Medical Toxicology of Occupational and Environmental Exposures

Volume I

Metals and Metalloids: Clinical Assessment, Diagnostic Tests, and Therapeutics

DONALD G. BARCELOUX

Edited by Robert B. Palmer

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MEDICAL TOXICOLOGY OF OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES

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MEDICAL TOXICOLOGY OF OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES

Volume 1

Metals and Metalloids: Clinical Assessment, Diagnostic Tests, and Therapeutics

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To My Wife, Kimberly,
Fifty years ago, a chance meeting in the Rome Train Station led to a life full of love, companionship, and a conversation that has continued through all these years. Your counsel and support made all the difference and life worthwhile.

To my adult children (Colin and Shannon) and their spouses (Taylor and Michael),
I am proud of your accomplishments, compassion, resilience, and the knowledge the world is a better place because of your presence.

Donald G. Barceloux, MD

To My Wife, Karen,
We intended to try to benefit the professional organizations through those endless committee and board meetings. Little did I know I would be the true beneficiary. Your love, kindness, and friendship, not to mention sage counsel, far exceed anything I could have ever hoped for.

To my daughter Abigail, who knows far more about metals chemistry than I ever will, and her husband, Michael. Your accomplishments are immense. But the real joy is the two of you falling for one another – beginning far too literally with a skydiving adventure.

Robert B. Palmer, PhD

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FOREWORD

The multivolume *Medical Toxicology of Occupational and Environmental Exposures* covering metals, radiation, and cancer is the eagerly awaited third instalment in the seminal series of medical toxicology textbooks written by Dr. Donald G. Barceloux. The first two books focused on natural substances and drugs of abuse, respectively, and have quickly established themselves as reference works in their respective fields. The comprehensive coverage of topics coupled with a consistent and easy-to-follow organization of content have made them indispensable companions of physicians and researchers alike. The newest addition to the series, created by Dr. Barceloux and edited by Dr. Robert B. Palmer, is a worthy successor to the first two books. Once again, the focus is on naturally occurring and man-made toxic threats that all medical toxicologists will have heard of but few will have had first-hand experience with. This is precisely what makes this work so valuable.

The first volume literally comprises an A–Z of all there is to know about the clinical toxicology of metals and metalloids, from aluminum to zirconium. The 36 chapters naturally include well-known toxic metals such as arsenic, cadmium, lead, and mercury on which there is a wealth of clinical and monitoring data available. Summarizing and organizing this information makes these chapters almost textbooks in their own right, covering their subjects in a breadth and depth rarely seen in other publications. This is exemplified by the chapter on arsenic which not only covers the well-known toxic inorganic arsenicals but also includes sections on gallium arsenide, organic arsenic, and arsine gas. Even chapters on metals that are rarely encountered in clinical practice offer a wealth of information, e.g. the chapter on beryllium boasts 167 references. And who would know where to look for information on the toxicokinetics of rare earths, or whether tellurium is a human teratogen? It is the attention to this kind of detail that sets *Medical Toxicology of Occupational and Environmental Exposures: Metals and Metalloids* apart.

In contrast to standard textbooks on clinical toxicology, *Medical Toxicology of Occupational and Environmental Exposures: Metals and Metalloids* is not only aimed at those working in the treatment of the poisoned patient. As the most comprehensive source of information in its field, it will equally be an invaluable reference for occupational physicians and hygienists as well as scientists and researchers in environmental health disciplines. Indeed, anyone concerned with the human health risk assessment and risk management of exposure to metals and metalloids, whether they work in regulatory agencies, industry, or universities, will benefit from this truly interdisciplinary work that will stand the test of time.

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PREFACE

This volume, *Metals and Metalloids*, in the multivolume *Medical Toxicology of Occupational and Environmental Exposures* is a continuation of the *Medical Toxicology Series* that began with *Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals* and *Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants*. The *Medical Toxicology Series* provides in-depth, evidence-based coverage of the most important human toxins. Similar to the rest of the *Medical Toxicology Series*, the goal of this volume is the creation of a comprehensive and convenient reference to answer questions regarding medical toxicology issues. The volume on *Metals and Metalloids* presents the basic and clinical science associated with exposure to these elements and their compounds.

The reader will recognize the similarities of the template in this volume with the template in previous books in the *Medical Toxicology Series*. This organizational consistency allows easy location of the appropriate information necessary for decisions regarding properties, sources, effects, regulation, and management of toxic exposures to metals and metalloids. General section headings include history, identifying information, physical characteristics, exposure, environmental fate, dose effect, toxicokinetics, histopathology, clinical response, diagnostic testing, health surveillance, and treatment.

Medical toxicology is a field often dependent on relatively weak scientific evidence (case reports, case series, retrospective analyses), resulting in the increased risk of perpetuating equivocal treatment regimens and even folklore. This volume provides the relevant evidence base to determine the clinical consequences, treatment, and safety measures important for the reduction of injury from excessive exposures to metals and metalloids. References are documented to validate the information and provide sources for further inquiry. Although this unique volume provides a medical toxicologist's perspective for exposures to metals and metalloids, the coverage contains input from a variety of disciplines including other clinical specialties, public health physicians, and research scientists. Since guidelines and regulations change with time, the organizations' websites should be consulted for any updates of specific guidelines and regulations.

The choice of topics in this volume reflects our desire to expand communication between medical toxicologists and practitioners in related fields. Our hope remains that this interdisciplinary, evidence-based approach will increase communication between traditional clinical settings and fields aligned with medical toxicology including those in laboratories, academic settings, and regulatory agencies. We anticipate this approach will encourage more inquiry into the pathophysiology, clinical effects, biomarkers, treatment, and prevention of illnesses related to metal and metalloid exposures.

Donald G. Barceloux, MD, Author
Robert B. Palmer, PhD, Editor
November 26, 2024

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John Wiley & Sons' Staff

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Pomona Valley Hospital Medical Center

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UCLA Emergency Department Colleagues

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DONALD G. BARCELOUX, MD

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REVIEW PANEL

The critical reviews and clinical insights of the distinguished Review Panel were much appreciated as an invaluable method to validate the scientific basis of *Medical Toxicology of Occupational and Environmental Exposures: Metals and Metalloids*.

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VOLUME 1

METALS and METALLOIDS: CLINICAL ASSESSMENT, DIAGNOSTIC TESTS, and THERAPEUTICS

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Chapter 1

ALUMINUM

HISTORY

Although the identification of aluminum as a metal occurred in 1827, the Romans used alum (hydrated aluminum sulfate) for the purification of water and the preparation and staining of hides.[1] In Europe, the commercial production of aluminum as a metallic pigment began shortly after the development of the Hall–Heroult electrolytic process in 1886. This process became the major industrial process for smelting aluminum by dissolving aluminum oxide (alumina from bauxite ore) in molten cryolite and electrolyzing the molten salt bath.[2] The first reported case associating aluminum toxicity with memory loss, ataxia, tremor, and muscle tics occurred in 1921.[3] Massive exposure to finely divided pyrotechnical aluminum flake powders during World War II in Germany caused fibrotic lung disease (aluminosis); ~20 years later, McLaughlin et al. reported the case of a ball mill operator with an occupational exposure to aluminum and aluminum oxide (Al_2O_3) during the production of flake powders; he presented with pulmonary fibrosis and encephalopathy (poor memory, speech disorder, myoclonic jerks, convulsion, focal weakness).[4]

In the middle of the 20th century (1944–1979), aluminum powder (e.g., McIntyre powder) was released in mines as a prophylactic agent to coat silica particles and prevent silicon-induced fibrotic reactions. Mortality studies of Australian cohorts exposed to aluminum dust prophylactically did not support the effectiveness of aluminum as a protective agent for silicosis.[5] This study suggested the possibility of increased risk of cardiovascular disease and Alzheimer's disease in the exposed cohort; however, the increase was small (SMR = 1.38) and not statistically significant with wide confidence intervals. An analysis of postmortem aluminum concentrations suggested pulmonary aluminum concentrations were similar in eight workers receiving McIntyre Powder and occupationally exposed workers.[6] The medical use of aluminum increased significantly in the 1950s when aluminum was prescribed as a phosphate binder to patients with chronic renal failure. By 1972, Alfrey et al. recognized an encephalopathy in patients on dialysis characterized by progressive dementia, myoclonus, facial grimacing, diffuse pain, and seizures.[7] This epidemic of dialysis dementia vanished when excess aluminum was eliminated from the dialysate.[8] In the early 1980s, a syndrome of encephalopathy, metabolic bone disease, and microcytic anemia occurred in dialysis-dependent children receiving aluminum-containing antacids.[9] Calcium carbonate gradually replaced aluminum-containing antacids in patients with chronic renal failure because of the lack of toxicity and the superior binding of calcium carbonate to phosphates compared with aluminum.[10] Parenteral solutions (e.g., total parenteral nutrition) were recognized as sources of aluminum loading, particularly in children; in 1990, the US FDA recommended that the aluminum concentration of these solutions not exceed 25 μg/L followed in 2004 by a daily recommended intake of 5 μg/kg.

PHYSIOCHEMICAL PROPERTIES

Aluminum is the third most abundant element in the earth's crust after oxygen and silicon, comprising about

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8% of the earth's crust and belonging to Group 13 (Group IIIa) along with boron, gallium, indium, and thallium.[11] Most aluminum compounds are solids with high melting points. Pure aluminum is a light, malleable, silvery-white metal that easily conducts both heat and electricity; however, the high reactivity of aluminum limits the existence of the metallic state in the earth's crust. The only natural oxidation state of aluminum is Al^{3+} with an ionic radius and chemical behavior similar to Fe^{3+}. Because aluminum has a small radius and an avid affinity for oxygen, this metal exists almost exclusively as aluminum oxides (bauxite) or aluminosilicate compounds (clays, feldspars, and micas). The resistance of aluminum to corrosion results from the rapid formation of aluminum oxide following exposure to oxygen, water, or other oxidants.

The pH determines the solubility of aluminum compounds; therefore, the physiological milieu strongly affects the affinity of Al^{3+} for hydroxide ions and the subsequent precipitation of the complex. Only small amounts of free aluminum exist in solutions within pH 6.5–7.4. Aluminum salts of chloride, nitrate, and sulfate are water-soluble, whereas metallic aluminum, aluminum oxide, and other aluminum salts (hydroxide, phosphate, silicate) are very poorly water-soluble. Aluminum hydroxides and aluminum phosphates are some of the least soluble aluminum salts, but both compounds contribute to aluminum exposure.[12] Aluminum oxide nanoparticles (<100 μm) more easily diffuse across biological membranes than larger particles.[13] At pH 7.0, the solubility of aluminum hydroxide and aluminum sulfate is limited (2.5 mg/L);[14] however, the solubility of aluminum salts increases as the pH deviates from neutral. Aluminum hydroxide binds hydrogen ions in an acid medium, whereas aluminum hydroxide releases hydrogen ions in an alkaline medium. In acidic aqueous conditions of the stomach (i.e., pH 2), aluminum occurs primarily as a monomolecular hexahydrate, $Al(H_2O)_6$, which is the "free" form of Al^{3+}. As pH increases to near-neutral conditions in the intestines, the insoluble precipitate (aluminum hydroxide, $Al(OH)_3$) forms. Table 1.1 lists the physical properties and identifying information of aluminum and common aluminum salts.

EXPOSURE

Commercial Processes

Aluminum exists naturally in bauxite, cryolite, feldspars, micas, and silicates. The major source of commercial aluminum is bauxite; this mineral contains aluminum hydroxide, silica, ferrous oxide, and smaller amounts of cryolite (Na_3AlF_6). The production of this metal via electrolytic reduction of the raw material involves the following: 1) the refining of bauxite (Bayer Process) under high temperature, pressure, and strong caustic solution to form alumina (aluminum oxide), 2) the electrolytic reduction of the hydrate by the Hall–Heroult process to produce aluminum in the reduction cells (pots), and 3) the casting of aluminum into ingots. During this chemical process, the aluminum leaches from the bauxite as sediment containing aluminum oxide (alumina). During the electrolysis of molten cryolite, the electrothermal process produces pure aluminum that precipitates on carbon cathodes in the furnace of a carbon-lined steel reservoir. Typically, ~200 pots are arranged in potlines within buildings called pot-rooms. Prebake technology has gradually replaced the older Søderberg pots, resulting in more efficient hooding, improved fume extraction, and reduced exposure to a variety of dust, fumes, and gases. Potential exposures to chemicals during the electrolysis of aluminum include tar oils, polyaromatic hydrocarbons (3,4-benzo(*a*)pyrene),[15] carbon monoxide, sulfur dioxide, and airborne fluorides (F^-, HF, sodium aluminum tetrafluoride).[16] In a study of 17,089 aluminum smelter workers followed from 1950–2004, the incidence of lung, bladder, and buccal cancer increased significantly ($P < 0.001$) with exposure to benzo(a)pyrene.[17]

Uses

Aluminum is an extremely versatile metal with myriad of uses as a structural material in the manufacture of food containers, insulating materials, automobile and airplane manufacturing, machinery, electrical products, and cooking utensils. Because pure aluminum lacks strength, most aluminum used in metallurgy involves the production of aluminum-based alloy castings and wrought aluminum products. The wire form of aluminum is used in welding, whereas the powder form is a constituent of paints, pyrotechnic flakes, and solid rocket propellants. Other applications for aluminum compounds include the following: antacids (hydroxide, phosphate), deodorants (chloride hexahydrate, hydroxide, phosphate, carbonate, silicate), abrasives (trioxide), petroleum cracking (anhydrous chloride), water purification (sulfate, alums), leavening agent (acidic sodium phosphate), grain fumigant (aluminum phosphide), emulsifying agent (basic sodium phosphate), acidifying agent (sulfate), anti-caking agent

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TABLE 1.1. Physical properties and identifying information of aluminum and aluminum salts.

Physical Characteristic	Aluminum	Aluminum Carbonate	Aluminum Chloride	Aluminum Fluoride	Aluminum Hydroxide
CAS RN	7429-90-5	53547-27-6	7446-70-0	7784-18-1	21645-51-2
Molecular formula	Al	$Al_2O_3 \cdot CO_2$	$AlCl_3$	AlF_3	$Al(OH)_3$
Molecular weight (g/mol)	26.98	NA	133.34	83.98	78.01
Color	Silver-white	White	White to gray-green	White	White
Physical state	Malleable metal	Aggregates or powder	Hexagonal plates	Hexagonal crystals	Bulky powder
Odor	Odorless	NA	Pungent	NA	NA
Melting point (°C)	660	NA	192.6	1,291	300
Density (g/mL, 20°C)	2.70	NA	2.48	3.10	2.42
Water solubility	Insoluble	Insoluble	Reacts violently[a]	5.59 g/L (25°C)	Insoluble
Vapor pressure	1 mm Hg (1,284°C)	NA	1 mm Hg (100°C)	1 mm Hg (1,238°C)	NA
Odor threshold					
Water	NA	NA	0.5 mg/L	NA	NA
Air	NA	NA	NA	NA	NA

Physical Characteristic	Aluminum Nitrate	Aluminum Oxide	Aluminum Phosphate	Aluminum Sulfate
CAS RN	13473-90-0	1344-28-1	7784-30-7	10043-01-3
Molecular formula	$Al(NO_3)_3$	Al_2O_3	$AlPO_4$	$Al_2(SO_4)_3$
Molecular weight (g/mol)	213.00	101.94	121.95	342.14
Color	Colorless	White	White	White, lustrous
Physical state	Rhombic crystals	Crystalline powder	Infusible powder	Crystals to powder
Odor	NA	Odorless	NA	Odorless
Melting point (°C)	73	~2,000	>1,460	770 (decomposes)
Density (g/mL, 20°C)	NA	4.0	2.56	1.61
Water solubility (25°C)	Very soluble	Soluble cold water[b]	Insoluble	Very soluble
Vapor pressure	NA	1 mm Hg (2,158°C)	NA	~0

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.
[a] Produces heat and hydrochloric acid on contact with water; [b] 0.98 mg/L, insoluble in hot water.

(silicate), color additives (aluminum lakes), the brewing and paper industry (bentonite, zeolite), the catalyst for the manufacture of rubber and wood preservatives (chloride), glass and ceramic production (borate), soap and paint industry, and food processing. Alum is a series of double sulfate salts of monovalent cations (i.e., principally aluminum, potassium, other aluminum sulfates) used to reduce the turbidity of drinking water. The sulfate of aluminum dissolves in water to form aluminum hydroxide, resulting in precipitation along with suspended organic matter. Aluminum chloride ($AlCl_3$) is a skin and mucous membrane irritant used as a fine powder in the petroleum cracking and polyisoprene production industries. Military applications have the greatest potential for aluminum nanoparticles, particularly coatings, fuels, and propellants.

Sources

The primary sources of exposure to this common metal for the general population are natural rather than anthropogenic processes.[11] In the environment,

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aluminum is always found in combination with other elements (aluminosilicates, oxides, hydroxides). Exposure to Al occurs daily, primarily via food (<10 mg) and drinking water (<1 mg).[18] The inhalation of airborne dust particles provides a much smaller contribution to the daily intake of Al (<0.1 mg/day). Potential sources of relative higher Al exposure for the general population include the use of aluminum-containing consumer products (e.g., antiperspirants, antacids, cosmetics). Exposure of the general population to anthropogenic sources of aluminum is primarily indirect. These sources include increasing dissolution of aluminum in the soil as a result of acidification from acid rain and enhanced wind and water erosion from cultivated land.[19]

Air

Aluminum exists in air primarily as aluminosilicates associated with particulate matter. The primary source of aluminum in the atmosphere is dust from the erosion of ores and rock material on the surface of the earth as well as volcanic activity. Only ~13% of the aluminum present in the atmosphere is released from anthropogenic sources with the major contributors being aluminum smelting, coal combustion, and commercial production of fuel and ores.[20] In urban environments, vehicle exhaust accounts for ~1–9% of the aluminum released into the ambient air.[21] Aluminum concentrations in urban air range from 0.4–10 ng/m^3 compared with background levels of 0.005–0.18 ng/m^3 in rural areas.[22,23] Aluminum concentrations in ambient air samples from aluminum plants are several orders of magnitude higher than in typical urban settings. In a study of 235 workers employed at 15 US plants producing various aluminum products, the median concentration of respirable and total aluminum in personal breathing samples was 25 μg/m^3 and 100 μg/m^3, respectively.[24] The percentage of particles deposited in the lungs depends on particle size; typically, about 20% of particles in the range of 0.1–0.3 μm are deposited in the alveolar region. In contrast to sparingly soluble Al particles, hygroscopic water-soluble Al salts may increase in size in the humid environment of the respiratory tract, thereby decreasing the deposition of inhaled Al particulates in the alveolar region. Higher ambient Al concentrations may occur during aluminum smelting (mean = 310 μg/m^3, range 40–900 μg/m^3 in 7 UK secondary smelters),[25] metal inert-gas (MIG) welding of aluminum cylinders (2,900 μg/m^3),[26] plants producing large flakes of pyrotechnical Al powder (5,000–21,000 μg/m^3),[27] and corundum (aluminum oxide) processing (1,600–7,400 μm^3).[28] Experimental studies suggest that fumes from MIG welding of aluminum may contain ozone up to 250 μg/m^3, potentially affecting lung function.[29]

Soil

The content of aluminum in the soil varies widely in different locations as a result of several factors (e.g., pH, volcanic activity). Aluminum is the third most abundant element with soil concentrations ranging from 700–100,000 mg/kg.[30] The aluminum concentration in urban street dust ranges from 3.7–11.6 μg/kg.[19] Most Al resides in bauxite rocks (hydrous aluminum oxides) or soil as insoluble Al silicates (e.g., feldspars, micas). Aluminum in the soil complexes with sodium and fluoride (cryolite). Weathering results in the formation of aluminum hydroxide.

Water

Although aluminum is ubiquitous in natural waters, the Al concentration in surface water is usually low (<0.1 mg Al/L) because aluminum solubility is very low in water with a pH >5.5. High humic acid content and acid precipitation increase aluminum content of groundwater. Ash from volcanic eruptions (e.g., Mt. Saint Helens) may increase Al concentrations in water up to 1 mg/L.[31] Aluminum concentrations in the ocean are much lower (i.e., <0.001 mg/L) than in lakes or streams.

High aluminum concentrations develop only when the pH is <5; this situation is unusual because the pH of naturally occurring water typically ranges from 6–9.[30] The median aluminum concentration in drinking water is highly variable ranging up to ~1 ppm.[32] Higher Al concentrations occur in water from treatment facilities using aluminum sulfate (alum) as a flocculent. In a study of US drinking water samples, the median Al concentration from facilities using alum was 0.224 mg/L compared with 0.043 mg/L for water samples that did not contain alum as a flocculent.[32]

Diet

Aluminum Intake

The primary (i.e., ~90–95%) source of aluminum for the general population is food, particularly food additives (e.g., acidifiers, buffers, emulsifiers, anti-caking agents, leavening agents, stabilizers, thickeners) in grain products, salt, and processed cheese.[33] Most adults ingest <15–24 mg of Al daily with ~1–10 mg derived from natural sources. Aluminum-containing medication and food additives account for ~5–7 mg.[19,34] The mean daily intake of Al from food in Bombay, India, was

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~6 mg with the total daily intake from inhalation and ingestion ranging ~2–12 mg.[35] The poor absorption of aluminum from the gastrointestinal tract limits daily Al absorption to ~0.3–0.5% of the daily intake.[36] Drinking water accounts for the small amount of the remaining Al exposure because the bioavailability of Al in drinking water is low (<1%).[37] Drinking water typically contributes <1–5% of the total daily Al intake by the general population.[38,39]

Foodstuffs

Aluminum (metallic aluminum, aluminum sulfate, sodium aluminum phosphate) is an approved food additive in the United States and the United Kingdom. Aluminum sodium silicate helps smooth icing on cakes in concentrations up to 1.5%.[40] These aluminum additives are more important sources of aluminum intake in the United States than in Europe.[33] Aluminum occurs naturally in tea and some vegetables. Sources of aluminum in food include processed cheese, cornbread, bay, herbs, spices, tea, some soy-based milk products, baking powder (prepared cake mixes), pancake mixes, self-rising flour, and pickled vegetables.[41] In a study of German foods, the order of increasing aluminum content was as follows: beverages, food of animal origin, and food of plant origin.[42] Table 1.2 lists the aluminum concentrations of some selected foods.

The aluminum content of beverages from aluminum cans is generally higher (noncola drinks, 33.4 μmol/L; cola drinks, 24.4 μmol/L) than that of beverages from bottles (5.6–8.9 μmol/L).[43] Both pH and container type influence the aluminum content in beverages with a pH of about 3.8 being the optimum pH for the transfer of Al from the container to the liquid. The aluminum content in a survey of beer containers was greatest in draft beer and least in beer bottles.[44] Dietary citric acid increases the absorption of oral aluminum loads (e.g., antacids) as a result of the formation of the more soluble Al-citrate complexes.[45] Because aluminum is abundant in the soil, some foods (e.g., carrots) may contain high Al concentrations (1,520–4,050 μg/100 g).[46]

Containers and Heating

Although cooking acidic food (tomatoes) in uncoated aluminum utensils or placing acidic food (vinegar, fruit

TABLE 1.2. Estimated aluminum concentration in selected foods. (Adapted from Soni et al.).[11]

Food Type	Aluminum Concentration (mg/100 g)	Food Type	Aluminum Concentration (mg/100 g)
Animal Products		*Vegetables*	
Cheese, natural	1.57	Beans, green cooked	0.34
Cheese, processed	29.7	Spinach, boiled	2.5
Hamburger	2	Potato, cooked (India)	1.08
Fish, (cod) cooked	0.04	Potato, baked (USA)	2.6
Milk	0.07	Spinach, canned	1.17
Fruits		*Nuts*	
Apple sauce	0.01	Peanut butter	0.02
Banana	0.04	Walnuts	0.02
Grains		*Herbs and Spices*	
Bran, wheat	1.28	Bay	43.6
Bread white	0.3	Cinnamon	8.2
Bread, whole wheat	0.54	Oregano	60
Rice, cooked	0.17	Pepper, black	14.3
Pancake, from mix	6.9	Thyme	75
Muffins, blueberry	12.8	Basil	30.8
Tortilla, flour	12.9	Celery seeds	46.5
Cornbread	40	Sage	40.4
Other			
Cocoa	4.5		
Pickles (aluminum additives)	3.92		
Cream substitute	13.9		
Baking powder	2,300		
Salt (aluminum additives)	16.6		
Tea in bag, dry	128		

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juice, lemons) in aluminum containers can increase the amount of aluminum in the food, the increase does not usually appear sufficient to cause adverse effects.[47,48] Cooking in aluminum containers causes a statistically significant increase in the Al content of some foods; cooking rhubarb in an aluminum saucepan increased the aluminum content in the meal from 0.1–25 mg.[23] A Swedish cross-sectional study suggested the use of aluminum utensils add 2 mg daily Al intake.[49] The mean Al intake from the diets of 105 Swedish women was 13 mg (range, 1.2–99 mg) compared with 7.8 mg (range, 1.2–24 mg) in 41 diets with little or no use of aluminum. In a study of Belgian adults, the estimated contribution of kitchenware to the diet was 7-fold less than that of food based on leaching models for food contact materials and surface area determined by in-house validation surveys.[50] A case report associated the chronic injection of an oral methadone solution heated in an aluminum pot with Al toxicity (admission Al = 180 μg/L) in an intravenous methadone addict with mild to moderate renal failure.[51] The symptoms of aluminum toxicity (seizures, ataxia, dysarthria, cognitive decline) occurred after ~3–4 years of regular intravenous injections; determination of causation is limited by the use of multiple drugs of abuse. Rarely, a delayed, toxic (spongiform) leukoencephalopathy manifested by apathy, cerebellar signs, confusion develops after inhalation of pyrolysates from heating heroin on aluminum foil ("chasing the dragon"). A 46-year-old woman with heroin dependence presented with acute behavioral changes and MRI images consistent with toxic encephalopathy.[52] Later, she developed difficulty making decisions (abulia), catatonia, and akinetic mutism before recovering.

Infant Formula

In general, the aluminum content of human breast milk and cow milk is very low (<0.05 mg/L).[53] Risks of aluminum toxicity are documented only for infants with renal failure exposed to high aluminum concentrations from drugs or dialysate fluid and preterm infants receiving high Al-containing parenteral nutrition.[54] The mean aluminum concentration in breast milk in one study was 49 μg/L, whereas the Al concentration of most baby formulas is <500 μg/L.[55] The aluminum concentration is ~10–20-fold higher in cow milk and ~100-fold greater in soy-based formulas than breast milk.[56] A study of seven infants with renal failure suggests that low-phosphorous infant formula produces no greater risk of aluminum toxicity than ingestion of a regular diet.[57]

Medical Therapy

Antacids

The use of maximum recommended daily doses of aluminum hydroxide-containing antacids substantially increases the daily aluminum intake up to 5 g.[58] Aluminum hydroxide antacids contain ~32 g Al/L. Under normal circumstances, poor absorption prevents aluminum toxicity; however, aluminum encephalopathy has occurred in uremic patients given large amounts of aluminum-containing antacids.[9] The administration of citrate in the form of calcium salts,[59] effervescent analgesic tablets,[60] or Shohl's solution[61] markedly increases aluminum absorption; the co-administration of citrate and aluminum-containing antacids may produce aluminum encephalopathy in dialysis patients.

Sucralfate

Sucralfate is a basic aluminum salt that contains 21% aluminum by weight. The bioavailability of aluminum in sucralfate increases at low pH, but aluminum absorption of this product in patients with normal renal function is not clinically significant.[62] A 21-day course of 4 g sucralfate daily significantly increased the serum aluminum level in 6 patients with chronic renal failure to 0.83 ± 0.48 μmol/L compared with patients without renal failure (0.24 ± 0.17 μmol/L).[63] Case studies suggest that the administration of sucralfate to patients with renal failure may produce an aluminum encephalopathy.[64,65]

Intravenous Solutions

Increased aluminum and osteomalacia may occur in patients receiving long-term total parenteral nutrition (TPN), even in patients with normal renal function.[66] The replacement of casein with amino acids substantially reduced the stainable aluminum on the surface of mineralized bone.[67] Infusions of purified albumin during plasmapheresis may increase plasma aluminum concentrations 5-fold,[68] although the clinical significance of this exposure to aluminum remains unclear. An acute encephalopathy developed in patients with renal dysfunction after the administration of intravesical irrigations of alum (ammonium aluminum sulfate) for severe urinary hemorrhage.[69,70,71,72]

Dialysis Fluid

Significant amounts of aluminum may diffuse across the dialysis membrane with plasma Al concentrations >10 μg/L potentially occurring during hemodialysis.[73] Because aluminum binds to nondialyzable plasma

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constituents, little aluminum typically passes into the dialysate.[74] Consequently, aluminum accumulates in the plasma of dialysis patients during hemodialysis. Techniques (e.g., reverse osmosis, deionization) almost eliminate aluminum from the dialysate.

ENVIRONMENTAL FATE

As an element, Al does not degrade in the environment. This element is highly reactive; consequently, aluminum does not exist as a free metal in nature.[23] Aluminum enters the air from the erosion of soil and combustion of coal, primarily as aluminosilicates associated with particulate matter. Transport of aluminum to soil occurs primarily through the deposition from the atmosphere. Aluminum exists naturally only in the trivalent oxidation state. Consequently, the fate of aluminum in the soil and water depends upon the chemical interactions of anions and water as well as the physical characteristics of the local environment (underlying geological materials, hydrological flow paths, soil–water interactions).[19] The presence of high concentrations of dissolved organic matter (i.e., fulvic acid) increases the amount of dissolved aluminum in streams and lakes. At pH >5.5, aluminum exists predominately in the undissolved form (i.e., gibbsite (aluminum hydroxide) and aluminosilicates). The mobility of Al in the soil increases as the pH decreases. Adsorption of Al into clay may limit mobility. Bioconcentration of Al in plants is limited, although Al uptake increases in a few plants (e.g., tea) grown on acidic soil. Because of the toxicity of aluminum to aquatic animals, Al does not bioaccumulate in the food chain.[23]

DOSE EFFECT

Because absorption of aluminum from the gastrointestinal tract is poor and aluminum excretion is rapid, the ingestion of aluminum compounds seldom produces toxicity unless renal dysfunction causes the accumulation of aluminum in the body. Healthy individuals on normal diets sustain little risk of aluminum toxicity including those cooking with aluminum pans.[75,76] Susceptible patients include patients with renal failure and premature infants receiving parenteral nutrition.[77] There is little risk of acute aluminum toxicity. The administration of 40 mg Al/kg/day as montmorillonite (loosely bound clay minerals containing hydrated aluminum silicates) to healthy adults for up to 90 days was not associated with any adverse effects.[78]

TOXICOKINETICS

Absorption

Oral

Factors that affect the absorption of aluminum include the bioavailability of the specific aluminum salt administered, the effect of pH on aluminum speciation and solubility, and dietary factors. Volunteer studies indicate that adults with normal renal function absorb between 0.1–1% of an oral dose of aluminum following ingestion depending on the solubility of the specific aluminum compound and the presence of complexing agents (organic acids, amino acids, silicates, carbohydrates, nucleotides, phosphates).[31,79] The presence of carboxylic acids (e.g., citric, lactic) enhances the absorption of aluminum, whereas the presence of phosphate or dissolved silicate decreases the absorption of aluminum.[23] Most of the gastrointestinal absorption of aluminum occurs in the acid media of the stomach, whereas very little absorption occurs in the duodenum. The poor bioavailability of aluminum significantly limits the oral toxicity of aluminum, particularly water-insoluble, hydrated aluminum silicates.

The bioavailability of aluminum from drinking water averages ~0.3% compared with an average bioavailability of ~0.1% from food;[80] the presence of food, calcium, or magnesium does not alter the bioavailability of aluminum in drinking water.[81] Unabsorbed aluminum hydroxide combines with phosphates in the gastrointestinal tract; the resultant aluminum phosphates are insoluble and excreted in the feces. Animal experiments confirm the limited bioavailability (i.e., 0.27–2.18%) of aluminum salts (e.g., borate, chloride, citrate, glycinate, hydroxide, lactate, sucralfate) in solutions with pH ranging from 1.7–7.0.[82] In studies of fasted rats gavaged with doses of aluminum citrate normally present in the diet, the absorption of aluminum ranged from ~2–5%.[83]

Pulmonary

In contrast to the oral route of Al exposure in the general population, inhalation is the primary route of occupational exposure to aluminum. Pulmonary absorption of aluminum varies between aluminum processes depending on solubility and particle size. Typically, aluminum-containing welding fumes consist of particles <1 μm in diameter, whereas the particles in aluminum flake powders vary from 5–200 μm in diameter and 0.05–1 μm in thickness.[84] Studies of workers exposed to welding fumes suggest that some absorption of aluminum (i.e., ~2%) occurs following the inhalation

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of aluminum compounds based on increased urinary excretion of aluminum;[85] however, elevated plasma aluminum concentrations are usually small and the clinical significance of these concentrations appears limited. Based on limited industrial data, the bioavailability of soluble airborne Al is ~1.5–2% as a result of the conversion of Al to less soluble forms (aluminum oxides) in aqueous tissues.[24,80] A Scandinavian study of five aluminum sulfate workers suggests exposure to soluble Al at an aluminum sulfate plant may result in higher aluminum absorption (i.e., ~7%).[86] The mean, 8-hour time–weighted average aluminum concentration was 0.13 mg/m^3 with a range of 0.02–0.5 mg/m^3.

Dermal

Few data exist on dermal aluminum absorption; however, intact skin apparently acts as a barrier to aluminum absorption.[87] A case report of a 43-year-old woman using an aluminum chlorohydrate-containing antiperspirant daily for 4 years suggested some dermal aluminum absorption occurs based on an initial plasma aluminum concentration of ~10 µg/dL (normal reference range of <1 µg/dL) prior to cessation of deodorant use.[88] Limited studies of the dermal application of ^{26}Al chlorohydrate on human volunteers indicate that the bioavailability of Al in this form does not exceed 0.012%.[89] In an *in vitro* study of human donor skin, transdermal Al absorption was very small (i.e., ≤0.07% of the deposited aluminum) with a mean absorption rate of 1.8 µg/cm^2 for the aerosol base and 0.5 µg/cm^2 for the roll-on type antiperspirant.[90] The measured uptake was significantly higher on stripped skin (11.50 µg/cm^2) than normal donor skin (1.81 µg/cm^2).

Distribution

The amount of aluminum bound to serum proteins increases with increasing blood aluminum concentrations ranging 54–92% between serum Al concentrations of 7.8–152 µg/L.[91] Aluminum is bound to low and high protein fractions (transferrin, albumin) along with small-molecule plasma binders (bicarbonate, citrate, fluoride, phosphate). Under normal conditions, ~80–90% of plasma aluminum is bound to transferrin and, to a lesser extent, albumin with the remainder forming soluble, small-molecular complexes (e.g., citrate, phosphate) including hydrolyzed forms.[92,93] Aluminum closely follows the iron pathway in the extracellular environment of humans.[94]

The average healthy individual contains ~30–50 mg Al with the highest concentration (i.e., ~1/2 the body burden) in the skeleton (5–10 mg/kg wet weight).[95] Ingested aluminum distributes primarily to bone (i.e., ~50–60%) and, to a lesser extent, to lung (i.e., ~25%), muscle (10%), liver, spleen, and kidney.[96,97] The retention half-times for aluminum in bone are long depending on bone turnover. The estimated retention half-times in trabecular bone (20% turnover/year) are ~500 days compared with 29 years for cortical bone (3% turnover/year).[98] Under normal circumstances, Al does not accumulate in the body. The brain contains ~1% of the aluminum body burden (0.25–0.75 mg Al/kg wet weight).[23] In animal studies, the steady-state V_d is dose dependent, ranging from 38–1.175 L/kg.[91] Most of the inhaled aluminum dust remains in the lungs.

Elimination

In healthy patients with normal renal function, elimination of aluminum occurs almost exclusively (>95%) by renal excretion with biliary excretion accounting for ~2% of the absorbed dose;[99,100] however, biliary excretion is the major route of elimination in patients with renal failure.[101] Normal renal excretion of aluminum in humans is <20 µg/day, but daily urinary Al excretion can increase up to 3,800 µg in patients receiving aluminum-contaminated total parenteral nutrition solutions.[102]

Blood

Animal studies suggest the plasma half-life of aluminum is relatively short (<40 hours) when renal function is normal.[103] The plasma elimination half-life increases to ~85 days in dialysis patients given aluminum-containing antacids.[91]

Urine

Studies of urinary Al elimination in aluminum-exposed workers indicate the existence of at least a two compartment elimination phase: 1) a relative rapid elimination phase, and 2) a much slower compartment probably dependent on redistribution of Al from body stores (e.g., bone, lungs), duration of exposure, and solubility of the aluminum compound. Examination of welders exposed to aluminum indicates two functional compartments exist: 1) an easily exchangeable compartment for recently exposed welders (<1 year) with an estimated $t_{½}$ of 9 days, and 2) a deep compartment in welders exposed >10 years with an estimated $t_{½}$ > 6 months.[104] A field study of seven workers exposed to alumina (Al_2O_3), aluminum fluoride (AlF_3), and cryolite (Na_3AlF_6) in potrooms from an aluminum fluoride

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production plant demonstrated a mean initial urinary Al elimination half-life of 7.5 hours (range, 5–9 hours) based on urine samples collected over the weekend.[105] These workers were exposed to variable amounts of soluble and insoluble aluminum with a ratio typically <1.

The terminal urinary Al elimination half-life based on urine Al concentrations in retired aluminum workers is much longer than the general population depending on differences in particulate size, solubility, and subsequent absorption.[104,106] The calculated elimination half-life of urinary aluminum in 10 retired aluminum workers exposed to poorly soluble aluminum flake powders ranged from 0.7–8 years depending on the length of retirement (0.5–14 years).[84] In this study, the urinary elimination half-life of Al was nearly constant (5–6 weeks) after cessation of Al exposure for 4–5 weeks, despite a large variation in the duration of Al exposure (1–20 years). In contrast to the relatively small particulates released during welding (i.e., <0.4 μm), the much larger aluminum flakes form a long-term pulmonary aluminum pool with a slow, fixed elimination rate.

Maternal–Fetal Kinetics

In a study of the four stages of breast milk production (colostrums, transitional milk, early mature milk, mature milk), the concentrations of microelements decreased with advancing lactation stages.[107] The mean aluminum concentration in samples from 45 lactating women in each lactation stage ranged from 56.45 ± 22.77 ng/mL in colostrum samples to 13.44 ± 6.28 ng/mL in mature breast milk samples.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Aluminum has no known physiological role in mammals; under normal circumstances, the amount of aluminum in the body is small. The mechanism of aluminum toxicity is not well defined. Al competes in biological systems with cations (e.g., magnesium) despite differences in the oxidation states.[23]

Central Nervous System

Aluminum-containing phosphate binding agents increase gastrointestinal aluminum absorption and predispose patients with renal dysfunction to aluminum toxicity including ataxia, dysmetria, tremors, hyperreflexia that progresses to cognitive and motor dysfunction.[108] Aluminum toxicity occurs almost exclusively in patients unable to excrete dietary aluminum. The pathogenesis of aluminum encephalopathy remains unclear. Animal studies indicate that aluminum inhibits many enzymes in the brain including acetylcholinesterase, ADP-ribosylation, acetyltransferase, cytosolic and mitochondrial glycolysis, monoamine oxidase, and dihydropteridine reductase.[109] Existing data suggest that aluminum may inhibit neurological processes that determine the uptake of γ-aminobutyric acid, choline, glutamate, and serotonin by replacing magnesium on DNA-protein binding sites. The comparatively slow release of aluminum from neurological sites would cause dysregulation of protein synthesis in the central nervous system (CNS).[110] Neuropathological changes include nerve cell atrophy and death, stromal spongiosis, and proliferation of astrocytes and microglia in the cerebral cortex, basal ganglia, and thalamus.

Alzheimer's Disease

Pathology

The characteristics of Alzheimer's disease are senile plaques with β-amyloid and aluminosilicate deposits at the core, neurotransmitter deficits (decreased cholinergic activity), and neurofibrillary tangles identified as helical filaments in damaged neurons. Alzheimer's disease results from both genetic and environmental factors with neurofibrillary tangles and amyloid-β oligomers accounting for <50% of the cognitive impairment. The neurofibrillary tangle is the characteristic pathological feature of Alzheimer's disease; this lesion contains primarily aluminum. Higher concentrations of both aluminum and silicon in the form of aluminosilicates are found in the central region of senile plaque cores compared with the distribution of other inorganic constituents. This finding suggests that aluminosilicates may be involved in the early initiation of senile plaques;[111] however, increased brain aluminum concentrations occur in other diseases that do not produce dementia (e.g., hepatic and renal failure, metastatic carcinoma, amyotrophic lateral sclerosis).

Etiology

Animal models of aluminum toxicity demonstrate pathological changes similar to those found in Alzheimer's disease; however, significant differences also exist between aluminum encephalopathy and Alzheimer's disease.[103] In 1973, Crapper et al. suggested aluminum was a potential neurotoxic factor in Alzheimer's disease because of elevated aluminum concentrations in the postmortem examination of the brains

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of these patients;[112] however, there was no elevation of aluminum concentrations in postmortem samples of hair, serum, or cerebrospinal fluid.[113] Banks et al. suggested that aluminum alters the blood–brain barrier,[114] but the potential role of aluminum and its neurotoxic mechanism await further clarification. Other potential mechanisms for the effect of aluminum on the development of Alzheimer's disease include the effect of aluminum on the phosphatidylinositol-derived second messenger system[115] and the elevated basal levels of inflammatory markers present in Alzheimer's disease.[116]

Pathological studies in humans do not support a strong causal link between Alzheimer's disease or dialysis-associated encephalopathy and aluminum exposure.[117] Case-control studies of patients using antacids for peptic ulcer disease have not demonstrated an excess incidence of Alzheimer's disease.[118] Other factors that may contribute to the formation of Alzheimer's disease include slow viruses or virions (most favored etiology, although unproved) and autoimmune processes. Aluminum toxicity is one of several theories on the etiology of this disease; however, there is no direct evidence to support a primary role for aluminum in the etiology of Alzheimer's disease.[19,119] Consequently, the association between dementia and aluminum exposure remains unproven.[120]

Pulmonary

Although long-term exposure to stamped aluminum powder used in pyrotechnics potentially produces pulmonary fibrosis, most other types of aluminum particles do not appear fibrogenic. Potential toxic exposures in aluminum-producing facilities include dusts (alumina, carbon, cryolite, fluorides), fumes, gases (hydrogen fluoride, sulfur dioxide), trace elements (chromium, nickel, vanadium), and strong electromagnetic fields. The cause of potroom asthma is not well established. A cross-sectional study of potroom workers did not reveal a difference in immune function between workers who did or did not develop asthma.[121] The similarity of serum IgE concentrations in potroom asthma with and without asthma and evidence of airway inflammation suggests an irritant, nonimmunological mechanism.[122] In a study of 7 aluminum smelters in Australia and New Zealand, the incidence of occupation asthma was correlated with the geometric mean total fluoride concentration as measured by personal samples of employees undertaking anode changing.[123]

Bones

Chronic renal failure patients on long-term hemodialysis develop high serum and tissue aluminum concentrations, especially in bone. Children with azotemia,[124] infants receiving aluminum-contaminated intravenous solutions,[66] and uremic neonates drinking powdered milk with high aluminum content[125] are particularly susceptible to this complication. Aluminum reduces bone resorption by multiple mechanisms including the following: 1) production of a relative phosphorus deficiency by binding to phosphorus; 2) enhancement of calcium excretion by prevention of calcium uptake into bone; 3) inhibition of the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (active form); and 4) reduction of parathyroid hormone secretion.[126] Quantitative bone histology in uremic children with excessive aluminum loads in their bone demonstrates osteomalacia and/or a lack of mineralization that resolves with the removal of the aluminum.[31] The histological characteristics of this vitamin D-resistant osteomalacia include deranged membranous bone formation characterized by the accumulation of osteoid matrix along with decreased lamellar and osteoid bands, reduction of osteoclasts and osteoblasts, and poor mineralization. The effect of aluminum on bone occurs mainly in trabecular bone rather than the less metabolically active cortical bone. Aluminum localizes in patients with aluminum-induced osteomalacia at the interface between osteoid and calcified matrix in trabecular bone based on the azurine stain.[1] Consequently, the presence of aluminum in bone inhibits the incorporation of calcium into the matrix.

The cause of osteomalacia in renal failure is probably multifactorial, but the exact mechanism of the effect of aluminum on bone remains unclear. Proposed mechanisms include direct effects on crystal seeding and growth as well as disturbances of collagen formation and impaired mineral entrance. Indirect effects include altered vitamin D metabolism, increased vitamin D resistance,[127] and osteoblast inhibition. The effect of aluminum on parathyroid hormone secretion is controversial. One theory assumes that the deposition of aluminum in bone blocks the incorporation of calcium into osteoid, leading to osteomalacia. The prevention of calcium deposition in bone results in elevated serum calcium concentrations as the calcium returns to the circulation; subsequently, the elevated serum calcium concentration inhibits the release of parathyroid hormone by the parathyroid glands.[128]

Blood

Aluminum may be a contributing factor to the development of uremic toxins, a functional deficiency in erythropoietin, and microcytic anemia during chronic renal insufficiency.[129] Animal experimentation as early

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as 1929 demonstrated that aluminum toxicity produced anemia similar to lead poisoning.[130] Even in the absence of severe anemia or microcytosis, aluminum contributes to the microcytic, hypochromic anemia of chronic renal disease, probably by impairing iron utilization or enhancing fecal iron/zinc elimination.[78,131] Modest accumulation of aluminum (<100 μg/L) probably inhibits hemoglobin synthesis based on a study using a 3-month course of deferoxamine treatment.[132] Iron binding of transferrin-binding sites is probably an important mechanism in the production of aluminum-induced microcytic anemia.

Postmortem Examination

Although the postmortem examination of the brain from a hemodialysis patient dying from aluminum encephalopathy revealed some immunohistochemical staining by phosphorylated neurofilaments, there were no neurofibrillary tangles, neuropil threads, or senile plaques associated with Alzheimer's disease.[133] The autopsy demonstrated nerve cell atrophy in the cerebral cortex along with mild loss of spongiosis of the stroma and proliferation of astrocytes. Five months before her death, her serum aluminum concentration was 195 μg/L.

CLINICAL RESPONSE

Medical Therapy

Children and adults with kidney disease have an elevated risk of aluminum toxicity along with preterm infants. Elevated aluminum concentrations (serum Al 150–350 μg/L) are associated with dialysis-associated encephalopathy and dialysis-associated osteomalacia[129] that require 3–7 years of dialysis for clinical expression.[134,135] Symptoms usually develop insidiously over months to years in chronic renal failure patients unless dietary aluminum loads are excessive. In dialysis patients with high Al body burdens, microcytic anemia is a common finding. The erythrocyte Al concentration correlates with decreases in the MCV and hematocrit. In a study of dialysis patients with Al overload comparing the highest and lowest quartiles of erythrocyte Al concentrations, these reductions were dose-dependent.[136]

Neurological

Aluminum-induced dialysis encephalopathy is pathologically distinct from Alzheimer's disease with epidemiological evidence insufficient to link aluminum to Alzheimer's disease. The most common neurological features of dialysis encephalopathy beginning with the most frequent include the following: multifocal seizures, disturbance of speech, mood change, dyspraxia other than of speech, myoclonus, gait disorder, episodic confusion, intellectual deterioration with poor concentration and short-term memory loss, and changes in personality and behavior.[137] Typically, these symptoms are episodic; however, the disease may be fatal in the absence of measures to reduce the Al load.[138] Nonspecific symptoms often precede major symptoms including malaise, anxiety, depression, and loss of memory and concentration. Premature infants with reduced renal function may develop excessive aluminum concentrations and an encephalopathy when dialyzed with aluminum-containing fluid or receiving TPN with excessive Al loads.[139]

Bone

Bone fragility (dialysis-associated osteomalacia) occurs in renal dialysis patients with high body burdens of aluminum (plasma Al concentrations >63 μg/L).[135] Typical features of vitamin D-resistant osteomalacia include progressive bone pain, fractures, bone deformities, and proximal myopathy.[1] Bone pain is an early sign of dialysis-associated osteomalacia, particularly in the back and feet. Dialysis-associated osteomalacia and encephalopathy are clinically distinct manifestations of aluminum toxicity that may present as separate clinical illnesses. The presence of osteomalacia does not necessarily indicate the presence of an encephalopathy as many patients with dialysis-associated osteomalacia do not have clinical evidence of cognitive impairment.[98] The oral administration of aluminum hydroxide to infants with renal disease has been associated with the development of bone disease.[140]

Acute Oral Toxicity

Aluminum compounds have relatively low acute toxicity as a result of poor gastrointestinal and pulmonary absorption, particularly the water-insoluble hydrated aluminum silicates. Attapulgite (palygorskite) is an aluminum-containing absorbent used in large doses for Traveler's and HIV/AIDS-related diarrhea without acute systemic effects.[141] The systemic toxicity associated with the ingestion of aluminum phosphide results from the formation of phosphine gas rather than the absorption of aluminum.

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Environmental Exposure

The acute toxicity of aluminum is low with little evidence of acute toxicity following dietary exposure in the general population.[142] Epidemiology studies do not clearly demonstrate a causal link between the aluminum concentrations in drinking water and the incidence of Alzheimer's disease. Some,[143,144] but not all[119] epidemiological studies demonstrate a statistically significant positive association between chronic aluminum intake from drinking water and cognitive decline or dementias (e.g., Alzheimer's disease). Some of these studies also report inverse associations between other factors (low pH, silicon, fluoride) and dementias. An 8-year follow-up study of 3,777 subjects from southwestern France detected a relative risk of Alzheimer's disease after adjustment for age, gender, educational level, place of residence, and wine consumption of 2.14 (95% CI, 1.21–3.80) for subjects exposed to Al concentrations exceeding 0.1 mg/L.[145] However, there was no dose-response relationship between aluminum concentrations in drinking water and Alzheimer's disease. The bioavailability of Al is low (<1%), and drinking water represents a small fraction (1–2%) of the daily Al intake. Consequently, unidentified confounders probably contribute to the positive results in these epidemiology studies. There is no epidemiological evidence to suggest that environmental (e.g., drinking water, ambient air) Al exposure causes bone fragility.[146]

Occupational Exposure

Lungs

Pulmonary Fibrosis

Pulmonary fibrosis (i.e., aluminosis in Sweden) has been reported in some,[147] but not all, studies of workers heavily exposed to fine aluminum dust in the aluminum industry. Frequently, co-exposure to silica occurs with the handling of aluminum ores (e.g., bauxite, corundum). The combined exposure to dust from these ores has been associated with pulmonary fibrosis (Shaver's disease),[148] but studies of workers exposed only to aluminum dust are contradictory. Severe pulmonary fibrosis developed in workers exposed to some aluminum metal dyes in Germany, Sweden, and England.[149] Pulmonary aluminosis was associated with the use of submicron-sized aluminum pyrotechnic flakes that were lubricated with a nonpolar aliphatic oil. The contribution of the oil to the development of pulmonary pathology was limited because other processes that used polar lubricants did not produce pulmonary abnormalities.[150] Exposure to low-temperature transitional aluminas in aluminum chemical refineries, high-temperature transitional aluminas in smelters (i.e., after 1960), and high-fired alpha-aluminum oxide found in potteries indicated that these aluminas demonstrate minimal, if any, fibrogenic potential.[151]

As a result of improved working conditions in recent decades, the occurrence of aluminum pneumoconiosis is rare. Several studies of aluminum workers and Chinese workers exposed to fine aluminum dust did not demonstrate excess cases of pulmonary fibrosis, although exposure to aluminum oxide during abrasive production was a *suspected* cause in nine workers with abnormal chest X-rays.[152] A case report associated chronic interstitial pneumonia of a predominantly desquamative pattern with work as an electric arc welder based on the presence of aluminum in alveolar macrophages;[153] however, a cross-sectional study of 64 aluminum welders did not reveal an excess of pulmonary disease.[154] The use of high-resolution CT scans demonstrated ill-defined, small, rounded opacities predominately in the upper lung regions in 24% ($n = 15$, mean exposure = 15 years) of 62 men working in 2 Al powder producing plants.[155] The CT findings suggested an alveolitis that had not progressed to fibrosis. Several of the affected workers had low plasma and urine Al concentrations; hence, other factors may have contributed to the development of mild alveolitis.

Asthma

A persistent, asthma-like syndrome ("potroom asthma") develops in workers exposed to fumes from the electrolytic extraction of aluminum (Hall–Heroult process) that often improves following removal from work.[156] The pot (Søderberg or prebake type) is the electrolytic cell where the reduction of alumina occurs; the surrounding building is the potroom. Some,[157] but not all, studies of potroom workers have demonstrated an increased incidence of asthma and chronic bronchitis. Although the occurrence of asthma is associated with the duration of employment in potrooms (OR = ~3 for 10 years of employment), studies have not demonstrated a statistically significant increase in asthma in potroom workers compared with the general population.[158] Risk factors for the development of potroom asthma include smoking, family history of asthma, and exposure to fluoride particulates and perhaps sulfur dioxide,[159,160] The incidence of potroom asthma has dramatically decreased with improvements in fume extraction systems at these plants, and there is no direct evidence that exposure to aluminum alone produces asthma in these workers.[123] Occupational asthma has not been

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associated with the separation of alumina (Al_2O_3) from bauxite ores (Bayer process).[158]

Central Nervous System

Reports on the cognitive effects of exposure to aluminum are conflicting with most studies using small populations, questionable methodology, inadequate exposure assessment, and poor control of confounding variables.[19] Case reports suggest that workers with aluminosis may develop central nervous system (CNS) dysfunction and dementia.[161] The first case report associating CNS abnormalities with occupational aluminum was published in 1962.[4] A 49-year-old ball-mill operator in an aluminum flake powder factory developed seizures, memory loss, dysarthria, and increased left hemiparesis after working for over 13 years in this factory. He died of bronchopneumonia within 1 year; however, no imaging studies were reported to clarify the etiology of his CNS abnormalities. Three aluminum smelter workers developed spinocerebellar degeneration without peripheral nerve involvement.[162] These three workers received long-term, low-dose exposures to aluminum in the same environment; all three displayed a lack of coordination, intention tremor, and cognitive deficits consistent with potroom palsy. The direct effect of aluminum is unclear in these cases because bone aluminum concentrations were normal.

Welders

Some case series and epidemiological studies report an increased prevalence of neurological symptoms in workers exposed to airborne aluminum concentrations exceeding current workplace standards. However, these symptoms are often not associated with objective evidence of neurological abnormalities or correlated to aluminum exposure or biomarkers. In a study of metal inert-gas welders separated into high, medium, and low exposure groups based on the sum of Monday-morning urine Al and concurrent serum Al concentrations, there were statistically significant differences in some symptoms (fatigue, mild depression, memory, concentration) between the high and low exposure groups.[163]

In a cross-sectional study of 38 aluminum welders and 44 railway track welders without lead, manganese, or aluminum exposure (controls), acute CNS symptoms were statistically more common in aluminum welders than controls, particularly fatigue.[164] These complaints increased with increasing urine aluminum concentrations. Complaints of pain and aches over the preceding 6 months were statistically less common in aluminum welders than controls. There were no significant differences between the two groups for symptoms related to tremor, peripheral nervous system symptoms, chronic fatigue, sleep disturbances, or chronic neurological symptoms related to mood, memory, or sensory systems. Additionally, there was no significant difference in the responses of the two groups to the Q16 questionnaire. A cross-sectional study of 98 aluminum welders with a median of 6 years exposure to aluminum welding fumes and 50 nonexposed car-production workers from the same plant did not reveal any statistically significant differences between welders and controls on a variety of tests including Q16 questionnaire, physical examination, or neuropsychological testing.[165] The annual measurement of the mean pre-shift and post-shift urinary Al was ~52 µg/g and 58 µg/g creatinine, respectively, whereas the median respirable air dust was 0.47 mg/m^3 and 0.67 mg/m^3. Welders typically do not develop an encephalopathy manifested by impaired memory, disorientation, or dementia.

Potroom Workers

There were frequent complaints of poor coordination, poor memory, impairment in abstract reasoning, and depression in a case series of 25 potroom workers examined at an occupational clinic for work-related illness.[166] However, there were no direct measures of aluminum available to confirm the extent of their aluminum exposure. In a cross-sectional study of 63 current and former aluminum potroom workers employed for at least 10 years, there was a statistically significant increase in responses to questions regarding depression, difficulty buttoning, and incoordination when compared with 37 cast house and carbon plant workers at the same facility.[167] However, tests of arm, hand, and leg tremor as well as measures of postural stability demonstrated no significant differences between the two groups. A cross-sectional study of aluminum potroom and foundry workers, aluminum welders, and workers exposed to aluminum during the production of flake powder did not demonstrate any consistent neurological effects in the exposed workers when compared with mild steel workers (controls).[168] Outcome measures included responses to mood and symptoms questionnaires and results from neuropsychological testing. The median duration of exposure and blood aluminum concentrations for the smelter workers, flake powder workers, aluminum welders, and mild steel workers (controls) were 15 years and 1.0 µg/L, 8 years and 9.0 µg/L, 15 years and 3.0 µg/L, and 12 years and 1.0 µg/L, respectively.

Skin

A unique dermatological condition developed in Canadian and Soviet workers at an aluminum plant.[169] These

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workers acquired skin telangiectases chiefly on the upper parts of their bodies (chest, back, shoulders, forearms, neck, face) characterized by 1–30 mm round, sharply demarcated, nonpruritic red macules that blanched on applied pressure. These lesions occurred primarily in aluminum workers in the Søderberg electrolysis process, which releases more aromatic hydrocarbons than the newer pre-bake process. Most workers develop these lesions within 20 years of working in these facilities. These lesions were dermatological abnormalities that were not associated with other diseases (e.g., ischemic heart disease).[170] There is no direct evidence that aluminum caused these lesions. Aluminum can produce a delayed-hypersensitivity granuloma in the skin when injected under the skin for tattooing.[171] Contact allergy to aluminum is extremely rare considering the ubiquity of aluminum in the environment.[172]

Bone

There is no epidemiological evidence to suggest occupational Al exposure causes bone fragility.[146]

Reproductive Abnormalities

Few human data are available on the teratogenicity of aluminum. There is no direct evidence that the ingestion of aluminum produces clinically significant alterations in the reproduction of animals or humans at concentrations present in the environment or workplace. Aluminum does cross the placenta and is excreted in breast milk.[173] Rodent models indicate that parenteral Al doses of 50 and 100 mmol as $AlCl_3$ cause growth retardation, delayed ossification, and malformations when administered during early organogenesis; however, these high aluminum concentrations produce maternal toxicity.[174] Furthermore, the severity of the effect is highly dependent on the form of Al administered; the use of nitrates confounds the interpretation of the studies because of the ability of nitrates to cause fetal damage.

Carcinogenesis

There is no direct evidence that aluminum is a carcinogen in humans or animals. Rats did not develop an excess of tumors following the ingestion of drinking water containing 5 ppm Al during a study that lasted the whole lifetime of the rats. Epidemiological studies have not demonstrated a consistent association between aluminum exposure and breast cancer risk. Case-control studies did not detect a causal link between antiperspirant use and breast cancer risks;[175,176] consequently, current epidemiological data are inadequate to confirm an association linking antiperspirant use and breast cancer.[177]

The International Agency of Research on Cancer (IARC) lists aluminum production as a group 1 carcinogen.[178] Statistically significant excesses of lung cancer[179,180,181] and bladder cancer[169] were reported in some, but not all, epidemiological studies of aluminum workers. Most of these studies involve the older Søderberg aluminum reduction plants where relatively high concentrations of polycyclic aromatic hydrocarbons occurred, particularly in the anode production areas and to a lesser extent in the potrooms. A historical cohort study of 4,213 men who worked >5 years at a Søderberg aluminum reduction plant demonstrated a statistically significant excess incidence (SIR = 1.69, 90% Cl 1.06–2.57) of bladder cancer but not of lung cancer.[182] In an updated cohort study of Canadian Søderberg smelter workers, Poisson regression analysis correlated the standardized mortality and incidence ratios for stomach and bladder cancer to cumulative exposure to coal tar pitch volatiles measured as benzene-soluble materials and benzo(a)pyrene.[183] Although the overall rate of lung cancer was similar to the general population, the risk of lung cancer in these workers also increased in a dose-dependent relationship (P_{trend} <0.001). As prebake technology gradually replaced the older Søderberg pots, cancer mortality and incidence decreased.

A Canadian study of 4,396 men working in a newer prebake smelter for at least 3 months detected no overall excess of standardized cancer mortality or incidence ratios with the exception of mesothelioma and kidney cancer.[184] There was no significant trend for cancer incidence and duration of exposure, and the incidence of lung and bladder cancers was similar to the general population. Consequently, confounders (e.g., coal tar oils, smoking) probably account for the excess rates of cancer in the earlier studies on Søderberg workers rather than direct exposure to aluminum. Cancer mortality and incidence studies of bauxite mine and alumina refinery workers have not detected an increased risk of cancer including lung and bladder cancers.[185]

DIAGNOSTIC TESTING

SI Conversion Units

1 μmol/L = 27.03 μg/L
1 μg/L = 0.037 μmol/L
1 μmol/mol creatinine ~3.05 mg/g creatinine
1 mg/g creatinine ~0.30 μmol/mol creatinine

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Analytical Methods

Flameless atomic absorption spectrometry is a simple, quick method of determining aluminum levels.[186] The earlier use of neutron activation and flame atomic absorption spectrophotometry has been replaced by flameless atomic absorption spectrometry because of the greater sensitivity and the smaller sample size necessary for the latter process.[187] The detection limit of Zeeman (flameless) absorption spectrometry is ~1 μg/L, and the precision is about 3–6%.[188] Speciation of aluminum is a complex process because of the influence of pH on Al species, contamination, and instability of some Al species.[189]

Sample contamination is a major problem with the analysis of aluminum concentrations in biological fluid because of the low Al concentrations in mammals and the high Al concentrations in the environment. Improper storage conditions result in the loss of aluminum and contamination of the storage vials. Leaching of aluminum occurs on the surface of glass vessels stored at 4°C.[190] The best storage conditions are polypropylene or polystyrene containers stored at −20°C with acidification of urine and dialysis fluid.

Biomarkers

Intravenous challenge doses of deferoxamine (DFO)[127] are a controversial method of assessing the total body burden of aluminum that is not currently recommended. One study suggested baseline plasma aluminum concentrations of 200 μg/L are highly specific (93%) but not sensitive (43%) for aluminum-induced bone disease, whereas the same plasma aluminum concentrations after deferoxamine infusion (40 mg/kg over 2 hours) are highly sensitive (94%), but not very specific (50%) for aluminum-induced bone disease.[191] The DFO infusion test is negative when the plasma aluminum concentration is <150 μg/L. The aluminum content of hair is too variable to reliably predict aluminum intoxication.[192] Hair aluminum concentrations in the scalp do not correlate well with daily or cumulative aluminum intake, plasma aluminum concentrations, or stainable bone aluminum concentrations.[193]

Blood

The distribution of Al between serum and plasma is similar; however, data on the distribution of Al between plasma/serum and red blood cells are conflicting. Some authors report the approximately equal distribution of Al between plasma and erythrocytes, resulting in similar Al concentrations between whole blood, plasma, and serum.[80] The mean whole blood/serum Al ratio in a series of healthy Italians was 1.67 as measured by flame atomic absorption spectrometry.[194] In a study of plasma and erythrocytes from rats and patients on dialysis, the distribution between the two was near unity.[195] The mean Al concentration in blood samples from four renal dialysis patients with Al concentrations of >100 μg/L was ~8% higher in whole blood than plasma.[196] However, the aluminum erythrocyte/plasma ratio was ~0.1 in subjects followed 3 months after the ingestion of ^{26}Al in a citrate-containing drink.[98] The difference is partially explained by variations in the solubility of different Al compounds. Serum is the preferred blood sample because some anticoagulants (e.g., heparin, citrate) may contain aluminum.

General Population

The serum aluminum concentrations in individuals from the general population without excessive exposure are usually <5–10 μg/L.[197] The estimated 95% upper limit of serum Al based on data from 21 Finnish laboratory workers without exposure to antacids was 2.7 μg/L as measured by graphite furnace/atomic absorption spectrometry.[198] The distribution of plasma aluminum in the general population follows a log-normal pattern; a study of subjects with normal renal function and no excessive intake of aluminum demonstrated plasma aluminum concentrations with an upper 95% CI <0.175 μmol/L (4.73 μg/L).[199] Substantial interindividual variation in plasma aluminum concentrations occurs. Whole blood Al concentrations may exceed serum and plasma Al concentrations. In a cross-sectional study of 85 healthy infants (median age, ~10 months) with normal renal function and no history of parenteral nutrition or aluminum-containing pharmaceutical use, the median whole blood aluminum concentration was 15.4 μg/L with a range of 0.9–952 μg/L.[200] There was no statistically significant correlation between blood Al and the estimated Al dose from vaccines. The authors did not explain the reason for the 7 outliners ranging from 98–952 μg/L. Without those 7 outliers, the median whole blood Al concentration was 14.3 μg/L (95% CI: 11.6–18.2 μg/L).

The administration of high doses of aluminum-containing antacids to infants[201] and adults in critical care units[202] increased plasma Al concentrations up to 40 μg/L; the patients did not develop symptoms of aluminum intoxication. These patients had normal renal function. Blood aluminum concentrations should be interpreted cautiously because some differences exist between chronic toxicity in patients with similar serum aluminum concentrations.

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Dialysis Patients

Typical serum aluminum concentrations are <50 μg/L in asymptomatic patients on chronic hemodialysis compared with <5–10 μg/L in the general population.[197] Clinical studies of renal dialysis patients indicate serum Al is a biomarker for total body burden and clinical effects (dialysis-associated bone disease and encephalopathy).[135] Serum aluminum concentrations may exceed 50 μg/L in patients with chronic renal failure following ingestion of 60 mL of aluminum hydroxide daily for 2 weeks.[203]

Serum aluminum levels of >60–100 μg/L indicate increased absorption and the potential for aluminum-related bone disease.[204] Typically, symptoms of encephalopathy (e.g., confusion and delirium) do not develop in patients with chronic aluminum intoxication until the serum aluminum concentration exceeds 100 μg/mL. Clinical symptoms of encephalopathy are frequent when serum aluminum concentrations are >200–300 μg/L.[205,206,207] In a renal dialysis center, 27 patients developed nausea, vomiting, and hypercalcemia after the replacement of a water conduit pipe containing Al- and Ca-rich cement mortar that provided tap water.[208] In antemortem blood samples from 7 patients dying after developing seizures, sepsis, and coma, the mean serum aluminum concentration was 808 μg/L (range, 359–1,189 μg/L) compared with 255 μg/L (range, 113–490 μg/L) in 17 survivors.

Occupational Exposure

Al concentrations in blood and urine do not correlate well to Al concentrations in brain or bones of aluminum-exposed workers;[98] only about 0.1% of the total body burden of aluminum exists in the blood. Serum aluminum concentrations are indirect measures of the total body burden of aluminum because aluminum is highly protein bound. Aluminum concentrations in the blood should be interpreted in relation to cumulative aluminum exposure because chronic, low-dose exposure may produce excess aluminum concentrations in the tissues without high (>100 μg/L) plasma aluminum concentrations.[209] In a nonrandomized study involving 28 potroom workers followed for 3 years after the construction of a modern aluminum smelter, the mean serum aluminum concentration was 6.41 ± 1.61 μg/L with air samples never exceeding the ACGIH-TLV of 10 mg/m^3.[210] The mean serum Al concentration doubled during the first year before becoming relatively stable during the next 2 years as the urine Al concentration continued to increase.

Urine

General Population

In the general population without exposure to typical amounts of Al, the urinary Al concentration is usually <10–15 μg/L. The mean Al concentration in 766 spot urine samples excluding the first voided specimen from healthy Italians was 10.9 μg/L (range, 2.3–19.5 μg/L) compared with 6.4 μg/L (range, 1.5–29.6 μg/L) for 178 British citizens as measured by electrothermal/atomic absorption spectrophotometry.[211] In urine samples from 44 healthy Finnish population without antacid use, the Al concentration was 8.9 ± 4.9 μg/L with a range of 1.9–22.2 g/L as measured by graphite furnace atomic absorption spectrometry (GFAAS) method with Zeeman background correction and corrected to a relative density of 1.024.[198] The estimated 95% upper limit for Al in urine was 16 μg/L.

Occupational Exposure

Workweek urine Al concentrations reflect both recent exposure and the body burden of aluminum, particularly in workers exposed to insoluble aluminum in ambient air; there are limited data on the use of pre-shift and first morning of the workweek urine samples as a means to measure the total body burden of aluminum by reducing the influence of recent aluminum absorption. In general, post-shift and end-of-week urine samples reflect primarily recent exposure; pre-shift and first-day-of-week urine samples reflect primarily body burden. For recently exposed workers, urine sampling during the workweek reflects recent exposure more than the body burden. The timing of urine samples depends on recent exposure history and the solubility of the Al compound. Urine and blood Al concentrations during a work shift (i.e., pre- and post-shift) are relatively constant for aluminum welders given a constant Al dust exposure; therefore, the timing of these samples during the shift is not critical for recent Al exposure.[212] In welders chronically exposed to aluminum, the Monday morning pre-shift Al urine probably reflects the total body burden; sample timing during the workday (i.e., pre-shift or post-shift) is probably not important in determining the Al body burden.[213] Occupational studies suggest that urine Al concentrations are more sensitive to recent fluctuations in airborne aluminum concentrations than serum or plasma Al.[214] The occurrence of unexpectedly high urine Al concentrations should prompt a search for Al-containing food and drugs, sample contamination, or highly concentrated urine, particularly if present in first-day-of-the-week samples. Normalization of urine aluminum concentrations to creatinine clearance is usually not necessary

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because aluminum clearance correlates to urine output and indirectly specific gravity rather than creatinine clearance.

Bone

Histological examination of bone biopsy material is a measure of the total body burden of aluminum because the bone is the main storage organ of aluminum in the body;[215] however, there are few data on noninvasive techniques (e.g., X-ray fluorescence) to determine the usefulness of these techniques for biomonitoring. Histochemical stains typically demonstrate no aluminum in bone specimens at aluminum concentrations below 50 mg/kg bone. The mean aluminum concentration in bone biopsies from three cases without renal disease was 6.4 mg/kg dry weight (range, 3.6–8.1 mg/kg dry weight) compared with 124.6 mg/kg dry weight (range, 71.2–194.0 mg/kg dry weight) for biopsies from three autopsies of individuals requiring dialysis during their lifetime.[100] In this study, a bone biopsy from a patient with normal renal function and a 25-year history of ingesting large doses of aluminum contained 24.1 mg Al/kg dry weight. Following an incident involving contamination of drinking water with aluminum sulfate,[96] serial bone biopsies demonstrated the presence of stainable aluminum for up to 18 months.[216]

Abnormalities

Blood

Manifestations of aluminum toxicity include hypercalcemia and a microcytic, hypochromic anemia that may or may not respond to iron therapy.

Neurophysiological

EEG abnormalities characteristic of aluminum encephalopathy in dialysis patients exposed to elevated aluminum concentrations include episodic bursts of spiking, high-voltage activity on a background of slow-wave activity.[217] Consistent abnormalities on the EEG have not been detected in epidemiological studies of aluminum-exposed workers. In a study of 17 Swedish aluminum welders, the amount of delta and theta activity in the quantitative EEG correlated positively and the amount of alpha activity negatively with serum Al concentrations.[218] In an expanded Swedish study of 65 aluminum welders and 25 mild steel welders (referents), the slowing of alpha activity did not reach statistical significance; there were no characteristic pathological EEG changes in the aluminum welders.[163] However, there were more diffuse ($P = 0.005$) and epileptiform ($P = 0.02$) abnormalities in the aluminum welders compared with the mild steel welders.

Neuropsychological

Clinical and occupational (smelting, welding, grinding) studies over the last several decades evaluating neuropsychological tests on aluminum-exposed subjects suggest the possibility of mild adverse effects, primarily in welders (e.g., complex attention tasks, information processing in working memory, visuospatial recall, and analysis); however, the neuropsychological data on dose-response are conflicting. These cognitive abnormalities are more easily detected when performance normally declines with age. A meta-analysis of 9 occupational studies of aluminum workers (5 aluminum welders, 3 aluminum production workers, 1 aluminum smelter) based on estimates of effect sizes included 449 exposed workers (welding, smelting, electrolysis) and 315 controls. The mean urine Al concentrations in the studies of exposed workers ranged from 13–133 μg/L.[219] The study evaluated overall effect sizes for 6 neuropsychological/psychomotor tests with 10 variables. The variables included seven attention tests (simple reaction time, digit span forward/backward, digit symbol computerized/noncomputerized, trail making A), two motor performance tests (Santa Ana dexterity preferred/nonpreferred hand), and one construction test (block design). Although nine of the overall effect sizes suggested inferior performance in the exposed groups, only the overall effect size on the paper version of the digit symbol test was statistically significant.

Miners and Salvage Workers

A study of workers exposed to McIntyre powder (15% finely ground elemental aluminum, 85% aluminum oxide) demonstrated decreased performance on examinations of cognitive function compared with a control group, but there were no significant differences in the prevalence of neurological diseases.[220] The standard dose prior to each underground shift was 35.6 mg/m^3 for 10 minutes. A cross-sectional study of 30 aluminum salvage workers and 60 controls without aluminum exposure did not detect statistically significant differences in the Mini-Mental State Examination, verbal short-term memory (Digit span), or clock drawing test.[221] None of the exposed workers exceeded the Biological Tolerance Value of 200 μg/L in urine; the mean Al concentration in end-of-shift urine samples from these workers was 11.59 ± 10.09 μg/L ($\text{mean}_{\text{controls}} = 4.37 \pm 3.67$ μg/L). The urine Al concentrations in the exposed workers were

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lower than those of railway workers in the Sjögren study of aluminum welders (median = ~22 μg/L).

Welders

Cross-sectional and longitudinal studies of aluminum welders generally demonstrate no statistically significant differences in neuropsychological tests between aluminum-exposed workers and controls. Although these studies do demonstrate some correlation between a few neuropsychological parameters and urine or blood Al concentrations, there are no consistent decrements in specific domains (e.g., motor, memory, verbal, visuospatial). A 4-year longitudinal study compared 41 Al welders in the train and truck construction industry with 37 controls (unexposed assembly workers) on neuropsychological scores in verbal intelligence, attention, logical thinking, memory, and psychomotor skills. Aluminum exposure ranged from 5–8 mg/m^3; biomonitoring data demonstrated pre-shift plasma and urine Al concentrations of 13–16 μg/L and 88–140 μg/g creatinine, respectively, in samples from the welders. Twenty welders and 12 controls completed the study. Explorative regression and covariance analyses demonstrated a correlation between premorbid intelligence and neuropsychological scores but no correlation between performance and Al exposure; additionally, there was no difference between performance scores in the two groups (i.e., 20 welders, 12 controls) over the 4-year study.

A study of 17 aluminum welders with a history of ~4 years of aluminum exposure and a mean urine aluminum concentration of 2.8 μmol/L (75.7 μg/L) with a range of 0.9–6.1 μmol/L (24.3–164.9 μg/L) demonstrated no abnormalities on neuropsychological testing, when compared with established reference levels.[218] However, the authors suggest that aluminum may affect short-term memory, learning, and attention based on decreased scores on these tests with increasing urine aluminum concentrations. In a cross-sectional study of 38 aluminum welders, there were statistically significant differences in 4 tests of motor function between the aluminum welders and a control group of 44 railway track welders.[164] These differences included the following tests: tapping speed, nondominant hand only, pegboard, dominant hand only, and two motor tasks on the Luria–Nebraska motor scale. These changes did not correlate to urine aluminum concentrations. There were no differences between the 2 groups in the scores on tracking tasks, simple reaction time, symbol digit coding, digit span, or vocabulary. This study did not control for age. In a study of 92 male Al welders in the automobile industry and 50 nonexposed construction workers in the same industry and of similar age (35–39 years), symptoms and neuropsychological scores (i.e., verbal intelligence, logical thinking, psychomotor behavior, memory, attention) did not differ between the two groups over the 4-year study period.[222]

A cross-section study of 20 aluminum welders with a mean aluminum exposure of about 8 years and mean urine aluminum concentrations of ~50 μg/L at the time of examination demonstrated significantly better performance on measures of reaction times and hand steadiness than 20 construction workers.[223] However, the welders reported a statistically significant increase in the mean number of neuropsychological symptoms (2.5 vs. 1.6) compared with the control group of construction workers. A cross-sectional study of 98 aluminum welders with a median of 6 years of exposure to aluminum welding fumes demonstrated a small, but significant decrease in simple reaction time, when compared with education and age-matched controls (i.e., car-production workers).[165] The study detected no other neuropsychological abnormalities (i.e., block design, trail-making, standard progressive matrices, recall of digits, psychomotor performance, verbal intelligence). In a study of metal inert-gas, welders separated into high, medium, and low exposure groups based on the sum of Monday-morning urine Al and concurrent serum Al concentrations, there were mild differences in scores on some, but not all, neuropsychological tests of attention (Bourdon–Wiersma cancelation test, counting backward, dual task), memory (memory for designs), and verbal abilities (synonyms).[163] There were no significant differences in the scores for the low- and medium-exposure groups. The scores were adjusted for age and lead exposure but not for any hold tests.

Pulmonary Function Tests

Most cross-sectional studies of aluminum workers have not detected changes in the FEV_1 and FVC,[224] whereas one study demonstrated a mean reduction in FEV_1 of 0.29–0.39 L in workers exposed >20 years to Al-containing dust when compared with predicted values.[225] A review of respiratory disorders in aluminum smelter workers reported increased mortality from chronic obstructive pulmonary disease and longitudinal decline in FEV_1 in aluminum potroom workers consistent with potroom asthma; however, the causative agent or agents of potroom asthma remain unknown.[226] Detecting pulmonary function abnormalities in workers exposed to aluminum dust is complicated by the difficulty in separating smoking effects and other pulmonary toxins from the effect, if any, of aluminum exposure. In a study of potroom workers, impairment of lung function secondary to occupational exposure

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occurred only in nonsmokers with statistically significant reductions ($P < 0.001$) in FVC, FEV_1, and PEF compared with controls.[227] At the present time, no current immunological test establishes the diagnosis of potroom asthma.

HEALTH SURVEILLANCE

Risk Assessment

The development of tissue damage as a result of aluminum exposure depends on the length of the exposure and the amount of aluminum deposited in the tissue.[228] In a study of hemodialysis patients receiving $Al(OH)_3$ for up to 7 years as a phosphate binder, the no-observable-adverse-effect-level (NOAEL) was 13 mg/kg/day as total Al. The calculated oral reference dose (RfD) was 1.3 mg/kg/day using an intraspecies uncertainty factor of 10; this value corresponds to a maximum concentration of 9 mg total Al/L in drinking water assuming a 70-kg person consumes 2 L of drinking water/day and adjusting for a default 20% relative source contribution.[78] This drinking water concentration exceeds the US EPA secondary maximum contaminant level (MCL) for total Al of 0.05–0.2 mg/L. However, the domestic use of water with high Al concentrations is unlikely because of the turbidity associated with these concentrations.

Environmental Monitoring

US Occupational Health and Safety Administration (OSHA) set the PEL–TWA for metal dust as Al at 15 mg/m^3 as total particulate and 5 mg/m^3 as the respirable fraction in order to prevent physical irritation from the dust. The American Conference of Governmental and Industrial Hygienists Threshold Limit Value Time–Weighted Average (ACGIH TLV–TWA) for metallic Al dust is 10 mg/m^3. These two organizations have set the same standard for the following Al exposures as TWA: pyro powders, 5 mg/m^3; welding fumes, 5 mg/m^3; soluble salts, 2 mg/m^3; and alkyls, 2 mg/m^3. The California Primary Drinking Water Action Level is 1 mg Al/L based on the lack of adverse effects of 125 mg Al/day and a 10-fold safety factor for sensitive individuals (e.g., hemodialysis patients). In California, the secondary action level of 200 µg/L is designed to prevent any cloudiness that results from aluminum in drinking water; however, in the European Economic Community, the 200 µg/L level is the maximum admissible Al concentration in raw water supplies for small water treatment facilities (100 µg/L for large water treatment facilities). Table 1.3 lists current regulations and guidelines for exposure to aluminum.

TABLE 1.3. Regulations and guidelines for aluminum exposure.

Type	Values
	ACGIH
TLV–TWA (8-hour)	1 mg/m^3 (insoluble Al respirable particulate matter)[a]
BEI (urine)	None
	NIOSH
REL–TWA (10-hour)	
Metallic Al	10 mg/m^3 (total dust)
	5 mg/m^3 (respirable fraction)
Aluminum oxide	15 mg/m^3 (total dust)
	5 mg/m^3 (respirable fraction)
IDLH	None
	OSHA
PEL–TWA (8-hour)	
Metallic Al (General industry)	5 mg/m^3 (total dust)
(Shipyard industry)	15 mg/m^3 (total dust)
Aluminum oxide	5 mg/m^3 (respirable fraction)
	DFG
BAT	60 µg/g creatinine (welding fumes, end-of-shift)
MAK	1.5 mg/m^3
	FIOH
BAL	162 µg/L (pre-shift, first-day-of week)[b]
	ATSDR
MRL	1 mg/kg/day (oral intermediate/chronic)
	WHO
Drinking water	≤200 µg/L (small water treatment facilities)
	≤100 µg/L (large water treatment facilities)
	EFSA
Daily food intake	1 mg Al/kg body weight

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; BAL = biological action level; BAT = biological tolerance level (biologische Arbeitsstoff-Toleranzwerte); BEI = biological exposure indices; DFG = Deutsche Forschungsgemeinschaft; EFSA = European Food Safety Authority; FIOH = Finnish Institute of Occupational Health; IDLH = immediately dangerous to life and health; MAK = maximum workplace concentration (maximale Arbeitsplatz-Konzentration); MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; TLV = threshold limit value; TWA = time-weighted average; WHO = World Health Organization.
[a]Metallic aluminum, stamped aluminum, aluminum oxide, aluminum in bauxite ore dust, or emery; there is no recommendation for soluble aluminum compounds because of inadequate data; [b]Corrected to a relative density of 1.021.

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Biological Monitoring

The objective of aluminum biomonitoring is the prevention of harmful aluminum concentrations in the lungs and other target organs (brain, kidneys, lungs). The ubiquity of Al complicates the biomonitoring of exposed workers from potential sample contamination, the presence of Al in food and drinking water, the ingestion of Al-containing drugs (antacids), and the use of Al-containing products (antiperspirants). The concentration of Al in urine and blood depends on the intensity of recent exposure, the solubility of the form of Al, and the body burden. The inhalation of fine particles of poorly soluble aluminum salts causes the retention of Al in the lungs, whereas soluble Al compounds do not accumulate in the respiratory tract.

Blood

Monitoring aluminum is substantially different in dialysis patients than in workers with occupational Al exposure. In patients with severe renal insufficiency, serum/plasma Al concentrations reflect total body burden of aluminum and potential Al toxicity.[213] Plasma Al concentrations exceeding 190 µg/L are associated with an increased risk of bone disease and encephalopathy in hemodialysis patients.[229] Increased monitoring of serum/plasma Al concentrations and enhanced health surveillance are recommended for dialysis patients with serum Al concentrations of >60–100 µg/L because of the potential increased adverse effects suggested in clinical studies.[230,231]

In subjects with normal renal function, urinary excretion of aluminum is a more sensitive indicator of the absorption of aluminum than the plasma/serum Al concentration. A study of 31 workers exposed to aluminum in a bauxite mining process did not demonstrate a statistically significant difference between the serum aluminum concentration of the workers and the control group (wood processors).[232] Although the mean plasma aluminum concentration of workers currently exposed to aluminum flake powders was only slightly above (12.5 µg/L) the upper range of normal urinary concentration of aluminum was 80–90 times higher (200 µg/L) than nonexposed workers.[233]

Urine

On a group basis, airborne aluminum concentrations (i.e., primarily the respirable fraction of finely-divided, poorly soluble Al compounds) correlate to urine Al concentrations. Biomonitoring of urinary Al is useful for Al exposures in the grinding, cutting, polishing, and thermal spraying of aluminum, aluminum welding (e.g., MIG/MAG-welding), production, and use of Al powders, and aluminum smelting. In a study of 12 workers exposed for 6 hours to 2.5 mg/m^3 aluminum-containing welding fumes from a metal inert gas welding process, the mean urine Al concentration increased from 13.5 ± 4.1 µg/L (baseline) to 23.5 ± 7.3 µg/L (immediately postexposure).[234] The urine Al concentrations returned to baseline within ~1 week. The pre-exposure and postexposure plasma concentrations were not statistically different.

In contrast to occupational exposure to poorly soluble Al salts (e.g., welders), long-term occupational Al exposure (e.g., Al sulfate production workers) typically exhibits urinary Al concentrations only slightly higher than local controls.[86] Urinary Al roughly quantitates the Al exposure during the production/use of soluble Al salts (sulfates, chlorides, nitrates), but the results are difficult to interpret following mixed exposure to soluble and insoluble Al compounds (e.g., potroom exposures).[197] In a study of potroom and Al fluoride production workers exposed to Al_2O_3 and AlF_3, post-shift urinary Al concentrations of 200 µg/g creatinine corresponded to an airborne Al exposure of 1.36 mg/m^3 during the shift.[24] Biomonitoring of aluminum in electrolytic reduction processes has limited value because the main chemical hazards are fluorides and polycyclic aromatic hydrocarbons.

Available data suggest that 150 µg Al/g creatinine in urine at the end of the shift is a safe biological limit value,[213] although some authors suggest limiting occupational exposure to sparingly soluble Al compounds to <62 µg Al/g creatinine (3 µmol/L).[197] A post-shift Al concentration of 200 µg/g creatinine and 400 µg/g creatinine correlated to Al concentrations in ambient air of 1.04 mg/m^3 and 2.25 mg/m^3 as soluble Al.[105] However, some studies suggest that subtle adverse neurological effects may occur in welders with urine Al concentrations in the range of 110–160 µg/L.[163] A longitudinal study of 32 workers from an Al powder-producing plant did not detect any statistically significant differences in scores on a battery of neuropsychological tests or the event-related P300 potentials when compared with age- and education-matched, unexposed controls from the same plant.[235] Follow-up 5 years later with 21 of the 32 workers did not demonstrate any significant differences in scores between the workers (15 still exposed, 6 formerly exposed) and the control group. Urine samples from the 21 workers and 30 controls at the initial examination contained median aluminum concentrations of about 77 µg/g creatinine (98.8 µg/L) with a range of 4.6–321.4 µg/g creatinine (5.0–336.6 µg/L) compared

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with a median of 9 μg/g creatinine (7.6 μg/L) and a range of 1.9–51.8 μg/g creatinine (1.9–51.8 μg/L) for the 30 controls.

TREATMENT

Mechanism of Action

Deferoxamine (DFO) is a recognized, specific aluminum chelator that effectively removes aluminum from patients with dialysis-associated encephalopathy,[236] microcytic anemia, and osteomalacia.[237] Chelation is also associated with improvement of symptoms in these patients.[238] Theoretically, 1,000 mg DFO binds 41 mg Al, but the removal of the Al-deferoxamine complex by dialysis is relatively inefficient because DFO does not remove significant amounts of aluminum bound to transferrin. The affinity of DFO for ferric iron as measured by the stability constant is ~9 orders of magnitude greater than aluminum, whereas the stability constants are much lower for essential elements (calcium, copper, magnesium, zinc) than aluminum. Consequently, iron deficiency may occur during DFO therapy, but clinically significant reductions in other essential elements are unlikely.

Pharmacokinetics

In the presence of substantial aluminum stores in bone, the plasma aluminum concentration increases two to four times above the baseline aluminum concentration with the maximum concentration occurring 24–48 hours after administration of DFO.[191]

Indications

The most common presentation of aluminum toxicity is the exposure of renal dialysis patients to excessive phosphate binders or aluminum-contaminated dialysis fluids, resulting in osteomalacia and/or encephalopathy;[61,239] however, aluminum poisoning in renal dialysis patients is now rare in developed countries with modern renal replacement therapies. The administration of aluminum-containing TPN solution may cause aluminum toxicity (osteopenia, pathological fractures) in premature neonates with immature renal function.[77] Case reports also suggest an acute encephalopathy may develop in patients with renal dysfunction treated with alum (aluminum potassium sulfate) for a hemorrhagic bladder.[240]

Although no randomized controlled clinical trials are currently available, the National Kidney Foundation (K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease) and Kidney Disease Improving Global Outcomes (KDIGO) Work Group provide recommendations for treating these patients based on case reports and expert opinion. Indications for the use of deferoxamine include symptomatic dialysis patients with serum Al concentrations between 60 and 200 μg/mL;[135,241] however, aluminum-associated bone disease may correlate better to Al concentration in bone than serum. The Kidney Disease Improving Global Outcomes guidelines for evaluation and treatment of dialysis-induced bone disease recommend using bone biopsy rather than serum.[242]

Dosage

The DFO dose depends on renal function, chronic vs. acute aluminum exposure, and concern about minimizing the risk of encephalopathy from DFO-induced redistribution of mobilized aluminum to brain in patients with high serum Al concentrations (>200 μg/mL). In dialysis patients, DFO is infused weekly in doses of 5 mg/kg[243] to 15 mg/kg[51] during the last hour of dialysis in order to reduce the loss of DFO in the dialysate.[244] The occurrence of adverse effects to deferoxamine may require DFO treatment 1 and 5 hours before dialysis. For the treatment of acute aluminum intoxication from bladder irrigation with alum, the administration of DFO 6–8 hours prior to daily dialysis was associated with clinical improvement within 3 days and normalization of mental status within 3 weeks.[245] After clinical improvement, hemodialysis decreased to three times per week. The duration of DFO/hemodialysis therapy for chronic aluminum intoxication is long-term ranging from 1–9 months. For dialysis patients with chronic aluminum overload, the use of lower thrice-weekly DFO doses of 0.5 mg/kg[246] or 2.5 mg/kg weekly[247] may be sufficient based on case series; however, there are limited pharmacokinetic data to determine the most efficacious dose.

Adverse Effects

Dialysis-associated encephalopathy has complicated DFO use in chronic renal failure patients with very high serum aluminum concentrations (>200 μg/mL) from prior parathyroidectomy or redistribution of the mobilized aluminum.[248] The weekly DFO dose should be reduced to 5 mg DFO/kg body weight in these patients. Other potential complications of DFO therapy include systemic hypersensitivity reactions, hyperparathyroidism, hypocalcemia, low serum ferritin,

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iron deficiency, adult respiratory distress syndrome, and systemic infections (*Yersinia*, *Mucor*).[249]

Adjunctive Treatment

In vitro and *in vivo* studies suggest that coated charcoal hemoperfusion and hemodialysis almost double the removal of aluminum from dialysate compared with hemodialysis alone;[250] however, few human data are available to determine the efficacy of combined hemoperfusion/hemodialysis and charcoal cartridges are difficult to obtain in the United States. Calcium disodium ethylenediaminetetraacetic acid does not appear as effective as deferoxamine in chelating aluminum.[251] The efficacy of deferiprone and deferasirox for aluminum toxicity is not well studied; both of these iron chelators also chelate essential elements (e.g., copper, zinc).[252] Sources of aluminum should be identified including aluminum in the dialysis water and the use of aluminum-containing medications. The current practice involves the use of calcium carbonate together with minimum amounts of aluminum-containing phosphate binding antacids when necessary.

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Chapter 2

ANTIMONY

ANTIMONY AND ANTIMONY SALTS

HISTORY

The use of antimony for cosmetic and medicinal purposes dates back to antiquity.[1] Chaldeans manufactured vessels and vases from the black sulfide salt of this metal as early as 4,000 BC. Antimony sulfide was a cosmetic for the embellishment of eyes and eyelashes in Roman times; in Arab countries, women also used antimony (*al-kohl*) to paint their eyes. Although Paracelsus documented the toxicity of tartar emetic (antimony potassium tartrate) in his book *Opera omnia* in 1556, the medicinal use of antimony was reintroduced in 1657 when King Louis XIV recovered from typhoid fever allegedly after the administration of an antimony compound by an unknown physician.[2] For the next several hundred years, trivalent antimony compounds (e.g., tartar emetic) were popular remedies for a variety of purposes including cathartic, diaphoretic, emetic, expectorant, irritant, antidiarrheal agent, antipyretic, skin preparations, and sedative.[3] During the 17th and 18th centuries, drinking wine stored in antimony cups was a popular method for inducing vomiting, purging, and sweating. Dr. James' Fever Powder contained ~33% antimony oxide in addition to potassium tartrate. This product was a popular constituent of the domestic medicine chests of people during the 18th and 19th centuries, including Queen Victoria.[4] Oliver Smith, one of the great English authors of the 18th century, died after developing a severe gastroenteritis following the ingestion of James' Powder for a febrile illness.[5]

The industrial use of antimony on a large scale began in the 19th century. A purification process for gold involved the use of antimony sulfide to form an alloy. Importation of antimony ore (stibnite, Sb_2S_3) in northeastern England occurred from 1870–2003. Processing of this ore involved roasting with charcoal or coke and the collection of the volatile oxide fumes to refine pure antimony. Toxicity associated with dusty conditions in these processing plants included rash (antimony spots), rhinitis, sore throat, bronchitis, conjunctivitis, perforations of the nasal septum, discolored teeth, and gastrointestinal irritation.[6] Excess pneumoconioses and lung cancers occurred in the antimony ore processors during the middle 20th century, but the etiology of these illnesses probably resulted from co-exposure to silica and arsenic.[7] Tartar emetic has been a poisoning agent since the Middle Ages; the infamous modern poisoner, Graham Frederic Young, used a mixture of antimony and thallium to poison his victims.[8]

The use of tartar emetic for dysentery decreased during the American Civil War as a result of the association of tartar emetic with the development of serious intestinal lesions.[9] In 1918, Christopherson demonstrated the efficacy of antimony potassium tartrate in the treatment of schistosomiasis in humans.[10] Later, antimony injections were used successfully to treat cutaneous and visceral leishmaniasis. By the late 1920s, the use of trivalent antimony compounds (anthiomaline, antimony sodium tartrate, stibophen) was replaced by less toxic pentavalent antimony drugs including the sodium

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stibogluconate salt of antimony (Pentostam, meglumine antimoniate).

PHYSIOCHEMICAL PROPERTIES

Antimony, bismuth, and arsenic belong to Group 15 (Group Va) in the periodic table that shares similar chemical and biological properties. Antimony is a metalloid with physiochemical properties between metals and nonmetals similar to arsenic. The two stable isotopes of antimony are ^{121}Sb and ^{123}Sb with natural abundances of 57.25% and 42.75%, respectively. ^{125}Sb is a fission product of nuclear fuel preprocessing plants and nuclear explosions with a half-life of 2.7 years. Pure elemental antimony is a brittle, silvery-gray metalloid that crystalizes in a feathery pattern. This metal is stable under normal conditions. Antimony tarnishes little in dry air; this metal oxidizes slowly to blackish-gray mixtures of antimony and antimony oxide.[2] The expansion of antimony during solidification is a useful property for lead–antimony alloys in printing type.

Of the four oxidation states (3−, 0, 3+, 5+), the most common and stable form in the environment is Sb^{3+}. Trivalent forms of antimony occur as thioantimonites *in vivo* after reacting with sulfhydryl groups. Pentavalent antimony is an oxidizer that converts to Sb^{3+} in acidic media. In contrast to most inorganic antimony compounds, antimony potassium tartrate has relatively high water solubility as demonstrated in Table 2.1 on the physical properties and identifying information on antimony and antimony forms complex ions with organic and inorganic acids (e.g., tartrate).

EXPOSURE

Processes

In nature, antimony occurs primarily as the sulfur ore (stibnite, Sb_2S_3) and, to a lesser extent, as an oxide

TABLE 2.1. Physical properties and identifying information of antimony and antimony compounds.

Physical Characteristic	Antimony	Antimony Pentasulfide	Antimony Pentoxide
CAS RN	7440-36-0	1315-04-4	1314-60-9
Molecular formula	Sb	Sb_2S_5	Sb_2O_5
Molecular weight (g/mol)	121.75	403.80	323.5
Valence	0	+5	+5
Color	Silvery white	Yellow	Yellow
Physical state	Solid	Solid	Solid
Odor	Odorless	Odorless	NA
Melting point (°C)	630.5	75 (decomposes)	380 (decomposes)
Density (g/mL, 20°C)	6.688	4.12	3.78
Water solubility (25°C)	Insoluble	Insoluble	Very slightly soluble
Vapor pressure	NA	NA	NA

Physical Characteristic	Antimony Potassium Tartrate	Antimony Trichloride	Antimony Trioxide	Antimony Trisulfide
CAS RN	28300-74-5	10025-91-9	1309-64-4	1345-04-6
Molecular formula	$Sb_2C_8H_4K_2O_{12}\cdot 3H_2O$	$SbCl_3$	Sb_2O_3	Sb_2S_3
Molecular weight (g/mol)	333.93	228.11	291.50	339.69
Valence	+3	+3	+3	+3
Color	Colorless	Colorless	White[a], colorless[b]	Black[c], yellow-red[d]
Physical state	Solid	Solid	Solid	Solid
Odor	Odorless	Sharp, unpleasant	Odorless	NA
Melting point (°C)	100	73.4	656	550
Density (g/mL, 20°C)	2.6	3.14 (25°C)	5.2[a]; 5.67[b]	4.64[c]; 4.12[d]
Water solubility (25°C)	83 g/L (cold)	99 g/L	Very slightly soluble	1.75 mg/L (18°C)
Vapor pressure	1 mm Hg (886°C)	1 mm Hg sublimes (49.2°C)	1 mm Hg (574°C)	NA

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number; *NA* = not available.
[a]Senarmontite; [b]Valentinite; [c]Stibnite; [d]Amorphous.

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(valentinite and senarmontite, Sb_2O_3); arsenic is a common constituent of the former ore. The antimony content in these ores ranges from 5–60%. Antimony is a common constituent of lead and copper ores; consequently, Sb is a byproduct of the smelting of lead ores.

Oxidation of the sulfide ore in gas-fired roller furnaces produces oxide fumes (Sb_4O_6), which are collected in a baghouse. Bagging operations are one of the major antimony sources of contamination in the production process.[11] Reduction of the oxide fumes allows the escape of sulfur dioxide. Chemical analysis of airborne dust at these smelting facilities indicates the dust consists primarily of antimony oxides and antimony trioxides (39–89%) and lesser amounts of antimony pentoxide (2–8%), ferric trioxide (1–4%), and arsenic oxide (0.2–6.5%).[12] Until 1972, arsenical slags were byproducts of the removal of arsenic during the production of metallic antimony for antimony–arsenic alloys in the battery industry.[13]

Uses

Industry

Antimony is a brittle compound that is not easily fabricated; therefore, antimony is a common constituent of metal alloys (e.g., lead, tin, copper). The use of antimony up to 2.5% in grid metal of lead storage batteries to increase the mechanical firmness of lead is now uncommon. Potential byproducts of using antimony in lead starter batteries include antimony trioxide (Sb_2O_3) and stibine (SbH_3). Intermetallic compounds (e.g., AlSb) are constituents of thermoelectric devices (e.g., infrared detectors). Semiconductor production uses high-purity antimony. Other uses of antimony compounds include the production of white paint pigment (trioxide), the manufacture of munitions, fireworks, and lubricants for brake pads (antimony trisulfide), ceramics, electrolytic generation of hydrogen (filling of hydrogen balloons), ruby glass (antimony trisulfide), and the creation of fire-proofing chemicals and textiles (antimony trioxide). Antimony oxychloride ($Sb_6O_6C_{14}$) is an effective flame retardant when added to materials as a result of reaction of hydrogen and hydroxy radicals to reduce the rate of flame propagation; heating these materials causes smoldering rather than bursts of flame. The use of flame-retardant clothing by firefighters is not associated with increased exposure to antimony as monitored by urine antimony concentrations.[14] Antimony trioxide is used in the manufacture of ceramics and glass as an agent to remove bubbles and stabilize colors; in plastic, antimony is a bromine receptor for the flame retardants in these objects. Additionally, SbO_3 is an esterification agent in the stabilization of polyester resins and a polycondensation catalyst for plastic polyethylene terephthalate bottles.

Medical Therapy

Anthroposophical medicines (i.e., alternative medicine prescribed based on the spiritual philosophy of Rudolf Steiner) sold in the United Kingdom may contain up to 5% elemental antimony. Trivalent antimony compounds are no longer used for medicinal purposes because of unacceptable side effects and difficulty with drug administration. The pentavalent salt, sodium stibogluconate, remains the drug of choice for visceral leishmaniasis secondary to African *Leishmania donovani* in combination with paromomycin.[15] The trivalent antimony compound, tartar emetic (antimony potassium tartrate, tártaro emético), is a treatment for alcoholism and *Schistosomiasis japonicum* in several countries.[16]

Sources

Antimony is a nonessential element for humans; the daily intake of antimony ranges from 2–29 μg with an average intake of ~5 μg.[17] Antimony is a constituent of tobacco averaging 0.1 mg/kg dry weight; the bioavailability of antimony in smoke is ~20% as measured by neutron activation analysis.[18] The bioavailability of antimony is dependent both on the speciation and physiochemical properties (e.g., antimony present in mineral lattices is almost inert).

Air

Release of Sb into the environment results from both natural and anthropogenic sources (e.g., antimony mines, heavy-duty brake pads), with the former source accounting for about 40% of the emissions of Sb into the air.[19] Coal-fired power plants, metal smelting, and refining and refuse incineration are the major anthropogenic sources of antimony. Because antimony is a relatively volatile metal, combustion processes cause the formation of fine (<1 μm) particles that are not efficiently trapped by air pollution control devices. Workplace ambient air may contain Sb concentrations ranging up to 1–10 mg/m^3.[20]

Soil

Most of the antimony released to the environment partitions into soil; however, antimony is present in soil in very low concentrations (1–8.8 mg/kg, mean =

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0.48 mg/kg). Little data are available on the adsorption of Sb to soil, but limited data suggest that antimony is relatively mobile under diverse environmental conditions.[21]

Water

Most of the antimony in water is associated with particulate matter. Antimony appears in water as a result of the weathering of soil and of the discharge from anthropogenic sources; however, antimony concentrations in surface waters are usually low (0.02–0.1 μg/L).[21] Concentrations of antimony in groundwater and surface water are similar.

Diet

The mean daily Sb intake is relatively small compared with other common trace metals. In 1,319 samples from the French National Total Diet Study, the mean value for Sb was 0.03 μg/kg bw with a 95% upper limit of 0.07 μg/kg bw.[22] For the general population, drinking water is the most important dietary source of antimony.[2] Cereals, fruit, vegetables, meat, poultry, and freshwater fish contain relatively small amounts of Sb (i.e., 1–10 ng/g wet weight). Radiochemical neutron activation analysis of homogenized composites from 12 table-ready foods obtained during the US FDA Total Diet Study Program demonstrated Sb concentrations ranging from 0.22–2.81 ng/g wet weight.[23] The highest Sb concentrations occurred in shrimp, baked potatoes, clams, and oysters. Antimony trioxide is a polycondensation catalyst in the production of polyethylene terephthalate (PET); leaching of antimony from containers may cause migration of the antimony into drinks (e.g., orange juice) or food.[24] The amount of antimony migrating into bottled water varies with varying storage conditions and containers from different countries. Antimony concentrations in containers may increase near to regulatory limits (e.g., 6 μg/L) with prolonged storage time (e.g., 6–12 months), high temperatures (e.g., 60–80°C), and use of new, recently manufactured bottles.[25] The mean antimony concentration in pristine groundwater increased from 1.7 ± 0.4 ng/L ($n = 6$) to 26.6 ± 2.3 ng/L ($n = 3$) following 6 months of storage in Canadian PET bottles and 281 ± 38 ng/L ($n = 3$) in German PET bottles.[26] In a study of six samples of ready-to-eat foods (pasta, fish fillets, cannelloni), the amount of antimony migrating from the PET container to the food after cooking ranged from 1.8–4.7 μg.[27] Although Sb may leach from plastic polyethylene terephthalate bottles,[28] typical use of plastic beverage bottles does not significantly increase urinary Sb concentrations.[29]

ENVIRONMENTAL FATE

Once released into the atmosphere, antimony particles settle slowly to the ground. Both wet and dry deposition contribute to the transfer of antimony from the air to the surface of the earth. The estimated atmospheric half-lives for antimony and antimony trioxide are 2.8 days and 4.6 days, respectively; the atmospheric half-lives of sub-micron particles of Sb may range up to 30 days.[30] Consequently, antimony may be deposited far from anthropogenic or natural sources. Once released into the atmosphere, the reactions of atmospheric oxidants transform antimony into antimony trioxide. Transportation of antimony into surface water results from the weathering of rocks as well as anthropogenic sources. Antimony occurs in seawater and aerobic freshwater primarily in the 5+ oxidation state (i.e., antimoniate), whereas trivalent antimony predominates in anaerobic environments (e.g., bed sediment). Sediment is a significant sink for antimony. Methylation of antimony by microorganisms (e.g., *Scopulariopsis brevicaulis*, *Clostridium* spp.) in anaerobic water and rotting wood (*Phaeolus schweinitzii*) reduces antimony to dimethylstibonic acid and methylstibonic acid.[31,32]

DOSE EFFECT

Gastrointestinal symptoms begin following the ingestion of >30–60 mg Sb. The ingestion of 2–6 g of trivalent antimony may produce serious toxicity, whereas 10–15 g is a potentially fatal dose. Pentavalent antimony compounds are less toxic than trivalent antimony compounds. A 4-hour infusion of 8.5 g pentavalent antimony (sodium stibogluconate) produced mild elevation of liver enzymes and a 43% reduction of the baseline white cell count, but the patient did not develop serious cardiac or liver toxicity.[33] Vomiting developed in a worker following the ingestion of antimony tartrate (tartar emetic)-contaminated lemonade that contained an estimated 0.53 mg Sb/kg body weight.[34] Oral dosing in pharmacological aversion therapy for the induction of vomiting ranged from ~25–140 mg.[16] The ingestion of ~500 mg tartar emetic by a 19-year-old man produced severe gastroenteritis and dehydration that resolved over 48 hours with supportive care.[35] He was lost to follow-up.

TOXICOKINETICS

Absorption

Most antimony compounds are poorly absorbed (i.e., <1%) from the gastrointestinal tract, and the strong

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emetic properties of these compounds further limit the absorption of large Sb doses. The absorption of trivalent compounds (trichloride, tartrate) is probably <10% based on an estimated range of absorption of 2–7% in animal studies.[36] Once absorbed, relatively small amounts (<5–10%) of the pentavalent form are reduced to the trivalent form.[37,38] In a pharmacokinetic study of 29 men receiving 600 mg intramuscular pentavalent antimony daily for 10 days, the mean time to peak Sb concentration was 1.34 ± 0.09 hours with a range of 0.5–2 hours.[39] Data on the absorption of antimony from the lung are limited, but animal experiments suggest that the lung rapidly absorbs and distributes antimony following inhalation.[40]

Distribution

The estimated total body burden of antimony in the general population is very low (i.e., ~7.9 mg).[30] Trivalent compounds bind avidly to cells and remain bound to erythrocytes disrupting hemoglobin function. The volume of distribution of pentavalent antimony compounds approximates total body water. In a study of 29 men with cutaneous leishmaniasis receiving 600 mg Sb daily for 10 days, the mean V_d was 45.7 ± 2.6 L with a range of 30.5–86.8 L.[39] The patients weighed 60–70 kg; however, individual weights were not reported. Highly vascular organs (e.g., spleen, liver, kidney, thyroid, bone) contain the highest Sb concentrations.[41] A study of smelter works exposed to ambient antimony indicates inhaled lung deposition of antimony may persist for several years. In a pathological study of 40 deceased, former smelter workers and 11 age-matched, nonexposed men from a nearby rural area, the median antimony concentration in the exposed workers was 315 μg/kg compared with 26 μg/kg in controls.[42]

Elimination

The rate and route of Sb elimination depend on the valence of the compound. The kidney slowly excretes trivalent compounds with 10% recovered in the urine after 24 hours and 30% recovered after 1 week.[43] In contrast to inorganic arsenic, antimony is not methylated *in vivo*; most absorbed trivalent antimony is eliminated in the feces after conjugation with glutathione. Some enterohepatic recirculation probably occurs.[44] The estimated urinary elimination half-life of trivalent antimony in workers at a starter battery production plant was ~95 hours.[45] Excretion of pentavalent antimony compounds occurs primarily in the urine. The kidney excretes pentavalent compounds more rapidly than trivalent compounds with 90% of a parenteral dose eliminated by 24 hours.[46] The elimination of pentavalent follows a multicompartment model with a rapid initial distribution phase followed by slower elimination phase. Primate studies suggest the intracellular conversion of pentavalent Sb to the trivalent form occurs during the resultant slow terminal elimination phase (i.e., 30–140 days) of trivalent Sb.[47] In a study of 12 young adults receiving 600 mg pentavalent antimony IM daily for 3 weeks, the mean terminal Sb elimination half-life from the blood was ~9.5 hours as measured by flameless atomic absorption spectrophotometry.[48] At the end of treatment, the kidneys excreted ~40% of the intramuscular dose of Sb during the first 24 hours after injection. Following the intramuscular injection of pentavalent compounds (stibogluconate, meglumine antimoniate) in 10 subjects, the mean half-life during the initial phase was ~2 hours compared with 76 hours for the terminal elimination phase based on a three-compartment model.[49] The slow terminal elimination phase may represent the *in vivo* conversion of pentavalent antimony to the trivalent form; small amounts of Sb may persist for many days (e.g., >50 days) after prolonged courses of pentavalent Sb.[50] The daily applications of trivalent antimony (antimony potassium tartrate) over 10 days did not result in Sb accumulation in the experimental animals.[51]

Maternal–Fetal Kinetics

Pentavalent antimony is excreted in breast milk. In a case report of a lactating mother receiving 20 mg pentavalent antimony/kg IV for leishmaniasis, the serum/breast milk ratios 4 hours and 23 hours after the last IV dose were 2.8 and 0.2, respectively.[52] The mean peak antimony concentration occurred 4 hours after the IV dosing.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Like arsenic, antimony has a strong affinity for sulfhydryl groups on many enzymes; however, antimony is less toxic than arsenic on a dose-response basis. Antimony potassium tartrate is a potent emetic with both local irritating and central emetic effects. Trivalent antimony compounds inhibit phosphofructokinase, which is an energy source for intracellular parasites. The exact mechanism of toxicity in humans remains unclear; *in vitro* studies suggest that antimony may inhibit pyruvate dehydrogenase complex and ATP production similar to arsenic by limiting acetyl coenzyme A from entering the Krebs cycle.[53]

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CLINICAL RESPONSE

Medical Therapy

Cardiotoxicity is the most serious side effect in patients treated with antimony compounds for parasitic infections. Conduction delays, prolongation of the QT interval, and ST-T wave abnormalities occur commonly in patients administered trivalent antimony compounds; rarely, ventricular dysrhythmias may develop. Minor electrocardiographic changes usually occur after therapeutic doses of pentavalent antimony compounds, but high doses of these compounds may cause life-threatening dysrhythmias.[54] Prolongation of the corrected QT interval (i.e., $QT_c > 500$ msec) and concave ST segments are the most significant prognostic signs of the development of serious cardiotoxicity. In a UK case series of 65 British travelers returning with New World cutaneous or mucosal leishmaniasis, each patient received a 21-day course of 20 mg/kg intravenous sodium stibogluconate daily.[55] Six asymptomatic patients developed a QT_c interval ≥450 msec or ≥50 msec increase above baseline in the third week of therapy. An 81-year-old man in this case series developed episodes of ventricular tachycardia without cardiovascular compromise. He had hypokalemia and a QT_c of 567 msec that resolved after normalization of the serum potassium concentration and resolution of the dysrhythmia.

Acute Oral Toxicity

The clinical presentation of acute antimony poisoning is similar to arsenic poisoning with the exception that neurotoxicity does not usually occur following Sb poisoning. Gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain) begin within 4–6 hours after ingestion of toxic doses (i.e., >30–60 mg Sb); gastroenteritis can cause severe dehydration as a result of intractable vomiting and diarrhea. Hepatic necrosis, coagulopathy, hepatic encephalopathy, and acute tubular necrosis may occur in severe cases of acute Sb poisoning.[56] High antimony doses can cause corrosion of the upper gastrointestinal tract and massive gastrointestinal bleeding, particularly in elderly patients.[41]

Occupational Exposure

Lungs

Although antimony in high concentrations is a respiratory irritant, co-exposure to arsenic complicates the interpretation of reports on Sb toxicity. Acute exposure to high ambient concentrations of antimony oxide and other ores can produce severe pulmonary edema along with cutaneous burns and pruritic papules that progress to pustules (*antimony spots*). Transient exposure to fumes of hydrochloric acid and antimony trichloride was associated with upper respiratory tract irritation from the HCl as well as gastrointestinal distress (abdominal pain, nausea, vomiting, anorexia), and headache; symptoms resolved within 1 week without sequelae.[57]

A simple pneumoconiosis was associated with the inhalation of antimony trioxide/pentoxide by workers with at least a decade of antimony exposure at antimony sulfide smelters. The clinical presentation was similar to other mild pneumoconioses (e.g., siderosis, stannosis, baritosis).[12] The etiology of pneumoconiosis may be mixed; consequently, the role of antimony in this disease remains unclear because of the presence of several confounders (e.g., silica, arsenic oxide, sodium hydroxide, ferric oxide). Animal studies indicate that exposure to dust from antimony ore produces mild, transitory pneumonitis, but neither the ore nor trivalent antimony induces progressive chronic inflammation of the lung.[58] A case series of workers at a smelter processing antimony sulfide ore associated work at the smelter with laryngitis, pharyngitis, rhinitis, and conjunctivitis; however, co-exposure to arsenic in the ores complicates interpretation of the study.[20] A case report associated exposure to high concentrations of antimony pentachloride with the development of pulmonary edema (presumably noncardiogenic); however, there was no ambient air monitoring to determine the actual exposure.[59] Two of the three workers died.

Skin

A pustular dermatitis is a recognized effect of exposure to antimony compounds (e.g., tartrates, trioxides) in antimony smelters,[60] welding,[61] production of grinding wheels,[62] and the use of metallic antimony for the manufacture of brazing rods.[63] These antimony spots are characterized by gray-white papules and pustules that surround sweat and sebaceous glands. Eczema may develop in areas of irritation that eventually form lichenification. Typically, these lesions appear on the legs, arms, back of neck, and scrotum during summer months as a result of heat and sweating. The face, hands, and feet rarely have lesions.[13] These lesions disappear following cessation of antimony exposure. Antimony chloride is a strong caustic.[64]

Heart

Although cardiotoxicity is a complication of the medicinal use of pentavalent antimony, there is no direct

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evidence that Sb exposure at concentrations typically present in the work environment causes or exacerbates cardiac disease. Exposure to antimony in the workplace primarily involves trivalent Sb. Older literature suggest inhalation of high Sb concentrations in the workplace may cause cardiomyopathy with prominent T-wave depression and dysrhythmias;[62] however, the documentation of exposure levels and confounding variables limit regarding the causation of these cardiovascular effects.

Carcinogenicity

Neither the IARC nor the US National Toxicology Program lists metallic antimony as a potential animal or human carcinogen. The IARC lists antimony trioxide as possibly carcinogenic to humans (Group 2B) based on animal data, whereas antimony trisulfide is listed as unclassifiable (Group 3). Both trivalent and pentavalent antimony compounds are usually negative in non-mammalian genotoxicity testing, whereas the former is positive and the latter negative in mammalian test systems.[65] A statistically significant excess of lung cancer occurred in workers exposed to fumes from the antimony smelting process before 1960 when compared with standardized national cancer rates.[13] Workers in antimony smelters before 1960 were exposed to antimony and antimony oxides at ambient air concentrations exceeding current standards by 20 times in addition to arsenic and arsenic oxides, sulfur dioxide, and polycyclic aromatic hydrocarbons. The excess risk of lung cancer disappeared after the 1960s when arsenic concentrations decreased in these processes.[66] The minimum latency period between first exposure and death from lung cancer for the pre-1960 cohort was 20 years. Exposure of rats to Sb concentrations ~100 times above the current TLV (50 mg Sb_2O_3/m^3) for 1 year at 7 hours/day and 5 days/week produced a statistically significant excess of lung neoplasms in female but not in male rats.[67] In this study, the appearance of interstitial pulmonary fibrosis usually preceded the development of lung tumors.

DIAGNOSTIC TESTING

Analytical Methods

Analytical methods for the quantitation of antimony (Sb^{3+}, Sb^{5+}) in biological samples include flow injection-hydride generation atomic absorption spectrophotometry (limit of detection, 0.5–1 μg/L),[68] anodic stripping voltammetry and graphite furnace atomic absorption spectrometry (LOD, 20–25 μg/L),[69] inductively coupled plasma/mass spectrometry (ICP/MS; LOD, 0.03 μg/L; coefficient of variance, 4%),[70] and neutron activation (NAA; LOD, 5 μg/L). Currently, ICP/MS is the most common method for detection of antimony; this method is more sensitive than older techniques (e.g., NAA). Consequently, the use of older methods may overestimate the antimony concentration in biological samples from the general population when a significant number of samples are below the LOD.

Only NAA does not require digestion of the sample. Losses of antimony as the chloride salt during the volatilization step of sample preparation for atomic absorption spectrophotometry may occur. The use of online ion chromatography/inductively coupled plasma/mass spectrometry allows the speciation of antimony compounds with LOD_s of trivalent and pentavalent in the range of 0.16 μg/L.[50]

Biomarkers

Blood

Pentavalent compounds bind poorly to erythrocytes; therefore, these pentavalent compounds typically produce much higher plasma antimony concentrations than similar doses of trivalent compounds. As a result of the very small fraction of pentavalent antimony bound to erythrocytes, plasma and whole blood antimony concentrations are similar following the administration of these compounds.[50] Trivalent Sb concentrates in erythrocytes; therefore, whole blood Sb concentrations are higher than serum or plasma Sb concentrations following absorption of trivalent Sb compounds.

General Population

Antimony is a trace element that occurs in small quantities in the blood. Several European studies indicate that Sb concentrations range from 0.03–3.5 μg/L (mean = 2.16 μg/L) in whole blood and from 0.01–1.7 μg/L (mean = 0.3–0.5 μg/L) in serum.[71,72] In a study of schoolchildren from rural areas of Kwazulu/Natal, South Africa, whole blood antimony concentrations ranged from <0.03–3.82 μg/L (median = 0.39 μg/L) compared with 1.40–4.35 μg/L (median = 2.08 μg/L) in whole blood samples from adults living in Dearborn, Michigan, as measured by inductively coupled plasma/mass spectrometry (LOD, 0.03 μg/L).[70] The mean whole blood antimony concentrations were 0.85 ± 0.90 μg/L and 2.51 ± 1.11 μg/L, respectively. In a French study of 100 healthy adults, the median antimony concentration in plasma samples was 0.11 μg/L (95% reference range, 0.03–0.15 μg/L) compared with 0.08 μg/L (95% reference range, 0.05–0.13 μg/L) in whole blood samples as measured by ICP/MS.[73] The LOQ was 0.02 μg/L and

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0.03 μg/L, respectively, with inter-assay imprecision of ~4–5%.

Medical Therapy

In a study of 12 Brazilian patients with cutaneous leishmaniasis receiving intravenous injections of 20 mg Sb^{5+}/kg/day for 20 days, the mean plasma Sb concentration prior to the last dose was 210 ± 19 μg/L with a range of 61–452 μg/L.[74] The blood samples were collected from 5 minutes to 48 hours prior to the last injection. Half of the patients reported arthralgias and myalgias during the course of treatment. The baseline plasma Sb concentrations for 18 Brazilian patients in this study were 3.39 ± 3.12 μg/L. In a study of 29 patients receiving a 10-day course of intramuscular 600 mg pentavalent antimony daily, the peak Sb concentration ~1.5 hours after injection was 8,770 ± 390 μg/L.[39] Ten patients received 5 mg Sb^{5+}/kg bodyweight intramuscularly for 30 days or 60 days; whole blood samples were collected 24 hours after the last dose. The mean steady-state Sb concentration in whole blood samples was 220 ± 7 μg/L.[50] Prior to initiation of therapy, the baseline mean whole blood Sb concentration was 0.69 μg/L.

Environment

Cross-sectional studies of subjects living in areas contaminated with antimony from mining activities indicate that antimony does not easily transfer from soil to humans. In a German study of 89 residents exposed to heavily Sb-contaminated soil (i.e., up to 776 mg/kg), the mean whole blood Sb was 0.89 μg/L compared with 0.69 μg/L in 49 referents as measured by graphite furnace/atomic absorption spectrometry after microwave digestion.[75] The mean amount of Sb excreted in 24-hour urine samples from the exposed group was 1.03 μg compared with 1.61 μg for the referents.

Overdose

Following an IV dose of 1,400 mg sodium stibogluconate (20 mg/kg), the serum antimony concentration in a 27-year-old woman 15 minutes after the infusion stopped was 85,000 μg/L.[52] The inadvertent infusion of 8,500 mg of sodium stibogluconate (143 mg/kg) over 4 hours produced a serum antimony concentration of 210,000 μg/L 30 minutes after the infusion stopped.[33] The serum antimony concentration 3½ and 8 hours later was 27,500 μg/L and 4,600 μg/L, respectively. No serious effects developed.

Urine

Typical urine Sb concentrations in the general population without occupational exposure are <0.1 μg/L as measured by more sensitive analytical methods (e.g., inductively coupled plasma/mass spectrometry).[76] In a French study of 100 healthy adults, the median antimony concentration in urine samples was 0.04 μg/L (95% reference range, 0.02–0.08 μg/L) as measured by ICP/MS.[73] The LOQ was 0.009 μg/L with inter-assay imprecision of ~5%. Pentavalent antimony is the predominant Sb species in human urine with traces of trivalent antimony and pentavalent organic Sb (e.g., trimethyl Sb) as measured by liquid chromatography coupled with ICP/MS.[77] Ten patients received 5 mg Sb^{5+}/kg bodyweight intramuscularly for 30 days or 60 days; spot urine samples were collected 24 hours after the last dose. The mean steady-state Sb concentrations in urine samples were 38,000 ± 800 μg Sb/g creatinine.[50] Prior to initiation of therapy, the baseline mean urine Sb concentration was 2 μg/g creatinine.

Abnormalities

The chest x-ray in workers with antimony pneumoconiosis generally demonstrates small, rounded and irregular opacities (p, s type).[78] Although chest x-rays may demonstrate numerous small opacities in the middle and lower lung fields, large opacities and massive fibrosis are not characteristic of antimony-associated pneumoconiosis. No specific clinical finding or laboratory abnormality distinguishes this pneumoconiosis from other types of simple pneumoconioses.

Biochemical abnormalities typically associated with antimony toxicity include mild leucocytosis, evidence of dehydration (e.g., elevated BUN/creatinine ratio), and rhabdomyolysis; measures of hepatic and renal function usually remain normal when fluid imbalance is corrected.[35,41,56] In a case series of 65 returning travelers treated with a 21-day course of pentavalent sodium stibogluconate, a majority developed asymptomatic elevations of serum amylase and hepatic aminotransaminases.[54] Mild to moderate hyperkalemia, anemia, and hepatorenal dysfunction may occur in severe cases along with rhabdomyolysis.[79] Electrocardiographic abnormalities associated with the therapeutic use of trivalent antimony (tartar emetic) include reduced T wave amplitude, T wave inversions, and QT prolongation.[80]

HEALTH SURVEILLANCE

The ACGIH currently recommends TLV–TWA for antimony of 500 μg/m^3. This recommendation corresponds to the NIOSH REL–TWA and the OSHA PEL–TWA. The US EPA maximum contaminant level

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for antimony in drinking water is 6 μg/L. Preplacement physical examinations should include comprehensive medical and work histories with emphasis on the skin, respiratory tract, and cardiac systems. Laboratory tests should include a chest x-ray, an electrocardiogram, and screening pulmonary function tests.

Blood

In a Taiwanese study of 103 optoelectronic workers with some exposure to antimony, the mean whole blood Sb concentration obtained during physical examinations prior to work was 0.72 ± 0.72 μg/L; these workers had co-exposure to arsenic (mean = 8.58 ± 6.36 ppb).[81] These values were similar to the mean whole blood Sb concentration (0.64 ± 0.64 μg/L) in 67 office workers without occupational exposure to antimony. The mean whole blood antimony concentration in a convenience sample of 15 Brazilian port workers exposed to Sb from heavy-weight brake pads was 27 ± 9 ng/kg as measured by hydride generation/atomic fluorescence spectrometry.[82] The end-of-work week venous samples from 14 formation workers exposed to median ambient air trivalent Sb concentration of 12.4 μg/m^3 (range, 0.6–41.5 μg/m^3) contained a median of 10.1 μg/L (range, 0.5–17.9 μg/L).[45]

Urine

In a Taiwanese study of 103 optoelectronic workers with some exposure to antimony, the mean urine Sb concentration obtained during physical examinations prior to work was 0.46 ± 0.22 μg/L.[81] These values were similar to the mean urine Sb concentration (0.30 ± 0.43 μg/L) in 67 office workers without occupational exposure to antimony. In a German study of 45 batch mixers exposed to trivalent antimony trioxide during glass manufacturing, the median urinary Sb concentration was ~5 μg/L with a range of 1.5–15.7 μg/L as measured by hydride generation and electrothermal atomic absorption spectrometry.[83] The concentrations of trivalent antimony trioxide in three personal air samples from the batch mixing area were <50 μg/m^3, 720 μg/m^3, and 840 μg/m^3. In a study of 32 workers from 6 art glass manufacturing plants exposed to trivalent Sb, the biological monitoring concentrations of Sb were higher than in the previous study. An exposure of 500 μg Sb/m^3 corresponded to an estimated total urinary Sb concentration of 49 μg/L as measured by electrothermal atomic absorption spectrometry.[84] The median Sb concentrations in ambient air samples from two plants were 14.0 μg/m^3 (n = 10; range, 3.9–31.0 μg/m^3) and 23.0 μg/m^3 (n = 14; range, 4.7–412.0 μg/m^3). Ambient air concentrations of antimony may not correlate to urinary antimony concentrations when airborne exposure to antimony is relatively low (e.g., 1–2 μg/m^3).[85] There are no biological exposure limits for antimony as a result of the limited occupational data on antimony exposure and the difference in urinary excretion between trivalent and pentavalent Sb compounds. Preliminary data suggest that an 8-hour exposure to 500 μg/m^3 increases the urinary Sb concentration to 35 μg Sb/g creatinine.[44] The end-of-work week urine samples from 14 formation workers exposed to median ambient air Sb concentration of 12.4 μg/m^3 (range, 0.6–41.5 μg/m^3) contained a median of 15.2 μg/g creatinine (range, 3.5–23.4/g creatinine).[45]

TREATMENT

There are little data to guide treatment and treatment primarily is supportive. Chelation with British Anti-Lewisite (BAL) is a potentially useful treatment for serious antimony exposures based on structural similarity to arsenic; however, there are inadequate clinical data to evaluate the efficacy of BAL for antimony toxicity. 2,3-Dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA) are oral analogs of BAL that may provide an alternative to BAL therapy, but there are few data on the use of DMPS (50 mg every 8 hours) or DMSA (100 mg PO tid) for antimony poisoning. Several literature reviews suggest the use of DMSA based on the chemical similarity (e.g., high electronegativity, high affinity to sulfur-containing chelating agents) with arsenic.[86,87] All cases of serious antimony poisoning should be monitored closely for the development of dysrhythmias, fluid depletion, hepatorenal dysfunction, hepatic encephalopathy, and electrolyte imbalance.

STIBINE GAS (ANTIMONY HYDRIDE)

STIBINE GAS

The reaction of elemental antimony with hydrogen produces the highly toxic gas (stibine, antimony hydride, SbH_3) in the 3− oxidation state. This reaction occurs during the reduction of antimony compounds, the electrolysis of basic or acidic solution and Sb-containing cathodes, or following the reaction of acids with metal

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TABLE 2.2. Physical properties and identifying information of stibine gas.

Physical Characteristic	Stibine Gas
CAS RN	7803-52-3
Molecular formula	SbH_3
Molecular weight (g/mol)	124.77
Valence	−3
Color	Colorless
Physical state	Gas
Odor	Disagreeable (similar to H_2S)
Melting/boiling points (°C)	−88/−17
Density (g/mL)	2.204 (at boiling point)
Water solubility	4.1 g/L (0°C)
Vapor pressure	>760 torr (20°C)
Conversion factor (25°C, 760 torr)	1 ppm = 5.1 mg/m^3 1 mg/m^3 = 0.196 ppm

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number

antimonides or antimony alloys. Stibine is a colorless gas with a disagreeable odor. Table 2.2 lists some physical properties and identifying information of stibine gas. Stibine gas evolves from the exposure of Sb alloys to acids and electrolysis or from the action of hydrogen on metallic Sb. This substance decomposes slowly in to elemental antimony and hydrogen. Oxidation of stibine gas in air forms antimony trioxide and water. In a study of workers exposed to trivalent antimony and stibine gas, the initial elimination half-life of antimony was similar (i.e., ~95 hours) following exposure to either substance.[45]

Few clinical data are available on the effects of stibine gas exposure. Interpretation of existing data is complicated by coexposure to arsenic in sources of stibine gas; however, existing data suggest stibine and arsine (AsH_3) gases produce similar effects. Clinical features of stibine gas exposure include hemolytic anemia, myoglobinuria, renal failure, weakness, profuse vomiting, nausea, headache, abdominal and low back pain, and hematuria.[88] Vomiting is usually prominent. The off-gassing of hydride gases including stibine gas generated from the effect of fungal degradation on fire retardants in PVC cot mattress covers was suggested as a possible cause of sudden infant death syndrome (SIDS);[89] however, there are insufficient data to establish a causal link.[90] *In vitro* studies indicate that antimony volatilization from PVC in cot mattresses does not occur under normal environmental conditions; off-gassing of antimony requires heating 80–100°C.[91] For stibine gas, the ACGIH TLV–TWA, US OSHA PEL, and the NIOSH REL are 0.1 ppm (0.5 mg/m^3). Treatment for stibine gas poisoning is supportive. There is no human evidence that BAL improves clinical outcomes after stibine gas exposure.[92] Few human data are available on the efficacy of exchange transfusion following stibine gas exposure; however, exchange transfusion is a potential option in the clinical setting of acute renal failure, hemolysis, or rhabdomyolysis.

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Chapter 3

ARSENIC

ELEMENTAL AND INORGANIC ARSENIC

HISTORY

Arsenic has a long history of abuse as a common, inexpensive homicidal agent and use as a medicinal agent in Greco-Roman and traditional Chinese medicine. Commercial applications of arsenicals in modern ages include a wood preservative, pesticide, veterinary anthelminthic, and ant paste; however, many of these arsenical products have been replaced by less toxic substances. Arsenic poisoning also occurs from the accidental addition of arsenic to commercial products. In 1955, the Morinaga Dry Milk Company produced arsenic-contaminated milk when a disodium phosphate stabilizer contained 5–8% of a soluble inorganic arsenic compound expressed as arsenous acid. The estimated arsenic concentration in the reconstituted milk was ~4–7 mg/L with a maximum of 4 months of exposure. Over 12,000 infants developed arsenic poisoning (fever, hyperpigmentation, hepatomegaly, anemia) with at least 130 infant deaths.[1] Follow-up studies suggest significantly increased mortality occurred in the survivors.[2]

Poisoning

The nonspecific, widespread effect of this odorless, tasteless compound enhanced the popularity of arsenic as a homicidal agent causing slow, painful deaths.[3] In one of the first recorded cases of arsenic poisoning, Nero poisoned Britannicus in 55 AD to solidify his position as Emperor of Rome. During the early Middle Ages, poisoning was a prevalent part of social and political life. Arsenic gained a reputation as "inheritance powder;" legendary arsenic poisoners included Cesare Borgia, Teofania di Adamo, Marie Madeleine, and later in the 19th century, Goeie Mie ("Good Mary") of Leiden, The Netherlands. The latter poisoner distributed arsenic trioxide-laced hot milk to over 100 victims. Other famous arsenic poisoners include Herbert Armstrong, Marie Besnard, and Marie Lafarge. Acute diarrhea associated with arsenic poisoning was easily confused with cholera. The German–Swedish apothecary and pharmacist, Carl Wilhelm Scheele, developed the Scheele test for detecting arsenic.[4] Heating a mixture of arsenic with metallic zinc and nitric acid produced arsine gas (AsH_3) that was detectable as a garlic odor; however, the test was unreliable and inadmissible in court. The British chemist, James Marsh, improved the Scheele test by heating the trapped arsine gas in a funneled tube to form a gray metallic film ("arsenic mirror") and hydrogen gas. The development of the Marsh test in 1836 allowed the detection of 20 μg of arsenic by conversion of arsenic to arsine gas with nitric acid and the modified Scheele test.[5] Sufficient arsenic was collected as a silver-black deposit on a cold ceramic bowl to provide visual proof of the presence of arsenic. The popularity of arsenic as a homicidal agent declined significantly after the development of this test and the subsequent conviction of the celebrated poisoner,

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Marie Lafarge, in September 1840.[6] Her controversial trial was the first legal case using forensic evidence to convict, when the Dean of the Paris Faculty of Medicine, Mathieu Orfila, confirmed the presence of arsenic in her husband's body using the Marsh test.[7]

Activation analyses of authenticated hairs of Napoleon correlated arsenic concentrations to clinical symptoms of chronic arsenic poisoning as recorded in the written diaries of his exiled companions.[8] In the month before his death, Napoleon complained of coffee-ground vomiting, yellow skin, scleral icterus, weight loss, and anorexia. Other complaints in the preceding year included right scapular pain, nausea, headaches, weakness, coughing, and abdominal distension. Although elevated arsenic concentrations occurred in hair samples reportedly from his scalp before and during his incarceration at St. Alba,[9] the contribution of arsenic to the death of Napoleon remains speculative. Another author attributed the final phase of Napoleon's chronic illness to the ingestion of calomel (mercurous chloride) flavored with oil of bitter almonds that formed mercuric cyanide. Besides arsenic exposure, Napoleon received several compounds that would potentially predispose him to hypokalemia, QT prolongation, and sudden death from ventricular fibrillation including quinine from Jesuit's bark, antimony in tartar emetic, and mercurous chloride in calomel.[10] An interdisciplinary analysis of the medical data recorded during Napoleon's internment indicated that his clinical course was not consistent with chronic arsenic toxicity.[11] An official autopsy performed by Francesco Antommarchi soon after Napoleon's death documented an upper gastrointestinal bleed and a perforated 10-cm-cancerous tumor in the lesser curvature of his stomach with cancer as the listed cause of death. His father also died of stomach cancer. The autopsy included no histological confirmation of the stomach cancer, as was the custom in the early 1800s; his autopsy contained no confirmation of any stigmata of chronic arsenic poisoning (Mees' lines, alopecia, hyperkeratosis, hyperpigmentation). Potential sources for the arsenic in hair samples from Napoleon include the volatilization of trimethylarsine from arsenic compounds in wallpaper, hair products, clothing, food wrappers, medicines, and well water.[12] Green copper arsenite (Paris green, Scheele's green) pigments were common constituents of wallpapers in the early 1800s; molds are capable of releasing trimethylarsine from damp wallpaper.[13] X-ray fluorescence spectroscopy of a wallpaper sample from the room where Napoleon died suggested the wallpaper was capable of off-gassing sufficient trimethylarsine to produce illness, but probably not death.

Medical Therapy

Hippocrates, Aristotle, and Pliny the Elder wrote about the medicinal properties of arsenicals. Hippocrates used arsenic sulfides (realgar, orpiment) for the treatment of ulcers; the Greek physician, Dioscorides, used orpiment as a depilatory.[14] In China, the Nei Jing Treaty recommended arsenic for the treatment of periodic fever. Si-Miao Sun (581–682) used an arsenic-containing medicine (orpiment, realgar, arsenic trioxide) for the treatment of malaria. In 1786, Thomas Fowler published a study on the treatment of malaria with a solution of potassium arsenite (Fowler's solution, Liquor Mineralis). This solution was widely administered for a variety of diseases (e.g., malaria, syphilis) until the mid-20th century. Beginning in the middle of the 19th century, a variety of arsenic-containing compounds including Fowler's solution (1% potassium arsenite), Asiatic pills (arsenic trioxide), Donovan's solution (AsI_3), and De Valagin's elixir (arsenous acid/hydrochloric acid) were remedies for a variety of ailments (e.g., rheumatism, asthma, chorea, tuberculosis, diabetes, fever, skin and blood abnormalities, nutritional disturbances, syphilis, trypanosomiasis).[3] Erasmus Wilson first described arsenical keratoses of the palms and soles in 1868.[15] By the early 1900s, physicians began substituting less toxic organic arsenicals for inorganic arsenic compounds. Although traditional Chinese and Western medicine used inorganic arsenic compounds to treat cancer for several hundred years, the popularity of inorganic arsenic as a treatment for chronic myelogenous leukemia did not increase significantly until the 1930s; however, adverse effects from the high arsenic doses limited the use of inorganic arsenic compounds. Beginning in the 1970s and 1980s, successful Chinese and Indian studies resulted in a resurgence of the use of arsenic trioxide for the treatment of acute promyelocytic leukemia in combination with all-*trans*-retinoic acid.[16] The key driver for this disease results from the fusion of the retinoic acid receptor α gene (*RAR*α) on chromosome 17 to the promyelocytic leukemia gene (*PML*) on the long arm of chromosome 15 (15q) that creates the PML-RARα fusion protein, producing the fusion protein responsible for acute promyelocytic leukemia. Arsenic binds to thiol groups on this protein.[17]

Environment

Arsenic is a constituent of arsenopyrite (FeAsS); this sulfide mineral commonly occurs in association with copper and iron ores. Consequently, arsenic trioxide

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is a byproduct of the smelting of these ores. Agricola and Paracelsus described arsenic poisoning in miners in the 15th and 16th centuries.[18] Arsenic is an occasional contaminant of well water and food. At the beginning of the 20th century in Salford, England, the ingestion of arsenic-contaminated beer was associated with the development of gait disturbances and sensorimotor neuropathy.[19] The cause of the Staffordshire beer epidemic was the use of arsenic-containing Spanish pyrite as a source of sulfuric acid to produce inverted sugar during the brewing process. In 1955, the contamination of sodium phosphate stabilizer in infant formula caused over 12,000 cases of arsenic poisoning in Japanese infants including 130 deaths.[20] Clare Booth Luce developed arsenic intoxication while she was the American Ambassador to Italy in the 1950s; the source of her poisoning remains unknown.[21] A review of 17 cases of arsenic toxicity during the 1980s in Minnesota demonstrated the following distribution of etiologies: accidental (41%), suicidal (41%), homicidal (12%), and malingering (6%).[22] The source of the vast majority of these poisonings was Terro Ant Killer®. A retrospective review of arsenic exposures reported to a poison control center during the 1980s indicated that exposure of children to arsenic primarily involved sodium arsenate in ant poison.[23,24] In 1989, the US EPA instituted the phase out of certain arsenic-containing ant poisons to reduce arsenic exposure in US children.

Chronic arsenic poisoning results from the natural contamination of drinking water with arsenic in several areas of the world including Argentina, Bangladesh, Chile, China, Finland, Hungary, India, and Mexico. Additionally, sporadic contamination of drinking water wells may result from the mining of ores (gold, silver, copper, lead, tin) that contain arsenic sulfides. The largest epidemic of arsenic poisoning occurred in Southeast Asia with an estimated 1.5 million inhabitants in West Bengal, India, and 21 million inhabitants in Bangladesh exposed to drinking water containing >50 μg arsenic/L.[25] In these inhabitants, consumption of high arsenic concentrations in drinking water up to 3.4 mg/L from tube wells was associated with the development of skin lesions (hyperpigmentation, hyperkeratosis, gangrene).[26,27] These tube wells have been installed in Bangladesh since the 1940s as a means to avoid microbial contamination. During the 1960s and 1970s, the United Nations Children's Fund (UNICEF) worked with the Department of Public Health Engineering to provide approximately one million wells, consisting of 5-cm-tubes inserted up to 200 m into the ground and capped with hand pumps; the arsenic concentration in the drinking water was not analyzed prior to the installation of these wells. Additional tube wells were installed privately in the 1970s and 1980s; by the end of the 1980s, 97% of the population drank water from tube wells. KC Saha at the Department of Dermatology at the School of Tropical Medicine in Calcutta, India, identified the first cases of arsenic-induced skin lesions in the early 1990s.[28] In Bangladesh, confirmation of arsenic contamination in tube-wells occurred in 1993 in the Nawabganj district. Ecological studies in Taiwan and Argentina during the 1990s suggest an elevated prevalence of skin and bladder cancers following chronic exposure to arsenic in drinking water.[29] Blackfoot disease is a unique peripheral vascular disease resulting from continuous exposure to arsenic-contaminated well water. Retrospective case-control studies of liver, lung, and bladder cancer in areas of Taiwan where Blackfoot disease is endemic suggest an elevated incidence of these cancers.[30]

PHYSIOCHEMICAL PROPERTIES

Elemental arsenic is a reactive transitional, nonessential element that belongs to Group 15 (Group VA) of the periodic table along with antimony, bismuth, nitrogen, and phosphorus. Arsenic is a naturally occurring metalloid capable of combining with metals or nonmetals to form inorganic (arsenites, arsenates), organic compounds (methyl and phenyl arsenates), and nonmetal/metal combinations (arsenopyrite, FeAsS). Arsenic occurs in the following four valence states: −3 (arsine), 0 (elemental), +3 (arsenite, AsO_2^-, including monomethylarsonite and dimethylarsenite), and +5 (arsenate, AsO_4^{-3}, including monomethylarsonate and dimethylasinate). Metallic arsenic is a brittle, crystalline, brilliant steel-gray metalloid that turns black upon exposure to air. Elemental arsenic is water-insoluble. Arsenite is the dominant form under reducing conditions, whereas arsenate is the stable form in well-oxygenated environments.[31] Heating arsenic-containing ores to 193°C releases arsenic fumes that combine with precipitation to form "white arsenic" (arsenic trioxide) in water. From a toxicological perspective, the major classifications of arsenic compounds include inorganic arsenic, metalloid arsenides, organic arsenic, and arsine gas. Figure 3.1 illustrates the chemical structure of some toxicologically relevant trivalent and pentavalent arsenic compounds.

Inorganic trivalent arsenic compounds include arsenic trioxide, arsenic trichloride, and sodium arsenite. Arsenic salts exhibit a wide range of solubilities depending on the redox potential and the pH. Arsenic trioxide is slightly soluble in water and forms arsenite in highly alkaline solutions. The aqueous solubility

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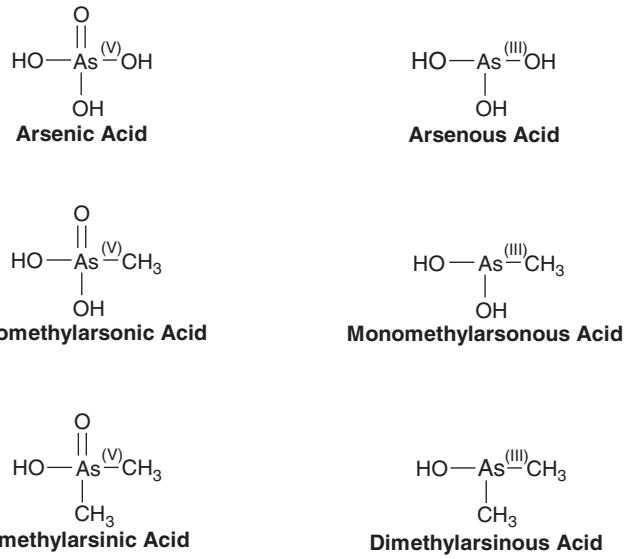


FIGURE 3.1. Chemical structures of toxicologically relevant trivalent arsenic (III) and pentavalent arsenic (V) compounds. (Adapted from Ren et al.).[32]

of arsenic trisulfide (0.0005 g/L at 18°C) is relatively low compared with arsenic trioxide (17 g/L at 16°C). The interaction of concentrated hydrochloric acid with arsenic trioxide produces arsenic trichloride. Pentavalent inorganic compounds include sodium pentoxide, lead arsenate, calcium arsenate, and arsenic acid. Arsenate is a phosphate analog; organisms living in elevated arsenate environments require high concentrations of phosphate to avoid arsenic toxicity. Both sodium arsenite and sodium arsenate are highly soluble in water. Inorganic arsenic compounds can change valence in water depending on the pH and the presence of other substances.[33] The oxidation of trivalent arsenic is more rapid in alkaline solutions than acidic solutions, whereas pentavalent inorganic arsenic is relatively stable in neutral and alkaline solutions.[34] The reduction of pentavalent inorganic arsenic increases as the pH decreases. Tables 3.1 and 3.2 list the identifying data and physical properties of some common inorganic arsenic compounds.

TABLE 3.1. Physical properties and identifying information of elemental arsenic, arsenic acid, and arsenic oxides. (Data from ATSDR).[35]

	Arsenic	Arsenic Acid	Arsenic Pentoxide	Arsenic Trioxide
Formula	As	H_3AsO_4	As_2O_5 or As_4O_{10}	As_2O_3 or As_4O_6
Synonym	Metallic arsenic, arsenic black	Orthoarsenic acid	Arsenic (V) oxide, arsenic acid anhydride	Arsenic oxide, white arsenic, arsenous acid anhydride
CAS RN	7440-38-2	7778-39-4	1303-28-2	1327-53-3
Valence	0	+5	+5	+3
Molecular weight (g/mol)	74.92	141.95	229.84	197.84
Color	Silver-gray	White	White	White
Physical state	Solid	Solid	Solid	Solid
Melting point (°C)	817 (28 atm)	35.5	Decomposes at 315	312.3 (claudetite)
Density (g/mL, 20°C)	5.778 (25°C)	2.2	4.32	3.865 (cubic) 4.15 (rhomboid)
Odor	Odorless			Odorless
Water solubility	Insoluble	302 g/L at 12.5°C	2,300 g/L at 20°C	17 g/L at 16°C
Vapor pressure	7.5×10^{-3} at 280°C	NA	NA	2.47×10^{-4} at 25°C

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.

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TABLE 3.2. Physical properties and identifying information of sodium arsenite and arsenates. (Data from ATSDR).[35]

Property	Calcium Arsenate	Sodium Arsenate	Sodium Arsenite
Formula	$Ca_3(AsO_4)_2$	Na_2HAsO_4	$NaAsO_2$
Synonym	Calcium orthoarsenate	Disodium arsenate	Sodium metaarsenite
CAS RN	7778-44-1	7778-43-0	7784-46-5
Valence	+5	+5	+3
Molecular weight	398.08	185.91	129.91
Color	Colorless	Colorless	Gray-white
Physical state	Solid	Solid	Solid
Melting point (°C)	1.455	57	615
Density (g/mL, 20°C)	3.62	1.87	1.87
Odor	Odorless	Odorless	Insufficient data
Water solubility (g/L)	0.13 (25°C)	Soluble	Very soluble

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.

EXPOSURE

Production Processes

Arsenic compounds (e.g., arsenic trioxide) are byproducts of lead, copper, and gold extraction. Smelting of arsenic-containing ores (e.g., arsenopyrite (FeAsS)) during these processes releases gaseous arsenic that electrostatic precipitators collect as crude flue dust. Roasting this dust oxidizes the gaseous arsenic to arsenic trioxide (white arsenic). Aluminum oxide is the main impurity in this process. The primary process for the production of elemental As is the reduction of arsenic trioxide with charcoal; however, low demand limits the production of elemental As. Currently, there is no domestic production of elemental or arsenic trioxide in the United States.[35]

Uses

Processes that produce arsenic include high-temperature combustion, waste incineration, household waste disposal, glassware production, semiconductor and bronze production, nonferrous smelting, lead and copper alloys, galvanizing, ammunition production, and the production of certain chemicals (dyes, wood preservatives, pesticides, pyrotechnics, drying agents for cotton and oil). Elemental arsenic is an alloying element in ammunition and solders, an antifriction additive for bearings, and a strengthening agent in lead-acid storage battery grids. Arsenic trioxide and arsenic acid are decolorizers and fining agents in the production of bottle glass and other glassware. Previously, the manufacture of pesticides (arsenic acid, arsenic pentoxide, arsenic trioxide, sodium arsenate), rodenticides, herbicides (calcium arsenate, lead arsenate, sodium arsenite), and other agricultural products accounted for a majority of inorganic arsenic uses.[36] Less toxic products are currently replacing these products. Commercial applications of arsenical compounds include pesticides, herbicides, glassware, marine paints, alloy makers, and pigment production. Although most medicinal uses of inorganic arsenic have been replaced by more effective and less toxic drugs, arsenic trioxide is now an approved treatment for acute promyelocytic leukemia and melarsoprol (aromatic arsenical) for trypanosomiasis in the United States.[37] Rarely, arsenic toxicity develops following the consumption of homeopathic medicines, manifested by melanotic skin lesions and polyneuropathy.[38]

Sources

Arsenic is a natural constituent of sulfide minerals (e.g., arsenopyrite, FeAsS). The arsenic concentrations in various types of igneous rocks range from <1–15 mg/kg with an average value of ~2 mg/kg.[31] The major anthropogenic sources of arsenic in the environment are the smelting of nonferrous metals and the production of energy from fossil fuels.[31] Food and, to a much lesser extent, water represent the major sources of arsenic exposure for the general population. The mean daily intake of total arsenic in a reference group from the Midwestern US was 0.13 μg/kg body weight.[39] These arsenic concentrations are usually below the arsenic concentrations that produce toxicity. The typical concentrations of arsenic in the air are relatively low (<80 ng/L). Case reports of arsenic toxicity secondary to environmental exposure (e.g., 9–11 mg/L well water) are rare in developed countries.[40] Most human health problems associated with environmental arsenic exposure result from the chronic ingestion of As-contaminated groundwater in Asia including Bangladesh, West Bengal,

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China (Inner Mongolia), Taiwan, Cambodia (Upper Mekong River Basin), and northern Vietnam (Red River Delta).[41] Arsenic concentrations in groundwater in the Mekong Delta of Cambodia ranged from 1–1,610 μg/L in Cambodia (mean = 217 μg/L) and from 1–3,050 μg/L (mean = 159 μg/L) in the Red River Delta of northern Vietnam.[42]

Air

With the exception of workers exposed to arsenic fumes, inhalation is not a major source of exposure for the general population. Even in situations where arsenic-contaminated coal is used to fire open indoor cooking and drying pits, arsenic-contaminated food accounts for most of the daily exposure to arsenic.[43] High-temperature processes (e.g., coal-fired power generators, burning vegetation, volcanic activity) release arsenic to the atmosphere, primarily in the oxidized, pentavalent (As^{5+}) state.[44] Arsenic in ambient air occurs primarily as a mixture of arsenate and arsenite oxides with few organic arsenic compounds.[35] Typical background concentrations of As in ambient air are 0.2–1.5 ng/m^3 for rural areas, 0.5–3 ng/m^3 for cities, and <50 ng/m^3 for industrial sites.[31] Mean arsenic concentrations in remote areas of the United States range from <1–3 ng As/m^3 compared with 20–30 ng As/m^3 in the ambient urban air.[45] The higher concentrations present in urban air usually result from the emissions from coal-fired power plants. Arsenic concentrations in ambient air near nonferrous metal smelters may reach 2,500 ng/m^3.[46]

Soil

Concentration

In soil, arsenic exists as a complex mixture of mineral phases (e.g., co-precipitated, sorbed, dissolved species), primarily as sulfide complexes (e.g., iron pyrites (FeAsS), orpiment (As_2S_3), realgar (As_2S_2)). The heating of ores containing these sulfide complexes produces a white powder (arsenic trioxide). Arsenic is the 20th most abundant element in the crust of the earth, although the concentration of arsenic varies substantially between different locations.[47] Generally, the natural As concentrations in soil range from 1–40 ppm with a mean of 5–7 ppm.[48] Arsenic occurs in natural soil near active geothermal areas in concentrations up to 20 ppm.[49] Soils near arsenic-containing sulfide ores may contain As concentrations of several orders of magnitude higher than typical mean As concentrations. In a study of 15 samples from 2 English counties with a long history of mining and smelting, the mean total arsenic concentration in soil was 4.45 ppm with a range of 0.345–52.6 ppm.[50] About 80% of the arsenic released to the environment from anthropogenic sources partitions into the soil. Fossil fuel combustion, application of pesticides, and disposal of solid wastes are the main sources of these releases. US coals contain relatively small amounts of arsenic compared with other coals in the world (e.g., Slovakia). In a study of US coals, bituminous coal contained the highest concentration of arsenic (mean = 23.5 ppm) compared with a mean of 2.7 ppm for sub-bituminous coal and a mean of 5.0 ppm for lignite coal.[51]

Soil samples from an area of high natural arsenic concentrations near a closed arsenical pesticide-producing plant contained As concentrations ranging from 32–1,597 mg/kg soil.[52] Speciation of the arsenic demonstrated that trivalent arsenite species averaged 44.8% of total arsenic in rock and ranging from 0.32–56% in soil. The median As concentration in 15 surface soil samples from South Australia was 3.9 ± 2.0 mg/kg compared with 0.6 ± 0.55 mg/kg for 6 Tasmanian soil samples.[53] Chromated copper arsenate is a wood preservative used in pressure-treated wood. Studies of decks built with arsenate-treated wood indicate that arsenic concentrations in soil samples below the deck may exceed US EPA standards for arsenic.[54] The contamination does not usually migrate beyond the immediate area below the deck; however, indoor sanding of the treated wood may release airborne arsenic concentrations exceeding current indoor workplace standards.[55]

Bioavailability

The bioavailability of arsenic species is not well defined, but current evidence indicates that the bioavailability of arsenic in soil is relatively low. Using a rat model, the estimated bioavailability of trivalent and pentavalent arsenic ranged from 1.02–9.87% and 0.26–2.98%, respectively. In a study of female monkeys, the oral bioavailability of arsenic in soil and dust was 19% and 14%, respectively, after normalization of the intravenous recovery data.[56] Animal models indicate that bioavailability does not correlate to leachates using water with a pH of 1.0 (acidic) or 7.0 (neutral). The degree of arsenic solubility in soil depends on several factors including mineral phase, particulate size, soil oxidation–reduction potential, and type of inorganic compound. In a study of soil near the Anaconda, Montana smelter, arsenic existed primarily as the sparingly soluble arsenic oxides and phosphates.[57]

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A Danish study compared a group of adults and children from an area of high arsenic soil concentrations (mean ~20 ppm) with a control group from an unpolluted area.[58] There was no statistically significant difference in the mean urine concentrations of inorganic arsenic or methylated metabolites between subjects from the area of high and low arsenic soil concentrations. The urine arsenic concentrations in the children of both groups were higher than in adults. A study of children (<6 years old) residing in the area of an old smelter demonstrated a correlation between soil arsenic concentrations and total speciated arsenic in urine samples, but the low arsenic concentrations suggested that the bioavailability of arsenic in contaminated soil was low.[59]

Water

Arsenic is widely distributed both in surface and groundwater, primarily as inorganic arsenic. The presence of As in groundwater results from a variety of factors including the intrusion of geothermal water, dissolution of sulfide minerals or oxyhydroxide ions, drainage from thermal springs and geysers, atmospheric depositions, and natural weather and leaching.[60] Most arsenic in well-oxygenated natural waters exists in the soluble pentavalent form (arsenate) rather than the less soluble trivalent form (arsenite).[61] The background concentration of As in open ocean seawater is ~1–2 μg/L with dissolved forms consisting of arsenate, arsenite, monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA).[31]

Arsenic concentrations in groundwater typically average ~1–2 μg/L, except in some western and north-central US states with volcanic rock and arsenic-containing sulfide mineral deposits high in arsenic (i.e., As concentrations up to 3,400 μg/L).[35] In wells contaminated by arsenic from local tin mines, arsenite represented <5% of the total arsenic species in shallow wells compared with ~39% of the total arsenic in deep wells.[62] Sediments in aquatic systems often contain higher concentrations (e.g., 0.1–4,000 ppm As) compared with surrounding rivers and lakes.[63]

The average daily intake of total arsenic from water is about 5 μg. Substantially higher arsenic intake occurs in some developing countries (e.g., Bangladesh, lowland Nepal), where arsenic contaminates tube wells used for drinking water.[64] In drinking water systems in developed countries, arsenic concentrations typically range from 0.2–10 μg/L with 99% of all systems containing <50 μg/L.[65] Most epidemiological studies indicate that arsenic concentrations in drinking water above 400 μg/L may produce toxicity, whereas As concentrations of <100 μg/L are not usually associated with toxicity. The US EPA maximum contaminant level (MCL) for As is 50 μg/L water (50 ppb). The US EPA ambient water quality standard for fish consumption is 17 ppt arsenic (0.017 μg/L) and 2.2 ppt arsenic (0.0022 μg/L) for fish and water consumption.

Diet

For the general US population, food is the primary source of arsenic. Other significant factors that modify total arsenic exposure include tap water, gender (males typically consume more water than females), smoking, and habitual seafood consumption (organic As).[66] Estimates of the average daily intake of *total* arsenic ranged from 38 μg in Canadian subjects (range 15 μg in young children to 59 μg in young adults)[67] to 110–348 μg in Japanese subjects.[68] Of the total As in the diet, inorganic arsenic averages about 35–40%. The estimated daily US intake of arsenic averages ~50 μg elemental As depending on age and seafood consumption.[69] Substantial differences in the estimated daily intake of arsenic probably result from differences in the temporal consumption of seafood[70] with estimates ranging from ~40–60 μg in the adults from 6 Canadian cities to 160–280 μg in Japanese adults from Shiga Prefecture.[71] Analysis of seafood products from Spain indicated that the highest arsenic concentration occurred in white fish, followed by blue fish, mollusks, crustaceans, and preserved fish.[72] Although seafood mostly contains the less toxic, methylated forms of arsenic, small amounts of inorganic arsenic may occur in seafood.[73] Typically, the As concentration in freshwater fish is <1 ppm (fresh weight). In a market basket survey, the total arsenic concentration in fish fillets ranged from 160 ppb wet weight in freshwater fish to 2,360 ppb wet weight in saltwater fish.[74] The average inorganic arsenic concentrations in these samples were ≤2 ppb wet weight. The inorganic arsenic content in saltwater fin fish was somewhat higher (5–38 ppb) in other studies.[68,75] Meat, poultry, grains, cereal products, and oils contain lesser amounts of arsenic (average 19–24 ppb) than seafood.[67,76] In a study of the US diet, the highest As concentrations occurred in seafood followed by rice, mushrooms, and poultry.[77] Terrestrial mushrooms contain relatively high concentrations of nontoxic arsenobetaine; store-bought mushrooms may contain low total arsenic concentrations with the predominant species being inorganic arsenic.[78] In 14 samples of store-bought mushrooms, the average total arsenic concentration was 0.20 mg/kg (ppm) dry mass with a range of 0.02–1.3 mg/kg. Rice may contain substantial amounts of arsenic depending on the surrounding soil. Boiling the fruiting bodies

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in rice water containing high As concentrations (i.e., 47–450 μg/L) may substantially increase the release (i.e., bioavailability) of As from parboiled and non-parboiled rice.[79] Although most vegetables adsorb As on their surface, the As content in most leafy vegetables is relatively low, even though local water may contain relatively high As concentrations.[80] The amount of arsenic in foods obtained through foraging or hunting (country foods) is highly variable. In a Canadian study, the total arsenic concentrations were as follows (wet weight): berries, 0.6–21 mg/kg; Labrador tea, 1.9 mg/kg; mushrooms, ≤46 mg/kg; and hare muscle tissue, 0.007–0.6 mg/kg.[81] The latter two foods contained substantial amounts of organic arsenic species including arsenobetaine.

In arsenic-contaminated regions of Bangladesh and India, drinking water is the main source of arsenic exposure when drinking water As concentrations exceed 50 μg/L. For residents exposed to drinking water below this standard, diet becomes an important source of arsenic. In a study of 47 women from Pabna, Bangladesh, the median daily total arsenic intake was 48 μg from food and 4 μg from drinking water.[82] Inorganic arsenic accounted for 82% of total arsenic, and about one-third of these residents exceed the World Health Organization's provisional tolerable daily intake of 2.1 μg total As/kg. Irrigation of rice and vegetables with arsenic-enriched groundwater is an important pathway of arsenic exposure in the Ganga–Meghna–Brahmaputra basin in West Bengal. In general, the arsenic content in fleshy vegetables (beans, tomatoes, peas, lentils) grown in this region is less than that of leafy (cabbage, spinach) and tuberous (potatoes, radish) vegetables.[80] The estimated daily *total* arsenic intake for adults and children in this region was 560 μg and 393 μg, respectively, as measured by flow injection hydride generation atomic absorption spectrometry.[83] Inhalation of arsenic from well water during bathing is probably not a significant route of exposure for acute or chronic toxicity.[84] Ayurvedic medicine is a potential source of chronic arsenic toxicity, particularly dermatological drugs. A case series of three Indians associated the ingestion of arsenic-contaminated Ayurvedic medicine (As > 0.1 mg/kg) with clinical features of chronic As toxicity (hyperpigmentation, hyperkeratosis, peripheral sensory neuropathy, pedal edema, gastrointestinal disturbances).[85]

In terrestrial foods, the percentage of inorganic arsenic ranges from 25–100% compared with elemental and organic arsenic species. In a market survey of 40 foods, the highest inorganic arsenic concentrations occurred in raw rice (74 ppb wet weight), flour (11 ppb), grape juice (9 ppb), and cooked spinach (6 ppb).[74] Consequently, diets high in rice (e.g., gluten-free) are potential sources of relatively elevated inorganic As concentrations compared with standard diets.[86,87] A study of 112 composite foods in the Canadian diet revealed that the highest mean total arsenic concentration occurred in fish (1,662 ppb) followed by cereals (24.5 ppb), meat and poultry (24.3 ppb), and fats and oils (19 ppb).[67] Arsenic may contaminate wine produced from grapes sprayed with arsenic-containing insecticides in concentrations up to 530 ppb, primarily as trivalent arsenite.[88] This study did not detect organic arsenic compounds in the wine (LOD, 1 ppb As). Arsenic accumulates primarily in the exoskeleton of invertebrates and fish livers.

Lifestyle

Homeopathic medications may contain arsenic concentrations ranging from 0.005–323 μg/g remedy.[89,90] Rare case reports associate the use of Chinese herbs with the cutaneous manifestations of arsenic poisoning including hyperpigmentation, palmar and plantar hyperkeratosis, and transverse lines of the fingernails.[91] The burning of arsenic-treated wood in home stoves can produce toxicity.[92] Arsenic compounds may contaminate moonshine whiskey.[93]

Arsenic occurs in processed tobacco products including cured tobacco leaves and some smokeless tobacco products. The US EPA estimates that As concentrations in tobacco leaves average ~1.5 ppm (1.5 μg/cigarette).[94] In a study of 17 commercial tobacco snuffs, the mean As concentration was 0.23 ± 0.06 μg/g dry weight.[95] Exposure to arsenic from tobacco products depends on the type of product, growing conditions (arsenic content), and parameters of product use (e.g., frequency, smoking techniques, duration of use). Arsenic yields in mainstream cigarette smoke range from 0–1.4 μg/cigarette depending on growing conditions and smoking techniques.[96] The IARC estimates the arsenic content in mainstream smoke from a standard cigarette averages 40–120 ng.[97] The mean As concentration in machine-generated mainstream smoke from 34 different products from the US cigarette market evaluated by the Reynolds Tobacco Company was 12.7 ng/cigarette with a range of 4.8–18.4 ng/cigarette.[98] In this study, analysis of NHANES data (2003–2008) did not detect a statistically significant difference in total urinary arsenic concentrations between tobacco smokers and nonsmokers. The study defined smokers as individuals who used cigarettes in the last 5 days.

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ENVIRONMENTAL FATE

Most arsenic in the environment exists in rock or soil. Speciation determines the interaction of arsenic with the environment.[31] Because most arsenic compounds adhere to soil or sediment, these compounds migrate only a short distance as a result of leaching. Soluble forms of arsenic may move much farther in rivers than insoluble forms. In the atmosphere, arsenic appears as particulates, primarily <2 μm in diameter.[99]

Air

Arsenic is released to the atmosphere primarily as arsenic trioxide and, to a lesser extent, as arsine gases. Arsenic in the atmosphere is a mixture of trivalent and pentavalent arsenic compounds because arsenic trioxide and methyl arsines oxidize to pentavalent As. Photolysis does not contribute significantly to the fate of arsenic in the atmosphere. The residence time of these particles in air depends on the size and meteorological conditions, but the average time is ~7–10 days.[100,101]

Soil

The mobility of As in soil is highly dependent on speciation, soil type, and pH.[31] In general, As released to the soil is relatively nonmobile as a result of the binding of As to soil particles, particularly iron and manganese oxides, aluminum and manganese hydroxides, manganese compounds, clay minerals, and organic material in the form of arsenate.[101] Acidic environments and strongly absorbant soils limit the mobility of arsenite and arsenate species. *In vitro* studies indicate that arsenate transport is strongly inhibited at pH 4.5 and 6.5, whereas transport increases rapidly at pH 8.5.[102] The enhanced transport of arsenate at pH 8 is consistent with the pH dependence of surface complexation reactions (e.g., ligand exchange mechanism) describing arsenate sorption by metal oxide minerals.

Arsenite is moderately unstable in the presence of oxygen, whereas arsenate is strongly absorbed by soils under aerobic conditions and rapidly desorbed under anaerobic conditions. Rainwater may leach soluble forms of arsenic into groundwater or surface water; soil microorganisms may release small amounts of arsines into the atmosphere. Microorganisms may convert sparingly soluble forms of arsenic into more soluble forms that are capable of migrating into groundwater. The top 1.37 m of contaminated soil near a copper acetoarsenite-manufacturing plant adjacent to Calcutta contained arsenous acid, arsenic acid, and methylated forms (methylarsonic acid, dimethylarsinic acid), but only inorganic arsenical compounds appeared in the borehole at levels below 1.37 m.[103] The transformation of arsenic in soil is complex similar to the transformation that occurs in water. Arsenate predominates in aerobic soils, whereas arsenite predominates in slightly reduced soils (e.g., during flooding). Reduction of desorbed arsenate to arsenite increases the mobility of arsenic in soils. Certain terrestrial plants may accumulate substantial amounts of As via absorption through the roots.[100] However, a study of a grassland ecosystem contaminated by arsenic (arsenopyrite) indicated that the potential for bioaccumulation of arsenic is small.[104]

Water

In water, arsenic undergoes a variety of complex transformations including biotransformation, ligand exchange, and oxidation–reduction reactions.[63] The predominant form of arsenic in surface water is pentavalent arsenate because of the positive redox potential and relatively low pH values that result from the interaction of atmospheric oxygen and carbon dioxide.[105] Oxidation of arsenite to arsenate occurs via chemical reactions and microbial activity (chemolithoautotrophic arsenite oxidizers). Microbial species (e.g., α-*Proteobacteria*) use oxygen as the terminal electron acceptor, arsenite as the electron donor, and carbon dioxide as the carbon source.[106,107] Aquatic microorganisms may also reduce pentavalent arsenate to methylated, trivalent arsenite, or other trivalent arsenic compounds via dissimilatory arsenate-reducing prokaryotes.[108] The predominant form of arsenic in groundwater is arsenate, but significant amounts of arsenite may occur depending on local geology and the characteristics (pH, sulfide content, oxidation–reduction potential, salinity, temperature) of the water, particularly in anaerobic environments.[109] Although there are limited data, the accumulation of As in biota is usually not clinically significant. Limited bioconcentration of As may occur in aquatic organisms, particularly in algae and invertebrates with bioconcentration factors ranging from 1–17.[35] Bioconcentration factors for As in fish are usually <5.[31] Biomagnification of As in the aquatic food chain is probably not clinically significant as most arsenic appears as the relatively nontoxic organic form.[110,111] Additionally, the accumulation of As in the edible portion of plants is usually low with As accumulation generally occurring in the roots rather than the leaves or fruits.[60]

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DOSE EFFECT

The toxicity of an arsenic compound depends on the physical state (gas, solution, powder), the particle size, solubility, the rate of absorption and elimination, and the presence of other constituents. Additional factors include the inherent toxicity of the specific arsenic compound and less quantifiable parameters (hand–mouth transfer, particle retention in lungs, mucociliary clearance to gastrointestinal tract). Pentavalent As (arsenate or organic form) is less toxic than trivalent As (arsenite or inorganic form) based on its lower solubility. In general, the insoluble salts of arsenic (arsenic trioxide, lead arsenate) and organic alkane arsonate possess substantially less toxicity than the more soluble inorganic arsenic compounds (sodium arsenite, arsenic acid, arsenous acid).[112,113] The least toxic form is elemental arsenic. The WHO maximum recommended daily intake of arsenic is 2 μg ingested inorganic arsenic/kg body weight.[114]

Trivalent Arsenic

Acute Toxicity

The toxicity of inorganic arsenic depends on both solubility and particle size (e.g., the rate of dissolution is inversely proportional to particle diameter). The estimated dose of trivalent that produces serious toxicity and death in children is ~1 mg/kg and 2 mg/kg, respectively.[115] The ingestion of about 9–14 mg of arsenic trioxide by a 16-month-old infant produced serious toxicity that required chelation therapy.[116] The acute, adult toxic dose of arsenic trioxide ranges from 5–50 mg. The estimated lethal range for adults is 200–300 mg arsenic trioxide, although survival occurs at higher levels (1.4 g arsenic trioxide, 2.15 g arsenous oxide, 10 g arsenic trioxide) in adults following aggressive treatment.[117,118,119] A 77-year-old dentist arrived at the hospital 5 hours after the suicidal ingestion of 4 g arsenic trioxide.[120] He received chelation with BAL, and he survived following the development of nonhemolytic anemia and gastritis with superficial ulcerations. The experimental use of arsenic trioxide for refractory acute promyelocytic leukemia involves daily doses of 20–30 mg for up to 60 days.[121] In a series of acute promyelocytic leukemia patients treated with 0.1 mg arsenic trioxide/kg, 3 of 10 patients died suddenly 9–15 days after initiating treatment.[122] Case series document the occurrence of QTc prolongation and torsade de pointes during the use of arsenic trioxide (10–20 mg/days) in patients with hematological malignancies.[123]

A 57-year-old amateur geologist presented to an urban emergency department 13 hours after the intentional ingestion of estimated 84 g arsenic that he obtained from crushing a chicken egg-sized rock of orpiment (arsenic trisulfide).[124] He was asymptomatic in the emergency department with sinus tachycardia (129 bpm) and a normal QTc interval (387 msec). He was treated with whole bowel irrigation and hydration, but no chelation. He remained asymptomatic, and he was transferred to an inpatient psychiatric unit.

Chronic

Chronic inhalation of air containing >0.8 mg trivalent As/m^3 causes irritation of the mucous membranes and hoarseness.[125] Analysis of exposure-risk relationships in several occupational cohorts suggests that cumulative pulmonary exposure to arsenic concentrations exceeding 0.75 mg/m^3 year is associated with an increased risk of lung cancer.[31,126] Arsenic in drinking water occurs primarily in the form of inorganic arsenate or arsenite depending on the pH and the presence of reducing or oxidizing agents.[127] The evidence of subclinical neuropathy when total arsenic concentrations in drinking water are <300–1,000 μg/L is conflicting; potential causes for the inconsistent results include genetic polymorphisms altering arsenic metabolism, nutritional status (e.g., selenium, folate), and lifestyle factors (e.g., body mass index, cigarette smoking).[128] In a review of data up to the late 1990s, the National Research Council concluded that there was no consistent evidence of peripheral neuropathy in residents following chronic exposure to total arsenic in well water below 1,000 μg/L.[129] A review of relevant epidemiological studies with individual-level data indicated an estimated threshold level near 100 μg/L (range, 50–150 μg/L) for inorganic arsenic in drinking water and urinary bladder, lung, and skin cancers consistent with the value (~65 μg/L) calculated based on mechanistic *in vitro* and *in vivo* investigations.[130] In a cross-sectional study of 147 Alaskan residents exposed to total arsenic in well water ranging from 1–4,781 μg/L, there was no dose-response relationship between the arsenic concentration in the well water and either neurological signs or nerve conduction velocities.[131] Similarly, a cross-sectional study from Inner Mongolia compared nerve conduction velocities in 32 residents ingesting well water with low arsenic concentrations (mean = 5.3 μg/L) with 109 residents with higher arsenic exposure (mean = 158.3 μg/L).[132] There were no statistically significant differences in motor or sensory nerve conduction velocities between the two groups. Other studies suggest the

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possibility of subclinical neuropathy in residents chronically exposed to arsenic concentrations in well water below 1,000 μg/L. A cross-sectional study of 320 Mongolian farmers with exposure to a mean total arsenic concentration of 270 μg/L in well water suggested a correlation between vibration thresholds of fingers and arsenic concentration.[133] A similar cross-sectional study of 137 residents in Bangladesh found deficits in vibration thresholds (Vibraton II Sensitivity Tester) of toes, but not fingers.[134] The mean total arsenic in well water for residents in the latter study was 115 μg/L. A retrospective case-control study of arsenic-associated skin lesions in West Bengal, India, suggested that the development of skin keratoses and hyperpigmentation requires at least 10-year exposure to arsenic concentrations in drinking water exceeding 100 μg/L.[135] However, the average latency period for documented arsenic-induced skin lesions on 42 individuals was 19–23 years with peak arsenic concentrations in the drinking water of controls averaging about 180 μg/L.

Pentavalent Arsenic

Widely used arsenic-containing ant killers usually consist of the pentavalent form of arsenic. For example, Terro Ant Killer (Senoret Chemical Co., Kirkwood, MO) contains 2.28% sodium arsenate (0.91% inorganic arsenic) and 1 mL of this product contains 27.7 mg of sodium arsenate (11.2 mg elemental arsenic). Poison center specialists may manage accidental ingestion of small amounts (<5 mL) of this substance in the home.[136] Most of these products are no longer available in the United States.

TOXICOKINETICS

Absorption

Ingestion

Both animal and human studies indicate that the gastrointestinal tract absorbs soluble forms of trivalent arsenic and pentavalent arsenic almost completely based on studies of arsenic elimination in the feces and urine; however, little absorption of insoluble arsenic (e.g., arsenic selenide) occurs following ingestion.[137,138] The bioavailability of As in soil is probably less than that of in food. In a pilot study of the bioavailability of As in soil, the estimated relative bioavailability of soil As was 54.3% (95% CI: 40.3–68.4%) compared with As in food.[139] The uptake of As^{5+} and As^{3+} occurs via phosphate transporters and aquaglyceroporins, respectively.[140] The absorption of arsenic trioxide following ingestion would be less than the more soluble forms of inorganic arsenic. Factors that affect the amount of arsenic absorption include particle size and the pH of the stomach content.

Inhalation

The absorption of arsenic following inhalation depends on the particle size and the chemical form. Little human data exist to estimate the amount of arsenic absorbed after inhalation. A study of eight terminal lung cancer patients inhaling smoke from radioactive arsenic-containing cigarettes demonstrated retention of ~20–40% of the inhaled dose with ~75–80% of the arsenic absorbed within 4 days.[141] The estimated pulmonary absorption of arsenic from the air in an arsenic smelter was ~42% based on measurements of ambient air samples and urine inorganic arsenic (inorganic species plus methylated metabolites).[142]

Dermal

Little quantitative data are available on the cutaneous absorption of arsenic compounds. Case reports of arsenic toxicity following cutaneous exposure to arsenic acid and arsenic trichloride indicate that some arsenic compounds are absorbed through the skin;[143] however, cutaneous absorption of arsenic is probably low, except in cases of damaged skin.[144]

Distribution

Both trivalent and pentavalent forms of arsenic diffuse out of the blood within hours, initially accumulating in the kidney, liver, and lungs. The clearance of arsenic from these tissues is relatively rapid with long-term storage of arsenic occurring in hair, skin, thyroid gland, lens, skeleton, and the squamous epithelium of the gastrointestinal tract following chronic ingestion.[33] Autopsy data in humans indicate that relatively high arsenic concentrations occur in the following tissues: bone, hair, nails, skin, and teeth.[145] Within 30 hours after ingestion, arsenic deposits in the hair. The hair of an individual dying within 6–8 hours of an arsenic overdose does not usually contain arsenic.

Trivalent arsenic tends to accumulate to a greater extent than pentavalent arsenic compounds. Following the fatal ingestion of trivalent arsenic trioxide, the highest concentrations of total arsenic occurred in the liver and kidneys with the blood arsenic concentrations ranging from 0.2–14% of the As concentrations

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present in tissues as measured by electrothermal atomic absorption spectrometry.[146] Trivalent arsenic was the predominant species in these tissues. Methylated species were more common in tissues with high lipid content. The sulfhydryl groups on keratin in the skin and hair preferentially bind trivalent arsenic compounds, whereas pentavalent compounds (e.g., arsenate) have an affinity for the bone because of their chemical similarity to phosphate. Only small amounts of arsenic penetrate the blood–brain barrier. The normal body burden in adults is ~20 mg of arsenic.[3]

Biotransformation

Humans metabolize arsenic primarily in the liver via the two following basic processes: 1) oxidation/reduction reactions that interconvert As^{3+} and As^{5+}, and 2) oxidative methylation with arsenite methyl transferase enzymes. DMA (dimethylarsinic acid) is the major metabolite with the urine containing lower concentrations of As^{3+} (inorganic arsenite), As^{5+} (inorganic arsenate), and MMA (monomethylarsonic acid) depending on multiple factors (e.g., chemical form, dose, species, route of exposure, time since exposure, genetic polymorphisms).[35] Epidemiological studies suggest the presence of some functional genetic polymorphisms in arsenic methylation among different ethnic groups.[147] In a study of healthy volunteers in the United Kingdom, the mean proportion of total urinary arsenic as dimethylarsenate was higher for the Somali Black-African group (50%) than the Asian (16%) or Caucasian (22%) groups.[148] The concentration of total arsenic was also significantly lower in the Somali Black-African group compared with the other two groups.

In the cytosol, rate-limited methylation occurs via: 1) oxidative methylation via *S*-adenosylmethionine and arsenic–sulfur intermediates, and 2) reductive methylation via conjugation of arsenite with glutathione. Arsenic triglutathione acts as a substrate for *S*-adenosylmethionine-dependent arsenite methyltransferase in the latter reaction.[149] Although vitamin B_{12}, coenzyme B_{12}, and methyl B_{12} can be methyl donors, the major methyl donor is adenosylmethionine.[150] The enzyme, methyltransferase, is a 42-kDa protein that is encoded by *cyt19* genes.[151] Arsenite methyltransferase was previously known as *cyt19* (*as3mt*) gene.

Biotransformation of inorganic arsenic involves methylation to pentavalent dimethylarsinic acid (DMA) and, to a lesser extent, to pentavalent methylarsonic acid (MMA, monomethylarsonic acid) and reduction of pentavalent arsenic (As^{5+}) to trivalent arsenic (As^{3+}). The reduction of pentavalent arsenic can occur non-enzymatically in the presence of a thiol (e.g., glutathione) or via reductases (e.g., glutathione-*S*-transferase).[152] The liver is the primary site for arsenic methylation. Methylation occurs enzymatically via the oxidative addition of methyl groups to trivalent arsenic with glutathione as a reducing agent and *S*-adenosylmethionine as the methyl donor.

Figure 3.2 demonstrates the classic metabolic pathway for the biotransformation of arsenate to dimethylarsinic acid. Methylation of pentavalent arsenic requires a two-electron reduction of arsenate (As^{5+}) to arsenite (As^{3+}) prior to the oxidative addition of a methyl group. Several studies of urine samples from residents exposed to high concentrations of inorganic arsenic in well water suggest that trivalent monomethylarsonous acid (MMA) and, to a lesser extent, dimethylarsinous acid (DMA), are metabolic intermediates of the biomethylation pathway in these subjects.[153,154] An alternative biotransformation pathway displayed in Figure 3.3 exists that involves the nonenzymatic formation of glutathione complexes with arsenite, resulting in the formation of arsenic triglutathione. The subsequent methylation of arsenic triglutathione forms monomethyl arsenic glutathione and ultimately MMA or DMA depending on glutathione concentrations.[150] Methylation of monomethyl arsenic glutathione to dimethylarsinic glutathione (DMAG) occurs in high-glutathione environments, whereas hydrolysis of MADG to trivalent MMA occurs in low-glutathione environments.[150,155] Consequently, the classical inorganic arsenic pathway converts MMA^{5+} to the more toxic trivalent MMA, while the alternative pathway converts trivalent MMA to the less toxic pentavalent MMA.

A substantial difference in the biotransformation of arsenic compounds exists between species. Squirrel monkeys, chimpanzees, marmosets, tamarins, and guinea pigs methylate little or no As species, whereas humans and the most common laboratory animals (hamster, rat, mouse, rabbit, rhesus monkey) extensively methylate As species via arsenite methyltransferases.[156] Furthermore, the ratio of MMA/DMA is substantially higher in humans than in common laboratory animals.[31] Additionally, there are relatively large interindividual variations in the methylation of inorganic arsenic; reduced methylation capacity (i.e., decreased dimethylarsinic acid to monomethylarsonic acid ratio) may increase susceptibility to the health effects associated with chronically high arsenic exposure.[151] Little conversion of cacodylic acid (DMA) and arsanilic acid to inorganic arsenic occurs in humans.

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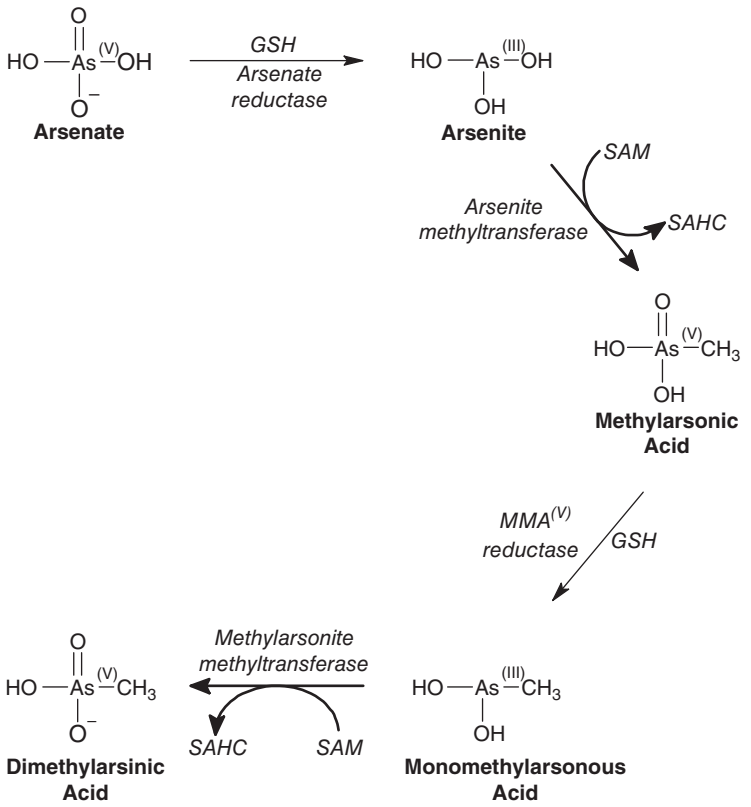


FIGURE 3.2. The classic pathway for biotransformation of inorganic arsenic. The pathway includes: 1) reduction/oxidation reactions that interconvert As^{5+} and As^{3+}, and 2) methylation reactions that convert As^{3+} to MMA^{5+} and DMA^{5+}. *Abbreviations:* GSH = reduced glutathione; SAM = *S*-adenosylmethionine; SAHC = *S*-adenosylhomocysteine. (Aposhian et al.).[153]

Elimination

Humans eliminate inorganic arsenic metabolites rapidly in the urine, primarily as dimethyl arsenic.[157] The kidney excretes almost all the absorbed dose of inorganic arsenic within 4 days, but small amounts of arsenic appear in the urine even after 10 days as a result of a triphasic renal excretion pattern that develops within 4–8 hours after absorption. The biological half-lives of trivalent arsenite and pentavalent arsenate are roughly similar depending on the amount of methylation that occurs.

Human retention studies with the pentavalent arsenic acid (^{74}As) demonstrated a three-compartment model with mean half-lives of ~2, 9.5, and 38 days.[158] These compartments account for 65.9%, 30.4%, and 3.7% of the total excretion of pentavalent arsenic, respectively, over 103 days. After 2–4 weeks, the skin, hair, and nails contain most of the arsenic as a result of the high sulfhydryl content of keratin in these tissues. Feces and sweat are minor excretory pathways.

In the general population and workers exposed to arsenic, the urinary excretion of an absorbed dose of inorganic arsenic varies as follows: DMA (60–70%), MMA (10–20%), and unchanged inorganic arsenic (10–30%).[159,160] In a study of 93 pregnant women exposed to inorganic arsenic in drinking water in Chile, the urine contained the following arsenic species: DMA, 79–85%; inorganic arsenic, 8–16%; and MMA, 5–6%.[161] This variability may result in variable sensitivity to disease with individuals having a higher proportion of inorganic arsenic and MMA along with reduced concentrations of DMA being more susceptible to the development of skin or bladder cancer.[162] Experimental and observational studies indicate a variety of factors that influence the methylation of inorganic As including dose, route of administration, species of arsenic, population group, and nutritional status.[163,164] The efficiency of methylation decreases with increasing doses of inorganic arsenic. Based on a Taiwanese study of residents chronically exposed to high arsenic concentrations in well water, women methylate inorganic arsenic more efficiently than men and the efficiency of methylation decreases with age.[165] Saturation of the metabolic pathways for arsenic probably occurs following severe intoxication (e.g., suicide

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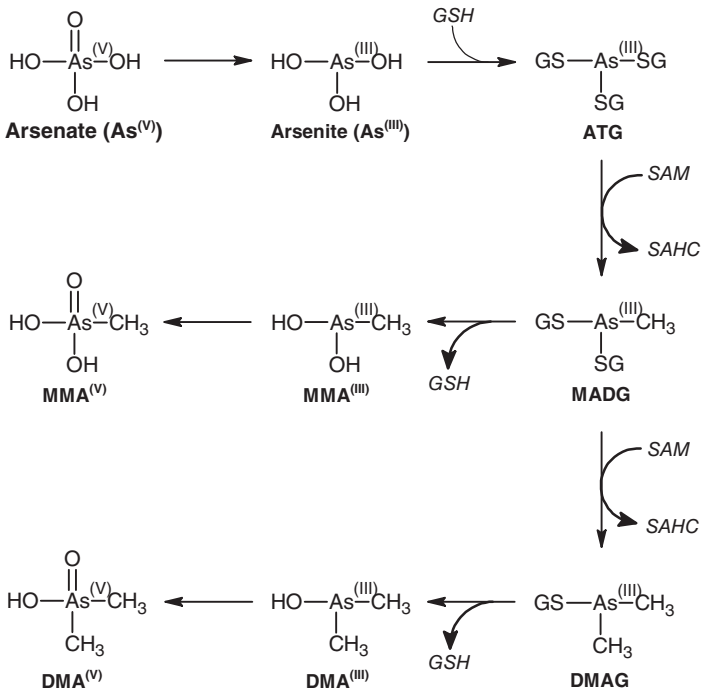


FIGURE 3.3. Alternate biotransformation pathways for inorganic arsenic. The methylation of arsenic triglutathione forms monomethyl arsenic glutathione and ultimately MMA^{3+} or DMA^{3+} depending on glutathione concentrations. In high-glutathione environments, methylation of monomethyl arsenic glutathione to dimethylarsinic glutathione (DMAG) occurs, whereas hydrolysis of MADG to trivalent MMA occurs in low-glutathione environments. Compared with the classical inorganic arsenic pathway, the alternative pathway converts MMA^{3+} to the less toxic MMA^{5+}. *Abbreviations:* ATG = arsenic triglutathione; DMA^{3+} = dimethylarsinous acid; DMA^{5+} = dimethylarsinic acid; DMAG = dimethylarsinic glutathione; GSH = reduced glutathione; MADG = monomethyl arsenic glutathione; MMA^{3+} = monomethylarsonous acid; MMA^{5+} = monomethylarsonic acid; SAHC = *S*-adenosylhomocysteine; SAM = *S*-adenosylmethionine.

attempt, acute arsine toxicity) rather than occupational exposure to trivalent arsenic.[166] Although the methylation of inorganic arsenic varies between individuals in different populations, the daily variation in inorganic arsenic methylation within a specific individual is small.[167]

Maternal–Fetal Kinetics

There are little human data on the transfer of arsenic across the placenta. The low molecular weight and poor protein binding of inorganic arsenicals favor the passage of arsenic from the placenta to fetal blood. In a study of 125 urban women delivering healthy singlets, the arsenic concentration was lower in umbilical cord blood than maternal blood.[168] The mean whole blood total arsenic concentration in maternal blood was 6.91 ± 5.32 μg/L (upper quartile, 8.55 μg/L) compared with 5.41 ± 4.81 μg/L (upper quartile, 6.41 μg/L) in cord blood. The percentage of samples below the LOD (0.1 μg/L) was 1.6% and 2.4%, respectively, as measured by ICP/MS. The arsenic was not speciated. Animal studies suggest that both As^{3+} and As^{5+} distribute into the embryo, but there are little data on the sites of uptake.[169]

Breast milk does not usually contain significant amounts of arsenic despite relatively high maternal arsenic exposure; consequently, arsenic exposure may be lower in breastfed infants than bottle-fed infants depending on the arsenic concentration in tap water. A study of infants in New Hampshire indicated tap water contributed ~70% of the arsenic exposure in bottle-fed infants.[170] In the study of 10 lactating Andean women with exposure to high arsenic concentrations (~200 μg/L) in well water, the mean total arsenic concentrations in their blood and urine were 10 μg/L and 320 μg/L, respectively.[171] The mean concentration of arsenic detected in human milk was 2.3 μg/kg fresh weight (range 0.83–7.6 μg/kg). In a study of the four stages of breast milk production (colostrums, transitional milk, early mature milk, mature milk),

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the concentrations of microelements decreased with advancing lactation stages.[172] The mean arsenic concentration in samples from 45 lactating women in each lactation stage ranged from 1.50 ± 1.50 ng/mL in colostrums samples to 0.16 ± 0.24 ng/mL in mature breast milk samples. In a study of 226 breast milk samples from lactating women in Bangladesh, 39 samples contained detectable arsenic concentrations.[173] The median detectable As concentration in breast milk samples from lactating women with arsenical skin lesions was 30 ng/mL (range, 15–44 ng/mL; $n = 11$) compared with 12 ng/mL (range, 2–49 ng/mL; $n = 28$) in lactating women without skin lesions. Although the infants' arsenic burden was relatively high, maternal urine arsenic concentrations did not correlate to arsenic concentrations in breast milk. In a prospective study of 120 mother–baby pairs in a Bangladesh study published in an open access journal, maternal urinary and breast milk arsenic concentrations were weakly correlated to infant arsenic concentrations at 1 month and 6 months of life.[174]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanisms of Action

Although there are no data from human studies that As is an essential metal, animal studies suggest that low arsenic concentrations may be essential to some animals.[175] Abnormalities detected following the administration of arsenic-deficient (10 ng As/g diet) diets included decreased concentrations of *S*-adenosylmethionine in the liver and pathological alterations of the heart muscle.[176]

Mechanism of Toxicity

Trivalent

Acute Toxicity

The mode of trivalent arsenic toxicity is not well understood. In animal experiments on arsenic intoxication, the main form of arsenic bound to tissues is trivalent arsenic rather than pentavalent arsenic or methylated metabolites.[177] Arsenite is electrophilic. Trivalent arsenic does not form complexes with nitrogen or phosphorus, but As^{3+} can replace nitrogen by binding to carbon. This compound interacts with thiol groups in the body by binding to electron-rich sulfhydryl groups on proteins and causing oxidative stress (activation of c-Jun *N*-terminal kinase/stress-associated protein kinase and formation of reactive oxygen species).[178] However, most arsenite toxicity probably results from the susceptibility of many critical enzymes (e.g., pyruvate dehydrogenase, other dehydrogenases) to deactivation by binding thiol-containing active sites.[179] Arsenite compounds bind to the sulfhydryl cofactor (dihydrolipoate), thereby causing inhibition of pyruvate and succinate oxidative pathways as a result of limiting the conversion of dihydrolipoate to lipoate.[119] Thus, inhibition of pyruvate dehydrogenase produces depletion of cellular citrate and blockade of the citric acid cycle. Carbohydrate depletion and depletion of the reductive energy supply that result from the inhibition of gluconeogenesis are major consequences of the inhibition of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase enzymes.[180]

QT prolongation, *torsade de pointes*, and sudden death are adverse effects following the treatment of acute promyelocytic leukemia with arsenic trioxide. Predisposing factors for the development of these complications include prior treatment with cardiotoxic chemotherapeutic agents (e.g., all-trans retinoic acid, anthracycline-based drugs) and electrolyte imbalance (e.g., hypokalemia, hypomagnesemia). Studies of HERG- and KCNQ1+KCNE1-transfected CHO cells indicate arsenic trioxide blocks I_{Kr} and I_{Ks} tail currents at therapeutically relevant concentrations; additionally, As_2O_3 activates a time-independent potassium current ($I_{K\text{-}ATP}$) that maintains normal repolarization.[181] The competing effects of these three potassium currents result in variable QT prolongation and ventricular dysrhythmias.

Cancer

Like most carcinogenic metals, arsenic is not genotoxic and does not form DNA adducts; however, *in vitro* studies indicate inorganic As causes oxidative DNA damage through alterations of aneuploidy (i.e., abnormal diploid number) and DNA repair via epigenetic mechanisms (DNA methylation, histone modifications, miRNA alterations) depending on the dose.[182,183] The former mechanism results from disruption of spindle tubulin,[184] whereas the latter results from inhibition of P53 signaling.[185] Potential mechanisms for the development of cancer following arsenic exposure include cocarcinogenesis, epigenetic dysregulation (i.e., heritable changes in gene expression with no dependence on DNA sequencing), chromosomal instability, tumor promotion, altered cell proliferation or DNA methylation, and the formation of reactive oxygen species.[32,186] A cross-sectional, dose-response study of generally healthy individuals in Bangladesh did not find evidence of an association between arsenic concentration

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(water, blood, urine) and measures of oxidative damage (plasma protein carbonyl, 8-oxo-deoxyguanosine).[187] Arsenite inhibits glutathione reductase, lowers intracellular concentrations of reduced glutathione, increases oxidative stress, and activates caspase 3 and the apoptosis pathways.[188] Trivalent arsenic is an indirect animal carcinogen in doses of >400 μg/day through promotion rather than a direct genotoxic effect.[189] Arsenic probably acts through epigenetic mechanisms (e.g., DNA methylation, microRNA expression, posttranslational histone modifications) by modulating the signaling pathways responsible for cell growth.[190,191] Arsenic does not react directly with DNA or cause gene mutations, except at very high doses; however, arsenic does cause gene amplification and chromosomal damage at lower doses as well as enhancing the mutagenesis of other agents. Arsenic produces carcinogenic effects in some *in vitro* tests (sister-chromatid exchange, gene amplification).[192,193] These tests indicate that arsenite is the primary carcinogenic agent; the carcinogenic activity of arsenate probably results from its conversion to arsenite and the subsequent formation of reactive metabolites that interact with critical cellular sulfhydryl groups and cause cytotoxicity along with regenerative cell proliferation.[194] This mechanism of toxicity suggests a nonlinear, threshold dose-response relation for noncancer and cancer end points.[195] Arsenite inhibits DNA repair and methylation as well as increasing the formation of radicals and the activation of the proto-oncogene *C-Myc*.[196] However, none of these potential mechanisms are well-accepted etiological events for arsenic carcinogenesis. The data on the carcinogenicity of arsenic in animals are limited; the extrapolation of animal data to humans is also limited by the lack of adequate animal models of cancer following exposure to arsenic.

Pentavalent

Arsenate is structurally similar to inorganic phosphate. Pentavalent arsenicals are less reactive and cause fewer biological effects than trivalent arsenicals. Potential mechanisms for the acute toxicity of arsenic include the reduction of pentavalent arsenic to trivalent arsenic and the replacement of phosphate in biological reactions.[32] Arsenate uncouples oxidative phosphorylation by the formation of unstable arsenate esters. Although pentavalent arsenic does not directly affect enzymes, this form of arsenic inhibits high-energy bonds by competitive substitution of arsenate for phosphate (arsenolysis).[3] Although glycolysis continues, the substitution of arsenate for phosphate reduces the amount of ATP formed; therefore, the cell produces less ATP. Consequently, both the pentavalent and trivalent forms of arsenic limit energy-linked functions of the mitochondria; however, arsenolysis appears less important in the production of arsenic toxicity than the arsenite (As^{3+})-induced inhibition of sulfhydryl groups. Additionally, arsenate can mimic the phosphate moiety of pyridoxal phosphate, resulting in the inhibition of several reactions including conversion of DOPA to dopamine and 5-hydroxytryphtophan to 5-HT.[197]

At relatively high doses, the weight-of-evidence indicates that dimethylarsinic acid (DMA) is a multi-organ tumor promoter in rodents and a complete carcinogen in the bladder of rats.[198] The incidence of bladder tumors increased in male F344 rats administered 50 ppm pentavalent DMA in drinking water for 2 years, but not in rats given 12.5 ppm DMA in drinking water for 2 years.[199] The relevance of these effects to human arsenic exposure remains unclear because large doses were required and because of the presence of species differences in the toxicokinetics of DMA.

Pathological Changes

Cardiovascular System

Vasodilation occurs initially in response to small doses of arsenic, but transudation of the fluid reduces preload, leading to reflex arteriolar constriction. Decreased contractility causes direct myocardial depression. QT prolongation and T-wave inversion may persist months after clinical recovery. The chronic ingestion of high arsenic doses produces the Blackfoot disease characterized by vasospasm, peripheral vascular insufficiency, and gangrene. The contamination of artesian well water primarily with pentavalent arsenic[200] and another substance (fluorescent humic substance) is an area of study into the etiology of this endemic peripheral vascular disease along the southwestern coast of Taiwan.[201] Statistically significant reductions in the amount of selenium and iron along with marked elevations of arsenic were detected in the hair of patients with the Blackfoot disease, particularly in the patients with severe disease.[202] As a result of the implementation of a tap water supply system, drinking water and cooking no longer involved the use of highly arsenic-contaminated water after the mid-1970s. Mortality related to peripheral vascular disease declined gradually for ~25–27 years following cessation of consumption of this arsenic artesian well water, suggesting a causal relationship between high arsenic exposure and peripheral vascular disease.[203]

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Gastrointestinal Tract

Dilation of splanchnic vessels causes submucosal vesicle formation. Rupture of these vesicles leads to rice water stools and bleeding. Subsequently, a protein-losing enteropathy may develop.

Kidney

Pathological changes associated with acute arsenic toxicity include acute tubular necrosis and renal cortical necrosis based on a case report of a 39-year-old man presenting with anuria and azotemia after consuming moonshine whiskey; he required peritoneal dialysis temporarily.[204] His admission serum arsenic concentration was 331 μg/L. Samples of the moonshine whiskey were not available for analytical confirmation. He also had an elevated serum lactic dehydrogenase concentration (10-fold over reference value); there were no measurements of urine myoglobin.

Skin

Arsenic-induced skin lesions include palmar erythema, local edema, hyperkeratosis, hyperpigmentation, atrophy, pyoderma, palmoplantar ulcerations, and skin cancer (intraepithelial squamous cell carcinoma *in situ* or Bowen's disease, multiple basal cell carcinomas). Hyperpigmentation is usually the earliest cutaneous manifestation of arsenic toxicity, particularly in heavily pigmented areas (e.g., groin, areola).[205,206] Within these hyperpigmented areas, scattered areas of hypopigmentation may occur that resemble raindrops. Hyperkeratotic papules on the palms and soles are common, but diffuse keratosis on the palms and soles is rare. There are no histological features that reliably distinguish arsenical keratoses or Bowen's disease from similar lesions produced by exposure to sunlight. Arsenic-induced Bowen's disease has the same histological features as other forms of Bowen's disease.

Neuromuscular System

Axonal degeneration is the predominant change associated with inorganic arsenic-induced peripheral neuropathy. Single, acute doses of arsenic produce Wallerian degeneration and various stages of nerve fiber degeneration in myelinated and unmyelinated axons.[207] Resorption of myelin and destruction of axon cylinders lead to stocking-glove distal sensory neuropathy followed by muscle atrophy. Theories on the pathophysiological effect of arsenic on peripheral nerves involve the disruption of axon function that initially produces segmental demyelination and then eventually distal axonal degeneration.[208] Key features of muscle biopsies following severe rhabdomyolysis include myofibrillar disruption, mitochondrial abnormalities, abundant cytoplasmic vacuoles containing lipids, and peri-fascicular, hyper-contracted fibers.[209]

Metabolic/Hepatic

Negative nitrogen balance, hepatic fatty degeneration, central necrosis and cirrhosis, and hypothyroidism may occur during arsenic toxicity. Although chemical hepatitis is uncommon following an acute arsenic ingestion, chronic arsenic poisoning may produce hepatic veno-occlusive disease, sinusoidal dilation, and perisinusoidal fibrosis, perhaps by direct injury to the vascular endothelium.[210] In a rat model of promotion, arsenic was one of seven chemicals fed to rats in drinking water at environmentally relevant concentrations (3.1 ppm As, 31 ppm As, 310 ppm As).[211] The mixture did not act as a promoter of preneoplastic foci in the rat liver.

Postmortem Examination

Anatomic changes noted on autopsy after fatal acute exposure to arsenic include hepatocellular and renal tubular necrosis, intense visceral congestion, pulmonary edema, hemorrhages and ulceration of the gastrointestinal tract, and subendocardial hemorrhages with interstitial myocarditis. Death usually results from circulatory failure, and the myocardium often demonstrates widespread foci of necrosis, but leucocyte diapedesis may not be present.[212]

The major types of lung cancer include small cell carcinomas and non-small cell carcinomas (squamous cell carcinoma, adenocarcinoma). In a postmortem study of biopsies from 1,786 East German uranium miners dying of lung cancer between 1957–1990, polytomous logistic-regression analysis suggested that arsenic exposure was associated with non-small cell carcinomas (squamous cell carcinoma, adenocarcinoma).[213] The highest fraction of squamous cell carcinoma occurred in miners with the highest exposure to arsenic, radon, and quartz (silicon); in miners with silicosis, the proportion of adenocarcinomas increased with elevated arsenic exposure. However, this study was retrospective, and control of confounding factors (e.g., smoking, quartz, radon) required retrospective estimates of exposure. Only about 7% of the German uranium miners were nonsmokers based on a sample size of 539; there was no smoking data on 1,247 of the 1,786 miners in the study. Smoking is associated with a higher risk of squamous

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cell carcinoma and small cell lung cancer than adenocarcinoma, whereas the cell type associated with arsenic and skin cancer is squamous cell cancer.

CLINICAL RESPONSE

Medical Therapy

Rare case reports associate the use of arsenic trioxide for the treatment of acute promyelocytic leukemia with QT prolongation and ventricular tachycardia.[214] Several patients on arsenic trioxide therapy developed QT prolongation and *torsade de pointes* during the terminal phase of their illness; these patients also had additional risk factors (sepsis, hypokalemia, hypomagnesemia, hypoxia).[123] In a case series of 10 patients with acute promyelocytic leukemia on daily arsenic trioxide therapy, 2 patients died suddenly without identifying the cause of death on autopsy.[122] These patients were not monitored; however, a third patient on continuous cardiac monitoring developed QT prolongation along with respiratory distress prior to the development of asystole. Other case reports associate the development of high-grade AV block with an incomplete right bundle-branch block with arsenic trioxide therapy that resolved after chelation.[215]

Acute Oral Toxicity

Prominent gastrointestinal symptoms (e.g., vomiting, bloody diarrhea, severe abdominal pain, burning esophageal pain) develop within 30 minutes to 2 hours after ingestion of toxic doses of inorganic arsenic. Garlic odor on the breath and salivation may occur. Severely poisoned patients develop multiorgan failure and cardiac decompensation characterized by shock secondary to vasodilation and myocardial depression (e.g., cold clammy skin, cyanosis, weakness, lightheadedness). The development of cerebral edema leads to headaches, lethargy, delirium, coma, and convulsions. Death usually results from circulatory failure within 1–4 days.[119] Prolongation of the QT interval may occur during episodes of serious arsenic toxicity in the absence of hypokalemia, hypomagnesemia, or hypocalcemia.[216] Typically, these patients demonstrate gastrointestinal disturbances, leukopenia, and paresthesias. Rarely, polymorphic ventricular tachycardia (*torsade de pointes*)[217] or ventricular fibrillation occurs during severe As intoxication.[218] *Torsade de pointes* also occurs during the use of arsenic trioxide as a chemotherapeutic agent for acute promyelocytic leukemia.[123] Late sequelae of acute inorganic arsenic toxicity include jaundice, renal failure, and peripheral neuropathy. Intracerebral hemorrhage has occurred after the parenteral use of arsenical compounds for syphilis. Intense abdominal pain, bloody diarrhea, albuminuria, and a garlic odor suggest acute arsenic toxicity. Other clinical features of severe arsenic poisoning include hepatorenal dysfunction, adult respiratory distress syndrome, and serious cardiac dysrhythmias. The differential diagnosis for inorganic arsenic toxicity includes Addison's disease, other heavy metals (thallium), Guillain–Barré syndrome and other peripheral neuropathies, Korsakoff's syndrome, porphyria, and septic shock.

Skin

Biopsies of large keratotic papules from patients with arsenic toxicity reveal an extremely thickened stratum corneum and multiple layers of compacted parakeratotic cells around an epidermal crater.[61] Granular layers below these cells are reduced or absent. The differential diagnosis of an absence of the granular layer includes ichthyosis vulgaris, pityriasis rotunda, Bowen's disease, and psoriasis. Rete pegs may extend into the upper dermis. Aggregation of tonofilaments and the absence of the granular layer are highly suggestive of arsenic-induced keratosis.[61,219] Pathological features of arsenic toxicity include alopecia (late), brittle fingernails, and Mees' lines of striated leukonychia (horizontal white lines that appear after the exposed nail bed area grows to the exterior). The latter finding is not specific to arsenic poisoning, as these discolorations represent dysfunctional growth of the nail matrix rather than deposition of arsenic. Mees' lines also occur in other diseases (e.g., thallium poisoning, congestive heart failure, chronic renal disease, chemotherapeutic drugs).[220] Rarely, direct dermal contact with arsenic compounds produces local inflammation that leads to the formation of blisters.[221] Rare case reports associate the application of extremely high dermal doses of arsenic (30% arsenic solution in isopropyl alcohol to the entire body) with severe burns and bullae, vomiting, respiratory distress, hypotension, oliguria, and death.[222] The arsenic species was not reported.

Neurological

A subacute, commonly ascending peripheral neuropathy frequently develops within 10 days–3 weeks of a massive overdose of inorganic arsenic. Numbness and paraesthesias appear first, followed by weakness in the distal lower extremities. The neuropathy evolves over 2–5 weeks; the severity of the clinical course is variable with a majority of the patients developing a

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TABLE 3.3. Clinical features of acute and chronic arsenic toxicity. (Adapted from Gorby).[3]

System	Acute Symptoms	Chronic Symptoms
Skin	Hair loss, Mees' lines 2–3 weeks after ingestion	Hyperpigmentation, facial edema, hyperkeratosis, Bowen's disease, cancer
Neurological	Hyperpyrexia, tremor, convulsions, coma	Polyneuropathy, tremor, encephalopathy
Gastrointestinal tract	Vomiting, bloody or rice-water diarrhea, dysphagia, abdominal pain, mucosal erosions	Nausea, vomiting, diarrhea, anorexia, weight loss
Liver	Fatty infiltration	Hepatomegaly, jaundice, cirrhosis
Kidney	Renal tubule and glomerular damage, uremia	Nephritis
Hematological		Bone marrow hypoplasia with pancytopenia, basophilic stippling
Cardiac	ST-T wave abnormalities, prolonged QTc interval, atypical ventricular tachycardia, ventricular fibrillation	

severe distal sensorimotor polyneuropathy.[207] Recovery from peripheral neuropathy is usually slow and often incomplete. Facial nerve palsies[221] and phrenic nerve involvement[223] are rarely associated with exposure to arsenic. Encephalopathy is a common complication of acute inorganic arsenic poisoning manifested by seizures, delirium, and progressive obtundation. Persistent, chronic encephalopathy (Korsakoff-like psychosis) occurs rarely following acute exposure to massive doses of arsenic.[224,225] Table 3.3 outlines the clinical and pathological findings of acute and chronic arsenic poisoning.

Environmental Exposure

The diagnosis of chronic arsenic toxicity may be difficult because the presentation is insidious and nonspecific, particularly premeditated poisoning.[226] Early features involve the gastrointestinal tract (diarrhea, abdominal pain) and the skin (hyperpigmentation and hyperkeratosis, especially on the palms and the soles in half of the cases). A large case series of chronic inorganic arsenic toxicity secondary to contaminated drinking water suggested that melanosis is the earliest cutaneous sign of chronic arsenic toxicity with keratosis (dry, irregular, papular skin lesions) appearing later.[227] Papular keratosis and ulcerative lesions appear less frequently.[228] A symmetrical sensory neuropathy with paresthesias and loss of vibratory or position sense is a potential complication of chronic As exposure. Other signs and symptoms of chronic intoxication include localized edema (face, ankles), sore throat, stomatitis, pruritus, coryza, lacrimation, salivation, perspiration, garlic odor, vitiligo, and alopecia. Late sequelae of chronic arsenic poisoning include a Wernicke-like encephalopathy, gangrene of the extremities (endarteritis obliterans), esophageal varices secondary to portal hypertension,[229] lung cancer and nasal septal perforations,[230,231] and possibly multiple visceral tumors including hepatic angiosarcoma.[232]

Skin

Skin lesions are the first visible symptoms of chronic arsenic exposure.[233] The chronic ingestion of drinking water from arsenic-contaminated well water (up to 2 mg As/L) produced the following lesions: keratosis of the palms and soles, hyperpigmentation, Bowen's disease (squamous cell carcinoma *in situ*), hypopigmentation, and superficial basal cell carcinomas.[228,234,235] Melanosis, keratosis, and leukomelanosis (small hypopigmented macules) may also occur on the tongue, gums, and lips.[236] The duration of the latency period of these skin lesions is dose-dependent. Typically, the estimated latency period for these skin lesions is ~10–20 years,[135] although some studies suggest that children under 10 years of age may develop arsenic-induced skin lesions (i.e., melanosis) within a few years of exposure to highly arsenic-contaminated drinking water.[237] Reducing the inorganic arsenic exposure from drinking water decreases the incidence and severity of arsenic-induced dermatological disorders.[238] In a study of 550 Bangladesh residents with skin lesions from arsenic exposure, resolution of the skin lesions occurred in 65 patients over 10 years.[239] Lower baseline arsenic concentrations were significantly associated with increased odds of resolution.

Noncancerous areas of hyperpigmentation primarily occur on the trunk, pressure points, and intertriginous areas. This brown-gray pigmentation has oval-shaped areas of normal pigmentation that produce the appearance of raindrops. New lesions appear as multiple brownish patches and plaques covered with thick scales and crusts arising from areas of normal skin. Keratosis

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begins on the palms and soles as small (0.4–1 cm), hard, yellowish papules without central depressions that progress to verrucous lesions.[240] After an ~10–20-year latency period, these keratotic lesions may develop into squamous cell carcinomas, but they have a low incidence of metastasis.[241] Some[242] but not all studies[243] of patients with hyperkeratosis and Bowen's disease suggest an association between the occurrence of these adverse effects and internal malignancies (lung, urothelial renal cancer). However, the positive studies did not demonstrate a consistent biological gradient.

Nervous System

Chronic exposure to inorganic arsenic produces an insidious sensorimotor peripheral neuropathy over a few weeks to a few months depending on dose, characterized initially by numbness and paresthesias of the soles of the feet and hands followed by mild weakness in the extensors of the feet and hands. Pain and paresthesias are typically more severe in the feet than in the upper extremities.[233] The earliest symptoms of arsenic neuropathy are symmetrical sensory changes. Continued exposure results in severe distal stocking-glove-type sensorimotor neuropathy that persists despite the cessation of exposure. Neurological signs include reduced pinprick sensation, reduced or absent vibratory perception, and decreased perception of joint position.[237] Motor features are much less common than sensory symptoms, ranging from mild extensor weakness of distal muscles to diffuse weakness and muscle atrophy in severe cases.[244] The differential diagnosis of neuropathy associated with arsenic includes alcoholism, amyloidosis, cancer, diabetes mellitus, diphtheria, dysproteinemias, Guillain–Barré syndrome, intermittent porphyria, nutritional deficiencies, paralytic shellfish poisoning, tick paralysis, uremia, and lead toxicity.

A meta-analysis suggested a negative effect of environmental arsenic exposure exceeding current guidelines on neurodevelopment in children aged 5–15 years as measured by Full Scale IQ, particularly verbal and performance domains with less effect on memory tests.[245] Most of the included studies (n = 18) were cross-sectional designs in populations (e.g., Bangladesh, Mexico, China, Taiwan) with high arsenic exposure by current standards and substantial heterogeneity in the results. The estimated negative effect was 0.5 Full Scale IQ point for children with As exposure of 118–194 μg/L in drinking water or 51–117 μg/L in urine. Two cross-sectional studies on the relationship between urine arsenic concentrations and behavioral disorders did not demonstrate a significant effect. The median urinary total arsenic concentration in the first-grade Mexican children (6–7 years) was 52.5 μg/L,[246] whereas the mean urinary total As concentration in the Bangladesh children (8–11 years) was 81.2 μg/L ± 75.2 μg/L.[247]

Cardiovascular

Retrospective cohort studies in southwestern Taiwan, India, and Chile associate high arsenic concentrations (>500 ng/mL) in drinking water with carotid atherosclerosis,[248] ischemic heart disease,[249] and hypertension,[250,251] when compared after multivariate adjustment with cohorts lacking excessive arsenic exposure in drinking water. Blackfoot disease (vasospasm, peripheral vascular insufficiency, gangrene) occurred primarily in Taiwan.[252] The causal association between hypertension and exposure to inorganic arsenic in drinking water is unclear because there are few data and significant methodological limitations (e.g., lack of prospective studies). An Argentinean study of 225 Andean women with a median urine arsenic concentration of 200 μg/L (range, 22–545 μg/L) suggested the cardiovascular effects of arsenic may vary between different populations.[253] In this study, urinary arsenic concentrations were inversely related to diastolic (P = 0.002) and systolic (P = 0.081) blood pressures without evidence of increased inflammation as measured by cytokine concentrations.

In a review of eight studies (mostly cross-sectional design) that compared the highest and lowest categories of arsenic exposure, the pooled odds ratio was 1.27 (95% CI: 1.09–1.47, P-value for heterogeneity = 0.001, I^2 = 70.2%).[254] However, the pooled OR for the five studies with moderate to high arsenic exposure was not statistically significant (OR = 1.15, 95% CI: 0.96–1.37, P-value for heterogeneity = 0.002, I^2 = 76.6%). The substantial heterogeneity suggests the estimated risks may not accurately reflect the true value. Examination of data from the 2003–2008 US National Health and Nutrition Examination Survey did not detect an association between systolic or diastolic hypertension and low to moderate arsenic exposure (<50 μg/L) common in the United States.[255] The median total urine arsenic concentrations were 8.3 μg/L (interquartile range, 4.2–17.1) compared with 3.6 μg/L (interquartile range, 2.0–6.0) for DMA and 1.4 μg/L (interquartile range, 0.3–6.3) for arsenobetaine. After multivariable adjustment, the odds ratio of hypertension for a 2-fold increase in total arsenic was 0.98 (95% CI = 0.86–1.11); similarly, there was no statistically significant increase in the odds ratio for hypertension after a 2-fold increase in urine DMA.

Studies on the mortality from cardiovascular disease in areas of long-term, low to moderate arsenic

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concentrations (<50–100 ng/mL) in drinking water are inconsistent.[256] Some studies suggest an increased risk for cardiovascular and cerebrovascular disease from inorganic arsenic exposure below these concentrations. In the prospective cohort Strong Heart Study of 3,575 American Indians followed for 18 years, hazard ratios comparing the highest and lowest quartiles of arsenic concentrations (>15.7 vs. <5.8 μg/g creatinine) were statistically significant for *incident* cardiovascular (HR = 1.32, 95% CI: 1.09–1.59, P_{trend} = 0.002) and coronary heart disease (HR = 1.30, 95% CI: 1.04–1.62, P_{trend} = 0.006), but not incident stroke (HR = 1.47, 95% CI: 0.97–2.21, P_{trend} = 0.032).[257] The hazard ratios were also elevated for coronary heart disease (HR = 1.71, 95% CI: 1.19–2.44) and stroke *mortality* (HR = 3.03, 95% CI: 1.08–8.50) after adjustment for sociodemographic factors, body mass index, lipids, and smoking. These results were based on a single urinary inorganic plus methylated arsenic concentration without measurement of arsenic drinking water concentrations; the definition of arsenic exposure was total urinary inorganic arsenic species (inorganic arsenic plus DMA and MMA species) at baseline examination. Hence, the arsenic exposure over the course of the study was unknown. The highest and lowest quartiles were >15.7 μg/g creatinine and <5.7 μg/g creatinine, respectively. Additionally, the population had a relatively high prevalence of diabetes and cardiovascular disease.

Mortality from hypertensive heart disease was increased in Mormon women (but not men) in Millard County, Utah, exposed to <200 ng As/mL in drinking water based on historical records of arsenic exposure in the community. A cohort study in Bangladesh reported a dose-response increase in mortality from cardiovascular disease in relation to arsenic concentrations in wells with a hazard ratio of 1.16 (95% CI: 0.96–1.40) for households exposed to 50–149 μg/L in drinking water.[258] In a prospective cohort study in Bangladesh with a 6-year follow-up, 28.9% (range, 1.4–60.0%) of deaths from heart disease were attributable to arsenic concentrations of >12 μg/L in well water. A prospective study of 208 cases of fatal and nonfatal heart disease in Bangladesh demonstrated a statistically significant increase in the adjusted hazard ratio for heart disease (aHR = 1.20, 95% CI: 1.04–1.38), but not for stroke (aHR = 1.08, 95% CI: 0.90–1.30), for each 112 μg/L increase in well water inorganic arsenic.[259] Classification of disease was based on interviews with 5% of death certificates available for review. Examination of urinary dimethylarsinic acid/monomethylarsonic acid ratios suggested an increased risk of heart disease in subjects with incomplete methylation capacity (i.e., lower DMA/MMA ratio). The lack of clear mechanisms of toxicity, potential unmeasured confounding, and the difficulty extrapolating beyond the study population limit definite conclusions regarding the role of arsenic in cardiac mortality and the development of cardiac disease. Retrospective cohort and ecological studies have not demonstrated an association between arsenic exposure and mortality from cerebrovascular disease.[260,261]

Occupational Exposure

Systemic inorganic arsenic toxicity (excluding cancer) occurs rarely following occupational exposure. In a study of copper smelter workers funded by the former Smelter Environmental Research Association, mortality from all cases of death combined and all cancers combined was not elevated including the most specific cause of death categories, when compared with national and local mortality rates.[262] The exception was a significant association between arsenic exposure and lung cancer in a southwestern US smelter that processed ores with relatively high As content. Similarly, an updated mortality study of 2,422 copper smelter workers in southeastern Tennessee did not demonstrate elevated mortality in most categories of nonmalignant deaths. There was limited evidence of a trend for increasing cumulative As exposure and cerebrovascular disease, but not heart disease when compared with national and local mortality rates. The most common effect of occupational exposure to arsenic is local irritation of the upper respiratory tract (e.g., hoarseness, nasal irritation, perforated septum), particularly in industries with relatively high arsenic ambient air concentrations (smelting As-containing ores, pesticide application). Clinical peripheral neuropathies, primarily sensory, are potential complications of excessive occupational exposure to arsenic (e.g., total urinary As, 250 μg/L).[263] In a study of 21 copper smelter workers exposed to arsenic ($mean_{urine}$ = 11.91 ± 9.5 μg/L; duration, 18.1 ± 7.8 years), complaints of paresthesias were correlated to duration of exposure (P = 0.05), but not to urinary or airborne arsenic concentrations.[264] The difference in sural nerve conduction velocity between exposed and 16 nonexposed workers matched for smoking and age was statistically significant, but the reduction in sural nerve conduction velocity did not correlate to urinary or airborne As concentrations.

Carcinogenesis

Arsenic and inorganic arsenic compounds are recognized as human carcinogens based on studies of workers

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exposed to arsenic during mining and copper smelting. Both the International Agency for Research on Cancer (IARC Group 1) and the US National Toxicology Program list arsenic and certain arsenic compounds as known human carcinogens. Occupational exposure to inorganic arsenic in the mining and copper smelting industries is associated with an increased risk of cancer, particularly lung cancer. Epidemiological studies of cancer following medical treatment with inorganic arsenic indicate an excess incidence of skin cancers;[265] associations between medical or occupational exposure to arsenic and other non-cutaneous, non-pulmonary cancers (e.g., hepatic angiosarcoma, renal cell cancer, transitional cell bladder carcinoma[266]) are less consistent. Similarly, consumption of high arsenic concentrations in well water has been associated with an increased incidence of skin cancers (i.e., squamous cell and basal carcinomas, but not melanomas);[267] the association of other types of cancer (e.g., bladder) with environmental exposure to arsenic is less clear. Variation in cumulative arsenite dose, genetic polymorphism (*NAT2* slow acetylator and *GSTM1* null genotypes), and differences in arsenic methylation capacity (i.e., high MMA/low DMA) may account for some of the heterogeneity in these studies.

In a mortality study of a Southwestern Taiwanese cohort with a high incidence of Blackfoot disease and exposure to high arsenite concentrations in well water, age-adjusted standardized mortality rates were elevated for liver, lung, and bladder cancer.[268] However, after adjustment for risk factors (age, gender, education, smoking habits), only bladder cancer mortality was elevated in a dose-response relationship based on questionnaires about the duration of well water exposure from 1910 to the early 1970s. Average arsenic concentrations and cumulative arsenic exposure did not demonstrate a similar dose-response relationships, and the 95% confidence limits were very high for all categories. An ecological study of residents of Antofagasta, Chile, exposed to a mean arsenic concentration in drinking water of 870 μg/L for ~12 years demonstrated increased SMRs for bladder cancer (SMR = 18.1, 95% CI: 11.3–27.4), laryngeal cancer (SMR = 8.1, 95% CI: 3.5–16.0), and liver cancer (SMR = 2.5, 95% CI: 1.6–3.7).[269] These rates were based on death certificates and national mortality rates.

Childhood cancers are not typically associated with exposure to environmental sources of inorganic arsenic.[270] A long-term prospective Japanese study of 6,104 survivors of arsenic poisoning during infancy did not detect a statistically significant excess cancer mortality (SMR = 1.2, 95% CI: 1.0–1.5) when compared with Osaka residents.[271] Individual exposure data were not available; however, 130 infants died of arsenic poisoning during this epidemic. The average follow-up for this 1955 epidemic was about 24 years.

Lung

Environmental Exposure

There are limited data on the risk of lung cancer from exposure to inorganic arsenic in drinking water; most of the existing studies have methodological limitations (e.g., poor exposure data, lack of adjustment for potential confounders). However, the results of these studies consistently reveal a statistically significant association between exposure to high arsenic concentrations (>100 mg/L) and lung cancer.[272] A case-control study of 152 lung cancer cases and 419 controls from different hospitals demonstrated a trend of increasing cancer risk with increasing arsenic concentrations in drinking water based on historical estimates of arsenic exposure.[273] There was no speciation of arsenic in the drinking water. For residents in Northern Chile with a 65-year exposure to 200–400 μg As/L water, the odds ratio for lung cancer was 8.9 with 95% CI = 4.0–19.6. There was some evidence of synergy between cigarette smoking and the ingestion of arsenic-contaminated drinking water.[274] In a case-control study of multiple chemical exposures in 304 lung cancer cases, the odds ratio for lung cancer in smokers (>10 cigarettes/day) with arsenic exposure to >335 μg/L in drinking water was 16 (95% CI: 6.5–40) compared with controls (<11 μg As/L drinking water, never-smokers).[275] Secondhand smoke exposure did not significantly alter the odds ratio. The International Agency for Research on Cancer (IARC) concluded that high concentrations of arsenic in drinking water are probably causally related to primary lung cancer.[276] Previously, only inhaled carcinogens were causally related to lung cancer.

Occupational Exposure

A study of copper smelter workers exposed to arsenic trioxide revealed a progressive, dose-related increase in the respiratory cancer mortality rate (two to nine times normal) that was correlated with the cumulative arsenic dose.[277] Exposure to arsenic trioxide was the primary cause of lung cancer in a cohort of smelter workers after adjustment for cigarette smoking and exposure to SO_2.[262] Most,[278] but not all[279] epidemiological studies of cohorts exposed to arsenic demonstrate synergic effects of cigarette smoking on the development of lung cancer with the effect being somewhere between additive and multiplicative. A study of copper smelter workers demonstrated a relative excess of adenocarcinomas and a slight excess of oat-cell cancer compared with other

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types of lung cancer (e.g., squamous cell).[280] A mortality study of workers formulating arsenic for pesticides (lead arsenate, calcium arsenate, copper acetoarsenite, magnesium arsenate) demonstrated an approximate 3-fold elevation (SMR = 333, 95% CI: 218–433) of the standardized mortality rate for respiratory cancers in workers first exposed to arsenic compounds before 1940 and followed until 1974.[281] In a follow-up study, the risk ratio for respiratory cancer in the time interval 1974–1982 was smaller (SMR = 116, 95% CI: 53–220); the results were not statistically significant.[282]

Skin

Medical Therapy

The medicinal use of inorganic arsenic compounds (Fowler's solution, potassium arsenite) has been associated with an increased incidence of skin cancer, but not with other types of internal cancer.[283] Follow-up studies of cancer following medical treatment with arsenic demonstrate an increased incidence of skin cancers, but the association between other types of cancer and arsenic is also less clear. A cohort study of 478 patients treated with Fowler's solution (potassium arsenite) demonstrated a significant excess of bladder cancer (5 cases observed/1.6 expected, $P = 0.05$).[243] There were no other causes of excessive deaths.

Environmental Exposure

Skin cancers (squamous cell, basal cell) are the most prevalent malignancy associated with arsenic ingestion in highly exposed populations drinking arsenic-contaminated drinking water. The three types of cutaneous tumors associated with chronic arsenic toxicity are arsenical keratosis, multiple basal cell carcinomas, and Bowen's disease.[284] The presence of these markers of chronic As exposure suggests an increased risk of internal cancers, particularly lung and urothelial cancers.[242] In contrast to skin cancers produced by UV light or X-rays, arsenic-induced skin cancers develop in areas not exposed to sunlight or X-rays. Preferential formation of arsenical keratoses occurs in areas of friction and trauma (e.g., palms, heels, toes). The most common form of skin cancer associated with arsenic exposure arises from areas of hyperkeratosis (squamous cell carcinomas). Multiple basal cell carcinomas may occur in non-hyperkeratinized areas of the skin. Some hyperkeratotic lesions and squamous cell carcinomas *in situ* may progress to invasive carcinoma.[240] Although metastasis of some cutaneous squamous cell cancers may occur, the incidence and mortality from metastatic skin lesions are low. Malignant melanomas are not usually associated with arsenic ingestion.[267]

Bowen's disease is a form of *in situ* squamous cell carcinoma that usually appears *de novo* as solitary plaques on glabrous skin. Consequently, there are no preexisting skin lesions (e.g., arsenical keratosis). About 15–20% of a group of patients with arsenic-associated Bowen's disease developed invasive squamous cell carcinomas.[285] Tseng et al. demonstrated a dose-response relationship between inorganic arsenic in contaminated well water and the development of skin cancer among residents of Taiwan where the Blackfoot disease was prevalent.[286] The mean latency period following arsenic exposure for Bowen's disease is ~10 years and ~18–20 years for invasive squamous cell carcinoma.[287] A case report associated the development of skin cancer with latency periods of 20 years and 23 years following the chronic ingestion of ~1 mg arsenic/day (cumulative total of ~8 mg As) from contaminated well water.[288] Although epidemiological studies link the development of skin cancer with exposure to arsenic-contaminated well water, the cumulative dose required to produce these skin cancers remains controversial. An ecological study of the mortality rates of skin cancer in US counties with open-pit copper mines did not demonstrate elevated skin cancer rates in the counties with the mines.[289]

Occupational Exposure

The interpretation of studies of occupational exposure to arsenic and skin cancer is complicated by multiple confounding variables; the results of these studies are inconsistent.

In a case-control study of 618 incident cases of nonmelanoma skin cancer (515 basal cell carcinomas, 70 squamous cell carcinomas) and 527 hospital-based controls aged 30–79 years, the lifetime prevalence of occupational arsenic exposure in cases and controls was 23.9% and 15.5% (statistically nonsignificant).[290] The odds ratio for nonmelanoma skin cancer was elevated in the high vs. low arsenic exposure groups (OR = 1.94, 95% CI: 0.76–4.95) based on expert evaluation of lifetime arsenic exposure, but the difference was not statistically significant. Adjustment of the odds ratio suggested that co-exposure to sunlight and arsenic may increase the prevalence of nonmelanoma skin cancer, but the ratio was based on four cases. Overall, the support for an association between arsenic exposure in the workplace and skin cancer was weak.

Genitourinary

Studies of environmental, but not occupational arsenic exposure suggest an association with genitourinary cancer. Several mortality studies of Taiwanese and Japanese populations exposed to high arsenic concentrations in

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well water suggest an increased bladder cancer risk;[30,291] however, other case-control studies have not detected a dose-related increase in the incidence of bladder cancer following exposure to lower mean arsenic concentrations (i.e., <100 μg/L) in well water.[292] A review of studies of bladder cancer mortality data in endemic areas of southwest Taiwan with the Blackfoot Disease secondary to high arsenic concentrations in well water determined that arsenic exposure concentrations alone did not explain the increased bladder cancer mortality rates in these areas.[293] In an ecological study of a region of Northern Chile where average arsenic concentrations reached 570 μg/L before 1970, the standardized mortality ratio between 1989 and 1993 for bladder cancer was elevated in men (SMR = 6.0, 95% CI: 4.8–7.4) and women (SMR = 8.2, 95% CI: 6.3–10.5).[294] A case-control study of residents in Utah with exposure to much lower concentrations of arsenic in drinking water (mean = 5 μg/L, range 0.5–160 μg/L) did not detect an elevated risk of bladder cancer.[295]

Another case-control study in Northern Chile of 122 kidney cancer cases and 640 population-based controls detected a dose-related response (P_{trend} = 0.008) between cumulative As exposure based on standardized questionnaires and renal pelvis and ureter cancers. The adjusted odds ratio of renal and ureter cancers for >25 mg As was 10.35 (n = 5, 95% CI: 2.57–41.64) compared with 5.49 (n = 12, 95% CI: 2.02–14.88) for cumulative As exposure 10–25 mg As. The trends in cumulative As exposure for renal cell cancer and all kidney cancers were not statistically significant.

Reproductive Abnormalities

Data on humans are limited to a few case reports of adverse reproductive outcomes and acute maternal arsenic toxicity[296,297] along with several ecological studies of drinking water and airborne exposure near point sources of arsenic.[298,299] Although the ecological studies suggest an association between inorganic As exposure and adverse pregnancy outcomes (low birth weight, spontaneous abortion, neural tube defects, cardiac anomalies), the marginal adjusted odds ratios, poor exposure data, and lack of control of confounding variables limit conclusions regarding the causal effect between environmental arsenic exposure on adverse pregnancy outcomes.[300] In a prospective, nested, community-based study of 1,578 pregnant women in Bangladesh, linear regression analyses suggested a statistically significant negative effect between low maternal urine total As concentrations (<100 μg/L at 8 weeks and 30 weeks of gestation) and the following birth outcomes: birth weight (−1.68 ± 0.62 g/μg As/L); head circumference (−0.05 ± 0.03 mm/μg As/L); and chest circumference (0.14 ± 0.03 mm/μg As/L).[301] Adjustment for asset scores, body mass index, and other covariates decreased the effect size for birth weight, but the effect remained statistically significant. However, there was no dose-effect association between maternal As concentration and birth weight when evaluated over the full range of arsenic exposure (median, 95 μg/L; range, 6–978 μg/L). Additionally, there were no further negative effects (i.e., no biological gradient) for maternal As exposure above 100 μg/L. About 1/3 of the women were malnourished, and ~2/3 engaged in betel nut chewing during pregnancy. A clinical pilot study of 27 Japanese survivors of the arsenic contamination from the Morinaga Dry Milk incident and 23 age-matched, unexposed local controls suggested abnormalities in bone metabolism.[302] The average height of the exposed group was 6.5 cm less than the unexposed group (P = 0.02). The mean serum alkaline phosphatase was also higher in the exposed group (233 ± 63 U/L, P = 0.01) than the unexposed group (191 ± 44 U/L). A 35-year-old woman received arsenic trioxide for acute promyelocytic leukemia; 9 months later, she conceived and delivered a healthy infant at 39 weeks, gestation.[303] In a study of CD-1 mice and New Zealand White rabbits, there were no dose-related developmental effects in either species at doses that did not produce maternal toxicity.[304] The developmental NOAEL for mice and rabbits in this study was 7.5 mg As/kg/day and 0.75 mg/kg/day, respectively.

DIAGNOSTIC TESTING

SI Conversion Units

1 nmol/L = 0.075 μg/L
1 μg/L = 0.013 μmol/L
1 nmol/mol creatinine ≈ 0.75 μg/g creatinine

Analytical Methods

Total Arsenic

Flame and graphite furnace atomic absorption spectrometry are the most common analytical procedures for the detection of *total* arsenic in biological samples.[31,305] Heat atomizes arsenic and a source transmits radiation through the atomic vapor of arsenic as a photoelectric detector measures the intensity of radiation that

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passes unabsorbed. Sample preparation techniques (e.g., gaseous hydride procedure) are necessary prior to atomic absorption spectrometry (AAS). In order to measure total arsenic, special steps (e.g., acid digestion with nitric or sulfuric acid) are necessary to degrade all organic arsenic species to inorganic arsenic.[306] Other analytical techniques for quantitating total arsenic include neutron activation analysis and X-ray fluorescence. The latter procedure does not require sample preparation. For analysis of a wide range of trace elements including total arsenic, inductively coupled plasma mass spectrometry is a well-recognized technique that has greater sensitivity and a larger elemental range than inductively coupled plasma atomic emission spectrometry or electrothermal atomic absorption spectrometry.[307] Confirmation of arsenic in contaminated water requires a 250-mL sample collected in Nalgene bottles that may need acidification with concentrated nitric acid.

Arsenic Species

Speciation of arsenic in biological specimens is important because traditional measurements determine total arsenic concentrations; this value may overestimate arsenic toxicity because of the contribution of organic arsenic species with relatively low toxicity (methylarsonic acid, dimethylarsinic acid, arsenobetaine, arsenocholine) to the total arsenic concentration.[308] The three steps of speciation are sample preparation, species separation, and detection. Generally, the separation of inorganic arsenic species from organic arsenic species involves the use of chromatographic separation procedures (e.g., liquid chromatography) prior to the introduction of the sample into the detection system (e.g., spectrometry). The combination of chromatographic separation (HPLC) with element-specific detection (e.g., AAS, inductively coupled plasma/mass spectrometry (ICP/MS), inductively coupled plasma/atomic emission spectrometry (ICP/AES), inductively coupled plasma/dynamic reaction cell/mass spectrometry (ICP/DRC/MS)) provides a sensitive method for the speciation of arsenic at the low concentrations present in the environment.[309,310] ICP/MS is the most specific method, and sensitivities can range up to 1,000 times greater than other methods.[311] Organic solvents in the mobile phase may interfere with the detection of arsenic species as measured by ICP/AES. The use of water extraction with high-performance liquid chromatography coupled with hydride generation and inductively coupled plasma mass spectrometry (HPLC/HG/ICP/MS) allows the speciation of arsenic in hair.[312]

Solvent extraction with toluene followed by graphite furnace-AAS separates inorganic arsenic from mono- and di-methylated arsenic species.[313] However, this method does not determine the concentration of individual organic arsenic species (e.g., arsenobetaine). A hydride generation technique also separates inorganic arsenic (trivalent and pentavalent) from organic arsenic of marine origin, but the technique does not detect individual organic arsenic species. After acid digestion of the sample, the hydride generation technique measures total arsenic. Organic arsenic species (arsenobetaine, arsenocholine, arsenosugars) do not form arsine with sodium borohydride; therefore, these relatively nontoxic arsenic species are not measured by this method. The cold trapping speciation technique measures inorganic arsenic and its major methylated metabolites (MMA and DMA). The estimated detection limits for these three compounds by hydride cold-trapping technique were 1.0 ng, 1.3 ng, and 3 ng, respectively.[314] The difference between total arsenic and value from the cold trapping speciation technique is the arsenic attributed to marine origin. An intercomparison study of analytical methods for the speciation of arsenic in human urine indicated that current techniques are not precise or accurate at arsenic concentrations of <5 µg/L.[315] Arsenic species are relatively stable in urine samples stored at low temperatures (4°C, −20°C). Arsenic speciation profiles are similar in most urine samples before and after storage at –20°C for 8 months even without preservative.[316] Although dilute acids (pH 4.5) are added to urine samples in order to reduce the adsorption of trace elements from sample containers, the use of strong acidification alters the concentrations of arsenic species in the urine sample. Speciation analysis of arsenic primarily has been applied to environmental samples,[317] although detection limits of 0.3–0.4 µg As/L urine were achieved with the use of LC and ICP/MS.[318]

The Gutzeit test provides immediate qualitative confirmation of arsenic exposure, but this test is not specific for arsenic exposure. The procedure includes the following:

1. Add 5 mL of urine to a test tube.
2. Add several drops of sulfuric acid and several granules of zinc.
3. Cover the tube with filter paper wetted with two drops of silver nitrate.
4. Black or brown discoloration indicates the presence of arsenic but does not distinguish between As^{5+} and As^{3+}.

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Biomarkers

Blood

Clearance of As from the blood is initially rapid with a first-phase elimination half-life of inorganic arsenic of ~2 hours; therefore, blood arsenic concentrations reflect very recent (i.e., 4–6 hours) exposure. Consequently, the serum arsenic concentration is relatively low soon after the ingestion of potentially dangerous amounts of arsenic compared with urine As concentrations. Although the biological half-life of inorganic arsenic in the blood is relatively short, the half-life of the methylated metabolites of inorganic arsenic in the blood is longer (range 5–20 hours).[319] As a result of the short half-life of inorganic arsenic in the blood, blood arsenic concentrations are less useful measures of recent arsenic exposure (1–2 days) than urine arsenic concentrations unless exposure occurred on the same day as the collection of the blood sample.

Whole blood levels of arsenic exceed the plasma arsenic concentration by several fold because arsenic concentrations are higher in erythrocytes compared with the serum and plasma. In a study of 25 patients with chronic arsenic toxicity (melanosis, keratosis) and no arsenic exposure for 2 years, the erythrocytes contained 72% of the total arsenic compared with 28% in plasma; the whole blood/plasma ratio was ~3.57:1.[320] Speciation of the total arsenic indicated that arsenic species are not evenly divided between erythrocytes and plasma, as demonstrated in Table 3.4.

General Population

Typical values of arsenic in whole blood from subjects without occupational exposure to arsenic range from 1–5 μg arsenic/L, whereas the whole blood arsenic concentration ranged from 6–123 μg/L in samples from residents living in communities with well water containing up to 393 μg As/L.[321] In an Italian study of 148 residents without occupational exposure to arsenic and no recent ingestion of seafood, the total blood arsenic concentration averaged ~5.1 ± 6.9 μg/L (range, 0.5–32 μg/L).[322]

TABLE 3.4. Distribution of arsenic species between plasma and erythrocytes in a study of 25 patients with chronic arsenic toxicity. (Based on Mandal et al.).[320]

Species	Plasma[a]	Erythrocytes[a]
Arsenobetaine	16.7	22.5
Arsenite	21.1	77.5
Monomethylarsonic acid	27.1	ND
Dimethylarsinic acid	35.1	ND
Total arsenic	28	72

Abbreviation: ND = not detected.
[a] Percentage of total arsenic (sum of trivalent and pentavalent arsenic).

Overdose

On admission 20 hours after the ingestion of 13 mg As_2O_3, the blood of a 23-year-old pharmacist contained 410 μg As/L.[117] His prior weakness, profound diarrhea, and vomiting resolved, and he complained only of constricted visual fields. He was treated with 5 days of BAL until he developed mildly elevated serum aminotransferases. His paresthesia and muscle weakness with bilateral footdrop resolved within 3 weeks; he was discharged without residual symptoms. A 25-year-old man presented to the hospital several hours after ingesting 8 g of As_2O_3 with abdominal pain and vomiting; the admission total serum arsenic concentration was 0.15 μg/mL.[323] He developed multiorgan failure and died 8 days later, despite intensive supportive care and BAL chelation.

Postmortem

The reported range of postmortem blood As concentrations is large. The arsenic concentration in postmortem samples of heart blood (left cardiac chamber) and the aorta from a termite control company employee found dead at his home was 6.3 μg/mL and 5.1 μg/mL, respectively.[324] The stomach contained 196 mg of arsenic (i.e., equivalent to 255 mg of arsenic trioxide) indicating a suicide. Postmortem blood (site not specified) from a 38-year-old man dying in the hospital 14 hours after ingesting a massive dose of A_2O_3 contained 20.1 μg/mL as measured by spectrophotometry compared with 16.2 μg/mL in postmortem blood from a 63-year-old man dying in the hospital 8 hours after ingesting ~15 g A_2O_3.[325] A 32-year-old man died in the hospital after developing an idioventricular rhythm and cardiac arrest 6 hours after admission for hypotension, dehydration, and gastrointestinal symptoms.[326] His wife admitted adding arsenic to his food including a large dose on the day of admission. His postmortem blood arsenic concentration (site not reported) was 7.2 μg/mL. A 28-year-old chemist developed profuse vomiting, diarrhea, hypotension, and renal failure after intentionally ingesting an estimated 75 g of arsenic trioxide.[327] He died 16 hours after ingestion despite intensive care; his postmortem blood (site not specified) contained 2,300 μg As/L.

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Urine

Total (Inorganic and Organic) Arsenic

Urinary total arsenic concentrations measure both inorganic and organic arsenic; the corresponding value reflects recent exposure (1–3 days) to arsenic.[328] In contrast to total arsenic concentrations, total speciated (inorganic) arsenic measures inorganic species plus the methylated metabolites of inorganic arsenic with the exclusion of organic arsenic species. The 95th percentiles for total urinary arsenic and total speciated arsenic (arsenic acid, arsenous acid, dimethylarsinic acid, monomethylarsonic acid) in the 2003–2004 US National Health and Nutrition Examination Survey (NHANES) were 65.4% and 18.9%, respectively.[310] The latter value represents inorganic-related arsenic species. Inorganic arsenic species were detected (LOD, 0.6–1.2 μg/L) in the following percentages (age ≥6 years): arsenic acid, 7.6%; arsenous acid, 4.6%; trimethylarsine oxide, 0.3%; and monomethylarsonic acid, 35%. The geometric mean of the total urinary arsenic concentration in this population was 8.30 μg/L (95% CI: 7.19–9.57 μg/L). The main species contributing to the total urinary arsenic concentration were dimethylarsinic acid (geometric mean = 3.71 μg/L) and arsenobetaine (geometric mean = 1.55 μg/L); however, the contribution of arsenobetaine to the overall total urinary arsenic concentration increased as the overall total urinary arsenic concentration increased.

Baseline total urinary arsenic concentrations are stable over the course of the day and from day-to-day in the same individual unless there is a recent, large ingestion of arsenic.[329] Total urinary arsenic concentrations may remain elevated for 1–2 months after severe acute arsenic intoxication. The relative proportion of trivalent (As^{3+}) and pentavalent (As^{5+}) species in the urine is pH dependent. Three to four days after ingestion, the methylated forms of inorganic arsenic (monomethylarsonic acid, MMA; cacodylic acid or dimethylarsinic acid, DMA) predominate in the urine as a result of biotransformation.[330] Approximately 24 hours after the intentional ingestion of As_2S_3 (orpiment), the total As in a spot urine sample was 1,490 μg/L; the patient complained of nausea, but otherwise, he remained asymptomatic during his hospitalization.[124]

Concentration Concentrations of total urinary arsenic are usually <30–50 μg/L with concentrations between 100–200 μg/L suggesting excessive arsenic exposure in the absence of heavy seafood consumption or occupational arsenic exposure within the last 7 days.[331] Interpretation of total urinary arsenic concentrations in the general population and workers requires a dietary history within the last 48 hours because methods that analyze total arsenic concentrations include the relatively nontoxic, trimethylarsenic (organic) compounds (e.g., arsenobetaine, arsenocholine) that are common constituents of marine foods (e.g., fish, shellfish, octopus, shrimp, mussel, seaweed, kelp, health food).[332,333]

In a cross-sectional study of 788 adults from the 2003–2004 National Health and Nutrition Examination Survey (NHANES), the median total urinary arsenic concentration was 7.1 μg/L.[334] The subset of this cohort without a history of recent seafood intake had a median total urinary arsenic concentration of 3.4 μg/L. In a study of spot urine samples from 4,276 participants in the 2003–2006 NHANES, the median total urine arsenic concentrations in participants without seafood consumption within 24 hours of sampling were 7.3 μg/L compared with 24.5 μg/L in participants reporting seafood consumption.[335] Dietary recall interviews conducted during the examination phase of NHANES using an automated multiple-pass method provided information on seafood intake during the past 24 hours prior to sampling. The median urinary arsenobetaine was 0.9 μg/L in participants without a history of recent seafood consumption compared with 10.2 μg/L in participants with a history of recent seafood consumption. There is substantial interindividual variation in the total urinary arsenic concentrations even in the absence of significant seafood consumption. In a study of American Indian communities, the median total urinary arsenic concentration ranged from 6.4 μg/g creatinine (90% CI: 3.9–15.2 μg/g creatinine) in Oklahoma to 16.9 μg/g creatinine (90% CI: 8.1–29.2 μg/g creatinine) in Arizona.[336]

Time Course Following the ingestion of single doses of inorganic sodium arsenite, methylarsonic acid (MMA), or cacodylic acid (dimethylarsinic acid, DMA), the kidneys excrete ~½ of the As^{3+} dose and ¾ of As dose in MMA and DMA within 4 days.[337] In this study, ~13% of the MMA dose was methylated to DMA, whereas the kidneys excreted the DMA unchanged (i.e., without metabolism). In a study of copper smelter workers exposed to arsenic trioxide, the approximate mean urinary half-lives were as follows: As^{3+}, 12 hours; As^{5+}, 8 hours; MMA, 20 hours; and DMA, 40 hours.[338] Consequently, DMA becomes the primary methylated arsenic species in the urine 1 week after arsenic ingestion with DMA accounting for 60–80% and MMA for 10–20% of urinary arsenic excretion.[50] The remainder of urinary arsenic excretion is unchanged in inorganic arsenic species. The time course of arsenic species in urine varies with time as a result of the methylation

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of inorganic arsenic. Initial excretion of arsenic during the first 48–96 hours involves unchanged inorganic arsenic; subsequently, progressively increasing amounts of MMA and DMA appear in the urine.

Seafood Ingestion of seafood increases the total urinary arsenic species, depending on the amount ingested and the type of seafood. The heavy consumption of seafood within 1–2 days of testing can increase the total urine arsenic concentration up to 1,500–2,000 μg/L;[339] the history of heavy consumption of seafood with 2 days of urine collection indicates the need to repeat the urine collection 2–3 days after ingestion. In a study of volunteers, the ingestion of seafood increased the total urinary arsenic species over baseline values as follows: tuna, 180%; crab, 280%; herring, 640%; and mackerel, 690%.[340] The ingestion of seafood also increased the urinary concentration of the methylated metabolites of inorganic arsenic, but relatively small increases in the urinary concentrations of inorganic arsenic occurred. Changes in the distribution of urinary arsenic species (e.g., trivalent, pentavalent, methylated metabolites) are not sensitive indicators of recent seafood consumption.[341]

Environment The mean total arsenic concentrations in the urine samples from a European reference population were 17.2 ± 11.1 μg/L as measured by AAS with organic arsenic species accounting for about 70% of the total arsenic concentration.[322] Inorganic arsenic and the methylated metabolites accounted for about 30% of total urinary arsenic.

Most excretion of organic arsenic from seafood occurs within 48 hours of ingestion. The mean total urinary arsenic concentration of 75 Vietnamese residents without occupational exposure to arsenic or seafood consumption within the previous 48 hours was 62.4 ± 11.6 μg/L as measured by AAS.[342]

Total Speciated (Inorganic) Arsenic

Current analytical methods allow the differentiation of inorganic arsenic and methylated metabolites of inorganic arsenic from the organic arsenic species (arsenobetaine, arsenocholine, arsenosugars) present in seafood.[343,344] Unlike the urinary excretion of complex organic arsenic compounds (arsenobetaine, arsenocholine) unchanged, most inorganic arsenic compounds are methylated to DMA (pentavalent dimethylarsinic acid, cacodylic acid) with smaller amounts of MMA (pentavalent monomethylarsonic acid) and MMA (trivalent monomethylarsonous acid). As determined by these techniques, total speciated arsenic (As_{itm}) measures inorganic arsenic (arsenite, arsenate) and the methylated metabolites (MMA^{5+}, MMA^{3+}, DMA^{5+}, DMA^{3+}) with organic arsenic species excluded. Although these methods exclude most organic arsenic species present in seafood, the presence of substantial amounts of di-methylated forms of inorganic arsenic (DMA) in some seafood (e.g., bivalves) and seaweed complicates interpretation of urine assays using methods (e.g., hydride generation technique) that report the total speciated arsenic concentration as the sum of inorganic arsenic and methylated metabolites. In a study of the arsenic species in seafood, inorganic arsenic species accounted for about 3% of the total arsenic in the flesh of mussels, but the flesh of other fish (ray, cod, sole, plaice, seabream) contained little inorganic arsenic.[75] Additionally, some arsenosugars in seafood are metabolized into DMA. Therefore, the consumption of seafood within several days of sampling can complicate the interpretation of results from analytical methods using speciation.

Individual Variation There is substantial interindividual variability in the ratio of unchanged inorganic arsenic, total MMA, and total DMA as a result of differences in methylating capacity and the subsequent pattern of the urinary excretion of arsenic metabolites. Factors that potentially alter the arsenic methylation capacity include individual genetic differences, age, arsenic dose, sex, pregnancy (estrogen), dietary and lifestyle (smoking, ethanol), and cooking.[345] The presence of relatively high concentrations of monomethylarsonic acid suggests inefficient methylation and the potential for increased susceptibility to chronic arsenic toxicity as a result of the intracellular accumulation of the toxic metabolite, MMA (trivalent monomethylarsonous acid). In contrast to substantial interindividual variation in methylation capacity, there are relatively minor intraindividual differences in the urinary arsenic metabolites. Several epidemiology studies suggest that individuals with relatively high urinary inorganic arsenic and MMA concentrations along with relatively low urinary DMA concentrations are more susceptible to the development of skin and bladder cancer.[346,347]

Environment Typically, the average total urinary speciated arsenic concentration (i.e., arsenate, arsenite, MMA species, DMA species) in the general population is <10 μg/L.[348] In a study of 37 German adults without occupational exposure to arsenic, speciation of the urine demonstrated the following arsenic species: pentavalent dimethylarsenate (DMA), 81%; pentalvalent methylarsonate (MMA), 10%; and inorganic As, 9%.[349] Trivalent MMA is an intermediate in the formation of trivalent

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DMA that varies substantially in urine samples. In a study of Romanian residents, trivalent MMA was not detectable in residents exposed to 2.8 μg As/L in their drinking water, whereas trivalent MMA represented an average of 7% of the speciated As in residents exposed to 161 μg/L in their drinking water.[153] The total urinary speciated arsenic (As_{itm}) from residents near point sources (e.g., As smelting or mining) may be higher than that from unexposed reference populations. In a pilot study of 24 residents near As mining and smelting sources, the mean As_{itm} (inorganic arsenic plus metabolites) concentration for the exposed and unexposed control group was 13.4 μg/g creatinine (range 2.7–58.9 μg/g creatinine) and 4.2 μg/g creatinine (range 2.5–5.3 μg/g creatinine), respectively, as measured by LC/ICP/MS.[50] In a study of 49 Stockholm residents, the mean As_{itm} and total organic As (As_{org}) concentrations were 12 μg/g creatinine (range 2.2–52 μg/g creatinine) and 49 μg/g creatinine (range 2.1–434 μg/g creatinine), respectively.[350]

Hair

As a result of the high affinity of arsenic for keratin, arsenic accumulates in hair, reflecting an integrated exposure depending on the growth rate of the hair (e.g., ~2–3 months for scalp hair). Although As in hair is an indicator of past As exposure, hair analysis is not a specific method for confirming chronic toxicity because this method does not discriminate between externally deposited arsenic and arsenic found within the hair shaft. Washing procedures may not remove all As from external contamination as arsenic in water and dust binds to the sulfhydryl groups in keratin and other proteins in hair based on studies of residents switching from As-contaminated well water to bottled water.[84] Sampling hair on the nape of the neck near the skin minimizes the chance of external contamination. Establishing reference ranges for As is complicated by the issue of external As contamination as well as the limited data available on the influence of age, hair sampling location and growth rate, gender, hair color, and ethnicity on As hair concentrations. The As hair concentrations in a convenience sample of 271 non-occupationally exposed US adults were below the LOD (1.10 μg/g) as measured by inductively coupled/argon plasma emission spectrometry.[351] In populations chronically exposed to arsenic in drinking water, the total arsenic concentration in hair ranges from 1–>9 μg/g.[12] As a result of external contamination and analytical issues, the total arsenic concentration in hair does not correlate well to total arsenic in drinking water.[352] Postmortem hair samples from 24 Chinese cases of accidental death demonstrated a mean concentration of 0.4 ± 0.22 μg As/g.[353]

The diagnosis of arsenic toxicity requires a correlation of the hair analysis to other samples (blood, urine) and the clinical presentation. In general, the presence of endogenous arsenic in the hair at concentrations exceeding 10 μg/g suggests chronic exposure, whereas arsenic hair concentrations exceeding 45 μg/g suggest high arsenic exposures.[12] External contamination of hair shafts may produce arsenic concentrations in the range of several thousand ppm (μg/g). The presence of high arsenic concentrations in hair and low urine arsenic levels after chelation indicates external contamination of the hair sample. The use of HPLC/HG/ICP/MS to analyze hair samples from two Chilean populations exposed to arsenic-contaminated drinking water demonstrated four arsenic species (As^{3+}, As^{5+}, pentavalent DMA, pentavalent MMA^{5+}).[312] Following chronic exposure to drinking water containing an average total arsenic concentration of 1.25 mg/L consisting almost exclusively (>99%) As^{5+}, the average As^{3+} and As^{5+} concentrations in 21 hair samples were 3.75 μg/g (range 0.23–13.72 μg/g) and 0.45 μg/g (range 0.1–1.52 μg/g), respectively. Thus, arsenite was the main arsenic species in hair, despite the consumption of water containing almost exclusively arsenate species. Methylated arsenic species accounted for <2% of the total arsenic extracted from the hair samples. Similar results were reported in a study of residents of As-affected areas in West Bengal, India. In that study, using the same analytical technique, Table 3.5 lists the approximate percentage of As species in scalp hair clipped at various locations on the head.[354]

Segmented hair analysis of full-length hairs using graphite furnace atomic absorption spectrophotometry is expensive, but this method provides an approximate estimate of the time since exposure and the amount

TABLE 3.5. Speciation of arsenic in hair and nails from residents of West Bengal, India, exposed to arsenic-contaminated drinking water without exposure to seafood. (Based on Mandal et al.).[354]

	Hair[a]	Nails[a]
Arsenite	60.9	58.6
Arsenate	33.2	21.5
Monomethylarsonic acid	2.2	7.7
Dimethylarsinic acid	3.6	3.0
Dimethylarsinous acid	ND	9.2

Abbreviation: ND = not detected.
[a] Percentage of total arsenic. These residents were not exposed to organic arsenic (e.g., arsenobetaine, arsenocholine) because of a lack of exposure to seafood.

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of exposure based on the rate of hair growth (i.e., ~1–1.3 cm/month).[355] Because of the difference in the growth rate of hairs from different parts of the body, the use of sequential analysis of individual hairs is more accurate than analysis of bulk or aligned hair samples. Full-length hairs should be marked with a clear indication of which end is the root. The distribution of arsenic in the length or cross-section of hair shafts does not distinguish between external contamination and endogenous arsenic.[12] Results from hair analysis of arsenic must be interpreted cautiously because of the propensity of As from external contamination (e.g., washing with As-containing water) to irreversibly bind to sulfhydryl groups and other proteins in the hair; hence, measurements of hair arsenic should be confirmed by urine and blood arsenic analysis.

Nails

Analysis of As in fingernails and toenails has the same advantages and limitations as measuring As concentrations in hair including the binding of arsenic from external sources to sulfhydryl groups in keratin proteins in the nail matrix; concentrations of As species in these two matrices are similar, but not identical, as demonstrated in Table 3.5. Nails grow more slowly than hair with average daily growth rates of about 0.1 mm for fingernails and 0.03–0.05 mm for toenails; however, the nail growth rate varies with age and individual nails. In general, As concentrations in toenail clippings reflect an integrated exposure over 12–18 months, depending on the growth rate, sample length, and the presence of external contamination.[356] Consequently, As concentration in toenail clipping varies substantially in the general population. In a study of 440 Michigan residents, the median As concentration in toenail clippings was 0.06 μg/g with a range of 0.003–1.26 μg/g.[357] Arsenic concentrations in nails from healthy subjects without excessive exposure to arsenic ranged from 0.02–2.9 ppm with a mean of 0.36 ppm.[358] Significantly higher arsenic concentrations (4.55 ± 2.25 ppm) were detected in subjects exposed to arsenic-contaminated well water.[359] Equations to correlate arsenic levels with arsenic concentration in nails have been formulated,[360] but the validity of these equations requires confirmation. Toenail arsenic concentrations have been proposed as a long-term biomarker of total arsenic exposure to drinking water exceeding 50 μg As/L and an alternative to the variability of urine arsenic concentrations,[361] but further validation of the exposure-response curve is necessary to validate this biomarker.

Abnormalities

Unabsorbed arsenic trioxide may appear as radiopaque flecks in the stomach.[362] Arsenic is radiopaque;[363] however, abdominal radiographs do not often demonstrate the radiopacity of arsenic in the gut because of rapid As absorption. The cerebrospinal fluid from patients with arsenic intoxication does not usually contain cells or increased amounts of protein.

Electrophysiology

Characteristic changes of inorganic arsenic-induced peripheral neuropathy begin with reduced sensory nerve conduction followed by decreased motor nerve conduction amplitude initially with only minor changes in motor nerve conduction velocity.[364] Reduction in motor nerve velocity is a later finding in chronic arsenic intoxication. Electromyography usually demonstrates denervation in the distal lower extremities.[365] Recovery from the electrophysiological effects of acute arsenic poisoning begins within a few weeks, but the residual slowing of nerve conduction velocity and decreased sensory nerve potentials may persist for several years.[207] Early electrodiagnostic testing may not distinguish arsenic toxicity from an acute inflammatory demyelinating polyradiculopathy (Guillain-Barré syndrome).

Electrocardiography

Occasional case reports associate electrocardiographic abnormalities with acute arsenic poisoning including heart block, nonspecific ST-T wave abnormalities, QTc prolongation, ventricular tachycardia (*torsade de pointes*),[217,218] and ventricular fibrillation.[366] A 34-year-old man developed syncope with polymorphic ventricular tachycardia along with clinical features of arsenic poisoning and a markedly elevated serum arsenic concentration.[367] The serum electrolytes were normal, and the electrocardiogram demonstrated dramatic QTc prolongation (660 msec) and T-U wave alternans.

In a Phase II trial of arsenic trioxide in the treatment of acute promyelocytic leukemia, QT prolongation occurred in all eight patients studied during the induction phase.[368] Four of these patients developed nonsustained ventricular tachycardia requiring antiarrhythmic drugs. Several studies suggest an association between chronic exposure to high arsenic concentrations in well water and QT prolongation. In a cross-sectional study of 280 men and 355 women from southwestern Taiwan exposed to arsenic in well water, the prevalence of QTc prolongation increased with

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arsenic concentrations exceeding 700 μg/L.[369] In a Bangladesh study of 1,715 participants in the Health Effects of Arsenic Longitudinal Study, QTc prolongation, as defined by a QTc of ≥460 msec in women and ≥450 msec in men, was associated with the highest quartile of arsenic exposure only in women (OR = 1.61, 95% CI: 1.00–2.58). The adjusted odds ratio of QTc prolongation in women for each standard deviation in well water arsenic concentration (108.7 μg/L) was 1.24 (95% CI: 1.05–1.47). The mean QTc interval for the 237 participants with QTc prolongation was 484 ± 45.0 msec.

Blood

Rare case reports associate acute arsenic poisoning with severe rhabdomyolysis.[209] Hematological abnormalities following arsenic poisoning include basophilic stippling of karyorrhexis of erythrocytes, normochromic, normocytic anemia, aplastic anemia, eosinophilia, leukopenia, thrombocytopenia, erythroid hyperplasia, megaloblastic anemia,[370] bone marrow hyperplasia, and myelodysplastic syndrome.[371] The most common hematological abnormalities resulting from chronic arsenic toxicity in the order of frequency are leukopenia, anemia, and thrombocytopenia.[372] A study of 40 workers exposed to arsenic detected a significant correlation between the concentration of glycosylated hemoglobin and the arsenic concentration in the urine of these workers. However, the clinical significance of these concentrations remains unclear.[373]

Urine

A study of 36 individuals exposed chronically to elevated As concentrations in drinking water demonstrated increased excretion of urinary porphyrins.[374] The threshold concentration was 1 mg As/g creatinine. Patients above this concentration had significant reductions in coproporphyrin III excretion, decreased coproporphyrin III/coproporphyrin I ratio, and increased excretion of urinary porphyrins compared with controls. The contaminated well water contained 92% pentavalent arsenate and 8% trivalent arsenite.

HEALTH SURVEILLANCE

Preplacement and annual physical examinations should include a chest X-ray and a careful examination of the skin for hyperpigmentation and keratosis.

Risk Assessment

Ingestion

The US EPA calculated a chronic oral reference dose (RfD) of 0.3 μg As/kg/day for inorganic arsenic based on an NOAEL of 0.8 μg As/kg/day for dermal effects and possible vascular complications in a Taiwanese farming population exposed to arsenic in well water[286] and an uncertainty factor of 3. The lack of arsenite-induced direct genotoxicity suggests the possibility of a nonlinear dose-response curve for arsenic-induced cancer with the potential for a threshold.[375]

Drinking Water

The WHO provisional guideline for drinking water is 10 μg As/L, but many areas in the world (Bangladesh, West Bengal, India, China, Taiwan, Mongolia, Finland, Hungary, Chile, Argentina, Thailand) substantially exceed this standard.[376] Epidemiological data from these regions with high arsenic concentrations (>150 μg/L) demonstrate a strong association between arsenic exposure and the risk of cancer (skin, lung, bladder). However, the risk of exposure to lower arsenic concentrations (<100 μg/L) is less well-defined because of the small sample size (i.e., power to detect OR <1.5–2), difficulty estimating past arsenic exposure (i.e., exposure misclassification), and potential confounding (e.g., smoking, radon).[377] Some studies suggest a threshold level near 100 μg/L based on analysis of cancer mortality data from Taiwanese villages with the endemic Blackfoot disease.[378] Comparison of dose-response data from different studies is complicated by potential variations in arsenic species (As^{3+}, As^{5+}, organic As), toxicity, interaction of trace elements (selenium, antimony, zinc),[379] population behavioral patterns, reliability of exposure measures, misclassification, and alternate exposure pathways for arsenic.[62,380] The magnitude of the estimated carcinogenic potency of arsenic ranges from cancer unit risk of 1×10^{-3} to $\sim 15 \times 10^{-3}$ depending on the linearity of the dose-response data.[381] Other potential factors that may modulate the effect of low doses of arsenic include genetic polymorphism, nutrition and other dietary factors, and the presence of a threshold for the saturation of the inorganic arsenic detoxification pathways at high doses.[382] However, a study of residents exposed to arsenic concentrations ranging from 17–980 μg/L in well water did not detect a threshold for the methylation of inorganic arsenic at the concentrations present in the well water.[383] The geometric mean of total speciated arsenic in the urine of current users of the well water was 58 μg/L with

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a range of 3–500 μg/L. Inorganic arsenic, MMA, and DMA represented about 19%, 9%, and 68%, of the mean speciated arsenic concentrations, respectively.

Skin

The current public drinking water standard for arsenic in the United States is 10 μg/L based on a low-dose linearity model and extrapolation of skin cancer risks from exposure to 170–800 ppb in the study of Taiwanese residents by Tseng et al.[286] Using US EPA methods, the estimated lifetime risk of developing skin cancer for an American male ingesting 1 μg As/kg/day is $\sim 15 \times 10^{-3}$. This risk estimate is highly dependent on the type of model used to extrapolate the risk of cancer to the doses of arsenic near the regulatory standard of 10 μg As/L. Using maximum likelihood estimation and a multistage Weibull model with nonzero linear and quadratic coefficients of dose, the lifetime risk of developing skin cancer for the same scenario was 1.3×10^{-3}.[384] Major limitations of the use of the Tseng data for low-dose extrapolation of cancer risk include the lack of exposure data for individuals and the absence of prevalence data for skin cancer in individual villages.[385] A single value represented the arsenic exposure at each village, and there were only three data points for skin cancer rates because these rates were grouped into three exposure categories.

In a longitudinal study of 11,746 participants in Bangladesh, the estimated risk of developing nonmalignant skin lesions was increased at drinking water concentrations of <50 μg total arsenic/L.[386] Based on linear dose-response analyses, the estimated excess relative risk of nonmalignant skin lesions for a 10 μg/L increase in total arsenic concentration in tube well water was 0.122 (95% CI: 0.087–0.171) as measured by graphite furnace atomic absorption spectrometry (limit of detection = 5 μg/L). When the result was near or below the detection limit, the sample was reanalyzed by inductively coupled plasma/mass spectrometry (detection limit of 0.1 μg/L).

Bladder

Species-specific arsenic toxicity, limited data on arsenic effects at low concentrations, and interindividual variables (e.g., smoking, arsenic methylation) complicate risk assessment of developing bladder cancer following environmental arsenic exposure.[387,388] Most evidence for an association between arsenic in drinking water and bladder cancer derives from studies of populations exposed to high arsenic concentrations (>150 μg/L) in drinking water.[29] In contrast to data from exposure to high arsenic concentrations, increased mortality from bladder or lung cancer is not clearly associated with exposure to well water containing arsenic concentrations below 150 μg/L.[389] A population-based bladder cancer case-control study of Michigan residents did not detect an increased risk of bladder cancer (OR = 1.10, 95% CI: 0.65–1.86) in residents exposed in their lifetime to >10 μg As/L drinking water, when compared with controls (<1 μg As/L).[390] A meta-analysis of eight studies of bladder cancer and low-level arsenic exposures (<100 μg/L) did not indicate that low-level arsenic exposure is an independent risk factor for bladder cancer.[391] The summary relative risk estimates (SRRE) for never-smokers were <1.0, whereas the SRRE for ever-smokers was slightly, but not statistically significantly elevated (SRRE = 1.24, 95% CI: 0.99–1.56). An update of this meta-analysis with data from two new publications yielded a slightly elevated, but non-statistically significant, summary relative risk estimate for the nine studies of 1.07 (95% CI: 0.95–1.21; $P_{\text{heterogeneity}} = 0.543$).[392] The predicted risk of bladder cancer from these studies was lower than the extrapolated risk from the high-exposure Taiwanese studies, particularly for never-smokers.

Chen et al. stratified Taiwan residents into four groups (<0.1 ppm, 0.1–0.29 ppm, 0.3–0.59 ppm, and ≥0.6 ppm) based on the median arsenic concentration in village well water.[393] The excess risk of developing bladder cancer as well as liver, lung, and kidney cancers following daily As exposure to 10 μg/kg was similar for men and women, assuming men consumed 3.5 L/day of well water and women consumed 2.0 L/day of well water. The calculated lifetime excess risk of males developing bladder cancer following this dose (i.e., corresponding to 0.2 ppm As in well water) was 1.2×10^{-2} compared with the following other cancers: liver, 4.3×10^{-3}; lung, 1.2×10^{-2}; and kidney, 4.2×10^{-3}.

Lung

Most,[291,394] but not all,[279] studies of workers exposed to inorganic arsenic indicated that smoking and arsenic act synergistically to increase the risk of lung cancer with the effects being intermediate between additive and multiplicative.[395] In the former study, no cases of lung cancer were detected among cases exposed to well water containing inorganic concentrations of arsenic of <50 μg/L.[291] A cohort study of residents from arseniasis-endemic areas in Taiwan did not detect a statistically significant increase in the relative risk of lung cancer in residents exposed to well water concentrations of <100 μg As/L.[394] After adjusting for age, an ecological study of lung cancer in Taiwan detected increased lung cancer mortality in populations exposed to well water containing inorganic arsenic concentrations of

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>640 μg/L, but statistically significant increases in lung cancer mortality were not detected in populations exposed to drinking water containing inorganic arsenic concentration below this concentration.[396]

Inhalation

The USEPA inhalation unit risk factor for As is 4.3×10^{-3} based on excess lung cancer mortality in the Asarco and Anaconda smelters in the Western United States. The Texas Commission on Environmental Quality reevaluated the As inhalation unit risk factor based on updates of the Asarco[397] and Anaconda[398] smelters along with data from a Swedish copper smelter cohort study.[399] Based on these data, the group recommended a value of 1.5×10^{-4}. This value correlates to 1/100,000 excess lung cancer deaths at 0.067 μg/m^3. Radon progenies frequently contaminate arsenic-containing materials, complicating the interpretation of cancer data from workers exposed to arsenic.[400] To date, the USEPA has not accepted a reference concentration (RfC) for chronic As inhalation.

Environmental Monitoring

Because arsenic is a recognized carcinogen, US OSHA regulations require the use of protective equipment (respirators, clothing), clean facilities (change areas, designated dining areas), engineering controls whenever employees are exposed to arsenic concentrations exceeding OSHA PEL; the goal is to control As ambient air concentrations to the lowest possible concentration below the PEL. Ambient air concentrations exceeding the action level (5 μg As/m^3) require the use of medical surveillance, protective equipment, notification, engineering controls, and training to reduce arsenic exposure. Regulated areas above the PEL require respiratory protection for the workers and prohibition on oral substances (food, beverages, gum, tobacco). The ACGIH established an 8-hour TLV–TWA of 10 μg/m^3 for inorganic arsenic based on the presence of an elevated risk of lung cancer (SMR 213, n = 47) in copper smelter workers exposed to mean airborne total arsenic concentration of 200 μg/m^3.[401] Table 3.6 lists the standards and recommendations for inorganic arsenic.

TABLE 3.6. Regulations and guidelines for inorganic arsenic exposure including the metal.

Exposure Limit	Values
ACGIH	
TLV-TWA (8-hour)[a]	
Elemental and inorganic arsenic	10 μg total As/m^3
BEI (urine)	35 μg inorganic As plus methylated metabolites/g creatinine[b]
NIOSH	
REL (15-minute ceiling)	2 μg As/m^3
IDLH	5 mg As/m^3
OSHA	
PEL-TWA (8-hour)	10 μg As/m^3
Action level	5 μg As/m^3
US EPA	
Carcinogenicity classification	A (known carcinogen)
Oral slope factor	1.5 per mg/kg/day
Inhalation unit risk	4.3×10^{-3} per μg/m^3
MCL	10 ppb (10 μg/L) As
RfD	0.3 μg/kg/day
Tolerance for residues–citrus, fruits	0.35 ppm As
US FDA	
Bottled drinking water	10 μg As/L
ATSDR	
MRL	
Oral acute	5 μg/kg/day
Oral chronic	0.3 μg/kg/day

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; BEI = biological exposure indices; IDLH = immediately dangerous to life and health; MCL = maximum contaminate level; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = reference dose; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency; US FDA = US Food and Drug Administration.
[a] Cancer notation for elemental and inorganic arsenic; [b] End of shift/end of workweek. Includes elemental arsenic and soluble inorganic arsenic compounds excluding gallium arsenide and arsine.

Biological Monitoring

Blood

The mean total blood concentration of arsenic from four glass workers exposed to airborne arsenic concentrations of 4.5–619 μg/m^3 was 30.7 μg/L (range, 8–48 μg/L) compared with a mean of 13.4 μg/L (range, 0.5–37 μg/L) for relatively unexposed store clerks.[322] Arsenic elimination from the blood is rapid; therefore, urine is the preferred sampling site for assessing occupational As exposure.

Urine

After the ingestion of inorganic arsenic, part of the dose is methylated and smaller amounts are

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excreted unchanged in the urine. In general, the kidney excretes ~10–25% of the absorbed inorganic As dose unmethylated.

Method

Although organic arsenic compounds (e.g., arsenobetaine, arsenocholine) are not relevant to the determination of arsenic toxicity, the critical dose metric for biological monitoring of arsenic exposure (i.e., total inorganic arsenic, oxidation state, DMA, MMA) remains unclear. Using the sum of speciated inorganic arsenic (trivalent, pentavalent) and major metabolites (DMA species, MMA species), the estimated biological equivalents (BE) based on the US FDA reference dose and the Agency for Toxic Substances and Disease Registry minimal risk level is 6.4 µg/L urine.[402] The BE is a screening tool to evaluate the margin of safety for current exposure guidelines; this level does not predict the likelihood of adverse health effects in individuals or populations.

The measurement of total speciated (inorganic) arsenic as a biomarker of occupational exposure to arsenic is a method to reduce the effect of diet on total urinary arsenic concentrations.[403] However, the consumption of certain types of seafood can increase the urinary DMA excretion, particularly when ingested within 24 hours of exposure, resulting in an elevation in the total urinary speciated arsenic.[340] The most complete assessment of occupational exposure includes total inorganic arsenic and arsenic speciation. Alternatively, evaluation may begin with total urinary arsenic with speciation of samples outside normal ranges.

Concentration

Total Speciated Arsenic Typical ranges of the components of As_{itm} in the urine of arsenic-exposed workers are as follows: pentavalent arsenate, 1–6%; trivalent arsenite, 11–14%; monomethylarsonic acid (pentavalent MMA), 14–18%; and dimethylarsinic acid (pentavalent DMA), 63–70%.[404] Using the speciation method during a study of workers exposed to arsenic, the average concentrations (µg As/g creatinine) of urinary speciated arsenic (As_{itm}) were as follows: unexposed controls, 4.4; workers in the electronics industry, <10; timber treatment workers applying arsenical wood preservative, 47.9; glassworkers using arsenic trioxide, 79.4; and chemical workers engaged in manufacturing inorganic arsenicals, 245.[404] About 70–75% of the urinary elimination of As_{itm} (inorganic As + metabolites) occurs within 3–4 days after exposure.

For workers exposed to arsenic trioxide at a geometric mean of 17 ± 3.1 µg As/m^3, the geometric mean of As_{itm} (inorganic arsenic plus metabolites) was 79 ± 2.4 µg As/g creatinine with a maximum of 328 µg As/g creatinine.[142] In a study of a copper smelter, the time-weighted average (TWA) ranged from 1–746 µg As/m^3 and the urinary As_{itm} ranged from 2–850 µg/L.[405] The calculated mean concentrations of urinary As_{itm} for workers exposed daily to ambient air concentrations of 10 µg As/m^3 and 50 µg As/m^3 were ~30 µg/L and 70 µg/L, respectively, corrected to a specific gravity of 1.024. The mean urinary As_{itm} concentration in a group of 40 workers using arsenic-containing products was 22.3 nmol As/mmol creatinine (maximum, 294.5 nmol As/mmol creatinine); the mean in urine samples from 26 referents without occupational exposure to arsenic was 12 nmol As/mmol creatinine.[373] The best correlation between ambient arsenic air concentrations and urine arsenic species occurred when the sum of As^{3+} and As^{5+} was measured in urine samples collected within 8 hours of the cessation of exposure. Urine DMA concentrations did not correlate well to ambient air As concentrations because of the confounding dietary exposure.

Based on a study of workers exposed to arsenic trioxide at a sulfuric acid chemical factory, the official permissible exposure limit of OSHA (10 µg/m^3) correlated to total inorganic arsenic plus methylated metabolites of ~28 µg/g creatinine.[406] A study of boiler cleaning operations in a Slovak coal-fired power plant examined the relationship between airborne exposure to pentavalent arsenic and urinary concentrations of inorganic arsenic and methylated metabolites.[407] The 8-hour time-weighted mean arsenic air concentration was 48.3 µg/m^3 (range, 0.17–375 µg/m^3; 90% particles ≤3.5 µm). The predicted mean concentration of urinary inorganic arsenic plus methylated metabolites was 13.2 µg/g creatinine (95% CI, 10.1–16.3 µg/g creatinine). This concentration is substantially below (i.e., 1/3) the urinary concentrations of inorganic arsenic and methylated metabolites predicted from studies of workers exposed to trivalent arsenic in copper smelters. This study suggests that As bioavailability may vary between industries, depending on particle size distribution, composition of matrix, and the type of arsenic compound.

Total Arsenic Most occupational studies of arsenic exposure involve exposure to arsenic trioxide vapors and arsenic-containing dust in copper smelters and refineries. Some of these studies measured total urinary arsenic concentrations rather than inorganic arsenic plus methylated metabolites. The total arsenic concentrations were measured in the urine of workers from two copper smelters[401,408] with airborne arsenic concentrations ranging up to 3,400 µg As/m^3 and a lead–acid

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storage battery factory with maximum airborne particulate arsenic concentrations of 5.1 μg/m^3 and a maximum arsine concentration in breathing-zone air samples of 49 μg/m^3.[409] The overall average predicted total urinary arsenic concentrations following exposure to airborne concentrations of 10 μg As/m^3 was 33.4 ± 8.7 μg/g creatinine based on these three studies. In a study of 14 copper smelter workers exposed to airborne arsenic concentrations up to 194 μg/m^3 (geometric mean = 17 μg/m^3), the mean urinary concentration of inorganic arsenic and methylated metabolites was ~49 μg/g creatinine. Another study of copper smelter workers measured airborne arsenic concentrations up to 1,000 μg/m^3 and corresponding urinary concentrations of inorganic arsenic plus methylated metabolites. Exposure to airborne arsenic concentrations of 10 μg/m^3 correlated to speciated urinary arsenic concentrations of ~25 μg/L.[410] Assuming a urinary creatinine concentration of 1.13 g/L, this value correlates to ~22.1 μg/g creatinine.

The physiochemical properties of the arsenic species, matrix composition, and particle distribution may alter the relationship between airborne As exposure and the urinary excretion of inorganic arsenic and methylated metabolites at a specific plant.

In a study of 24 copper smelter and arsenic trioxide refinery workers exposed primarily to trivalent arsenic, the concentrations of inorganic arsenic (As^{3+}, As^{5+}) and metabolites MMA (monomethylarsonic acid) and DMA (dimethylarsinic acid) were analyzed in urine from 0–20 hours after exposure.[338] The best correlation between the time-weighted average of arsenic in the air (range, 0.8–45 μg/m^3) and urine arsenic species was the sum of As^{3+} and As^{5+} in urine samples collected 0–8 hours postexposure. An inorganic As concentration of 5 μg/L urine correlated to an 8-hour TWA of 10 μg As/m^3. The predicted end-of-shift urinary concentration of inorganic arsenic plus methylated metabolites following exposure to airborne arsenic concentrations of 10 μg/m^3 was ~35 μg/g creatinine.

Sample Collection

Although previous studies of arsenic-exposed workers used total urine As at the end of shift as a biomarker, the currently recommended method for monitoring workers exposed to inorganic As is the determination of inorganic As and methylated metabolites. Use of this method reduces the influence of organic arsenic compounds that do not contribute significantly to toxicity.

The urine should be collected during the mid-to late week.[405] Analysis of the urine from workers with elevated arsenic concentrations should be repeated, particularly if the consumption of seafood occurred within 48 hours. Speciation helps determine the contribution of arsenic related to seafood consumption when the total urinary As is elevated. Over 99% of the arsenic in most, but not all, seafood occurs in the organic form. However, microorganisms may release inorganic arsenic from arsenobetaine present in some marine animals (e.g., mussels), and some marine organic compounds release dimethylarsinic acid in the body.[75] Consequently, the consumption of seafood within 48 hours of the collection of urine samples should be avoided in order to accurately interpret the sum of inorganic and methylated metabolites.

TREATMENT

Decontamination

In the absence of contraindications, gastric lavage is an option for decontamination when the patient presents within the first 1–2 hours postexposure and activated charcoal is not indicated. However, there are inadequate data to determine if these measures improve clinical outcomes. Case reports suggest exposure to arsine fumes from the interaction of stomach acids with large quantities of arsenic trioxide can cause local skin and mucous membrane irritation in health care workers administering these decontamination measures.[411] The presence of radiopaque material in the stomach after lavage is an indication that decontamination measures were inadequate. Whole bowel lavage is an alternative decontamination measure if the radiopaque material is past the pylorus, but data are inadequate to evaluate the efficacy of this measure. Decontaminate any exposed skin. The efficacy of activated charcoal is unclear because of the limited data on the adsorption of various inorganic arsenic compounds to activated charcoal. Case reports suggest the use of alkaline irrigation of the stomach (i.e., 60 mEq $NaHCO_3$/L at 1 L/hour in the proximal fundus with drainage via a pyloric tube) improves the decontamination of radiopaque arsenic;[412] however, there are inadequate data to confirm the efficacy of this procedure, particularly in the setting of multiple therapies. If repeat KUB demonstrates residual radiopaque material in the colon, colonic irrigation via a colonoscope is an option to remove arsenic concretions.[413]

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Elimination Enhancement

Arsenic is not readily dialyzable; early dialysis removes relatively small amounts of arsenic compared with the total body burden of arsenic.[414] In a case of massive arsenic ingestion (10 g sodium arsenate), hemodialysis accounted for about 20% of the elimination of pentavalent arsenic in combination with BAL.[415] Continuous venovenous hemofiltration combined with hemodialysis and peritoneal dialysis removed negligible amounts (i.e., about 0.5% of the estimated dose) of arsenic over an 11-day period in a patient surreptitiously administered ~10 g of arsenic trioxide.[416] Hemodialysis is useful primarily as an adjunct for the removal of the BAL-arsenic complex when renal failure occurs.[417] Experimental evidence suggests that other chelating agents (e.g., DMPS or 2,3-dimercapto-1-propane sulfonic acid, DMSA or meso-dimercaptosuccinic acid) do not cross hemodialysis membranes.[418]

Chelating Agents

Chelation therapy should be administered early (within several hours if possible) to prevent serious toxicity in acute As exposures when the patient is symptomatic. A spot total urine arsenic concentration (2–4 hours after an acute arsenite exposure) exceeding 200–300 μg/L is an empiric indication for early chelation.[23] Arsenic is rapidly cleared from the blood following chelation; urine arsenic concentrations typically return to normal within 7–14 days after the ingestion of inorganic arsenic. Although chelation may increase urinary arsenic excretion after chronic arsenic exposure, the efficacy of chelation for chronic arsenic poisoning is unclear. Neurological symptoms frequently persist in patients with peripheral neuropathy despite the prompt use of BAL or DSMA for acute arsenic trioxide poisoning.[412,419]

British Anti-Lewisite Compound (BAL)

The use of this traditional heavy metal chelator is indicated in all serious acute arsenic exposures except arsine gas. The actual dosage range depends on the severity of exposure. The usual regimen of BAL for the treatment of arsenic toxicity is as follows: 3–5 mg/kg intramuscularly every 4 hours for 2 days; 3 mg/kg intramuscularly every 6 hours for 1 day; and then 3 mg/kg intramuscularly every 12 hours for 7 days until symptoms clear or the urine concentration decreases to <50 μg As/24 hour. Little data exist to guide the duration of treatment. Typically, the duration of BAL treatment is 5–10 days, followed by 14–19 days of oral succimer (DMSA) 10 mg/kg twice daily. A 50-mg dose of BAL combines with a maximum of 30 mg of arsenic.[420]

BAL therapy is effective for hematological manifestations of chronic arsenic poisoning, but this type of chelation probably does not improve chronic neurological symptoms. Side effects include nausea/vomiting, abdominal pain, myalgias, urticaria, burning sensation in the oropharynx (lips, mouth, throat), fever, conjunctivitis, rhinitis, lacrimation, salivation, diaphoresis, headache, anxiety, irritability, transient leukopenia, mild hepatic aminotransferase elevation, hypertension, and allergic reactions to peanut oil in BAL. Some relief of adverse effects results from administration of 1–1.5 mg diphenhydramine (Benadryl)/kg intramuscularly or by mouth every 6 hours.

2,3-Dimercaptosuccinic Acid (DMSA)

Animal experiments suggest oral BAL analogs may improve symptoms of acute arsenic trioxide poisoning,[421] primarily when administered within 1–2 hours of intoxication.[422] Efficacy decreases rapidly with an increasing interval between poisoning and chelation. Compared with BAL, DMSA has lower toxicity, oral administration, and a higher therapeutic index, particularly for the treatment of chronic arsenic toxicity.[423] Although DMSA enhances arsenic excretion from the soft tissue body stores several fold following acute organic arsenic poisoning, there are inadequate data to determine which chelating agents improve clinical outcomes following acute or chronic arsenic intoxication. The lipophilic properties of DMSA limit the ability of this compound to remove metals from the brain and bone.

Administration

The typical oral DMSA dose is 10 mg/kg t.i.d. for 5 days, followed by twice-daily administration for an additional 2 weeks. Maculopapular and vesicular rashes may develop during therapy; however, cessation of DMSA chelation rarely is necessary. A recommended chelation end-point is a 24-hour urinary arsenic concentration of <50 μg/L.[424] Arsenic inhibits T cell activation and IgG/IgM formation, resulting in reactivation of varicella-zoster and herpes simplex viruses;[425] suspicious rashes should be cultured and acyclovir administered as indicated.

Acute Toxicity Several case reports of acute trivalent (As_2O_3)[426] and pentavalent arsenic (sodium methanearsonate herbicide)[427] poisoning temporally associate the administration of DMSA with increased arsenic

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excretion and good clinical outcome. The intentional ingestion of 4–8 g DMSA during chelation therapy for an arsenic trioxide overdose was not associated with adverse effects other than a minimal elevation of serum ALT.[428] Incomplete recovery from arsenic-induced peripheral neuropathy may occur despite chelation therapy, with permanent impairment of nerve conduction.

Chronic Toxicity Although rodent studies suggest some improvement with DMSA use in chronic arsenic intoxication,[429] the efficacy of DMSA in chronic arsenic poisoning is unproven.[430] A 3-week course of DMSA did not improve the symptoms of a group of patients who ingested excessive amounts of arsenic from well water when compared with the control group (no treatment).[431] The use of DMSA in a 39-year-old woman with tetraplegia secondary to chronic arsenic poisoning reduced serum arsenic concentration; however, the neuropathy did not improve despite chelation.[432] The arsenic source was never identified; chelation therapy began about 2 months after she was hospitalized with a peripheral neuropathy.

2,3-Dimercapto-1-propanesulfonic Acid (DMPS)

A few studies and case reports from Europe and Australia suggest DMPS may be more effective than DMSA for arsenic intoxication; however, DMPS is not a USFDA-approved chelator for arsenic toxicity. Although some US compounding pharmacies carry DMPS, its availability is limited and fatal anaphylactic reactions have occurred following the use of non-pharmaceutic DMPS preparations. Analysis of urine samples from volunteers suggests DMPS chelates trivalent MMA; the latter is the substrate necessary for the biomethylation of arsenic from pentavalent MMA to pentavalent DMA.[433] Consequently, the urine from these subjects contained relatively more pentavalent MMA and less pentavalent DMA compared with pre-chelation concentrations.

Some case reports describe improvement in neurological outcome that began after intravenous DMPS therapy was initiated because for the continuing deterioration of the patient despite oral DMSA[434] and intramuscular BAL therapy.[435] The suicidal ingestion of an estimated 600 mg-dose of arsenic trioxide was treated promptly with 12 days of DMPS (patient left after 12 days); trivalent and pentavalent inorganic arsenic accounted for ~40% of the urinary output of arsenic during treatment.[436] DMPS administration in these patients involved oral DMPS (4–8 mg DMPS/kg q6h) or intravenous DMPS (3–5 mg q4h by slow IV infusion over 20 minutes) when the patient could not tolerate oral fluids (hypotension, severe diarrhea, vomiting, or intestinal ileus).

A randomized, placebo-controlled, single-blind trial of 11 patients hospitalized for chronic arsenic intoxication treated with DMPS (100 mg 4 times/day on weeks 1, 3, 5, and 7) demonstrated a statistically significant improvement in observed clinical scores during the first 3 months after therapy when compared with 10 controls (placebo).[437] Significant improvements in clinical scores of the treatment group occurred for weakness, lung disease, and pigmentation, whereas no significant difference occurred in hematological or biochemical parameters. Arsenic exposure ceased in both groups during the study; both groups had statistically significant improvements in clinical scores when compared with pre-study values. A similar randomized, placebo-control study of DMSA did not demonstrate statistically significant differences in clinical scores between treatment and placebo groups.[438] Potential observer bias and short-term follow-up limit conclusions regarding the efficacy of DMPS for chronic arsenic intoxication based on this study.

Penicillamine

This compound provides adjunctive therapy in serious ingestions[439,440] producing fewer adverse reactions than BAL. The efficacy of D-penicillamine is controversial; animal studies have not supported the effectiveness of this drug in the treatment of arsenic toxicity.[441] Serious side effects from D-penicillamine usually occur from long-term use (optic neuritis, nephrotoxicity). Sensitivity reactions to penicillamine include fever, rashes, leukopenia, eosinophilia, and thrombocytopenia. The dose for adjunctive chelation in children is 100 mg penicillamine/kg/day for 5 days in 4 oral doses up to 1 g/day and up to 500 mg 4 times a day in adults. The administration of penicillamine should be reconsidered following a 5-day rest period when symptoms reappear or when the urine arsenic concentrations remain elevated. The use of penicillamine is contraindicated in penicillin-sensitive patients.

Supplemental Care

1) Follow fluid/electrolyte balance carefully because arsenic causes vasodilation. Treat hypotension with fluids before using vasopressors.
2) Obtain an electrocardiogram and monitor the cardiac rhythm. The treatment for *torsade de*

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pointes includes magnesium, restoration of potassium balance, and overdrive pacing along with the avoidance of Class IA antiarrhythmic drugs (procainamide, quinidine, disopyramide).

3) Follow renal and hepatic function with serum creatinine and hepatic enzymes.
4) Obtain a baseline chest X-ray. Pulmonary edema is a rare complication, and respiratory failure secondary to neuromuscular weakness may develop several weeks after severe poisoning.[442]
5) Review any underlying disease and observe for complications of anemia, particularly in patients with cardiopulmonary disease.
6) Treatment options for arsenical keratoses includes topical chemotherapy, electrodessication and curettage, cryosurgery, and excisional surgery.

TABLE 3.7. Some physical properties and identifying information of gallium arsenide.

	Gallium Arsenide
Formula	GaAs
Synonym	Gallium monoarsenite
CAS RN	1303-00-0
Valence	−3
Molecular weight (g/mol)	144.64
Color	Dark gray
Physical state	Solid
Melting point (°C)	1,238
Density (g/mL)	5.31
Odor	Odorless[a]
Water solubility (20°C)	Very low

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.
[a] May emit garlic-like odor is in contact with water.

GALLIUM ARSENIDE

PHYSIOCHEMICAL PROPERTIES

The oxidation state of arsenide compounds ranges from 0 (elemental state) to 3− (nonmetallic), whereas only the oxidation state of gallium arsenide (GaAs) is 3−.

Gallium arsenide is a poorly soluble, synthetic metalloid that does not exist naturally. This crystalline solid is resistant to reactions with air and water in the wafer form; however, chemical properties of GaAs change (e.g., water solubility substantially increases) following the grinding of this metalloid into low micron-sized particles. Strong acids (e.g., nitric acid) decompose gallium arsenide into gallium and arsenic oxides. Table 3.7 lists some physical properties and identifying information of gallium arsenide. Hydrolysis of gallium arsenide in high-concentration hydrochloric acid produces arsine; however, these conditions are not usually present in animals or the environment. Gallium arsenide has greater electron mobility and substantially less electrical capacitance than silicon.

EXPOSURE

The use of gallium arsenide, indium arsenide, and aluminum arsenide occurs mainly in the semiconductor industry (telecommunications, solar cells, space research) with gallium arsenide being the most common arsenide in this industry. High electron mobility and saturation velocity along with desirable electromagnetic and photovoltaic properties favor the use of gallium arsenide in high-speed semiconductor and optoelectronic devices. Gallium arsenide is an important component of photoelectric chemical cells, light-emitting diodes, laser diodes, photodetectors, microwave devices, and semiconductors. The semiconductor industry uses arsine for the epitaxial growth of gallium arsenide in the manufacture of light-emitting diodes and as a doping agent in silicon-based, solid-state electronic devices.[443] Potential exposure to GaAs occurs during the formation of GaAs-silicon wafers, sandblasting GaAs ingots, and maintenance of these work areas. Although workers in the electronics industry using gallium arsenide are exposed to arsenic and arsine, the typical occupational exposure to arsenic during the production of optoelectronic devices and integrated circuits is below current work standards.[444,445]

ENVIRONMENTAL FATE

Gallium arsenide is a synthetic compound without natural sources in the environment. After anthropogenic release to the environment, gallium arsenide undergoes slow dissolution and oxidation to gallium trioxide and arsenite based on *in vitro* studies.[446] The low solubility of GaAs and its binding to other materials in solution limit the toxicity of this metalloid following environmental release.[447]

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TOXICOKINETICS

The bioavailability of GaAs is relatively low. In rodent studies, the intratracheal administration of single doses of 10, 30, and 100 mg/kg of GaAs particles to rats produced dose-dependent increases in arsenic concentrations, but the gallium concentration in blood was not detectable.[446] Similarly, the oral administration of 10, 100, and 1,000 mg/kg did not produce detectable gallium concentrations. Rodent studies suggest that arsenic bioavailability is substantially greater following intratracheal administration than ingestion based on analyses of urinary porphyrins and blood arsenic. Regardless of the route, excretion of arsenic and gallium occurred almost primarily in the feces. Arsine gas is not a byproduct of GaAs biotransformation in animals.

HISTOLOGY AND PATHOPHYSIOLOGY

The toxicity of GaAs is limited by poor solubility and the composition of materials that bind or solubilize gallium.[447] In animal studies, the target organs are the lungs and testes, but some inorganic arsenic oxides may be released from absorbed GaAs. Although there are limited data, animal studies suggest that indium arsenide produces more pulmonary toxicity than GaAs based on intratracheal administration of equimolar doses of GaAs, indium arsenide, and aluminum gallium arsenide to hamsters.[448] The latter metalloid was the least toxic.

CLINICAL RESPONSE

There are few data on the toxicity of GaAs in humans. In animal models, the lungs and testes are target organs following inhalation. The poor solubility and bioavailability of GaAs limit the toxicity following ingestion. Gallium arsenide is not listed as a substance reasonably anticipated to be a carcinogen by the US National Toxicology Program. Although the IARC determined that there is inadequate evidence of carcinogenicity of gallium arsenide in humans and limited evidence in experimental animals, the IARC lists gallium arsenide as carcinogenic to humans (Group 1) based on the biotransformation of GaAs to inorganic arsenic species in the body and concern that gallium may contribute to the formation of lung tumors in female rats.[449] Although data are limited, existing studies are not suggestive of an overall or site-specific excesses of mortality or cancer incidence in semiconductor manufacturing plants including semiconductor wafer fabrication in cleanrooms using GaAs.[450,451] Conclusions are limited by the small number of selected cancers and the relatively young age of exposed workers.

The issue of whether lung tumors occurring in these studies result from particulate-induced inflammation and increased proliferation rather than the primary carcinogenic effect of GaAs remains controversial.[452] Long-term animal studies indicate that GaAs exposure increases the incidence of lung tumors in female rats, but not in male rats, male mice, or female mice. In a 2-year study of 50 male and 50 female Fischer 344/N rats exposed by inhalation to gallium arsenide concentrations of 0, 0.001, 0.1, or 1 mg/m^3 6 hours/day, 5 days/week, there was a clear neoplastic response in the lungs and adrenal medulla of female rats.[453] The predominant non-neoplastic pulmonary effect was alveolar proteinosis followed by chronic active inflammation. Although inflammatory and proliferative lesions developed in the respiratory tract of the male rats, there was no evidence of carcinogenic activity in male rats. These studies used small particles of GaAs formed by mechanical treatment that destroyed the crystalline structure normally present in the workplace.[452]

DIAGNOSTIC TESTING

Methods for the determination of gallium in ambient air include hydride generation/atomic fluorescence spectroscopy and instrumental neutron activation analysis.[454] Monitoring of occupational exposure to gallium arsenide typically involves analysis of arsenic concentrations rather than gallium because of the limited analytical techniques for the determination of gallium.

HEALTH SURVEILLANCE

Biological monitoring of GaAs usually involves monitoring speciated arsenic in urine using arsenic recommendations and standards. The NIOSH recommended ceiling value is 0.002 mg/m^3 for GaAs, but there are no regulations specifically for GaAs exposure.

TREATMENT

Treatment is based on the amount of inorganic arsenic exposure.

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ORGANIC ARSENIC

HISTORY

Erasmus Wilson first described arsenical keratoses of the palms and soles in 1868.[15] By the early 1900s, physicians began substituting less toxic organic arsenicals (sodium cacodylate, sodium arsanilate) for the use of inorganic arsenic compounds as a treatment for pellagra, malaria, and sleeping sickness. In 1910, Nobel laureate Paul Ehrlich (1854–1915) developed the organic arsenical, arsphenamine (Salvarsan) for the treatment of syphilis and trypanosomiasis.[455] Between 1910 and the introduction of penicillin in the 1940s, arsphenamine was the primary drug available to treat syphilis; however, the treatment of syphilis with intravenous arsenicals was prolonged (>18 months), alternating with previously used mercury or bismuth treatments. Nausea, vomiting, and rapid oxidation of arsphenamine complicated the treatment of syphilis with arsenicals. The use of arsenic compounds for the treatment of diseases associated with protozoa, helminths, amoeba, and spirochetes was superseded by more effective antimicrobial therapy. Melarsoprol [2-(*p*-(4,6-diamino-*s*-triazin-2-ylamino)phenyl)-1,3,2-dithiarsolane-4-methanol] is still used to treat trypanosomiasis.

Organic arsenic-based chemical warfare agents include Adamsite (phenarsazine chloride, CAS RN: 578-94-9), Clark 1 (diphenylchloroarsine, CAS RN: 712-48-1), Clark 2 (diphenylcyanoarsine, CAS RN: 23525-22-6), and Lewisite (dichloro(2-chlorovinyl)arsine, CAS RN: 541-25-3). Nazi Germany produced arsine oil (50% phenyldichloroarsine, 35% diphenylchloroarsine, 5% arsenic trichloride, 5% triphenylarsine) as chemical weapons during World War II.[456] The Japanese Imperial Army synthesized diphenylchlorarsine and diphenylcyanoarsine as emetic-type chemical weapons during World War II under the code name Agent Red No. 1. Case reports associate the development of neurological abnormalities (speech difficulty, diplopia, gait disturbance, myoclonus, ataxia, hyperreflexia) with the consumption of well water contaminated with diphenylarsinic acid, a degradation product of these chemical weapons.[457,458]

PHYSIOCHEMICAL PROPERTIES

Common organic arsenic compounds include arsanilic acid (4-aminophenyl arsonic acid), dimethylarsinic acid (cacodylic acid, DMA), monomethylarsonic acid (pentavalent MMA), and the trivalent intermediate metabolite of inorganic arsenic, monomethylarsonous acid (trivalent MMA). Most organic arsenic compounds are pentavalent compounds that are positively charged quaternary "arsenonium" salts without a covalent bond to an oxygen atom. Arsenobetaine $[(CH_3)_3As^+CH_2COO^-]$ and arsenocholine $[(CH_3)_3As^+CH_2CH_2OH]$ are common constituents of seafood; arsenosugars frequently occur in seaweed. Cooking alters the concentration of arsenic species in seafood; this process transforms arsenobetaine to trimethylarsine oxide and tetramethylarsonium ion.[459] Table 3.8 lists identifying information and physical properties of common organic arsenic compounds.

EXPOSURE

Uses

Traditional uses of organic arsenic compounds since the 1940s include weed control (herbicide) and wood preservation; these compounds were introduced as substitutes for the more toxic inorganic arsenic compounds. Several organic arsenic compounds are herbicides including sodium methanearsonate (weed control on cotton and turf), disodium methanearsonate (weed control), calcium acid methanearsonate (post-emergent weed control on lawns), and cacodylic acid (defoliant, herbicide). The latter herbicide is a highly soluble organic arsenic compound that in the powder form is called Agent Blue. This herbicide contained 4.7% cacodylic acid and 26.4% sodium cacodylate.[460] Most organic arsenical pesticides are banned by the USEPA with the exception of sodium methanearsonate (methanearsonate, MSMA) used as a broadleaf weed herbicide on cotton. The use of chromated copper arsenic as a wood preservative has been phased out in US residential construction and most industrial applications. Other organic arsenicals are agricultural antimicrobials in animal and poultry feeds including arsanilic acid, sodium arsanilate, and 3-nitro-4-hydroxyphenylarsonic acid (roxarsone).[35]

Sources

Environment

Inorganic forms of arsenic are the predominated species in ambient air with minor amounts of organic arsenic.[35] In soil, organic arsenic may be mineralized to inorganic arsenic compounds or arsine depending on moisture

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TABLE 3.8. Physical properties and identifying information of organic arsenic compounds. (Data from ATSDR).[35]

	Arsanilic Acid	Arsenobetaine	Dimethylarsenic Acid	Disodium Methane-Arsonate	Methylarsonic Acid
Formula	$C_6H_8AsNO_3$	$(CH_3)_3As^+CH_2COO^-$	$(CH_3)_2HAsO_2$	$CH_3Na_2AsO_3$	$CH_3H_2AsO_3$
Synonym	4-Aminophenyl arsonic acid	Fish arsenic	Cacodylic acid, DMA^{5+}	DSMA	Methylarsenic acid, MMA^{5+}
CAS RN	98-50-0	64436-13-1	75-60-5	144-21-8	124-58-3
Molecular weight (g/mol)	217.04	178.06	138.01	185.95	139.98
Color	White		Colorless	Colorless	White
Physical state	Solid	Solid	Solid	Solid	Solid
Melting point (°C)	232	204–210	195–196	>355	161
Density (g/mL)	1.957				
Odor	Odorless		Odorless		
Water solubility (g/L)	Slight		660 (25°C)	1,000	Soluble

	3-Nitro-4-Hydroxy-Phenylarsonic Acid	Sodium Arsanilate	Sodium Dimethylarsinate	Sodium Methanearsonate
Formula	$C_6H_6AsNO_6$	$C_6H_7AsNO_3Na$	$(CH_3)_2NaAsO_2$	$CH_3NaHAsO_3$
Synonym	Nitrophenol arsonic acid, Roxarsone	Atoxyl	Sodium cacodylate	MSMA
CAS RN	121-19-7	127-85-5	124-65-2	2163-80-6
Molecular weight (g/mol)	263.03	239.05	159.98	161.96
Color	Pale yellow	White	Colorless	
Physical state	Solid	Solid	Solid	
Melting point (°C)			200	115–119
Water solubility (g/L)	Slightly soluble	Soluble	830 (20°C)	570 (25°C)
Odor		Odorless	Slight odor	

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.

content and aerobic conditions (e.g., anaerobic conditions favor the formation of arsine, whereas aerobic conditions favor the formation of inorganic arsenates). Severe contamination of underground aquifers occurred as a result of the gross contamination of soil with copper acetoarsenite (Paris-Green) ranging up to 51,000 mg As/kg soil.[103] The concentration of organic arsenic in open waters is low (0.01–7.4 ppb) with most samples <0.3 ppb.[461] The main organic species in freshwater are DMA and its degradation product, MMA; these species are usually present at lower concentrations than inorganic arsenic species.

Food

Marine organisms normally contain arsenic, predominately as organic arsenic including arsenobetaine (invertebrates, fish) and arsenosugars (macroalgae). In the environment, microorganisms convert inorganic arsenic to the organic, dimethyl, and trimethyl forms that accumulate in fish. The arsenic content in edible marine fish and shellfish typically contain ~85–>90% organic arsenic (e.g., arsenobetaine, arsenocholine, dimethylarsinic acid) with ~10% inorganic arsenic.[35] However, the inorganic arsenic content in seafood may be highly variable. In a dietary study of Japanese adults, trimethyl arsenic compounds, dimethylarsinic acid, monomethylarsonic acid, and inorganic arsenic accounted for ~48%, 27%, 4%, and 6% of the total arsenic intake, respectively.[68] Arsenobetaine, a trimethyl arsenic compound, is the primary organic arsenic species in seafood (e.g., fin fish) with arsenocholine, tetramethylarsonium ion, and monomethylarsonic acid generally accounting for small portions (i.e., <4–5%) of the total arsenic present in seafood.[462,463] Trimethyl arsenic compounds originate primarily in fish, shellfish, octopus, and shrimp, whereas dimethyl arsenic compounds occur in seaweed and humans following the biomethylation of inorganic arsenic. Dimethylarsinic acid appears in most seafood items with DMA representing ~20–25% of the total arsenic content.[464] Arsenosugars (arsenoribosides) are the predominant organic arsenic species in seaweed,

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algae, and some marine animals (e.g., scallops) that feed on algae.[465,466] The Asian seaweed product nori contained 17–28 μg As/g dry weight; this product is processed from red algae.[467] Almost all of the arsenic was present as arsenosugars. In a study of 18 algae food products from Spain, the concentration of total arsenic ranged from 2.3–141 mg/kg dry weight with *inorganic* arsenic accounting for 0.15–88 mg/kg dry weight.[468] Other, less common organic arsenic species in seafood include trimethylarsine, trimethylarsine oxide, and tetramethylarsonium salts.[462]

Bioconcentration factors for As are lower in freshwater invertebrates and fish than in marine organisms.[31] Mean As concentrations in whole samples from fish and seafood usually average ~4–5 ppm As with a range up to 170 ppm As, depending on the source.[67,469] Although traditional seafood is the primary source of arsenosugars, other foods contain arsenobetaine and other arsenosugars including edible seaweeds, mushrooms, rice, spices, and meat products using fish meal as feed.[348]

ENVIRONMENTAL FATE

Arsenic in the atmosphere is a mixture of trivalent and pentavalent arsenic compounds as a result of the oxidation of arsenic trioxide and methyl arsines to the pentavalent state. Biotransformation of As in the environment involves redox changes between arsenite and arsenate, reduction and methylation, and biosynthesis of organic arsenic compounds. The biomethylation of arsenic maximizes near-neutral pH, whereas acidic pH limits biomethylation. Organic arsenical pesticides do not degrade by hydrolysis or soil photolysis. The reduced conditions of swamps and bogs favor the formation of arsine, methylated arsenical compounds, and elemental arsenic.

DOSE EFFECT

Pentavalent arsenic (As^{5+}, arsenate or organic form) is less toxic than the trivalent form (arsenite or inorganic form) based on its lower solubility. Although dimethylthioarsinic acid is pentavalent, this organic compound is highly reactive with thiol substances, and its toxicity in rodent studies is similar to that of trivalent monomethylarsonous acid (MMA).[470] The toxicity of organic arsenic depends on the specific organic compound. Sodium methanearsonate (monosodium methylarsonate, MSMA) is a selective pre-emergent herbicide that contains concentrated organic (pentavalent) arsenic. The ingestion of an estimated 500 mL of 16% MSMA by a 20-year-old cocaine-dependent man was associated with nausea, vomiting, transient hypotension, elevated hepatic aminotransferases, and renal insufficiency.[471] He was lost to follow-up after receiving DMSA chelation. The ingestion of up to 240 mL of 47% MSMA by a 16-year-old adolescent was associated with vomiting, generalized abdominal pain, weakness, and paresthesias.[472] She received 192 mg of British anti-Lewisite 12 hours after ingestion, followed by a 14-day course of dimercaptosuccinic acid. At follow-up 6 weeks after discharge, she had a normal physical examination without alopecia, Mees' lines, or objective evidence of neuropathy.

TOXICOKINETICS

Absorption

The organic arsenical compounds found in seafood are well absorbed by the gastrointestinal tract.[75] In a study of mice and hamsters receiving 40 mg As/kg body weight as dimethylarsinic acid, ~75–85% of the dose was detected in the urine and feces.[473]

Biotransformation

With the exception of arsenosugars, most organic arsenic compounds do not usually undergo biotransformation. Oxidation of arsenocholine to arsenobetaine occurs rapidly following the absorption of this compound from fish, but essentially no biotransformation of arsenobetaine or arsenocholine occurs *in vivo*. The metabolism of arsenosugars is more complicated than arsenobetaine metabolism. Dimethylarsenate is the main metabolite of biotransformation of arsenosugars with minor metabolites including dimethylarsinoylethanol.[474] In a study of a volunteer ingesting ~70 g of arsenosugars, analysis of urine samples indicated the presence of 12 metabolites including the major metabolite, dimethylarsenate, along with smaller amounts of dimethylarsinoylethanol and trimethylarsine oxide.[475] The remaining metabolites were not identified. Consequently, organic arsenic compounds contribute little to the total body burden of arsenic.

Elimination

The renal elimination of most organic arsenic is more rapid (i.e., ~1 day) than the elimination of inorganic arsenic species with ~75–85% excreted as DMA and MMA. The kidneys excrete arsenobetaine within

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48 hours, primarily as the unchanged compound.[476,477] During experimental studies, the elimination half-life of sodium arsenite was approximately twice as long as the elimination half-life of arsenobetaine (30 hours vs. 18 hours, respectively) as measured by arsine generation/atomic absorption spectrometry (AG/AAS).[478] In a study of 6 volunteers ingesting a fish meal containing 13.6 ppm As (wet weight), the kidney excreted a majority of the organic arsenic dose within 2 days, but ~23% of the arsenic dose remained in the body 9 days after ingestion.[479]

Maternal–Fetal Kinetics

Laboratory analysis of the placentas of mothers treated with organic arsenic compounds (arsphenamine, neoarsphenamine) in the 1920s indicated that arsenic accumulated in the fetus.[480,481] However, none of these studies linked arsenic concentrations in cord blood with adverse pregnancy outcomes.

CLINICAL RESPONSE

The most prominent symptoms during organic arsenic intoxication (methyl arsine sulfide, methyl arsine bislaurylsulfide, ammonium salts of ferric methyl arsonic acid) were abdominal pain and vomiting.[482] Acute arsenical dermatitis previously was a common manifestation of the use of arsenic (arsphenamine) as a treatment for syphilis. Signs of this dermatitis included a generalized erythematous papular, pustular, and/or bullous eruption that sometimes evolved into erythema multiforme bullosum or an exfoliative dermatitis.[483]

As reported by the Mississippi Poison Control Center in 2011, seven teenagers inadvertently ate an estimated 2–4 oz of fish fried in sodium methanearsonate herbicide. All developed early gastrointestinal symptoms (nausea, vomiting, loose stool) that resolved in 12 hours. The admission whole blood arsenic concentrations ranged from 348–613 μg/L. They were treated with dimercaprol for 24 hours and succimer for 19 days. None of these teenagers developed any long-term toxicity.

DIAGNOSTIC TESTING

Speciation of arsenic usually requires separation procedures prior to quantitation by a detection system (e.g., atomic absorption spectrometry, inductively coupled plasma/atomic emission spectrometry, inductively coupled plasma/mass spectrometry). Most analytical techniques for measuring arsenic in biological samples do not accurately quantitate arsenobetaine because of the inability of arsenobetaine to form a hydride and the quantitatively different response to electrothermal AAS than inorganic arsenic. The detection of arsenobetaine and arsenocholine requires liquid chromatography to separate these arsenic species because these organic arsenic species are not volatile. Detection limits below 1 μg As/L can be achieved with liquid chromatographic separation combined with inductively coupled plasma instrumentation with mass spectrometry or atomic emission spectrometry (ICP/MS, ICP/AES). The use of high-performance liquid chromatography (HPLC) with ICP/MS allows the speciation of arsenic in plasma and the quantitation of arsenobetaine.[484]

The biological half-life of organic arsenic in the blood is relatively short (4–6 hours). Volunteer studies also indicate that the kidney excretes ~70% of a dose of organic arsenic in fish within 3 days via the urine;[479,485] however, case reports suggest that occasionally organic arsenic concentrations in 24-hour urine samples may exceed 2,000 μg/L soon after a seafood meal.[486] A 54-year-old diabetic with distal extremity paresthesias ate two lobster tails 5 days prior to the collection of a 24-hour urine sample.[487] The urine contained a total arsenic concentration of 4,749 μg/L (3,769 μg/g creatinine). Speciation of the urinary arsenic demonstrated no inorganic or methylated arsenic; a subsequent 24-hour, seafood-free urine sample contained 30 μg/L (21 μg/g creatinine). The concentrations of these arsenic species in urine stabilize after the second day of the workweek. Following a meal containing arsenobetaine, this arsenic species is usually rapidly absorbed and eliminated mostly unchanged with a biological half-life of ~18 hours compared to 30 hours for arsenite.[337]

HEALTH SURVEILLANCE

The US OSHA 8-hour TWA PEL for organic arsenic in the air is 500 μg/m^3. Arsenic standards and guidelines for food, water, and biomonitoring are based on total or inorganic/metabolite concentrations.

TREATMENT

Most organic arsenic species lack clinically significant toxicity. Treatment is primarily supportive. A 20-year-old cocaine-dependent man drank ~500 mL of a 16% pentavalent sodium methanearsonate herbicide solution; he received four 5-day courses of 30 mg DMSA/kg/day.[471] The initial serum and urine arsenic concentrations were 2.871 mg/L and 78.92 mg/L, respectively. He recovered without sequelae; there were no adverse effects attributed to the DMSA therapy.

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ARSINE

PHYSIOCHEMICAL PROPERTIES

Arsine (CAS No. 7784-42-1) is a colorless, nonirritating gas that volatilizes from arsenic compounds upon addition of an acid; this gas has relatively poor odor warning properties (i.e., substantially below currently recommended ambient air concentrations).[488] The odor threshold of the mild, garlic-like smell is ~1.5–3 mg/m^3.[443] Although arsine gas is a strong reducing agent that deposits arsenic following exposure to light and moisture, *in vitro* studies indicate that arsine cannot reduce organic disulfides to thiols at physiological pH (7.4).[489] Arsine is heavier than air (i.e., ~2.5); thus, this gas accumulates in relatively low areas. The production of arsine gas occurs following the contact of nascent hydrogen with arsenic or following the exposure of metallic arsenide to water. Volatile arsine (AsH_3) gas also forms following the exposure of labile hydrogen to elemental arsenic or arsenic oxides. Arsine gas is slightly soluble in water and boils at 62.5°C. The presence of acidic water or borohydride promotes the formation of arsine gas. Decomposition of arsine gas into arsenic occurs following exposure to light and elevated temperatures.[490]

EXPOSURE

The primary use of arsine gas (AsH_3) is a dopant in the semiconductor industry during the production of microchips and the epitaxial growth of gallium arsenide. Arsine exposure may occur while recycling various grades of gallium arsenide chips during degassing processes[491] or during the burnishing of metal with dilute acidic arsenic trioxide solutions.[492] Oil combustion may release arsine into the atmosphere.[35] Marine environments typically do not release arsine into the atmosphere. In seawater, marine algae transform arsenate into nonvolatile methylated arsenic compounds (methylarsonic and dimethylarsinic acids) rather than arsine.[493] Potentially, arsine may be released from metal refining, acidified metal, or acid cleaning of metal castings, particularly castings with galvanized metal.

ENVIRONMENTAL FATE

Methyl arsine compounds undergo oxidation in the atmosphere to form pentavalent compounds. After releasing to the atmosphere, oxidation of volatile arsine compounds to nonvolatile species occurs followed by distribution of these As species back to the surface.[35] Biomethylation and reduction of nonvolatile arsenic compounds (arsenite, arsenate) by terrestrial microorganisms produce volatile arsine compounds (e.g., methyl arsine, dimethyl arsine, alkyl arsine) depending on soil conditions (oxygenation, moisture). High-moisture conditions favor alkyl arsine, whereas aerobic conditions favor methyl arsine compounds.[494] The chemical instability of arsine limits the conversion of arsine to inorganic arsenic oxides as arsine decomposes in water within a few hours to elemental arsenic and hydrogen.[447]

DOSE EFFECT

Arsine gas (AsH_3) is the most toxic form of arsenic. Immediate death occurs at arsine gas concentration of 150 ppm. Estimated fatal exposures include 30 minutes of exposure to 25–50 ppm and <30 minutes at 100 ppm.

TOXICOKINETICS

Although there are few data on the absorption of arsine in humans, arsine absorption probably crosses the alveolar membranes rapidly based on the appearance of symptoms within a few hours after exposure to arsine gas. *In vitro* studies indicate that arsine rapidly distributes to erythrocytes after absorption, particularly in rat red blood cells.[495] Rats are much more susceptible to arsine-induced hemolysis than humans. Case reports suggest that arsine is rapidly metabolized to As^{3+}, to a lesser extent, As^{5+}, then to MMA and DMA. In a worker exposed to arsine gas at a recycling factory, the approximate biological half-lives of arsenic species in the blood were as follows: As^{5+}, 43 hours; As^{3+}, 30 hours; and MMA^{5+}, 96 hours.[491] The biological half-life of DMA was not calculated because the urinary DMA concentration was increasing near the end of the 5-day study.

Renal elimination accounts for most of the arsenic excretion from arsine metabolism. The biological half-life of arsenic species in the urine was ~15–20 days in a worker exposed to arsine at a recycling plant.[491] In a urine sample collected 6 days after his exposure, speciation of the urine detected the following values: As^{5+}, <1%; As^{3+}, 14%; MMA, 20%; and DMA, 65%. The excretion of arsenobetaine following arsine exposure is small compared with these four species. In a worker exposed to arsine gas during metal burnishing, the arsenic elimination in the urine

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was triphasic with biological half-lives of 28 hours, 59 hours, and 9 days.[492] Urinary arsenobetaine concentrations were slightly higher than expected from seafood consumption.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Arsine binds directly to erythrocytes and produces dose-dependent hemolysis as a result of irreversible damage to the cell membrane. Although the presence of hemoglobin is a necessary component of arsine toxicity, the exact mechanism is not well delineated. *In vitro* studies indicate that arsine gas releases heme in the presence of oxyhemoglobin, but not in the presence of carboxyhemoglobin.[496] How arsine interacts with hemoglobin molecules (e.g., sixth ligand position of the Fe^{2+} of heme) is unclear. Oxidative stress and interaction with sulfhydryl groups on the Na^+/K^+ ATPase pump are probably not important mechanisms of arsine-induced hemolysis. Although arsine causes a diffuse, direct cytotoxicity at high doses, *in vitro* studies indicate that unchanged arsine gas produces oxidative stress, but not direct cell toxicity at arsine concentrations up to 1 mmol.[489] At this concentration, trivalent arsenic causes both oxidative stress and cell death. *In vitro* experiments indicate that arsine concentrations in the range of 0.2–0.3 mmol are models of hemolytic, near-lethal arsine doses.[447]

Pathological Changes

Renal biopsies of patients with kidney damage secondary to arsine gas exposure typically demonstrate an acute interstitial nephritis with preservation of glomeruli.[497] Abnormalities in tubular cells include mitochondrial degeneration (dense matrix, small size, variable shapes), rupture of outer mitochondrial membranes, and disruption of cristae.[498] Additionally, electron microscopy demonstrates vacuolated structures (lysosomes) containing dense granular material.

CLINICAL RESPONSE

The classic presentation of arsine exposure involves a latent period of 2–24 hours, followed by the onset of abdominal pain, hemolysis, jaundice, and subsequently, oliguric renal failure.[499,500] Constitutional (headache, lightheadedness, malaise, weakness) and gastrointestinal (nausea, vomiting, abdominal pain) complaints predominate initially. Susceptible patients may develop congestive heart failure or neurological deficits, in part from lowered oxygen-carrying capacity secondary to hemolysis. Hyperkalemia and anemia with dark red urine (hemoglobinuria) indicate severe hemolysis; the latter may persist for 3–4 days. Bronze-colored skin may also appear, but jaundice and hepatotoxicity occur rarely. Renal failure is usually associated with hemolysis, probably as a result of myoglobinuria. An arsenic-hemoglobin complex may concentrate in the kidney, contributing to renal damage. Sudden death resulting from overwhelming arsenic exposure may occur in the absence of pulmonary edema and hemolysis. Rarely, permanent renal dysfunction may result from severe exposure to arsine gas.[501]

Signs of chronic arsenic poisoning may follow acute arsine gas exposure including coryza, paresthesias, garlic perspiration, hyperpigmentation, keratosis, hair loss, Mees' lines, and anemia. Chronic arsenic toxicity from prolonged low-dose arsine exposure may occur in the industrial setting; clinical features include a hoarse voice, perforated nasal septum, anemia, and gastrointestinal distress. Renal damage is rare with this type of arsenic exposure. There are few data on the mutagenicity or carcinogenicity of arsine gas in experimental animals or humans.

DIAGNOSTIC TESTING

Conversion Factors

1 mg arsine gas/m^3 = 0.309 ppm
1 ppm arsine gas = 3.24 mg/m^3

Analytical Methods

Techniques to speciate arsenic in biological samples after arsine exposure include liquid chromatography/inductively coupled plasma/mass spectrometry.[502] The analysis of air samples by graphic furnace atomic absorption spectrometry after nitric acid desorption and a nickel matrix modifier allows the detection of arsine concentration in the range of 1–200 µg/m^3.[31]

Biomarkers

At admission 34 hours after arsine gas exposure, a worker had vomiting, hematuria, and hemolysis; during the 5-day hospitalization, he required four blood

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transfusions.[491] The total serum arsenic concentrations at admission and discharge were 245 μg/L and 97 μg/L, respectively. A 46-year-old man was accidentally exposed to arsine gas at work.[503] Within 6 hours, he developed nausea, vomiting, paresthesias, fatigue, and dark urine. His blood arsenic concentration at admission was 1,250 μg/L. His renal function deteriorated, and he received supportive care, plasma/erythrocyte exchanges, and hemodialysis. His kidney function returned to baseline within 1 month. Total urinary arsenic concentrations do not correlate well to clinical arsine gas toxicity.

Abnormalities

Acute arsine gas exposure may cause free plasma hemoglobin and decreased serum haptoglobin within 3–24 hours after exposure. In addition to hemolytic anemia, substantial leukocytosis may occur with bandemia and toxic granulations. Other laboratory changes include abnormal urinalysis (proteinuria, hematuria, white cell clumps), elevated serum creatinine phosphokinase, and increasing serum creatinine.[504]

HEALTH SURVEILLANCE

The ACGIH TLV-TWA for arsine gas is 0.005 ppm (0.016 mg/m^3). In a study of 21 ion implanter maintenance engineers at 3 semiconductor plants, 22 of 45 area air samples contained detectable arsine concentrations with mean arsine concentrations ranging up to 2.9 ppb (9.4 μg/m^3); 15 of the 35 personal air samples contained detectable arsine concentrations with a geometric mean arsine concentration in positive samples of 0.07 (range, 0.01–1.66 ppb).[505] The presence of arsenic on wipe samples, the relatively low airborne arsine concentrations, and the increase in the total urinary arsenic concentration of 1.0–7.8 μg/g creatinine during ion implant maintenance suggested ingestion as a predominant pathway of exposure. In a study of 48 workers at a lead-acid battery plant exposed to arsine concentrations ranging up to 49 μg/m^3, exposure to 15.6 μg/m^3 in personal air samples correlated to total urinary arsenic concentrations of 50 μg/L.[409] The airborne As exposure of these workers was mixed as ambient air samples detected particulate As concentrations up to 5.1 μg/m^3; the history of individual As exposure was not well defined including a lack of dietary history.

TREATMENT

Stabilization

In the presence of dangerous ambient arsine concentrations, self-contained breathing apparatus, a full-face mask, protective clothing, and boots should be worn. Wash the skin of the victim copiously. Insert an intravenous line, administer fluids, and provide oxygen and cardiac monitoring during transport.

Elimination Enhancement

Anecdotal case reports suggest that patients with severe arsine poisoning may benefit from exchange transfusion as a method to improve oxygenation and reduce renal tubular necrosis. When free hemoglobin concentrations exceed 1.5 g/dL, exchange transfusion should be considered because this procedure may remove significant amounts of arsenic trapped in erythrocytes during the early phase of toxicity.[492] However, existing clinical data are not sufficient to decide if exchange transfusion is superior to blood transfusion alone. In a study of 12 patients treated with plasma exchange for severe acute arsine poisoning, the total fresh frozen plasma used for replacement fluid ranged from 1,400–4,000 mL.[506] The total arsenic removed by the plasma exchange ranged from 55.4–177.4 mg. The authors observed that the arsine-induced hemolysis associated with arsine poisoning in these cases terminated rapidly during plasma exchange. Hemodialysis is limited to the support of renal function rather than the removal of arsine or other arsenic compounds. Chelation therapy with BAL is not useful acutely because chelation does not prevent hemolysis. Current data are inadequate to determine if BAL therapy prevents renal failure or reduces the incidence of chronic arsenic poisoning after acute arsine exposure.

Supplemental Care

Blood samples should be monitored for hyperkalemia, hemolysis, liver damage, and rhabdomyolysis for at least several days. Maintain a urine flow of 2 mL/h/kg in patients who demonstrate hemolysis. Alkalinization of the urine is a therapeutic option if rhabdomyolysis develops; however, the clinical efficacy of alkalinization in addition to fluid replacement in this setting is unproven.

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Chapter 4

BARIUM

ELEMENTAL BARIUM AND POORLY ABSORBABLE BARIUM SALTS

HISTORY

Barium (Ba) is the heaviest divalent alkaline metal existing in nature primarily as barite ($BaSO_4$) and witherite ($BaCO_3$). Scheele discovered barium in 1774; the name originates from the Greek word *barys*, meaning heavy. Medicinal uses for barium salts (e.g., terra ponderosa, $BaCO_3$; muriata, $BaCl_2$) from the 17th–19th centuries included administration as a diuretic, depilatory, and emetic;[1] soon thereafter, muscle paralysis was a recognized complication of barium treatment primarily involving barium chloride and barium carbonate.[2] The use of insoluble barium sulfate as a radiopaque gastrointestinal contrast media began in 1910.[3] Few adverse effects were associated with the use of barium sulfate, despite its widespread use. In Brazil, the use of barium contrast media highly contaminated with soluble barium compounds (carbonate, sulfite) resulted in 44 illnesses and 9 deaths, primarily from ingestion.[4] Six of the 44 cases resulted from the rectal administration of the barium contrast. The industrial poisoning of workers by barium is rare unless exposed to soluble barium compounds.

PHYSIOCHEMICAL PROPERTIES

Barium is a dense alkaline earth metal belonging to Group 2 (Group IIA) of the periodic table.[5] This highly reactive metal readily combines with halogens, oxygen, and sulfur to form halides, oxides, and sulfides. Elemental barium is a silver-white, soft metal that is relatively volatile. Powdered barium easily ignites in the presence of air or other oxidizing agents. Consequently, barium exists in the divalent state in nature rather than the elemental form; the only oxidation state of barium in nature is the divalent form. Elemental barium combines readily with most metals to form alloys; barium reduces the halides, oxides, and sulfides of less reactive metals to form the corresponding metal. In moist environments, barium sulfide may decompose in to barium carbonate with the evolution of hydrogen sulfide gas. Barium sulfate is poorly water-insoluble; barium oxide and sulfate are odorless compounds. Barium oxide reacts rapidly with carbon dioxide in water to form barium hydroxide and barium carbonate.

Table 4.1 lists the physical properties and identifying information of common poorly water-soluble barium compounds. These properties are similar to those of other alkaline earth metals (calcium, strontium). The acetate, chlorate, and nitrate salts of barium are very soluble in water, whereas the arsenate, carbonate, chromate, fluoride, oxalate, phosphate, and sulfate salts of barium are poorly water-soluble. Acid-soluble barium salts include acetate, carbonate, chloride, hydroxide, nitrate, and sulfide. The solubility of all these salts increases with decreasing pH with the exception of barium sulfate.

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TABLE 4.1. Physical properties and identifying information of elemental barium and poorly absorbable barium compounds. (Based on WHO).[5]

Property	Barium	Barium Oxide	Barium Sulfate
CAS RN	7440-39-3	1304-28-5	7727-43-7
Synonym	–	Barium monoxide or protoxide, baryta	Artificial heavy spar; barytes, barium sulfate
Chemical formula	Ba	BaO	$BaSO_4$
Physical description	Silvery-yellow metal	White-yellow powder/cubic or hexagonal crystals	White crystals
Molecular weight (g/mol)	137.327	153.326	233.391
Melting point (°C)	727	1,972	1,580
Boiling point (°C)	1,897	NA	NA
Density (g/mL)	3.62	5.72	4.49
Water solubility	Reacts with water	1.5 g/100 g (20°C)	0.00031 g/100 g (20°C)
Vapor pressure (mmHg)	0.000665 (630°C) 0.998 (1,050°C)	Essentially zero	NA

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.

EXPOSURE

Commercial Processes

The primary source of barium is the mineral barite ($BaSO_4$) and less commonly witherite ($BaCO_3$). During the production of barium compounds, high-temperature sintering with charcoal reduces barite and witherite to their more reactive forms (i.e., barium sulfide and barium oxide, respectively).

Uses

Barium is a valuable nonmagnetic metal because of its high specific gravity, low abrasiveness, and chemical stability. Commercial uses for barium include oil and gas drilling muds, automotive paints, dyes, fireworks, stabilizers for plastics, case hardening steels, bricks, tiles, lubricating oils, jet fuel, vulcanization of rubber, and pesticides.[6] Table 4.2 lists products that may contain barium salts. Oil and gas industries use most (i.e., 85–95%) industrially produced barium as weighting agents for drilling mud in oil and gas wells.[5] Barium sulfate is used as a contrast medium for the gastrointestinal tract because the extreme insolubility substantially limits barium absorption from the GI tract. Barium chlorate and nitrate are used to produce yellow-green flames during the ignition of fireworks; in contrast to barium sulfate, these barium salts are very water-soluble and highly toxic.

Sources

Barium is a highly reactive metal that exists naturally in the stable divalent state primarily as inorganic complexes, primarily as carbonates and sulfates. This metal is ubiquitous as almost all living organisms contain barium.[8] For the general population, exposure to barium occurs via the ingestion of water and food, usually at low concentrations.

TABLE 4.2. Commercial uses of barium salts. (Modified from Johnson and Van Tassell).[7]

Salt	Uses
Acetate	Lubricants, fabrics, mordant (printing)
Carbonate	Ceramic glazes, enamels, chrome cleaner, marble substitutes, paper manufacturing, pesticides, rat poison, rubber manufacturing
Chloride	Acid dyes, equine purgatives, isotope (bone scan), glass manufacturing, pesticides, rat poison
Chlorate	Dyeing, explosives, matches, pyrotechnics (green)
Fluoride	Embalming, enamels, glass manufacturing
Hexafluorosilicate	Insecticides
Hydroxide	Pesticides, rat poison
Sulfide	Depilatory, luminous paints, rubber

Air

Barium is ubiquitous in air, primarily in the form of barium sulfate and carbonate from industrial emissions; however, limited data exist on the levels of barium in air. Higher barium concentrations occur near smelters;[9] however, surveys have not detected significantly higher ambient barium concentrations with industrialization. Consequently, the correlation between industrial sources of barium and barium concentrations in surrounding ambient air is relatively poor.[6] Coal ash contains widely variable amounts of barium that enter

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the ambient air as barium particulates.[6] The barium concentration in ambient air is typically <0.05 μg/m.[3,5] A US survey revealed ambient barium concentrations ranging from 0.0015–0.95 μg/m^3.[10]

Soil

Barium is a relatively abundant element that combines with other elements in soil and rocks. Concentrations of barium in soil range from 100–3,000 μg/g.[5] Nuclear explosions produce radioactive barium (^{140}Ba, ^{143}Ba), but the short half-life and small concentrations of radioactive barium in the fallout limit the significance of barium in the environment after atmospheric testing. Barium probably is not very mobile in soil because of the formation of insoluble salts except under some acidic conditions. Barium apparently does not undergo biotransformation other than the formation of divalent cations.

Water

Barium concentrations in seawater range from 2–63 μg/L with a mean concentration of ~13 μg/L.[6] Almost all surface waters contain barium as a result of the leaching of barium from sedimentary rocks into groundwater, and the barium concentration depends on local geological and chemical conditions. Rivers transport soluble barium compounds over long distances, and most barium in surface water reaches the ocean unless removed by precipitation with sulfate ions.

Diet

The average daily intake of barium ranges from ~4–25 μg/kg bodyweight depending on age and food consumption. In a study of 156 inhabitants of the Midwestern United States, the mean daily dietary intake of barium was 14 μg/kg bodyweight with an upper 90% of 16 μg/kg (95% CI: 13–23 μg/kg). Barium intake is substantially higher in infants and toddlers than in adults.[11] Typically, barium concentrations in food and herbs are below amounts considered potentially toxic as well as below recommended limits for daily intake.[12] The barium content of most foods is <4 ppm with bread accounting for the largest portion (i.e., ~20%).[6] Although barium is present in many plants, it does not generally accumulate in most plants in significant enough quantities to produce toxicity. Of all edible portions of plants, Brazil nuts contain the highest barium concentrations ranging from 1,500–3,000 mg/kg.[13,14] Barium is not an essential element in humans.

Drinking water is an important source of exposure to barium for the general population. Studies of drinking water in the United States indicate that the barium concentration ranges up to 10 mg/L with average barium concentrations of 1–30 μg/L.[15,16,17] In a survey of flushed drinking water samples from representative residences in the Midwestern United States, the average barium concentration was 30 μg/L with an upper 90% of 77 μg/L (95% CI: 51–120 μg/L), as measured by inductively coupled plasma/mass spectrometry.[18] There was little difference in the barium concentration between flushed and standing water. The US EPA limit for barium in drinking water under the Safe Drinking Water Act is 1 mg/L.

ENVIRONMENTAL FATE

Barium is a highly reactive and abundant metal being the 14th most abundant element in the earth's crust averaging about 425 ppm. In natural conditions, barium occurs almost exclusively in the divalent (+2) state combined with inorganic complexes. The most important features of the partitioning of barium in the environment are wet and dry deposition on the earth's surface, adsorption to the soil, leaching from geological formations to groundwater, and biomagnification in the food chain.

Air

The main mechanism of barium removal from the atmosphere is wet and dry deposition. Barium rapidly oxidizes in moist air. The residence time of barium in the air is usually several days, depending on rainfall, particulate size, and the chemical composition of the particulate matter.[6] Consequently, barium released into the air is not widely dispersed.

Soil

Barium is poorly mobile in the soil as a result of the adsorption of barium to soil particulates, particularly clay minerals; barium forms relatively water-insoluble metal oxides and hydroxides, but not soluble complexes with fulvic or humic acids. The presence of organic matter and the precipitation of barium by high concentrations of anions (carbonate, sulfate) limit the migration of barium in soil.[6] In general, barium mobility in soil increases with the formation of water-soluble salts (e.g., acetate, chloride, hydroxide, nitrate), particularly with decreasing soil pH.

Water

In aqueous media, barium precipitates as water-insoluble salts (e.g., carbonate, sulfate); barium does not

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hydrolyze appreciably except in highly alkaline environments (i.e., pH ≥10). Appreciable concentrations of barium sulfate occur in natural water as a result of high sulfate concentrations, particularly in ocean water. Sedimentation removes a large portion of the barium from surface water, primarily in the form of barium sulfate (barite). The high content of sulfate in ocean waters enhances the formation of barite, particularly at locations where rivers enter the ocean. Other poorly soluble barium compounds include arsenate, chromate, fluoride, oxalate, and phosphate. In the marine environment, the bioconcentration factor for barium in marine plants is ~1,000; however, the bioconcentration factor for terrestrial plants appears much smaller.[6] Some plants (e.g., legumes, forage plants, Brazil nuts, corn, mushrooms) accumulate barium with bioconcentration factors ranging from 2–20 in tomatoes and soybeans.[19] The residence time of barium in aquatic systems is several hundred years.[5]

DOSE EFFECT

Poorly absorbed barium salts (e.g., barium sulfate) are relatively nontoxic compared with water-soluble Ba salts, particularly the acid-soluble barium salts (acetate, carbonate, chloride, hydroxide, nitrate, sulfide). Deaths associated with barium enemas typically involve the contamination of the barium solution with toxic substances, rupture of internal organs, or perforation of the intestines.[20]

TOXICOKINETICS

Absorption

The oral absorption of barium compounds depends on water solubility, the presence of food in the intestines, sulfate content of food, and stomach acidity. Tracer studies in dogs suggest some absorption of poorly soluble $^{131}BaSO_4$ occurs in the lung following dust exposure with a biological half-life of 8–9 days.[21] Recent studies also indicate some absorption of barium sulfate occurs during radiographic procedures as measured by the appearance of barium in the urine.[22]

Distribution

Barium preferentially deposits in active sites of bone growth (i.e., ~90%), teeth, and to a lesser extent in muscle and lung;[8] rodent studies suggest that barium storage in kidneys, liver, spleen, heart, brain, and hair is small based on tracer studies with $^{140}BaCl_2$.[23] The average body burden of barium in an adult is ~22 mg with ~90% present in the skeleton and the remainder in soft tissue.[8,24] In soft tissue, the highest barium concentrations are found in the eye, particularly in the pigmented parts of the eye (e.g., choroid).[25] Studies in rodents suggest that skeletal uptake of barium decreases with age.[26]

Elimination

Elimination of barium occurs primarily in the feces with only small amounts (<2–10%) of an ingested or injected dose of barium appearing in the urine.[27] The body clears a majority (i.e., ~75%) of the absorbed barium dose within 3 days with prolonged terminal excretion (1–6 weeks) based on a limited tracer ^{133}Ba study in a human volunteer.[28] Analysis of barium kinetics in this subject suggests a three-compartment model with biological half-lives of ~3½ days, 34 days, and 1,033 days.[29]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Barium is a trace mineral with no proven physiological role in the human body. Like other divalent ions (e.g., calcium, magnesium), barium may affect muscle function when absorbed into the body. Barium is a physiological antagonist of potassium that is associated with hypokalemia from impairment of passive K^+ efflux rather than increased urinary/fecal potassium losses or alteration of the sodium–potassium pump.[30] The poor solubility of these barium salts limits alteration of potassium concentrations and muscle function.

CLINICAL RESPONSE

Medical Therapy

Contrast media contains extremely insoluble and relatively nontoxic barium sulfate. In a case report, hypotension and disseminated intravascular coagulation occurred after the rupture of a barium enema balloon. *In vitro* experiments suggest that the barium sulfate may have contributed to endotoxemia by generating bradykinin.[31] Commercially available barium preparations contain a number of additives including acacia, bentonite, benzoate, carboxymethylcellulose, methylparaben, polyethylene glycol, saccharin, silica, and simethicone. Systemic allergic reactions that develop

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following the administration of barium-containing contrast media most likely result from a hypersensitivity reaction to the additives rather than barium toxicity.[32] Acute aspiration of low-density barium sulfate (100% weight/volume) during radiographic procedures may cause hypoxemia secondary to alveolar shunting and ventilation–perfusion mismatches.[33] The aspiration of high-density barium sulfate (250% weight/volume) may cause an intense acute inflammatory reaction in the alveoli along with life-threatening disruption of gas exchange.[34] The aspiration of gastric fluid enhances the effects of barium aspiration.[35] Although barium aspiration produces dramatic opacities on chest X-ray, emphysema and pulmonary fibrosis do not usually occur.

Acute Oral Toxicity

Barium and *insoluble* barium compounds (e.g., barium sulfate) have low oral toxicity.

Environmental Exposure

There is no clear, consistent association between barium exposure in the general population and mortality. An epidemiology study suggested that communities with relatively high barium concentrations (≥2.0–10 mg/L) in drinking water had statistically significantly higher mortality rates for all causes, heart disease, arteriosclerosis, and all cardiovascular disease than communities with little or no barium (nondetectable to 0.2 mg/L) in drinking water.[36] The death rate ratios were 1.107, 1.143, 1.152, and 1.136, respectively. However, this study had a number of methodological limitations including poor control of confounding variables (calcium, magnesium, sodium) and wide variation in the study population (population size, duration, and amount of exposure). Other studies with similar limitations have not detected increased mortality in populations with relatively barium concentrations in drinking water when compared with the general population.[37]

Occupational Exposure

Case series suggest that chronic occupational exposure to fine dust composed of barium oxide or sulfate produces a relatively benign pneumoconiosis (baritosis). Workers exposed to finely ground barium including barium salts for many years may develop fine punctate and annular lesions on their chest X-rays; these lesions rarely progress to larger nodular lesions.[38] Typically, the lesions resolve after exposure ceases with no significant symptoms or decline in pulmonary function.[39] Cases of pneumoconiosis associated with barium miners usually involve chronic exposure to silica; barium is not typically found in the lungs of these workers.[40]

Carcinogenesis

Barium is not a recognized human or animal carcinogen.

DIAGNOSTIC TESTING

Inductively coupled plasma/atomic emission spectrometry (ICP/AES) is a fairly rapid and sensitive analytical method for the quantitation of barium in biological samples with a limit of detection (LOD) in the range of 0.25 µg Ba/L urine and 0.4–0.6 µg Ba/L blood.[41] Accuracy (% relative error) as measured by inductively coupled plasma/optical emission spectrometry (ICP/OES) after microwave digestion of blood and urine samples spiked with 15 µg Ba/L was 4% and 7%, respectively.[42] The atomic-line emission spectra for barium is 455.50 nm; this value overlaps with boron, resulting in spectral interference when the boron concentration exceeds 100 mg/L. ICP/AES is also a method for the determination of barium in food and several other metals (Al, Sr, Ti) with a lower limit of quantitation of ~10 ppm.[43,44] Neutron activation analysis is an alternative to ICP/AES that requires minimal sample preparation, but the costs are more expensive and the sensitivity is much lower (LOD, 66 µg/L plasma) than ICP/AES; consequently, the current use of NAA is limited.[45] Flame/atomic absorption spectroscopy lacks adequate sensitivity for the detection of barium concentrations in biological solutions below 10 µg/L. Electrothermal atomic absorption spectroscopy (EC AAS) is a common analytical technique for measuring barium in air, water, and soil; this technique is complex and time-consuming, particularly for the analysis of multiple elements.[46] Acid digestion with nitric acid is the most common method of preparation. Methods recommended by the USEPA for the determination of barium in water include flame atomic absorption spectroscopy (Methods 208.1 and 7080) and graphite furnace atomic absorption spectroscopy (Methods 208.2 and 7081); the limit of detection for these techniques is 100 µg/L and 2 µg/L, respectively.[6]

HEALTH SURVEILLANCE

Table 4.3 lists international and US regulations and guidelines related to barium and barium compounds.

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TABLE 4.3. Guidelines and regulations for exposure to metallic barium and insoluble barium sulfate.

Substance	Value
	OSHA
PEL–TWA	
Barium sulfate	15 mg/m^3 (total dust)
	5 mg/m^3 (respirable fraction)
	ACGIH
TLV–TWA	
Barium	0.5 mg/m^3[a]
Barium sulfate	5 mg/m^3[b,c]
	NIOSH
REL–TWA	10 mg/m^3 (total dust)
Barium	0.5 mg/m^3
Barium sulfate	
(total dust)	10 mg/m^3
(respirable fraction)	5 mg/m^3
	WHO
Drinking water quality guideline	1.3 mg/L
	US EPA
MCL	2 mg/L (drinking water)
10-day health advisory 10-kg child	0.7 mg/kg (drinking water)
Carcinogenicity classification	Not classifiable as to human carcinogenicity
	US FDA
Bottled drinking water	2 mg/L

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; MCL = maximum contaminate level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; TLV = threshold limit value; TWA = time-weighted average; US EPA = United States Environmental Protection Agency; US FDA = United States Food and Drug Administration; WHO = World Health Organization.
[a]Eye, skin and gastrointestinal irritant; [b]Inhalable particulate matter; [c]The value is for particulate matter containing no asbestos and <1% crystalline silica.

TREATMENT

Elemental barium and nonabsorbable barium salts (oxide, sulfate) are relatively nontoxic. Decontamination measures are usually unnecessary. Patients with symptoms of barium toxicity should be treated similarly to poisoning from absorbable barium salts (see Treatment section below); other etiologies for their illnesses should be considered.

ABSORBABLE BARIUM SALTS

HISTORY

Medicinal use of barium included the administration of barium salts as emetics, diuretics, and depilatories, as well as treatment for a variety of diseases (scrofula, scabies, rickets, asthma, tumors, congestive heart failure). By the end of the 19th century, the medical literature documented ~30 cases of barium poisoning, primarily as a result of the substitution of soluble barium salts in medicine and the contamination of flour by barium carbonate. During the early 20th century, barium chloride was administered for the treatment of heart block.[47] In 1930, a Canadian medical missionary, A. Stewart Allen observed an illness (*Pa Ping*) in what is now Leshan, China; the illness began with periodic episodes of paresthesias and gastrointestinal symptoms (nausea, vomiting, diarrhea) that progressed to respiratory paralysis, areflexia, ascending paralysis, and occasionally death.[48] Subsequent investigations of Chinese food poisoning cases with clinical presentations similar to familial periodic paralysis documented the presence of high barium chloride in contaminated salt consistent with barium-induced hypokalemia.[49] The substitution of soluble barium carbonate for barium sulfate in cream administered during gastrointestinal radiographic procedures produced stiffness of the mouth, blurred vision, severe hyporeflexia, and weakness in seven patients.[50] Several episodes of severe barium poisoning resulted from the contamination of food by toxic barium salts. An epidemic of food poisoning occurred in Israel when barium carbonate contaminated potato flour was used in making sausage.[51] Approximately 100 people developed extreme gastrointestinal irritation, weakness of the limbs, dry mouth, headache, testicular pain, and paresthesias as well as bulbar and respiratory weakness in severe cases. Contamination of food with barium carbonate caused illness in 13 Taiwanese family members and one death.[52]

PHYSIOCHEMICAL PROPERTIES

Table 4.4 lists the physical properties and identifying information of absorbable barium compounds. The following barium salts are very water-soluble: acetate, chloride, and nitrate. Although barium carbonate

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TABLE 4.4. Physical properties and identifying information of absorbable barium compounds and relatively water insoluble barium carbonate.

Property	Barium Acetate	Barium Carbonate	Barium Chloride	Barium Hydroxide	Barium Sulfide
CAS RN	543-80-6	513-77-9	10361-37-2	17194-00-2	21109-95-5
Synonym	Barium diacetate	Barium monocarbonate	Barium dichloride	Barium dihydroxide	Barium sulfide
Chemical formula	$Ba(C_2H_3O_2)_2$	$BaCO_3$	$BaCl_2$	$Ba(OH)_2$	BaS
Physical description	White powder[a] White crystal[b]	Crystals	Crystals	White powder[a,b] White crystal[c]	Colorless crystal or gray powder
Molecular weight (g/mol)	255.416[a] 273.431[b]	197.336	208.232[a] 244.263[d]	171.342[a] 189.357[b] 315.464[c]	169.393
Melting point (°C)	110 (decomposes)	1,555	962[a] 120[d] (decomposes)	408[a] 78[c] (decomposes)	2,229
Boiling point (°C)	NA	NA	1,560[a]	NA	NA
Density (g/mL)	2.47[a] 2.19[b]	4.2865	3.9[a] 120[d] (decomposes)	3.743[b] 2.18[c]	4.3
Water solubility (g/100 g)	79.2/100 g (25°C)	0.0014 (20°C)	37.0 (25°C)	4.91 (25°C)	8.94 (25°C)
Vapor pressure (mmHg)	NA	Essentially zero	Essentially zero	0[b] (15°C) 11.4[c] (15°C)	NA

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.
[a] Anhydrous; [b] Monohydrate; [c] Octahydrate; [d] Dihydrate.

is poorly water-soluble, both barium carbonate and barium chloride are soluble in the acidic pH of the stomach. Barium carbonate and chloride are odorless compounds, whereas barium sulfide is a sulfurous compound. Barium sulfide slowly decomposes in water, forming barium hydroxide and barium hydrosulfide. Additionally, barium sulfide undergoes slow oxidation in solution to form elemental sulfur and various oxidized sulfur species (sulfate, sulfite, thiosulfate, polythionates).[6]

EXPOSURE

Uses of barium compounds include processes in the brick, ceramic, photographic, and chemical manufacturing industries, as displayed in Table 4.2.[6] The chemical manufacture of most barium compounds begins with barium sulfide. Barium styphnate is a 2,4,6-trinitroresorcinol salt derived from styphnic acid used as a propellant in the production of explosives, whereas barium chlorate is a constituent of fireworks that produces green smoke on incineration. Barium carbonate, hydroxide, and chloride are pesticides. Barium compounds generally are not available to the public except for certain pesticides, fireworks, and depilatories. Rarely, epidemics of barium poisoning result from contamination of food sources (e.g., table salt, flour). Suicidal ingestions of soluble barium compounds often involve persons with access to chemistry laboratories.[53]

DOSE EFFECT

Serious toxicity occurs following the absorption of 200–500 mg of Ba in a soluble salt with potentially fatal Ba amounts near 1,000 mg depending on access to medical care. A 52-year-old man survived the ingestion of an estimated Ba chloride dose of 13 g after developing severe weakness, hypokalemia, respiratory failure, and renal dysfunction; at 3 months, the only sequelae was a serum creatinine of 1.4 mg/dL (baseline, 0.9 mg/dL).[54] A 39-year-old woman developed severe hypokalemia, paralysis, and respiratory failure after the intentional ingestion of 40 g of barium carbonate; all symptoms resolved within 7 days after intensive supportive care including intubation.[55] Recovery also occurred after the development of severe hypokalemia, metabolic acidosis, and respiratory failure following the ingestion of 12 g Ba as barium chloride[56] and 12.8 g Ba as barium sulfide.[57] The latter patient recovered completely within 30 hours of treatment. Studies of epidemics of barium carbonate

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poisoning suggest that children are less susceptible to muscle weakness and paralysis, perhaps as a result of reduced stomach acidity and decreased conversion of the carbonate salt to the more absorbable chloride salt. However, the number of children in epidemics of barium poisoning is too small to reach definitive conclusions regarding pediatric susceptibility.[58]

TOXICOKINETICS

Absorption

The acid in the stomach converts barium salts (e.g., barium carbonate) into the absorbable form, barium chloride; then, absorption of barium occurs beyond the pylorus. The gastrointestinal tract absorbs both acid-soluble and water-soluble barium compounds; however, the amount absorbed is compound-dependent and highly variable ranging from 3–60%.[59] The International Commission for Radiation Protection (ICRP) estimates that the gastrointestinal absorption of barium is as follows: adults, 20%; children aged 1–15 years, 30%; and infants, 60%.[60] All segments of the respiratory tract absorb soluble salts of barium relatively well.[61] Studies of aerosolized barium compounds in animals suggest that the respiratory tract of dogs absorbs ~50–75% of inhaled barium chloride or barium sulfate,[62] whereas the nasal epithelium of hamsters absorbs ~65% of an insufflated barium chloride dose similar to gastrointestinal absorption.[63] Dermal absorption of barium compounds from intact skin is minimal, but toxicity may occur when wounds are contaminated by soluble barium compounds. Animal studies suggest that peak barium concentrations occur rapidly (i.e., within ~1 hour) following ingestion.[64]

Distribution

Barium is primarily distributed to bone (i.e., ~90%) with ~1–2% of the total body burden in muscle, adipose, skin, and connective tissue.[8]

Elimination

Following the injection of 72–80 kBq of carrier-free ^{133}Ba in 6 volunteers, excretion of the barium was primarily fecal with the fecal/urinary clearance ratio ranging from 6–15 during the first 2 weeks after administration.[65] Fecal and urinary excretion during the first 2 weeks accounted for ~90% of the intravenous barium dose. Following the intravenous administration of soluble Ba^{2+}, the barium excretion followed a three-compartment model with biological half-lives of 3.6, 34.2, and 1,033 days, respectively.[29] Barium does not undergo biotransformation in humans.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Barium is a competitive potassium channel antagonist that blocks the passive efflux of intracellular potassium, resulting in a shift of potassium from extracellular to intracellular compartments.[66] Seventeen *KCNJx* genes grouped into seven subfamilies ($K_{IR}1.x$–$K_{IR}7.x$) code channel proteins that modulate the potassium inward rectifier current and the inward rectifier channels. These channels affect the resting membrane potential in excitable cells, and repolarization in cardiac myocytes is important in the regulation of the heart rhythm, cardioprotection during ischemia, insulin secretion, and water homeostasis.[67] The inward rectifier channels are very sensitive to barium ion-dependent blockade. During acute intoxication, barium directly stimulates striated, cardiac, and smooth muscle, resulting in gastrointestinal hypermotility, hypertension, and muscle cramps. Muscle paralysis develops after initial stimulation as the intracellular translocation of potassium reduces the resting membrane potential and decreases muscle excitability.[54] Barium is the only alkaline earth metal capable of producing hypokalemia as a result of the intracellular shift of potassium rather than the blockade of the sodium–potassium pump.[68] Total body stores of potassium remain normal, and the hypokalemia reflects an intracellular shift of potassium stores. Changes in muscle biopsy consistent with hypokalemic periodic paralysis are not seen following barium-induced paralysis.[55]

Pathological Changes

Pathological findings in patients dying from barium chloride poisoning are nonspecific (e.g., severe pulmonary edema, hypokalemia, petechial hemorrhages of the gastric, and small bowel mucosa).[50,69] In a case series of four accidental deaths from barium chloride poisoning, postmortem examination demonstrated subendocardial hemorrhage in the ventricles, fatty changes in the liver, vacuolar changes in the proximal tubular epithelium, mild hyaline droplet degeneration of the proximal convoluted tubules, and aggregates of amorphous, flocculent foamy material in the renal tubules.[70] Internal organs were edematous with visceral petechiae.

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CLINICAL RESPONSE

Acute Oral Toxicity

Marked hypokalemia, hypertension, and progressive skeletal muscle weakness characterize toxicity from the absorption of some barium salts (e.g., carbonate, chloride, sulfide); the clinical pattern of toxicity from absorbed barium salts is similar. Characteristically, barium toxicity follows three stages: 1) acute gastroenteritis with mild paresthesias; 2) loss of deep tendon reflexes with the onset of muscle weakness; and 3) progressive muscle paralysis.[71] Following large ingestions of toxic amounts of acid- or water-soluble barium salts (acetate, carbonate, chloride, hydroxide, nitrate, sulfide), severe gastrointestinal irritation develops within 30–60 minutes, followed within 2 hours of ingestion by hypertension tachycardia, severe hypokalemia,[72,73] and neuromuscular effects (muscle twitching, myoclonus, paresthesia, hyporeflexia, profound weakness). The clinical course may progress to hypotension, progressive flaccid paralysis, intractable hypokalemia,[74] metabolic acidosis, respiratory failure, and death.[4,75] The vomiting and diarrhea typically resolve within 24 hours for survivors. Table 4.5 lists the symptoms associated with acute barium poisoning in 226 patients reported in the medical literature.

The cervical and intercostal muscles are particularly susceptible to barium toxicity; extensor muscle groups are usually affected before the flexor groups begin in the upper extremities.[57] Paresthesias typically begin around the mouth and neck followed by the hands and feet within several hours. The dose-dependent paralysis begins peripherally and progresses centrally with respiratory failure being a common complication of barium poisoning. Rhabdomyolysis,[7] renal failure,[54] respiratory arrest,[76] and occasionally cardiac dysrhythmias (ventricular tachycardia, *torsade de pointes*, transient asystole, decreased ventricular conduction, atrial fibrillation) may result from an acute barium ingestion.

Occupational Exposure

Occupational poisoning from barium compounds is unusual. A chrome-plating worker developed gastrointestinal distress, progressive muscle weakness, rapid paralysis, and renal dysfunction after a large quantity of barium carbonate powder blew into his face while cleaning chrome tanks.[77] Barium poisoning may occur when penetrating wounds or burns are contaminated by soluble barium compounds. Hypertension, ventricular bigeminy, hypokalemia, and vomiting without paralysis developed in a jackhammer operator when he broke into a furnace area containing molten barium chloride.[78] Muscle paralysis and weakness may persist for 1 week; however, there are no documented musculoskeletal sequelae of acute barium poisoning. Workers exposed to finely ground barium salts for many years develop fine punctate and annular lesions on their chest X-rays (baritosis) that rarely progress to larger nodular lesions or pulmonary dysfunction.[38]

Reproductive Abnormalities

Barium probably crosses the placenta because studies of stillborn rodents demonstrate the presence of barium.[79] During a food poisoning epidemic resulting from the use of barium carbonate-contaminated flour, the ingestion of toxic amounts of barium in the first and third trimesters of pregnancy was not associated with adverse effects on the fetus.[7] These women had gastrointestinal symptoms without serious hypokalemia or muscle weakness.

Carcinogenesis

Neither the IARC nor the US National Toxicology Program lists barium or barium salts as suspected carcinogens with the exception of barium chromate. The latter salt is a member of the group of hexavalent chromium compounds for which there is sufficient evidence of carcinogenicity (IARC Group I: carcinogenic to humans). A 2-year study of male and female rats and mice receiving barium chloride hydrate in drinking water did not detect evidence of carcinogenicity in either species.[80] Nephropathy occurred in both female and male mice.

DIAGNOSTIC TESTING

Conversion Factors

1 μmol/L = ~56 μg/L
1 μg/L = ~0.018 μmol/L

Analytical Methods

Analytical techniques for measuring barium and barium compounds in biological and environmental samples include flame atomic absorption spectroscopy (FAAS), graphite furnace atomic absorption spectroscopy (GFAAS), X-ray fluorescence spectroscopy (XFS), neutron activation analysis (NAA), direct

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TABLE 4.5. Clinical signs and symptoms associated with acute barium toxicity in a case series of 226 patients. (Adapted from Bhoelan et al.).[67]

Affected System	Symptoms/Signs	Patients (%)
General conditions		
	Dizziness	88 (38.9)
	Headache	52 (23.0)
	Coma	48 (21.2)
	Speech problems	44 (19.5)
	Weakness	17 (7.5)
	Sweating	7 (3.1)
	Feeling cold	5 (2.2)
	Vision problems	4 (1.8)
	Consciousness (reduced)	3 (1.3)
	Drowsiness	1 (0.4)
Cardiovascular		
	Arrhythmias	134 (59.3)
	Effects on pulse rate	96 (42.5)
	Hypertension	38 (16.8)
	Hypotension	14 (6.2)
	ECG abnormalities	28 (4.9)
	Effects on heart rate	7 (3.1)
	Collapsed	5 (2.2)
	Cardiovascular failure	3 (1.3)
Respiratory		
	Respiratory arrest/failure	59 (26.1)
	Dyspnea	46 (20.4)
	Effects on respiration rate	32 (14.2)
	Respiratory muscle weakness	6 (2.7)
	Respiratory muscle paralysis	5 (2.2)
	Cyanosis	5 (2.2)
Gastrointestinal		
	Vomiting	213 (94.2)
	Diarrhea	177 (78.3)
	Abdominal pain	95 (42.0)
	Abdominal colic	87 (38.5)
	Gastroenteritis	86 (38.1)
	Nausea	59 (26.1)
Neuromuscular		
	Absent or abnormal reflexes	130 (57.5)
	Paralysis	125 (55.3)
	Muscle weakness	95 (42.0)
	Dilated pupils	89 (39.4)
	Dysarthria	9 (4.0)
	Quadriparesis	9 (4.0)
	Convulsions	4 (1.8)
	Heaviness in limbs	3 (1.3)
	Tenesmus	3 (1.3)
Sensory		
	Tingling	86 (38.1)
	Paresthesia	21 (9.3)
	Sensory diminished	1 (0.4)
Metabolic		
	Hypokalemia	39 (17.3)
	Acidosis	9 (3.9)
	Abnormal temperature	5 (2.2)
Others		
	Speech problems	4 (1.8)
	Shock	2 (0.9)

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current argon plasma-atomic emission spectroscopy (DCAP/AES), inductively coupled plasma/mass spectrometry (ICP/MS), inductively coupled plasma/atomic emission spectrometry (ICP/AES; LOD, 0.6 µg/L),[81] scintillation spectroscopy, and spectrography.[6] ICP/AES (Method 7300) is a technique recommended by NIOSH for analyzing soluble barium compounds in air with a limit of detection of 0.005 µg per sample (~0.005 µg/m^3); this method is 400 times more sensitive than FAAS (NIOSH Method 7056). The use of ICP/MS allows the isotopic analysis of barium and the determination of the source of environmental emissions. Limits of detection for ICP/MS for environmental (e.g., water)[82] and biological (e.g., urine)[83] samples using ICP/MS are 0.001 µg/L and 1 µg/L, respectively. This method is much more sensitive than X-ray fluorescence spectroscopy, neutron activation analysis, or spectrography. All of these techniques measure total barium concentrations in the sample without speciation.

Biomarkers

Blood

Case reports suggest barium is not equally distributed between serum and whole blood. In a patient intentionally ingesting barium chloride, the serum barium concentration 3 hours after admission was 20.45 µg/L compared with 150 µg/L in whole blood.[53]

General Population

Most of the barium in the blood resides in the plasma/serum with the erythrocytes containing little barium. In a study of 141 healthy adult Norwegians (age 21–87 years), the median Ba concentration in serum samples was ~60 µg/L with a range of ~30–98 µg/L as measured by ICP/AES after microwave digestion.[84] In a French study of 100 healthy adults, the median barium concentration in plasma samples was 111 µg/L (95% reference range, 90–154 µg/L) compared with 59 µg/L (95% reference range, 46.4–77.6 µg/L) in whole blood samples as measured by ICP/MS.[85] The LOQ was 7.0 µg/L and 0.19 µg/L, respectively, with inter-assay imprecision ~3–5%. The barium concentrations in these two studies are substantially higher than other studies, suggesting the possibility of methodological issues (e.g., barium contamination from glass containers). Whole blood barium concentrations in human clinical specimens collected before 1996 ranged from 0.5–2.5 µg/L.[86] The mean whole blood Ba concentration in 25 healthy Italians was 1.2 ± 0.26 µg/L (range, 0.47–2.9 µg/L) with a reference range of 0.47–2.4 µg/L as measured by NAA and several AAS techniques.[87] In a study of 130 German volunteers without occupational exposure to barium, the mean whole blood Ba concentration was 0.8 µg/L (95% CI: 0.4–1.2 µg/L) with a range up to 1.9 µg/L as measured by ICP/MS.[88]

Overdose

Approximately 24 hours after the intentional ingestion of barium carbonate, a 39-year-old woman was intubated for respiratory failure and complete flaccid paralysis; her plasma barium concentration was ~2.8 mg/L as measured by inductively coupled plasma/atomic emission spectrometry the potassium concentration was ~2.2 m Eq/L.[55] She survived with intensive supportive care; her peak plasma barium concentration was ~7.8 mg/L. Three hours after the ingestion of an estimated 20 g barium chloride, a 39-year-old woman arrived at the emergency department with cyanosis, confusion, general muscle weakness (serum K+ = 1.3 mEq/L), respiratory failure requiring intubation, and a history of the acute onset of profuse vomiting.[53] On admission, her serum and whole blood barium concentrations were 20.45 and 150 ng/mL as measured by inductively coupled plasma/mass spectrometry; her serum potassium was 1.3 mEq/L. She received hemodialysis within 1 hour of admission; she survived without complications.

Postmortem

A 39-year-old man died ~6 hours after reporting the ingestion of barium despite supportive care and advanced cardiac life support. His postmortem blood (site not specified) drawn 3 hours after death contained 2.16 mg Ba/L.[69] The barium concentration in postmortem blood (site not reported) from a 49-year-old man dying at the scene despite attempted resuscitation following the ingestion of barium chloride was 9.9 mg/L, as electrothermal atomic absorption spectrometry (EC AAS).[89] In a case series of four deaths from barium chloride poisoning, the postmortem blood (site not specified) contained barium concentrations ranging from ~16–22 mg/L (ppm).[70]

Hypokalemia secondary to barium poisoning is difficult to detect at autopsy because of the rapid passive diffusion of intracellular potassium into the blood after death; however, vitreous potassium concentrations are often relatively low when drawn within a few hours after death. Rapid analysis of fresh tissue with electron-probe analysis helps localize intracellular potassium, whereas freezing of tissue interferes with the analysis of the intracellular potassium concentration.

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URINE

Barium in urine is usually below 0.05 µmol (~2.8 µg)/24-hour urine volume and 8 µg/L in spot urine samples from the general population.[90] In the 3rd US National Report on Human Exposure to Environmental Chemicals, the geometric mean of barium was 1.43 µg/L with an upper 95% limit of 7.14 µg/L. The mean urinary Ba concentration in 35 healthy, unexposed Italians was 2.7 ± 0.5 µg/L (range, 0.25–10.1 µg/L) with a reference range of 0.25–5.7 µg/L.[87] In a French study of 100 healthy adults, the median Ba concentration in urine samples was 0.89 µg/L (95% reference range, 0.17–3.8 µg/L) as measured by ICP/MS.[85] The LOQ was 0.07 µg/L with inter-assay imprecision of ~8%. The mean Ba concentration in urine samples from 1,437 US patients was 3.5 ± 2.2 µg/L with a range of 1.0–7.0 µg/L as measured by ICP/MS.

Abnormalities

Hypokalemia after overdose may be severe (i.e., <2.0 mEq/L).[91] The total body potassium probably remains relatively stable during barium intoxication; rebound hyperkalemia frequently occurs after treatment of barium intoxication including the use of potassium supplements.[30] During the time the muscles are flaccid from severe hypokalemia, the EMG is electrically silent. Serum magnesium concentrations usually remain normal, but hypophosphatemia may occur rarely along with evidence of rhabdomyolysis (↑ creatine kinase, ↑ myoglobin).[92] Electrophysiological abnormalities during acute barium intoxication include loss of the F waves, loss of the H reflexes, and low-amplitude compound muscle action potentials.[93] These changes indicate involvement of the gamma efferent fibers, the proximal segments of the reflex arch, and the neuromuscular junction. Although barium is not directly cardiotoxic, rare case reports associate severe barium intoxication with elevated serum troponin I concentrations.[7,94] Barium compounds are radiopaque; small concretions appear in the intestine and colon following ingestion of these compounds.

HEALTH SURVEILLANCE

Table 4.6 lists international and US regulations and guidelines related to soluble barium compounds. The Agency for Toxic Substances and Disease Registry derived an intermediate-duration oral minimal risk level (MRL) for barium of 0.2 mg/kg/day based on a No-Observed-Adverse-Effect-Level (NOAEL) of 65 mg Ba/kg/day and a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 115 mg Ba/kg/day for increased kidney weight in female rats exposed to barium chloride during a US National Toxicology Program study;[80] the uncertainty factor was 100 (10-fold, animal to human extrapolation; 10-fold, human variability) with a modifying factor of 3 to account for the lack of an adequate developmental toxicity study. The chronic-duration oral MRL was 0.2 mg/kg/day based on a $BMDL_{05}$ (benchmark dose corresponding to the predicted 5% incidence of the selected effect) of 61 mg

TABLE 4.6. Regulations and guidelines for exposure to soluble barium salts.

Substance	Value
OSHA	
PEL–TWA (8-hour)	
Barium (soluble compounds)	0.5 mg/m^3 (as barium)
ACGIH	
TLV–TWA[a] (8-hour)	
Barium (soluble compounds)	0.5 mg/m^3
NIOSH	
IDLH	
Barium chloride	50 mg/m^3
REL–TWA (10-hour)	
Barium chloride	0.5 mg/m^3
WHO	
Drinking water quality guideline	0.7 mg/L
USEPA	
MCL	2 mg/L (drinking water)
10-day health advisory 10-kg child	0.7 mg/kg (drinking water)
Carcinogenicity classification	Not classifiable as to human carcinogenicity
USFDA	
Bottled drinking water	2 mg/L
ATSDR	
MRL	
Oral intermediate soluble barium salt	0.2 mg/kg/day
Oral chronic soluble barium salt	0.2 mg/kg/day

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; IDLH = immediately dangerous to life and health; MCL = maximum contaminate level; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; TLV = threshold limit value; TWA = time-weighted average; US EPA = United States Environmental Protection Agency; US FDA = United States Food and Drug Administration; WHO = World Health Organization.

[a] There are few data on the biological monitoring of workers exposed to soluble barium compounds; therefore, the ACGIH does not publish a recommended biological exposure index.

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Ba/kg/day for nephropathy in male mice from the same study and an uncertainty factor of 100 (10-fold, animal to human extrapolation; 10-fold, human variability).

Although several epidemiological studies suggest an inverse relationship between cardiovascular mortality and barium concentrations of <1 ppm in drinking water,[37,95] a cross-sectional study of residents in an area with relatively high barium concentrations (7–10 ppm) in drinking water demonstrated higher cardiovascular mortality in the study group compared with a nearby area with low barium concentrations. The study did not control for water softness (i.e., high barium concentrations in water are usually associated with high calcium and magnesium concentrations), ethnicity, or other confounders for cardiovascular mortality. A subsequent study of the same area did not detect a statistical difference in blood pressure between residents of the same two areas with high (mean = 7.3 ppm) and low (mean = 0.1 mg/L) barium concentrations in drinking water.[96]

An experimental study of 10 healthy volunteers compared a variety of known risk factors for cardiovascular disease following exposure to the following barium concentrations in drinking water as barium chloride: 2 weeks of 0 ppm, 4 weeks of 5 ppm, and 4 weeks of 10 ppm.[97] There were no statistically significant changes in blood pressure, electrocardiographic monitoring, plasma cholesterol, serum lipoprotein or apolipoprotein, serum potassium or glucose, or urine catecholamine concentrations when compared to baseline (0 ppm).

TREATMENT

Decontamination

The rapid onset of vomiting following the ingestion of barium salts limits the effectiveness of lavage. The oral administration of magnesium or sodium sulfate has the theoretical advantage of precipitating barium salts as insoluble barium sulfate. The intravenous use of magnesium salts has the theoretical concern of precipitating barium in the intravascular spaces. Consequently, oral administration or the addition of 5–10 g of magnesium sulfate to lavage fluid is probably the best decontaminating method. Sodium sulfate (60 g) is an alternate agent for magnesium sulfate. Activated charcoal is probably not effective.

Enhancement of Elimination

Although barium is eliminated primarily through the feces, some case reports suggest renal replacement therapies (e.g., intermittent hemodialysis and continuous venovenous hemodialysis) improve clinical outcomes by aiding the stabilization of serum potassium concentrations; the contribution of enhanced barium elimination from hemodialysis remains unclear. A 22-year-old former chemistry student arrived at the emergency department with altered mental status, *torsade de pointes*, increased muscle tone, and a serum potassium concentration of 1.5 mEq/L.[98] He was treated with infusions of saline, potassium 10–30 mEq/L/hour, sodium bicarbonate, and magnesium sulfate. Ten hours after the presentation, his mental status improved, but he complained of muscle pain and weakness. Four hours of venovenous hemodialysis were associated with rapid resolution of his symptoms along with normalization

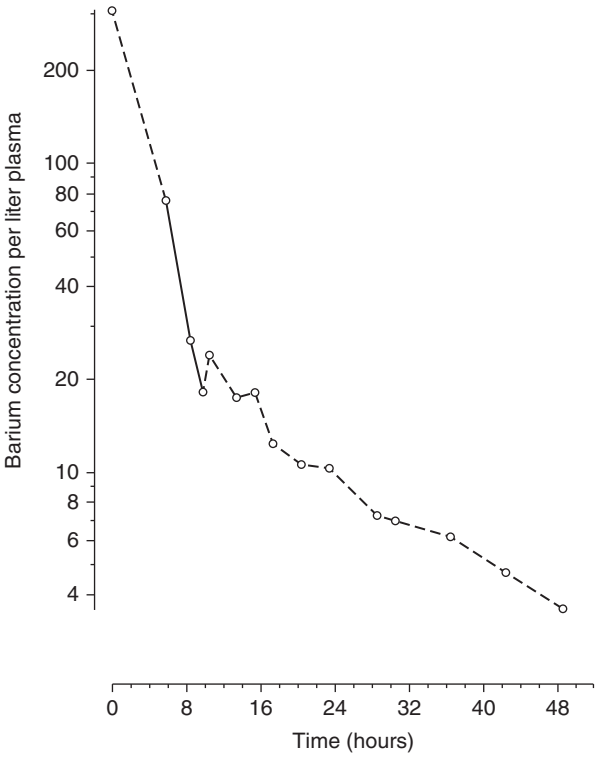


FIGURE 4.1. Plasma barium concentrations in a 22-year-old man after ingesting barium carbonate dissolved in hydrochloric acid. The patient was admitted to the hospital ($t = 0$) about 2 hours after ingestion. The solid line represents the plasma barium concentration during hemodialysis (200 mL/minute) using inductively coupled plasma/optical emission spectroscopy. The dashed line before hemodialysis is the estimated plasma barium concentration before the first measurement, whereas the dashed line after hemodialysis represents the barium concentration measured up to 48 hours after hemodialysis. The approximate plasma barium half-life during hemodialysis was 1.9 hours compared with 18 hours for the half-life after hemodialysis. (Adapted from Schorn et al.).[100]

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of his serum potassium and a substantial reduction in his serum barium concentration. Another case report described the rapid improvement in muscle strength and mental status following the use of hemodialysis (dialysate potassium concentration, 4 mEq/L) 3 days after admission.[99] Her serum potassium concentration increased from admission (1.1 mEq/L) to 4 mEq/L following an IV potassium infusion. However, her respiratory failure and profound weakness persisted until the completion of hemodialysis and concomitant reduction in her serum barium concentration.

Although several case reports describe reductions in serum barium concentrations during dialysis, few pharmacokinetic data document barium clearances during hemodialysis. A 22-year-old man arrived at the emergency department 1.5 hours after ingesting barium carbonate dissolved in hydrochloric acid.[100] Hemodialysis began ~7 hours after ingestion with the dialysate containing sodium bicarbonate and 4 mEq/L potassium. As displayed in Figure 4.1, the serum barium half-life during hemodialysis was 1.9 hours compared with a terminal half-life of ~18 hours. The use of continuous venovenous hemodiafiltration during acute barium intoxication reduced the elimination half-life of barium to 6 hours with an ~3-fold increase in the clearance of barium compared with renal elimination.[101] A potential application of hemodialysis in severe barium poisoning is the correction of hypokalemia by the use of high potassium doses in the dialysate (e.g., double the normal dialysate potassium concentration or 7 mEq/L) in the dialysate, particularly in patients with renal dysfunction. Careful monitoring of serum potassium concentrations is necessary in these patients.

Supplemental Care

The mainstay of treatment is the stabilization of vital signs and the aggressive treatment of hypokalemia. Large potassium doses of oral and intravenous potassium may be necessary immediately to correct hypokalemia in patients with severe barium poisoning.[102] Within the first 19 hours of treatment, a 24-year-old man, who intentionally ingested a Ba-containing facial depilatory, received 260 mEq IV potassium; his serum potassium concentration increased from 2.7 mEq/L at admission to 3.9 mEq/L 19 hours after admission.[57] A 30-year-old Ba-intoxicated patient with a markedly widened QRS received 240 mEq/L of IV potassium over 7 hours; his serum potassium increased to 2.0 mEq/L and his ECG normalized.[72] After 4 hours of hemodialysis, he was extubated and his muscle weakness resolved. Monitor the electrocardiogram, the cardiac rhythm, and the serum potassium closely over the first 24 hours.[54] The administration of potassium and continuing barium elimination may cause rebound hyperkalemia;[75] patients generally tolerate mild hypokalemia in the setting of barium poisoning because of the protective effects of barium on cardiotoxicity.[29] Administer generous amounts of fluid replacement while monitoring the urine and serum for evidence of renal failure.

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Chapter 5

BERYLLIUM

HISTORY

The French chemist, Vauquelin, discovered beryllium in 1798 while synthesizing beryllium hydroxide. Both Wohler and Bussy isolated the metal in 1828; the latter named the metal glucinium because of the sweet taste of its salt.[1] Commercial production did not begin in the United States until the recognition of the usefulness of beryllium in weapons production, fluorescent lighting, nuclear energy, and aerospace in the 1930s. Beryllium is the lightest among the solid, chemically stable elements with special properties (e.g., extremely hard, nonmagnetic, high electric and thermal conductivity, radiotranslucent) beneficial to modern technology. In 1933, the first medical reports of acute pneumonitis secondary to beryllium exposure appeared in the German literature.[2] The first major use for beryllium in the United States was the production of phosphors (beryllium phosphorus) in fluorescent lighting. During World War II, the first reports of acute chemical pneumonia in US workers extracting beryllium oxide were published.[3] Many cases of acute and chronic lung disease occurred among workers in the early fluorescent lighting industry. The use of beryllium in the fluorescent lighting industry ceased in 1951.

Chronic exposure to beryllium causes a chronic granulomatous pulmonary disease in a small percentage of sensitized, beryllium-exposed workers that is similar to sarcoidosis and miliary tuberculosis.[4,5,6] The term Salem sarcoid was applied to the granulomatous lung disease that appeared in fluorescent lighting manufacturing workers in Salem, Massachusetts.[7,8] Subsequently, Hardy discovered inhaled beryllium as the cause of this disease. The Salem workers also developed granulomatous skin lesions and acute contact dermatitis from exposure to soluble beryllium salts.

In the 1940s, beryllium was used during the development of nuclear weapons and nuclear power.[9] An acute pneumonitis appeared in US workers refining beryllium. Beginning in 1947, chronic beryllium disease developed in some residents living near beryllium production facilities and some family members of beryllium workers, presumably as a result of para-occupational exposure to beryllium-contaminated clothing.[10,11] Implementation of the 1949 recommendations of the Atomic Energy Commission concerning work practices, air concentrations, emissions, and ventilation systems drastically reduced cases of granulomatous disease associated with occupational and environmental exposure to beryllium. Between the 1960 and the early 1990s, only one case of chronic beryllium disease was reported following nonoccupational exposure to beryllium.[12]

In 1951, Harriet Hardy established the US Case Register (for beryllium disease) in Boston. The National Institute for Occupational Safety and Health (NIOSH) now manages this case registry, and the registry now contains over 800 cases.[13] A similar registry in the United Kingdom contains about 60 cases.[14] Exposure of earlier workers to dust and fumes of various beryllium compounds (oxides, fluoride, sulfate) occurred during extraction and fabrication of beryllium, whereas the majority of beryllium exposures in the current work environment occur in industries that fabricate or machine beryllium-containing alloys.[15] Current uses include alloys for space exploration, military equipment, electronics, and nuclear reactors.[16,17] Although

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improved work practices and environmental controls have markedly decreased the number of cases of chronic beryllium disease, genetic susceptibility and prolonged Be exposure increase the risk of Be sensitization and chronic beryllium disease in manufacturing processes using beryllium (e.g., beryllium oxide ceramics, nuclear weapons production facilities).[18,19]

PHYSIOCHEMICAL PROPERTIES

Beryllium is an odorless, nonmagnetic, corrosion-resistant metal that possesses the lowest thermal neutron adsorption cross-section of any metal. This strong, lightweight metal has several attractive physiochemical properties including radiotransparency, electrical conductivity, corrosion resistance, and the generation/reflection of neutrons. The stability, exceptional strength, and heat-absorbing properties allow many technological applications. Physicochemical properties affect the toxicity of beryllium ions. Case reports associate acute beryllium disease with exposure to high doses of low-fired beryllium oxide, but not exposure to high-fired (1,540°C) beryllium oxide.[20]

Pure beryllium is a brittle, steel-gray metal that possesses unique properties as the fourth-lightest element in the periodic table. The brittleness of this stiff metal allows the spread of insoluble Be particles during the machining and other beryllium processes. Beryllium occurs naturally only as the ^{9}Be isotope. The physical properties of low absorption of neutrons and high-scattering cross-section favor the use of beryllium as a moderator and reflector of structural material in nuclear plants. Low density along with resistance to oxidation, strength, and high modulus of elasticity produces beryllium alloys that resist high centrifugal forces. However, most alloys contain beryllium concentrations of ~3–4% because of the brittleness of beryllium compounds and the low solubility of most elements in beryllium. The exception is lockalloy (62% Be, 38% Al).

There are two oxidation states, Be^{0} (metallic) and Be^{2+} (divalent). The chemical properties of beryllium and aluminum compounds are similar including a high affinity for oxygen that provides corrosion resistance. The solubility and size of beryllium particles probably affect the risk of developing beryllium sensitization and chronic beryllium disease.[21] Metallic Be is not soluble in water at neutral pH. Water hydrolyzes cationic beryllium salts to form insoluble hydroxides or hydrated complexes at physiological pH of 5–8, but at pH >8 more soluble beryllate salts form. Most beryllium salts (e.g., oxide, carbonate, anhydrous sulfate, hydroxide) are practically insoluble in water, whereas water-soluble beryllium salts include chloride, fluoride, nitrate, phosphate, and sulfate (tetrahydrate). Beryllium salts are odorless. At physiological pH (7.2), beryllium ore materials and beryllium hydroxide are more soluble than beryllium oxide and metallic beryllium. Table 5.1 lists the identifying information and physical properties of beryllium and beryllium compounds.

TABLE 5.1. Identifying information and physical properties of metallic and divalent beryllium. (Based on WHO).[1]

Property	Be	BeF_2	$Be(OH)_2$	BeO	$BeCl_2$	$BeSO_4$	$BeCO_3$
Synonym	Metallic beryllium	Beryllium fluoride	Beryllium hydroxide, dihydroxide, or hydrate	Beryllium oxide or monoxide	Beryllium chloride or dichloride	Beryllium sulfate	Beryllium carbonate (basic)
CAS RN	7440-41-7	7787-49-7	13327-32-7	1304-56-9	7787-47-5	13510-49-1	13106-47-3
Valence	0	2	2	2	2	2	2
Molecular weight (g/mol)	9.012	47.01	43.03	25.01	79.92	105.07	112.05
Color	Gray	Colorless	White	White	Colorless	Colorless	White
Physical state	Solid hexagonal	Glassy, hygroscopic mass	Amorphous powder or crystalline solid	Amorphous powder	Needles	Tetragonal crystals	Powder
Melting point (°C)	1,287–1,292	555	Decomposes with heat	2,508–2,547	405	550–600 (decomposed)	No data
Density (g/mL)	1.846	1.986	1.92	3.016	1.899	2.443	No data
Water solubility (mg/L)	Insoluble	Very soluble	3.44	Very sparingly	Very soluble	Insoluble	Insoluble

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.

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EXPOSURE

The principal source of beryllium exposure for the general population is the combustion of fossil fuels, particularly near power plants that burn coal containing high Be concentrations. The highest risk of Be exposure occurs in individuals involved in the manufacturing, fabrication, or reclamation of beryllium. Most studies of workers in these industries involved exposure to materials containing relatively high beryllium concentrations (i.e., 20–65 wt%); however, most beryllium alloys currently contain <4% beryllium (e.g., commercial wrought copper–beryllium) with the exception of lockalloy. As a result of improved work practices and better control of emissions, people living near beryllium-emitting industries have only a slightly increased risk of developing diseases related to Be exposure. Smokers may inhale high concentrations of beryllium depending on the source of the tobacco. Smoking may triple the daily consumption of beryllium.[22] Some mantles from camping lanterns contain high concentrations of beryllium nitrate that volatilize within the first 15 minutes of igniting.[23]

Commercial Processes

The United States is the leading producer of beryllium ores and consumer of Be products.[15] Mining of beryllium occurs primarily from naturally occurring silicates (bertrandite, beryl ore). Production in the United States occurs only in Utah via the SX-carbonate process from bertrandite ($4BeO_2SiO_2\ H_2O$, 15% Be by weight). The United States imports beryllium from Argentina and Brazil, where the main beryllium silicate ore is beryl ($Al_2Be_3Si_6O_{18}$, 5% Be by weight).[24] Byproducts of metallic beryllium production from beryllium-containing ores include beryllium carbonate, tetrahydrate sulfate, and hydroxide. Beryllium sulfate results from the leaching of the ore with sulfuric acid; then, aqueous ammonium carbonate converts the beryllium sulfate to basic beryllium carbonate. The subsequent heating of beryllium carbonate yields beryllium hydroxide, beryllia (starting material for the production of the metal), and beryllium alloys. The arc furnace method is used to form beryllium-copper alloy by reducing beryllium oxide with carbon in the presence of molten copper.

Two other commercial methods called the fluoride and sulfate processes convert the commercial ore, beryl ($Be_3Al_2Si_6O_{18}$), to beryllium hydroxide. The sulfate process involves the alkaline or heat processing of beryl with the addition of strong sulfuric acid, while the fluoride process involves the sintering of beryl with sodium silicofluoride or sodium fluoroferrate and the leaching of the solution with caustic soda. The consumption of beryllium has been decreasing since 1987 because of decreased demand in the defense and aerospace industries as well as concern about the potential health hazards.[1] Examination of the ambient air during beryllium machining operations indicates that >50% of the particles in the breathing zone of the workers are >10 μm in aerodynamic diameter.[25] Using a personal impactor, this study demonstrated median time-weighted beryllium averages ranging from 0.13 $\mu g/m^3$ in lapping processes to 0.74 $\mu g/m^3$ in deburring operations.

Uses

Industrial uses of beryllium involve primarily free metals, beryllium alloys, and beryllium oxide. Beryllium-copper and other alloys account for ~75–80% of Be production as a result of favorable commercial properties (e.g., good electrical/thermal conductivity, high strength and hardness, corrosion/fatigue resistance, non-magnetic, non-sparking).[15] The addition of 2% Be to copper substantially increases the strength of the alloy without reducing thermal or electrical conductivity. Bauxite is the principal source of aluminum, and these aluminum-bearing rocks contain variable amounts of beryllium depending on the source. Emissions from the pot used in the aluminum smelting process may contain beryllium, but the sensitization rate of aluminum smelter workers to beryllium is low compared with beryllium-exposed workers in other industries.[26] Beryllium exposure may occur in industries that do not produce or process this metal including the following: 1) abrasive blasting operations using Be-containing coal or copper slag; 2) welding of specialized Be-copper or other Be-containing electrodes/fluxes; 3) fabrication of Be alloys; or 4) recycling of Be-containing metals.[27] Workers at risk of developing Be sensitization include work involving Be metal production, melting and casting Cu-Be alloy, processing Be-containing rod and wire products, ceramics production, machining Be, Be metal production, and analytical laboratories using Be.[28] Beryl is a gemstone (green emerald, light blue aquamarine, yellow beryl). Beryllium phosphate has no commercial uses. Table 5.2 lists the common uses of specific beryllium compounds.

Sources

Human exposure to beryllium occurs primarily in the workplace. Machinists working directly with beryllium

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TABLE 5.2. Commercial uses of metallic beryllium, beryllium alloys, and beryllium oxide. (Based on WHO).[1]

Form	Uses
Metallic Be	Aircraft disc brakes, turbine rotor blades, space vehicles optics and instruments, heat shields, aircraft/satellite structures, missile guidance systems, nuclear reactor neutron reflectors, nuclear warhead triggering devices, nuclear fuel elements, precision instruments, rocket propellants, navigational systems, mirrors, high-speed computers, audio components, X-ray transmission windows
Be-copper alloy	Aircraft engine parts, springs; high-frequency electrical connectors and relays; precision instruments; bushings and bearings in aircraft and heavy machinery; non-sparking tools; submarine cable housing and pivots; wheels and pinions; switches in automobiles; molded plastics; radar; telecommunications; factory automation; computers; home appliances; instrumentation and control systems; tubing in oil and drilling equipment; connectors for fiber optics; and integrated circuits
Be-aluminum alloy	Aircraft and spacecraft construction material
Be-copper-cobalt alloy	Nozzles for gas/oil burners, electronics (springs, switches, contacts, electrodes), bushings, bearings, soldering iron tips
Be-nickel alloy	Aircraft and spacecraft parts, glass molding, diamond drill bits, springs, electrical connectors
Be-nickel-chromium alloy	Crowns and bridges as an alternative to gold
Be oxide	High-technology ceramics, nuclear reactor components, electronic heat sinks, electrical insulators, substrates for high-density electrical circuits, gyroscopes, military vehicle armor, rocket nozzle crucibles, gas lantern mantels, microwave oven components, thermocouple tubing, laser structural components, automotive ignition systems, radar electronic countermeasure systems

metals and alloys are particularly susceptible to developing beryllium sensitization.[29] The general population typically is exposed to trace amounts of beryllium in ambient air, food, and water.

Air

The emission of beryllium from natural sources (volcanic particles, windblown dust) is small compared with the emission from man-made sources. The combustion of coal (average Be content 1.8–2.2 μg/g) in power plants represents the major source (i.e., ~95%) of man-made Be emission.[22] Other anthropogenic sources include metal fabrication, beryllium oxide production, municipal waste combustion, and ore processing. Beryllium enters the atmosphere as beryllium oxide. Potential sources of local elevated ambient Be concentrations include beryllium extraction plants, ceramic plants, foundries, incinerators, machine shops, municipal waste incinerators, propellant plants, and rocket-motor test ranges.

The annual average Be concentration in rural ambient air in the United States is typically nondetectable (<0.03 ng/m^3). Beryllium concentration in urban air is usually higher due primarily to the burning of coal and fuel oil; between 1982–1992, the average annual ambient air concentration of Be in Detroit, Michigan, ranged from 0.02–0.2 ng/m^3 with a median atmospheric Be concentration of ~0.2 ng Be/m^3.[15]

Soil

This metal exists in nature as a component of coal, oil, soil, rocks, and volcanic dust rather than as a pure metal. Beryllium is an uncommon element in soil, present in variable concentrations with average Be soil concentrations of 0.6 mg/kg in the United States,[15] compared with ~2.5–5 mg/kg soil and a range up to 40 mg/kg worldwide.[1,30] The Be concentration usually increases with the increasing content of silica and alkali. Although Be binds strongly to fulvic acid in the soil, beryllium has a stronger affinity for aluminum in clay than iron oxides and most organic materials. The most important source of environmental exposure to beryllium is the burning of coal, typically at concentrations of 100 mg Be/kg coal. Both coal ash and municipal waste ash present in landfills constitute a major source of beryllium in the environment.[15]

Water

The Be concentration in surface waters is in the low ng/L range with the concentration in seawater ~10 times less (i.e., <0.5 ng/L). Anthropogenic sources of beryllium in surface water are primarily the discharge of industrial wastewater effluents. The geometric mean of total beryllium in US surface water is usually <70 ng Be/L. Only 5.4% of the samples of US drinking water contained beryllium concentrations of >10 ng/L; the

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mean beryllium concentration in the positive samples was 190 ng/L.[31] In a review of analytical studies of US tap water, the mean Be concentration was ~13 ng/L (range, 10–70 ng/L)[32] compared with <10 ng/L (LOD; range, <10–20 ng/L) in 18 samples of domestic mineral water.[33] Within the pH range (4–8) typically present in the environment, the strong absorption of beryllium into finely dispersed sediment limits the migration of beryllium into groundwater. In general, the bioconcentration of beryllium in plants and animals is low.[15] Existing data suggest that significant bioconcentration of Be in water by aquatic species does not occur.[34]

Diet

There are limited data on the total daily Be intake in the general population. The estimated daily intake of Be in nonsmoking adults ranges from 5–100 μg with the primary source being food (root, tuber, forage crops on acidic soil); typical Be concentrations range from <1– to ~20 μg/kg fresh weight.[32] In a Japanese study of hospital diets, the average daily Be intake was ~84 μg as measured by inductively coupled plasma mass spectrometry.[35] Most plants absorb only small amounts of beryllium from the soil with little Be translocation (i.e., <25 μg/kg fresh weight) to edible parts of the plant. Foods with the highest Be content include kidney beans, crispbread, peas, parsley, and pears.[15] Biologically significant biomagnification of beryllium in plants and animals probably does not occur because the bioconcentration factor is <1,000; limited data suggest this value for beryllium ranges from 19–100.[15]

Lifestyle

Beryllium is a minor constituent of cigarette smoke in some samples with yields in mainstream smoke ranging from nondetectable to 0.0005 μg/cigarette in a review of 12 analytical studies; 8 of these studies had nondetectable quantities of beryllium in mainstream smoke.[36] The source of the beryllium is unclear; there are inadequate data to determine the quantity of beryllium present in commercial mainstream cigarette smoke.

ENVIRONMENTAL FATE

Air

Beryllium enters the atmosphere primarily as beryllium oxide particles. Most of these particles have a mean mass aerodynamic diameter of <2.5 μm; and therefore, the atmospheric life of these particles is short (i.e., about 10 days).[37]

Soil

The reaction of beryllium in soil includes hydrolysis of soluble salts, complexation with ligands (e.g., humic substances), and anion exchange (e.g., sulfate to carbonate). There are little data on the biotransformation of beryllium in soil. In general, beryllium adheres tightly to most types of soil.[30] The common beryllium silicates are highly insoluble in aqueous solutions and relatively resistant to weathering.

Water

The mobility of beryllium in water is low; however, water-soluble complexes of hydroxides form with beryllium at high pH, increasing solubility and mobility. Most beryllium in the aqueous environment is bound either to suspended matter or sediment. Little beryllium is dissolved in natural waters, except in acidic, organic-rich continental river waters.[24] The estimated residence time of beryllium in the ocean is a few hundred years. Most reactions in water involve the conversion of one beryllium salt to another. Hydrolysis of soluble beryllium salts produces beryllium hydroxides that are relatively insoluble at the pH of most natural waters.

DOSE EFFECT

Most of the information relating to dose-response in humans results from observing the effect of the inhalation of beryllium salts in the work environment. Although very little information is available on the dose-response of beryllium following ingestion, the oral route is probably not a significant route for the development of beryllium-associated disease.

Acute Toxicity

Inhalation of beryllium salts (fluoride, sulfate, chloride, oxide, hydroxide) or metallic dust in concentrations of >25–100 μg Be/m^3 may produce acute respiratory symptoms in workers ranging from irritation of the mucous membranes in the nose and throat to acute bronchitis and chemical pneumonitis.[10,38] Almost all

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workers develop these acute respiratory symptoms at Be concentrations of >1 mg/m^3; these acute symptoms are absent at Be concentrations of <15–25 μg Be/m^3. Although the vast majority of patients recover completely after an acute exposure, animal studies suggest that symptoms of chronic beryllium disease may appear years after a high-dose, acute exposure.[39]

Chronic Toxicity

The prevalence of chronic beryllium disease has declined dramatically since the implementation of an occupational exposure standard of 2 μg Be/m^3; however, significant variability occurs in the latency and the dose-effect relationship of this disease. Although there is currently no consistent association between mean, cumulative, and peak Be exposure and beryllium sensitization and/or chronic beryllium disease, respiratory disease is unlikely following Be exposure of <0.03–0.2 ng/m^3 in ambient air.[15]

Pregnancy may be a risk factor because a majority of the fatal cases in females listed in the US Beryllium Case Registry were pregnant. Cross-sectional studies suggest that beryllium sensitization may occur in a few individuals at mean ambient air concentration of <2 μg Be/m^3, particularly in jobs that involve short-term exposure (i.e., 1 year) to relatively high peak Be concentrations in air.[40] Five cases of chronic beryllium disease occurred among workers exposed to beryllium oxide fumes at a precious metals refinery from 1972–1985.[41] Four of these individuals worked in the furnace area, where the mean Be concentration in time-weighted-average personal air samples collected during 2 weeks in 1983 was 0.52 μg/m^3; however, this cross-sectional analysis of air samples may or may not reflect past or recent beryllium exposure of these workers. Consequently, the current occupational standards may not protect all workers from sensitization and the potential to develop beryllium disease.[1] A study of beryllium workers in a beryllium-copper alloy manufacturing plant did not detect sensitization to beryllium below airborne beryllium concentrations of 0.01 μg/m^3 based on the lymphocyte proliferation test.[42]

TOXICOKINETICS

Absorption

Inhalation is the primary route of exposure to beryllium with the amount absorbed depending on dose, solubility, and particle size; the upper airways filter particles of >5 μm, whereas particles 0.5–5 μm reach the alveoli. The mean mass median aerodynamic diameter of Be particles in various operations of a Be extraction and processing plant was 5.0–9.5 μm as collected by an 8-stage impactor and measured by electrothermal atomic absorption spectrometry;[43] the estimated alveolar Be deposition was 3–5% for nasal breathing and 9–13% for mouth breathing based on the International Commission on Radiological Protection lung model. However, other factors (e.g., beryllium speciation, particle size, surface area) besides airborne Be mass may affect the risk of developing chronic beryllium disease (CBD).[44]

Although few human data are available, animal studies suggest that the lungs retain and slowly adsorb beryllium.[45] The residence time of insoluble Be compounds (e.g., metallic Be) may be years based on the presence of Be in the lungs years after exposure ceases.[15] The gastrointestinal tract poorly absorbs beryllium; animal studies suggest that <1% of an ingested dose crosses the epithelium of the gastrointestinal tract.[46] Dermal absorption of beryllium through intact skin probably contributes little to the total body burden of beryllium unless Be contaminates ulcerated skin.

Distribution

Most beryllium in the blood circulates as a colloidal phosphate rather than as citrate or hydroxide salts. Following inhalation, long-term storage of beryllium occurs in lung tissue, particularly in pulmonary lymph nodes. Most of the retained beryllium eventually deposits in the skeleton. Substantial variation exists in the beryllium concentration between patients with similar exposure; there are more patients with high body burdens of beryllium and no disease than patients with chronic beryllium disease.[47]

Elimination

Although beryllium and beryllium salts are not biotransformed, animal studies suggest that the partial conversion of one salt to another may alter the water solubility of the beryllium compound.[45] Following ingestion, most of the beryllium appears in the feces because of the poor oral absorption of beryllium. The kidney excretes most of the absorbed beryllium in urine. The biological half-life of beryllium following inhalation in a group or by workers exposed to beryllium dust ranged from 2–8 weeks.[48] The residence time of beryllium in the lung lasts up to several years depending on the solubility of the beryllium salt. Animal studies indicate that the ionized soluble forms of beryllium (e.g., citrate) leave the lung rapidly (4 days), whereas non-ionized soluble forms have rapid (1–60 days) and slow (0.6–2.3 years) phases of elimination.[49]

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HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

The lung is the primary target organ for beryllium toxicity following inhalation. The role of dermal exposure in beryllium sensitization remains undefined.[50] Two types of pulmonary disease result from the inhalation of beryllium dust and salts: an acute chemical pneumonitis and chronic interstitial granulomatous lung disease. The acute form of the disease probably results from the direct cytotoxic injury caused by exposure to high Be concentrations. Beryllium is a potent inhibitor of phosphorylated enzymes (e.g., alkaline phosphatase). A suspected mechanism for the acute effects of beryllium involves the impairment of key protein phosphorylation. Beryllium probably combines with un phosphorylated enzymes and interferes with the competition of magnesium for these enzymes.[51] Fibrosis is not necessarily a consequence of an acute inflammatory response to beryllium.

An immune reaction to the inhaled beryllium causes chronic beryllium disease (CBD) following the deposition and long-term retention of beryllium in the lungs. The number of antigen-specific T cells (Be-responsive CD4+ T cells) in the blood increases during the transition from Be sensitization to CBD.[52] Following the accumulation of Be-responsive CD4+ T cells in the lungs, granulomas form from cytokine release. Exposure to Be triggers T cell proliferation in these granulomas from the production and release of proinflammatory T helper 1 (Th1) type cytokines (e.g., tumor necrosis factor-α, γ-interferon, interleukin-2).[53] Subsequently, chronic lung inflammation and slowly progressive pulmonary fibrosis develop.

In these patients, beryllium probably acts as a hapten that binds to proteins and peptides in the lungs, resulting in the beryllium–peptide becoming physically associated with a major histocompatibility complex (MHC) Class II molecule. The T cell contains a receptor (T cell antigen receptor) that recognizes the MHC Class II-beryllium–peptide complex; along with CD4+ cells, these T cells produce cell proliferation through the production of lymphocyte growth factor (interleukin-2) and accumulation of beryllium-specific CD4+ (helper/inducer) cells.[54] Special antigen-presenting cell surface molecules (coded by the *HLA-DPB1* gene) facilitate the recognition of beryllium by the T cells.[55] The transition of T cells from a central memory to an effector memory phenotype characterizes the development of chronic beryllium disease (noncaseating granulomas, fibrosis). After T cell activation, the accumulation of inflammatory cytokines (IFN-γ, TNF-α, IL-2, IL-6, IL-10) along with macrophages and activated T cells perpetuates the granulomatous inflammation.

Susceptibility to Be sensitization and chronic beryllium disease has a genetic component; a substantial number of these individuals have the human leukocyte antigen (*HLA*) Class II marker, HLA-DPB1 E69. However, the risk of beryllium sensitization is multifactorial as not all patients with beryllium sensitization have known a HLA mutation. This susceptibility may result from polymorphisms in HLA-DPB1 and DRB1 alleles that cause overrepresentation of HLA-DPB1 alleles with glutamic acid at position 69 of the β chain (E69) as well as polymorphisms in cytokines (*TGF-β1*) and interleukin genes (*IL-1A-1142*, *IL-1A-3769*, *IL-1A-4697*).[56,57] The non-*02 E69 alleles and E69 homozygotes are associated with increased odds for beryllium sensitization and CBD compared with *02 alleles and E69 heterozygotes, respectively. In a study of 386 US workers in a nuclear weapons facility, any E69 carriage increased the odds of developing CBD.[19] Compared with E69 negative genotypes, a single E69 positive *02 allele increased the odds for beryllium sensitization (OR = 12.01, 95% CI: 4.28–33.71) and chronic beryllium disease (OR = 3.46, 95% CI: 1.42–8.43).

Of the 630 known DNA sequence variants of *HLA-DPBI*, 204 are *HLA-DPB1 E69* with at least 1/3 of the US population containing E69 marker. The prevalence of CBD increases substantially in Be workers with any 2 E69 alleles or an E69 allele with the most electronegative charge (i.e., −9) when compared with Be workers not having the E69 allele or only 1 E69 allele.[58] In the US population, the most common E69 allele is *02:01 with a surface charge of −7.[59] Genetic and other factors also affect Be sensitivity and progression to CBD because the prevalence of the supra-allelic E69 marker of genetic risk far exceeds the prevalence of Be sensitization and CBD and ~25% of workers with CBD do not carry the *HLA-DPB1 E69* gene variant.[60] E69 marker is a risk factor for beryllium sensitization, but not chronic beryllium disease; the large prevalence of E69 in the general population indicates the presence of E69 has a low positive predictive value for beryllium sensitization.[61]

Pathological Changes

The acute reaction of tissue to Be is a nonspecific inflammation similar to the reaction of tissue to other mucosal irritants.[20] Similarly, the hallmark of chronic reaction of tissue to Be exposure is a noncaseating epithelioid granuloma that is indistinguishable from

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similar lesions caused by extrinsic allergic alveolitis, sarcoidosis, and other forms of pulmonary inflammation associated with chronic granulomas.[62] Although granulomas may appear in different types of tissue including lymph nodes, spleen, liver, myocardium, kidney, and bone, chronic beryllium disease (CBD) is primarily an interstitial granulomatous disease of the lungs without extrapulmonary lesions.[63] A mononuclear cell interstitial infiltrate and varying degrees of fibrosis are usually present during the examination of lung biopsies of patients with CBD.

Beryllium is an unusual metal that produces cell-mediated immune responses. In animal models, the initial inflammatory response is indistinguishable from the histopathological changes caused by strong irritants.[64] Table 5.3 describes the four phases of histopathological changes seen in CBD. Phases II and III involve the formation of noncaseating granulomas in response to an immunological reaction to beryllium.

The pathological hallmark of chronic beryllium disease is the formation of non-necrotic epithelioid cell granulomas that are indistinguishable histologically from those seen in Crohn's disease, zirconium granulomas (skin only), extrinsic allergic alveolitis, tuberculosis, and sarcoidosis. These granulomas consist of closely-knit epithelioid histiocytes (transformed macrophages) cells with a collar of lymphocytes (predominantly CD4+ T cells), scattered plasma cells, and fibroblasts.[65] Eosinophils are not usually present in these granulomas. Rarely, other metals (aluminum,[66] titanium[67]) have been associated with the formation of noncaseating granulomas and hypersensitivity. The distribution of granulomas in the lung is similar to that of sarcoidosis (subpleural, interlobular septae, around bronchovascular bundles).

TABLE 5.3. Histological phases in chronic beryllium disease (CBD). (Kribel et al.).[9]

Phase	Histological Changes
I	Nonspecific inflammatory responses develop along with cellular exudation, emphysema, and obliteration of the normal lung architecture that may progress to fibrosis. Permanent changes may not occur following mild Be exposure.
II	"Foamy" macrophages appear that contain phagocytized Be particles. Peribronchial lymphoid tissue proliferates with lymphocytes visible in the intracellular septae and around Be particles.
III	Formation of granulomas with focal accumulation of macrophages, epithelioid cells, and multinucleated giant cells.
IV	Interstitial fibrosis occurs along with hyperplasia of alveolar septae.

The epithelioid cells contain a variety of cytoplasmic inclusion bodies.[68] Schaumann bodies are concentrically laminated spherules containing calcium and iron impregnated glycoproteins with central birefringent crystals.[69] The presence of Schaumann bodies in fibrotic lungs indicates the previous presence of granulomatous disease. Schaumann bodies are not pathognomonic for chronic beryllium disease (CBD); these lesions are often present in patients with sarcoidosis, less often in patients with tuberculosis or Crohn's disease, and rarely in patients with extrinsic allergic alveolitis.[68] The final phase is progressive, interstitial fibrosis that is characteristic of many pulmonary toxins. The prominence of alveolitis helps distinguish CBD from sarcoidosis and indicates a poorer prognosis.[63] Beryllium persists for many years in the lung granulomas from patients with CBD, even after occupational Be exposure ceases.[70] Most of the Be in the lungs of patients with CBD resides in the chronic lung granulomas, and Be concentrations in histologically normal lung tissue are similar in Be-exposed patients with and without CBD. The presence of high concentrations of beryllium in postmortem lung tissue helps confirm the diagnosis of CBD in the presence of clinical and radiological findings consistent with CBD. However, high concentrations of beryllium are not required for the diagnosis of CBD; high concentrations of beryllium may be present in lung tissue without CBD.[71]

CLINICAL RESPONSE

Beryllium is a cutaneous sensitizer and primary skin irritant that produces contact dermatitis, skin granulomas, and ulcers.[72] High Be concentrations cause inflammation and edema in the affected tissue including conjunctivitis and periorbital edema. Acute beryllium disease implies that the duration of illness is less than 1 year and that the disease involves inflammation of the skin, the respiratory tract, and the mucous membranes.

Acute Toxicity

Exposure to Be concentrations from 25–100 $\mu g/m^3$ causes a pneumonitis indistinguishable from other causes of chemical pneumonitis along with conjunctivitis, dermatitis, pharyngitis, and laryngotracheobronchitis.[73] Initial symptoms include dry cough and progressive shortness of breath with exertion. Diffuse bilateral alveolar infiltrates may appear on chest X-ray within a few weeks of the onset of symptoms consistent with chemical pneumonitis. The clinical course is often

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mild but may progress rapidly to death; some symptoms may persist over a year.[74] In contrast to chronic beryllium disease and sarcoidosis, the clinical features of acute beryllium disease and acute sarcoidosis (Löfgren syndrome) differ. The latter typically has a benign course that resolves in most patients in contrast to the occasional fulminant pulmonary disease culminating in cor pulmonale associated with acute beryllium disease. Additionally, some systemic effects (e.g., erythema nodosum, acute reactive arthritis, uveoparotitis) occur in sarcoidosis but not in acute beryllium disease.[75]

Environmental Exposure

Soon after the discovery of chronic granulomatous pulmonary disease (CBD) among beryllium manufacturing workers in the 1940s,[7] case reports from 1948–1969 documented the presence of a similar disease in residents of communities surrounding Lorraine, Ohio, associated with para-occupational and/or Be exposure in ambient air.[10] In 1959, a series of 21 cases of community-acquired chronic beryllium disease in residents without occupational Be exposure living up to 8 km from a beryllium facility was published.[76] Similar cases did not appear in the medical literature until a case series of five definite and three probable community-acquired CBD cases diagnosed from 1999–2002 living near a Reading, Pennsylvania, beryllium manufacturing and fabricating facility was published in 2008.[77] All these cases have been long-term residents since the 1950s. The lead author testified in court on behalf of the plaintiff community members.

Beryllium is a lightweight metal that occurs naturally in the soil at low concentrations as beryllium silicate. Extraction of Be salts from the soil and formation of metallic or ceramic Be is associated with beryllium sensitization and chronic beryllium disease; however, insufficient evidence associates these adverse effects with exposure to environmental Be silicates.[63]

Occupational Exposure

Lungs

Acute beryllium disease usually follows within several days of massive Be inhalation or within several weeks following prolonged exposure to high ambient air Be concentrations; resolution typically occurs within several months after cessation of beryllium exposure. Depending on the dose, duration, and type of exposure, signs and symptoms of acute beryllium disease in the lungs range from mucosal irritation to tracheobronchitis, chemical pneumonitis, and fatal noncardiogenic pulmonary edema.[78] Although almost all cases of acute beryllium disease occurred before 1950 as a result of beryllium concentrations (50–100 $\mu g/m^3$) exceeding current workplace standards, sporadic cases of acute beryllium disease still occur.[79] Large exposure to soluble beryllium salts (primarily fluoride) causes upper respiratory tract irritation (conjunctivitis, rhinitis, bronchitis), whereas exposure to the less soluble beryllium salts and oxide fumes produces chemical pneumonitis. Symptoms include progressive cough with sputum, dyspnea, substernal chest pain, malaise, anorexia, and cyanosis. Although most cases of acute beryllium disease recover without sequelae within 1–6 months, some individuals develop chronic beryllium disease years after an acute massive Be exposure.[80,81]

Skin

Cutaneous manifestations of Be exposure include contact dermatitis, dermal granulomas, and beryllium ulcers. Soluble Be salts (fluoride, sulfate, chloride, nitrate) can hydrolyze to free acids causing edema and contact dermatitis (papules, vesicles, pustules, eczematous lesions).[82] Workers exposed to vacuum-cast beryllium metal, pure beryllium metal, and beryllium hydroxide have not developed these skin lesions.[83] Symptoms usually begin within 1–2 weeks, suggesting a delayed allergic reaction. The introduction of either soluble or insoluble beryllium compounds underneath the skin through abrasions or lacerations produces nodular scars and chronic ulcerations. These lesions contain granulomas that are painless; the skin lesions usually appear several years after the introduction of beryllium into the skin.[84] In contrast to sarcoidosis, erythema nodosum is not associated with Be sensitization.

Chronic Beryllium Disease

Chronic beryllium disease (CBD) is a systemic granulomatous disease that is similar to sarcoidosis and principally affects the lungs, lymphatic system, and the skin of sensitized individuals (<15–20% of the exposed population).[15] Most exposed workers do not develop beryllium sensitization or chronic beryllium disease with the incidence varying widely across industries using beryllium. Involvement of organs outside the lungs does not usually occur without the presence of pulmonary lesions; with pulmonary disease, hepatic lesions occur occasionally and cardiac involvement is rare.[85] In contrast to sarcoidosis (e.g., erythema nodosum, uveitis), extrapulmonary manifestations of CBD are rare today.[86] The prevalence of granulomatous interstitial lung disease (CBD) in beryllium industry workers

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previously averaged ~1–3% with a prevalence of hypersensitivity ranging up to 20% in high-risk industries,[87,88] whereas currently the estimated prevalence of CBD ranges from 0–7.8% and Be sensitization of ~1–15%.[89] The vast majority of cases of CBD occur in the beryllium production industry (machining, lapping, forming, firing); however, rare cases of CBD have developed in workers exposed to copper-beryllium alloys containing Be concentrations as low as 2%.[90,91] In a cross-sectional survey of the latter group of workers, the prevalence of Be sensitization using the beryllium blood lymphocyte test was 1% in comparison to 0.9–10% for beryllium sensitization in workers from the beryllium production industry.[92] This disease may occur in workers at nuclear weapons facilities during the processes of decontamination or decommissioning.[93]

The prevalence of beryllium sensitization is low when the overall Be exposure is low (e.g., workers at conventional munitions facilities).[94] In a case-control study of workers at a nuclear weapons facility, logistic-regression analyses demonstrated a statistically significant relationship between CBD and measures of beryllium exposure (mean, cumulative), whereas Be sensitization was not directly associated with either mean or cumulative Be exposure.[95] Beryllium is a ubiquitous metal; sensitization may occur in new hires without known prior Be exposure.[96] Longer latency periods are associated with less severe disease.[97] Several studies of workers with CBD indicate smoking prevalence is lower in beryllium workers than without CBD.[29] In a cross-sectional study of 895 current workers at a nuclear weapons production plant, 17 workers (1.9%) had Be sensitization (consistently abnormal BeLPT results).[98] The beryllium-sensitized individuals did not significantly differ from the whole cohort in cigarette smoking status or pack-years; additionally, there were no differences in gender, age, history of atopic disease, prevalence of respiratory symptoms, spirometric abnormalities, or profusion of small opacities on chest X-rays.

Stages

Classification of chronic beryllium disease based on sensitive immunological techniques involves the following three stages: 1) beryllium sensitization (positive blood or lung Be lymphocyte proliferation test (BeLPT)) with no other laboratory evidence of disease; 2) subclinical chronic beryllium disease in asymptomatic, sensitized individuals with additional evidence of pathological abnormalities in the lung; and 3) clinical chronic beryllium disease.[99] Beryllium sensitization, as defined by a positive BeLPT result, can progress to chronic beryllium disease; however, not all sensitized individuals develop CBD. Individuals with subclinical chronic beryllium disease are sensitized to beryllium along with histological evidence of lung granulomas in the absence of clinical effects. Some impairment of lung function may be detectable in the absence of symptoms. Slight alterations in lung function during exercise were observed in ~60% of individuals with subclinical CBD; no other consistent alterations in lung function were found. The individuals with clinical CBD have Be sensitization, histological evidence of lung granulomas, respiratory symptoms, abnormal chest X-rays, and/or altered lung function. The disease may progress in the absence of continuing Be exposure.

Presentation

Manifestations of CBD are consistent with an allergic inflammation of the lungs that is associated with secondary changes in other tissues. Chronic beryllium disease usually develops from 10–20 years up to 40 years after the first Be exposure with the onset of symptoms typically ranging from a few months to 25 years.[38,100] The rate of progression from beryllium sensitization to CBD is highly variable, but the rate of sensitization and CBD increases with increasing cumulative exposure.[101] Patients with CBD typically present with nonspecific generalized symptoms or respiratory findings including weight loss, dyspnea, cough, chest pain, fatigue, malaise, night sweats, arthralgias, and cor pulmonale. Dyspnea on exertion is the most common presenting symptom. Physical features depend on the severity of the disease and include bibasilar crackles, hepatosplenomegaly, clubbing, lymphadenopathy, and, in severe cases, cor pulmonale and right-sided heart failure.[102] The cardiac effects probably result from a response to impaired lung function and cor pulmonale rather than a direct effect of beryllium on the heart.

Diagnosis

The combination of adequate Be exposure and evidence of beryllium sensitization (positive beryllium lymphocyte proliferation test) combined with histopathological features of noncaseating granulomas define CBD; however, this pathognomonic histopathological lesion is indistinguishable from similar lesions seen in sarcoidosis. In contrast to sarcoid, ocular involvement, parotid disease, and acute reactive arthritis are absent in chronic beryllium disease. Table 5.4 outlines the diagnostic criteria for beryllium-induced diseases. The route of exposure primarily involves inhalation, although other routes (oral, resuspension from clothing) may contribute to sensitization.[103]

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TABLE 5.4. Diagnostic criteria for beryllium-induced health effects. (Adapted from Maier).[100]

Diagnosis	Criteria	Tests	Abnormality
Beryllium sensitization	1. Beryllium sensitization	Blood BeLPT	Positive
	2. Histopathological evidence of CBD	Lung biopsy	None
Subclinical CBD	1. Beryllium sensitization	Blood BeLPT	Positive
	2. Histopathological evidence of CBD	Lung biopsy	Noncaseating granulomas, mononuclear cell infiltrate
	3. No respiratory symptoms or physiological abnormalities		
CBD	1. Beryllium sensitization	Blood BeLPT	Positive
	2. Histological evidence of CBD	Lung biopsy	Noncaseating granulomas, mononuclear cell infiltrate
	3. Clinical symptoms	History	Cough, dyspnea
	4. Physical abnormalities	Physical exam	Crackles
	5. Laboratory abnormalities	PFTs, exercise testing, ABG	Abnormal

Abbreviations: ABGs = arterial blood gases; BeLPT = beryllium lymphocyte proliferation test; CBD = chronic beryllium disease; PFTs = pulmonary function tests.

Carcinogenesis

The US Toxicology Program lists beryllium and beryllium compounds as known human carcinogens based on sufficient evidence of carcinogenicity from studies in humans. Several epidemiological studies of workers indicate a an increased risk (OR = 1.5–2) of lung cancer in workers exposed to beryllium.[104,105] A mortality study of 16,115 Be workers employed from 1925–2008 in seven facilities using soluble/mixed Be and eight facilities using insoluble Be compounds reported increased lung cancer mortality occurring predominantly in workers initially employed before 1955 in two soluble/mixed Be facilities (Lorain, Reading).[106] Be workers employed after 1955 or workers employed at any time in plants using only insoluble Be materials did not experience elevated lung cancer mortality rates.

A meta-analysis of six studies of US male Be workers employed in 1940–1969 and followed through 1988 demonstrated a mean SMR of 1.26 (range, 0.99–1.69) based on US national rates.[30] Interpretation of these studies is complicated by selection bias, confounding with other carcinogens (sulfur mists, cigarette smoking), limited exposure data, and accurate estimation of the expected number of lung cancer deaths. Some,[1] but not all,[107] reviews of these design flaws suggest that a significantly elevated risk of lung cancer probably does exist in cohorts of beryllium workers. A nested case control study of 142 lung cancer cases in beryllium workers associated cumulative, average, and maximum beryllium exposure with lung cancer after a 20-year lag.[108] The study did not adjust for birth year, and direct information on smoking was not available. Reanalysis of this study for the birth year (and presumably for the difference in smoking rates) demonstrated an association between average/maximum beryllium exposure and long-term cancer risk; cumulative beryllium exposure was not associated with a dose-related increase in the risk of lung cancer.[109] Information on smoking was incomplete in most of these studies; therefore, the data do not permit an evaluation of the effects of smoking and Be exposure. Data from the US Beryllium Case Registry suggest a 3-fold increased lung cancer mortality risk (95% CI: 1.0–6.2) for individuals with acute beryllium disease, but there was no statistically significant increased risk (95% CI: 0.1–3.7) in individuals with chronic beryllium disease.[110]

Following a review of beryllium carcinogenicity,[111] the IARC classified beryllium as a Group 1 compound (human carcinogen), in part because of the dose-related increased lung cancer incidence in a retrospective cohort mortality study among 9,225 male workers employed at 7 beryllium processing facilities for at least 2 days from 1940–1969[112] and a cohort mortality study on 689 patients from a case registry with beryllium disease.[113] In the former study, the standardized mortality ratio (SMR) for lung cancer in the total cohort was 1.26 (95% CI: 1.12–1.42), whereas the SMR for the latter study was 2.00 (95% CI: 1.33–2.89). Factors favoring the increased incidence of lung cancer in these cohorts included the following: 1) the highest risk occurred in plants with the highest rate of acute beryllium disease and individuals with acute beryllium disease; 2) workers hired before

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the 1950s had greater excess lung cancer risk and presumably the higher Be exposure; and 3) the consistent excess of lung cancer in most plant locations. The IARC noted several limitations of these studies including the low excess lung cancer risk, poor exposure data, and little adjustment of confounding variables (e.g., smoking); consequently, controversy remains regarding the interpretation of the results. Levy et al. recalculated the data from SMRs for lung cancer in the cohort study of 9,225 beryllium processing workers using city mortality rates rather than county or US rates along with a different indirect method for adjusting for smoking.[114] This reanalysis did not detect statistically significant increases in the incidence of lung cancer among beryllium workers. A subsequent pooled, cause-specific mortality study of 9,192 workers in 7 US Be processing plants demonstrated an increased standardized mortality ratio (SMR) for lung cancer of 1.17 (95% CI: 1.08–1.28). The standardized rate ratios (SRRs) for lung cancer were higher for higher quartiles of cumulative exposure lagged 10 years including the 2nd (1.56), 3rd (1.66), and 4th (1.97) quartiles. Reanalysis of this study indicated the lung cancer risk increased monotonically, but modestly, in the full cohort of three of these Be plants by tenure and most subgroups based on plant and date of hire; however, regression-based point-wise confidence bands did not clearly separate lung cancer risks for low- and high-Be exposure groups.[115] In animals, the development of lung tumors following exposure to beryllium is species-specific. Rats and monkeys are very susceptible, whereas rabbits, hamsters, and guinea pigs do not usually develop lung tumors.[1]

Reproductive Abnormalities

There are few human data on the reproductive and developmental effects of beryllium. Although animal data on these effects is limited, current data do not indicate that beryllium exposure at the current workplace or environmental concentrations causes adverse reproductive effects.

DIAGNOSTIC TESTING

SI Conversion Units

1 nmol/L = 9.012 mg: = 0.009 ng/mL
1 ng/L = 0.111 nmol/L
1 ng/g (blood) ≅ 1 ng/mL

Analytical Methods

Before the 1960s, analytical methods for the determination of Be in biological and environmental samples involved spectrometric, spectrophotometric, and fluorometric techniques. Subsequent use of gas chromatography/electron capture detection allows limits of detection (LOD) in the range of <1 ppb; however, the technique requires skilled technicians and the volatilization of Be to a derivative (e.g., trifluoroacetylacetone).[116] Current methods to measure airborne Be exposure analyze total mass per cubic meter of air by using size separation techniques and atomic absorption spectrometry; standard methods include both inductively coupled plasma/mass spectrometry (ICP/MS, NIOSH 7300 method) and graphite furnace atomic absorption spectrophotometry (GFAAS, NIOSH 7102 method). The limit of detections for these two techniques is 0.005 ppm and 0.03 ppm, respectively. Flame atomic absorption spectrometry and atomic emission spectrometry (AES) lack sufficient sensitivity to quantitate Be concentrations in biological media. High concentrations (500 mg/kg) of aluminum and silicon interfere with beryllium analysis by atomic absorption spectrometry; whereas high iron concentrations interfere with the 243.86 nm beryllium emission line used in ICP-AES.

Methods to evaluate the physiochemical properties of Be include Auger microscopy, scanning electron microscopy (SEM) coupled with X-ray energy-dispersive spectrometry (EDS), transmission electron microscopy (TEM) with EDS or electron energy loss spectroscopy (EELS), X-ray diffraction, and time-of-flight/secondary-ion mass spectrometry (TOF/SIMS) in positive mode. TEM is complementary to SEM as the former analyzes particles of <0.5 μm compared with ≥0.5 μm for the latter. In a study of dust collected by dry-grab sampling technique in four Quebec factories (aluminum smelter, magnesium processing, electrolyte processing, electrolytic pools treatment), only TOF/SIMS, ICP/MS, and GFAAS detected Be in the dust samples.[117] The advantage of TOF/SIMS was the determination of Be particle size distribution at low Be concentrations (<0.01%, range 58–146 ppm) and small particle size (mostly <10 μm).[118] These techniques did not determine the chemical speciation of the beryllium in the dust samples.

Biomarkers

Patients with CBD have an abnormal immune response to Be (lymphocyte proliferation test), and transbronchial biopsies demonstrate evidence of noncaseating granulomas or mononuclear cell interstitial infiltrate. The

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diagnostic criteria for classic chronic beryllium disease (CBD) include the following: 1) documented exposure to beryllium; 2) consistent clinical and radiographic features; 3) presence of granulomas; 4) evidence of beryllium in tissues; and 5) hypersensitivity to beryllium.[119] The finding of beryllium in granulomas from tissue is diagnostic of chronic beryllium disease. Laser microprobe mass spectrographic analysis allows the detection of beryllium in standard histological sections of granulomas in tissue with light microscopy.[120] Although some studies suggest a difference in the serum concentration of proinflammatory cytokines (IFN-γ, IL-2, IL-6, TNF-α),[121] upregulation of *CD55* or downregulation of *CXCL9*, the evaluation of proinflammatory cytokines with existing technologies (e.g., SELDI-TOF using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) remains challenging to differentiate chronic beryllium disease, beryllium sensitization, and sarcoidosis.[122] Blood and urine Be concentrations are not currently used as biomarkers of Be exposure.

Blood

Lymphocyte Proliferation Test

The blood or bronchoalveolar lavage from a vast majority of patients with chronic beryllium disease (CBD) demonstrates *in vitro* lymphocyte sensitization when challenged with Be salts; however, some patients with evidence of hypersensitivity may have only subclinical disease.[123] A confirmed abnormal beryllium lymphocyte proliferation test (BeLPT) without evidence of lung disease is diagnostic of beryllium sensitivity, whereas the presence of granulomatous inflammatory response in the lungs with an abnormal BeLPT is diagnostic of chronic beryllium disease. The BeLPT documents the beryllium-specific blast transformation of lung lymphocytes obtained either through peripheral blood or through bronchoalveolar lavage. The sensitivity of a single abnormal BeLPT is relatively low (i.e., 66–88%) and increases with repeat testing.[124] However, the BeLPT is highly specific with low false-positive rates of 1–3% and higher false-negative rates (~30%) depending on the prevalence of beryllium sensitization in the population.[125] Final reports typically involve four options (normal, borderline, abnormal, uninterpretable). A single abnormal result usually should be confirmed with an additional test to establish beryllium sensitization. The demonstration of two abnormal or an abnormal plus a borderline BeLPT minimizes the risk of false-positive results. Uninterpretable or borderline results require repeat testing with subsequent actions (e.g., continued surveillance, referral for clinical evaluation) depending on the results and individual patient factors.[126] Options for inconsistent results in highly suspicious cases include transbronchial biopsies and bronchoalveolar lavage for BeLPT cells.

A substantial portion of workers with a positive BeLPT develop CBD (e.g., 6–8%/year), but studies on the exact rate are inconsistent. In a study of 55 Be-sensitized workers, 17 (31%) developed CBD over a mean of ~4 years (range, 1–9.5 years) of follow-up.[127] The progression rate to CBD was 6–8%/year. Overall, low methodological quality on studies of Be-sensitized workers limits conclusions regarding the exact percentage of BeLPT-positive workers who eventually develop the disease.[128] Additionally, data on the percentage of sensitized workers who develop the disease despite cessation of Be exposure are limited. The BeLPT does not efficiently separate CBD from Be sensitization or predict the progression from Be sensitization to CBD. A study of Beryllium BioBank participants suggests consideration of the intensity and total hours of Be exposure as well as the absolute BeLPT (i.e., rather than positive/negative based on cut points) may improve the predictive value of this test for the development of CBD.[129,130]

The beryllium lymphocyte proliferation test on blood samples (30–40 mL blood in heparinized tubes and shipped to the laboratory within 30–48 hours) is the method of choice for the medical screening of workers for beryllium sensitization. Laboratories with substantial experience for detecting beryllium sensitization include National Jewish Health (Denver, Colorado) and the Oak Ridge Institute for Science and Education the (Oak Ridge, Tennessee). The use of bronchoalveolar lavage fluid is a more sensitive and specific test medium for the diagnosis of Be hypersensitivity than peripheral blood based on studies correlating the degree of blast transformation with the severity of the clinical disease;[131] the presence of a positive beryllium lymphocyte proliferation test on lavage fluid indicates CBD.[18,132] Substantial variation in the sensitivity of the blood lymphocyte transformation test occurs between different laboratories.[133] Slightly positive blood tests may occur in healthy workers with Be exposure and sensitization, but the clinical course of these patients remains variable. Borderline BeLPT results are usually repeated with split samples sent to two different laboratories. Beryllium patch tests historically were an alternate method to diagnose CBD in patients with equivocal blood tests;[134] however, the Be patch test is usually not used currently because of concern about the development of Be sensitization in Be-naïve individuals.[89] Table 5.5 compares the differential features of chronic beryllium disease, sarcoidosis, and extrinsic allergic alveolitis. Poor

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TABLE 5.5. Comparison of findings in chronic beryllium disease, sarcoidosis, and extrinsic allergic alveolitis. (Adapted from Jones Williams).[14]

Finding	Chronic Beryllium Disease	Sarcoidosis	Extrinsic Allergic Alveolitis
Occupational exposure	Yes	No	Yes
Beryllium in tissues	Yes	No	No
Erythema nodosum	No	Yes	No
Bilateral hilar adenopathy	Uncommon	Common	No
Bone cysts	No	3%	No
Skin tests			
Tuberculin	Negative	Negative	Unaltered
Kveim	Negative	Positive	Negative
Be lymphocyte transformation test	Positive	Negative	Negative
Circulating precipitins	No	No	Yes
↑ Serum angiotensin-converting enzyme	Not prominent	Common	Uncommon
Granulomas	Yes	Yes	Yes
Alveolitis	Prominent	Inconspicuous	Prominent
Prognosis	Poor	Good	Good

positive predictive value and ethical considerations limit the use of the HLA-DPB1E69 biomarker as a screening test.[135]

Beryllium Concentration

There are few data on blood beryllium concentrations. Typical background Be concentrations in blood are <1 ng/mL (ng/g). In a study of 10 subjects without known occupational exposure to beryllium, the mean serum Be concentration was 1.0 ± 0.4 ng/mL (ng/g) as measured by flameless atomic absorption spectrometry.[136] In a French study of 100 healthy adults, the 95% reference range for beryllium was below the limit of quantitation (0.10–0.14 µg/L) in whole blood and plasma samples as measured by ICP/MS.[137]

Urine

Background urinary beryllium concentrations in the general population is <1 ng/mL. In the Third National Health and Nutrition Examination Survey (NHANE-SIII) of the US population, most urine samples from >5,000 participants contained nondetectable beryllium concentrations (95% CI: <0.13 ng/mL).[138] Similarly, the beryllium concentration in urine samples from 100 healthy French volunteers was below the limit of quantitation (0.05 µg/L) in almost all subjects.[137] A study of 496 US residents without known exposure to beryllium detected urine Be concentrations in 67% of these residents with a mean Be concentration of 0.28 ng/mL (0.22 ng/g creatinine) and an upper 95% limit of 0.79 ng/mL (0.62 ng/g creatinine) as measured by inductively coupled argon plasma mass spectrometry and Zeeman graphite furnace atomic absorption spectrometry (LOD, 0.1 ng/mL).[139] In a study of 10 men without known occupational exposure to beryllium, the urine from smokers of nonfiltered cigarettes contained substantially higher serum Be concentrations (2 ng/mL) than the mean (0.9 ± 0.5 ng/mL) of all subjects as measured by flameless atomic absorption spectrometry.[136]

Abnormalities

Imaging

Beryllium is radiolucent. The classic radiographical feature of chronic beryllium disease is an interstitial disease (i.e., nonnecrotizing granulomas) consistent with a predominant upper lobe fibronodular process (small, round, and reticular opacities) and hilar adenopathy with radiographical abnormalities usually lagging behind the development of symptoms and physiological impairment.[140] Radiographical examinations typically reveal opacities in the lung following chronic Be exposure. There are three radiographical stages of chronic beryllium poisoning as follows: 1) fine diffuse granularity in the lungs; 2) diffuse reticular pattern; and 3) appearance of distinct nodules and honeycombing.[141] Other abnormalities include diffuse, bilateral reticular opacities, and honeycombing. The hilar adenopathy typically is mild, bilateral, and associated with parenchymal changes (linear scars).[142] Typically, the hilar adenopathy

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is less prominent in CBD than sarcoidosis.[143] Radiographical imaging of the chest is similar in CBD and sarcoidosis.

Pulmonary Physiology

Pulmonary function testing is not a reliable screening test for CBD. Although most epidemiological studies of beryllium workers have not demonstrated decrements in pulmonary function,[4,81,141] a recent cross-sectional study found small decrements in pulmonary function after long-term Be exposure. In this study, a cumulative exposure of 100 μg Be/m^3/year (i.e., 50-year exposure to the current TLV–TWA of 2 μg Be/m^3) was associated with a decrease of 220 mL in the FVC and 150 mL in the FEV_1.[144]

A variety of patterns of pulmonary function abnormalities occur in workers with CBD including obstructive, restrictive, or mixed defects with slowly declining gas exchange (i.e., reduced CO diffusing capacity, DL_{CO}) and a mild obstructive pattern being the most common physiological abnormality in current workers. A study of 41 workers with CBD revealed the following three patterns: 1) restrictive defect (20%); 2) obstructive defect (39%); and 3) isolated reduction of carbon monoxide diffusing capacity (36%).[145] Characteristic changes in advanced disease are a restrictive disease with reduced vital capacity, decreased total lung volume, and a reduction in the DL_{CO}. CBD may be subclinical with normal pulmonary function tests;[146] however, cardiopulmonary exercise testing may reveal abnormalities in early disease when static physiological values are normal.[147]

Direct arterial blood gas measurements during exercise testing may help distinguish between CBD and beryllium sensitization, but the interpretation of pulse oximetry during testing is more complicated because indirect measures of oxygen saturation misclassify some patients. Exercise tolerance testing is the most sensitive indicator of physiological impairment in patients with CBD, particularly exercise capacity.[146] Other abnormalities include elevated dead space to tidal volume ratio (V_d/V_t), low resting PaO_2, low diffusing capacity, and increase in the arterial-alveolar (A-a) gradient at maximum exercise. Abnormalities on bronchoalveolar lavage (BAL) include leukocytosis, lymphocytosis, and an abnormal lymphocyte proliferation test.

Blood

The Kveim test is consistently negative in patients with CBD, but the high false-negative rate of this test in sarcoidosis limits the ability of this test alone to differentiate between sarcoidosis and chronic beryllium disease (CBD). Occasionally, hypercalcemia develops and the appearance of renal stones is common in workers with CBD.[1] In patients with chronic beryllium disease, there are no direct effects on typical blood parameters (white blood cell counts, hematocrit, differential white blood cell percentages) or serum chemistry panels including hepatorenal function.[48,148]

HEALTH SURVEILLANCE

Risk Assessment

The estimated tolerable concentration for the non-cancer health effects of Be is 0.02 μg/m^3 based on the LOAEL for chronic beryllium disease in exposed workers using a total uncertainty factor of 10.[15,30] The inhalation unit risk of 2.4×10^{-3} was derived for Be based on the risk of lung cancer in exposed workers. However, the data were limited by the small increases in lung cancer risks, incomplete smoking histories, lack of control of other potential carcinogens, and limited Be exposure data.[30] The risk of developing chronic beryllium disease is relatively low despite long-term exposure based on cross-sectional studies. In a cross-sectional study of 50 Be sensitized workers from a cohort of 1,875 current/former nuclear weapons research and development facility workers undergoing Be sensitivity testing, the mean duration of employment was ~18 years.[149] Five of the workers had CBD (0.3% of the total cohort), and three had the probable disease. None of these workers had severe diseases. The mean latency from the first possible Be exposure to evaluation was 32 years. Three workers had definite CBD and 2 had probable CBD of 11 sensitized workers in the low Be exposure group, whereas 2 sensitized workers had definite CBD and 1 worker had probable CBD in the moderate Be exposure group of 28 sensitized workers. None of the sensitized workers in the high Be exposure group of nine workers had evidence of CBD. A study of 5,436 US beryllium workers using best-fitting power and categorical models with mean daily weighted average (DWA) beryllium exposure based on job exposure matrices suggested a statistically significant excess lifetime risk of lung cancer following DWA beryllium exposure of 4 μg/m^3.[150] In general, the risk of beryllium sensitization and CBD is substantially less in beryllium mine and ore extraction workers compared with workers exposed to beryllium oxide particles; the occurrence of CBD in workers solely exposed to beryllium at the former facilities is extremely rare.[21,151]

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Environmental Monitoring

Table 5.6 lists the standards and regulations for beryllium in the United States. The machining operations involving beryllium alloys produce irregularly shaped particles. A study of these processes demonstrated that the mass median sieve diameters of particles produced by sawing beryllium metal, the beryllium-nickel, and beryllium-copper alloys were 130 μm, 230 μm, and 300 μm, respectively.[152] With the use of high velocity, low volume exhaust systems, and special ventilation shrouds, the ambient air Be concentration was <0.07 μg/m^3; the Be air concentration in the shrouds was <2 μg/m^3. The current Be standards require maintenance of a beryllium work area, respiratory protection (powered air-purifying respirator), protective clothing, and equipment to reduce dermal exposure.[153] The previous standard for beryllium emissions remains unchanged.

The ATSDR recommends a chronic-duration oral minimal risk level (MRL) for Be of 2 μg/kg/day based on benchmark analysis of a chronic dog feeding study involving the administration of beryllium sulfate in the diet to 5 male and 5 female dogs for 143–172 weeks.[154] At Be doses of 12 mg/kg/day (males) and 17 mg/kg/day (females), ulcerative lesions in the small intestine occurred in 9 of 10 dogs, whereas only 1 dog developed similar lesions at 1 mg/kg/day. There were no observable gastrointestinal effects at lower doses. The ATSDR did not recommend a MRL for inhalation because of inadequate data and the lack of animal studies with a reliable no-observed-adverse-effect level (NOAEL) for respiratory effects.

TABLE 5.6. Regulatory and guidelines for beryllium exposure.

Exposure Limit	Value
OSHA	
PEL–TWA (8-hour)	0.2 μg/m^3
Action level	0.1 μg/m^3
STEL–TWA (15-minute)	2 μg/m^3
NIOSH	
REL–TWA (10-hour)	<0.5 μg/m^3
IDLH	4,000 μg/m^3[a,b]
ACGIH	
TLV–TWA (8-hour)	2 μg/m^3
STEL–TWA (15-minute)	10 μg/m^3
US FDA	
Bottled water allowable limit	4 μg/L
US EPA	
RfC (chronic inhalation exposure)	0.02 μg/m^3
RfD (chronic oral exposure)	2 μg/kg/day
EPA carcinogenic unit risk (daily)	4.3 mg/kg (oral)
	2.4×10^{-3} mg/kg (inhalation)
MCL (US Federal drinking water guidelines)	4 μg/L
ATSDR	
MRL (chronic oral)	2 μg/kg/day
MRL (chronic inhalation)	No recommendation

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; MCL = maximum contaminate level; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency; US FDA = US Food and Drug Administration; WHO = World Health Organization.

[a] As a carcinogen, NIOSH recommends reducing exposure to the lowest concentration feasible; [b] Values are based on the NIOSH Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHs) (1994). As a recognized human carcinogen, the current recommendation is to reduce the concentration to the lowest feasible.

Biological Monitoring

Although the risk of acute beryllium pneumonitis is dose-related, the latency, onset, severity, and progression of chronic beryllium disease (CBD) are highly variable and poorly related to exposure because the disease results from a Type IV hypersensitivity reaction.[155] The immune-mediated etiology of CBD complicates the interpretation of Be concentrations in blood and urine. The detection of beryllium in blood or urine indicates beryllium exposure; however, Be concentrations in biological samples do not correlate well to the total body burden of beryllium or CBD. The blood and urine from patients with CBD may not contain detectable Be concentrations.[156] There are limited data on the use of blood and urine beryllium concentrations as measures of beryllium exposure. Beryllium concentrations in blood and urine of individuals exposed to beryllium range from nondetectable to 3 μg/L.[157,158] In a study of 65 metallurgical workers in steel and copper alloy plants exposed to relatively low ambient air Be concentrations (median = 0.03–0.31 μg/m^3), the urinary Be concentration ranged from <0.03 (LOD)–0.54 μg/L.[159] For workers in the copper alloy plants with median ambient air concentrations of ~0.3 μg Be/m^3, the median urinary Be concentration ranged from 0.2–0.4 μg/L compared with Be concentrations of <0.03 μg/L (LOD) in urine samples from the control group (assembly workers). Based on regression analysis of air and urine samples, inhalable Be dust concentrations of 0.2 μg/m^3 correlated to urine Be concentrations of 0.12–0.15 μg/L.

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Medical Screening

The Occupational Safety and Health Administration released an updated final ruling on allowable beryllium exposure and increased requirements for worker screening in 2017 with implementation beginning in 2019 as displayed in Table 5.7.[153] This ruling expanded the beryllium requirements to shipyard and construction industries as well as increasing worker screening requirements.[160] Current final US OSHA rules require repeat Be exposure monitoring within 6 months for Be exposure of $\geq 0.1\,\mu g/m^3$ (action level) and within 3 months if the exposure exceeds the TWA PEL ($0.2\,\mu g/m^3$) or STEL ($2\,\mu g/m^3$).

Preemployment physical examination should include pulmonary function tests, chest X-ray, and a careful history of previous respiratory disease and allergies. However, there is no definite evidence that workers with preexisting diseases are at greater risk of developing CBD.[161] As a screening test for the detection of CBD, the beryllium lymphocyte proliferation test is more sensitive and specific than a chest X-ray, spirometry, or clinical examination.[18] The BeLPT identifies >70% of cases of CBD. Sensitization may occur within a few months of beginning employment in a beryllium machining plant.[162] US OSHA rules require medical examination every 2 years or when exposure exceeds the action level for 30 days/year.

A positive BeLPT requires a repeat test for confirmation. Two positive tests imply sensitization to beryllium, and these workers need further evaluation for the presence chronic beryllium disease (PFTs, chest X-ray, consideration for bronchoalveolar lavage and biopsy). Workers who develop positive LPT probably require removal from further Be exposure. Cohort and case-control studies of beryllium workers with beryllium sensitization and CBD indicate an association between these effects and *HLA-DPB1 E69*.[163] This *HLA-DPB1 E69* genotype encodes a glutamic acid at position 69. HLA markers may regulate the development of sensitization or disease, but the specific alleles (HLA-DPB1 E69, HLA-DRB1 S11) and mechanisms for their effects require further elucidation. Currently, there are inadequate data to use genetic markers (e.g., Glu69) as screening tests for beryllium-related health effects.[143]

TABLE 5.7. Occupational Safety and Health Administration (OSHA) 2017 final ruling for beryllium exposure. (Based on Occupational Safety and Health Administration (OSHA)).[153]

Requirements	Updated Ruling
Industries using beryllium in the workplace	Adds construction and shipyards.
Personal protective equipment	Appropriate protection of skin, eyes, and lungs (negative pressure/powered air-purifying respirators).
Screening requirements	Exposure to $0.1\,\mu g\ Be/m^3$ for >30 days/year.
Screening frequency	Every 2 years or sooner.

TREATMENT

Pulmonary

The first goal of management is the cessation of beryllium exposure. Workers with positive responses to the lymphocyte transformation test may require removal from any environment that contains beryllium. For patients with CBD, corticosteroids are the primary modality of treatment; however, there are no well-controlled clinical trials to determine how the administration of steroids changes the natural history of chronic beryllium disease. Because lifetime treatment with steroids is usually required to provide symptomatic relief and improve lung function, the desirable dose is the lowest effective dose (e.g., alternate daily dose of 20–40 mg prednisone) with dose reductions considered every 2–3 years using PFTs as measures of relapse. Short-term high-dose (60–80 mg prednisone/day) therapy may be necessary. After clinical improvement, the corticosteroid dose may be tapered as tolerated. Clinical improvement usually occurs within 2–3 months of the initiation of steroid treatment.[164] These patients should be monitored closely for the development of opportunistic respiratory infections (e.g., aspergilloma)[165] and right-sided heart failure. Inhaled steroids may be administered early in the disease course with short-acting bronchodilators if needed for symptomatic improvement. Few data are available on the use of methotrexate or newer immunosuppressive therapies (e.g., infliximab)[166] to reduce steroid side effects.

Patients with acute beryllium disease are also treated with high-dose steroid therapy. Controlled clinical trials of steroid treatment in CBD are not available to guide the duration of treatment. Some patients develop prolonged remission after steroid treatment, whereas other patients continue to deteriorate. Methotrexate and other anti-inflammatory agents (azathioprine, cyclophosphamide, mycophenolate, infliximab) are alternative treatments for patients that develop serious adverse reactions or do not respond to steroid treatment with dosages similar to the treatment of sarcoidosis.

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General treatment is similar to that for other patients with end-stage lung disease including cessation of smoking and yearly immunizations with pneumococcus and influenza vaccines. There are few clinical data on the use of chelating agents in the treatment of beryllium toxicity. Consequently, there are inadequate data to recommend the use of chelating agents for beryllium toxicity. 1,2-Dihydroxybenzene-3,5-disulfonic acid (Tiron) and calcium disodium EDTA are potential chelating agents based on experimental studies in rodents.[167] There are no data on the use of tumor necrosis factor inhibitors in patients with CBD.

Skin

Wounds contaminated with beryllium should be irrigated copiously and thoroughly debrided. These wounds should be followed closely for the development of delayed healing, chronic ulcerations, and the formation of granulomas. Complete excision is necessary for chronic skin lesions that result from the entrapment of beryllium in the skin. Acute cutaneous eruptions from Be exposure should be treated with soaks or compresses, topical corticosteroids, and the avoidance of further direct contact with beryllium.

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Chapter 6

BISMUTH

HISTORY

Both inorganic and organic bismuth have a long tradition of medicinal use. At the beginning of this century until the antibiotic era started, bismuth tartrate and bismuth salicylate in oil were used to treat syphilis, either alone or in combination with organic arsenic compounds. Occasionally, osteoporosis and/or osteomalacia developed in the pelvis, femur, and vertebrae of patients treated with these bismuth compounds. Briefly, in the 1930s, bismuth subnitrate was administered for hypertension and diuresis.[1] An acute, usually reversible, renal failure developed following the oral or intramuscular administration of bismuth triglycollamate and bismuth thioglycollate for stomatitis, upper respiratory tract infections, and warts.[2,3] The use of inorganic bismuth preparations continues for a variety of gastrointestinal complaints (subcarbonate, subgallate, subsalicylate, subnitrate, tartrate), hemorrhoidal irritation (subgallate, resorcinol), and minor skin irritation (subgallate, formic iodide, subnitrate).

In the early 1970s, the first cases of bismuth encephalopathy (confusion, ataxia, myoclonus, psychiatric symptoms) occurred in an Australian patient receiving bismuth subgallate as an ileostomy deodorant.[4] Over the next 5 years, in France and surrounding countries (Austria, Belgium, West Germany), an epidemic of >900 encephalopathies was reported in patients receiving high cumulative, annual doses (i.e., 20 g bismuth over 0.25–20 years) of relatively water-insoluble, lipophilic bismuth salts including bismuth subgallate and bismuth subnitrate.[5,6,7] Most patients recovered fully following the cessation of bismuth therapy. Although the exact source and etiology of this epidemic were never identified, bismuth salts (e.g., subgallate) were withdrawn from several countries. Later cases of bismuth encephalopathy occurred in Turkey and South Africa.[8] Despite higher overall per capita consumption of the same bismuth salts, bismuth encephalopathy was rarely associated with these bismuth salts in the United States.[9] Currently, the administration of bismuth preparations is increasing as a result of the recognition that the use of colloidal bismuth subcitrate and subnitrate promotes the healing of gastroduodenal ulcers and chronic gastritis, in part by antibacterial activity against *Helicobacter pylori*.[10]

PHYSIOCHEMICAL PROPERTIES

Bismuth (CAS RN: 7440-69-9) is a brittle heavy metal (atomic weight, 208.98 g/mol) that belongs to Group 15 (Group Va) of the periodic table along with arsenic and antimony. Bismuth appears as a pinkish-white crystalline structure that possesses high electrical resistance and the lowest thermal conductivity of all metals except mercury. The density of bismuth is 9.7 g/cm^3 with a melting point of 271.3°C. Of the two naturally existing valences (+3, +5), the trivalent form is the most abundant and chemically stable. Most inorganic salts of bismuth are poorly soluble in water, but their solubility increases in the presence of substances (citrate, tartrate, sorbitol) that reduce pH. The composition of most bismuth salts is complex with these compounds appearing as mixtures of salts both in lightly and heavily hydrated forms.[11] Although the exact structure requires further

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elucidation, colloidal bismuth subcitrate probably forms a solution containing particles of bismuth, citrate, oxychloride, and hydroxyl group depending on pH.[12]

EXPOSURE

Uses

Commercial

Most bismuth consumed in the United States appears in low-melting alloys and metallurgical additives used in electronic and thermoelectric applications.[13] Bismuth is also a catalyst, an industrial chemical, a pigment in cosmetics, and a substitute for lead in shotgun pellets. Potential nanotechnological uses of Bi include super-structured nanonetworks of BiOCl and nested nanonetworks of Bi_2S_3 as components of electronic devices, sensors, filters, and photocatalysts.[14]

Medicinal

Bismuth is available in a variety of over-the-counter medications for the treatment of indigestion/diarrhea (subsalicylate, subgallate, subcarbonate), hemorrhoids (subcarbonate, subgallate, resorcinol), minor skin irritation (subgallate, formic iodide, subnitrate), and diaper rash. Another indication is the use of colloidal bismuth subcitrate (De-Nol™, bismuth tripotassium dicitrate or tripotassium dicitrate bismuthate) in the treatment of gastric and duodenal ulcers caused by *H. pylori*. Colloidal bismuth subcitrate is a soluble, complex salt of citric acid that precipitates at pH <5. This bismuth preparation inhibits the digestion of protective gastric mucosa, bioactive proteins, epidermal growth factor-induduced proteolysis, and the proliferation of *H. pylori*.[15] Bismuth subsalicylate is an effective agent for the treatment of travelers' diarrhea and dyspepsia. Bismuth iodoform paraffin paste is a wound-packing and hemostatic agent that reduces wound colonization and promotes granulation tissue formation.

Production Processes

Bismuth in ores exists primarily as bismite (bismuth oxide) and bismuthite (bismuth sulfide); these minerals commonly occur in association with tin oxide, lead sulfide, and copper sulfide ores. The most common process for the production of bismuth is pyro-metallurgic separation during lead and copper refining.

Sources

Data on the presence of bismuth in the environment are limited. The daily intake of bismuth from water and food is ~20 µg, whereas the daily inhalation of bismuth is small (<0.01–0.76 µg) as a result of low Bi concentrations in ambient air (i.e., urban air, <0.07 µg/m^3; rural air, <0.001 µg/m^3).[16] Bismuth concentrations in soil average ~1 mg Bi/kg, whereas the bismuth concentration in rocks ranges from 0.1–0.3 mg Bi/kg (ppm) in sandstone.[13] The total Bi concentration in four seawater samples near the San Diego coastline ranged from 0.13–2.0 ng/L as measured by hydride generation/atomic absorption spectrophotometry.[17] The mean total Bi concentration in 164 dissolved river water samples from a summary of 4 Japanese studies was 12.7 ± 43.4 ng/L compared with 28.1 ± 103.2 ng/L in 162 particulate samples from the same area, as measured by inductively coupled plasma/mass spectrometry (ICP/MS).[18] For 24 dissolved and 23 particulate lake water samples, the mean bismuth concentrations were 17.7 ± 82.0 ng/L and 52.7 ± 167.9 ng/L, respectively. The mean bismuth concentrations in 29 dissolved and 23 particulate water samples from coastal seawater were 24.0 ± 34.4 ng/L and 12.1 ± 9.1 ng/L, respectively.

ENVIRONMENTAL FATE

Few data are available on the transportation and distribution of bismuth in the environment. Currently, there is little evidence that bismuth is present in the environment at concentrations that produce toxicity.

DOSE EFFECT

Pharmaceutical Preparations

Most over-the-counter bismuth medications contain 1–2% bismuth. Bismuth subsalicylate (Pepto-Bismol) yields 200 mg Bi/30 mL (1.75% solution), and salicylate intoxication is more likely to develop following an acute overdose of bismuth subsalicylate than bismuth intoxication.[19] One De-Nol (colloidal bismuth subcitrate) tablet contains about 108 mg bismuth. Because most bismuth compounds are poorly absorbed from the gastrointestinal tract, most toxicity results from the chronic ingestion of these compounds. No clinically significant changes in the spectral analysis of the electroencephalogram or nerve conduction studies were detected in 66 patients receiving either colloidal bismuth subcitrate (n = 22; 480 mg/day) or bismuth subnitrate (n = 20;

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1.8 g/day) for 2 months, when compared with controls ($n = 24$) receiving ampicillin.[20]

Overdose

A 19-year-old recovered from the ingestion of 21 tablets of bismuth triglycollamate (1.5 g bismuth) after a period of renal insufficiency.[3] Renal failure and neuropathy developed after the single ingestion of 11–12 g bismuth (100 De-Nol tablets), but there was no evidence of an encephalopathy; recovery occurred within 2 weeks of ingestion.[21] A 68-year-old man with poor renal function ingested 864 mg bismuth daily for 2 months; he developed mental status changes with hallucinations and ataxia that resolved within 4 months of the cessation of bismuth therapy.[22]

TOXICOKINETICS

Absorption

Although bismuth absorption from the gastrointestinal tract is poor (<0.33%) for most insoluble salts (e.g., nitrate),[23] substantial interindividual and intraindividual variation occurs, probably as a result of differences in factors affecting absorption including gastric emptying, stomach pH, and dissolution rate of tablets.[24] Animal studies suggest that absorption of bismuth occurs in the duodenum.[25] Human data on absorption are limited. Rapid peak plasma bismuth concentrations occur after the ingestion of single oral doses of colloidal bismuth subcitrate (bismuth tripotassium dicitrate, De-Noltab). In a study of 16 healthy adults ingesting 2 De-Noltab (216 mg Bi), median peak bismuth concentration occurred 30 minutes (range, 15–105 minutes) after ingestion; the peak plasma bismuth concentration was >50 μg/L in 14 subjects and >100 μg/L in 9 subjects.[26] The median steady-state bismuth concentration following the ingestion of 4 bismuth tripotassium dicitrate tablets (108 mg Bi/tablet) daily for 6 weeks in plasma samples from 9 patients was 17 μg/L.[27]

The peak plasma Bi concentration is lower after the ingestion of bismuth subsalicylate or bismuth subnitrate than colloidal bismuth subcitrate.[28] In an experimental study of 10 healthy, fasting volunteers, the peak plasma Bi concentration was 1.7 μg/L (range, 0.8–5.3 μg/L) 4 hours after the ingestion of three 30-mL doses of bismuth subsalicylate.[29] Following multiple bismuth subcitrate doses, steady-state plasma Bi concentrations occur after ~4 weeks with plasma Bi concentrations rarely exceeding 50 μg/L.[30] In a study of healthy adults receiving multiple doses of bismuth tripotassium dicitrate, the mean steady-state plasma Bi concentration occurred 18 days (range, 7–29 days) after beginning Bi treatment with mean peak Bi concentration of 38.3 μg/L (range, 7.6–58.3 μg/L).[31] Rodent studies suggest that bismuth in shotgun pellets implanted intraperitoneally is absorbed and distributed throughout the body; the clinical effects of retained bismuth bullets remain unclear.[32,33]

Distribution

In the blood, relatively large amounts of bismuth appear in erythrocytes. The highest concentrations of bismuth occur in the kidney, regardless of the route of administration or the type of salt.[11] An autopsy study of 22 patients given intramuscular injections mostly of bismuth salicylate during the 1930s revealed the following median values in mg/kg (ppm): kidney, 33.3; liver, 6.8; spleen, 1.6; colon, 1.3; lung, 0.9; brain, 0.6; and blood, 0.5.[34] In French patients dying of bismuth encephalopathy, the highest Bi concentrations appeared in the thalamus and cerebellar cortex; the Bi concentration was twice as high in the gray matter as white matter.[35]

Elimination

Bismuth elimination occurs primarily in the urine and, to a lesser extent, in the feces with the Bi concentration 10 times higher in bile than plasma. The exact contribution of renal excretion and biliary secretion of bismuth remains undetermined; the contribution of each route probably depends on the salt and the dose. Bismuth continues to accumulate for up to several months during chronic dosing with bismuth subcitrate. In a study of healthy volunteers, the mean plasma Bi elimination half-life changed from 18 hours after a single Bi dose to 13–22 days (mean = 20.7 days) after up to 4 weeks of multiple colloidal bismuth subcitrate doses.[31] Consequently, a washout period of 8 weeks is recommended between multiple courses of bismuth subcitrate therapy. The International Commission on Radiological Protection (ICRP) recommended the following biological half-lives for bismuth in the body: whole body, 5 days; liver, 15 days; bone, 13.3 days; spleen, 10 days; and kidney, 6 days.[36] In a study of nine patients receiving daily bismuth tripotassium dicitrate for 6 weeks, elevation of urine bismuth concentrations over baseline 12 weeks after cessation of treatment suggested the accumulation of this bismuth dose.[27]

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HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Bismuth is not an essential element for mammals. In general, heavy metals (e.g., bismuth) form strong covalent bonds with sulfhydryl groups on proteins, resulting in the inhibition of vital enzymes. In animal models, bismuth alters the metabolism of certain heavy metals (copper, zinc) and induces the formation of low-molecular-weight metallothionein-like proteins, particularly in the kidney.[37] Animal studies indicate that bismuth produces conformational changes in the membranes of mitochondria in the liver and the proximal tubule of the kidney; these changes occur along with impairment of enzyme activity in these membranes.[38] The etiology and mechanism of toxicity of the encephalopathy that occurred in France following the consumption of bismuth have never been firmly established.

Chronic ingestion of bismuth subsalicylate may produce black pigmentation of the tongue.[39] This compound reacts with hydrogen sulfide produced by anaerobic bacteria in the mouth to form bismuth sulfide. The latter chemical is an insoluble black bismuth salt that discolors the tongue. In contrast to the black, hairy tongue, the acquired pigmentation is not associated with enlargement of the filiform papillae of the tongue.

Pathological Changes

Following an overdose of bismuth subcitrate, a dose-dependent change occurs in the renal tubular epithelial cells of the kidney, beginning with vacuolation and eventually producing necrosis. These renal changes are associated with proximal renal tubular dysfunction (glucosuria, aminoaciduria, phosphaturia); the changes are usually reversible. Intranuclear inclusion bodies are often present in the renal tubular epithelium during autopsies of patients treated with intravenous bismuth for syphilis; these lesions are usually strongly Schiff-positive when stained by PAS and a hematoxylin counterstain.[40] Typically, the inclusion bodies are spherical, hyaline, refractile bodies with a brown tinge, appearing more often in the nuclei than the cytoplasm. Although some studies do not suggest these inclusion bodies are bismuth,[41] animal studies with x-ray microanalysis indicate the presence of bismuth.[42]

There are no pathological changes in the brain or in the kidney that are specific to bismuth toxicity. Postmortem examinations of patients with suspected bismuth-associated encephalopathy demonstrate bismuth accumulation in neurons and glial cells in various parts of the brain (e.g., cerebellum, neocortex, thalamus), particularly in the vascularity of the cerebellum as measured by silver enhancement of bismuth crystallites by autometallography.[43] Gliosis and neuronal loss are usually not present. Electron microscopy demonstrates the presence of bismuth in the vascular basement membranes and lysosomes. Postmortem examination of a 20-year-old woman with bismuth encephalopathy demonstrated nonspecific anoxic lesions (Ammon's horn, cortex, basal ganglia) along with widespread loss of Purkinje cells in the cerebellum; she died after 5 weeks in the hospital from septicemia.[44] The case report did not describe the course of her oxygenation; the thalamus, hypothalamus, subthalamus, and white matter were unremarkable. Autopsies of three patients dying from Bi-associated encephalopathy demonstrated the highest Bi concentrations in the frontal and occipital cortex, thalamus, and cerebellum; Bi concentrations ranged up to 25 μg/g compared with 0.01 μg/g in controls.[35]

CLINICAL RESPONSE

Most examples of bismuth toxicity result from chronic therapeutic use of soluble bismuth compounds. Some bismuth compounds are associated with reversible myoclonus and encephalopathy that require 2–10 weeks to resolve spontaneously.[45] Chronic bismuth ingestion results in stomatitis, black spots in the mucosa and gums (bismuth lines), black pigmentation of the tongue (bismuth subsalicylate), salivation, and pathological fractures.[5]

Medical Therapy

Encephalopathy

Over 1,000 cases of myoclonic, subacute progressive encephalopathy in patients on prolonged courses of bismuth therapy were reported in France in the 1970s, along with isolated cases in Australia,[46] Belgium, Switzerland, Spain, and Germany. The major clinical features included a prolonged prodromal phase characterized by impairment of gait and writing, deterioration of antegrade and retrograde memory, inattentiveness, insomnia, and behavioral changes followed by the subacute development of confusion, dysarthria, ataxic gait, difficulty standing, apraxia, and myoclonus over 24–48 hours. Table 6.1 lists the frequency of signs and symptoms in 698 patients with bismuth encephalopathy. Most patients recovered within 2–6 weeks of cessation

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TABLE 6.1. Clinical features in 698 patients with bismuth encephalopathy. (Adapted from Slikkerveer).[11]

Category	Clinical Feature	Percentage of Total Patients
Neurological		
	Myoclonus	80
	Trembling	59
	Memory Disturbances	56
	Writing Disturbances	53
	Dysarthria	52
	Inability to Walk	38
	Unsteady Gait	36
	Insomnia	35
	Sphincter Troubles	30
	Status Epilepticus	28
	Somnolence	25
	Headache	25
	Motor Deficit	20
	Gait Disturbance	20
	Coma	13
	Diplopia	5
Neuropsychiatric		
	Confusion	79
	Poor Concentration	60
	Thought Abnormalities	58
	Mental Disturbance	36
	Excitation	35
	Depression	32
	Anxiety	27
	Hallucination	17
	Delirium	16
Other		
	Shoulder Stiffness	8
	Renal Impairment	5
	Osteonecrosis of Humeral Head	3
	Bismuth Gum Lines	0.3

of bismuth therapy. Some neuropsychological symptoms (affective disorder, reduced cognition, insomnia, tremor) persisted in the most severely affected patients.[5] Case reports associated the chronic use of bismuth nitrate with panic attacks and a major depressive disorder,[47] whereas the prolonged use of colloidal bismuth subcitrate (bismuth tripotassium dicitrate) was linked to the development of neurotic symptoms.[48] However, a definite causal relationship between bismuth compounds and neuropsychiatric symptoms was not clearly established.

Nephropathy

The chronic use of bismuth triglycollamate, bismuth diallyacetate, and bismuth thioglycollamate previously has been associated with reversible impairment of the proximal tubules of the kidney that occasionally leads to renal failure. An 8-year-old girl developed nausea, vomiting, malaise, low-grade fever, and anuria after ingesting an unconfirmed amount of bismuth sodium triglycollamate given to her by her sister; the estimated amount was 18 g (plasma bismuth = 300 μg/L 1 week after admission).[49] The patient recovered after ~1 week of hemodialysis. Renal function and development remained normal at follow-up examination 3 years after the incident. A 16-year-old adolescent girl developed renal failure (serum creatinine = 19.9 mg/dL) 10 days after ingesting 18 g of colloidal bismuth subcitrate; the serum bismuth concentration was 495 μg/L on admission.[50] Normal renal function returned 9 weeks after admission.

Osteoarthropathy

Demineralization and osteonecrosis are reported complications in patients receiving high Bi doses parenterally for syphilis and orally for gastrointestinal symptoms; these complications are usually but not always associated with encephalopathy.[51] These bone lesions occurred primarily in the humeral head, thoracic vertebrae, and, less commonly, the femoral head.[11,52] Typically, these bony lesions occur in patients with severe bismuth-induced myoclonic jerks and encephalopathy. In a case series of 59 cases of bismuth-associated encephalopathy reported in the 1970s, eight women had boney lesions confined to the humeral head and thoracic vertebrae including 6 fractures of the humeral neck and three compression fractures of the thoracic spine.[5] All these patients had serum Bi concentrations exceeding 1,500 μg/L.

Acute Oral Toxicity

Several case reports associated the development of acute renal failure with large, intentional ingestions of colloidal bismuth subcitrate.[21,53] A 17-year-old girl presented to the emergency department with nausea, vomiting, and acute tubular necrosis with anuria 7 days after intentionally ingesting 7.5 g bismuth subcitrate (300 mg Bi).[54] She required hemodialysis for ~1 week. A 22-year-old woman developed Fanconi's syndrome and acute renal failure after the intentional ingestion of 5.4 g of colloidal bismuth subcitrate; she was anuric 3 days after ingestion, requiring 2 weeks of hemodialysis.[55] Within 6 weeks, her renal function was normal. A 2-year-old boy developed renal dysfunction and oliguria 2 days after the ingestion of 28 De-Nol tablets (colloidal bismuth subcitrate 8.4 g).[56] He received 10

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days of peritoneal dialysis with the return of normal renal function 3 weeks after ingestion. Encephalopathy occurred in none of these patients.

Environmental Exposure

In general, bismuth exposures from the environment are relatively low with little evidence of toxicity from these sources.

Occupational Exposure

Bismuth toxicity in the workplace is not well documented. Even though exposure to bismuth in the work environment occurs commonly, there is little evidence of toxicity resulting from bismuth exposure in industry.[57]

Reproductive Abnormalities

Although human and animal data are limited, there is no current evidence to indicate that Bi is a reproductive toxin at concentrations normally present in the environment or during medical treatment with Bi compounds. In a case series of 45 patients with Bi-associated encephalopathy, three women were pregnant and delivered normal neonates.[58] Presumably, the fetus was exposed to high Bi concentrations throughout pregnancy; the estimated Bi concentration in cord blood from one neonate was 250 μg/L.

Carcinogenesis

Although data are limited, there is no evidence that bismuth compounds are carcinogenic in animals or humans. Neither the IARC nor the US National Toxicology Program list bismuth or bismuth compounds as suspected carcinogens.

DIAGNOSTIC TESTING

SI Conversion Units

1 μM = 208.98 μg/L

1 μg = 0.00478 μmol

Analytical Methods

The current method of choice for the determination of bismuth concentrations in biological samples includes inductively coupled plasma/mass spectrometry (LOD, 0.007 μg/L; RSD 5–14%),[59] electrothermal atomic absorption spectrophotometry (ET/AAS), inductively coupled argon plasma/atomic emission spectrometry (LOD, 0.04 μg/L, RSD, <6%),[60] and atomic absorption spectrophotometry with hydride generation (HG/AAS; LOD, 0.225 μg/L).[61] Interpretation of Bi concentrations using ET/AAS is complicated by the volatility of Bi at temperatures necessary to remove the matrix. The use of electrothermal/atomic absorption spectrometry with platinum as a matrix modifier to decrease Bi volatility allows a limit of detection of 25 ng/g wet weight.[62] In a study of trace elements in urine, temperature (frozen, refrigerated, room temperature) and chemical additives (dilute hydrochloric acid, nitric acid, boric acid, potassium pyrosulfate) did not significantly change the bismuth concentrations when stored over 65 days as measured by inductively coupled plasma/mass spectrometry.[63]

Biomarkers

Blood

Medical Therapy

The interpretation of studies on bismuth blood concentrations is complicated by the lack of standardized analytical techniques, variation in types of blood samples (whole blood, serum, plasma), insufficient size of study groups, and the failure to distinguish normal from therapeutic concentrations.[64] Currently, there are inadequate data to determine the difference in Bi concentrations between different types of blood samples. In a study of 75 healthy adult subjects, the reference range for bismuth in plasma was <0.1 (LOD) to 3.5 μg/L.[65] In general, blood bismuth concentrations are <50 μg/L during therapy with the current regimen of bismuth compounds.[66] In a study of healthy volunteers receiving either colloidal bismuth subcitrate (480 mg/day) or bismuth subnitrate (1.8 g/day) for two months, the mean, posttreatment serum Bi concentrations were 17.2 ± 9.7 μg/L and 5.4 ± 2.8 μg/L, respectively, as measured by electrothermal/atomic absorption spectrometry.[20] The baseline serum Bi concentration in controls and treated patients was <1 μg/L. In a study of 19 healthy volunteers, the serum bismuth concentration ranged from <0.007 (LOD) to 0.67 ng/L with the serum from 10 of these volunteers being below the LOD as measured by ICP/MS.[59]

Overdose

Toxicity may occur in patients with blood Bi concentrations of >100 μg/L; patients with Bi-associated encephalopathy have large variations in the blood Bi concentration. A chronically ill, 76-year-old woman

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presented with confusion, poor appetite, insomnia, myoclonus, and malnutrition.[67] She had a history of chronic bismuth subsalicylate use; serum bismuth was 242 μg/L ~1 week after admission. Improvement began ~1 month after admission; her mental status returned to normal 18 months after admission with a normal activity level. A 56-year-old woman presented with two weeks of progressive confusion, difficulty concentrating, myoclonic jerks, hand tremors, gait instability, and visual hallucinations.[68] A blood bismuth concentration during her workup was 397 μg/L; her myoclonus, rigidity, and visual hallucinations (but not her mental status) resolved by discharge 10 days after admission. In a case series of 45 patients with Bi-associated myoclonus and encephalopathy, the serum Bi patients with bismuth encephalopathy was ~680–700 μg/L.[69] In a patient with renal dysfunction, behavioral changes, incontinence, visual hallucination, and ataxia developed after the ingestion of 48 g Bi over 2 months.[22] The whole blood Bi concentration was 880 μg/L. Fifty days after admission, his whole blood Bi concentration was 46 μg/L, and his neurological exam and electroencephalogram returned to normal.

Urine

The elimination half-life of bismuth is longer in urine (20–30 days) than plasma.[11] In a study of 75 healthy adult subjects, the reference range for bismuth in urine was 0.3–4.6 μg/L.[65] The LOD was 0.1 μg/L as measured by hydride generation/atomic absorption spectrophotometry (HG/AAS).[61] The mean bismuth concentration in urine samples from 14 students and laboratory employees was 1.94 ± 1.26 μg/L with a range of 0.52–3.89 μg/L as measured by HG/AAS. In a case series of 45 patients with Bi-associated myoclonus and encephalopathy, the urine Bi concentration ranged from 200–9,600 μg/L.[58] A 67-year-old man with sacral chondroma developed myoclonus and encephalopathy (confusion, disorientation, delusions, agitation) within 10 days after debridement and packing of his extensive sacral tumor with bismuth iodoform paraffin paste.[70] His urine Bi concentration 14 days after packing and prior to chelation with DMPS was 2,800 μg/L.

Spinal Fluid

Substantial interindividual variation also occurs in CSF bismuth concentrations in patients with Bi-associated encephalopathy averaging ~50–60 μg Bi/L. In a case series of 45 patients with Bi-associated myoclonus and encephalopathy, the CSF Bi concentration ranged from 10–100 μg/L.[58]

Abnormalities

The electroencephalogram (EEG) is characteristic of bismuth encephalopathy in most cases with generalized spike-wave complexes suggestive of myoclonus that is epileptic in origin.[71] Monomorphic waves at 3–5 Hz appear in the temporal-rolandic and frontal areas, unaffected by eye opening or photostimulation.[58] This rhythm spreads to the occipital regions where alpha rhythms disappear. A diffuse beta rhythm of low voltage develops in most patients, but spikes or other features of paroxysmal activity are usually absent. In a case series of 70 French patients with Bi-associated encephalopathy and myoclonus, paroxysmal phenomena on the EEG and generalized clonic epileptic seizures occurred only when the serum Bi concentration was <1,500 μg/L.[72] Bismuth is radiopaque; increased density may appear in the cortex of the cerebral hemispheres and the basal ganglia along with residual Bi in the gastrointestinal tract. No significant changes occurred in the CSF.

HEALTH SURVEILLANCE

There are no well-defined environmental or biological exposure limits for Bi or Bi compounds with the exception of the intermetallic compound, bismuth telluride (Bi_2Te_3), used in the semiconductor industry. The ACGIH TLV–TWA for selenium sulfide-doped bismuth telluride is 5 and 10 mg/m^3 for undoped bismuth telluride. The NIOSH REL–TWA is 10 mg/m^3 (total, un-doped Bi_2Te_3) and 5 mg/m^3 for respirable Bi_2Te_3, whereas the OSHA PEL–TWA is 15 mg/m^3 (total Bi_2Te_3) and 5 mg/m^3 for respirable Bi_2Te_3. Typical urine Bi concentrations in subjects without occupational exposure are <20 μg/L; Bi toxicity is rare in subjects with blood Bi concentrations of <50–100 μg/L.

TREATMENT

The main treatment for bismuth intoxication is the cessation of bismuth therapy along with supportive care. Decontamination measures may be effective for large single ingestions within the first 1–2 hours post-ingestion, but little data are available to guide treatment. Whole bowel irrigation is a potential decontamination measure if the abdominal x-ray indicates large quantities of bismuth in the intestines.

Little data are available to determine the optimal treatment. Symptomatic patients with blood bismuth concentrations exceeding 200–300 Bi/L are candidates for chelation. Based on animal studies and limited human data,[22,73] DMPS (2,3-dimercapto-propane-1-

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sulfonic acid) and DMSA (2,3-dimercaptosuccinic acid) given in doses of 30 mg/kg/day until symptoms abate are the chelating agents of choice.[74] Case reports document increased urinary Bi following treatment with DMPS,[70] but the absence of pharmacokinetic data and the presence of other factors affecting clinical symptoms (e.g., removal of Bi packing, hemodialysis) prevent conclusions regarding the efficacy of chelation therapy in cases of Bi encephalopathy. Sixteen hours of hemodialysis preceded by the intravenous administration of DMPS removed 4.7 mg of Bi, whereas hemodialysis alone did not increase Bi clearance.[73] In some case reports, DMPS was stopped because of clinical deterioration despite substantial reduction in plasma Bi concentrations and increased urinary Bi excretion.[71]

Although renal clearance of bismuth increases after the administration of BAL, the clinical effectiveness of BAL (dimercaprol) for bismuth toxicity has been inconsistent.[75] In a study of rats receiving 250 µmol/kg of 1 of 6 chelators (BAL, deferoxamine, DMPS, DMSA, sodium-calcium EDTA, D-penicillamine, thiopronine) daily for 3 days, BAL and DMPS produced the highest urinary Bi elimination.[74] BAL was the only chelator that effectively lowered brain bismuth concentrations, whereas EDTA increased brain bismuth. The authors opined that DMPS and DSMA were possibly the most useful chelators of bismuth with BAL reserved for very severe intoxications. In a study of 24 volunteers receiving either 30 mg/kg DMSA or DMPS after 28 days of colloidal bismuth subcitrate (480 mg/day) therapy, the blood bismuth concentration increased within the first 4 hours (DMSA > DMPS), followed by a ~50-fold increase in the urine bismuth concentration during the first 24 hours.[76] Treatment with BAL should be reserved for severely intoxicated patients without peanut allergies. Animal studies do not support the use of D-penicillamine.[77] Hemodialysis does not significantly increase Bi elimination; treatment with hemodialysis should be limited to patients with renal failure.[21]

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Chapter 7

BORON AND BORON COMPOUNDS

BORON AND BORATES

HISTORY

The Babylonians imported borax (sodium tetraborate) over 4,000 years ago as a flux for shaping gold.[1] Borax has been a cleaning agent since the Greek and Roman Empires. Although its use in mummifying, metallurgy, and medicine has been attributed to the Egyptians, the first documented use of borax occurred in the 8th century, when Arab traders brought the mineral tincal to Mecca and Medina. Tibetan lakes are probably the earliest sources of borax that were shipped over the Himalayas to India. As early as the 12th century, European goldsmiths used borax flux. Gay-Lussac and Sir Humphry Davey independently isolated and identified elemental boron in 1808 by heating boron oxide with metallic potassium. Reports of boric acid poisoning appeared in the late 19th century as a result of the use of this compound as an anticonvulsant.[2] Borax was a common food preservative prior to the 20th century, particularly in meat. Dr. Harvey Wiley was the chief of the United States Department of Agriculture Bureau of Chemistry (forerunner of the US Food and Drug Administration) when food manufacturing became a mass production industry in the early 1900s.[3] Under the authority of the Pure Food and Drug Act of 1906, he banned the use of borax as a preservative; his decision was upheld by the US Supreme Court in 1911.

PHYSIOCHEMICAL PROPERTIES

Elemental boron is the only metalloid and electron-deficient, nonmetallic element in Group 3 (Group IIIb) of the periodic table that includes aluminum, gallium, indium, and thallium. At room temperature, pure boron is a hard, brittle metalloid that functions as a semiconductor. The chemistry of boron is complex with the interaction of boron with other compounds resembling the chemistry of silicon and carbon. As a result of the high affinity of boron for electronegative atoms (e.g., oxygen), elemental boron occurs primarily as inorganic salts (i.e., borates) rather than elemental boron in nature. The two stable isotopes of boron are ^{10}B and ^{11}B. In its natural state, boron (B) exists as a mixture of about 20% ^{10}B and the remainder as ^{11}B isotopes.

Boron has a high affinity for oxygen, resulting in the formation of borates; reduced boron compounds (alkyls, aryls, halides, hydrides) readily oxidize and hydrolyze, limiting the commercial value of these compounds.[4] Hence, boron exposure primarily involves inorganic boron compounds. In water, at temperatures above 100°C, boron forms boric acid and other boron compounds. The theoretical composition of borax is 52.7% sodium tetraborate, $Na_2B_4O_7$ (36.5% boric oxide, 16.25% sodium oxide), and 47.24% water of crystallization; borax hydrolyzes in solutions to produce a mildly alkaline solution of $Na_2(B_4O_5(OH)_4)\cdot 8H_2O$. At 20°C, the pH of a 5% solution of borax is ~9.3 compared with 11.4 for a 5% solution of sodium metaborate ($NaBO_2\cdot_nH_2O$, CAS RN: 7775-19-1). Sodium perborate

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TABLE 7.1. Physical properties and identifying information for boron and selected boron compounds (ATSDR).

Property	Boron	Boric Oxide	Borax	Sodium Tetraborate
CAS RN	7440-42-8	1303-86-2	1303-96-4	1330-43-4
Molecular formula	B	B_2O_3	$N_2B_4O_7{\cdot}10H_2O$	$Na_2B_4O_7$
Atomic weight (g/mol)	10.811	69.62	381.373	201.22
%B (by weight)	100	31.1	11.34	21.5
Melting point (°C)	2,075	450	75 (decomposes)	743
Boiling point (°C)	4,000	1,500	NA	1,575 (decomposes)
Density (g/mL)	2.35[a] (25°C)	1.8[a]	1.73	2.367
Water solubility	Insoluble	4% (20°C)	59.3 g/L (25°C)	3.1% (25°C)

Abbreviations: CAS RN = Chemical Abstract Service Registry Number; NA = not available.
[a]Amorphous form.

($NaBO_3$, CAS RN: 7632-04-4) is the hydrolytically unstable persalt of boron that reacts with water to form stable sodium metaborate and hydrogen peroxide. The addition of activators to solutions of perborate compounds at normal washing temperatures allows the use of these compounds as bleaches. The multi-center nature of boron results in the formation of a diverse array of covalent networks, rings, cages, and clusters that produces strong covalent bonds with electronegative elements (e.g., fluorine, oxygen). The vapor pressure of boron and borates at room temperature is negligible. Table 7.1 lists some identifying characteristics and physiochemical properties of boron and boron compounds.

EXPOSURE

Production Processes

Turkey is the largest producer of borate products in the world, exporting mineral concentrates including ulexite ($Na_2O{\cdot}CaO{\cdot}5B_2O_3{\cdot}16H_2O$), colemanite ($2CaO{\cdot}3B_2O_3{\cdot}5H_2O$), and tincal ($Na_2B_4O_7{\cdot}10H_2O$) as well as other refined borax products. In the United States, the entire production of borates occurs in the Mohave Desert of Southern California from the Kramer deposit at Boron, California. This deposit is the largest borate deposit outside of Turkey. The production of boron results from the chemical reduction of boron-containing ores by reactive metals, either by nonaqueous electrolytic reduction or through thermal decomposition. In the latter process, ore collected from open-pit mines is crushed and dissolved with steam with the resulting borax solution crystallized, washed, and kiln-dried after the removal of insoluble compounds by sedimentation. This process produces borax with either 5 or 10 mol of water, depending on the temperature at crystallization. Heating the hydrated form of borax to molten glass followed by cooling produces anhydrous borax, as does pulverizing the glass to a fine powder.

Uses

Fiberglass accounts for about 77% of the production of boron minerals with ~2/3 produced for fiberglass insulation and ~1/3 for fiberglass textiles. In fiberglass, boric oxides increase mechanical strength and chemical durability. The production of low-thermal expansion glasses and heat-resistant Pyrex accounts for ~18% of boron production compared with ~5% for enamels, ceramic glazes, and frits. The addition of borates to glass removes bubbles and improves the formation of finished glass products. Elemental boron is used as a neutron absorber in nuclear reactors. Boron also appears in cosmetics, soaps and cleansers, fertilizers for boron-deficient plants (apples, sugar beets, oil palms, alfalfa), leather tanning, and antifreeze.[5] Borax contributes to the softening of hard water by precipitating calcium to form calcium borates as well as reacting as a buffering and mild alkalinizing agent. Sodium perborate is an effective bleach, but activators (e.g., organic acyl derivatives) are necessary to hydrolyze perborate at temperatures <60°C.[1] Previously, boron was a food preservative in Europe and Asia. Boron trichloride is part of the chemical vapor deposition process for the production of boron filaments, whereas boron tribromide is a catalyst in the manufacture of proprietary pharmaceuticals.

Product Formulations

Sources of boron in products include insecticides (e.g., Harris Famous Roach Tablets (boric acid), Roach-Pruf (orthoborate)), soaps (e.g., Boraxo Powdered Hand Soap), and contact lens solutions. Sodium borate, sodium biborate, sodium pyroborate, and sodium tetraborate (borax cleaners) contain 21.5% boron by weight. Sodium borate solutions (Dobell's) contain 1.5 g sodium borate, 1.5 g sodium bicarbonate, and 0.3 mL liquified phenol. Boric anhydride, boron oxide, boron

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trioxide, boric oxide, boron sesquioxide, borax, and tincal (tinkal) are 33% boron by weight. The following is the percentage by weight of other boron compounds: sodium perborate (oxidizer in tooth powders and toothpastes), 7.3%; sodium metaborate, 16.44%; magnesium perborate, 14%.

Sources

Borates are the most common boron-containing compounds in sediments and sedimentary rock as a result of the highly stable bonds formed between boron and (electronegative) oxygen species. The weathering of these formations probably accounts for greater exposure of the general population to boron than releases from a limited number of industrial sources.[6] Except for boric acid and sodium borate, the limited solubility of boron compounds substantially reduces their bioavailability. Ingestion of food (primarily fruits and vegetables) and water are the major sources of boron for the general population. Exposure to boron-containing insecticides and cosmetics may increase boron exposure. The western United States contains boron-rich deposits; therefore, this population probably has a relatively higher boron exposure than residents of other parts of the United States.

Air

Natural sources of borates in the atmosphere include oceans and geothermal steam. Evaporation of seawater is the biggest contributor of boron to ambient air.[4] The release of boron compounds occurs from natural and anthropogenic sources. The latter sources include coal-fired and geothermal steam power plants, fiberglass manufacturing facilities, and rockets. There are few data on the boron concentration in ambient air; however, air is probably an insignificant source of boron exposure for the general population. Estimated boron concentration in air averages $\sim 2 \times 10^{-5}$ mg/m^3 with a range of $<5 \times 10^{-7}$–8×10^{-5} mg/m^3.[7]

Soil

The concentration of elemental boron in the earth's crust is ~10 ppm. A study of US soils revealed that boron concentrations ranged up to 300 mg/kg with a geometric mean of 26 mg/kg.[5] Boron-containing ores include the following: borax, colemanite, kernite, tincalconite, tourmaline, and sassolite. Boron is released to the soil both from natural sources (rainfall, weathering, desorption, or decay of boron-containing matter) and from man-made sources (fertilizers, pesticides, fly ash, sewage sludge).[8] Boron is an essential nutrient for plants at concentrations of ~0.5 ppm boron.

Water

The major source of boron in water is the weathering of clay-rich sedimentary rocks containing boron; boron concentrations in natural waters depend on the geographic location of boron-rich deposits.[6] Some contamination of water occurs as a result of run-off from industrial and agricultural uses of boron-containing materials. High boron concentrations exist naturally in marine sediments and sedimentary rocks in the form of borosilicates. The average boron concentration in samples of sewage effluent in California was 1 mg/L. In England, a study of municipal sewage from a treatment plant revealed boron concentrations ranging from 2.5–6.5 mg/L.[9]

Typically, the boron concentration in surface freshwater is <0.1–0.5 mg/L.[7] Unusually high boron concentrations (e.g., 0.31–15.2 mg/L) occur in the water supplies of northern Chile,[10] while the water supplies of the Kutahya Province of Turkey contain boron concentrations in water samples ranging from 2.05–29 mg/L.[11] In the San Joaquin Valley of California, where groundwater is near boron-rich soils of marine origin, the median boron concentration was 4 mg/L with a range up to 120 mg/L.[6]

Diet

The range of the average estimated daily intake from all sources of boron in the United States ranges from 0.5–3 mg with a mean of 1.5–2 mg.[12] In a study of US diets (Continuing Survey of Food Intakes by Individuals), the reported mean daily intake of boron for male and female adults were 1.17 mg and 0.96 mg, respectively, with a range of 0.02 to over 9 mg.[13] The median daily boron intake in adult male vegetarians is higher (1.47 mg) than in the general population. In areas with high boron content in drinking water (e.g., northern Chile), daily boron intake may reach 27 mg (0.45 mg/kg).[14]

Food is the primary source of exposure to boron for the general population, particularly fruits (avocado), grains, wine, legumes, nuts, and vegetables. Plant-based foods are a richer source of boron than animal-based foods. Boron is an essential plant nutrient, occurring naturally in all plant foods. Milk and coffee account for the largest contribution of boron to the diet because of the volume of these items in the diet.[15] Analysis of foods with the highest boron content demonstrated the following concentrations (wet weight): raisins,

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2.20 mg/100 g; peanut butter, 1.45 mg/100 g; peanuts, 1.70 mg/100 g; dried fruits, 1.87 mg/100 g; and avocados, 1.22 mg/100 g.[13] Dairy products, meats, fish, and most grains are poor sources of boron. Wine consumption may add several mg of boron daily.

Most surveys of drinking water do not report boron concentrations. Existing data suggest that boron concentrations in drinking water are highly variable depending on the geographical source of the water. Analysis of US public water supplies indicates that drinking water typically contains <1 mg B/L with maximum boron concentrations ranging up to 3–4 mg/L.[16] Boron in US drinking waters probably does not pose any significant human health risk in most locations. Conventional water treatment methods (coagulation, filtration, sedimentation) do not remove significant amounts of boron.

ENVIRONMENTAL FATE

Boron is a nonvolatile metalloid compound that combines with most other elements. Although changes in the specific form of boron may occur during transport through the environment, transformation and degradation of boron do not occur in the environment.

Air

Boron released to the atmosphere may exist in the form of aerosols or particulate matter as borates, boron oxides, borides, boranes, borazines, or organoboron compounds.[5] Borates are relatively water soluble; therefore, wet or dry deposition releases these compounds to the surface of the earth relatively quickly. The atmospheric half-life of boron compounds is probably measured in days, depending on atmospheric conditions and particle sizes.

Soil

The extent of adsorption to soil depends on pH and the chemical composition of the soil with maximum adsorption occurring in the range of 7.5–9.[17] The greatest adsorption results from soils that contain high concentrations of aluminum oxides, iron oxides, and hydroxides. The adsorption of boron in some soils may not be reversible. Most boron compounds are transformed into borates in the soil as a result of the presence of moisture. Water leaching and incorporation into plants remove these borate compounds from soils.

Water

In natural waters, boron compounds readily hydrolyze to form the weak monobasic acid (H_3BO_3) and the monovalent anion $B(OH)_4^-$. Because borate ions in solution are fully oxidized, aerobic processes are unlikely to affect speciation; therefore, biotransformation does not affect the behavior of boron species in the environment. The adsorption of boron by clays is the main mechanism for removal of boron from natural waters.[6] Bioconcentration of boron by organisms from water is unlikely because of the low octanol/water partition coefficient (0.175) of boron. Boron does accumulate in aquatic and terrestrial plants, but biomagnification of boron in the food chain does not occur.[4]

DOSE EFFECT

Like carbon and silicon, the chemistry of this metalloid is very complex depending on temperature, pH, and the interaction of borates with oxygen. In aqueous solutions, boron forms $B(OH)_3$ (boric acid); presumably, the toxicokinetics and toxicity of boron relate to the effects of boric acid. However, the amount of boric acid formed will vary depending on local environmental conditions and the type of boron product. Hydrated borax typically contains 52.7% sodium tetraborate, $Na_2B_4O_7$ (36.5% boric oxide, 16.25% sodium oxide), and 47.24% water of crystallization.

Acute Toxicity

Borax is an alkaline salt that is an irritant to the upper respiratory tract in sufficient doses. In a study of 629 borax workers, inhalation of borax dust (boric oxide, sodium tetraborate) at ambient air concentrations exceeding 4–14.6 mg/m^3 was associated with acute irritation of the upper airway as measured by weighted mean total particulate borax in personal samples.[18] Symptoms included eye irritation, dryness of the upper respiratory tract, dry or productive cough, epistaxis, chest tightness, and sore throat, primarily in the higher exposure categories. Borax concentrations of <1.1 mg/m^3 as total particulate were not associated with signs or symptoms of acute irritation. A study of 79 workers exposed to sodium tetraborate dust did not demonstrate any significant differences in the potency of anhydrous sodium borates compared with other sodium borates at a geometric mean of ~3 mg/m^3, total dust.[19]

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Chronic Toxicity

In the older medical literature, a review of 175 cases associated the daily ingestion of 6–20 g of borax for several months with a wide range of toxicity.[20] These doses correspond to 2.12 g boron/day. The clinical details and differential diagnoses in these case reports were limited using obsolete analytical techniques. A prospective study of 303 workers exposed to an arithmetic mean daily boron concentration of 0.45 mg/m^3, total dust (0.02 mg boron/m^3) did not detect any significant change in the FEV_1 over a period of 7 hours.[21]

TOXICOKINETICS

Absorption

Uptake of boron occurs almost exclusively (i.e., >98%) as undissociated boric acid regardless of the form of inorganic borate (e.g., boric acid, borax, boron in the diet) because of the high pKa of boron. Absorption from the following procedures is sufficient to produce toxicity: irrigation of skin with altered permeability, irrigation of serous cavities, enemas, and intravenous injections. Limited human data indicate that intact skin absorbs little boron; however, significant amounts of boron may be absorbed across broken skin or across mucous membranes. In an *in vitro* study with human skin and a dose simulating bathing conditions in 5% borax, the mean absorption was 0.41% of the applied dose.[22] In volunteers administered ^{10}B-enriched 5% borax and 10% disodium octaborate tetrahydrate (DOT) aqueous solutions topically, the mean percent dose absorbed was 0.210 ± 0.194% for the borax solution and 0.122 ± 0.108% for the DOT solution as determined by urinary boron concentrations.[23] The flux and permeability constant for the borax solution were 0.009 µg/cm^2/hour and 1.8×10^{-7} cm/hour compared with 0.01 µg/cm^2/hour and 1.0×10^{-7} cm/hour, respectively, for the DOT solution.

Distribution

The distribution of boron occurs throughout the body by passive diffusion, particularly to the brain, liver, and kidneys.[24] The volume of distribution of boron is relatively small (i.e., <total body water). In animals, boron does not accumulate in soft tissue or fat; bone is a repository for absorbed boron with relatively high boron concentrations compared with other tissues.[25,26]

Elimination

The kidney excretes almost all (i.e., >90%) of the absorbed dose of boron with a relatively rapid excretion rate. The kidneys excrete ~50% of an absorbed dose during the first 24 hours with most of the rest of the dose eliminated in 5–7 days. Little, if any, metabolism of borax occurs in the body.

Maternal–Fetal Kinetics

No data are available on the kinetics of boron in the fetus. Boron occurs in the milk of lactating mothers with concentrations typically ranging from ~11–110 µg/L milk depending on boron concentrations in the environment. In a St. Johns, Canada, study of 28 lactating mothers within 12 weeks of delivery, the mean boron concentration in breast milk was relatively stable, ranging from 10–60 ng/mL (mean = ~30 ng/mL).[27] In a study of 35 lactating mothers from areas in Chile and Argentina with high environmental boron concentrations, the geometric mean breast milk/blood boron ratios from 3 cohorts residing in different areas were ~60–80%.[28] The geometric mean boron concentration in drinking water samples ranged from ~5,000 ng/mL (San Antonio de los Cobres, $n = 4$) to ~8,000 ng/mL (Arica, $n = 9$) with marked interindividual variation compared with 187 ng/mL in the control city (Santiago, $n = 6$). The study used whole blood samples for mothers in San Antonio de los Cobres (GM = 430 ng/mL), whereas plasma samples were collected in Arica (GM = 380 ng/mL) and Santiago (GM = 35 ng/mL). However, the erythrocyte and plasma boron concentrations were highly correlated ($r_s = 0.99$).

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Current evidence suggests but does not provide definitive proof that boron is an essential element in humans with suspected effects on cell membrane function, hormone metabolism, normal bone growth, calcium metabolism, and enzyme reactions.[29] In some bacteria, boron-containing biomolecules are involved in cell-to-cell communication; several important biomolecules in humans have a high affinity for boron including *S*-adenosylmethionine and NAD^+. Some studies suggest homeostatic control of boron in humans.[30] Boron is an essential element in vascular plants, particularly for plant growth and cross-linking in cellular membranes/extracellular matrix.[31,32]

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The mechanism of boron toxicity is not known. The most sensitive endpoints of toxicity in animals are developmental and reproductive toxicity. In rats that ingested boron for 10–14 weeks, cerebral succinate dehydrogenase activity was increased, suggesting that alterations in electron transfer in the respiratory chain of the mitochondria may contribute to the boron toxicity.[33]

CLINICAL RESPONSE

Acute Oral Toxicity

The oral toxicity of borates is relatively low depending on the amount of boric acid formed and primarily involves irritant effects.

Occupational Exposure

The presence of excessive ambient air boron concentrations exceeding 4 mg/m^3 has been associated with acute irritant effects including dryness of the upper respiratory tract, productive cough, epistaxis, chest tightness, and sore throat.[18] To date, long-term adverse pulmonary effects (radio graphical abnormalities, reduced FEV_1, FVC) have not been detected in studies of workers exposed to boron compounds.[5,18] Animal studies suggest that boron trifluoride is a more severe pulmonary irritant than other boron compounds,[34] but little human data are available. Contact dermatitis occurred in workers exposed to alkanolamine borate compounds used in metalworking fluids at concentrations of 10–30%; the dermatological effects appeared independent of the alkalinity of these compounds.[35]

Reproduction Abnormalities

Although exposure of animals to high doses of boron as boric acid causes reproductive abnormalities in rodents, there are few data on similar effects in workers exposed to borates. A cross-sectional study of 500 male workers exposed to average ambient air concentrations of 17.6–44.8 mg boron/m^3 as sodium borate for a mean of 18 years did not detect an effect on fertility as measured by the standard birth ratio.[36]

Carcinogenesis

Neither the International Agency for Research on Cancer nor the US National Toxicology Program lists boron or boron compounds as carcinogenic agents. There are little data on the carcinogenicity of boron. To date, *in vitro* studies do not indicate that boron is genotoxic.[37,38] A study of mice fed boron for 103 weeks did not detect a significantly increased incidence in the number of tumors.[39] A 2-year study of mice ingesting 400–500 mg boric acid/kg/day (low dose) and 1,100–1,200 mg boric acid/kg/day (high dose) did not demonstrate any significant excessive incidence of tumors.[40]

DIAGNOSTIC TESTING

SI Conversion Units

1 g borax = 10.5 mmol boron = 0.113 g boron
1 g anhydrous borax = 0.215 g boron
1 ppm boron = 0.4421 mg boron/m^3
1 mg boron/m^3 = 2.262 ppm boron

Analytical Methods

Several issues specific to boron compounds complicate the interpretation of analytical results for boron in biological samples. Boron concentrations are usually reported either as total boron or boron species (borates). As a result of the lack of convenient, commercial methods to speciate boron in borate, the percentage of boron in borate species is inferred from the percentage of boron in the borate species being analyzed. Consequently, susceptibility of borates to weight change from uptake/loss of water (i.e., instability of hydration state) and the type of sampler will affect the accuracy of analytical results.[41] The latter issue involves the difference in weight measured as total dust (NIOSH Method 0500) and inhalable particles (Institute of Occupational Medicine sampler).[42] Complications in sample preparation result from the ubiquity of boron in the environment, the low boron concentration in biological samples, and the volatility of boron compounds. These difficulties include certification and preparation of standards, contamination from Teflon vessels during microwave digestion, boron losses during freeze-drying, B isotopic variations, reagent backgrounds, and instrumental interferences.[43]

The most common analytical procedure to analyze boron in biological materials involves digestion of the sample in hot acid or base, followed by an analysis of the resulting solution by inductively coupled plasma/atomic emission spectrometry (ICP/AES). High-temperature atomic spectrometric methods (e.g., ICP/AES) are sensitive methods for the detection of boron in biological

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and environmental materials. The limit of detection for boron in air samples using NIOSH method 7303 (hot acid digestion followed by ICP/AES) is 9.4 ng/L. Inductively coupled plasma/mass spectrometry (ICP/MS) is a more rapid method requiring a small sample size with limits of quantitation in blood samples near 1 µg/L (inter-assay imprecision, ~3–5%) and 0.25 µg/L (inter-assay imprecision, ~1%) in urine samples.[44]

The measurement of the $^{10}B/^{11}B$ isotopic ratio allows the separation of anthropogenically derived boron from natural sources of boron in groundwater.[45] The natural abundance of ^{10}B and ^{11}B is specific to a location; thus, the $^{10}B/^{11}B$ isotopic ratio varies depending on the anthropogenic and groundwater sources of boron.[46] Atomic absorption analysis is not an effective method, and colorimetric curcumin and carmine methods are outdated.[5] The turmeric paper test (i.e., turning the yellow turmeric paper red in the presence of boric acid and hydrochloric acid) lacks specificity as a result of many false-positive reactions.[24]

Biomarkers

Blood

The geometric means for serum samples from 397 healthy, urban male and 583 female Japanese residents were 79.8 µg/L (95% CI: 33.3–191.2 µg/L) and 67.9 µg/L (95% CI: 29.5–154.9 µg/L), respectively, as measured by ICP/AES (LOD, 5 µg/L).[47] With the exception of the 50–69-year-old age group, the boron concentrations increased with age. In a convenience sample of 15 Chinese workers employed at boron mines or processing plants producing borax or boric acid, the mean serum boron concentration was 499 ± 790 ppb (µg/L; range, 20–3,569 ppb) compared with 96 ± 91 ppb (range, 3–536 ppb) for community controls from the same area of high environmental boron concentrations.[48] The mean serum concentration for a convenience sample of 15 Chinese residents without occupational boron exposure from a different area (i.e., low environmental boron exposure controls from the same study) was 48 ± 24 ppb (range, 8–113 ppb) as measured as elemental boron by inductively coupled plasma/mass spectrometry. There are few data on the ratio of boron concentrations in plasma/serum and whole blood. In a French study of 100 healthy adults, the median boron concentration in plasma samples was 36 µg/L (95% reference range, 19–79 µg/L) compared with 26 µg/L (95% reference range, 14–44 µg/L) in whole blood samples as measured by ICP/MS.[44]

Urine

The presence of elevated total boron concentrations in the urine reflects recent exposure (i.e., several days). In a study from the early 1960s, the boron concentration in urine samples from 148 healthy working adults without known exposure to boron compounds ranged from 40–6,600 µg/L (mean = 919 µg/L; median = 715 µg/L) as measured by a spectrographic method after acid digestion.[49] In a study of 102 Japanese electronic workers without occupational boron exposure, the distribution of boron concentrations in urine samples was lognormal with a geometric mean of 798 µg/L (95% CI: 398–1,599 µg/L).[50] The urine was normalized to a specific gravity of 1.024. The mean total boron concentration in urine samples from 118 Italian residents was 1,890 µg/L (95% CI: 490–3,290 µg/L) as measured by ICP/AES.[51] The maximum urine boron concentration was 7,800 µg/L. A Chinese study compared post-shift urine boron concentrations in 15 workers producing borax and boric acid with those of 15 unexposed control workers living near the plant.[48] The mean post-shift urine boron concentration in the exposed workers was 19.3 mg/g creatine (range, 1.4–168 mg/g creatinine) compared with 4.8 mg/g creatinine (range, 0.8–50.7 mg/g creatinine) for local controls. The estimated daily boron intake for the exposed workers was ~41 mg compared with ~3 mg for local controls; however, the study did not separately report the inhalable boron concentration in workplace personal air samples. The mean end-of-shift total boron concentrations in urine samples from 14 workers exposed to airborne borax concentrations (range, 3.3–18 mg/m^3) measured gravimetrically ranged from 3.16–10.72 µg/mg creatinine.[52]

HEALTH SURVEILLANCE

Environmental Monitoring

Table 7.2 lists the guidelines and regulations for occupational exposure to boron compounds. Gravimetric analysis of air samples for boron concentrations may be misleading compared with direct measurement of boron content because certain boron species can rapidly hydrate following the collection of air samples.[41] These guidelines are based on the irritation of boron to the skin, eyes, and respiratory tract. The lower concentrations recommended for the trifluoride and tribromide compounds reflect the greater pulmonary toxicity that occurs in animal studies when compared with other boron compounds.

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TABLE 7.2. Regulations and guidelines for exposure to boron compounds.

Substance	Level
OSHA	
PEL–TWA (8-hour)	
Boron oxide	
(total dust)	10 mg/m^3
(respirable fraction)	5 mg/m^3
Sodium tetraborates	10 mg/m^3
Ceiling	
Boron tribromide	10 mg/m^3 (1 ppm)
Boron trifluoride	3 mg/m^3 (1 ppm)
ACGIH	
TLV–TWA (8-hour)	
Sodium tetraborates	
Anhydrous	1 mg/m^3
Pentahydrate	1 mg/m^3
Decahydrate	5 mg/m^3
Boron oxide	10 mg/m^3
Ceiling	
Boron tribromide	1 ppm (10 mg/m^3)
Boron trifluoride	1 ppm (3 mg/m^3)
MRL Inhalation	
Acute-duration (≤14 days)	0.3 mg/m^3
MRL Oral	
Acute-duration (≤14 days)	0.2 mg B/kg/day
Intermediate-duration (15–365 days)	0.2 mg B/kg/day
NIOSH	
IDLH (30 minute)	
Boron trifluoride	100 ppm
WHO	
ADI	13 mg (adult)
IPCS	
TDI	0.4 mg/kg

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ADI = acceptable daily intake; IDLH = immediately dangerous to life and health; IPCS = International Programme on Chemical Safety; MRL = Minimum risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; TDI = tolerable daily intake; TLV = threshold limit value; TWA = time-weighted average; WHO = World Health Organization.

Biological Monitoring

There are no official biological guidelines for exposure to boron. Creatinine-corrected, post-shift urine boron concentrations are biomarkers for workers exposed to borax and boric acid; however, there are inadequate data to determine a reliable biological exposure limit. In a study of Chinese workers exposed to borax and boric acid in boron mines and processing plants, total boron concentration in post-shift spot urine samples correlated with total boron concentrations in 24-hour urine samples (Pearson correlation coefficient = 0.85, $P < 0.0001$) and with total boron concentrations in personal air monitoring (Pearson correlation coefficient = 0.83, $P < 0.0001$) as measured ICP/MS.[48] The mean post-shift urine boron concentration for 60 Chinese boron workers was 16 mg/g creatinine (range, 0.7–235.7 mg/g creatinine).[48] In this study, the post-shift boron concentration correlated well to total estimated boron exposure for the workers (Pearson correlation coefficient 0.90, $P < 0.0001$) and community comparisons (Pearson correlation coefficient 0.48, $P < 0.008$), but not for residents from areas of low boron exposure. Over the work week, there was no evidence of accumulation of boron in the body following these exposures.[52]

TREATMENT

Treatment is supportive.

BORIC ACID

HISTORY

Arabian physicians used boric acid as a cleansing agent in the first millennium. In the early 18th century, boric acid was administered in Europe as a sedative (Homberg's sedative salt), an anti-spasmodic, and an analgesic. Lister introduced the use of boric acid as an antiseptic in 1875;[53] since that time, this compound has also been a common constituent of ointments, skin lotions, medicinal powders, toothpaste, mouthwashes, topical astringents, and water softeners. Medicinal uses of boric acid solution included irrigation of pleural cavity, bladder, lower bowel, abscesses, inflamed joints, skin ulcers, and inflamed mucous membranes. Reports of boric acid poisoning appeared in the late 19th century as a result of the copious irrigation of internal organs with boric acid.[54] Routes of poisoning from boric acid include ingestion, intravenous, lavage of cavities, dermal (topical wound care, diaper dermatitis), and enemas. Fatalities have been associated with the accidental administration of boric acid to infants[55] and the ingestion of boric acid-contaminated food by adults.[56]

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PHYSIOCHEMICAL PROPERTIES

Boric acid is a colorless, odorless compound that appears in the form of crystals, white powder, or granules. This very weak monobasic acid is soluble in water, glycerin, and alcohol (~5%); chemically, this substance is a Lewis acid accepting OH^- rather than a proton donor. The chemical behavior of boron in aqueous media depends on pH and boron concentration.[1] Dilute aqueous solutions of boric acid at pH <7 contain primarily undissociated boric acid [$B(OH)_3$] and metaborates [$B(OH)_4^-$] species. In biological systems, boron associates with one or more hydroxyl groups. A teaspoon of 100% boric acid crystals contains about 2.9–4.4 g boric acid.

Because boric acid is weakly acidic (pKa 9.42), over 98% of boric acid exists in the form of $B(OH)_3$ in human blood at pH 7.4. Above pH 10, metaborate anion is the main species in the solution. Boric acid is stable to dehydration under all conditions in contrast to borax and low-hydrated borates.[41] Boric acid does not hydrate because there are no known higher hydrates. At elevated temperatures, boric acid dehydrates to form one of three metaboric acid crystal modifications ($B_2O_3 \cdot H_2O$). Table 7.3 lists some identifying data and physical properties of boric acid. Saturated solutions of boric acid contain 5.55% boron by weight.

EXPOSURE

Although used as a pH buffer in aqueous ophthalmic irrigation solutions, boric acid is no longer a common antiseptic agent. Uses of boric acid include the formulation of cosmetics, pharmaceuticals, and toiletries as well as the reduction of flammability of cellulose insulation, cotton mattresses, and wood composites. Boric acid and related sodium salts (sodium tetraborate decahydrate, sodium tetraborate pentahydrate, anhydrous sodium tetraborate, disodium octaborate tetrahydrate, anhydrous disodium octaborate, sodium metaborate) are constituents of registered pesticide products in the United States. The concentration of boric acid in seawater is ~4.5–5.5 mg/L with about 76% of the total inorganic boron in the undissociated form of boric acid.[38] At neutral pH (7.0), 98% of boric acid in dilute solution is present in the undissociated form. In water, boric acid is in equilibrium with borates, depending on water pH.

TABLE 7.3. Physical properties and identifying information of boric acid.

Physical Characteristic	Value
CAS RN	11113-50-1, 10043-35-3
Molecular formula	$B(OH)_3$
Molecular weight (g/mol)	61.83
%B (by weight)	17.5
Color	White
Physical state	Crystals, powder, granules
Odor	Odorless
Melting point (°C)	170.9
Density (g/mL)	1.435 (15°C)
Water solubility (g/L)	47.2 (20°C)
Vapor pressure	Negligible (20°C)

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number.

DOSE EFFECT

Acute Toxicity

A single ingestion of boric acid is frequently asymptomatic. Linden et al. documented several accidental ingestions that produced minimal systemic toxicity.[57] In this study, a 14-month-old child ingested an estimated 20 g of 50% boric acid without developing signs of intoxication. A 2-year-old child ingested 10 g boric acid; his only sign of intoxication was spontaneous emesis for 3 hours. A 28-year-old female ingested an estimated 297 g of 99% boric acid; she developed spontaneous vomiting within 1 hour. She received gut decontamination measures, and she was released the following day asymptomatic.

Human case reports suggest that the minimum lethal dose of boron (as boric acid) is ~2–3 g in infants, 5–6 g in children, and 15–20 g in adults; however, as noted above, symptoms based on the estimated dose are highly variable.[58,59] The estimated fatal dose of boric acid in 5 infants ranged from 4.5–14 g.[55] With supportive care, infants survived an estimated ingestion of 1.95–20 g boric acid.[55,57,60] A 77-year-old female presented to the hospital 23 hours after ingesting an estimated 30 g boric acid; she developed acute renal and cardiac failure.[61] Despite the use of hemodialysis and charcoal hemoperfusion, she died. An 82-year-old man accidentally ingested 30 g boric acid that was sold to him as magnesium sulfate by a pharmacist.[62] He developed headache, agitation, nausea, vomiting, and mild hypertension; he survived with supportive care and hemodialysis. Inhalation of borax and boric acid at ambient air levels of 4–14.6 mg/m^3 has been associated with acute

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irritation of the upper airway in the occupational setting.[63]

Chronic Toxicity

Valdes-Dapena et al. reported boron poisoning from the daily ingestion of 4–5 g boric acid for 3–4 weeks; however, they did not describe the clinical features of intoxication.[20] This dose corresponds to 2.12 g boron/day. In animals, the most sensitive toxic effect of boron is developmental toxicity in rats with a lowest-observed-adverse-effect level (LOAEL) of 13.3 mg/kg/day and a no-adverse-effect level (NOAEL) of 9.6 mg/kg/day.[64]

TOXICOKINETICS

Absorption

Boric acid is almost completely absorbed from the gastrointestinal tract. In a pharmacokinetic study of volunteers, ~94% of the ingested dose was recovered in the urine within the first 96 hours.[65] Limited human data indicate that intact skin absorbs little boron; however, significant amounts of boron may be absorbed across broken skin or across mucous membranes. No increase in the urinary excretion of boron occurred following the application of 15 g boric acid to a forearm for 4 hours.[66] An *in vitro* study on human skin demonstrated percutaneous flux values for the following boric acid solutions: 0.05%, 0.25 μg/cm^2/hour; 0.5%, 0.58 μg/cm^2/hour; and 5.0%, 14.58 μg/cm^2/hour.[22]

Distribution

Boric acid distributes rapidly after absorption via passive diffusion; the volume of distribution of boric acid is relatively small (i.e., <total body water).[67] In a study of eight young adult male volunteers receiving an intravenous boric acid dose of 562–611 mg, the distribution phases of the three-compartment model were 0.251 ± 0.099 , 0.456 ± 0.067 , and 0.340 ± 0.128 L/kg.[68]

Elimination

Boric acid is not metabolized in the human body. The kidneys excrete almost all of the absorbed dose of boric acid in the urine unchanged; therefore, renal clearance is the major determinant of the elimination half-life. Following the ingestion of boric acid solutions, the elimination half-life of boric acid is ~1 day.[67,69] In a study of eight young adult male volunteers receiving an intravenous boric acid dose of 562–611 mg (100–108 mg B), the mean plasma elimination half-life was ~21 ± 5 hours based on a three-compartment model.[68] The mean total renal clearance was 54.6 mg/minute/1.73 m^2 using the area under the curve. The mean renal clearance of dietary boron over 24 hours in 16 pregnant women was ~61 ± 37 mg/minute/1.73 m^2) compared with ~44 ± 22 mg /minute/1.73 m^2 for 15 nonpregnant women.[70] An analysis of 9 cases of boric acid poisoning revealed a mean serum half-life of 13.4 hours (range, 4–27 hours).[71]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

The mechanism of toxicity following boric acid poisoning is unknown. Postmortem findings in patients dying from boron toxicity are nonspecific (e.g., cerebral edema, pulmonary congestion).[72] Extensive vascular congestion, intravascular thrombosis, and widespread perivascular hemorrhage, along with degenerative changes in the neurons of the CNS appeared in autopsies of infants dying after ingesting boron-contaminated formula.[55] In addition, these autopsies demonstrated exfoliative dermatitis, neutrophilic infiltrate in the lamina propria of the small bowel, intracytoplasmic inclusion bodies in pancreatic acinar cells, renal tubular damage, liver congestion, and parenchymatous degeneration of the liver.[20] Some of these changes may be pre-terminal pathology rather than a direct effect of boron toxicity.

CLINICAL RESPONSE

Medical Therapy

Following repeated application of boric acid-containing ointments for diaper rash, chronic boron poisoning developed characterized by exfoliative dermatitis and renal toxicity (oliguria, renal tubular necrosis, renal failure).[20,24,73] Hyperthermia and hypothermia may occur. Neonates and young infants appear more susceptible than adults to chronic boron poisoning.

Acute Oral Toxicity

Irritation of the gastrointestinal tract (nausea, vomiting, blue-green diarrhea) begins within 1–2 hours following the ingestion of toxic amounts of boric acid. Although most accidental ingestions produce no symptoms, persistent vomiting and diarrhea may cause dehydration, shock, and coma following severe ingestion. A

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45-year-old man presented with vomiting, blue-green diarrhea, and dehydration 2 days after ingesting an estimated 280 g boric acid.[72] Seventeen hours after admission, he died after developing persistent hypotension, metabolic acidosis, oliguric renal failure, and pulseless electrical activity in his heart.

Classically, serious boric acid toxicity is associated with the "boiled lobster" syndrome, characterized by exfoliative dermatitis (erythema, desquamation 1–2 days post-ingestion).[74] The erythema is generalized; the rash usually resolves within 1–3 days. The rash may localize to the hands, feet, buttocks, scrotum, or face in less serious cases. Clinical features of serious boron toxicity in neonates and infants receiving large doses of boric acid include weakness, lethargy, irritability, restlessness, opisthotonus, tremors, hyperexcitability, delirium, convulsions, and coma.[55] After the intentional ingestion of a roach powder containing boric acid, a 56-year-old man developed desquamative dermatitis involving the axilla, inguinal crease, sacral area, and gluteal cleft with sparing of the palms and soles.[75] There were no genital or oral lesions; Nikolsky's sign was positive.

Environmental Exposure

There are few data on the toxicity of boric acid exposure to the environment.

Reproductive Abnormalities

Animals

Developmental studies in animal species (mice, rats, rabbits) indicate that high doses of boric acid cause developmental effects when fed to these animals at doses causing maternal toxicity. Several animal studies also demonstrate adverse reproductive effects on sperm formation when animals are fed high doses (1,750 ppm) of boron in the diet over 90 days.[76] These high doses of boric acid cause epithelial disorganization and loss of germ cells as well as decreases in the basal serum testosterone concentrations.[77] No developmental toxicity was observed in mice fed 55 mg boric acid/kg/day from gestational day 0–20[64] or in rabbits fed 125 mg boric acid/kg/day from gestational day 6–19.[78] The rat is the most sensitive species with a NOAEL of 9.6 mg B/kg/day for developmental toxicity, whereas the NOAEL for rabbits and mice were 22 mg B/kg/day and 43 mg B/kg/day, respectively.[79] The latter study demonstrated mild maternal effects and severe developmental toxicity (cardiovascular malformations) in rabbits fed 250 mg boric acid/kg/day. Inhibition of the release of mature sperm and testicular atrophy was seen in male mice feed >4,500 ppm boric acid over 9 weeks;[80] however, a threshold effect was observed at 2,000 ppm boric acid.

Human

Although boron affects male reproduction in laboratory animals following exposure to high boron doses, there is no clear evidence of male reproductive effects attributable to boron in studies of highly exposed workers. In a Chinese study of 945 men working in boron mining or processing including a subset of 16 heavily exposed workers with a mean estimated daily boron intake of 125 mg, there was no significant difference in reproductive outcomes between the workers' wives and the wives of 249 background control men after adjustment for potential confounders.[81] Additionally, there were no statistically significant differences in semen characteristics between all exposure groups and controls except for a reduction in the sperm Y:X ratio of boron workers. In a cross-sectional study of a nonrandom sample of 102 workers at plants producing borax, boric acid, and sodium perborate, analysis of sperm and hormone concentrations (FSH, LH, testosterone) did not detect any significant difference between controls, low exposure group, and high exposure group.[82] The estimated mean daily boron exposure of the highly exposed group was 14.45 ± 6.57 mg (range, 3.32–35.62 mg).

DIAGNOSTIC TESTING

SI Conversion Units

1 g boric acid = 16.2 mmol boron = 0.175 g boron

Biomarkers

Serum and plasma concentrations of boric acid are similar.[61]

General Population

Often, concentrations are reported as boric acid (borate) rather than boron. Because boron has an atomic weight of 10.81 compared with 61.8 for boric acid, the boric acid concentration is ~5.7 times heavier than an equivalent concentration of boron (i.e., 100 g boric acid/L = 17.5 g B/L). Therefore, 1 g boric acid contains 0.175 g boron. The mean whole blood concentration in 7 healthy adults was about 0.01 mg boron/L.[83]

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Overdose

Serum and urine boron concentrations document exposure, but the prediction of clinical effects based on boron concentrations must be done cautiously. A 14-month-old child remained asymptomatic with a serum boric acid concentration of 80 mg/L (14 mg boron/L) 4 hours after ingestion. Emesis developed in patients with the following serum boric acid concentrations: 530 mg/L 1 hour after ingestion; 580 mg/L 7 hours after ingestion; and 2,320 mg/L 1 hour post-ingestion.[57] Two hours after ingesting 75 g boric acid, a 45-year-old man was vomiting continuously with stable vital signs.[84] At that time, his serum boric acid concentration was 167.4 mg/L. He survived without sequelae after supportive care and hemodialysis. The serum boric acid concentration of an 82-year-old was 1,800 mg/L 3 hours after accidentally ingesting 30 g boric acid.[62] He survived with supportive care and hemodialysis without developing metabolic acidosis, hypotension, or renal dysfunction. Fifty-two hours after the ingestion of 280 g boric acid, a 45-year-old adult had a whole blood boric acid concentration of 450 mg boric acid/L.[72] The patient died shortly thereafter.

Postmortem

The blood borate concentration in a postmortem heart blood sample from an 18-month-old child was 83.16 mg/L.[85] The child was found in cardiopulmonary arrest at home after apparently ingesting roach powder containing boric acid; she was pronounced dead in the emergency department. The gastric contents from this child contained 60.48 mg borate/L.

Abnormalities

Dehydration may cause electrolyte (e.g., hypernatremia, hyperchloremia) and metabolic (e.g., acidosis) abnormalities following an overdose of boric acid.[55] Occasionally, evidence of renal damage (elevated serum creatinine) and liver damage (elevated aspartate and alanine aminotransferases) may develop after boron toxicity.[75,86]

HEALTH SURVEILLANCE

In rodents, the lowest-observed-adverse-effect level (LOAEL) was the development of reduced fetal body weight, minor skeletal changes, and a slight delay in maturation seen in rats fed 13.6 mg boron/kg/day as boric acid during gestation days 0–20.[87] Developmental toxicity in animal studies appears before reproductive toxicity. Based on the LOAEL value of 13.6 mg boron/kg/day as boric acid for developmental toxicity, an intermediate oral minimal risk level (MRL) of 0.01 mg boron/kg/day was derived using an uncertainty factor of 1000 (10 for extrapolation from animals to humans, 10 for human variability, and 10 for a LOAEL).[5] A study of rats fed diets containing doses of up to 8.75 mg boron/kg/day for 2 years did not detect any adverse effects (i.e., NOAEL).[76] The International Program on Chemical Safety Task Group from the World Health Organization derived a tolerable daily intake level of 0.04 mg B/kg/day using a NOAEL (no-observable-adverse-effect level) of 9.6 mg boron/kg/day from a similar developmental study[64] and an uncertainty factor of 25.[88] Using a benchmark dose for 5% reduction in fetal body weight of 10.3 mg B/kg/day based on the rat developmental toxicity data and an uncertainty factor of 78, Hasegawa et al. calculated a tolerable daily intake of 0.13 mg B/kg.[89]

The WHO provisional guideline for boron in water is 0.5 mg/L based on an NOAEL of 9.6 mg/kg/day in development studies, an uncertainty factor of 60, and a subsequent tolerable daily intake (TDI) of 0.16 mg/kg/day.[90] Ten percent of the TDI is allocated to drinking water (60 kg adult consuming 2 L water/day). Although there are few data, the chronic ingestion of boron exceeding these guidelines has not been associated with specific diseases.[11]

TREATMENT

Gut Decontamination

The effectiveness of gut decontamination in boron toxicity has not been studied. Most accidental ingestions (<200 mg boric acid/kg) of boron compounds (i.e., boric acid) require no measures of decontamination.[71] There are no data to confirm the efficacy of lavage in this setting. *In vitro* data indicate that activated charcoal does not adsorb boric acid well enough to be a practical alternative to other methods of decontamination.[91]

Enhancement of Elimination

Although the pharmacokinetic properties (i.e., low molecular weight, small volume of distribution) of boric acid suggest a potential role for hemodialysis, there are limited pharmacokinetic data on the efficacy of hemodialysis during the treatment of boric acid poisoning. Following the suicidal ingestion of an estimated

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21 g boric acid, 2 sessions of hemodialysis eliminated about 24% (5 g) of the estimated dose of boric acid.[92] The calculated total body clearance of boric acid during hemodialysis was 3.53 L/hour compared with 0.99 L/hour without dialysis. The serum half-life of boric acid decreased from 13.46 hours to 3.76 hours during dialysis. The renal clearance of boric acid following the suicidal ingestion of 75 g boric acid averaged 274 mL/minute during 2.5 hours of hemodialysis with a high-flux, high-efficiency polysulfone hemodialysis membrane (blood flow rate 400 mL/minute).[84] The serum boric acid concentration decreased from 15.44 to 1.83 mg/dL during this time period. The hemodialysis clearance of boric acid in an 82-year-old man with acute boric acid toxicity was 235 mL/minute with an extraction ratio of 70%.[62] In two young infants accidentally given boric acid in their formula, plasma boric acid concentrations decreased from 257 mg/L and 171.6 mg/L to <10 mg/L during continuous venovenous hemodialysis in 16 hours and 10 hours, respectively.[93] Removal of boric acid was 767 mg (mean clearance, 167 mL/minute/1.73 m^2) and 214 mg (mean clearance, 131 mL/minute/1.73 m^2), respectively.

Antidotes

There are no recognized antidotes for boron poisoning. Experimental data in rats suggest that *N*-acetylcysteine may reduce the renal toxicity of boric acid, but there are no human data.[94]

Supplemental Care

Patients with serious boron intoxications are frequently dehydrated; these patients should receive generous fluid replacement with close monitoring of renal function and electrolyte status. Diazepam (adult, slowly up to 10 mg intravenously; child, 0.1–0.3 mg/kg), lorazepam (adult, 1–2 mg IV), or midazolam are the drugs of choice to treat seizures. Respiratory insufficiency usually results from altered consciousness, except following direct pulmonary toxicity from exposure to boron trifluoride or boron tribromide.

BORANES

PHYSIOCHEMICAL PROPERTIES

Borane compounds (boron hydrides) have the general formula, B_nH_{n+4}; these compounds exist as very different structures than corresponding hydrocarbons as a result of the ability of boron to form multicenter bonds that are exclusively covalent. Pentaborane is a highly volatile, flammable liquid and a strong reducing agent that is highly toxic. Dimethylamine borane is a white solid with an amine odor at room temperature. In contact with water, this substance releases a flammable gas, whereas decomposition into unstable peroxides occurs after prolonged exposure to air. Diborane is a gas, and pentaborane is a volatile liquid, both with poor odor warning properties.[95] Based on studies from the 1950s, the median odor thresholds for boranes are as follows: decaborane, 0.3 mg/m^3; diborane, 2–4 mg/m^3; and pentaborane, ~2.5 mg/m^3.[96] Table 7.4 lists the physiochemical properties of the most common borane compounds.

EXPOSURE

Borane compounds are active reducing compounds previously used in the production of rocket fuel. Other uses for diborane include doping agent, rubber vulcanizer, accelerator of flame speed, and catalyst (olefin polymerization). Decaborane is also a catalyst for olefin polymerization. Pentaborane currently has no commercial uses. Manufacturing processes using dimethylamine borane include the production of thin-metal film, semiconductors, high-temperature printed circuit boards, floppy disks, and power transistors. Exposure to these compounds depends on their form.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

The mechanism of toxicity is not well-defined. Rodent and *in vitro* studies suggest that exposure to decaborane inhibits pyridoxal phosphate-requiring enzymes, possibly as a result of the reduction of pyridoxal phosphate by a substance formed non-enzymatically from the presence of decaborane in the aqueous environment of the body.[97] Animal studies indicate that decaborane exposure produces hypertension initially followed by hypotension, bradycardia, and myocardial depression (↓ myocardial contractile force).[98] In rodent studies, inhalation of high diborane concentrations produces primarily pulmonary damage.[99] Histological changes include vascular congestion, alveolar hemorrhage, atelectasis, degeneration of mucosal cells, and sloughing of the mucosal epithelium of the bronchi and bronchioles.

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TABLE 7.4. Physical properties and identifying characteristics of borane compounds.

Physical Characteristic	Decaborane	Diborane	Pentaborane
CAS RN	17702-41-9	19287-45-7	19624-22-7
Molecular formula	$B_{10}H_{14}$	B_2H_6	B_5H_9
Molecular weight (g/mol)	122.31	27.69	63.12
Color	Colorless	Colorless	Colorless
Physical state (standard temperature/pressure)	Crystalline solid	Gas	Liquid, volatile
Odor		Offensive, sweet	Pungent
Melting point (°C)	99.6	−165	−46.6
Boiling point (°C)	213	−92.5	60
Specific gravity	0.94 (25°C)	0.96 (air = 1)[a]	0.61 (0°C)
Water solubility (25°C)	Slightly soluble[b]	Insoluble[c]	Decomposes
Vapor pressure (mmHg)	0.05 (25°C)	>760	171 (20°C)
Odor threshold (mg/m^3, air)[96]	0.3 (0.06 ppm)	2–4 (2.2–4.4 ppm)	2.5 (1 ppm)

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number.
[a]Vapor density; [b]Decomposes in hot water; [c]Hydrolyzes in water to boric acid and hydrogen gas (H_2).

CLINICAL RESPONSE

The central nervous system is the primary target organ for borane compounds with varying severity of respiratory tract irritation. Most of the reports on the clinical effects of exposure to borane compounds used data from the 1940s and 1950s with very little analytical confirmation of workplace exposure. These clinical reports document dizziness, nausea, headache, and drowsiness as common symptoms of excessive exposure to these compounds; chest tightness and cough occurred more frequently after diborane exposure than decaborane or pentaborane exposure.[100] Additional symptoms of toxicity include muscle spasm, nervousness, restlessness, fatigue, tremor, ataxia, and convulsions.[101,102] Symptoms may develop soon after exposure to the volatile liquid, pentaborane, whereas symptoms (e.g., nausea, headache, dizziness) following decaborane exposure may be delayed 24–48 hours depending on the intensity of exposure. Respiratory tract irritation developed in two workers within 15 minutes of acute exposure to pentaborane, followed shortly thereafter by seizures, metabolic acidosis, coma, and cardiac arrest.[103] One worker died, and the other worker sustained postanoxic brain damage. Common symptoms reported in coworkers with milder exposure to pentaborane included lightheadedness, confusion, lethargy, insomnia, difficulty concentrating, nightmares, muscle jerks, headaches, and numbness. Separating the effects of post-traumatic stress from the direct effects of pentaborane was difficult; neuropsychological testing suggested the presence of some minimal brain dysfunction and major affective disorders 4–12 weeks after the incident.[104]

TABLE 7.5. Regulations and guidelines for exposure to borane compounds.

Exposure Limit	Value
OSHA	
PEL–TWA (8-hour)	
Decaborane[a,b]	0.3 mg/m^3 (0.05 ppm)
Diborane	0.1 mg/m^3 (0.1 ppm)
Pentaborane	0.01 mg/m^3 (0.005 ppm)
NIOSH	
REL–TWA (10-hour)	
Decaborane[a]	0.3 mg/m^3 (0.05 ppm)
Diborane	0.1 mg/m^3 (0.1 ppm)
Pentaborane	0.01 mg/m^3 (0.005 ppm)
REL–STEL (15-minute)	
Decaborane[a]	0.9 mg/m^3 (0.15 ppm)
Pentaborane	0.03 mg/m^3 (0.015 ppm)
IDLH	
Decaborane[a]	15 mg/m^3
Diborane	17 mg/m^3 (15 ppm)
Pentaborane	2 mg/m^3 (1 ppm)
ACGIH	
TLV–TWA (8-hour)	
Decaborane[a]	0.25 mg/m^3 (0.05 ppm)
Diborane	0.115 mg/m^3 (0.1 ppm)
Pentaborane	0.013 mg/m^3 (0.005 ppm)
STEL–TWA (15-minute)	
Decaborane[a]	0.75 mg/m^3 (0.15 ppm)
Pentaborane	0.039 mg/m^3 (0.015 ppm)

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; IDLH = immediately dangerous to life and health; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average.
[a]Skin notation; [b]Vacated, 1993.

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A case report associated the development of an axonal polyneuropathy with accidental exposure of a chemical worker to liquid dimethylamine borane.[105] Five days after being soaked with dimethylamine borane ($C_2H_{10}BN$, CAS RN: 74-94-2) following a pipe blowout, a 38-year-old man developed numbness and weakness in the distal limbs, dysphagia, slurred speech, and poor concentration. Nerve conduction studies and sural nerve biopsy confirmed axonal polyneuropathy. Some residual muscle weakness and sensory impairment persisted 1½ years after exposure.

DIAGNOSTIC TESTING

Conversion factors for borane compounds at 25°C and 760 mm Hg include the following: decaborane 1 ppm = 4.99 mg/m^3; 1 mg/m^3 = 0.200 ppm; diborane 1 ppm = 1.15 mg/m^3; 1 mg/m^3 = 0.873 ppm; and pentaborane 1 ppm = 2.58 mg/m^3; 1 mg/m^3 = 0.388 ppm. The recommended analytical method for diborane in ambient air is plasma emission spectrometry (NIOSH method 6006) at 249.8 nm with an accuracy of ±21.5% in the range of 0.06–0.25 mg/m^3.[106] There are currently no recommendations for the analysis of decaborane or pentaborane.

HEALTH SURVEILLANCE

Table 7.5 lists the regulations and guidelines for airborne exposure to borane compounds. There are no official biological exposure limits for these compounds.

TREATMENT

Treatment is supportive. The primary risk following severe acute exposure to high doses of borane compounds is central nervous system depression and suppression of the respiratory drive. Patients should be removed from further exposure, and contaminated skin should be washed thoroughly with soap and water after the removal of contaminated clothes. Case reports document symptoms of borane toxicity in first responders after providing medical care to workers with borane toxicity.[103] Appropriate protective gear should be worn when removing exposed patients from the source of borane toxicity. Symptomatic patients should be monitored for respiratory depression and cardiac dysrhythmias. Patients with altered consciousness may require respiratory support (supplemental oxygen, assisted ventilation). There are no antidotes for borane toxicity.

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Chapter 8

CADMIUM

HISTORY

The discovery of cadmium as a separate element occurred in 1814.[1] Early cases of cadmium toxicity primarily involved industrial exposure to cadmium dust in the latter 1800s and accidental ingestion of toxic cadmium salts (e.g., bromide).[2] By the early 1900s, cadmium toxicity was a recognized complication of the use of cadmium as an antiseptic and anthelmintic.[3] The industrial output of cadmium was relatively low until the early 1920s because cadmium is a byproduct of zinc production. The rapid expansion of the industrial uses of cadmium began in the 1940s, primarily as a result of the use of cadmium in electroplating; consequently, the body burden of cadmium in the general population has increased dramatically since 1900.[4] In 1946, inhabitants (primarily middle-aged women with low calcium and vitamin D intake) of the Jinzu River basin in Toyama Prefecture, Japan, began developing *itai-itai* (ouch-ouch) disease characterized by severe arthralgia, renal dysfunction, and osteomalacia.[5,6] This disease resulted from consumption of water and rice contaminated by cadmium from the discharges of a local zinc-mining operation, primarily affecting women. The use of traditional Japanese dress with wide hats to screen out sunlight with subsequent reduction in vitamin D synthesis contributed to the musculoskeletal symptoms of *itai-itai* in these women.[7] Gastrointestinal symptoms and renal dysfunction were relatively less prominent than musculoskeletal complications (osteomalacia, compression fractures of the spine). The full syndrome occurred only in postmenopausal women with a history of several pregnancies. Renal dysfunction usually involved the excretion of low-molecular-weight proteins, rarely involving impairment of urine concentrating ability.[8] Other incidents of environmental cadmium contamination include the Mae Sot District, Tak Province, Thailand, where discharges from a zinc mine contaminated local rice fields.[9]

PHYSIOCHEMICAL PROPERTIES

Cadmium (Cd) is a silver-white, soft, odorless metal that belongs to Group 12 (Group IIa) of the periodic table along with zinc and mercury. Cadmium rarely occurs in its metallic state because this metal readily forms a number of divalent inorganic salts. There is no evidence that cadmium forms stable covalent bonds with carbon in nature; therefore, organic cadmium compounds are not toxicologically important compounds.[10] Proteins bind most cadmium in mammals as inorganic salts. Table 8.1 lists the properties and identifying information of metallic cadmium and cadmium salts. Several cadmium salts (acetate, chloride, fluoride, nitrate, sulfate) are very soluble in water, whereas other salts (carbonate, oxide, sulfide) and metallic Cd are insoluble. In nature, the presence of oxygen and acids increases the solubility of cadmium salts. Cadmium has a relatively high vapor pressure compared with other metals, and cadmium oxides form quickly after the evaporation of cadmium. Cadmium is more volatile than lead. The presence of reactive gases (carbon dioxide, hydrogen chloride, sulfur dioxide, sulfur trioxide, water vapor) in the immediate

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TABLE 8.1. Physical properties and identifying information of cadmium and cadmium salts.

Property	Cadmium	Cadmium Carbonate	Cadmium Acetate	Cadmium Chloride	Cadmium Hydroxide
CAS RN	7440-43-9	513-78-0	543-90-8	10108-64-2	21041-95-2
Empirical formula	Cd	$CdCO_3$	$C_4H_6CdO_4$	$CdCl_2$	$Cd(OH)_2$
Molecular mass (g/mol)	112.41	172.42	230.50	183.32	146.41
Relative density (g/mL)	8.642	4.58[a]	2.341	4.047	4.79
Odor	odorless	odorless	slight vinegar odor	odorless	odorless
Melting point (°C)	320.9	Decomposes at 357	256	568	300
Boiling point (°C)	765	NA	Decomposes	960	Decomposes
Water solubility (g/L)	Insoluble	Insoluble	Very soluble	1,400 (20°C)	0.0026 (26°C)

Property	Cadmium Oxide	Cadmium Sulfide	Cadmium Sulfate	Cadmium Sulfite
CAS RN	1306-19-0	1306-23-6	10124-36-4	13477-23-1
Empirical formula	CdO	CdS	$CdSO_4$	$CdSO_3$
Molecular mass (g/mol)	128.40	144.46	208.46	192.46
Relative density (g/mL)	6.95[b]	4.82[c]	4.691	
Odor	odorless	odorless	odorless	odorless
Melting point (°C)	<1426	1750	1,000	Decomposes
Boiling point (°C)	Decomposes 900–1,000[d]	NA	NA	
Water solubility (g/L)	Insoluble	0.0013 (18°C)	755 (0°C)	Slightly soluble

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.
[a] g/mL at 20°C; [b] Amorphous powder, 8.15 g/cm^3 for crystals; [c] Hexagonal structure, 4.5 g/cm^3 for cubic structure; [d] Decomposes.

environment encourages the formation of cadmium salts (carbonate, chloride, sulfite, sulfate, hydroxide). The heating of cadmium alloys above 321°C produces a golden yellow smoke composed of cadmium oxide fumes compared with gray smoke from zinc fumes.[11] The relatively low melting point, excellent corrosion resistance, high thermoelectric conductivity, and high ductility favor the industrial use of cadmium.

EXPOSURE

Uses

The primary industrial application of cadmium salts is the use of cadmium hydroxide in electrode material of Ni–Cd rechargeable batteries; less commonly, cadmium is a constituent of pigments in plastic and glass as well as a component of protective metal plating on steel. Cadmium sulfide is a yellow to deep-maroon pigment present in some paints, glazes, ceramics, glass, and fireworks. The use of cadmium (Cd laurate, Cd stearate) as a stabilizer in plastics (PVC) and components of alloys has declined significantly. Uncommonly, cadmium is a constituent of semiconductors, ceramic glazes, phosphors for television sets and X-ray screens, and a neutron absorbant in nuclear reactors. A cadmium-containing Asian herbal preparation (*chui-fong tokwan*) was distributed illegally in the United States.

Commercial Process

Cadmium exists in nature primarily in association with zinc sulfide deposits (greenockite, sphalerite) at cadmium/zinc ratios of 1/100–1/1,000. Exposure to cadmium may occur at nonferrous foundries as a contaminant in special high-grade zinc, particularly in finishing workers and furnace operators.[12] A variety of products may contain cadmium as an impurity including phosphate fertilizers, cement, fossil fuels, iron, steel, and nonferrous metals (copper, lead, zinc). The production of cadmium (as cadmium oxide) is a byproduct of roasting of zinc-bearing ores with coke or the refining of lead and copper sulfide ores (galena, malachite). The separation of cadmium occurs by distillation or electrodeposition. Cadmium readily volatilizes during smelting, forming respirable cadmium oxide fumes that may cause cadmium toxicity.[13] This metal is also recovered from recycled, Cd-containing batteries.

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Sources

Air

Volcanic activity is the primary natural source of cadmium in the air; however, anthropogenic sources (e.g., mining/smelting zinc and lead, fuel combustion, phosphate fertilizers, waste disposal, pigment manufacturing plants) account for most of the cadmium present in ambient air. Mean total cadmium concentrations in air range from <1 ng/m^3 in remote areas[14] to 5–40 ng/m^3 in urban and industrial areas; emissions near anthropogenic sources may exceed 100 ng/m^3.[15] The main sources of airborne cadmium in the United States are the burning of fossil fuels and the incineration of municipal waste that contains rechargeable batteries and plastic.[16] Less common sources include the abrasive blasting of steel bridges.[17] The chemical form of cadmium in the air after combustion from the burning of fossil fuels, including tobacco smoke, is primarily a cadmium oxide aerosol.

Soil

The extensive natural distribution of cadmium in the soil occurs with Cd concentrations averaging ~0.1–0.5 mg/kg (ppm) soil, primarily in association with copper, lead, and zinc ores. In a study of agricultural soil remote from Cd sources, the Cd concentrations averaged 0.27 mg/kg.[18] Phosphate fertilizers contain 3–100 µg Cd/g fertilizer; these phosphate fertilizers are the major source of cadmium in agricultural soils.[12] Other sources of terrestrial cadmium include the land disposal of cadmium-containing waste and the application of sewage sludge containing cadmium. Soil Cd concentrations near long-established smelters may exceed 100 mg Cd/kg soil; contamination of the food chain may occur in areas surrounding these facilities.[19] The deposition of cadmium from the air may contribute significant amounts of cadmium to the soil near point sources of cadmium (e.g., smelters and pigment manufacturing plants).[20] In England, contaminated soil from cadmium mines (average, 87 ppm; range, 2–520 ppm) was not associated with adverse health effects, but local conditions may affect the translocation of cadmium from the soil through the food chain to humans.[21,22]

Water

Cadmium concentration in seawater is typically <0.1 µg/L; however, runoff from point sources of Cd may increase seawater Cd concentrations near harbors and estuaries.[23] In a study of the Spring River Basin containing lead and zinc mining and ore processing in the central United States, Cd concentrations in samples of surface waters under peak flow conditions ranged from <1.0–24 µg/L, whereas samples collected during base flow conditions contained Cd concentrations of <1.0–75.0 µg/L.[24] Groundwater seldom contains detectable concentrations of cadmium, unless local industrial or mining wastes contaminate these waters. Typical cadmium concentrations in drinking water are <1 µg/L (ppb) unless point sources of cadmium are nearby.[25] Soft or acidic water increases the leaching of cadmium and lead from distribution and household pipes, but drinking water contributes minor amounts to the total body burden of cadmium.

Diet

The estimated age-weighted daily intakes of cadmium in nonsmoking adult males and females living in the United States are 0.35 µg/kg/day and 0.30 µg/kg/day, respectively.[26] The difference primarily results from differences in gastrointestinal absorption. Total Diet Study by the US Food and Drug Administration during the early 1980s also indicates that the estimated daily amount of Cd ingested by the average US adult is ~30 µg Cd.[27] Food is the major source of cadmium exposure for the general population, with most foods containing some cadmium. Drinking water and ambient air (<0.5 µg Cd/day) are minor sources of cadmium in the diet for the general population, with the exception of tobacco smoke.[28] Cadmium typically occurs in its free ionic form in water, whereas Cd usually exists as a complex with a variety of ligands (e.g., metallothionein) in food.[29] In general, plant foods (e.g., rice, wheat, green leafy vegetables, potatoes, carrots) contain higher cadmium concentrations than eggs, milk, meat, and fish muscle. Soybeans, peanuts, and sunflower seeds have naturally high cadmium concentrations.

Rice is a leading source of increased Cd exposure in the Japanese population compared with the US population. The average daily intake of Cd in the Japanese diet decreased from ~37 µg during the 1977–1981 period to ~25 µg during the 1991–1997 period.[30] The amount of Cd in the Japanese diet correlated strongly to rice consumption. The actual daily contribution of food (1–3 µg Cd/day) to the total body burden of cadmium is much less than the total daily intake because of the limited bioavailability of cadmium. High-fiber diets and diets rich in shellfish increase the uptake of cadmium relative to the general population.[31] Some foods (e.g., kidney and liver (0.2–1.3 ppm), shellfish (0.1–4.7 ppm), leafy vegetables (0.01–0.06 ppm), potatoes, grains, and cereals) readily absorb cadmium from soil contaminated by phosphate fertilizers, polluted water, or sewage sludge.[1]

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The total Cd concentrations are typically higher in the following situations: 1) marine than terrestrial organisms, 2) older than younger organisms, 3) hepatorenal than other tissue, and 4) organisms living near than far away from point sources of cadmium.

The persistence of cadmium in the environment and the long biological half-life (10–30 years) of cadmium account for the accumulation of cadmium in the body with age. The scarcity of chromium in the 1940s resulted in the use of cadmium plating. Acute cadmium poisoning resulted from the acid leaching of cadmium from cadmium alloys in cooking utensils and containers.[32] Most ceramic wares do not now contain acid-leachable Cd concentrations that exceed US FDA standards (0.5 μg/mL).

Lifestyle

Tobacco plants accumulate cadmium depending on soil characteristics; consequently, measurable amounts of cadmium occur in tobacco leaves and mainstream cigarette smoke. Typically, tobacco leaves contain 1–2 μg Cd/g dry weight, resulting in ~0.5–1 μg Cd/cigarette.[33] The mean Cd content of 331 samples of cigarette tobacco from 20 different countries was 1.15 μg/g (range, 0.29–3.38 μg/g), as measured by flameless atomic absorption spectrophotometry after wet digestion with nitric, sulfuric, and perchloric acids.[34] Analysis of tobacco samples in commercial Finnish cigarettes produced from 1920–1984 suggests that the Cd content in tobacco remained relatively stable over those decades.[35]

Tobacco smoking is a significant cadmium source in the form of cadmium oxide for cigarette smokers because mainstream smoke from a cigarette yields 0–6.67 μg Cd depending on the Cd content in the tobacco and smoking characteristics (frequency, duration, intensity).[36] Cd occurs primarily in the particulate phase of smoke. In a study of Saudi Arabian cigarettes with a mean Cd content of 1.81 μg/g dry weight (range, 0.83–2.78 μg/g dry weight), the estimated Cd intake from smoking one pack of cigarettes ranged from 0.22–0.78 μg.[37] Smoking one pack of cigarettes per day doubles the daily intake of cadmium, in part because of the increased uptake of cadmium from the lungs compared with the gastrointestinal tract.[38] The inhalation of passive smoke apparently does not significantly increase blood cadmium concentrations.[39] In contrast to chromium, preliminary studies suggest that lung clearance reduces pulmonary cadmium concentrations after cessation of smoking. In a Finnish study of 45 autopsies, the mean cadmium concentration in the lungs of nonsmokers was 0.4 ± 0.4 μg/g dry weight compared with 3.0 ± 2.2 μg/g dry weight in smokers.[40] The Cd concentration in former smokers decreased to concentrations present in nonsmokers ~20 years after cessation of smoking.

Environmental Fate

Similar to other heavy metals, cadmium is not biodegradable; therefore, the environmental fate of cadmium depends on its physicochemical form.

Air

Cadmium and cadmium salts have negligible vapor pressures; however, combustion processes (e.g., municipal waste incinerators, nonferrous metal production) release small particles in the respirable range (<10 μm). These particles have a residence time of 1–10 days in the atmosphere that allows long-range deposition up to a few thousand kilometers.[23] Deposition of cadmium in urban areas is ~1 order of magnitude greater than the deposition of cadmium in rural areas. Dry deposition and precipitation remove cadmium from the atmosphere. Cadmium and cadmium compounds exist in the air as suspended particles derived from ocean spray, industrial emissions, volcanic discharges, and erosion of soil. Most cadmium appears in the air as cadmium oxide, but other compounds (sulfate, sulfide, chloride) may occur in the atmosphere. These cadmium compounds are stable and do not undergo photochemical reactions.

Soil

Cadmium does not form volatile compounds; therefore, partitioning of cadmium from soil to air does not occur, except through the erosion of cadmium-containing soil. Cadmium is relatively more mobile than most heavy metals (e.g., lead, mercury) with some cadmium leaching from the soil into water, especially under acidic conditions. The strong binding of cadmium to organic matter limits the mobility of Cd in soil.[41] Migration of cadmium depends on soil pH and the presence of organic matter; insoluble Cd salts disperse into sediments, whereas soluble Cd salts are mobile, potentially migrating into water sources. Cadmium accumulates at all levels of the food chain, particularly in plant leaves; however, experimental data suggest that the amount of Cd available for translocation decreases as the total soil Cd concentration increases.[42] Therefore, Cd soil concentrations are not directly correlated to Cd in the food chain unless extremely contaminated soil exists in the area. The binding of cadmium is relatively stronger in wetland than upland soils; thus, Cd is relatively more bioavailable under upland conditions.[43]

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Water

Cadmium is more mobile in an aqueous environment compared with other heavy metals (lead, mercury). Similar to the soil, the Cd concentration in water is inversely related to pH and the amount of organic material. Particulate matter rapidly adsorbs most cadmium released into freshwater, and the listed local conditions determine the amount of cadmium that precipitates onto the river bottom. The reducing and oxidizing potential of water does not affect the concentration of cadmium in water because cadmium exists almost exclusively in the 2+ (soluble) state. Photolysis is not an important mechanism for cadmium degradation in an aquatic environment. The partition of cadmium from water to the atmosphere is probably very limited as a result of the poor volatility of cadmium.

Biomagnification requires the transfer of the toxicant through the food chain by ingestion, whereas bioaccumulation involves the direct uptake of cadmium by each level of the food chain, independent of the uptake of lower levels in the food chain. The extent of the bioaccumulation of cadmium depends on the following factors: the physicochemical properties of the species of cadmium, the presence of other metals, physical conditions (pH, salinity, water temperature), the cation exchange capacity of the soil, and the plant species.[1] Aquatic and terrestrial organisms bioaccumulate and bioconcentrate cadmium, depending on water pH and humic content. Although cadmium accumulates at a variety of levels in the food chain, biomagnification of cadmium in the food chain does not occur because of the low bioavailability of cadmium and the tendency of cadmium to concentrate in the liver and kidney rather than muscle.[44]

DOSE EFFECT

Following both acute and chronic exposures to airborne cadmium, the accumulated dose rather than the deposited dose correlates best with a dose-effect relationship.[45]

Acute Toxicity

Inhalation

Case reports associate fatalities from acute chemical pneumonitis and pulmonary edema from estimated exposure to 50 mg Cd oxide/m^3 for 1 hour[46] and 8.6 mg Cd oxide/m^3 for 5 hours;[47] however, these calculations are questionable because the authors based these values on extrapolations from postmortem Cd concentrations in the lung rather than direct measurement of ambient air exposures. Animal studies suggest that exposure to cadmium at concentrations of >0.5 mg/m^3 may produce alterations in the epithelial cells of the lungs.[48]

Ingestion

Gastrointestinal symptoms develop after exposure to oral doses exceeding 0.07 mg Cd/kg.[23] The gastroenteritis produced by cadmium ingestion and the poor bioavailability of oral cadmium doses limit the acute systemic Cd toxicity, depending on the dose.[49] The estimated ingestion of 150 g cadmium chloride by a 17-year-old girl caused hypotension, respiratory arrest, metabolic acidosis, oliguria, and death, despite intensive care including chelation and intubation.[50]

Chronic Toxicity

Long-term exposure to high concentrations of airborne cadmium causes primarily pulmonary and renal effects. An increased prevalence of the urinary excretion of low-molecular-weight proteins occurs in workers exposed to 20–50 μg Cd/m^3 for 10–20 years and in some individuals in the general population ingesting 140–260 μg Cd/day.[51] Diabetic patients may be more susceptible to cadmium-induced renal proximal tubule dysfunction than nondiabetic patients based on the synergistic effect of diabetes and the cadmium body burden on the urinary excretion of β_2-microblobulin and *N*-acetyl-D-glucosaminidase in a cross-sectional European (Cadmibel) study of 2,327 residents of Cd-polluted and non-polluted areas.[52] In a Swedish population-based study of morning urine samples from 813 middle-aged women, regression analysis indicated an interaction between urinary *N*-acetyl-D-glucosaminidase concentrations and insulin-dependent diabetes (β = 2.3, P = 0.042), but not with non-diabetics (β = 0.8). However, the number of diabetics was insufficient to determine the lowest observed effect level. The estimate of the critical concentration in the renal cortex associated with probable kidney dysfunction in 50% of the general population is ~250 μg Cd/g tissue, whereas the critical level associated with renal dysfunction in 10% of the population is ~200 μg Cd/g tissue.[53,54] Pulmonary effects from exposure to cadmium occur exclusively following inhalation in the work environment with evidence of renal dysfunction. Host and nutritional factors influence the development of cadmium-induced bone changes that occur only after very high cadmium exposure.[51]

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TOXICOKINETICS

Absorption

The two main routes of Cd absorption are the lungs and gastrointestinal tract. Although limited human data are available, animal studies indicate that percutaneous absorption of cadmium is negligible, except under extreme circumstances. Dermal absorption of Cd is limited. The application of soluble cadmium compounds to the skin of guinea pigs resulted in the absorption of 1.8% of the cadmium over 5 hours.[55]

Inhalation

The uptake of cadmium from the lungs averages ~25% (range, ~10–50%) depending on a number of factors, particularly particle size.[51] The relatively greater cadmium absorption from cigarette smoke than ambient air probably results from small particle sizes and high alveolar deposition based on data from animal studies.[56] Atmospheric cadmium exists primarily as suspended particulates; therefore, particle size is the major determinant of cadmium deposition in the alveoli and pulmonary absorption. Less important factors include mucociliary and alveolar clearance, solubility, and transport through the epithelial lining of the lung. Soluble cadmium salts (chloride, sulfate) pass through the alveolar membrane more quickly than less soluble salts (oxides), but the majority (50–100%) of the cadmium dose delivered to the alveoli eventually will be absorbed, regardless of the solubility of the particular cadmium compound.

Ingestion

In general, absorption of metals in humans is variable depending on multiple factors including chemical species, environmental matrix that surrounds the metal, contents of the gastrointestinal tract, diet, age, and nutritional status (e.g., low iron stores). Limited observations of humans indicate that the bioavailability of cadmium compounds ranges from 2.2–9.0% with an average of ~3–5%.[10,57] Animal studies suggest that the presence of metallothionein-bound cadmium in food reduces Cd absorption and changes cadmium distribution;[58] however, the role of metallothionein in the gastrointestinal absorption of cadmium is probably minimal. Mice fed metallothionein-bound cadmium have higher cadmium concentrations in the kidney compared with mice fed similar amounts of cadmium chloride; these metallothionein-bound Cd-fed mice have comparatively lower Cd concentrations in blood and liver.[59,60] Patients with deficiencies of calcium, protein, iron, or zinc absorb relatively more cadmium than patients with normal concentrations of these elements. In a study of volunteers, the average absorption of 25 μg ^{115m}Cd from a test meal was 8.9 ± 2.0% in 10 subjects with low body iron stores (serum ferritin <20 ng/mL) compared with 2.3 ± 0.3% in 12 subjects with normal iron stores (serum ferritin >23 ng/mL).[61]

Distribution

The body burden of cadmium increases throughout life from ~1 μg at birth to ~20–30 mg by age 50, depending on environmental exposure and smoking. The body burden of Cd in workers exposed to high cadmium concentrations ranges up to 200–300 mg. Most cadmium in the body is bound to a small-molecular-weight, cysteine-rich protein (metallothionein).[62] In the blood, metallothionein binds cadmium, concentrating Cd primarily in the erythrocytes. Transport of Cd by the portal circulation results in the uptake of Cd by the hepatocytes, where the presence of Cd induces metallothionein synthesis, resulting in the sequestration of Cd as Cd–metallothionein complex. Although some uptake of the Cd–metallothionein complex occurs in the kidney, most Cd bound to metallothionein is not available for uptake by the tissues in the body. Cd is also loosely bound to other proteins (albumin, amino acids) and sulfhydryl compounds (glutathione, cysteine) in the blood; metallothionein binds a majority (~60%) of the cadmium in the red cells.

After chronic, low-dose cadmium exposure, about one-half of the body burden of cadmium exists in the kidneys and much smaller amounts (i.e., 20-fold less) in the liver. Autopsy data indicate that the body burden varies with age, sex, race, cigarette smoking, and cause of death.[63] The average Cd concentration in the renal cortex ranges from 11–100 mg/kg wet weight with the 90th percentile being about twice the median Cd concentration.[51] After exposure to the relatively higher Cd concentration in the workplace, the liver stores a greater portion of the cadmium burden. The development of cadmium-induced renal dysfunction results in the loss of cadmium from the renal cortex; in these situations, the cadmium concentration in the liver may substantially exceed the cadmium concentration in the kidney. Even in workers dying from the inhalation of cadmium fumes, the cadmium concentration in the lungs is less than renal or hepatic Cd concentrations.[64] Brain, bone, and fat contain relatively low cadmium concentrations. Postmortem examinations indicate that bone is not a major repository for cadmium, with Cd concentrations in bone being ~1,000-fold less

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than those in the renal cortex, depending on age and smoking status.[65]

Elimination

Cadmium does not undergo any direct metabolic conversion (e.g., oxidation, reduction, alkylation). The limited oral bioavailability (i.e., <5–10%) of cadmium results in the excretion of the majority of the ingested dose in the feces. Of the adsorbed cadmium dose, excretion occurs approximately equally in the urine and bile. Renal cadmium excretion is very slow and dose-dependent, probably as a result of the reabsorption of the metallothionein–cadmium complex by the epithelial cells of the proximal tubule at low Cd exposures. Biological half-lives of cadmium in the body are several decades. The amount of cadmium in the urine depends on the total body burden of cadmium, the presence of renal dysfunction, and, to a lesser extent, recent exposure. Increased urinary cadmium excretion occurs when proteinuria develops; high Cd concentrations exist in the absence of proteinuria only after short-term, high-dose exposure to cadmium.[66] The elimination of cadmium from blood follows a 2-compartment model with an initial whole blood elimination half-life of 2–4 months that reflects recent exposure and a slow compartment with a half-life of years (e.g., 7–16 years) reflecting the total body burden of cadmium.[67] Figure 8.1 demonstrates the cadmium elimination curve for a nonsmoking copper-cadmium alloy factory worker with renal tubular damage and a currently smoking worker without evidence of tubular dysfunction. Both workers were followed for up to 13 years after the cessation of cadmium exposure.

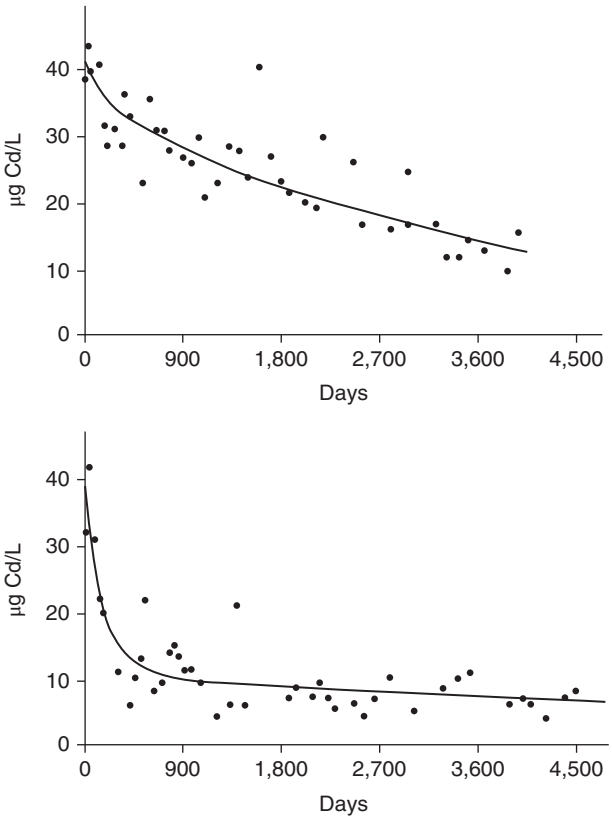


FIGURE 8.1. Blood cadmium elimination curve of two copper-cadmium alloy factory workers followed up to 13 years after cessation of cadmium exposure as measured by spectrophotometric and later atomic absorption methods. (Redrawn from Järup et al.).[67]

Maternal–Fetal Kinetics

There is a maternal–fetal gradient for blood cadmium, with the cadmium concentration in cord blood of neonates generally being lower than maternal Cd concentrations. In contrast to lead and mercury, the placenta is a selective barrier to the transplacental transport of cadmium through the synthesis of metallothionein.[68] This process reduces the cadmium concentration in newborn children to <50% of the maternal concentration.[69,70] Although the placenta selectively retains cadmium because of the synthesis of metallothionein, the placenta limits the transfer of cadmium from the mother to the fetus. In a study of mothers living in Chinese farmland containing cadmium concentrations up to ~9 mg/kg, the maternal blood to cord blood ratio ranged from ~1–99.[71] The cadmium concentration in maternal blood ranged from 0.8–25.2 μg/L with a median of 1.72 μg/L, whereas the cord blood cadmium concentration ranged from 0.02–1.48 μg/L with a median of 0.4 μg/L. Cadmium concentrations in human milk are 5–10% of the concentrations present in maternal blood.[72] In a study of the four stages of breast milk production (colostrums, transitional milk, early mature milk, mature milk), the concentrations of microelements decreased with advancing lactation stages.[73] The mean cadmium concentration in samples from 45 lactating women in each lactation stage ranged from 1.37 ± 0.94 ng/mL in colostrum samples to 0.34 ± 0.19 ng/mL in mature breast milk samples. Analysis of breast milk from smoking mothers suggests that the cadmium concentration in colostrums was significantly higher in smoking than never-smoking mothers; however, the sample size was small.

Chemical Interactions

Reduced iron stores increase cadmium absorption,[61] whereas oral zinc supplements reduce cadmium

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absorption. Increased susceptibility to cadmium-induced bone toxicity is associated with vitamin D, calcium, and protein deficiencies.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Cadmium is a nonessential trace metal that progressively accumulates in the body. The exact mechanism of toxicity for cadmium is unclear. Suspected mechanisms include cadmium binding to sulfhydryl groups on important enzymes, autophagy dysfunction, competition with essential trace elements (zinc, selenium), and interference with calcium-binding sites on regulatory proteins (e.g., calmodulin).[74]

Pathological Changes

Kidney

The kidney is the main target organ following chronic cadmium exposure as a result of the accumulation of Cd in the epithelial cells of the proximal tubule; the subsequent disruption of the resorptive capacity of the proximal tubule causes polyuria, glucosuria, and low-molecular-weight proteinuria. A low-molecular-weight cytosolic protein (metallothionein) selectively binds heavy metal ions including essential trace elements (copper, zinc) and more toxic metals (cadmium, mercury). Metallothionein is an important transport and storage protein that provides some protection against the toxic effects of cadmium in both the kidney and liver[75] as well as regulating the metabolism and function of copper and zinc.[76] In the blood, metallothionein binds cadmium; the glomerulus readily filters cadmium-metallothionein complex followed by reabsorption of the complex by the proximal tubule. Uptake of Cd-metallothionein by lysosomes in the epithelial cells of the proximal tubules results in the degradation of the complex and the release of Cd within the epithelial cell. When the free Cd^{2+} concentrations exceed 50–300 μg/g wet weight in the renal cortex, the free Cd^{2+} interacts with sulfhydryl groups on intracellular proteins to directly alter protein functions (e.g., metal-dependent enzymes), activates calmodulin, and induces oxidative stress leading to cell injury by either necrotic or apoptotic cell death.[77] Early changes induced by excess renal Cd may include alteration of cell–cell adhesion, cellular signaling pathways, and autophagic responses. Subsequently, cytosolic contents of the injured cells are shed into the urine and the reparative process begins in the damaged area where dedifferentiated cells migrate to the denuded area of the basement membrane and replace the injured cells. Animal studies suggest that increased β_2-microglobulinuria begins when the urine concentration of non-metallothionein-bound Cd exceeds 2 ppm, which corresponds to renal cortical Cd concentrations of 150–200 ppm (μg/g).[78] Cd-induced proteinuria progresses slowly and is probably irreversible following continued exposure to high Cd concentrations.[79] The initial renal lesion is proximal tubular dysfunction characterized first by proteinuria, and later by aminoaciduria and glycosuria. Renal failure is rare.[80]

Lungs

Acute exposure to Cd concentrations exceeding 5 mg/m^3 has been associated with the destruction of pulmonary epithelium and the development of tracheobronchitis, pneumonitis, and pulmonary edema. Abnormalities at the cellular level are similar to the damage caused by oxidative stress with alteration of multiple enzymes including catalase, glucose-6-phosphate dehydrogenase, glutathione peroxidase, and superoxide dismutase. Necrosis of Type I alveolar pneumocytes occurs with subsequent hyperplasia of Type II alveolar pneumocytes.

Cadmium is a probable lung carcinogen. Although the mechanism of toxicity is not clear, cadmium is a poor mutagen; this carcinogen probably acts indirectly through non-genotoxic mechanisms. Cadmium potentially induces cancer by multiple mechanisms including inhibition of DNA damage repair, aberrant gene expression, and inhibition of apoptosis. Although the generation of reactive oxygen species by cadmium-induced oxidative stress probably does not directly cause carcinogenic effects, reactive oxygen species play a central role in cadmium carcinogenesis by promoting the above mechanisms.[81]

Bone

Reduction in bone mineral density and increased risk of osteoporosis are complications in residents of cadmium-polluted areas, primarily in subjects with poor nutrition. Animal studies suggest a direct toxic effect of Cd on the bone, resulting in increased bone turnover and decreased bone mineralization. Usually, these subjects have renal toxicity with associated loss

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of calcium and phosphate along with alteration of vitamin D metabolism that may contribute to the formation of structural weakness in the bones. However, several studies suggest that cadmium may have a direct effect on bone resorption based on a correlation between bone resorption biomarkers (urinary hydroxylysylpyridinoline, lysylpyridinoline) and cadmium exposure, particularly in menopausal women.[82] In these studies, reduction in serum parathyroid hormone indicated that cadmium-associated calciuria results from bone resorption rather than decreased tubular resorption.

Postmortem Examination

An autopsy of a worker dying 12 days after exposure to high concentrations of yellow-brown smoke from the melting of copper scrap metal demonstrated diffuse alveolar damage characterized by an exudation of pneumocytes, organized exudate filling the alveolar sacs, interstitial fibrosis, and intra-alveolar hemorrhages. Presumably, this smoke contained high Cd concentrations; however, no analysis of the workplace exposure was reported.[83] The Cd concentration in the right upper lobe was 1.06 μg/g wet weight; no other postmortem values were reported. A 53-year-old steel erector died 5 days after melting cadmium-plated nuts and bolts in a closed space.[47] The postmortem examination demonstrated abnormalities in the respiratory tract and kidneys without significant changes in other organs. There was massive pulmonary edema, hyperemic trachea and bronchi, small pleural effusions, pulmonary consolidation, acute emphysema, and renal cortical necrosis. Histological examination of the kidneys demonstrated bilateral cortical necrosis with thrombosis of the intralobular arteries and afferent arterioles along with thrombotic occlusion of capillary tufts and infarction of many glomeruli. A 55-year-old man died 7 days after welding a cadmium-coated metal fixture that emitted a colored fume.[84] He developed cough and malaise followed by fever, chills, and respiratory distress 3 days later, which progressed despite penicillin therapy and supplemental oxygen. There was no analysis of cadmium concentrations or welding fumes to confirm the extent of cadmium exposure. Postmortem examination demonstrated marked pulmonary edema, thickened, edematous alveolar septae with lymphocytic infiltration and early fibrosis, and hyperplasia of the epithelial lining of the bronchi. The kidneys had occasional pigmented casts in the tubules, but no evidence of cortical damage.

CLINICAL RESPONSE

Acute Inhalation

The clinical features of cadmium-induced metal fume fever include fever, headache, dyspnea, pleuritic chest pain, conjunctivitis, rhinitis, sore throat, and cough developing 4–12 hours after exposure. Although this presentation is similar to acute illnesses caused by inhaling copper, zinc, and other metallic fumes, cadmium-induced metal fume fever may progress to a severe illness. At higher cadmium concentrations, acute chemical pneumonitis may progress to a fatal, acute respiratory distress syndrome.[85,86] Respiratory failure may occur 3–10 days later.[47,87] A 78-year-old nonsmoking man died of respiratory insufficiency 25 days after developing the clinical features of metal fume fever shortly after welding with solder containing 20–30% cadmium.[88] His autopsy demonstrated an elevated blood cadmium concentration (59.4 μg/L) and diffuse bronchopneumonia along with interstitial, perivascular and peribronchial fibrosis. The latter finding suggested preexisting pulmonary disease. Although pulmonary abnormalities on chest X-ray may persist for several months, most acute cases of cadmium-induced respiratory injury recover without sequelae.[89] The 4-year follow-up of a 34-year-old worker with a history of cadmium pneumonitis (cough, dyspnea, myalgia, fever) after a 1-hour exposure to cadmium fumes from welding revealed a normal physical examination and no respiratory complaints.[90] His single-breath diffusing capacity returned to normal, but his total lung capacity was somewhat decreased. A 51-year-old welder developed metal fume fever after welding plates of cadmium silver alloy; he returned to work at the same facility for the next 13 years without further cadmium exposure.[91] Subsequently, he developed progressive pulmonary fibrosis manifested by dyspnea, finger clubbing, basal crepitations, and chest X-ray abnormalities (nodules, diffuse patchy shadowing).

Acute Ingestion

Acute gastroenteritis after Cd ingestion is characterized by the sudden onset of vomiting, diarrhea, and abdominal pain. A large (150 g) ingestion of cadmium chloride produced facial edema, vomiting, hypotension, respiratory arrest, metabolic acidosis, pulmonary edema, oliguria, and ultimately death 30 hours after the ingestion.[50]

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Environmental Exposure

Investigation of the effect of excessive cadmium exposure in the general environment primarily involves the examination of the health effects of residents in several cadmium-polluted areas of Japan and China. These studies indicate that the primary target organs are the kidney and bones. The main source of cadmium for these cohorts was chronic ingestion of Cd-contaminated food in the diet. A cross-sectional study of morning spot urine samples from 1,753 middle-aged Japanese women (mostly aged 35–60 years) did not demonstrate clear evidence of renal tubular dysfunction in the general population without exposure to Cd-polluted areas.[92] Although urinary α_1-microglobulin and β_2-microglobulin concentrations were higher in residents with high urine Cd concentrations than residents with lower urine Cd concentrations, the prevalence of residents with microprotein concentrations above standard cutoffs was similar between residents with high and low cadmium concentrations.

Kidney

The earliest manifestation of Cd-induced renal damage in residents of Cd-polluted areas is the increased excretion of low-molecular-weight proteins (β_2-microglobulin, retinol-binding protein, α_1-microglobulin) along with urinary markers of cytolysis (e.g., *N*-acetyl-β-D-glucosaminidase). The health consequences of proximal renal tubular damage remain controversial including the reversibility of these elevated urinary biomarkers. Most environmental studies on Cd-related kidney injury are observational (i.e., case series) with several prospective cohort studies;[93,94,95] a review of these studies did not detect convincing evidence supporting a risk of progression to chronic renal disease or renal failure following environmental cadmium exposure as measured by declining glomerular filtration rate (GFR).[96] Some studies suggest the increased excretion of these markers is irreversible in some residents, but the concentrations may stabilize with a reduction in Cd exposure.[97] A prospective follow-up study of 102 Japanese residents from Cd-polluted areas of Nagasaki, Japan, suggested that these changes are irreversible in some residents.[98] From 1979–1989, the geometric mean urinary β_2-microglobulin of 28 residents over the age of 40 years increased from 1,135.8 μg/g creatinine to 1,999.7 μg/g creatinine ($P = 0.01$), despite the reduction in the urinary cadmium concentrations during this period as a result of soil remediation. In 1979, 29 residents had urinary β_2-microglobulin concentrations exceeding 1,000 μg/g creatinine; by 1989, 25 of these residents had urinary β_2-microglobulin concentrations exceeding 1,000 μg/g creatinine and 21 residents had higher Cd concentrations than the initial 1979 value.

Tubular proteinuria is frequently asymptomatic. Chronic exposure to very high cadmium concentrations may cause glomerular damage, resulting in decreases in glomerular filtration and reduced creatinine clearance. Some follow-up studies suggest that glomerular damage may also develop in residents of Cd-polluted areas. A follow-up study of 29 Japanese residents demonstrated an increase in the urinary protein concentration and a reduction in creatinine clearance during the study period, despite soil remediation and a reduction in the urinary cadmium concentrations.[99] Although the creatinine clearance did not improve during the 10-year study, the serum creatinine concentrations remained in the upper limits of normal reference ranges. The clinical significance of these values was not evaluated. Japanese cohort studies of the cadmium-contaminated Nagasaki Prefecture also suggest that cadmium-induced renal dysfunction is associated with increased mortality (SMR = 1.41, 95% CI: 1.07–1.83), but this association disappears as the cadmium exposure decreases.[100]

Current observational studies do not support a causal relationship between increased kidney stone risk and environmental or dietary Cd exposure based on urine and blood Cd concentrations.[101] In a Swedish population-based prospective cohort study using a self-administered questionnaire on diet and lifestyle at baseline to estimate dietary data and cadmium concentrations in food, the adjusted hazard ratios for kidney stones did not support a strong association between dietary cadmium and kidney stone risk in men (aHR = 0.97, 95% CI: 0.77–1.23, $n = 707$ cases) or women (aHR = 0.99, 95% CI: 0.89–1.43, $n = 290$ cases).[102]

Bone

Bone abnormalities (osteomalacia, decreased bone mineral density, osteoporosis) occur late in the course of chronic cadmium poisoning, usually in association with nutritional deficiencies associated with alterations in serum vitamin D and increased urinary loss of calcium and phosphorus with alteration of parathyroid hormone concentrations. Itai-itai disease (severe arthralgias, renal dysfunction, osteomalacia, alteration of long bones, multiple fractures) was endemic in the heavily Cd-polluted mining area in the Toyama Prefecture of Japan; this disease occurred primarily in malnourished residents and postmenopausal women. Urinary excretion of cadmium was high (30 μg/g creatinine), and stress fractures were common in these

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patients. Osteomalacia and osteoporosis as measured by a microdensitometer also occurred in Cd-exposed men with renal dysfunction, when compared with non-exposed male subjects; however, the difference in bone density between Cd-exposed and nonexposed men is substantially less than that between Cd-exposed and nonexposed women.[103]

Chronic low-level Cd exposure may also enhance renal loss of calcium and reductions in bone mineral density in populations outside Japan. In postmenopausal Belgian women living near zinc smelters (mean Cd soil concentration, 0.8–14.7 ppm Cd), a 2-fold increase in urinary cadmium correlated to a statistically significant ($P < 0.02$) reduction of 0.01 g/cm^2 in bone density.[104] A doubling of the urinary cadmium was associated with an increase (mean = 1.73, 95% CI: 1.16–2.57) in the relative risk of fractures in women. For women with urinary cadmium concentrations >1 μg/day, the incidence of bone fracture was 13.5/1,000 person-years. A study of 1,021 Swedish residents living in Cd-polluted areas near nickel-cadmium battery production plants demonstrated an ~3-fold increased risk of low forearm bone mineral density in the group with urinary cadmium of >3 nmol/mmol creatinine when compared with the lowest exposure group.[105] There was also a dose-response relationship between increasing cadmium concentrations in the group over 50 years of age and the risk of forearm fractures. In a population-based study of 820 upper-middle-aged Swedish women, multiple linear regression analysis detected significant negative associations between urinary Cd (median = 0.52 μg/L, 95% CI: 0.24–1.3 μg/L) adjusted to density (1.015 g/mL) and bone mineral density ($P = 0.047$).[106] The bone mineral density of women in the upper 99th percentile of urinary Cd concentrations averaged 5–6% lower than women in the bottom 1% of Cd exposure. Increasing urinary Cd was also associated with increasing bone resorption (urine deoxypyridinoline) and decreasing serum parathyroid hormone.

Cardiovascular System

Hypertension

Although some studies suggest an association between modest elevations in systolic blood pressure (1–2 mm Hg)[107] and blood cadmium concentrations, particularly in women,[108] there is no conclusive evidence that cadmium contributes to the development of essential hypertension in the general population.[109,110] Some studies suggest an elevated blood cadmium concentration in hypertensive patients compared with normotensive patients,[111] whereas other studies demonstrated no statistically significant difference in blood cadmium concentrations between the two groups.[80] Existing positive studies indicate that the effect of cadmium on blood pressure is relatively small compared with other confounding variables. The association between blood cadmium concentrations and blood pressure in the positive studies is stronger in never-smoking participants than in former smokers or current smokers. A study of 33,333 Swedish women did not detect an association between cadmium in the diet and cardiovascular disease (myocardial infarction, total cardiovascular disease, stroke).[112] For myocardial infarction, the multivariable-adjusted RR comparing the highest and lowest quartiles of cadmium exposure in the diet was 1.07 (0.88–1.29).

Cardiovascular Disease Mortality

Studies of the effect of cadmium exposure on cardiovascular mortality in the general population are inconclusive. A Belgian study of residents living near cadmium-producing plants did not detect a statistically significant increase in cardiovascular mortality among residents near the plants.[113] Cross-sectional analysis on data from the National Health and Nutrition Examination Surveys (NHANES), 1988–1994 survey, followed for mortality through 2,000 suggested associations between elevated cadmium exposure and increased risk of cardiovascular mortality in men, but not women. Among adult participants, the multivariable-adjusted hazard ratios associated with a 2-fold increase in creatinine-corrected urinary cadmium were 1.21 (95% CI: 1.07–1.36) in men and 0.93 (95% CI: 0.84–1.04) in women.[114] The hazard ratios for cardiovascular disease mortality were 1.36 (95% CI: 1.11–1.66) and 0.82 (95% CI: 0.76–0.89), respectively. Adjusted variables included smoking. Analysis of data from 8,989 participants in the US National Health and Nutrition Examination Survey followed for 4.8 years suggested that environmental cadmium concentrations were associated with increased cardiovascular mortality using Cox regression to analyze the cause of death based on death certificates.[115] Comparing cardiovascular disease mortality in patients with cadmium concentrations in the 80th (0.80 μg/L) and 20th (0.22 μg/L) percentiles, the multivariable-adjusted (smoking status, recent smoking, cumulative smoking dose, sociodemographic/cardiovascular disease risk) hazard ratio was 1.69 (95% CI: 1.03–2.77) for blood cadmium and 1.74 (95% CI: 1.06–2.83) for urine cadmium. Cadmium concentrations were strongly associated with smoking; study limitations (e.g., reliance on death certificates for outcome) prevent conclusions about causation. A meta-analysis of prospective studies on Cd blood concentrations and mortality from cardiovascular disease demonstrated an association of higher

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blood Cd concentrations with increased cardiovascular disease-related deaths (HR = 1.60, 95% CI: 1.21–2.10; I^2 = 21.4%); however, increasing urine Cd concentrations did not correlate to increased mortality from cardiovascular disease (HR = 1.27, 95% CI: 0.84–1.93; I^2 = 81.1%).[116] Cumulative Cd body burdens correlate better to urine than blood Cd concentrations. In this meta-analysis, estimated Cd intake was not associated with increased coronary heart disease mortality (HR = 1.02, 95% CI: 0.88–1.30).

Nervous System

Several studies have associated hair cadmium concentrations with disruptive behavior including children and US Navy recruits.[117] In a study of 149 children aged 5–16 years in a rural Maryland public school system, hair cadmium correlated inversely to intelligence (verbal IQ) and social achievement scores, but not motor function.[118] Interpretation of these studies is complicated by numerous study limitations including lack of control of confounding variables (home environment, parental IQ, lead exposure) and use of a weak cadmium biomarker (hair cadmium). In a prospective cohort study of 106 Chinese children followed for 4.5 years, cadmium umbilical cord concentrations correlated negatively with the Wechsler Preschool and Primary Scale of Intelligence Revised Edition after controlling for confounding variables. However, most studies of environmental cadmium exposure do not demonstrate a negative association between biomarkers of Cd exposure and neurodevelopment (IQ, behavior). A randomized clinical control trial did not demonstrate any statistically significant decrease in scores on intelligence quotient, neuropsychological function or behavior, and blood Cd concentration at 2 years of age, adjusted for concurrent blood lead, caregivers' IQ, and socioeconomic factors.[119] The median whole blood Cd concentration was 0.21 μg/L as measured by inductively coupled plasma/mass spectrometry. Separating the children into categories based on the whole blood Cd concentrations did not demonstrate any statistically significant differences between the groups, with the exception of the California Verbal Learning Test for Children.

Liver

Although cadmium accumulates in the liver, there is little evidence that liver damage occurs in humans exposed to cadmium commonly present in the environment.[120] A Japanese study of 607 nonsmoking and nondrinking women between the ages of 19–78 demonstrated no correlation between blood cadmium concentrations and serum hepatic transaminases.[121] The geometric mean values for the daily Cd intake and the serum cadmium concentration were 24.7 μg and 1.76 μg/L, respectively.

Occupational Exposure

The primary form of cadmium in occupational exposures is cadmium oxide with the primary target organs being the lungs and kidneys.[23] Following inhalation, the toxicity of different cadmium compounds is similar, despite some differences in solubility (e.g., cadmium sulfide, cadmium selenium sulfide). Chronic rhinitis and anosmia are frequent complaints among workers chronically exposed to cadmium. In a non-blinded study of 16 referents and 55 workers exposed to cadmium fumes during brazing, evaluation of olfactory function indicated that 13% of the workers were moderately or severely hyposmic compared with none in the referent group based on butanol detection threshold (local receptors in nasal epithelium) and odor identification (central processing).[122] Forty-four percent (n = 24) of the cadmium-exposed workers were mildly hyposmic compared with 31% (n = 5) of the referent group. The study did not exclude confounding factors (e.g., smoking); the smoking history of the referents was unknown. Yellowing of the teeth is a potential marker of chronic cadmium oxide exposure.

Lungs

Chronic obstructive pulmonary disease occurs frequently in workers exposed to cadmium, but the association between Cd exposure and the development of emphysema remains inconclusive, particularly in cigarette smokers exposed to multiple carcinogens in tobacco smoke.[123] Methodological considerations (e.g., small sample size, healthy worker effect, limited exposure data, diagnostic accuracy, confounding exposure to pulmonary toxins) limit conclusions from these studies. Early studies that did not control for confounding variables (e.g., smoking) demonstrated a significantly increased incidence of emphysema and chronic bronchitis in cadmium workers,[124] but several subsequent studies did not confirm an excess prevalence of respiratory disease.[125] In a study of 57 male workers using cadmium-containing solder (median calculated cumulative dose = 1.7 mg Cd-year/m^3; range, 0.34–9.9 mg Cd-year/m^3) and 31 referents matched for age and height, there was no statistically significant difference in pulmonary function (FVC, FEV_1, FEV%,

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single-breath nitrogen washout) between the two groups despite the presence of elevated β_2-microglobulinuria in 42% of the exposed workers.[126] Separation of the exposed group into exposure categories did not reveal any dose-response relationships between cadmium exposure and pulmonary function. More recent evidence favors some pulmonary effects from cadmium exposure, albeit small.[127,128] In a study of pulmonary function in 69 smoking and nonsmoking male volunteers (mean = 45 years) exposed to ambient air Cd concentrations of 0.008–1.53 mg/m^3 over several years in a cadmium alloy plant, the residual volume of the Cd-exposed workers averaged 8% higher than controls.[129] Workers with the highest cumulative Cd exposure had slightly larger differences (i.e., 10%). There were no statistically significant differences in the values of FVC, FEV_1, or diffusing capacity. In a study of lung function in 101 copper-cadmium alloy manufacturing workers with ≥1-year exposure to cadmium and referents matched for age, sex, and employment status, decrements in diffusing capacity (transfer coefficient) increased with cumulative cadmium exposure.[130] The FEV_1, FEV_1/FVC%, or both were ≥1.96 SD below published reference values in 33% of the cadmium workers and 17% of the references ($P < 0.05$), whereas the transfer factor was below those values in 19% of the cadmium workers and 3% of the referents ($P < 0.01$). Cigarette consumption was similar in the two groups. Estimation of the cumulative exposures of workers in these studies indicated that the ambient air concentrations of cadmium in these facilities were substantially higher than current workplace standards.

Kidney

The kidney is the main target and most sensitive marker of excessive chronic cadmium exposure. Renal tubular dysfunction is an early marker of renal dysfunction in cadmium workers, and low-molecular-weight proteinuria using sensitive markers (β_2-microglobulin, retinol-binding protein, α_1-microglobulin) is a frequent early finding.[131] Subtle defects in glomerular filtration may precede the onset of proximal tubular impairment as detected by increased urinary concentrations of transferrin and protein;[132] however, the presence of high molecular weight proteinuria usually occurs after the development of renal tubular dysfunction.

A case report associated an increased age-related decline in workers with evidence of proteinuria and/or evidence of renal tubular dysfunction; however, evidence of chronic kidney disease as measured by declining GFR is conflicting.[133] A review of 34 Cd-exposed groups including >3,000 subjects did not find consistent evidence of a rapid decline in GFR, despite the inclusion of older workers with proteinuria and heavy Cd exposure.[96] Heterogeneity, the risk of bias, and a lack of information on methods precluded a meta-analysis of the data from these studies. In a 5-year follow-up study of 23 workers removed from workplace exposure to cadmium because of increased urinary excretion of β_2-microglobulin and/or retinol-binding protein, the estimated reduction in glomerular filtration rate (GFR) over the 5 years was 31 mL/minute/1.73 m^2.[134] Direct measurement of the GFR was not available. The low-molecular-weight proteinuria associated with cadmium exposure is slowly progressive and may be irreversible despite cessation of exposure.[54,135] The hypercalcinuria following high cadmium exposures may increase urolithiasis risks; however, observational studies are inconsistent. In a cross-sectional study of 765 Swedish battery workers using the lowest tercile of cumulative cadmium exposure as referents (<250 μg-years/m^3), the incident rate ratio for self-reported kidney stones in workers with the highest cumulative Cd exposure (>5,000 μg-years/m^3) was elevated (incidence rate ratio, IRR = 3.0, 95% CI: 1.3–6.8), but not in the middle tercile (IRR = 1.6, 95% CI: 0.7–3.4).[136] The results were adjusted for age and calendar time, but not for additional risk factors; overall, the quality of the study was low. A meta-analysis of two cross-sectional and two case-control studies comparing the highest and lowest cadmium exposures on renal stone risks reported a summary odds ratio of 1.56 (95% CI: 1.13–2.14, $I^2 = 56.1\%$, $P_{\text{heterogeneity}} = 0.077$).[137] The few studies and substantial heterogeneity indicate the results may not reflect true causation.

Cardiovascular System

Most studies of workers exposed to cadmium have not detected increased mortality from cardiovascular disease. The exact role of cadmium in the development of hypertension in workers with renal dysfunction remains undetermined. In a study of 6,958 cadmium-exposed workers followed for 41 years (mean duration exposure = 12 years), there was no statistically significant increased mortality from hypertensive diseases (SMR = 119, 95% CI: 85–152), when compared with standardized mortality rates for England and Wales.[138] The SMR for circulatory diseases was 89 (95% CI: 84–94) for the total study period, whereas the SMR for ischemic heart disease was 92 (95% CI: 85–98) for the same period. There was also a statistically significant inverse association between cadmium exposure and cerebrovascular mortality. In a study of US cadmium production workers with cadmium exposure for at

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least 6 months, 1940–1969 and followed through 1978, mortality from diseases of the circulatory system in this cohort was lower than expected (SMR = 65, 95% CI: 49–85) including heart disease.[139]

Nervous System

Data on Cd-induced neurological injury are limited, with few data to document occupational exposure to cadmium as a cause of neurological abnormalities. Neurological injuries are not typically associated with cadmium toxicity. Several case reports associate cadmium exposure with neurological changes. A case report associated the development of sensorimotor peripheral neuropathy with cadmium exposure during work as a pipe fitter based on physical examination.[140] The nerve conduction studies and electromyogram were normal with the exception of slightly reduced recruitment of normal-appearing motor units. However, the association with cadmium was based on elevated hair cadmium concentrations that are poor biomarkers of occupational cadmium exposure. The urine cadmium concentration was 5 μg/L. A double-blinded epidemiological survey of 13 retired long-term Cd-exposed workers and 19 age-matched controls reported the presence of peripheral neuropathy in 7 (54%) exposed workers and 2 (11%) controls based on symptoms, physical examination (areflexia, anesthesia), and neurophysiological testing; the diagnosis of a peripheral neuropathy required abnormalities in only 2 of the 4 areas.[141] Multiple regression analysis indicated a correlation (OR = 1.26, 95% CI: 1.04–1.51) between the diagnosis of peripheral neuropathy and urinary Cd.

Reproductive Abnormalities

No conclusive evidence associates cadmium with teratogenic effects, either in animals or humans. Limited evidence in humans suggests the possibility that cadmium exposure causes a reduction in birth weight,[142] decreased height,[71] or prematurity.[143] However, there is no consistent pattern of reproductive abnormalities between various studies of the effect of environmental concentrations of cadmium on fetal development.[144,145] Although near-fatal doses of cadmium cause testicular necrosis in several animal species, a small study of male workers exposed to cadmium oxide fumes did not demonstrate decreased testicular hormones.[146] In a study of 83 Belgian smelter workers with a mean urine Cd concentration of 6.94 μg/g creatinine, the probability of a live birth did not differ between the exposed and 138 unexposed controls.[147] About 25% of the workers had evidence of microproteinuria. Fertility was similar in the two groups based on questionnaires regarding live births, age of the family, and date of marriage. The wives were not interviewed to determine confounding variables. Studies on the effect of cadmium exposure on sex hormones are also inconsistent. A study of 40 infertile Nigerian men with oligozoospermia (<20 million/cm^3) and 20 with azoospermia compared various measures of spermatogenesis with serum Cd concentrations as measured by atomic absorption spectrometry.[148] The serum Cd concentration correlated negatively to several measures of spermatogenesis (e.g., sperm density, motility, viability, morphology) and positively to serum testosterone, follicle-stimulating hormone, luteinizing hormone, and prolactin. The study did not control smoking. A population-based study of 263 Chinese men from Cd-polluted areas did not support the correlation between blood Cd and these sex hormones after adjustment for smoking, body mass index, and alcohol consumption.[149]

Carcinogenesis

The International Agency for Research on Cancer listed cadmium and cadmium compounds as human carcinogens (IARC Group 1) in 1993[150] and the US National Toxicology Program as a compound known to be a human carcinogen in 2000[151] based primarily on an increased risk of lung cancer in some occupational cohorts exposed to cadmium. The US EPA classifies cadmium as a probable human carcinogen (Group B1) by inhalation based on limited evidence of increased lung cancer in humans and sufficient evidence of lung cancer in rats. Mortality studies of cadmium exposure and an increased risk of lung cancer are inconsistent with both positive and negative results. Inadequate controls for confounding factors (e.g., smoking, co-exposure to metallic carcinogens), small numbers of lung cancer deaths, and poor correlation between lung cancer mortality and cumulative Cd exposure complicate the interpretation of these studies. Strong evidence from rat studies indicates that cadmium inhalation can cause lung cancer (pulmonary adenocarcinomas), but the evidence is less convincing in other animal species.

Lungs

Occupational Exposure

In several cohorts of workers exposed to cadmium (cadmium recycling facilities, nickel-cadmium battery plants, cadmium smelters/processing plants), the risk of death

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from lung cancer increased; however, a clear association between specific cumulative Cd exposure levels and lung cancer risk remains uncertain. In a meta-analysis of five occupational cohort studies following a mean of 31 years, the weighted relative risk for lung cancer was 0.68 (95% CI: 0.33–1.41) when comparing the highest and lowest cadmium exposure categories; the RR for three occupational case-control studies was 1.61 (95% CI: 0.94–2.75).[152] The lung cancer data do not demonstrate a linear dose-response.

Many epidemiological studies of occupational cadmium exposure are small with no control for confounding variables (e.g., smoking, arsenic, nickel).[153] Exposure to cigarette smoke significantly increases the whole blood cadmium concentrations; therefore, exposure to cigarette smoke is a confounding variable in epidemiological studies of workers exposed to cadmium. Reevaluation of the US smelter data indicated that cadmium is carcinogenic only in the presence of concomitant exposure to arsenic. After adjustment for age attained, year of hire, and Hispanic ethnicity, a reanalysis of the smelter data indicated a significant positive trend ($P < 0.05$) between cumulative Cd exposure and the risk of lung cancer mortality.[154] The trend was not significant in the absence of concurrent exposure to arsenic trioxide. The number of lung cancer deaths in this study was small ($n = 21$). A study of Swedish battery workers exposed to nickel hydroxide and cadmium oxide detected an increased overall risk of lung cancer (SMR 176, 95% CI: 101–287).[155] However, there was a significant dose-related increase in the risk of lung cancer only for combined exposure to cadmium and arsenic. A study of 926 male nickel-cadmium battery workers in the United Kingdom detected a statistically, nonsignificant elevation of the SMR (111, 95% CI: 81–148) for the exposed cohort, but the risk of lung cancer was not related to estimated cumulative cadmium exposure.[156] Although a review of these data suggested that the carcinogenic classification of probable human carcinogen would be more appropriate than human carcinogen,[157] the International Agency for Research on Cancer reaffirmed the designation of cadmium as a human carcinogen in 2012, primarily based on studies of American smelter workers.[158]

Environmental Exposure

Although a meta-analysis of three prospective population studies of lifetime environmental cadmium exposure based on urine cadmium concentrations and adjustment of lung cancer risk for age and smoking suggested a positive association (RR = 1.68, 95% CI: 1.47–1.92; $P < 0.0001$), the association between lung cancer and chronic cadmium inhalation by residents living near point sources of cadmium is inconsistent. In a meta-analysis of three cohort studies of the general population following a mean of 15 years, the weighted relative lung cancer risk comparing the highest and lowest cadmium exposure groups was 1.42 with a 95% CI of 0.91–2.23.[152] The lung cancer data do not demonstrate a linear dose-response. An increased cancer incidence has not been detected following the ingestion of cadmium in water and food including studies of high cadmium contamination in Japan. A mortality study in the English village of Shipham, where high cadmium concentrations occur in the soil, did not detect a significantly increased cancer incidence when compared with the cancer rates from an adjacent village.[159] The cadmium concentration in garden soil from Shipham ranged up to 360 ppm; these concentrations are substantially higher than cadmium concentrations (i.e., 3 ppm) typically found in polluted Japanese soils. A 17-year observational study of residents near Belgian zinc smelters suggested an association between environmental cadmium exposure (24-hour urinary cadmium excretion) and lung cancer.[160] The adjusted hazard ratio for lung cancer was 1.70 (95% CI: 1.13–2.57, $P = 0.011$) for a doubling of the 24-hour urinary cadmium excretion and 1.57 (95% CI: 1.11–2.24, $P = 0.012$) for a doubling of cadmium concentration in the soil. Adjustments for confounders included smoking and arsenic exposure; however, arsenic concentrations were calculated for only 26% of the study population. The association between lung cancer and cadmium exposure remained statistically significant only when calculating arsenic exposure by the geometric mean arsenic excretion within the 10 districts of the study and not with multiple-regression analysis. Based on a single urinary cadmium concentration at baseline and cancer mortality followed for up to 20 years, the Strong Heart Study of 3,792 American Indians compared baseline urine cadmium concentrations with annual cancer mortality.[161] The adjusted hazard ratio (aHR) comparing the 80th vs. the 20th percentiles of urine cadmium for lung cancer mortality was 2.27 (95% CI: 1.58–3.27) after adjusting for sex, age, smoking status, cigarette pack-years, and body mass index. Urine cadmium concentrations of the study group were not followed during the course of the study.

Prostate

The causal association between cadmium exposure and an increased cancer incidence in tissues other than the lungs is not definitive. The association of cadmium with prostatic cancer is relatively weak and inconsistent;[162,163] however, experimental animal studies

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indicate high cadmium doses produce tumors in multiple tissues of several species and strains by different routes of exposure, including the prostate.[164,165] Some early European epidemiological studies detected an increased risk of prostate cancer following cadmium exposure in the workplace, but more recent studies have not confirmed this relationship. In a cohort mortality study of 522 Swedish men exposed to cadmium for at least 1 year between 1940–1980 in a cadmium-nickel battery factory, the SMR for prostate cancer was 108 ($n = 4$) for all workers; however, the SMR for 295 workers with at least 5 years of Cd exposure and 20 years of latency (i.e., with substantially higher Cd exposure in earlier years) was 148 ($n = 4$). The latter was statistically significant. Several case-control studies of workers exposed to cadmium demonstrate marginal increases in the incidence of prostatic cancer among cadmium workers.[128,166] Other case-control studies did not associate an increased risk of prostate cancer with cadmium exposure.[167,168] The Strong Heart Study did not detect an association between baseline urine cadmium concentrations in the American Indian cohort and prostate cancer mortality during the 20-year study.[161] Rodent studies indicate that chronic inhalation of cadmium produces prostate tumors following cadmium exposure below the Cd concentrations necessary to cause testicular toxicity.[169] Accumulation and retention of prostatic cadmium appear highly androgen-dependent in these studies. Cadmium concentrations high enough to cause testicular necrosis are required to produce Leydig cell tumors in rodents.[170] Higher cadmium doses produce an increased incidence of prostate tumors in animals only following the preservation of testicular function by zinc treatment. Most oral studies in laboratory animals have not found significant increases in cancer incidence.[171] In animal studies, preneoplastic lesions of the prostate appeared in male rats, but these lesions were not dose-related.[169] A meta-analysis of cadmium exposure and the risk of prostate cancer suggests the risk is higher following occupational rather than environmental exposure; however, substantial heterogeneity among studies limits conclusions.[162]

Kidney

Several hypothesis-generating case-control studies suggest that chronic occupational exposure to high cadmium doses (i.e., exceeding current workplace standards) increases the risk of renal cancer, with typical relative risk estimates in the range of 1.3–2.0.[172,173] However, these epidemiological studies examined many types of exposure, and the cadmium exposure estimates were based primarily on questionnaires.

DIAGNOSTIC TESTING

SI Conversion Units

1 μg/L = 0.0089 μmol/L = 8.9 nmol/L
1 μmol/L = 112.4 μg/L
1 nmol/L = 0.112 ng/L
1 nmol/mmol creatinine ≈ 1.12 μg/g creatinine

Analytical Methods

Electrothermal atomic absorption spectrometry (ET/AAS) and inductively coupled plasma/atomic emission spectrometry (ICP/AES) are the most common methods for the determination of cadmium in biological and environmental samples; the limit of detection for the former is ~0.1 μg/L in blood and 1–10 μg/kg (ppb) in food and tissue.[1,51] The limit of detection (LOD) for biological samples using ICP/AES and microwave digestion was 0.15 μg/L.[174] Quality assurance programs (e.g., acid-washing, double-distilled water rinsing, reduced volatilization during analysis) are necessary to ensure that interference, contamination, and analyte loss do not invalidate the measurement of samples with low cadmium concentrations. Although the LOD of neutron activation analysis is relatively low (0.1–1 mg Cd/L), methodological problems limit the use of this analytical technique except for the determination of Cd in tissues (kidney, liver).[175] NIOSH Method 7300 for the determination of cadmium in ambient air (membrane filter, digestion with nitric and perchloric acid) has a LOD of 0.3 μg/L. EPA Method 1638 using inductively coupled plasma/mass spectrometry with nitric acid digestion can detect Cd in water samples with an LOD of 0.025 μg/L. Whole blood specimens should be collected in acid-cleaned, heparinized containers (glass or plastic) that do not contain heavy metal contamination; the specimens should be refrigerated until analysis.[176]

Biomarkers

Blood

Although the total body burden of cadmium is difficult to assess without a renal biopsy, the blood cadmium concentration is the best measure of recent (within the last several months) exposure with some contribution from long-term body burden.[177,178] Blood is typically superior to urine in the assessment of body burden for metals with long biological half-lives (i.e., cadmium) as a result of reduced variability in cadmium concentrations.[179]

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The plasma contains much lower cadmium concentrations than whole blood because most cadmium in whole blood resides in erythrocytes. In the general population, the plasma contains only ~30% of the cadmium in whole blood.[180,181] For workers chronically exposed to cadmium, the plasma contains substantially less Cd (i.e., ~13%) than whole blood, reflecting the increased contribution of the cadmium body burden.[182]

General Population

The whole blood Cd concentration in the unexposed general population is usually <0.5 μg/L with Cd concentrations exceeding 1 μg/L suggesting environmental or dietary Cd exposure. In the Canadian Health Measures Survey, the geometric mean cadmium concentration in adults was 0.42 μg/L (95% CI: 0.37–0.48 μg/L), similar to the geometric mean blood cadmium concentrations in adults from the US NHANES (men, 0.37 μg/L; women, 0.41 μg/L) and Germany (0.58 μg/L) studies.[183] The mean and median blood cadmium concentrations in the Korean National Health and Nutrition Examination Survey (958 men, 944 women) were 1.67 μg/L and 1.55 μg/L, respectively.[184] In a study of 588 nonsmoking Japanese women from 1991–1997, the geometric mean whole blood Cd concentration was 1.90 ± 1.86 μg/L. Whole blood Cd concentrations are relatively lower in children because of the slow excretion of Cd from the body and the accumulation of Cd with age. The median whole blood Cd concentration in a study of ~4,000 urban and rural German children was ~0.1–0.2 μg/L with an upper 95th percentile of <0.4 μg/L.[185]

Relatively higher whole blood cadmium concentrations occur in smokers and subjects with low iron stores than nonsmokers with normal iron stores. Analysis of US NHANES data from 1999–2006 demonstrated a statistically significant difference in the whole blood Cd concentration between cigarette smokers (GM = 0.95 μg/L) and nontobacco consumers (GM = 0.31 μg/L) after adjustment for gender, body mass index, age, ethnicity, and survey year.[186] The whole blood Cd concentrations were not significantly different between smokeless tobacco consumers and nontobacco users. In a regression model using NHANES data from 1999–2010, a history of smoking within the last 5 days was associated with an increase in the geometric mean blood Cd concentration of 55% (range, 40–71%); there was no statistically significant increase in the urine Cd concentration.[187] In a study of 1,811 New York City adults, the geometric mean whole blood Cd concentration was 0.77 μg/L (95% CI: 0.75–0.80 μg/L) compared with 1.53 μg/L in heavy smokers.[188]

Substantial geographical variation occurs in the blood cadmium of middle-aged men 40–59 years of age. An Italian study of urban residents demonstrated 95th percentile cadmium concentrations in nonsmokers and smokers of 1.4 μg/L and 2.3 μg/L, respectively, as measured by graphite furnace atomic absorption spectrophotometry.[189] A study of this age group indicated that the 95th percentile for nonsmokers was <2.0 μg Cd/L, whereas the whole blood cadmium concentration in 1% of men smoking >1 ppd exceeds 7 μg/L.[190]

Toxicity

Biological monitoring equivalents (BEs) are concentrations in blood or urine that correspond to the maximum existing health-based exposure guidelines. The calculated BEs in whole blood for the US EPA chronic RfD and the ATSDR chronic MRL are 5.3 μg/L and 4.4 μg/L, respectively;[191] these concentrations substantially exceed the blood cadmium concentrations in most individuals in the general population.

Postmortem

Case reports of antemortem and postmortem blood suggest the occurrence of postmortem redistribution.[192] In a study of 66 autopsies of adults (mean = 45.6 years) without known excessive Cd exposure, the geometric mean Cd concentration in postmortem femoral and cardiac blood was 2.59 μg/L and 11.81 μg/L, respectively.[193] Nine cases had postmortem blood cadmium concentrations ranging from 82–600 μg/L, as measured by inductively coupled plasma/dynamic reaction cell/mass spectrometry. Regression modeling indicated that the blood cadmium concentration increased with the postmortem interval ($P < 0.006$); the mean time between death and blood collection was 13.3 hours (range, 0.5–24.5 hours). The postmortem Cd concentrations were statistically higher than reference values in the general population. The smoking history was mostly unknown.

Urine

Urine Cd is predominately a measure of cumulative Cd exposure and renal Cd concentrations, but the urine Cd concentration does respond somewhat to recent Cd exposure. Following low cadmium exposures (i.e., general environmental, moderate occupational) in subjects with normal renal function, the urine cadmium concentration reflects total body burden.[194] In a study of 109 renal biopsies from healthy renal transplant donors, kidney Cd concentrations were strongly associated ($r_p = 0.70$, $P < 0.001$) with urine Cd concentrations adjusted for creatinine.[195] The relationship was nonlinear with relatively lower urine Cd concentrations at higher kidney Cd concentrations. The association between kidney Cd and whole blood

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Cd concentrations was weaker ($r_p = 0.44$, $P < 0.001$) than creatinine-adjusted urine Cd concentrations. Following high cadmium exposure, urine cadmium concentrations reflect recent exposure. Urine cadmium concentrations increase substantially when renal tubular damage releases intrarenal cadmium and reduces the further uptake of cadmium in the renal cortex.[196]

General Population

The most important determinants of urine cadmium concentrations in the general population are increasing age, smoking (>10 cigarettes/day), and residence in Cd-polluted areas (e.g., eating vegetables in Cd-contaminated soil).[197] Urine cadmium concentrations usually increase up to the age of 50 years and then decrease.[198] Typical urine Cd concentrations in residents from areas without excessive Cd exposure range from 0.4–1.0 μg/L (3.5–8.9 nmol/L) for nonsmokers and from 1.4–4.0 μg/L (12.5–35.6 nmol/L) in smokers; smoking approximately doubles the baseline urine Cd concentrations. In a Swiss study of 1,409 subjects over the age of 15 years, the median Cd concentration in 24-hour urine samples was 0.13 μg/L; the median Cd concentration for smokers was 0.19 μg/L compared with 0.11 μg/L for never-smokers.[199] The median Cd amount excreted in the 24-hour urine samples was 0.23 μg (95% upper CI: 0.81 μg). In the US NHANES III study (1988–1994) of 22,162 participants (6–>70 years), the mean value for urine cadmium was 0.57 μg/L (0.48 μg/g creatinine). In 7,970 urine samples from the 1999–2002 NHANES survey, the mean Cd concentration was 0.41 μg/L with an upper 95th percentile of 1.3 μg/L. These Cd concentrations were not associated with subclinical renal tubular dysfunction. In 2,848 urine samples from the US adult population in NHANES IV (2009–2010), the geometric mean was 0.179 μg/L and the median was 0.180 μg/L with a 95th percentile of 1.03 μg/L.[200] Urine cadmium concentrations increase with age and smoking. Urine cadmium concentrations averaged 1–2 μg/L in Japanese women from non-polluted areas; samples from other countries demonstrate lower mean urinary cadmium concentrations (0.54–0.88 μg/L).[198] A study of 588 nonsmoking women from 27 locations throughout Japan demonstrated a geometric mean urinary Cd concentration of 2.50 ± 2.14 μg/L compared with 4.39 ± 1.96 μg/g creatinine and 2.59 ± 1.92 μg/L for results corrected to a specific gravity of 1.016.[30] In a study of spot urine samples from middle-aged Japanese women, the grand geometric mean of the urine Cd concentration was 1.3 μg/g creatinine with a range of 0.8–3.2 μg/g creatinine.[92]

Toxicity

Early adverse effects of cadmium toxicity primarily involve the kidney and to a lesser extent the bones. Cadmium-induced renal dysfunction is unlikely in subjects with urine cadmium concentrations of <2 μg/L.[201] However, chronic exposure to low Cd concentrations (<2.0 μg/g creatinine) may cause subclinical increases in the urinary excretion of high molecular mass enzymes and low-molecular-weight proteins,[202] but the threshold concentration of elevated microproteins varies substantially between different studies and populations. In general, 5 μg Cd/g creatinine corresponds to ~100 μg/g renal cortex wet weight.[23] The following classes of proteins are measured in order to assess the effects of cadmium on the kidney: 1) high molecular mass enzymes (alanine aminopeptidase, AAP; *N*-acetyl-β-D-glucosaminidase, NAG), 2) intermediate molecular mass proteins (albumin, transferrin), and 3) low molecular mass proteins (β_2-microglobulin, β_2-M; retinol-binding protein, RBP; α_1-microglobulin, protein HC or α_1-M). Low molecular mass (M_r) proteins easily pass through the glomerulus and are reabsorbed by the proximal tubules. The earliest manifestation of renal tubular toxicity is the increased excretion of low molecular mass proteins (β_2-M, α_1-M, RBP) in the range of 0.5–3 μg Cd/g creatinine, reflecting subclinical dysfunction of proximal renal tubule reabsorption.[203,204] The intermediate M_r proteins (albumin, transferrin) measure glomerular filtration because under normal circumstances only small amounts of these proteins appear in the urine; however, defects in tubular reabsorption also increase the amount of these proteins in the urine because some of these proteins are filtered by the glomerulus and reabsorbed by the renal tubules. The high M_r proteins originate in the proximal renal tubular tissue, and these proteins (NAG, AAP) are usually more sensitive indicators of renal damage than the low M_r proteins (β_2-M, RBP, α_1-M).[205] A variety of factors affect the urinary concentration of these biomarkers including sex, age, body surface area, blood pressure, circadian rhythms, inter-day variability, aspirin, diabetes mellitus, hypertension, and rheumatoid arthritis.[206] Hence, the upper limits of normal depend on the reference population and individual characteristics. Some controversy exists over whether these measures of proximal renal function detect dysfunction before the impairment becomes irreversible.

In a study of 74 Japanese inhabitants with elevated urinary β_2-microglobulin concentrations followed 5 years after cessation of excessive Cd, the urinary β_2-microglobulin continued to increase during the 5-year follow-up in subjects with urine β_2-microglobulin concentrations exceeding 1,000 μg/g creatinine. The

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β_2-microglobulin concentrations in the other inhabitants remained stable (but did not decline).[207] Complications in establishing a definitive threshold concentration at which cadmium-induced renal toxicity begins include the ubiquity of cadmium and confounding factors (diet, individual kinetics, preexisting disease, vitamin deficiencies) that contribute to the development of renal disease following cadmium exposure.[208] Cadmium exposure increases urinary calcium concentrations by decreasing the uptake of calcium by renal tubules;[209] however, there are limited data correlating urine calcium concentrations and renal dysfunction.

Hair

Hair Cd concentrations are qualitative, but not quantitative measures of the body burden of cadmium. Although analysis of cadmium in hair has theoretical advantages, hair cadmium concentrations are not reliable predictors of toxicity or excessive occupational exposure as a result of external contamination and individual variation from differences in hair acidity.[210,211] Hair cadmium concentrations may be helpful as a screening test for the general population,[212] but the weak correlation between Cd body burden and hair concentrations limits the use of this test. In a study of 40 residents of a Cd-polluted area of Japan, hair cadmium concentrations correlated weakly or moderately to body burden; blood cadmium concentrations were much better measures of the cumulative cadmium dose.[213] A study of Cd hair concentrations in maternal and newborn hair suggested that the median cadmium hair concentration in newborns of currently smoking mothers was higher than that in newborns of maternal nonsmokers or past-smokers (i.e., stopped before the third trimester).[214] However, the confidence intervals were wide and Cd hair concentration did not discriminate between the groups on an individual basis. The median hair Cd concentration was not significantly different in another arm of the study comparing light smokers (9.1 ± 5.1 cigarettes/day) and nonsmokers.

Abnormalities

Blood/Urine

Microcytic anemia may develop in heavily exposed workers who usually, but not always, respond to iron therapy. Studies of populations exposed to high Cd concentrations in the diet have not detected evidence of a correlation between cadmium exposure and the presence of anemia.[215] Urine calcium concentrations may increase in patients with chronic exposure to high Cd concentrations.

Neuropsychological Testing

A cross-sectional study of 42 active and retired cadmium workers demonstrated slowing of visuomotor function and simple reaction time along with an increase in complaints consistent with peripheral neuropathy and equilibrium when compared with a nonexposed control group from the same company.[216] These abnormalities were correlated to the maximum urine cadmium concentration measured during the course of their employment. There were no statistically significant differences in neuropsychological scores for switching reaction times, finger tapping, or digit span. The neuropsychological test scores were adjusted for years in school, but not for other, more robust measures of intelligence (e.g., vocabulary). The study did not report nerve conduction studies in the exposed workers; therefore, the neurological complaints could not be correlated to objective evidence of peripheral nerve dysfunction. Neuropsychological testing demonstrated abnormalities of coordination, peripheral sensation, and prolonged reaction times in two workers exposed to cadmium during a fire when compared with reference norms.[217] There were no preexposure neuropsychological test scores to determine any postexposure changes or analyses of ambient air including no ambient cadmium concentrations. Because of the difficulties inherent in comparing neuropsychological test scores between groups, more studies are necessary to define the neurological effects of cadmium.

HEALTH SURVEILLANCE

Risk Assessment

Studies on the benchmark dose for estimating cadmium reference levels indicate that both renal function and osteoporosis are critical reference points. The World Health Organization established a lower 95% confidence limit of the benchmark reference dose (BMDL) for environmental cadmium exposure of 5.0 μg/g creatinine in urine. A review of Japanese data suggested a lower BMDL for cadmium of 1.5–3.2 μg/g creatinine in urine.[218] In a Chinese study of 83 female controls, 104 women from moderately Cd-polluted areas and 151 women from heavily Cd-polluted areas, the BMDL of urine cadmium associated with osteoporosis was 3.78–6.36 μg/g creatinine based on z-scores below −2 from dual-energy X-ray absorptiometry of the nondominant wrist.[219] The BMDL for low bone mass was somewhat lower (2.14–3.99 μg/g creatinine). The

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BMDL of urine cadmium for osteoporosis was substantially lower in women > 60 years of age than in women <60 years of age.

The ATSDR calculated the acute inhalation minimal risk level from a LOAEL of 0.088 mg Cd/m^3 as cadmium oxide based on a study of 5 male and 5 female F344 rats exposed to 0, 0.1, 0.3, 1, 3, or 10 mg cadmium oxide/m^3 (0, 0.088, 0.26, 0.88, 2.6, or 8.8 mg Cd/m^3) 6.2 hours/day, 5 days/week for 2 weeks.[220] The earliest histological abnormalities were alveolar histiocytic infiltrate along with focal inflammation and minimal fibrosis in alveolar septa in rats exposed to Cd concentrations of ≥0.088 mg Cd/m^3. The uncertainty factor was 300 based on factors of 10 for the use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability. The data were unsuitable for benchmark dose analysis because of the lack of data on the shape of the dose-response relationship below the 100% response level. To derive the chronic-duration inhalation MRL, the ATSDR used an analysis of European environmental exposure studies to estimate the internal dose (urinary cadmium expressed as μg/g creatinine) corresponding to a 10% excess risk of low-molecular-weight proteinuria (urinary cadmium dose, UCD_{10}).[23] The 95% lower confidence limit of the UCD_{10} ($UCDL_{10}$) was 0.5 μg/g creatinine; the estimated inhalation exposure to produce this value (in addition to dietary exposure) was 0.1 μg Cd/m^3. The MRL was derived from an uncertainty factor of 10 for human variability and the lack of human data. The chronic inhalation MRL was derived from the 95% lower confidence limit benchmark dose associated with a change of one standard deviation from the control that produced bone mineral density changes in rodents and an uncertainty factor of 100, whereas the ATSDR based the chronic oral MRL on the lower 95% confidence interval of the benchmark dose for low-molecular-weight proteinuria in human studies. The US EPA based their reference doses for water and food on the estimated chronic intake necessary to produce a kidney Cd concentration of 200 μg/g kidney tissue wet weight.

Environmental Monitoring

Airborne cadmium concentrations in the workplace vary substantially, depending on the type of industrial processes, engineering design, and working conditions. Historical estimates of occupational cadmium exposure indicate substantial decreases in ambient air concentrations in most industries since the mid-20th century. Examination of static area sampling results in a study of 926 UK nickel-cadmium battery workers demonstrated the highest mean Cd concentrations (range, 0.35–1.29 mg/m^3) from 1954–1963 compared with the lowest concentration from 1989–1992 (range, 0.002–0.03 mg/m^3).[156] In a study of Chinese Ni-Cd battery factory workers with renal damage and Cd exposure, the geometric mean of area sample was 2.17 mg/m^3 (range, 0.1–32.8 mg/m^3) as Cd oxide dust.[221] Based on reviews of airborne Cd concentrations in 697 areas and 236 personal samples of copper-cadmium alloy workers from 1951–1983, the estimated Cd exposure decreased from 0.6 mg/m^3 in 1926 to 0.056 mg/m^3 in 1980.[222] The US Occupational Safety and Health Administration (OSHA) reduced the permissible exposure limits (PEL) for cadmium by 95% to 5 μg Cd/m^3 for all cadmium compounds in 1992. Table 8.2 lists regulatory standards and recommended guidelines for cadmium exposure in air, water, diet, and biological samples.

Biological Monitoring

The most widely used measure of chronic cadmium exposure is urinary cadmium concentrations, but urine Cd concentrations do not reflect recent changes in cadmium exposure (e.g., first year of occupational Cd exposure) unless the recent Cd exposure is very high. The blood cadmium concentration is a better measure of current (i.e., within several months) exposure; therefore, this biomarker is the preferred biological exposure index during the first year of exposure and during changes in cadmium exposure.[223] Although cadmium is an IARC Group 1 (human) carcinogen, studies associating cytogenetic endpoints and cadmium exposure are inconsistent. As a result of study limitations (small sample size, selection bias, inadequate control of confounders, insufficient exposure data), there currently are inadequate data to correlate cadmium exposure to cytogenetic endpoints.[224]

Urine

Standard practice indicates that cadmium urine concentrations should be measured in μg Cd/g creatinine to correct for dilution, but there is controversy regarding the importance of adjusting the cadmium concentrations for urine density.[225,226] Dilute urine samples (i.e., specific gravity <1.010, urine creatinine <0.3 g/L) should not be used routinely for biological monitoring. Random urine sampling is sufficient because of the long urinary elimination half-life of cadmium. Urine

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TABLE 8.2. Regulations and guidelines for exposure to cadmium and cadmium compounds (as cadmium).

Exposure Limit	Value
OSHA	
PEL–TWA (8-hour)	5 μg/m^3 (action level 2.5 μg/m^3)
PEL-Ceiling	None
PEL-acceptable maximum concentration (30 minutes maximum during 8-hour shift)	None
NIOSH	
REL–TWA (10-hour)	Potential carcinogen[a]
REL–STEL (15-minute)	Potential carcinogen[a]
IDLH	9 mg/m^3
ACGIH	
TLV–TWA (8-hour)	10 μg Cd/m^3 as Cd for total particulate[b]
STEL (15-minute TWA)	None
Biological exposure indices	
Urine	5 μg/g creatinine
Blood	5 μg/L
US FDA	
Bottled water allowable limit	5 μg/L
US EPA	
RfC (chronic inhalation exposure)	None
RfD (chronic oral exposure)	
Food	1 μg/kg/day
Water	0.5 μg/kg/day
Carcinogenic inhalation unit risk	1.8×10^{-3} per μg/m^3
MCL water	5 μg/L
WHO	
Air quality guidelines	0.005 μg/m^3
Water quality guidelines	3 μg/L
ATSDR	
MRL Acute inhalation (<14 days)	0.03 μg/kg/day
Chronic inhalation (≥1 year)	0.01 μg/kg/day
Intermediate oral (15–364 days)	0.5 μg/kg/day
Chronic oral	0.1 μg/kg/day

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; EPA = (US) Environmental Protection Agency; FDA = (US) Food and Drug Administration; IDLH = immediately dangerous to life and health; MCL = maximum contaminate level; MCLG = maximum contaminate level goal; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average.
[a] Lowest feasible concentration; [b] 2 μg Cd/m^3 for the respirable particulate fraction.

specimens should be collected in acid-cleaned plastic or glass bottles, while avoiding the use of rubber or colored plastic. Sampling should occur outside the workplace after removing work clothes and showering to reduce Cd contamination. The pH of the container used for collecting urine samples to analyze β_2-microglobulin concentrations should remain above pH 5.5 because this enzyme degrades below pH 5.5.

Cadmium and Metallothionein

At low cadmium exposure (i.e., general environment, low-moderate occupational exposure), the Cd-binding proteins (e.g., metallothionein) are not saturated and the urine cadmium concentration reflects the body burden of cadmium and the critical target organ (kidney) concentrations.[227] Urine cadmium concentrations reflect recent exposure when the metallothionein binding sites

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are saturated during very high Cd exposures. As the intracellular Cd concentrations increase in the proximal renal tubule, epithelial cell injury develops resulting in substantially increased renal Cd and metallothionein excretion. Consequently, polyuria and proteinuria develop; then, urinary cadmium concentrations reflect substantial amounts of current exposure rather than total body burden.[182] Measurements of urine cadmium concentrations in workers with renal dysfunction do not accurately reflect workplace exposure. Cadmium follows the same transport pathways as intestinal absorption of essential elements and plasma proteins for urinary excretion; consequently, essential metal deficiencies and proteinuria may confound interpretation of the renal effects of cadmium at low concentrations, particularly in the presence of altered renal physiology.[228]

Metallothionein binds most urinary cadmium; therefore, metallothionein is a potentially sensitive indicator of the body burden of cadmium without the disadvantage of interference with external contamination.[229] A urine metallothionein concentration of 300 μg/g creatinine correlates to a urine Cd concentration of 3 μg/g creatinine; however, urine cadmium concentrations with or without correction for density remain the urine biomarker of choice for measuring cadmium body burden. The utility of using chelating agents to monitor cadmium burden remains unclear.

Low-Molecular-Weight Proteins

Classification of urinary proteins includes the following: 1) high-molecular-weight enzymes (microsomal alanine aminopeptidase, *N*-acetyl-β-D-glucosaminidase), 2) intermediate-molecular-weight proteins (albumin, transferrin), and 3) low-molecular-weight proteins (β_2-microglobulin, retinol-binding protein, α_1-microglobulin). The presence of excessive urinary concentrations of low-molecular-weight proteins is a biomarker of proximal renal tubule dysfunction, whereas increased urinary concentrations of intermediate-molecular-weight proteins indicate dysfunction in glomerular filtration. Beta$_2$-microglobulin is the most common measure of proximal renal tubular function; however, this biomarker is unstable in acidic urine and precautions are necessary to prevent degradation during storage. Urinary β_2-microglobulin concentrations of 300–1,000 μg/g creatinine confirm an excessive cadmium exposure with potentially reversible renal tubular dysfunction following cessation of Cd exposure, whereas concentrations ranging from 10,000–100,000 μg/g creatinine imply renal damage.[227] The presence of increased β_2-microglobulin is not specific for Cd-induced renal disease because the elevation of this microprotein occurs in renal disease (e.g., chronic pyelonephritis, urinary tract infections), increasing age, and other disease processes (e.g., congenital Fanconi syndrome).[230]

Urinary retinol-binding protein is also a sensitive indicator of decreased tubular reabsorption, but this low-molecular-weight protein is not specific for cadmium-induced damage in the kidney.[231] Retinol-binding proteins increase in the urine when proximal tubular reabsorption decreases for any cause; therefore, this nonspecific, low-molecular-weight protein supports but does not confirm an excessive cadmium exposure. At urine cadmium concentrations below 10 μg Cd/g creatinine, α_1-microglobulin (protein HC) and *N*-acetyl-β-D-glucosaminidase (NAG) isoenzymes may be sensitive markers of proximal renal tubular dysfunction.[232,233,234] In biological fluids, NAG is present in two major enzymatic forms (A or acidic, B or basic) and several minor forms (I_1, I_2, As, P). Although the B isoform is a more sensitive and reliable biomarker of Cd-induced renal damage than the isoenzyme A form, most analytical methods measure the sum of both forms. Total *N*-acetyl-β-D-glucosaminidase (NAG) is a secretory product (lysosomal enzyme) of the kidney that is a nonspecific marker of renal toxicity. Protein HC is a more stable marker in acidic urine than β_2-microglobulin;[235] however, the lack of data necessary to estimate the predictive value of these measures regarding the clinical course of renal function in subjects with early elevations of these markers limits the routine use of these biomarkers to assess cadmium-induced renal damage. Renal injury following chronic cadmium exposure is usually nonreversible.[236]

Biological Exposure Indices

US OSHA standards require biological monitoring of all cadmium-exposed workers at least annually.[237] If the urine Cd concentration exceeds 3 μg/g creatinine or the urinary β_2-microglobulin concentration exceeds 300 μg/g creatinine, the worker should receive a medical evaluation, the biological monitoring should be increased to every 6 months, and source of increased Cd exposure identified and remediated. Removal from cadmium exposure is required when the urine cadmium concentrations exceed 15 μg/g creatinine or urine Cd concentrations exceed 3 μg/g creatinine in the presence of elevated urinary β_2-microglobulin. United States OSHA standards also require removal from cadmium exposure when the urinary β_2-microglobulin exceeds 1,500 μg/g creatinine.

The World Health Organization recommends an exposure limit of 10 μg Cd/g creatinine and the introduction of control measures at an action level of 5 μg Cd/g creatinine. The presence of biomarkers

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of renal dysfunction (i.e., low-molecular-weight or high-molecular-weight proteinuria) occurs consistently at urine cadmium concentrations exceeding 10 μg Cd/g creatinine; this value corresponds to a cadmium concentration of 200 ppm (μg/g tissue) in the renal cortex.[238] Several studies suggest an increase in low-molecular-weight proteins (β_2-microglobulin, retinol-binding protein) when the urine cadmium concentrations exceed 5 μg Cd/g creatinine.[231,239,240] In a study of 65 Chinese smelter workers exposed to airborne Cd oxide concentrations ranging from 4–187 μg/m^3, 9 workers (13%) had low- or marginally low-molecular-weight proteins and/or high β_2-microglobulin values.[241] Of these nine workers, four had urine Cd concentrations of 5–10 μg/g creatinine (mean exposure duration = 11.6 years, range 2.5–1.2 years). Even though these changes are subclinical, studies suggest that Cd exposures producing these urine Cd concentrations may increase the age-related decline in renal function (i.e., glomerular filtration) even after cessation of Cd exposure.[28] The risk of permanent renal dysfunction at these urine Cd concentrations increases significantly, especially when urinary β_2-microglobulin concentrations exceed 300 μg/g creatinine.[227] The ACGIH recommended lowering the biological exposure indices to 5 μg Cd/g creatinine in 1993. The basis for this lower level of cadmium exposure is the prevention of early biochemical changes in the kidney; however, a direct link between the appearance of these biochemical changes and the subsequent development of permanent kidney damage remains controversial.[242]

Blood

Concentrations

Whole blood cadmium concentrations reflect both recent and long-term cadmium exposure; after exposure creases, the initial half-life is ~2–4 months followed by the terminal half-life of several decades. Several years after exposure ceases, the whole blood Cd concentrations reflect the total body burden. Elevated blood Cd concentrations occur within weeks of acute exposure and stabilize within a few months in the presence of continuing Cd exposure. The whole blood Cd concentration reflects the intensity of exposure.[157] In a study of 17 newly hired Swedish Cd-Ni battery factory workers, the whole blood Cd concentration increased for the first 3 months and then plateaued.[243] Typical whole blood Cd concentrations in Cd-exposed workers range from 5–50 μg/L with high-dose exposures producing whole blood concentrations up to 100–300 μg/L. In workers with moderate Cd exposure (whole blood <10 μg/L), the blood cadmium concentration reflects the amount of cadmium exposure within the last several months; however, as the body burden of cadmium increases from prolonged exposure, a greater portion of the blood cadmium results from contributions from the body burden of cadmium. Consequently, the blood cadmium concentration is most useful to assess recent changes in exposure to cadmium in workers with moderate exposures and evaluate the risk of renal damage after cadmium exposure ceases in workers with large body burdens of cadmium. Smokers have higher whole blood Cd concentrations than nonsmokers. In a study of 158 cadmium workers, the mean whole blood cadmium concentration in active smokers was 0.97 μg/L compared with 0.85 μg/L in nonsmoking workers without passive smoke exposure; the effect of smoking on blood Cd concentrations is greatest at Cd concentrations near the concentrations present following typical environmental exposure.[244] Blood cadmium concentrations also increase with age. Cumulative cadmium in the blood is a better measure of cumulative dose than the retrospective estimation of historical air cadmium concentrations.[245]

In a study of 18 men (9 smokers, 9 nonsmokers) employed in an alkaline battery factory with a mean duration of employment of 10 years (range, 2–29 years), the mean airborne Cd concentration collected in personal samplers was 7.6 μg/m^3 (95% CI: 7.1–8.8 μg/m^3), whereas the mean whole blood Cd concentration was 14.1 μg/L (CV = 17%). There was a statistically significant difference in the whole blood Cd concentration between smokers and nonsmokers, with the former being ~2-fold higher than the latter. Cadmium exposure exceeding whole blood Cd concentrations of 10 μg/L for 20 years was associated with an increased incidence of renal dysfunction. A study of cadmium workers revealed that 10% of the workers with blood concentrations of 10 μg Cd/L for 30–40 years had elevated excretion of low-molecular-weight proteins in their urine.[246]

Biological Exposure Indices

US OSHA standards require biological monitoring of all cadmium-exposed workers at least annually for urine cadmium, urine β_2-microglobulin, and blood cadmium.[237] Removal from cadmium exposure is required when the whole blood cadmium concentrations exceed 15 μg/L. If the whole Cd concentration exceeds 5 μg/L, the biological monitoring should be increased to every 6 months and the source of increased Cd exposure identified and remediated. The World Health Organization recommends an action level of 5 μg Cd/L and an upper limit of exposure of 10 μg Cd/L. Recently, the ACGIH recommended lowering the biological exposure index for cadmium from 10 μg Cd/L

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to 5 μg Cd/L. The new US OSHA standards require removal from exposure to cadmium when the blood cadmium concentration exceeds 15 μg Cd/L or the blood cadmium concentration exceeds 5 μg Cd/L in the presence of an elevation of urinary β_2-microglobulin. The German Biological Tolerance Value (BAT) is 15 μg Cd/L and is a temporary guideline for medical examination.

Medical monitoring

The purpose of the medical surveillance program is the periodic monitoring of cadmium workers for recent cadmium exposure, cadmium body burden, and potential or current kidney damage. The preplacement examination should include a comprehensive work and medical history with a careful record of smoking history, diet, and prior renal disease (e.g., chronic pyelonephritis, diabetes-associated renal dysfunction), prostate exam, screening pulmonary function tests, chest X-ray, and a complete blood panel (complete blood count, BUN, creatinine, alanine aminotransferase). Analysis of the urine should include cadmium concentration, albumin, glucose, and total and low-molecular-weight protein concentrations. Follow-up medical examinations depend on the results of biological monitoring. If the results are normal, the workers should be re-examined in 1 year and then biennially thereafter.

TREATMENT

Stabilization

The primary risk following severe acute exposure to very high cadmium oxide fumes is the development of metal fume fever (cough, upper respiratory tract irritation), the delayed development of pneumonitis, and potentially fatal pulmonary insufficiency. Patients should be removed from further cadmium exposure, and contaminated skin should be washed thoroughly with soap and water after the removal of contaminated clothing. Symptomatic patients should be monitored for respiratory insufficiency with pulse oximetry.

Gut Decontamination

Vomiting usually occurs after the ingestion of toxicologically significant amounts of cadmium. There is no evidence that cadmium binds to charcoal. Treatment is supportive with the replacement of fluid loss and antiemetic medication for nausea and vomiting. There are few human data to guide therapy following the ingestion of large doses of soluble cadmium compounds.

Elimination Enhancement

There are inadequate human or animal data to support the use of hemodialysis to increase the removal of cadmium. In a study of 100 male smokers on maintenance hemodialysis for chronic renal failure, the mean whole blood Cd concentration before hemodialysis was 6.22 ± 1.24 μg/L (95% CI: 5.45–6.99 μg/L) compared with 4.07 ± 1.53 μg/L (95% CI: 3.36–4.78 μg/L).[247] *In vitro* studies suggest that extra-corporeal complexing hemodialysis as an adjunct to chelation therapy may reduce the exposure of the kidney to the toxicity of chelating agents (e.g., EDTA); however, inadequate data are available to recommend this therapy.[248]

Chelation

Inadequate data are available to determine the effectiveness of chelating agents for acute or chronic cadmium poisoning; common antidotes tested include British Anti-Lewisite (BAL), calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$), 2,3-dimercaptosuccinic acid (DMSA), 2,3-dimercapto-1-propanesulfmonic acid (DMPS), and dithiocarbamate compounds (diethyldithiocarbamate, dimethyldithiocarbamate).[249] Animal studies suggest $CaNa_2EDTA$ and DMSA are effective chelating agents for acute cadmium toxicity when administered within 2–8 hours,[250,251] but the issues of unproven clinical efficacy and redistribution to other tissues (e.g., brain, kidney) remain a concern, particularly with $CaNa_2EDTA$.[252,253] The efficacy of chelating agents for improving chronic cadmium toxicity (i.e., renal dysfunction) is unproven. Binding of most plasma cadmium to proteins and other molecules (albumin, macroglobulin, metallothionein) limits the ability of chelating agents to eliminate cadmium from target organs of toxicity.[77]

British anti-Lewisite (BAL) increases cadmium nephrotoxicity; therefore, this chelator is not recommended for cadmium toxicity. As a result of the lack of effective chelating agents, chronic cadmium exposures require no chelation; treatment involves the removal of the person from sources of cadmium contamination. In a study of 17 workers removed from cadmium exposure for elevated urine cadmium and β_2-microglobulin concentrations, periodic administration of ethylenediaminetetraacetic acid (0.5 g IV EDTA/day for 3 days once a year) did not reduce chronic Cd-induced renal

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dysfunction.[254] Chelation therapy was administered 1989–1999 with the exception of 1992–1994. The reversibility of renal dysfunction was associated with urine Cd concentration below 10 μg/g creatinine at the time of removal from Cd exposure, whereas there was no reduction in Cd-induced renal damage in the workers with urine cadmium concentration above that value. The annual administration of EDTA had no beneficial effect on renal tubular dysfunction as measured by urinary β_2-microglobulin concentrations. Because of the lack of any clinically effective chelating agent, experimental work continues on new chelating agents (THP-12-ane N_4, monoesters of DMSA).[255,256] *In vitro* studies suggest that DMSA is superior to DMPS and *N*-acetyl-cysteine as a chelating agent to efficiently bind the Cd-metallothionein complex and theoretically enhance the urinary Cd excretion; however, these chelating agents also removed zinc.[257]

Supportive Care

Treatment of acute poisoning from cadmium fumes remains supportive with attention toward fluid and electrolyte balance, oxygenation, and the detection of chemical pneumonitis with respiratory failure. Screening tests include serum creatinine, urine analysis (creatinine, protein, glucose, amino acids, calcium), chest X-ray, arterial blood gases, and complete blood count. The treatment for chronic cadmium toxicity primarily involves supportive care and removal from exposure to cadmium sources.

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Chapter 9

CHROMIUM

The most stable and common form of chromium is the trivalent state (Cr^{3+}), whereas the most common commercial form of chromium is the strongly oxidizing, hexavalent state (Cr^{6+}). Elemental chromium (0) does not occur naturally on earth. Trivalent chromium is an essential trace metal necessary for the formation of glucose tolerance factors and the metabolism of insulin that has commercial applications in tanning and pigments. Commercial applications of Cr^{6+} compounds include corrosion inhibition, plating, glassware-cleaning solutions, wood preservatives, manufacture of safety matches, metal finishing, and the production of pigments.

TRIVALENT

HISTORY

In 1798, Vaquelin discovered the element chromium in the Siberian red lead ore, crocoite ($PbCrO_4$). Chromium is the sixth-most abundant element in the earth's crust. This metal always occurs in combination with other elements, displaying a wide variety of colors. Only meteorites contain free chromium; most chromium exists in chromite (Cr^{3+}) ore along with iron and oxygen.[1] The mining of chromite ore in the United States ceased in 1961; subsequently, the United States became totally dependent on foreign sources of chromium by 1985, until surface mining of chromite resumed in the late 2000s.[2]

PHYSICOCHEMICAL PROPERTIES

Table 9.1 lists the identifying information and physical properties of elemental and trivalent chromium. Although the oxidation states of chromium range from 2− to 6+, the important valences are Cr^{3+} and Cr^{6+}. Elemental chromium (Cr^0) does not occur naturally on earth. Most chromium compounds exist as halides, oxides, or sulfides. Most naturally occurring chromium exists in the trivalent state, predominantly combined with iron or other metal oxides. The most stable form of chromium is the trivalent oxide form that has low solubility and limited reactivity, resulting in limited mobility in the environment and low toxicity.[3] The divalent (chromous) form is a strong reductant; this form of chromium rapidly decomposes in air or water to the chromic (trivalent) state. Cr^{4+} (chromium oxide, CrO_2) and Cr^{5+} compounds are relatively unstable and occur infrequently in nature.

As indicated in Table 9.1, most trivalent chromium compounds are poorly water-soluble in pH 4–11 except acetate, chloride (hexahydrate), and nitrate salts. In alkaline media, trivalent chromium easily oxidizes to hexavalent chromium. Basic chromium sulfate is an unusual hexa-coordinate, a corrosive form of trivalent chromium that liberates up to 6 mol of hydrogen ions per mole and avidly binds proteins in tissues.[4] Although there is no direct evidence that biological systems can

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TABLE 9.1. Identifying information and physical properties of metallic, trivalent, and tetravalent chromium.

Physical Characteristic	Chromium	Chromium Chloride	Chromite	Chromium Oxide	Chromium Phosphate
CAS RN	7440-47-3	10025-73-7	1308-31-2	1308-38-9	7789-04-0
Synonym	Elemental chromium, chrome	Chromium trichloride	Chromite ore, ferro-chromite	Chromic oxide, chromium sesquioxide	Chromium ortho-phosphate, Amaudon's Green®
Molecular formula	Cr	$CrCl_3$	$FeCr_2O_4$	Cr_2O_3	$CrPO_4$
Molecular weight (g/mol)	51.996	158.35	223.84	151.99	146.97
Valence	0	+3	+3	+3	+3
Color	Steel-gray	Violet–purple	Brown–black	Green	Gray–brown or black
Physical state	Solid	Solid	Solid	Solid	Solid
Odor	Odorless	NA	NA	NA	NA
Melting point (°C)	~1900	~1150 (1300)[a]	>1,870	2435	>1800
Density (g/mL)	7.14 (28°C)	2.87 (25°C)	4.97	5.22 (25°C)	2.94 (32.5°C)
Water solubility (25°C)	Insoluble	Sightly soluble (hot water)	Insoluble	Insoluble	Insoluble
Vapor pressure (mm Hg)	1 (1616°C)	NA	NA	NA	NA

Physical Characteristic	Chromium Sulfate	Chromium Hydroxide Sulfate	Chromium Picolinate	Sodium Chromite	Chromium Dioxide
CAS RN	10101-53-8	12336-95-7	14639-25-9	12314-42-0	12018-01-8
Synonym	Sulfuric acid, Cr^{3+} salt, Chromitan B	Basic chromium sulfate	CrPic, chromium 2-pyridine-carboxylate		Chromium (Cr^{4+}) oxide
Molecular formula	$Cr_2(SO_4)_3$	$CrOHSO_4$	$C_{18}H_{12}CrN_3O_6$	$NaCrO_2$	CrO_2
Molecular weight (g/mol)	392.18	165.1	418.3	106.98	83.99
Valence	3	3	3	3	4
Color	Violet, red, peach	Green	Ruby red	NA	Black-brown
Physical state	Solid	Solid, powder	Crystal	NA	Solid
Odor	NA	NA	NA	NA	NA
Melting point (°C)	90–100	>900	NA	NA	300[a]
Density (g/mL)	3.012	1.25	NA	NA	NA
Water solubility (g/L)	Insoluble	2,000	0.001 (25°C)	NA	Insoluble
Vapor pressure (mm Hg)	NA	NA	NA	NA	NA

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.
[a] Decomposes.

convert trivalent compounds to hexavalent compounds,[5] *in vitro* studies suggest the possibility of the conversion of Cr^{3+} to Cr^{6+} by H_2O_2 or the glucose oxidase system.[6]

EXPOSURE

Production Processes

Chromite ore (Cr^{3+}) is the major source of chromium with the highest grade of ore ($FeOCr_2O_3$) containing slightly more than 50% chromic oxide (Cr^{3+}). Production of chromium metal involves the reduction of chromite ore with aluminum, carbon, or silicon followed by purification. Commercial production of basic chromic sulfate for the tanning industry typically involves the reduction of sodium dichromate with organic compounds (e.g., molasses) in the presence of sulfuric acid or the reduction of dichromate with sulfur dioxide. Limited amounts of chromite ores are mined in Oregon, but most chromite for the use of chromium in the United States is imported (South Africa, Kazakhstan, Russia, Zimbabwe).

Uses

The primary users of chromium compounds are the chemical, metallurgical (stainless steel, mild steel, high alloy steel), and refractory industries (heat-resistant). Commercial applications of trivalent chromium primarily involve leather tanning and the production of green, orange, red, and yellow pigments. The steel industry is

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a major consumer of chromium metal during the production of stainless steel. In addition to stainless steel, chromium applications in the metallurgical industry include the use of ferrochromium intermediates in cast irons and nonferrous alloys. The high melting point of chromium and its resistance to acid and alkali are ideal characteristics in the refractory industry. Chromium is a component of chrome and chrome-magnesite castables, chrome-magnesite firebricks in furnaces, and granular chromite in various heat-resistant applications. Trivalent chromium picolinate is an ergogenic aid and a dietary supplement for insulin-dependent diabetes mellitus and hypoglycemia; however, the use of chromium for these indications remains equivocal.[7,8] A meta-analysis of seven randomized clinical trials of patients with type 2 diabetes mellitus using >250 μg Cr^{3+}/day for 3 months suggested that Cr^{3+} supplementation reduced fasting blood sugar compared with placebo; HbA1c, body mass index, and lipids remained unchanged.[9] Although the commercial applications of natural isotopes (^{50}Cr, ^{52}Cr, ^{53}Cr, ^{54}Cr) are limited, radioactive isotope ^{51}Cr is commonly used in biomedicine.

Sources

Although air is the major route of occupational exposure to chromium, inhalation is a minor route of exposure for the general population.[10] Most chromium released into the environment results from human activities at stationary point sources (waste incineration, fuel combustion, industrial processes). Combustion and the processing of ore discharge mostly trivalent chromium into the environment as chromium oxide;[11] however, small amounts of hexavalent chromium occur in fly ash from coal-fired power plants[12] and soil near chromate manufacturing sites.

Almost all of the exposure of the general population to chromium results from the chromium in the diet with food and water accounting for a mean daily intake of ~60 μg and 2 μg, respectively.[2] The estimated mean daily intake of chromium from air is <0.2–0.4. Chromium picolinate is a popular supplement for weight loss and bodybuilding, despite the lack of proven efficacy.[13,14] This compound is also an experimental drug for the treatment of atypical depression.[15]

Air

Total chromium concentrations in US outdoor ambient air are usually low (median, <0.02 μg/m^3).[16] Typical total chromium concentrations in rural areas of the United States are <0.01 μg Cr/m^3, whereas concentrations in urban areas average 0.01–0.03 μg/m^3 with a range up to 0.6 μg/m^3.[17] Stationary fuel combustion accounted for slightly less than half of the total airborne emissions of chromium in Los Angeles between 1976–1980; releases from metal industries accounted for 26–45%.[18] Total chromium in fly ash typically ranges from about 300–600 μg/g fly ash.[19] Although hexavalent chromium (CrO_2Cl_2, CrO_3) is present in fly ash from coal-fired power plants, most chromium emitted into the ambient air from combustion processes and ore processing industries exists as Cr_2O_3 (Cr^{3+}).[10] Chromium is a constituent of cigarettes;[20] the presence of chromium in cigarette smoke may increase chromium concentrations in indoor air substantially above outdoor ambient air concentrations of chromium.

Soil

Chromium concentrations vary widely in soil depending on the composition of parent rocks. A collection of US soil samples demonstrated total chromium concentrations ranging from 1–2,000 mg/kg with a geometric mean of ~37 ± 2.37 mg/kg (estimated arithmetic mean, 54 mg/kg).[21] Deposition of commercial products containing chromium accounts for a majority of the chromium in soil; very high chromium concentrations in soil may result from the deposition of these commercial products in local areas (e.g., landfills).[22] Fertilizers may contain chromium as well as other metals (e.g., arsenic, cadmium, lead, nickel). In a study of Canadian tree planting operations using commercial bulk fertilizers, the total chromium concentration in six samples ranged from 50–114 μg/g (ppm) as measured by inductive coupled plasma/mass spectrometry.[23] The average soil concentration of total chromium underneath wood decks treated with a chromate-containing wood preservative was 43 mg/kg.[24] Most chromium in soil occurs as insoluble trivalent salts (oxide, carbonate). Bioaccumulation of chromium from soil to plants is relatively low, and biomagnification of chromium up the terrestrial food chain is unlikely.[25]

Water

Shallow ground water in the United States typically contains total chromium concentrations ranging from 2–10 μg/L compared with a mean chromium concentration of 0.3 μg/L in sea water.[26] The total chromium concentrations in US rivers range from <1–30 μg/L with a median of ~10 μg/L.[27] Chromium in the aquatic phase exists either in solubilized solution or suspended particles. Soluble chromium accounts for a small amount of the total chromium in water as both hexavalent and

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trivalent chromium. The major source of chromium in aquatic systems is domestic wastewater effluents. Less important sources of chromium in aquatic systems include the following sources in the order of importance: metal manufacturing, ocean dumping of sewage, chemical manufacturing, processing nonferrous metals, and atmospheric fallout.[22]

Diet

Food (e.g., meat, fish, fruits, vegetables) is the major source of chromium for most individuals; drinking water does not contribute significant amounts of chromium (<4 μg) to the diet unless total chromium concentrations exceed 25 μg/L.[10] The typical total chromium concentration in US drinking water averages 0.4–8.0 μg/L with a mean value of 1.8 μg/L; most values are below 5 μg/L.[28] Corrosion of the water pipes may increase the total chromium concentration up to 15 μg/L;[29] however, contaminated wells near anthropogenic sources of chromium may contain substantially higher chromium concentrations. The contribution of airborne chromium to the daily intake of chromium in persons without occupational chromium exposure is minimal (<0.2–0.6 μg) because of the very low total chromium concentrations in ambient air.

Trivalent chromium is probably an essential nutrient with an adequate daily intake of 20–45 μg in healthy adolescents and adults;[2] this value corresponds to the recommended daily intake of trivalent chromium for adults by the US Institute of Medicine in the National Academy of Sciences.[30] The US Food and Drug Administration recommends daily intake of total chromium is 120 μg. Studies of the US diet indicate that the amount of total chromium ranges from 25–224 μg/day with a mean of 60–79 μg/day.[31,32] A study of 32 volunteers indicated that the average daily diet of most people ranges from 10–40 μg Cr; the bioavailability of dietary chromium was dose dependent, ranging from 2% at 10 μg/day to 0.5% at 40 μg/day.[33]

The estimated daily oral intake of total chromium for UK infants (1 year), children (11 years), and adults is 33–45 μg, 123–171 μg, and 246–343 μg, respectively.[10] The reported daily intake of total chromium from the diet has decreased over the last few decades as a result of improved instrumentation and a reduction in contamination from sources (e.g., stainless steel containers).[34] Most fresh foods contain low total chromium concentrations including vegetables (20–50 μg/kg), fruits (20 μg/kg), and grains/cereals (40 μg/kg).[17] Foods high in chromium include green beans, broccoli, high-bran breakfast cereals, and some brands of beer and wine.[35] Frozen or canned vegetables, canned fruits, chicken eggs, seafood, and meat may contain up to 200 μg Cr/kg.[16] In a study of fish from 167 Northeastern US lakes, the mean total chromium concentration was 0.19 μg/g with a range of 0.03–1.46 μg/g.[36]

ENVIRONMENTAL FATE

Although there are limited data on the speciation of chromium, trivalent chromium is the predominant species in the environment.[10] The environmental fate of chromium depends on its chemical species. Trivalent chromium forms relatively inert precipitates, and this form of chromium may persist in soil or sediments. However, the bioavailability of trivalent chromium is limited.

Air

Chromium particles in air possess mass median diameters of ~1 μm.[37] Removal of chromium from the atmosphere occurs primarily by dry deposition and to a lesser extent wet deposition. Based on the size of chromium particles, the expected residence time in the air is <10–14 days. Chromium compounds do not volatilize from water. Canadian studies suggest that most (>90%) of the chromium in air is trivalent chromium.[10]

Soil

The mobility of trivalent chromium (i.e., predominant oxidation state) in soil is relatively poor, especially compared with other metals.[38] The fate of chromium in soil depends on the redox potential and pH of the soil. The presence of low levels of organic matter, oxygen, manganese dioxide, moisture, and brush fires facilitates the conversion of the trivalent form to the hexavalent form.[39] In most soils, chromium occurs primarily in the trivalent state (i.e., insoluble carbonate or oxide) that is relatively immobile because of its strong adsorption to organic particles.[40] Soluble chromium compounds are more mobile in soil, and the solubility of trivalent chromium in soil may increase as a result of the formation of soluble complexes with organic matter in acidic soil. Available evidence indicates that biomagnification of chromium in the aquatic food chain (water → marine organism) and bioaccumulation in plants (soil → above ground plant parts) are not clinically significant; most chromium absorbed from soil to roots is not translocated to above ground plant parts.[41] Additionally, biomagnification in the terrestrial food chain (soil → plants → animals) is unlikely.[2,26]

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Water

Chromium compounds do not volatilize from surface water to air; most of the aqueous chromium in surface water ultimately deposits in the sediment with residence times up to 18 years in lake water based on an analysis of water in the Great Lakes.[42] Soluble chromium accounts for a very small percentage (i.e., <0.002%) of the total chromium in water, and particles (iron oxide, clay, organic) suspended in water absorb most chromium.[2] The valence state of chromium in water depends on pH and redox potential in the aquifer. Trivalent chromium predominates under reducing conditions, typical of the more acidic conditions in deep groundwater. Although the oxidation of trivalent chromium to hexavalent chromium may occur in aerobic water, the oxidation half-life is very long (in years).[43] Biomagnification of chromium along the terrestrial food chain is unlikely because of the low bioavailability of chromium due to the formation of complexes with humic acid and the limited translocation of chromium to edible plant parts.[41,44]

DOSE EFFECT

Ingestion

Other than the corrosive chromium sulfate, trivalent chromium compounds are relatively nontoxic. In nutritional studies, no signs of toxicity occurred following the ingestion of up to 1 mg trivalent chromium/day.[45] In a Chinese study of the effects of trivalent chromium on cholesterol and glucose concentrations in type 2 diabetics, the daily administration of 1 mg chromium picolinate was associated with a reduction in the cholesterol and glucose concentrations.[46] Plasma chromium concentrations and the incidence of side effects were not reported in the study.

After intentionally ingesting 48 g basic chromium sulfate ($CrOHSO_4$), a 41-year-old woman developed hemorrhagic gastroenteritis, severe pancreatitis, renal failure, hypovolemia, and intractable cardiogenic shock; she died despite intensive care including hemodialysis.[4] A postmortem examination demonstrated erosive gastroenteritis of the entire gut, severe hemorrhagic pancreatitis, pulmonary congestion, and peritonitis. Basic chromium sulfate has unique chemical properties including the liberation of up to 6 mol hydrogen/mol and high affinity for proteins.

Dermal

Dermal penetration is much lower for trivalent than hexavalent chromium with dermal toxicity much lower for the former than the latter; however, dermal absorption rates alone do not explain the difference in sensitization potency.[47] The penetration rate depends on the time of exposure, pH, and concentration of the chromium solution, as well as the innate penetrating property of the individual chromium compound.[48,49] For trivalent chromium compounds, the penetrating property varies substantially between individual compounds (chloride > sulfate or nitrate). Trivalent chromium is the form that binds immune cells of the skin because hexavalent chromium is converted to trivalent chromium after skin penetration. Trivalent chromium has not been associated with dermatitis, whereas exposure to hexavalent chromium produces both a primary irritant dermatitis and a type IV hypersensitivity reaction.[50]

TOXICOKINETICS

Absorption of chromium occurs in the gastrointestinal tract and the lungs. Urinary excretion may take more than 14 days. The toxicity of chromium compounds is apparently related to the powerful oxidizing action of the hexavalent compound, which the acid milieu of the stomach converts to the less toxic trivalent form. Chromium is stored in all body tissues. The kidney excretes about 60% of the absorbed chromate dose within 8 hours after ingestion.[51] Elimination also occurs via the gastrointestinal tract. Small amounts of chromium are excreted in breast milk.[52]

Absorption

Inhalation

The exact bioavailability of respirable chromium particles (0.2–10 μm) is not known, but the lung probably absorbs soluble chromium compounds well based on the increased renal excretion of chromium following exposure to chromium lignosulfonate (Cr^{3+}).[53] The actual amount of absorption of chromium into the blood depends on a number of factors, including oxidation state, size, solubility, and the phagocytic activity of alveolar macrophages. In most cases, hexavalent compounds are more easily absorbed through the lungs compared with trivalent compounds, in part because of the relatively greater ease with which hexavalent chromium compounds traverse biological membranes. Animal studies suggest that the lungs absorb ~5–30% of respirable trivalent chromium particles.[2]

Ingestion

The absorption of chromium compounds from the gut is poor, averaging ~0.5–2% based on urinary excretion

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studies.[33] In contrast to Cr^{6+}, the large, octahedral complexes of trivalent chromium limit the transport of Cr^{3+} into cells via the ubiquitous nonspecific anion exchangers.[54] Based on the renal excretion of chromium, volunteers absorbed about 0.4% of a dose of chromium chloride (Cr^{3+}).[55] The absorption fraction of soluble trivalent chromium in chromium picolinate is greater than $CrCl_3$ based on renal excretion studies.[56]

Dermal

Trivalent chromium penetrates skin to a very limited extent, except following massive exposure to hot, acidic chromium sulfate that produces thermal and chemical burns.[57] In clinical studies, trivalent chromium penetrates human skin in variable amounts depending on several factors (concentration, pH, time of exposure, individual variability). Chromium sulfate traverses excised intact human epidermis very slowly compared with chromium chloride.[58]

Distribution

The body reduces most hexavalent chromium entering the body; thus, trivalent chromium accounts for the vast majority of total chromium in the body. After absorption, trivalent chromium binds to transferrin in plasma and distributes widely throughout the body with the exception of erythrocytes. *In vitro* studies indicate hexavalent chromium easily crosses erythrocyte cell membranes via anion carrier proteins, whereas little penetration of Cr^{3+} into erythrocytes occurs.[59,60] In an intravenous radioactive $^{50}Cr^{3+}$ tracer study in six volunteers, the trivalent chromium was distributed primarily to liver, spleen, soft tissue, and bone.[61] With the exception of the lungs, chromium concentrations in all other tissues decrease with age.[62] A study of autopsies of smelter workers revealed higher concentrations of total chromium in the lungs of the workers compared with controls, but the concentration of chromium in the liver and kidneys was similar to controls.[63] The excess concentrations of chromium in the lungs decreased as the period between death and retirement lengthened. Bone is also a potential repository for the long-term storage of chromium.

Elimination

Chromium exists in the body primarily as Cr^{3+}. The kidney rapidly excretes most of the absorbed chromium as trivalent chromium with little retention of chromium in tissues.[64] Biliary excretion accounts for ~10% of the elimination of chromium with smaller amounts of chromium appearing in sweat, milk, nails, and hair.[65] Renal excretion of chromium is rapid following exposure of workers to dust containing chromium lignosulfonate (Cr^{3+}).[53] In the urine of these workers, the half-time for trivalent chromium was 4–10 hours based on an open, one-compartment kinetic model. These urinary half-times are substantially shorter for trivalent chromium than for workers exposed to hexavalent chromium (15–41 hours)[66] or volunteers ingesting hexavalent chromium (mean = 39 hours).[67] Experimental studies on trivalent chromium kinetics in volunteers suggest a three-compartment model with the delayed release of chromium from a slow compartment ($t_{1/2}$ = months–few years). Following the intravenous administration of $^{51}Cr^{3+}$ to six healthy volunteers, the kinetic data fit a model with the plasma in equilibrium with fast ($t_{1/2}$ = 0.5–12 hours), medium ($t_{1/2}$ = 1–14 days), and slow ($t_{1/2}$ = 3–12 months) compartments as measured by a whole-body scintillation scanner.[61]

Maternal–Fetal Kinetics

Trivalent chromium traverses the placenta and occurs in all tissue with the exception of the lungs. The chromium concentrations in most tissues clear rapidly with the exception of the liver and kidneys; these organs retain neonatal tissue concentrations until the second decade of life.[68] In a case series of 10 pregnant women with MoM hip arthroplasties, the maternal whole blood chromium concentration at delivery was 1.28 ± 0.28 µg/L compared with 0.378 µg/L ± 0.17 in cord blood; the difference was statistically significant ($P < 0.01$).[69] The placental transfer rate for chromium was 29%, suggesting the placenta modulates the chromium transfer to the fetus. Most samples of breast milk from lactating women on regular diets contained <0.4 µg Cr/L with a mean of about 0.3 µg/L.[52]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

While current evidence suggests trivalent chromium is an essential trace metal necessary for the normal metabolism of cholesterol, fat, and glucose, the data are not definitive.[70] Rare case reports suggest that insufficient dietary intake of chromium produces a disease similar to adult-onset diabetes and cardiovascular disease;[33] however, there are no well-defined chromium-deficiency diseases in humans. The

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development of insulin-resistant diabetes in patients on parenteral nutrition that responds to supplementation with trivalent chromium suggests that Cr^{3+} is essential for normal energy metabolism.[71] The naturally occurring, low-molecular-weight oligopeptide, chromodulin (glucose tolerance factor), binds four equivalents of trivalent chromium. This complex may be involved in the auto-amplification mechanism in insulin signaling, but the role of chromodulin in energy metabolism remains unclear. Chromodulin binds chromic ions in response to an insulin-mediated chromic ion flux, and activation of tyrosine kinase activity occurs when the chromodulin-chromium complex binds to an insulin-stimulated insulin receptor.[72] Although trivalent chromium has the potential to form complexes with proteins and nucleic acids, hexavalent chromium first must be converted to the trivalent state before it combines with nucleic acids and proteins.[2] Trivalent chromium forms tight bonds with oxygen- and sulfur-containing ligands; some chromium complexes with histidine and cysteine are relatively inert because of these tight bonds.[73] Trivalent chromium potentiates the action of insulin, probably through a glutathione-like complex composed of niacin, trivalent chromium, and amino acids.[74] Chromium deficiencies in the diet could potentially produce elevated circulating insulin concentrations, hyperglycemia, hypercholesterolemia, elevated body fat, decreased sperm counts, reduced fertility, and a shortened life span.

Mechanism of Toxicity

Trivalent chromium is a weak sensitizing agent that may produce allergic dermatitis; however, *in vitro* studies indicate that the poor dermal penetration of trivalent chromium significantly limits cases of allergic dermatitis.[75] Although trivalent chromium is not a good sensitizer, case reports document positive bronchial provocation tests to trivalent chromium sulfate and nickel sulfate in an electroplater developing asthma symptoms within 1 week of starting employment.[76] Trivalent chromium is a mild pulmonary irritant compared with hexavalent chromium; however, chromium sulfate is a strong corrosive capable of causing direct damage to skin and mucous membranes. There is no apparent association of renal dysfunction with exposure to trivalent or metallic chromium.[2]

CLINICAL RESPONSE

Trivalent compounds generally have low oral toxicity with poor gastrointestinal absorption.

Acute Toxicity

A case report associated thrombocytopenia, anemia, hemolysis, liver dysfunction, and acute renal failure with the ingestion of 1.2–2.4 mg chromium picolinate (Cr^{3+})/day for 4–5 months by a 33-year-old woman.[77] The initial plasma chromium concentration during the second day of hospitalization was 4.6 μg/L (laboratory norm: 0.1–2.1 μg/L). No renal biopsy was performed to determine the cause of the renal failure other than hemolysis; therefore, the effect of chromium on the clinical features of this case report is unclear. Other case reports associate renal dysfunction with the use of dietary supplements containing chromium picolinate;[78] however, the lack of blood chromium concentrations and analysis of the supplements limits conclusions about causation.

Environmental Exposure

In addition to irritating effects, chromium compounds produce an allergic contact dermatitis characterized by acute or chronic eczema. A 63-year-old man developed chronic eczema after handling old chromium dioxide (Cr^{4+}) magnetic cassette tapes;[79] analysis of CrO_2 dust suggests that these tapes may release small amounts of Cr^{3+} and Cr^{6+} following prolonged contact with water or sweat.[80] Hexavalent chromium salts are the main skin sensitizers because they penetrate skin more easily than the trivalent compounds.[75] Consequently, Cr^{3+} sensitivity is much less common than Cr^{6+} sensitivity, primarily involving leather goods.[81] Leather products are a common source of chromium sensitization, particularly leather shoes;[82] both Cr^{3+} and Cr^{6+} are present in leather goods. In a study of 2,211 consecutive patients with suspected allergic contact dermatitis patch tested with 0.5% potassium dichromate (Cr^{6+}) and 13% chromium trichloride (Cr^{3+}), 71 (3.2%) patients had a positive reaction to Cr^{6+} and 31 (1.3%) had a positive reaction to Cr^{3+}.[83] No hexavalent-negative patients had a positive reaction to trivalent chromium.

In a study of 55 lifetime residents (30 men, 25 women) without clinical evidence of renal disease living near a chromium-contaminated landfill in New Jersey, analysis of four urine biomarkers (intestinal alkaline phosphatase, tissue nonspecific alkaline phosphatase, *N*-acetyl-β-D-glucosaminidase, microalbumin) did not demonstrate elevated values compared with reference concentrations.[84] The mean urinary total chromium concentration in 53 women and men was 0.3 ± 0.2 μg/L (0.3 ± 0.8 μg/g creatinine) with no statistically significant difference between women and men.

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A case report associated the use of chromium polynicotinate in combination with multiple vegetable extracts as a weight reduction program with the development of hepatitis (ALT 4371 IU/L, total bilirubin 20 mg/dL).[85] The liver biopsy demonstrated intralobular hepatocyte necrosis and a mixed intralobular and portal cellular inflammatory infiltrate with many eosinophils. The hepatitis resolved within 3 months after cessation of all supplements. The presence of confounding factors (e.g., *Peumus boldus*) limits conclusions regarding causation.

Occupational Exposure

Interpretation of the health effects associated with exposure to Cr^{3+} is complicated by concomitant occupational exposures to Cr^{6+} or other compounds that can induce adverse health effects including respiratory tract irritation. In studies of workers exposed primarily to trivalent chromium, the primary target organs are the immune and respiratory systems. Exposure of 236 workers to trivalent chromium in a ferroalloy metallurgy plant (mean airborne Cr^{3+}, 0.075 mg/m^3; Cr^{6+}, <0.001 mg/m^3)[86] and to metallic chromium in an alloy steel plant (mean = 0.61 mg Cr^0/m^3; mean = 7 years)[87] was not associated with adverse renal effects based on analysis of urinary biomarkers (total protein, albumin, retinol binding protein, renal tubular antigens, β_2-microglobulin alanine-aminopeptidase, *N*-acetyl-β-D-glucosaminidase, γ-glutamyl-transpeptidase, and β-galactosidase activities). A German mortality and morbidity study of trivalent chromium oxide and chromium sulfate production workers did not demonstrate an excess incidence of liver disease.[88] There are few data associating trivalent chromium exposure with alterations of the nervous system. A cohort study of 3,408 US chromate production workers processing chromite ore (mixed Cr^{3+} and Cr^{6+} exposure) did not detect an increased incidence of vascular lesions in the central nervous system of exposed workers; the proportionate mortality ratios for Caucasian and African American men were 78 (95% CI: 61– 98, $P < 0.05$) and 68 (95% CI: 44–101), respectively.[89] Current workers in chromium-related industries are typically exposed to chromium concentrations two orders of magnitude higher than the general population.[2]

Trivalent chromium has significantly lower dermal toxicity than hexavalent chromium as a result of the relatively slower penetration of the dermis compared with Cr^{6+};[47] consequently, trivalent chromium does not usually cause skin ulcers unless converted to the hexavalent form.[90] Trivalent basic chromium sulfate ($CrOHSO_4$) is an exception that may produce direct skin or mucous membrane damage following direct contact. Although Cr^{6+} is the species typically associated with allergic contact dermatitis, Cr^{6+} transforms to Cr^{3+} following penetration of the skin; the latter species binds to immune cells and produces dermal toxicity. Sensitivity to chromium may occur in some workers exposed to high concentrations of trivalent chromium compounds based on patch testing.[91]

Reproductive Abnormalities

Trivalent chromium is not a recognized reproductive toxin. Histological studies of rats exposed to 15.5 mg Cr^{4+}/m^3 for 2 years did not demonstrate pathological changes in the sex organs.[92]

Carcinogenesis

The International Agency for Research on Cancer (IARC) lists hexavalent chromium as a human carcinogen (Group 1), whereas metallic chromium and trivalent chromium are not classifiable as to human carcinogenicity (Group 3). Although chromium workers are often exposed to both trivalent and hexavalent chromium, there is no clear evidence that trivalent chromium exposure in these workers increases the lung cancer rate. The epidemiological studies of workers in the ferrochromium alloy industry exposed to Cr^0 and Cr^{3+} along with small amounts of hexavalent chromium are inconsistent,[93] whereas studies of workers exposed to Cr^{3+} in the tanning industry did not demonstrate an association between exposure to trivalent chromium and an increased incidence of lung cancer. In a US retrospective mortality study of 9,365 workers exposed to Cr^{3+} in 2 chrome leather tanneries from 1940 and followed to 1982, the standardized mortality rate (SMR) for tracheal and bronchial lung cancer in the 2 tanneries was 67 (95% CI: 40–106) and 93 (95% CI: 67–126) when compared to local cancer rates.[94] There was no increase in lung cancer rates with increasing duration of employment.

In a study of 2,357 chromate production workers exposed to both trivalent and hexavalent chromium, the relative risk of lung cancer mortality adjusted for smoking was similar for Cr^{3+} (RR = 1.32, 95% CI: 1.15–1.51) and Cr^{6+} (RR = 1.38, 95% CI: 1.20–1.63).[95] However, exposure to the two chromium species was highly correlated, and analysis of exposure to individual chromium species indicated that hexavalent chromium was the cause of the increased lung cancer risk. In combined proportional hazards models of $\log_{10}$ cumulative exposure for each 10-fold increase in cumulative

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exposure to Cr^{3+} and Cr^{6+}, the relative risk for Cr^{6+} exposure remained significant (RR = 1.66, $P = 0.045$), whereas the relative risk for Cr^{3+} was not statistically significant (RR = 0.17, $P = 0.449$).

Based on animal studies, there is inadequate evidence of carcinogenicity for metallic chromium (Cr^0) and some Cr^{3+} compounds (chromic oxide, chromium acetate). In experimental studies, trivalent chromium compounds produce genetic changes only in acellular or subcellular systems. Trivalent chromium compounds exhibit no genetic activity in cellular systems, probably because these compounds do not cross cell membranes.[96]

DIAGNOSTIC TESTING

SI Conversion Units

1 μmol/L = 52 μg/L
1 nmol/L = 0.052 μg/L
1 μg/L = 0.01923 μmol/L = 19.23 nmol/L
1 nmol/mmol creatinine ≈ 0.52 μg/g creatinine

Analytical Methods

Methods to quantitate chromium in biological media include graphite furnace atomic absorption spectrometry, neutron activation analysis, inductively coupled plasma/atomic emission spectrometry, gas chromatography/electron capture detection, and mass spectrometry. The former three methods are also used to quantitate chromium in environmental samples. Graphite furnace atomic absorption spectrometry is the most common method used to determine chromium concentrations in biological samples, but appropriate background correction methods (e.g., Zeeman effect background correction, continuum source echelle monochromator wavelength modulation) are necessary to ensure accuracy.[97] Available techniques typically do not separate trivalent chromium from hexavalent chromium. The use of acid digestion followed by quantitation with atomic absorption spectrophotometry allows the determination of hexavalent chromium concentrations in environmental samples (e.g., sediment, sludge, soil).[98]

Matrix interference, the previous lack of Standard Reference Materials, and very low Cr concentrations complicate the analysis of total chromium in biological samples. Prior to the mid-1970s, the inability of conventional atomic absorption spectrometry systems (e.g., electrothermal/atomic absorption spectrometry) to correct for the high nonspecific background absorption resulted in numerous erroneous values for chromium concentrations in biological samples (i.e., whole blood, serum, urine). Newer techniques (ICP/MS equipped with a dynamic reaction cell)[99] and the release of standard material by the National Institute of Standards and Technology improve the precision and accuracy of current chromium measurements.

The ubiquitous presence of chromium in laboratories and the low sensitivity of most methods require careful handling of the biological sample in the laboratory. Some plastic containers contain significant amounts of leachable chromium; therefore, special acid-washed specimen containers are necessary. Stainless steel utensils, scalpels, or trays should not be used to collect tissue specimens for analysis of chromium concentrations; plastic intravenous cannulas are preferable needles for drawing blood samples. Case reports suggest that 2-fold increases in whole blood chromium concentrations may occur following the use of metal cannulas containing chromium.[100] Trace-element-certified containers are often unavailable. Commonly available collection tubes for anticoagulated samples typically contain either ethylenediaminetetraacetic acid (EDTA) or sodium heparin (less often sodium lithium). Red cell lysis may occur after a few days of storage; hence, coagulated serum samples are preferable to plasma samples for the determination of chromium concentrations.

Biomarkers

Concentrations of chromium in the blood and urine document the extent of absorbed chromium when collected within 2 days of exposure and analyzed as discussed above. One study of tannery workers suggested that chromium hair concentrations were a determinate of exposure to trivalent chromium; however, external contamination complicates the interpretation of total chromium concentrations in hair samples.[101]

Blood

Plasma or serum chromium concentrations reflect recent exposure to hexavalent and trivalent chromium, whereas intracellular chromium concentrations reflect the burden of hexavalent chromium because only Cr^{6+} penetrates red blood cells. Three days after the ingestion of a wood preservative containing hexavalent chromium and arsenic, the erythrocyte Cr^{6+} concentration was 4,540 μg/L compared with total chromium concentrations of 2,180 μg/L in whole blood and 1,070 μg/L in plasma.[102] The patient underwent successful liver transplantation 6 days after admission.

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General Population

Prior to 1970, published serum total chromium concentrations in the general population were substantially higher than current values, probably from contamination (e.g., stainless steel needles) and less accurate analytical methods. In a review of analytical data from the 1970s and 1980s, typical serum total chromium concentrations for individuals in the general population with no hip implants or occupational exposure to chromium were 1–3 nmol/L (0.052–0.156 μg/L).[103,104] In a recent French study of 106 healthy adults without occupational exposure to chromium, the median whole blood total chromium concentration was 0.55 μg/L (upper 95%: 0.87 μg/L) compared with <0.29 μg/L (upper 95%: 0.79 μg/L) in plasma.[105] The mean whole blood chromium concentration in 519 healthy Italian adults without occupational chromium exposure was 0.23 ± 0.01 μg/L (estimated upper reference value, 0.45 μg/L), whereas 530 serum samples contained a mean total chromium concentration of 0.17 ± 0.01 μg/L (estimated upper reference range, 0.41 μg/L).[106]

Chromium-Cobalt Hip Implants

The concentration of chromium in blood samples from patients with long-term metal-on-metal total hip prostheses substantially exceeds values for the general population, but there are few data on the adverse effects of these elevated concentrations; the clinical significance of elevated chromium concentrations in these patients is unclear.[107,108] Typically, serum concentrations in patients with metal implants are elevated less for chromium (i.e., <1–5 ng/mL) than cobalt.[109,110] In an analysis of 43 studies representing 16 different metal-on-metal (MoM) implants with at least a mean follow-up of 1 year, the mean total chromium concentrations ranged from 1.3–2.2 μg/L in whole blood and 1.6–5.1 μg/L in serum. The median total chromium concentrations in whole blood ranged from 0.5–2.5 μg/L compared with 0.8–4.6 μg/L in serum.[111] This study did not detect any clear difference in chromium concentrations between the different implants; exclusion criteria included single-case reports and bilateral implants. In a 2-year follow-up study of 91 patients with unilateral hip arthroplasty, the median preoperative and 2-year postoperative erythrocyte chromium concentrations were not statistically different despite a mean increase of 1.15 ng/mL (range, 0.62–1.43 ng/mL) in the serum chromium concentration in individual patients with metal-on-metal, porous-coated chrome-cobalt femoral implants (DePuy Orthopaedics, Warsaw, IN).[112] The lack of a statistically significant difference between serum and erythrocyte chromium concentrations suggests that the increased serum chromium concentration resulted from trivalent rather than hexavalent chromium.

In a study of 29 patients with normal functioning unilateral hip protheses (54-mm femoral Birmingham Hip, Smith & Nephew, London, UK) followed 5–29 months after implantation, most of the chromium occurred in the serum and plasma fractions with minimal chromium concentrations in erythrocytes.[113] The mean chromium serum/whole blood ratio was ~2.3 with serum containing about 10 times higher chromium concentration than erythrocytes. *In vitro* and *in vivo* studies suggest the possibility that corrosion of stainless steel or cobalt-chromium (18–30% chromium) hip prostheses may produce Cr^{6+}, but the intracellular hexavalent chromium would be rapidly reduced to Cr^{3+} by the acidic medium of lysosomes based on Amberlite resin separation.[114] *Ex vivo* analysis of periprosthetic capsular tissue obtained during revision of MoM hip implants indicates that trivalent chromium phosphate (Cr_2O_3) is the predominant species in the tissue.[115]

In a 5-year follow-up study, the mean serum chromium concentration in patients with total hip arthroplasties was ~10-fold higher than controls without hip implants.[116] There was no statistically significant difference in the serum chromium concentrations between patients with metal-on-metal Birmingham hip resurfacing and metal-on-metal total hip arthroplasties. Similar elevations in serum chromium concentrations do not usually occur in patients with cobalt-chromium total knee arthroplasties.[117] Table 9.2 lists the erythrocyte and serum chromium preoperatively and 2-years postoperatively from this study. Both cup abduction angle and head size affect serum chromium concentrations after femoral implants.[118,119] Serum chromium concentrations in these patients decrease after the removal of the implant.[120]

Occupational Exposure

Case reports suggest that serum chromium concentrations increase substantially following the accumulation of chromium during occupational exposure, particularly following the inhalation of fumes containing chromium. After cessation of heavy exposure to chromium during the plasma cutting of stainless steel, the serum chromium concentrations of a stainless steel cutter decreased from 10.35 μg/L to 1.87 μg/L 8 years later with a half-life of 40–43 months, as measured by electrothermic atomic absorption spectrometry.[121] His major complaints were mucous membrane irritation and eczema. He developed a minor stroke 4 days after stopping work.

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TABLE 9.2. Median erythrocytes and serum chromium concentrations before and after unilateral hip arthroplasty. (Data from Engh et al.).[112]

Treatment Group	Preoperative[a] (Interquartile Range)	2-year Follow-up[a] (Interquartile Range)
RBC metal-on-polyethylene	1.00 (0.75–1.45)	1.10 (0.70–1.73)
RBC metal-on-metal 28 mm	1.20 (1.10–1.55)	1.10 (0.60–1.70)
RBC metal-on-metal 36 mm	0.90 (0.70–1.47)	1.20 (0.78–1.63)
Serum metal-on-polyethylene	0.20 (0.13–0.29)	0.17 (0.12–0.29)
Serum metal-on-metal 28 mm	0.22 (0.10–0.28)	1.29 (0.77–1.72)
Serum metal-on-metal 36 mm	0.21 (0.12–0.34)	0.91 (0.64–1.78)

Abbreviation: RBC = red blood cell.
[a] ng/mL.

Urine

Urine chromium concentrations reflect absorption of total chromium (i.e., Cr^{3+} and Cr^{6+}) primarily over the last 1–2 days, depending on the amount of prior exposure to chromium compounds. As a result of reduction of hexavalent chromium in the airways and blood after absorption, only trivalent chromium appears in the urine. Consequently, urinary chromium represents exposure to either or both of these species. Most analytical methods do not distinguish between trivalent and hexavalent chromium. Although trivalent chromium does contribute somewhat to the total chromium concentration, substantial portions of the total chromium may result from the reduction of hexavalent chromium. The use of organic chromium supplements (e.g., trivalent chromium picolinate) increases the renal excretion of chromium above background concentrations.[122] Although tobacco contains variable amounts of chromium, the impact of smoking on urine chromium concentrations is not well defined.

General Population

In recent studies of the general population with typical exposure to chromium, the *mean* total chromium concentrations in urine are usually <0.5 μg/L with a range of ~0.2–1.8 μg/L.[104,123] The estimated upper 95% CI for total Cr in urine samples from 189 adult Danish subjects was 0.68 μg/L.[124] The upper 95% reference limit in Finnish subjects without occupational exposure to chromium was 0.52 μg (0.01 μmol)/L.[125] In the National Health and Nutrition Examination Survey (NHANES III) of the US population, the mean total chromium concentration in urine was 0.22 μg/L (0.21 μg/g creatinine) with a 95 upper percentile concentration of 0.7 μg/L (0.60 μg/g creatinine) as measured by inductively coupled argon plasma/mass spectrometry.[126]

Occupational Exposure

The mean concentration in the urine of nonexposed workers was 0.11 ± 0.04 μg Cr/g creatinine as measured by graphite furnace atomic absorption spectrophotometry (GF/AAS).[127] In a study of 45 Chinese cement workers, the average urinary chromium concentration was ~6 times higher (45.5 μg/L) in nonsmoking workers with hand eczema than in nonsmoking workers with no skin disease (7.6 μg/L).[128] Multiple regression analysis of 890 volunteers from 8 different areas of Italy without occupational exposure to chromium did not detect a significant effect of smoking on urine chromium concentrations.[129]

HEALTH SURVEILLANCE

Environmental Monitoring

Incidental ingestion is the most important route of exposure to trivalent chromium, unless people consume garden vegetables grown in chromium-contaminated soil.[130] There is no clear evidence that exposure of the general population to chromium concentrations present in the United Kingdom produces adverse health effects.[10] Trivalent chromium possesses negligible risk because of its low inherent toxicity and low bioavailability.[131] The data on dose-response relationships for chromium compounds are very limited; the use of reference dose for trivalent data based on data for hexavalent chromium may lead to highly inaccurate assessments of risk.[132]

The ATSDR intermediate-duration inhalation minimal risk level (MRL) for insoluble trivalent chromium particulate compounds is 5 μg Cr^{3+}/m^3 based on a minimal LOAEL of 3 mg Cr^{3+}/m^3 for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation in the lung of rats in a 13-week study.[133] The intermediate-duration inhalation MRL for soluble

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trivalent chromium compounds MRL is 0.1 μg Cr^{3+}/m^3 based on the previous study. The US EPA reference dose (RfD) for oral exposure to insoluble trivalent chromium salts (i.e., chromium oxide/sulfate) of 1.5 mg/kg/day based on a NOAEL derived from administering 5% chromic trioxide (C_2O_3; 1,800 mgCr^{3+}/kg/day) to rats for over 2 years.[134] The current US EPA maximum contaminant level (MCL) of total chromium in drinking water is 50 μg/L.

Biological Monitoring

Although the absorption of trivalent chromium compounds is poor, increased urinary excretion of chromium occurs in limited studies of tannery workers exposed to trivalent chromium compounds.[53,135] Biological monitoring studies suggest that end-of-shift urinary chromium concentrations do not correlate well to trivalent chromium concentration in ambient air.[136]

TREATMENT

Treatment is supportive because trivalent chromium compounds are less toxic and generally not corrosive compared with hexavalent chromium compounds (e.g., chronic acid). Consequently, standard first aid measures are appropriate for decontaminating skin exposed to trivalent chromium. Dilution is the preferred first aid measure for the ingestion of corrosive trivalent chromium compounds (e.g., acidic chromium sulfate).

HEXAVALENT

HISTORY

Cummings first described the skin ulcers (chrome holes) associated with dermal exposure to hexavalent chromium (potassium dichromate) in 1827.[137] In 1928, Blair reported the development of skin and nasal ulcerations in 12 chrome platers.[138] The carcinogenesis of hexavalent chromium compounds was recognized in the late 19th century when nasal tumors were described in Scottish chrome pigment workers.[139] Case reports in the 1930s focused attention on the incidence of lung cancer in chromate workers; in 1936, lung cancer became an accepted work-related disease in German chromate workers.[140] In the 1960s and 1970s, chromium-containing slag was a substantial component of landfills in a variety of residential and commercial settings in Hudson County, New Jersey. Health concerns about exposure to this soil were based on experience with workers exposed to chromium. Epidemiological studies of chromate workers indicate an increased risk of death from lung cancer in workers exposed to hexavalent chromium (Cr^{6+}) compounds.[141,142] Hexavalent chromium compounds are both skin and pulmonary sensitizers, producing a generalized irritation of the conjunctiva and mucous membranes, nasal perforations,[143] and a dry, fissured contact dermatitis (e.g., blackjack disease in card players exposed to dichromate salts used to dye green felt).[144]

PHYSIOCHEMICAL PROPERTIES

Hexavalent chromium occurs in nature rarely, primarily in crocoite ($PbCrO_4$); therefore, most hexavalent chromates exist as a result of commercial production. The hexavalent compounds usually exist as oxides or oxohalides; however, at physiological pH, hexavalent chromium typically exists as an oxyanion $(CrO_4)^{-2}$ that resembles sulfate and phosphate oxyanions. The hexavalent form (chromate, Cr^{6+}) is a strong oxidizing agent, particularly in acidic media. The anionic transport system moves $(CrO_4)^{-2}$ into cells, where various intracellular reducing agents (e.g., ascorbic acid, cysteine, glutathione) ultimately reduce this oxyanion to trivalent chromium.[54] The reduction of dichromates to trivalent chromium increases with decreasing pH in the range 2–6, particularly in the presence of oxidizable organic matter.

Hexavalent chromium compounds (e.g., chromic acid, chromic trioxide, ammonium, potassium, and sodium dichromate) are soluble in water. In general, dichromates are more soluble than the corresponding chromate.[145] *Soluble* hexavalent chromium compounds traverse cell membranes and reduce spontaneously to trivalent compounds.[146] The pH of chromium compounds ranges from 0.5 (chromic acid) to 13 (ammonium dichromate). Table 9.3 lists identifying information and physical properties of hexavalent chromium compounds.

EXPOSURE

Production Processes

The roasting of chromite ore with soda ash produces sodium chromate and dichromate. The latter two compounds are the starting mixtures for most other hexavalent chromium compounds. The commercial production of lead chromate for use as a pigment involves the reaction of sodium chromate with lead nitrate or a reaction of lead monoxide with chromic acid solution.

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TABLE 9.3. Identifying information and physical properties of hexavalent chromium compounds.

Physical Characteristic	Chromic Acid	Calcium Chromate	Lead Chromate	Potassium Chromate	Sodium Chromate	Strontium Chromate
CAS RN	7738-94-5	13765-19-0	7758-97-6	7789-00-6	7775-11-3	7789-06-2
Synonyms		Chromic acid, calcium salt; Calcium Chrome Yellow	Chromic acid, lead salt	Chromic acid, dipotassium salt	Chromic acid, disodium salt, Caswell No. 757	Chromic acid, strontium salt
Molecular formula	H_2CrO_4	$CaCrO_4$	$PbCrO_4$	K_2CrO_4	Na_2CrO_4	$SrCrO_4$
Molecular weight (g/mol)	118.01	156.07	323.18	194.19	261.97	203.61
Valence	+6	+6	+6	+6	+6	+6
Color	Purple-red	Yellow	Yellow	Yellow	Yellow	Yellow
Physical state	Solid	Solid	Solid	Solid	Solid	Solid
Odor		NA	NA	Odorless	NA	NA
Melting points (°C)	196	NA	844	975	792	NA
Density (g/mL, 20 °C)	1.67–2.82	2.89	6.12 (15°C)	2.732 (18°C)	2.710–2.736	3.895 (15°C)
Water solubility (g/L, 20°C)	Very soluble	223	0.058	629	873 (30°C)	1.2 (15°C)
Vapor pressure (mmHg)	NA	NA	NA	0	NA	NA

Physical Characteristic	Zinc Chromate	Ammonium Dichromate	Potassium Dichromate	Sodium Dichromate	Chromium Trioxide
CAS RN	13530-65-9	7789-09-5	7778-50-9	10588-01-9	1333-82-0
Synonyms	Chromic acid, zinc salt	Chromic acid, diammonium salt	Chromic acid, dipotassium salt	Chromic acid, sodium salt	Chromic acid, chromium anhydride
Molecular formula	$ZnCrO_4$	$(NH_4)_2Cr_2O_7$	$K_2Cr_2O_7$	$Na_2Cr_2O_7$	CrO_3
Molecular weight (g/mol)	181.97	252.06	294.18	262	99.99
Valence	+6	+6	+6	+6	+6
Color	Lemon yellow	Orange	Red	Orange–red	Red
Physical state	Solid	Solid	Solid	Solid	Solid
Odor	Odorless	Odorless	NA	Odorless	Odorless
Melting points (°C)	NA	180[a]	398	356.7	197
Density (g/mL, 20 °C)	3.40	2.15 (25°C)	2.676 (25°C)	2.52 (13°C)	2.70 (25°C)
Water solubility (g/L, 20 °C)	Insoluble	Soluble	Soluble	Soluble	Soluble

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.
[a] Decomposes.

Uses

Exposure to hexavalent chromium compounds occurs primarily in the chemical, metallurgical, and refractory (heat-resistant) industries with the stainless steel industry accounting for the largest consumption of chromium. Commercial applications include corrosion inhibition, plating, glassware-cleaning solutions, wood preservatives, safety match manufacture, metal finishing, and pigments. The inclusion of chromium alloys and stainless steel increases hardness and resistance to corrosion with chromium concentrations typically ranging ~11–30%. Exposure to hexavalent chromium varies with and within occupations. In a German study of welders, spray painting, shielded metal arch welding, and flux-core arc welding of stainless steel were associated with geometric mean airborne exposure to hexavalent chromium of >5 μg/m^3, whereas the geometric mean Cr^{6+} exposure for gas metal arc welding of stainless steel, cutting, hard-chromium plating, and metal spraying in the chemical chromium industry was 1–5 μg/m^3.[147]

There are two types of chrome plating: 1) decorative plating where the base metal (e.g., nickel) receives a thin layer (0.5–1 μm) of chromium, and 2) hard plating where the layer is more corrosion-resistant and thicker (5–10 μm). Sufficient water-soluble chromates leach from zinc potassium chromate in primer paints to produce allergic reactions; the chromium concentrations in primers are much higher than water-soluble chromates in cement (0.0002–0.0008%).[148] Since 2000, the use of chromates in pigments for US paints, coatings, printing inks, ceramics, glass, plastic, and construction materials has declined.

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Sources

Combustion and the processing of ore discharge primarily trivalent chromium into the environment as chromium oxide;[11] however, small amounts of hexavalent chromium occur in fly ash from coal-fired power plants[12] and in soil near chromate manufacturing sites. The highest exposure to hexavalent chromium occurs during chromate production, ferrochrome and chrome pigment production, chrome plating, and stainless steel welding.[2] The chromium produced by the chemical industry exists primarily as hexavalent chromium; treatment of the waste requires conversion to trivalent chromium (i.e., Cr_2O_3) by reduction and precipitation of the hydrous oxide with lime or caustic soda.[2]

The composition of welding fumes is complex with the composition of these fumes varying depending on the type of welding, oxygen concentration, air contaminants, and the composition of the metal, fluxes, and electrodes.[149] Stainless steel is an alloy of iron, nickel, and chromium, whereas mild steel is an alloy of iron, carbon, and silicon. Consequently, the contribution of fumes from mild steel and high alloy steel welding to the chromium burden is minimal, whereas the fumes from the welding of stainless steel potentially contain chromium (Cr^{6+}) and smaller amounts of nickel.[150] Although stainless steel welding produces rapid uptake of presumably soluble hexavalent chromium compounds along with rapid (i.e., same day) excretion of these chromium compounds, the contribution of chromium in welding fumes to the total body burden of chromium is relatively small.[151] Biological monitoring of workers exposed to fumes from both metal inert gas and the manual metal arc methods of welding stainless steel indicates that these workers are exposed to relatively high total chromium concentrations compared with the tungsten inert gas process.[152] However, the metal inert gas method produces relatively smaller amounts of total chromium primarily as insoluble elemental and trivalent chromium compounds in contrast to the relatively high-soluble hexavalent chromium compounds produced by the manual metal arc method. In general, the increase in the systemic bioavailability of hexavalent chromium is very small to negligible for all welders.

Airborne sampling data suggest high blood Cr^{6+} occurs in workers grinding chromium-containing metal or near chromium electroplating tanks.[153] Most of the chromium particles in electroplating tanks are hexavalent (i.e., ~98%) with substantial variation in size ranging from small, respirable particles to large, unrespirable particles.[154] In a study of air samples from seven chromium electroplating factories, the geometric mean Cr^{6+} concentration was 89.7 μg/m^3 with a range of 0.7–168.3 μg/m^3.[155]

Air

The emission of hexavalent chromium from fossil fuel combustion and steel production accounts for ~2/3 of the airborne chromium in some urban areas.[156] The remaining chromium in air is in trivalent form. The speciation of chromium released from specific sources depends on a variety of factors including temperature and reactions with other elements.[157] The US EPA estimates that up to ~1/3 of the chromium released from anthropogenic sources into the atmosphere occurs as hexavalent chromium depending on the specific source.[158] Ambient air in the United States usually contains small amounts of *total* chromium with most airborne samples containing <100 ng/m^3 (median, <20 ng/m^3).[16]

In a study of 21 industrial sites containing chromate ore processing residues, the arithmetic mean hexavalent chromium concentration in particulates from outdoor air samples averaged 9.9 ng/m^3 with a range of 0.13–110 ng/m^3.[159] The mean ratio of hexavalent to total chromium averaged ~21% with a range of 4–60%. The mean background hexavalent chromium concentration of ambient air monitoring samples from Hudson County, NJ, was 1.2 ng/m^3 with a range of 0.2–3.8 ng/m^3.[160] Chromite ore processing residue was a fill material in several areas in Hudson County, NJ, with hexavalent chromium typically accounting for ~1–5% (maximum, 7%). The mean background concentration of total chromium was 4.5 ng/m^3 with a range of 1.5–10 ng/m^3. Although oxidation of trivalent chromium to hexavalent chromium can occur in the presence of manganese, simulation models suggest that typical conditions in the atmosphere favor the reduction of hexavalent chromium to trivalent chromium.[161]

Typically, indoor hexavalent chromium concentrations in ambient indoor air from nonsmoking households are lower (i.e., <1/2) than outdoor ambient air; smoking substantially increases indoor air concentrations of chromium. In a study of 24-hour ambient air samples from 33 residences in Hamilton, Canada, the geometric mean of the hexavalent chromium concentration was 0.20 ng/m^3 (range, 0.1–0.6 ng/m^3) in indoor air compared with 0.55 ng/m^3 (0.1–1.6 ng/m^3) in outdoor air.[162] Hexavalent chromium represented about 20% of the total chromium fraction in the ambient air samples.

Soil

Chromium in the aquatic phase of sediment exists either in solubilized solution or suspended particles. Soluble

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chromium accounts for a small amount of the total chromium in water as both hexavalent and trivalent chromium. Total chromium concentrations in Canadian soils ranged from 5–1,500 mg/kg with a mean of 43 mg/kg; however, few data on Cr^{6+} were reported.[26] A smaller percentage of total chromium in soil exists as the more mobile and soluble Cr^{6+} than Cr^{3+}. Higher Cr^{6+} concentrations in soil do not necessarily result in higher airborne Cr^{6+} concentrations based on an analysis of soil and indoor/outdoor air chromium samples in a study of 25 industrial sites in Hudson County, NJ.[163] Hexavalent and total chromium concentrations in indoor industrial air samples were 0.23–11 ng/m^3 and 4.1–130 ng/m^3, respectively, compared with 0.013–15.3 ng/m^3 and 1.9–84.5 ng/m^3, respectively, in outdoor industrial air samples.

Water

Total chromium concentrations in US rivers range from <1–30 μg/L (median, ~10 μg/L); however, analytical data on the concentrations of Cr^{6+} are limited. Chromium in the aquatic phase exists either in solubilized solution or suspended particles. Soluble chromium accounts for a small amount of the total chromium in water as both hexavalent and trivalent chromium. In a study of winter water samples from the Delaware River in Pennsylvania, the dissolved total chromium concentrations ranged from 0.57–1.30 μg/L with Cr^{6+} representing up to ~30% of the total Cr concentrations.[164] The total chromium concentrations decreased to 0.03–0.23 μg/L in the spring. Older studies suggest that Cr^{6+} concentrations in well water near point sources (e.g., chrome plating plants) may substantially exceed typical concentrations in groundwater.[165]

Diet

Total chromium concentrations in food are usually very low (i.e., <20–50 ppm).[17] Little data are available on the bioavailability or speciation of chromium compounds.

Although chromium may leach into some acidic foods that are in contact with stainless steel surfaces during harvesting, processing, or preparation, processing typically removes a large percentage of chromium from foods.[2] Typical total chromium concentrations in edible plants range from 0.02–0.05 μg/L with few data on Cr^{6+} concentrations.[17] Fish do not bioconcentrate chromium. The mean total chromium concentration in fish from 167 Northeastern US lakes was 0.19 μg/g (range, 0.03–1.46 μg/g).[36] In a monitoring survey of ~4,400 community and noncommunity water systems by the California Department of Public Health, 86% of the 2,432 samples contained Cr^{6+} concentration of ≤10 μg/L.[166] Only four water samples exceeded 50 μg/L. Sampling did not include agricultural wells, monitoring wells, or treatment facilities with both raw and treated samples. Total chromium concentrations in tobacco range widely between various sources (e.g., 0.24–14.6 μg/g); however, data on the valence and amount of chromium absorbed into the body as a result of smoking is limited. Typically, chromium content in tobacco smoke is higher than that of other metals (e.g., arsenic, beryllium, cadmium, chromium, cobalt, lead, manganese, mercury nickel).[167] In a study of Brazilian cigarettes, the mean total chromium content was 1.43 ± 0.63 μg/g dry weight as measured by graphite furnace atomic absorption spectrometry after desiccation and microwave-assisted digestion.[20] The content of chromium was the highest of five metals analyzed (As, Cd, Cr, Ni, Pb).

ENVIRONMENTAL FATE

Air

The primary process for the removal of chromium from the atmosphere is precipitation and subsequent deposition on the earth's surface. Although there are limited data on the persistence of chromium in the atmosphere, the estimated residence time is <10 days based on modeling, depending on the particle size. Experimental studies indicate that the presence of chlorine, MnO_2, and oxygen increases the formation of hexavalent chromium, whereas the presence of hydrogen, sulfur, sodium, and calcium inhibits the formation of hexavalent chromium.[168] In the atmosphere, hexavalent chromium may be reduced to trivalent chromium by various airborne ions including, in order of highest reducing power, hydrogen sulfide, sulfur, iron sulfide, ammonium, and nitrate.[169] The presence of vanadium and trivalent arsenic also enhances the reduction of Cr^{6+} to Cr^{3+}. Hydrogen and iron sulfide are particularly effective reducing agents in anaerobic environments with reducing half-lives of less than a few days. The estimated atmospheric half-life for this reduction is ~1–5 days.[169]

Soil

Hexavalent chromium is usually water-soluble and a potent oxidizer. Consequently, the mobility in soil is greater for hexavalent chromium than trivalent chromium.[170] Soluble hexavalent chromium compounds are more mobile in the soil than insoluble hexavalent compounds, but organic matter eventually reduces the

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hexavalent form to insoluble (and less mobile) trivalent chromic oxide (Cr_2O_3).[39]

Water

The migration of Cr^{6+} into groundwater is complex, depending on local soil conditions including soil characteristics (e.g., clay) and the presence of reducing agents (i.e., Fe^{2+}-containing minerals, organic matter).[171] The leachability of hexavalent chromium in the soil increases as the soil pH increases. The valence of chromium in water depends on the pH and the redox potential in the aquifer. As commonly occurs in drinking water, hexavalent chromium predominates in conditions of relative high pH that favor oxidation (shallow groundwater with pH 6–8). Although hexavalent chromium may persist in surface waters for extended periods (e.g., 4–18 years), ultimately organic matter and other reducing agents convert the hexavalent chromium to trivalent chromium with subsequent deposition in sediments.[42] Although oxidation of Cr^{3+} to Cr^{6+} can occur in aerobic environments (shallow, oxygenated aquifers), the process is slow. In an experimental study, the oxidation half-life of conversion of Cr^{3+} in lake water to Cr^{6+} was 9 years; the addition of MnO_2 reduced the oxidation half-life to 2 years.[43] Trivalent chromium predominates in the reducing conditions of deep, anaerobic groundwater. The chlorination of drinking water probably does not produce any significant amounts of Cr^{6+} as a result of the presence of complexing organic matter and low chromium concentrations.

DOSE EFFECT

Ingestion

Hexavalent chromium toxicity results from oxidizing and corrosive properties of the individual chromium compounds. An average lethal dose is ~1–3 g chromium compound depending on these physiochemical properties.

Chromic Acid

The intentional ingestion of an estimated 125 mL chromic acid by a 33-year-old electroplating worker was associated with refractory hypotension, acute renal tubular necrosis, and hepatic failure.[172] Electroplating fluid usually contains 20–40% chromic acid (no blood chromium concentration reported). He died 2 days after ingestion. Case reports document the survival of patients ingesting an estimated chromic acid dose of 5–15 g with intensive care including hemodialysis.[51,173]

Dichromate

The estimated ingestion of 1 g ammonium dichromate (~100 mg/kg) by a 22-month-old child was associated with severe gastroenteritis, acute renal tubular necrosis, hepatic injury with coagulopathy, hypotension, respiratory failure, and death 48 hours after ingestion.[174] The intentional ingestion of 2–3 g potassium dichromate (40–60 mg/kg) by a 17-year-old adolescent caused vomiting, nonbloody diarrhea, and epigastric pain; endoscopy demonstrated a small ulcer in the gastric fundus.[175] She developed renal tubular dysfunction based on substantially elevated urinary β_2-microglobulin and retinol-binding protein concentrations; however, glomerular filtration, creatinine clearance, and hepatic function remained normal.

A 17-year-old male died 18 hours after the estimated ingestion of 29 mg Cr^{6+}/kg (i.e., ~5 g $K_2Cr_2O_7$).[176] Prior to death, he developed methemoglobinemia, respiratory failure, hyperkalemia, severe erosion of the stomach and duodenum, disseminated intravascular coagulation (DIC), and gastrointestinal hemorrhage that failed to respond to intensive care. An 18-year-old man ingested ~5 g of potassium dichromate by history.[176] On admission, he was hypotensive and cyanotic (22% methemoglobinemia); shortly thereafter, a coagulopathy, hemorrhage, and cardiac arrest occurred. The initial blood chromium level was 58 mg/L.

Some case reports suggest that the lethal dose of hexavalent chromium may be somewhat lower (0.5–0.8 g). A 14-year-old boy developed an acute gastroenteritis and toxic hepatitis with renal failure, leading to anuria and death 8 days after ingesting 7.5 mg Cr^{6+}/kg body weight.[177] The use of dimercaprol (BAL), ascorbic acid, exchange transfusion, and peritoneal dialysis did not alter his clinical course. Postmortem examination demonstrated extensive liver and kidney damage along with high chromium tissue concentrations. Based on clinical reports, renal damage occurs following smaller Cr^{6+} doses than hepatic necrosis.[173,178]

Survival has been reported after large ingestions of hexavalent chromium. A 20-year-old man ingested about 45 g of a powder containing 70% $K_2Cr_2O_7$ (31.5 g potassium dichromate).[179] He immediately developed gastrointestinal symptoms (vomiting, hematemesis, diarrhea) and hypotension. He recovered after a prolonged hospital course that included hepatorenal failure and gastrointestinal bleeding. The estimated ingestion of 22.5 g potassium dichromate by a 48-year-old man was associated with vomiting, upper gastrointestinal bleeding, and anemia (Hct = 25%); he survived with

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mild elevation of hepatic transaminases and serum creatinine.[180] The serum chromium concentration 7 hours after ingestion was ~0.7 mg/L.

Dermal

The risk of sensitization to hexavalent chromium depends on the duration and amount of exposure. A review of the current medical literature indicated that the prevalence of chromium sensitization in cement workers chronically exposed to 10–20 ppm hexavalent chromium for years is about 4–5% compared with 0.5% in the general European population without occupational exposure to chromium.[181] Exposure to 20 ppm hexavalent chromium potentially may cause skin ulcers in nonsensitized workers. A substantial decrease in the number of sensitized cement workers occurred after the concentration of water-soluble chromate (Cr^{6+}) decreased to <2 μg/g (ppm) cement.[182] Based on patch testing, the release of <0.3 μg leachable chromates/cm^2 is associated with minimal sensitization of workers exposed to hexavalent chromium.[183] Experimental studies in humans indicate that exposure to 25–29 mg Cr^{6+}/L water[184] and 1,240 mg Cr/kg soil[185] should not cause allergic contact dermatitis in Cr^{6+}-sensitized individuals.

TOXICOKINETICS

Absorption

Inhalation

The precise bioavailability of respirable chromium particles (0.2–10 μm) is not known, but the lung probably absorbs soluble chromium compounds well. The actual amount of chromium absorbed into the blood depends on a number of factors, including oxidation state, size, solubility, and the phagocytic activity of alveolar macrophages. In most cases, hexavalent compounds are more easily absorbed through the lungs compared with trivalent compounds, in part because of the relatively greater ease with which hexavalent chromium compounds traverse biological membranes. Animal studies suggest that the lungs absorb ~53–85% of respirable hexavalent chromium particles (<5 μm).[2]

Ingestion

Following the ingestion of chromium doses normally present in the diet, the poor bioavailability of hexavalent chromium results from the reduction of hexavalent chromium to trivalent chromium in the stomach.[186] In a study of adult volunteers receiving single 10 mg doses of Cr^{6+} in 1 L drinking water, endogenous reducing agents within the upper gastrointestinal tract and the blood reduced virtually all (>99.7%) of the ingested dose of Cr^{6+} to Cr^{3+} prior to absorption into the blood.[67] Consequently, large doses of hexavalent chromium are required to bypass the reducing capacity of the stomach and enter the blood in toxicologically significant amounts. In a study of six volunteers ingesting chromite ore processing residue at a dose of up to 200 μg total chromium/day for 3 days, monitoring of the urine detected no significant change in the urine chromium concentration.[187] The residue contained ~10% hexavalent chromium.

Dermal

Hexavalent chromium penetration is limited, except following massive exposure that typically includes thermal and chemical burns. In clinical studies, potassium dichromate penetrates human skin;[188] the rates of absorption of sodium chromate (Cr^{6+}) from occluded patches on volunteers were concentration-dependent. One study demonstrated the following absorptive rates for Cr^{6+}: 1.1 μg/cm^2/hour for a 0.01 M solution, 6.4 μg/cm^2/hour for a 0.1 M solution, and 10 μg/cm^2/hour for a 0.2 M solution.[49] Immersion of four volunteers below their shoulders for 3 hours in a warm aqueous bath (91° ± 2.5°F) containing 22 mg Cr^{6+}/L as potassium dichromate resulted in the estimated total chromium absorption of $\sim 3.3 \times 10^{-5}$–4.1×10^{-4} μg/cm^2/hour based on analysis of urine chromium concentration over 5 days.[189] The lack of elevated plasma and erythrocyte chromium concentrations beyond the first day is consistent with the rapid penetration of hexavalent chromium in the dermis and conversion to trivalent state.

Distribution

In contrast to Cr^{3+}, hexavalent chromium rapidly penetrates red cells, where it binds to the β-chain of hemoglobin.[190] The hexavalent chromium complexes are sufficiently stable to persist for a substantial portion of the erythrocyte lifecycle. Within the erythrocyte, hexavalent chromium is reduced to trivalent chromium. This process may produce reactive intermediates, DNA- and protein-chromium adducts, and free radicals. Following ingestion of Cr^{6+}, chromium concentrates in white blood cells and the liver with the kidney and brain containing lower hexavalent chromium concentrations than leukocytes and liver.[177,191]

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Elimination

The half-life for chromium in urine following the ingestion of hexavalent chromium is longer than exposure to trivalent chromium with urinary half-times of workers exposed to hexavalent chromium ranging from 15–41 hours.[66] After ingestion of 0.05 mg Cr^{6+} as potassium dichromate in drinking water, the mean urinary excretion half-life of chromium in four volunteers was 39 hours.[67] About ¾ of the total dose was excreted in the first 4 days. The urine chromium concentration returned to baseline by 14 days after cessation of dosing. The relatively longer excretion half-lives following dosing with hexavalent chromium probably reflect incomplete reduction of Cr^{6+} to Cr^{3+} and the relatively longer retention of hexavalent chromium in the tissues.

Case reports suggest that serum chromium concentrations follow a two-compartment model after ingestion of high doses of hexavalent chromium. After an intentional ingestion of 22.5 g potassium dichromate, the serum chromium half-lives for the initial and terminal phases over 16 days were 3.16 ± 2.63 hours and 50 ± 27 hours, respectively, as measured by atomic absorption spectrometry.[180] The plasma half-lives of chromium after the accidental ingestion of potassium dichromate for these two phases over the 49-day-study were 5.6 hours and 191 hours, respectively.[192] Erythrocytes release hexavalent chromium slowly; the RBC chromium elimination half-life was >2-fold greater (440 hours) than the plasma elimination half-life. At the end of the study (49 days), the plasma and RBC chromium concentrations remained elevated. Kinetic studies in workers exposed to hexavalent chromium suggest the delayed release of chromium from a slow compartment ($t_{1/2}$ = months to a few years). In a study of four stainless steel manual metal arc welders exposed to soluble hexavalent chromium fumes, analysis of urinary chromium excretion suggested an exponential two-compartment model with a biological half-life in the slow compartment of 14 days to infinity.[193] Evidence for this slow compartment was not present in kinetic studies of patients with acute chromium toxicity when followed for 16 days.

Substantial individual variation in urine chromium concentrations occurs between individuals as a result of variations in individual reductive capacity for hexavalent chromium as well as confounders such as smoking, nutritional supplements, and beer consumption.[194] All three confounders increase urinary chromium. Consequently, in a *selected* population of "strong reducers," relatively high urine chromium concentrations may reflect more efficient elimination processes rather than a higher risk of toxicity. In chrome platers exposed to much higher hexavalent chromium concentrations compared with the general population, the renal elimination half-life of chromium was 2–3 days followed by a slow phase characterized by a renal elimination half-life of ~1 month.[195] Case reports suggest that the urinary elimination half-life of chromium may be prolonged in some workers exposed to heavy concentrations of fumes containing chromium. The half-life of chromium in urine samples obtained from a plasma cutter of stainless steel after he stopped working was ~129 months.[121]

Maternal–Fetal Kinetics

Hexavalent chromium traverses the placenta; the maximum chromium concentrations in most tissues are present at birth, with the exception of the lungs.[68]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

The mechanism of chromium toxicity is complex. *In vitro*, hexavalent chromium, but not trivalent chromium, produces strong oxidative and cytotoxic effects, resulting in DNA, protein, and membrane injury along with dose-dependent loss of cell viability.[196] The major defense against the action of hexavalent chromium in the lungs and stomach is the reduction of hexavalent chromium to trivalent chromium via an NADPH-dependent mechanism involving ascorbate. Animal studies indicate that glutathione plays an important role in the reduction of hexavalent chromium in erythrocytes; this compound also provides some reducing capacity in the lungs.[197] Mechanisms for renal tubular injury following acute ingestion of hexavalent chromium (dichromate, chromic acid) include hypotension, intravascular hemolysis, and a direct toxic effect of chromium on the tubular epithelial cells.

Skin

Hexavalent chromium is a skin and mucous membrane irritant as well as a powerful oxidizing agent. Some hexavalent chromium compounds (chromic acid, ammonium or potassium dichromate) are strong corrosives.[198] Sensitivity to chromium compounds depends on valence ($Cr^{6+} \gg Cr^{3+}$), water solubility, pH, amount, and the presence of reducing agents (e.g., iron sulfate).[199] Hexavalent chromium is a strong sensitizing agent capable of producing allergic dermatitis, particularly in the cement industry, where the dermal

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absorption of Cr^{6+} substantially increases when the pH exceeds 10.[75] The addition of iron sulfate during the kiln process reduces the conversion of Cr^{3+} in cement to Cr^{6+}.[200] Chromium sensitivity is a classic delayed-type (class IV) hypersensitivity reaction. A lag phase of 14 days is necessary for sensitized, antigen-specific T cells to form in the lymphatic system and diffuse into the skin. Subsequent dermal exposure to chromium releases cytokines and cytotoxic T cells, which produce dermal inflammation. The primary risk factors for the development of chromium sensitization are prior irritation of the skin and the chromium concentration present at the surface of the skin. Co-exposure to other metals (cobalt, nickel) is not a prerequisite for the development of chromium sensitization, although sensitization to these metals may occur in the same individual.

Carcinogenesis

Although most carcinogenic metals act primarily as epigenetic agents and weak mutagens, *in vitro* studies indicate Cr^{6+} is a genotoxic metal capable of forming DNA adducts and inducing mutations.[201] The production of oxidative DNA damage probably contributes to the human genotoxicity of hexavalent chromium compounds.[139] Cytotoxicity from deposition and excessive accumulation of particulate hexavalent chromium in the pulmonary bifurcation contribute to Cr^{6+}-associated lung cancer following intracellular Cr^{6+} absorption.[202] Intracellular reduction of hexavalent chromium produces oxidative stress, tissue inflammation, cytotoxicity, and subsequent DNA/protein damage; however, *in vitro* studies also indicate Cr^{6+} has epigenetic effects including DNA methylation and histone posttranslational modifications involving chromatin compaction and gene silencing. Increased cell proliferation enhances changes in DNA methylation and/or sequence substitutions.[201,203]

Hexavalent chromium is the primary species responsible for chromium toxicity,[204] although molecular damage probably results from the intracellular reduction of Cr^{6+} to intermediates (Cr^{5+}, Cr^{4+}, carbon-based radicals) and Cr^{3+} via nonenzymatic (ascorbate, cysteine, reduced glutathione) and enzymatic (cytochrome P450 reductase, glutathione reductase, mitochondrial electron transport complexes, aldehyde oxidase) antioxidants.[146,205] The greater potency of hexavalent chromium probably results from the higher redox potential of Cr^{6+} and the easier penetration of Cr^{6+} into cells.[206] The tetrahedral chromate ion more closely resembles the permeable sulfate and phosphate ions than the octahedral complexes of trivalent chromium. The higher redox potential of Cr^{6+} causes the rapid reduction of hexavalent chromium to reactive intermediates (Cr^{5+}, Cr^{4+}) and then to trivalent chromium. Oxidative reactions form complexes with critical macromolecules (peptides, proteins, DNA) that cause DNA stand breaks, DNA-protein crosslinks, and disruption of cellular signaling pathways.[207] Trivalent chromium may participate in some of these intracellular processes.

Pathological Changes

Lung

Hexavalent chromium is a strong pulmonary irritant that produces hyperemia,[208] thick nasal discharge, nasal ulcerations, and other inflammatory changes in the mucosa of the respiratory tract following exposure to high concentrations of chromium trioxide fumes.[209] Additionally, hexavalent chromium compounds are pulmonary sensitizers that cause bronchospasm and anaphylactoid reactions in sensitized workers.[210]

Hexavalent chromium compounds are recognized as human carcinogens. Although all pathological types of lung cancer occur following exposure to hexavalent chromium, small cell carcinomas and, to a lesser extent, poorly differentiated cancers predominate in post-mortem investigations of chromium workers dying of lung cancer.[211] In a Japanese study of 84 chromate production workers from a plant that ceased operation in 1975, autopsies of 13 ex-workers were performed before 1993.[212] Nine of the ex-workers had 16 lung tumors (13 squamous cell types and 3 small cell types). The incidence of squamous cell tumors was twice as frequent as age-matched controls with lung tumors. A majority of the lung tumors in these workers developed in central parts of the lung, particularly near major bifurcations where inhaled chromate particles are chronically retained.

Kidney

The acute ingestion of large amounts of hexavalent chromium produces acute tubular necrosis, marked interstitial changes, and renal failure.[213,214] The association of renal tubular dysfunction with exposure of workers to hexavalent chromium compounds is equivocal.[2] The glomeruli usually remain intact.[215]

Liver

Centrilobular hepatic necrosis, hepatic coma, and death occur after the acute ingestion of very large, acute

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doses of hexavalent chromium.[177] Postmortem analysis of a patient dying of hepatorenal failure 26 hours after receiving a purgative containing high hexavalent chromium concentrations demonstrated hepatic chromium concentration 20 times higher than in other tissues.[216]

A study of five workers in the chrome plating industry associated histological changes (lymphocytic and histiocytic infiltrates, hyperplasia of Kupffer's cells, necrosis) in the liver with exposure to hexavalent chromium.[217] However, most epidemiological studies of workers have not detected an increased incidence of liver damage.[155]

Postmortem Examination

Hexavalent chromium is a strong oxidizing agent that causes ulceration of the skin and gastrointestinal mucosa. The autopsy of a fatal ingestion of chromic acid demonstrated extensive necrosis of the gastrointestinal tract with esophageal perforation and a mediastinal hematoma anterior to the upper esophagus.[218] Histological examination of the liver revealed necrosis in 80% of the hepatocytes and fatty degeneration. Renal injury included dilated, atrophic renal tubules without necrosis and dilated glomeruli. Postmortem examination of other fatalities demonstrates centrilobular necrosis of the liver, pulmonary hemorrhage, hemoperitoneum, necrosis of the mucosal lining in the stomach,[176] and extensive cortical proximal convoluted renal tubular cell necrosis;[172] glomeruli appear relatively normal.[174]

CLINICAL RESPONSE

Acute Oral Toxicity

The ingestion of large doses of hexavalent chromium causes vertigo, thirst, abdominal pain, bloody diarrhea, and, in severe cases, coma and death. Serious complications include hepatorenal syndrome,[179] severe coagulopathy,[176] and intravascular hemolysis.[219] If the patient survives, the initial phase of shock, hepatic, and renal failure may develop within 1–2 days. Occasionally, renal dysfunction may persist after recovery from an acute overdose of hexavalent chromium.[216]

Although suicidal chromic acid ingestions are usually fatal, patients may survive the accidental ingestion of chromic acid with intensive care including hemodialysis.[51] Serious complications of an acute chromic acid ingestion include severe hemorrhagic gastroenteritis with yellow-green vomitus or hematemesis, hepatic necrosis, gastrointestinal hemorrhage and perforation, and acute tubular necrosis with renal failure.[51,173] Although chromic acid is a strong mineral acid that causes direct skin and extensive gastrointestinal tract ulcerations, serious end organ failure, and gastric hemorrhage may develop despite the absence of lesions in the mouth, larynx, or esophagus on endoscopy.[220] An intravenous chromic acid exposure resulted in nausea, vomiting, dark red urine, loose reddish stool, and renal failure that required temporary hemodialysis.[178]

Environmental Exposure

Ecological studies of populations exposed to hexavalent chromium as measured by chromium concentration in drinking water or geographical location near point sources are inconsistent; overall, most studies do not strongly support an association between cancer mortality and environmental chromium exposures. An ecological study of JinZhou Chinese province containing a ferrochromium plant compared mortality rates in four areas with low total chromium concentrations in drinking water (<0.001 mg/L) and five areas with relatively high chromium concentrations from 1970–1978.[221] Discharge from the plant to surface and drinking water began in 1961. In 1965, total chromium concentrations in well water samples from the high-chromium areas ranged from 0.6–20 mg/L with 15% of the well water containing <2 mg/L. Comparing high and low chromium exposure areas, the age-adjusted cancer mortality rate ratio for stomach cancer was elevated at 1.82 (95% CI: 1.11–2.91), whereas the rate ratio for lung cancer of 1.15 (95% CI: 0.62–2.05) and all cancers of 1.13 (95% CI: 0.86–1.46) were not significantly elevated. Re-analysis of cancer rates in the region by dividing the province into the industrial town of TangHeZi where the plant was located, unexposed agricultural village residents, and exposed agricultural residents did not confirm the elevated rate of stomach cancer deaths when using local rather than provincial rates.[222] The relative risks of lung and stomach cancers were similar for the chromium-exposed residents and residents of agricultural villages without chromium contamination; average total chromium concentrations in drinking water did not correlate to stomach or lung cancer rates.

Hexavalent chromium compounds were additives at water-cooling towers in three southern California, gas compressor facilities in the decades from the 1950s–1980s. An ecological study in Kings County and San Bernardino County, California compared cancer mortality in locations near natural gas compressor plants with areas distant from the plants based on zip codes.[223] Age-adjusted cancer mortality rate ratios (i.e., rate (areas near the plant)/rate (distant areas)) for

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1989–1998 were 1.03 (95% CI: 0.90–1.17) for lung cancer deaths, 0.93 (95% CI: 0.87–1.00) for all cancer deaths, and 0.98 (95% CI: 0.95– 1.02) for all deaths.

Occupational Exposure

The main target organs of hexavalent chromium toxicity are the skin and respiratory tract. A French mortality study of 4,227 stainless steel production workers from 1968–1984 detected excess deaths from liver cirrhosis compared to expected deaths (SMR = 174, 95% CI: 131–226; Observed/Expected = 55/31.6) based on national rates and matched for age, sex, and calendar time.[224] The study reported no measures of chromium exposure or regression analysis for potential confounding variables. Most mortality and morbidity studies of workers in the production of chromium compounds have not demonstrated an excess prevalence of liver disease.[142]

Kidney

Studies of renal function in chrome platers suggest the possibility that Cr^{6+} exposure exceeding $4\,\mu g/m^3$ may produce renal tubular dysfunction manifested by increased urinary excretion of β_2-microglobulin.[225] In a cross-sectional study of 115 Chinese chromate production workers with mean duration of chromium exposure of ~13 years and 60 local controls without Cr exposure, the incidence of urinary *N*-acetyl-β-D-glucosaminidase activity and β_2-microglobulin concentration above reference values was increased compared with controls.[226] Despite the mandatory use of personal protective equipment (M40 masks, rubber gloves/boots) and the lack of any airborne chromium concentrations exceeding $50\,\mu g/m^3$, the airborne chromium concentrations correlated to urine total chromium concentrations (mean = 17.41 μg/g creatinine); the airborne chromium concentration was not speciated. Therefore, the chromium exposure may have exceeded current workplace standards. The study did not report confounding variables. Other studies have not detected an increased prevalence of renal tubular dysfunction or reduced creatinine clearance. A cross-sectional Swedish study of 24 current chrome platers, 27 ex-chrome platers, and 37 referents demonstrated an increased incidence of elevated urinary β_2-microglobulin concentrations in current chrome platers (mean = 5.3 years), but not ex-chrome platers with >1 year Cr^{6+} exposure in the chrome plating plants followed 1940–1968.[227] Other epidemiological studies on chrome platers[228] and on stainless steel welders[229] have not consistently associated renal tubular dysfunction or reduced glomerular filtration with occupational Cr^{6+} exposure. In a study of 3,408 US chromate production workers processing chromite ore and followed 1937–1971, mortality from genitourinary disease was not significantly increased with a proportionate mortality ratio for Caucasian workers of 71 (95% CI: 40–117).[89] Chromium exposure and smoking data were not available.

Skin

Hexavalent chromium is a skin and mucous membrane irritant with some hexavalent compounds being strong corrosive agents. Chromic acid is a corrosive that produces inflammation and ulceration of the skin as well as allergic contact dermatitis in sensitized individuals. In addition, chromic acid burns can cause systemic toxicity even following relatively small burns. External burns of 10% of the total body surface caused by chromic acid may be fatal, whereas a 19-year-old man survived a 20% burn after developing hepatic damage, acute renal failure, and normochromic and normocytic anemia.[230]

In addition to the corrosive injuries produced by chromic acid, Cr^{6+} may cause allergic contact dermatitis or skin ulcers in sensitive individuals. Skin ulcers (chrome holes) develop slowly in exposed areas of the body (nasal septum, extremities) following exposure to hexavalent chromium, particularly in areas of the skin with loss of dermal integrity (e.g., index, middle fingers). These painless ulcers are usually well-circumscribed craters with intense inflammation and tenacious crusts.[231,232] These lesions heal in a few weeks following cessation of chromium exposure, often with atrophic or occasionally hypertrophic scars.

Immune System and Asthma

Occupational exposure to hexavalent chromium compounds may produce an allergic contact dermatitis characterized by eczema.[233] Chromium sensitization is a common cause of contact dermatitis in workers presenting to allergy and occupational clinics, particularly among workers in the building trades.[234] Although the chromium concentration in cement is low (<0.2%), chromium sensitivity is the most common type of sensitivity reaction in cement workers. As many as 8–9% of cement workers have positive patch tests for hexavalent chromium compounds, even though the incidence of allergic dermatitis is much less.[235] A study of volunteers from a referral clinic indicated that sensitivity to chromates (Cr^{6+}) in that population averaged 1.7%,[236] but the actual incidence for patients with normal skin and normal sensitivity is probably much less (0.1%). In a

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study of 230 automobile workers handling nuts and bolts coated with Cr^{6+}-containing chrome and diagnosed with skin disease (eczema, dermatitis), positive patch tests to potassium chromate occurred in 56 (24.3%) of exposed workers compared with 1 (0.15%) of 66 controls.[237] Among construction workers, hexavalent chromate in cement is the most common cause of allergic contact dermatitis; however, over the last several decades, the prevalence of allergic contact dermatitis in cement workers has decreased as a result of the reduction of hexavalent chromium concentrations in cement.[238]

Case reports associate the development of occupational asthma in chromium-sensitized workers with a variety of hexavalent chromium compounds including chromic acid vapors[210,239] metal plating with chromium,[76] chromate spray paint,[240] zinc chromate primer paint,[239] and chromium (Cr^{6+}) fumes from stainless steel welding.[241] Although the chromium content of cement is minute, case reports associate the development of allergic contact dermatitis and occupational asthma with cement exposure, particularly in smokers.[242,243] Nickel electroplating is more efficient compared with chromium electroplating that generates minimal amounts of Cr^{6+}. Some cross-reactivity to nickel may occur in electroplating workers with chrome-induced occupational asthma.[244] Sensitization to chromium may occur in occupational environments, where air concentrations to chromium are below permissible occupational limits.

The wide variation in lymphocyte subpopulations and modulation of cell populations by a wide variety of effectors limits interpretation of the effect of chromium on the immune system. In general, studies do not support the suppression of the immune system by chromium compounds. Comparison of a convenience sample of 15 plastics workers exposed to lead chromate (Cr^{6+}) demonstrates a 30–50% reduction in measures of CD4+ helper-inducer and natural killer lymphocytes compared with 15 healthy, unexposed controls; serum chromium concentrations and serum immunoglobulins IgA, IgG, and IgM were not significantly different between the two groups.[245] In an Italian study of 84 shoe, hide, and leather workers exposed to hexavalent chromium, the lymphocyte subpopulations (CD4+, CD8+, CD19+, CD16+/CD56+, CD4/CD8) were similar in exposed and unexposed workers.[246] An earlier study of 20 Italian tannery workers detected an increased proliferative response of peripheral blood mononuclear cells to concanavalin A, but the distribution of lymphocyte subsets (e.g., T cells, T helper lymphocytes, T cytotoxic lymphocytes, B cells, natural killer cells) was similar between the exposed and unexposed workers.[247] Personal air samplings of Cr^{6+} concentrations were not reported, but analysis of airborne total Cr and Cr^{6+} concentrations in similar factories suggested TWA concentrations of 90–100 $\mu g/m^3$ and 1–2 $\mu g/m^3$, respectively.

Respiratory Tract

Chronic exposures to chromate dusts and chromic acid fumes may cause conjunctivitis, lacrimation, sneezing, nose and throat irritation, rhinitis, cough, epistaxis, nasal obstruction, or ulceration, and/or perforation of the nasal septum.[155,248,249] Older studies of chromate production workers associated high exposure to dichromate and chromium trioxide (>10 Cr^{6+} $\mu g/m^3$) with an increased incidence of sinusitis, laryngitis, nasal polyps, and bronchitis; airborne chromium concentrations were not well-defined but involved both Cr^{3+} and Cr^{6+}.[250,251] In a cross-sectional study of 27 Korean electroplaters and 34 controls (male clerks from the same factory), the prevalence of nasal complaints (dry nose, crusting, nasal obstruction) was significantly increased in chromium workers compared with controls based on questionnaires.[252] Olfactometry testing demonstrated reduced olfactory thresholds in exposed workers without nasal complaints. Chemicals used in electroplating included chromic acid, sodium and potassium dichromate, hydrogen chloride, nitrous oxide, sulfuric acid, and nickel carbonate with the airborne concentration of Cr^{3+} and Cr^{6+} near or slightly above current workplace standards.

A statistically significant excess of deaths (SMR = 143; observed/expected, 41/28.66; $P < 0.05$) due to chronic obstructive pulmonary disease (COPD) was detected in UK chromate production workers first employed before 1945 based on national rates adjusted for geographical area and social class; there was no excess mortality from COPD in workers employed after that date.[253] The SMR for workers employed after process changes to reduce dust and chromate exposure demonstrated a significantly reduced SMR for COPD (SMR = 17; observed/expected, 1/5.88; $P < 0.05$). In a retrospective mortality study of 2,689 UK nickel/chromium platers employed at least 6 months 1946–1983, the SMR for mortality from respiratory diseases excluding cancer was 127 (observed/expected, 97/76.4; $P < 0.05$) based on national rates.[254] The primary exposure was chromium trioxide, but the chromium concentrations were not well documented. There was no direct correlation between the presence of chromates and the development of chronic obstructive pulmonary disease in a cross-sectional study of ferrochromium workers.[255] Methodological issues in these studies prevent the establishment of a definitive cause–effect relationship

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between chromate exposure and mortality from noncancerous pulmonary diseases, particularly the lack of smoking, chromium speciation, and confounder data.

Reproductive Abnormalities

Reproductive data on the effect of hexavalent chromium on human reproduction are limited, particularly for studies with analyses of airborne Cr^{6+} concentrations. In the current medical literature, the association between Cr^{6+} exposure and adverse child outcomes (birth defects, autism spectrum disorder, prematurity, small for gestational age) is weak.[256] A study of 30 tungsten inert gas stainless steel welders exposed to low concentrations of hexavalent chromium did not detect a statistically significant increase in sperm morphology, sperm mobility, or sex hormones (testosterone, follicle-stimulating hormone, luteinizing hormone) compared with referents.[257] In a study of women undergoing *in vitro* fertilization, the number of spontaneous abortions before 28 weeks in IVF-treated women impregnated by men exposed to stainless steel welding fumes ($n = 91$, 18%) and mild steel welding fumes ($n = 128$, 25%) was similar to controls ($n = 819$, 28%).[258] The risk ratio for pregnancies with paternal exposure to stainless steel was 0.6 (95% CI: 0.4–1.0). The same group earlier studied the occurrence of spontaneous abortions among 2,520 pregnancies of 1,715 married to metal workers in 1977–1987. The odds ratio of spontaneous abortions in couples with fathers exposed to stainless steel welding fumes was 0.78 (95% CI: 0.55–1.1) when compared with couples of unexposed fathers.[259] Occupational histories were based on questionnaires, and the occurrence of spontaneous abortions was confirmed on medical registries; no chromium concentrations were reported. A study of stainless steel and mild steel welders did not detect statistically significant differences in sperm morphology, sperm motility, or sex hormones (follicle-stimulating hormone, luteinizing hormone, testosterone) between welders and referents.[260] The study did not assess airborne concentrations of metals to determine dose-response.

Toxic oral doses of potassium dichromate (57 mg Cr^{6+}/kg/day) in drinking water caused severe developmental and fetal toxicity in rats including increased post-implantation loss, decreased cranial ossification, and decreased fetal weight.[261]

Carcinogenesis

The International Agency for Research on Cancer (IARC) and the US Toxicology Program recognize hexavalent chromium as a known human carcinogen. Increased risk of lung cancer occurs primarily in workers exposed to hexavalent chromium dust during the refining of chromite ore and the production of chromate pigments. Although individual studies suggest the possibility of an excess incidence of cancer at sites outside the lung, the results from these studies are inconsistent. Studies of chrome platers exposed to Cr^{6+} and other carcinogenic chemicals (e.g., nickel, sulfuric acid) found a significantly increased lung cancer risk in association with surrogate measures of Cr^{6+} exposure (e.g., duration of employment at jobs involving Cr^{6+} exposure); however, data on estimates of attributable risk of Cr^{6+} exposure remain unclear. Similarly, lung cancer rates are elevated in studies of chromate production workers with the rates declining as improved industrial hygiene methods reduced Cr^{6+} exposure. Results of studies of lung cancer rates in stainless steel welders exposed to Cr^{6+} and other potential carcinogens are inconclusive.

Lung

Based on positive responses in assays for genotoxicity, hexavalent chromium is the most potent genotoxic chromium species.[139] The solubility of these hexavalent compounds is a significant risk factor with the moderately soluble compounds (e.g., strontium and zinc chromates) associated with the greatest risk of lung cancer. The dose-related, increased risk of lung cancer is associated with the inhalation of hexavalent chromium in the occupational setting, primarily in populations of workers refining chromite ore or producing chromate pigments with high exposures to hexavalent chromium.[262,263] No increased risk of lung cancer was detected in a population-based, case-control study of tobacco-using workers with low to medium exposure to hexavalent chromium as determined by job history; however, the odds ratio of lung cancer among nonsmokers or former smokers was elevated (OR = 2.4, 95% CI: 1.2–4.8).[264] In the 1950s and 1960s, process modifications (i.e., elimination of calcium chromate by changing to lime-free processes) and improved environmental controls reduced exposure to hexavalent chromium compounds. A meta-analysis of cancer studies post-modification did not demonstrate a statistically significant excess of lung cancer; however, the combined studies lacked sufficient statistical power to exclude a moderate increase in the risk of lung cancer.[265] This risk of lung cancer decreases to baseline levels for the working population when newer technologies for reducing the amount of lime in the roast mix result in hexavalent chromium concentrations in ambient air of <1–5 $\mu g/m^3$.[266]

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Squamous cell and small cell carcinomas are the predominant cell types with the development of small cell carcinomas occurring after more intense exposures over shorter periods of time compared with the appearance of squamous cell carcinomas.[139]

The mean latency period for developing lung cancer in these workers ranged from ~13–30 years, although a few cases have appeared following 5 years of exposure to chromates.[267] In general, the minimal latency period for lung cancer is 10–15 years. Similar latency periods for the development of lung cancer have been reported in chromium chemical production workers (chromic acid mists) and workers exposed to lead and zinc chromates.[268,269]

Chromate Production

Epidemiological studies of chromate production workers demonstrate an increased risk of lung cancer mortality that has declined with improved industrial hygiene methods. These studies indicate that the risk of lung cancer increases with increasing cumulative exposure to hexavalent chromium.[270] An increased incidence of lung cancer (adjusted SMR = 197; observed deaths, 175) occurred in 1,422 workers exposed to hexavalent chromium in chromate production employed before changes to production processes in the late 1950s decreased hexavalent chromium exposure.[253] The study demonstrated no excess lung cancer deaths (adjusted SMR = 102, 95% CI: 56–171; observed deaths, 14) in 677 men employed after the changes in production processes. An etiological research study of 398 chromate workers at a new facility, where >99% of the personal breathing zone samples were <50 μg Cr^{6+}/m^3, did not demonstrate increased mortality.[271] The number of subjects was small, and the follow-up period was relatively short (15 years). A meta-analysis of 49 epidemiological studies of cancer outcomes primarily among chromate production workers employed after improvements in the production process demonstrated a SMR of 141 (95% CI: 135–147).[272] Limiting the analysis to high-quality studies controlled for smoking indicated that current hexavalent chromium exposure is a relatively weak carcinogen as the overall SMR for lung cancer decreased to 112 (95% CI: 104–119).

Chrome Plating

Some epidemiological studies demonstrated elevated lung cancer rates in chrome bath workers exposed primarily to soluble hexavalent chromium (i.e., chromic acid mists) when compared with referent populations. In these studies, the risk of lung cancer following exposure to chromic acid mists increased with the duration of exposure after adjustment for sex, age, and period from the first chrome work.[273] The risk of developing lung cancer is smaller and less consistent in chrome platers than in chromate production workers. In a study of 1,087 chrome platers exposed to chromic acid mist, the SMR was 185 (95% CI: 141–238; observed deaths, 60; $P < 0.001$) when compared to the general population in England and Wales.[274] However, there was no statistically significant difference in the SMR for lung cancer when comparing the exposed workers with a group of workers without known exposure to hexavalent chromium. In a prospective cohort study of 1,193 Japanese metal platers (626 chrome platers, 587 non-chromium platers), the overall SMR for all platers was 179 (95% CI: 102–290; observed deaths, 16).[275] However, there was no statistically significant difference in the SMR between the subgroups of chromium and non-chromium platers. The chromium platers worked in small-scale chromium plating plants in Tokyo, Japan, for at least 6 months. Extending the follow-up to 27 years resulted in an increased lung cancer mortality of borderline statistical significance (SMR = 146, 95% CI: 0.98–2.04; observed deaths, 28); the SMR was 1.09 (95% CI: 0.67–1.60; observed deaths, 20) in non-chromium platers.[276] Higher lung cancer risk occurred in chromium platers with earlier exposure, but not with increased duration of employment as a chromium plater. Smoking histories were not available.

Chrome Pigment Production

Some epidemiological studies suggest an increased incidence of lung cancer in workers exposed to hexavalent chromium (e.g., lead and zinc chromates) during chromium pigment production.[141] In some of these studies, the rate of lung cancer mortality increased (SMR = 190, 95% CI: 111–295) for workers with hexavalent chromium exposure over 30 years (1940–1982), but not with shorter Cr^{6+} exposure or the whole cohort.[277] Monitoring airborne chromium concentrations in later years indicated total chromium exposure for the cohort was >500 μg/m^3 with highly exposed workers exceeding 2,000 μg/m^3. The lack of control for confounders (smoking, nickel exposure) and poor exposure data (i.e., lack of speciation) limits conclusions regarding the contribution of hexavalent chromium to lung cancer rates.[278,279] In general, water-soluble chromates (sodium and potassium chromate, dichromates) are more potent carcinogens than less-soluble chromate compounds with the exception of calcium and zinc chromates.[280] Studies of end users of chromate (e.g., painting operations using chromate pigments) do not demonstrate a strong association between exposure to chromium compounds and the development of lung cancer.[281]

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Stainless Steel Welding

Workers in the stainless steel welding industry are exposed to hexavalent chromium and other potential carcinogens (e.g., nickel and asbestos); epidemiological studies of workers in this industry are inconsistent with increased lung cancer mortality rates in some sections of the industry.[282] Although a meta-analysis of five epidemiological studies suggested an increased pooled relative risk of lung cancer in stainless steel welders of 1.94 (95% CI: 1.28–2.93),[283] the differences in lung cancer risks between exposed welders and referents in four of the studies were not statistically significant. A historical follow-up study of arc welders exposed to fumes containing chromium and nickel demonstrated a nonstatistically significant increase (~20–30%) in the mortality from lung cancer compared with controls, but most of this excess mortality was attributed to smoking and asbestos exposure.[284] The ~30–40% increase in the incidence of lung cancer in welders does not correlate well with exposure to hexavalent chromium; a study of welders demonstrated little difference in the rates of lung cancer between stainless steel welders (chromium, nickel exposure) and mild steel welders (no chromium, nickel exposure).[285] In a Swedish study of 234 stainless steel welders with at least 5 years of exposure 1950–1965 and followed through 1984, the SMR for trachea, bronchus, and lung tumors was 2.49 (95% CI: 0.80–5.81; observed/expected, 5/2).[286] The median time-weighted average airborne total chromium concentration was 110 μg/m^3 ranging up to 750 μg/m^3. Eighty-five percent of the chromium measurements exceeded current workplace standards.

Environmental Exposure

There is little evidence that chromium causes lung cancer following lifetime exposure to hexavalent chromium in drinking water or airborne chromium exposure near point sources. In a mortality study of residents near gas compressor facilities that used hexavalent chromium as water-cooling additives, there was no significant increase in the mortality rates of cancer at any site when compared with mortality rates in surrounding communities.[223] In an ecological study of five Chinese agricultural villages with and four nearby villages without Cr^{6+} in their drinking water, the mortality rates from lung cancer, stomach cancer, and all cancers were similar without evidence of a dose-response relationship.[222] The risk of cancer from dermal or oral exposures to hexavalent chromium compounds is not well documented.[10] Hexavalent compounds for which there is evidence in animal studies for carcinogenicity include the following: barium chromate, calcium chromate, chromium trioxide, lead chromate, sodium dichromate, and strontium chromate.

Other Sites

Currently, there is a lack of conclusive evidence to associate hexavalent chromium exposure with an excess of cancer outside the respiratory tract.[287] Although individual studies suggest the possibility of an excess incidence of cancer at sites outside the lungs (nose, gastrointestinal tract), results from these studies are inconsistent.[253,288] In a study of 2,354 workers employed at a chromate production plant in 1950–1974, lung cancer mortality was elevated (SMR = 1.63, 95% CI: 1.42–1.86) using US mortality rates without evidence of increased mortality rates from other cancer sites.[289] A review of the carcinogenicity of hexavalent chromium reported suggestive evidence of an increased risk of cancer in nonpulmonary sites including bone, stomach, prostate, genital, renal, bladder, and blood (lymphoma, Hodgkin's disease, leukemia).[290] However, the evidence cited for this conclusion primarily involves mortality studies, many of which demonstrated nonsignificant increases in the SMR. Furthermore, the author failed to discuss the inherent weakness of mortality studies (selection bias, accuracy of exposure data, confounding) and the lack of well-designed cohort studies to support the development of cancer at sites distant from the sites of administration. Most of the studies cited for stomach cancer contained small numbers of observed cases and nonsignificant increases in the SMR.[291,292] A review of the chromium data in 1997 indicated that heterogeneity of reporting and reporting bias precluded the use of meta-analysis to determine the incidence of cancer at sites outside the lung.[265] Additionally, confounding complicates the interpretation of these studies including smoking, dietary factors, alcohol consumption, and socioeconomic status. Co-exposure to sawdust confounded the previous causal relationship between sinonasal cancer and chromates.[293] A more recent meta-analysis of 32 studies of gastrointestinal tract cancers detected an elevated meta-SMR of 1.49 only for esophageal cancer among four US cohorts (meta-SMR = 1.49, 95% CI: 1.06–2.09) with relatively high Cr^{6+} exposure.[294] Calculated meta-analysis summary relative risk (95% CI) using random effects models and inverse variance weighting methods was as follows: oral cavity = 1.02 (0.77–1.34), esophagus = 1.17 (0.90–1.51), stomach = 1.09 (0.93–1.28), colon = 0.89 (0.70–1.12), and rectum = 1.17 (0.98–1.39). A meta-analysis of 56 cohort and case-control studies and 74 individual relative risk estimates on stomach cancer suggested an association

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between hexavalent chromium exposure and stomach cancer.[295] The summary relative risk (sumRR) was 1.27 (95% CI: 1.18–1.38); these studies included workers in chrome plating, chromium production, leather works, and jobs with exposure to Portland cement. The sumRR for studies with increased risk of lung cancer was higher (sumRR = 1.41, 95% CI: 1.18–1.69), suggesting increased risk of stomach cancer following higher chromium exposure. Few studies controlled for confounding variables (e.g., smoking).

DIAGNOSTIC TESTING

Analytical Methods

In biological media, techniques for the determination of hexavalent chromium include complexation with diphenylcarbazide followed by solvent extraction and analysis by electrothermal/absorption atomic spectrometry (LOD, 0.2–0.5 μg/L)[296] and capillary electrophoresis/inductively coupled plasma/sector field/mass spectrometry.[297]

In environmental samples, ion chromatography is the most common technique for separating hexavalent chromium from environmental samples with flow-injection analysis a less common technique.[298] Techniques for quantitating hexavalent chromium in environmental samples include ion chromatography followed by ultraviolet–visible (UV–VIS) spectroscopy (air, NIOSH method 7605; water, EPA method 7199 or 218.7 for dissolved Cr^{6+}), complexation of chromate ions with 1,5-diphenylcarbazide (DPC) in strongly acidic solution followed by spectrophotometry (540 nm),[299] anion-exchange fast protein/liquid chromatography/electrothermal atomic absorption spectrometry (LOD, 0.035 μg Cr^{6+}/m^3),[300] absorptive stripping voltammetry,[301] complexation with pyrocatechol violet and *N*-(2-hydroxyethyl)ethylenendiamine-*N*,*N*′,*N*′-triacetic acid coupled with differential pulse adsorptive stripping voltammetry,[302] flow injection on-line sorbent extraction followed by complexation with sodium diethyldithiocarbamate and quantitation by electrothermal/atomic absorption spectrometry (LOD, 16 ng Cr^{6+}/L and 18 ng Cr^{3+}/L),[303] ion chromatography coupled with inductively coupled plasma/atomic emission spectrometry,[304] and complexation with ammonium pyrrolidinedithiocarbamate followed by high-pressure liquid chromatography with UV detection.[305,306] The limit of detection for hexavalent chromium using the latter method is 2.2 μg/L. Although the reaction of DPC with chromate is highly specific for Cr^{6+}, the presence of other metals (Cu^2, Fe^3, Hg^2, Mo^6, V^5) may compete with Cr^{6+} for the colorimetric reagent and lower the quantitative value of hexavalent chromium. Additionally, the use of spectrophotometry for the quantitation of Cr^{6+} (e.g., welding fumes) is usually inappropriate because the highly acidic solutions in the presence of magnetite (Fe_3O_4) reduce most of the Cr^{6+} to Cr^{3+}.[298] The use of a sampling filter impregnated with alkali decreases the reduction of Cr^{6+} when analyzing chromic acid mists, but the addition of magnesium hydroxide is important to prevent the air oxidation of trivalent chromium species to Cr^{6+}. Proper storage of water samples requires a pH ≥ 8 with ammonium ion-containing buffers to complex free chlorine; the presence of free chlorine oxidizes Cr^{3+} to Cr^{6+}.

Biomarkers

Blood

Plasma or serum chromium concentrations reflect recent exposure to hexavalent and trivalent chromium, whereas RBC chromium concentrations reflect the burden of hexavalent chromium because only Cr^{6+} penetrates red blood cells. Chromium concentrations in erythrocytes indicate the extent of hexavalent chromium exposure during the lifetime of the red blood cell. Low RBC chromium concentrations imply that the concentration of Cr^{6+} did not significantly exceed the reducing capacity for Cr^{6+} in the plasma, whereas RBC Cr concentrations often exceed plasma Cr concentrations ~3–5 fold several days after severe acute Cr^{6+} poisoning.[216] On the day of admission after accidentally ingesting potassium dichromate, the plasma and RBC chromium concentrations in blood samples from a 58-year-old man were 1,657 μg/L and 631 μg/L, respectively.[192] By 49 days postingestion, values were 5 μg/L and 129 μg/L, respectively.

The ratio of whole blood/plasma total chromium concentrations varies substantially with time after an acute ingestion as chromium diffuses into erythrocytes. In a fatal chromic acid ingestion complicated by massive gastrointestinal hemorrhage, the whole blood/plasma total chromium ratio was 2.1 3 hours after ingestion (Hct = 53%) compared with 1.75 11 hours after ingestion (Hct = 17%).[218] She died 1 hour later. The whole blood/plasma chromium ratio was ~2–3 several days after the use of dichromate-containing purgatives.[216]

General Population

There are few data on Cr^{6+} concentrations in whole blood samples from the general population, primarily because of the low hexavalent chromium exposure for individuals without occupational exposure to Cr^{6+}.

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Toxicity

Whole blood chromium concentrations above 2–3 mg/L are potentially lethal following acute exposure to hexavalent chromium.[217] Most case reports do not speciate blood chromium concentrations. A 15-year-old girl ingested potassium dichromate, vomited, and soon became comatose; she died within 12 hours of ingestion. The admission blood sample contained 35 mg Cr/L.[307] A 17-year-old adolescent died 18 hours after the ingestion of potassium dichromate from hypotension, DIC, and severe gastrointestinal hemorrhage, despite intensive care including the use of hemodialysis, hemoperfusion, and dimercaprol.[176] The whole blood chromium concentrations 3 hours and 13 hours after ingestion were 58 mg/L and ~27 mg/L, respectively. The total serum chromium concentration 7 hours after the intentional ingestion of potassium dichromate by a 48-year-old man was ~0.7 mg/L.[180] He survived after developing tarry stools, abdominal pain, diarrhea, chest pain, and mild elevation of his serum creatinine. The serum chromium concentration 1 day after the deliberate ingestion of potassium dichromate by a 16-year-old adolescent was ~2.4 mg/L.[308] Within 2 days, he developed hepatorenal failure requiring liver transplantation. He survived without hepatorenal dysfunction for at least 2 years after transplant. On admission to the emergency department with diarrhea and abdominal pain, the plasma chromium concentration in a 58-year-old man who accidentally ingested potassium dichromate was 2.09 mg/L.[192] He survived without developing hepatorenal dysfunction. A 55-year-old man survived the accidental ingestion of chromic acid after developing hemorrhagic gastroenteritis and hepatorenal dysfunction that required several days of hemofiltration.[220] Five hours after ingestion, his blood chromium concentration (sample type not reported) was 3.4 mg/L.

Urine

Urine chromium concentrations reflect absorption of chromium primarily over the last 1–2 days in patients without prior occupational exposure to chromium. As a result of reduction of hexavalent chromium in the airways and blood, only trivalent chromium appears in the urine. Consequently, urinary chromium represents exposure to either or both of these species. Most analytical methods do not distinguish between trivalent and hexavalent chromium. Although trivalent chromium does contribute somewhat to the total chromium concentration, substantial portions of the total chromium result from the reduction of hexavalent chromium.

Hair

External contamination of hair complicates the use of this biomarker as a measure of the severity and timing of hexavalent chromium exposure. Analysis of hair chromium could not distinguish the timing of an acute, accidental exposure to potassium dichromate in a woodworker using chromium as a pigment.[218] The use of hair analysis in the occupational setting is complicated by the difficulty of distinguishing chromium bound to the hair after absorption from external contamination. External contamination of the hair prevented the identification of the time of an acute ingestion of potassium dichromate. Chromium concentrations in hair are up to 1,000 times higher than serum chromium concentrations.

Abnormalities

Some hexavalent chromium compounds are strong oxidizing agents; therefore, methemoglobinemia potentially may develop. In a fatal case of potassium dichromate poisoning, methemoglobinemia occurred along with respiratory failure, gastrointestinal hemorrhage, and coagulopathy.[176] A case series of chromium-sensitized workers indicates that inhalational challenges with potassium dichromate produce a variety of reactions (immediate, dual, late) in response to the bronchial provocation tests including angioedema, erythema, pruritus, cough, wheezing, and bronchospasm.[309] Not all chromium-exposed patients with positive bronchial provocation tests have positive skin prick tests for potassium dichromate.[310]

HEALTH SURVEILLANCE

Risk Assessment

Occupational Exposure

Hexavalent chromium is a recognized lung carcinogen that causes elevated lung cancer rates in exposed workers (e.g., chromate and chromate pigment production), whereas no increased risk of lung cancer was detected in workers in the ferrochromium industry exposed to trivalent chromium.[53] In general, estimates of excess lifetime occupational risks of developing lung cancer in chromate production workers range from ~0.002–0.005 per μg Cr^{6+}/m^3. Based on Poisson and Cox regression analysis of the Painesville cohort at a chromate production facility, the estimated lifetime additional risk of lung cancer mortality associated with 45 years of occupational exposure to 1 μg Cr^{6+}/m^3

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was 0.00205 (90% CI: 0.00134–0.00291) for the relative risk model assuming a linear dose-response for cumulative exposure with a 5-year lag.[270] Extrapolating these data to a continuous environmental exposure resulted in an environmental unit risk of 0.00978 (90% CI: 0.00640–0.0138). Statistical tests did not detect a statistically significant increased risk of lung cancer below lifetime cumulative occupational exposures to hexavalent chromium below 1 mg/m^3-year. The exclusion of short-term workers defined by <1 year of employment limited information in the low exposure range. In an updated mortality study of 714 Painesville workers including 198 short-term workers, the standardized mortality ratio (SMR) remained elevated (SMR = 186, 95% CI: 145–228) for workers with cumulative exposure of >1.41 mg/m^3-years.[311] Using linear Cox model with unlagged cumulative exposure, the occupational unit risk was 20% lower (0.00166, 95% CI: 0.000713–0.00349) and the environmental unit risk was 15% lower (0.00832, 95% CI: 0.00359–0.0174) than in the previous study.

Extrapolation of exposure data from 2,372 men hired at a chromate manufacturing plant from August 1, 1950 to December 31, 1974 with mean cumulative exposure to hexavalent chromium of 0.134 mg/m^3-year indicated an estimated rate ratio of 2.44 (95% CI: 1.54–3.83) for a cumulative hexavalent chromium exposure of 1 mg/m^3-year as CrO_3.[312] The estimated excess lifetime risk of lung cancer mortality from exposure to 0.1 mg/m^3 (OSHA PEL) was 255 per 1000 (95% CI: 109–416).

Currently, there is substantial scientific debate about the following: 1) the mode of action (i.e., cytotoxic vs. genotoxic) of Cr^{6+}-induced cancer; and 2) the validity of extrapolating from high oral doses in rodents to chromium concentrations typically present in the environment using a linear model rather than a nonlinear threshold model reflecting the Cr^{6+} reductive capacity in the gastrointestinal tract.[313,314]

Using the multistage, low-dose linear extrapolation, the US EPA calculated an inhalation unit risk factor for airborne Cr^{6+} exposure of 0.012 per μg/m^3.[315,316] This value correlates to an upper 95% confidence limit of 1/1,000,000 for an airborne Cr^{6+} concentration of 8×10^{-5} μg/m^3. Revaluation of the inhalation unit risk factor by the Texas Commission on Environmental Quality using dosimetric adjustments and an uncertainty factor of 30 to points of departure with respect to tumor formation resulted in a value of 0.24 μg Cr^{6+}/m^3 (i.e., ~300 times higher than the US EPA estimate).[317] In this study, analysis of data from Crump et al.[270] and Luippold et al.[263] suggested possible threshold values of 1.00–2.70 mg/m^3 year for cumulative Cr^{6+} exposure; the most conservative point of departure selected for derivation of the cancer-based chronic inhalation reference value was 0.195 mg/m^3 year. In the Luippold study, over ¾ of the exposed cohort smoked. There are inadequate data to evaluate the effect of combined exposure to tobacco smoke and chromium on the risk of developing lung cancer.[318]

Environmental Exposure

The inhalation of Cr^{6+}-contaminated dust is a carcinogenic hazard; however, there is limited evidence causally linking oral or dermal environmental exposure to Cr^{6+} and increased lung cancer. Risk analyses of soil contaminated with hexavalent chromium indicate that soil concentrations limited to the range of 130–450 ppm Cr provide adequate protection against the development of allergic contact dermatitis, respiratory cancer, and systemic toxicity.[319] For persons living in residential properties, the estimated risk of lung cancer is <1:1,000,000 when the concentration of total chromium in the soil is <180 mg/kg (ppm). Risk analysis by an expert panel concluded that soils containing Cr^{6+} concentrations below 75 ppm or total chromium concentrations below 1,000 ppm with 5% Cr^{6+} did not pose a significant health hazard to nearby residents.[320] Studies of residents exposed to hexavalent chromium in ambient air have not detected an excess incidence of lung cancer in these subjects.[223,321]

The body possesses mechanisms in the lung and stomach to reduce hexavalent chromium to the less toxic trivalent chromium. Thus, at low levels of Cr^{6+} exposure, the body has the potential to reduce Cr^{6+} to Cr^{3+} before the former compound can interact with DNA. Current evidence, including the decline in the incidence of lung cancer in chromate workers after reduction in Cr^{6+} concentrations, suggests the possibility that a threshold for the carcinogenic potential of hexavalent chromium in humans may exist; however, the existence of a Cr^{6+} threshold for cancer remains controversial.[322]

Environmental Monitoring

Inhalation

The ATSDR MRL (minimal risk level) for intermediate- and chronic-duration inhalation exposure to Cr^{6+} as chromium trioxide mist or other dissolved hexavalent chromium aerosols and mists is 0.005 μg Cr^{6+}/m^3 based on a LOAEL of 0.002 mg Cr^{6+}/m^3 for upper respiratory effects in workers.[143] The MRL for intermediate-duration inhalation exposure to Cr^{6+} as particulate hexavalent chromium compounds is

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0.3 μg Cr^{6+}/m^3 based on a benchmark concentration of 0.016 mg Cr^{6+}/m^3 for increased lactate dehydrogenase activity in lung lavage fluid from rats.[323]

Oral

The ASTDR MRL for intermediate-duration oral exposure to Cr^{6+} is 5 μg/kg/day based on hematological changes (e.g., microcytic and hypochromic anemia) in rats,[324] whereas the MRL for chronic-duration oral exposure to Cr^{6+} is 0.9 μg/kg/day based on a benchmark dose of 0.9 μg Cr^{6+}/kg/day for diffuse epithelial hyperplasia of the duodenum in mice.[324]

The US EPA chronic oral reference dose (RfD) for soluble Cr^{6+} salts (e.g., potassium or sodium chromate, potassium or sodium dichromate) is 3 μg Cr^{6+}/kg/day based on a NOAEL for systemic effects in rats exposed to 2.5 mg Cr^{6+}/kg/day as potassium chromate in the drinking water for 1 year.[325] By inputting recent toxicology and mode of action data into physiologically-based pharmacokinetic and benchmark dose models, a reevaluation supported the current oral RfD of 3 μg Cr^{6+}/kg/day.[326]

Biological Monitoring

Table 9.4 lists the recommendations and standards for exposure to chromium, including the recommendations of the ACGIH for biological monitoring.

Urine

Urine chromium concentrations are the most practical method of monitoring occupational exposure to hexavalent chromium. Total chromium concentrations in urine samples from individuals without occupational exposure to chromium are usually <5 μg/g creatinine. Total chromium concentrations in the urine of workers must be interpreted cautiously because of the low sensitivity of current methods and because of the ubiquity of chromium in laboratories (i.e., cross-contamination). These methods do not routinely speciate chromium because chromium in urine is primarily Cr^{3+}; consequently, the urine chromium concentration reflects exposure to dietary and environmental Cr^{3+} as well as hexavalent chromium. End-of-shift urine chromium concentrations correlate to soluble hexavalent chromium concentrations, but not to insoluble hexavalent chromate or trivalent chromium compounds.[327] The pre-shift urine chromium concentration reflects both current and past chromium exposure as some accumulation of chromium occurs during the workweek that decreases slowly following cessation of exposure. In a study of a retired plasma cutter of stainless steel followed for 8 years, the urinary chromium half-life was 129 months.[121]

After several weeks of exposure to water-soluble hexavalent chromium, the end-of-shift, end-of-work week urinary chromium concentration should not exceed 30 μg Cr/g creatinine and the increase during a shift should not exceed 10 μg Cr/g creatinine.[328] In a study of 16 workers from an aircraft construction factory using hexavalent chromium adhesives (magnesium chromate) to finish off joints, exposure to airborne total chromium was low (0.2–1.5 μg Cr/m^3).[127] The corresponding amount of total chromium in the urine also was low (0.16–7.74 μg/g creatinine). Urine total chromium concentrations between 10–40 μg/L correlate with external exposure to 100 μg Cr^{6+}/m^3 based on studies of stainless steel welders using manual arc (MMA) and metal inert gas (MIG) methods, resulting in exposure to chromium trioxide concentrations up to 80 μg/m^3.[329] The median hexavalent chromium concentration in personal air samples of MIG welders was slightly higher (10 μg/m^3) compared with MMA welders (<4 μgm^3). The mean total chromium concentration in the urine of the 14 welders using only the MIG method was 64.5 ± 65.3 μg/L (range, 9.6–229.4 μg/L) compared with 35.1 ± 40.1 μg/L (range, 7.0–191.9 μg/L) for the 39 welders using only the MMA method. Confounding factors for increased urinary chromium include beer drinking, diabetes, occupational exposure to chromium, chromium supplementation, prostheses with chromium-containing alloys,[330,331] and exercise; however, these factors do not affect the concentration of chromium in erythrocytes.[332]

A study of welders exposed to chromium and nickel demonstrated a statistically significant increase in the rate of DNA single-strand breakage and the sister chromatid exchange frequencies when compared with unexposed controls.[333] However, there was no significant correlation between these measures and the results of the urine chromium or nickel concentrations. Almost all of the urine samples for the biological monitoring of these workers were below the current Biological Exposure Indices recommended by the American Conference of Governmental and Industrial Hygienists.

Blood

The concentrations of chromium in the erythrocyte may be a selective indicator of exposure to hexavalent chromium because Cr^{6+} is preferentially deposited in the red blood cell for its lifetime (110 days), whereas plasma chromium concentrations return to baseline

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TABLE 9.4. Guidelines and regulations for metallic chromium and chromium compounds.

Exposure Level	Value
	US EPA
MCL	
Drinking water	100 µg Cr/L
RfD	
Food/water	3 µg Cr^{6+}/kg/day
	1,500 µg Cr^{3+}/kg/day (insoluble Cr^{3+})
	US FDA
Recommended dietary allowance (RDA)	35 µg Cr/day (adults 19–50 years)
Bottled drinking water	100 µg Cr/L
Food	120 µg/day (total Cr)
	WHO
Air	
4×10^{-2} lifetime risk	1 µg Cr^{6+}/m^3
Drinking water	50 µg total Cr/L
	OSHA
PEL–TWA (8-hour)[a]	5 µg Cr^{6+}/m^3 (action level: 2.5 µg/m^3)[b]
	500 µg Cr/m^3 (Cr^{2+}/Cr^{3+})
	1,000 µg Cr/m^3 (Cr^0/insoluble salts)
	NIOSH
REL–TWA (10-hour)	0.2 µg Cr^{6+}/m^3 (chromic acid/hexavalent salts)
	500 µg Cr/m^3 (Cr^0/Cr^{2+}/Cr^{3+})
IDLH	15,000 µg Cr^{6+}/m^3
	250,000 µg Cr/m^3 (Cr^0/Cr^{2+})
	25,000 µg Cr^{3+}/m^3
	ACGIH
TLV–TWA (8-hour)	
	500 µg Cr/m^3 (Cr^0/Cr^{2+}/insoluble Cr compounds)
	3 µg Cr^{3+}/m^3 [b,c]
	0.2 µg Cr^{6+}/m^3 (Cr^{6+} compounds)[c,d]
TLV–STEL	0.5 µg Cr^{6+}/m^3 (Cr^{6+} compounds) [c,d]
BEI[e]	
Urine	0.7 µg Cr/L (total urinary Cr)[f]

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; BEI = biological exposure indices; IDLH = immediately dangerous to life and health; MCL = maximum contaminate level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency; US FDA = US Food and Drug Administration; WHO = World Health Organization.

[a] Defining the highest average chromium concentration in air to which a worker can be legally exposed;

[b] The Cr^{6+} standards do not apply to pesticide or Portland cement exposures or to activities where objective data demonstrate that the Cr^{6+} processes do not release ≥0.5 µg/m^3 as an 8-hour TWA under any expected conditions of use;

[c] Inhalable particulate matter;

[d] Skin/respiratory sensitization for water-soluble compounds;

[e] Water-soluble Cr^{6+} fumes;

[f] End-of-shift/end-of-week.

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concentrations within days following cessation of an acute exposure to hexavalent chromium.[334] Although Cr^{3+} does not easily penetrate the erythrocyte, Cr^{6+} is reduced in the erythrocyte to Cr^{3+}. In a study of 103 stainless steel welders using both the manual metal arc and the metal inert gas methods, the median total chromium concentration in erythrocytes was 0.60 μg/L compared with 9.00 μg/L in plasma.[329] The median airborne total chromium exposure for the former was 4 μg/m^3 compared with 10 μg/m^3 for metal inert gas welders. As a result of the differential absorption of chromium species by erythrocytes, measurements of total chromium in serum (or plasma) and whole blood help distinguish between exposure to different chromium species. Following exposure to trivalent chromium, increased serum or plasma chromium concentrations relative to erythrocytes suggest trivalent chromium exposure, whereas elevated total chromium in erythrocytes compared with plasma or serum suggests hexavalent chromium exposure. In a study of 22 workers exposed primarily to airborne chromium with a range of 0.008–0.212 mg Cr^{6+}/m^3 and 0.010–0.10 mg Cr^{3+}/m^3, the total chromium concentration in blood versus nonexposed controls was as follows: serum, 2.2 μg/L vs. 1.1 μg/L; erythrocytes, 8.9 μg/L vs. 1.0 μg/L; and whole blood, 6.9 μg/L vs. 1.4 μg/L.[136] The total chromium concentration in the blood of 15 basic chromium sulfate workers exposed primarily to trivalent chromium (0.046–1.689 mg/m^3) and small amounts of hexavalent chromium (0.002–0.023 mg/m^3) were as follows: serum, 3.1 μg/L; erythrocytes, 1.4 μg/L; and whole blood, 1.8 μg/L.

Insufficient data are available presently to correlate the development of lung cancer with the ratio of plasma and erythrocyte chromium concentrations. Substantial differences in the ability of individuals to reduce chromium in plasma complicate the interpretation of chromium concentrations in erythrocytes.[2] Individuals reducing Cr^{6+} quickly have relatively high urinary chromium concentrations and relatively low blood chromium concentrations compared with slow reducers.

Medical Monitoring

Medical surveillance of workers exposed to hexavalent chromium involves a pre-placement and annual physical examination that includes the following: 1) comprehensive work and smoking history; 2) potential conditions that would be exacerbated by exposure to chromium (skin and pulmonary sensitization, skin or mucous membrane diseases, kidney disease); and 3) evidence of dermatitis, mucous membrane irritation, or chrome ulcers. OSHA (http://www.osha.gov/Publications/OSHA-3373-hexavalent-chromium.pdf) requires initial examinations for all workers as well as annual examinations for any worker exposed to Cr^{6+} air concentrations exceeding the action level. At termination, a medical evaluation is required unless the worker had an evaluation within 6 months of the end of employment. Routine laboratory tests include baseline urinalysis, chest X-rays, and kidney function tests. Although annual chest X-rays are recommended after the age of 40, a study of chromate workers did not detect a significant improvement in 5-year survival of workers in the screening program.[335] Air monitoring activity is not required by US OSHA where initial monitoring indicates that the 8-hour TWA is below the action level (2.5 μg Cr^{6+}/m^3), whereas exposures between the action level and PEL (5 μg/m^3) require monitoring every 6 months. Above the PEL, OSHA required air monitoring every 3 months.

TREATMENT

First Aid

Treatment is supportive. Dilution is the preferred first aid measure for the ingestion of hexavalent chromium compounds because of their corrosive properties. Dermal exposure to chromic acid requires careful decontamination with copious amounts of saline. Systemic toxicity may result from relatively small burns (1%) even after decontamination. Chromic acid produces severe injury to the cornea characterized by infiltration, vascularization, and opacification. Following instillation of chromic acid in the eye, the eye should immediately be irrigated copiously with saline for at least 15–20 minutes or until the pH normalizes in the conjunctival sac. Subsequently, the eye should be evaluated by slit lamp examination to determine the extent of injury.

Gut Decontamination

Patients ingesting large doses of hexavalent chromium usually vomit profusely. Syrup of ipecac is contraindicated for hexavalent compounds because of their strong oxidizing properties. If the patient presents within 1–2 hours of ingestion, the careful insertion of a soft tube is appropriate in order to aspirate and lavage the stomach. Insufficient data are available to recommend the use of lavage with magnesium hydroxide. Although ascorbic acid reduces the more soluble chromium compounds (hexavalent) to the relatively poorly soluble ones (trivalent) *in vitro*,[336] there are no data on the effectiveness of ascorbic acid to reduce the absorption

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of hexavalent chromium when administered following lavage. Activated charcoal probably does not bind chromates well.

Antidotes

There are no currently available antidotes to remove hexavalent chromium and prevent the formation of reactive oxygen species. The efficacy of BAL, EDTA, DMPS, hemodialysis, and exchange transfusion for hexavalent chromium toxicity is unproven. *N*-acetylcysteine (NAC) is a potential antioxidant based on animal studies,[337] but human data are inadequate to evaluate the effectiveness of this regimen.

Enhancement of Elimination

Exchange transfusion and hemodialysis may reduce serum chromium concentrations,[338] but existing clinical data do not confirm the efficacy of these measures. A double-volume exchange transfusion removed only 3.77 mg Cr (i.e., 1.56 mg from plasma, 2.21 mg from erythrocytes) from a child following the ingestion of an estimated 1 g ammonium dichromate, whereas 3 hours of hemodialysis in this child removed only 0.17 mg chromium.[174] Hemodialysis is primarily a supportive modality rather than a method to enhance elimination; 5 hours of hemodialysis removed ~5 mg chromium from a 31-year-old man with an initial serum chromium concentration of 1.6 mg/L a few hours after accidental ingestion of potassium dichromate.[339] After the intentional ingestion of an estimated 22.5 g potassium dichromate by a 48-year-old man, 9 hours of hemodialysis removed only 3.3 mg chromium; this value represented ~0.16% of the estimated ingested Cr^{6+} dose.[180] Studies in dogs indicate that charcoal hemoperfusion removes only 1% of the estimated dose of hexavalent chromium following an acute dichromate poisoning.[340] Peritoneal dialysis does not effectively remove chromium from the blood. After 19 peritoneal dialysis runs, the clearance of chromium from the blood was estimated at ~24 mg/day in a 14-year-old child, who died after ingesting potassium chromate despite a reduction in the total serum chromium from 580 to 30 mg/dL.[177]

Supplemental Care

General

Renal failure generally occurs within 1–2 days of exposure; patients hospitalized for serious ingestions of chromates should be monitored for the development of renal failure. In general, the evaluation of a patient exposed to large oral doses of hexavalent chromium should include a urinalysis and CBC as well as laboratory assessment of liver and kidney function. Following exposure to high ambient air concentrations of hexavalent chromium, the evaluation should include a chest X-ray (pulmonary edema, infiltrates) and pulmonary function tests. Testing the urine for low-molecular-weight proteins (β_2 microglobulin, retinol binding protein) helps detect subtle changes in renal proximal tubule function in subjects exposed to low chromium concentrations, but the significance of any elevations of these biomarkers as predictors of chronic renal dysfunction remains unclear. Clinical availability of these tests in the United States is generally limited to specialty laboratories.

Supportive care also includes the correction of any fluid or electrolyte imbalance. Urine alkalinization may be necessary to help prevent renal injury due to massive hemolysis. Endoscopy may be necessary to evaluate the extent of esophageal and gastric burns. Liver transplantation is an option when severe hepatocellular necrosis results from the ingestion of potassium dichromate.[308]

Ascorbic Acid

There are no clinical studies to support the use of ascorbic acid after the ingestion of hexavalent chromium compounds or determine the potential complications (e.g., oxaluria) of this therapy. The intravenous administration of large doses (3 g ascorbic acid over 30–60 minutes) has been recommended for the reduction of chromate-induced renal toxicity based on uncontrolled, *in vitro* studies that suggest the reduction of hexavalent chromium to the less toxic trivalent form by ascorbic acid.[341] Subsequent animal studies indicated that large parenteral doses (0.5–5 g/kg) of ascorbic acid prevented renal toxicity *only* when administered within 1–2 hours following the administration of chromate.[342,343] In these studies, the delayed administration of ascorbic acid was associated either with no effect or with increased nephrotoxicity. A 24-month-old child recovered from the ingestion of up to 50 mL 10% sodium dichromate (serum chromium 0.21 mg/L 1 hour after ingestion) without the development of renal or hepatic toxicity.[338] Supportive care included the daily administration of ascorbic acid (1 g via nasogastric tube) as well as peritoneal dialysis and British Anti-Lewisite (BAL) therapy. A 49-year-old worker received burns to over 40% of his body from contact with hot chromic acid and 25% sulfuric acid.[344] Despite the use of 5 g ascorbic

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acid per day beginning on the day of injury, the patient developed anuria on the second day and died on the sixth day.

Skin

The topical application of 1% aluminum acetate wet dressings is an anecdotal treatment for chrome ulcers along with topical ascorbic acid. An animal study demonstrated that the application of 10% ascorbic acid *within 30 minutes* of the initiation of chrome ulcers significantly reduced the healing times of these ulcers.[345] This nonblinded study did not use statistical analysis to compare treatment times with controls. There are also case reports that associate the use of a 10% ascorbic acid as a preventive cream with the resolution of chromate-induced dermatitis over a period of several months,[346,347,348] but there are no clinical studies that compare the healing rate of chromate-induced dermatitis with controls (i.e., no ascorbic acid). The early excision of burns secondary to hot chromic acid may be considered to prevent systemic poisoning because the extent of tissue deposition is difficult to assess depending on clinical judgment.[349]

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Chapter 10

COBALT

HISTORY

The use of cobalt as a blue coloring agent for pottery, jewelry, and glass began in Egypt and Persia around 2,000 BC; currently, cobalt is an important constituent of blue glaze in Danish porcelain.[1,2] Leonardo Da Vinci was one of the first artists to use the bright blue pigment of cobalt in oil paints. Although blue pigments in Ming dynasty pottery and Venetian glass from the 15th century contained cobalt, copper comprised most of the blue pigment in earlier times. The Swedish chemist, George Brandt, first isolated cobalt in the 18th century; T.O. Bergman identified cobalt as an element in 1780.[3] The use of cobalt in industrial applications began in the 20th century. In the 1920s, the discovery that cobalt bound tungsten carbide into a hard substance began the use of this "hard metal" in a variety of important industrial applications (e.g., high-speed drills, cutting tools). Cobalt was a constituent of the first permanent magnetic alloy (alnico) developed during the 1930s. The use of cobalt has increased rapidly since World War II, reaching peak production in the mid-1980s. The development of rare-earth cobalt magnets that possess important power and size advantages contributed to the miniaturization of electrical and electronic equipment in the 1980s.

Cobalt is an essential element in humans necessary for the formation of vitamin B_{12} (hydroxocobalamin); this vitamin catalyzes reactions involving methionine synthesis, purine and folate metabolism, and formation of succinyl-CoA from methylmalonic acid. Excessive administration of this trace element may cause goiter and reduced thyroid activity. The medicinal use of a cobalt/iron formulation (Roncovite®) for the treatment of anemia in the 1940s was associated with blockage of iodine uptake by the thyroid gland.[4] Serious pulmonary complications from exposure to the dust from hard metals were first recognized in Germany during World War II.[5,6] In the industrial setting, cobalt is a common constituent of heat-resistant alloys and cobalt-containing hard metals. Chronic cobalt dust exposure from diamond polishing has been associated with "hard-metal pneumoconiosis" in industrial workers.[7] The acute form of this disease resembles a hypersensitivity reaction with malaise, cough, and wheezing; the chronic form can progress to pulmonary fibrosis and cor pulmonale.

In 1966, a syndrome characterized by pericardial effusion, elevated hemoglobin concentrations, and congestive heart failure occurred in heavy beer drinkers in Quebec City, Canada.[8] Similar cases were not reported in other parts of Canada where the cobalt concentration in beer was about 10 times lower. The following year, epidemics of "beer drinkers' cardiomyopathy" appeared in Omaha, Nebraska[9] and in Minneapolis, Minnesota.[10] Some Belgian breweries also added cobalt chloride to beer between 1959 and 1967, resulting in the occurrence of cardiomyopathies in heavy drinkers.[11] These cardiomyopathies occurred when local breweries added cobaltous chloride or nitrate as a method to reduce the effect of soap residues from electric dishwashers on the formation of foam. The fact that most of the cases developed in heavy drinkers ingesting cobalt doses substantially below doses previously used for refractory anemia suggests the occurrence of other factors necessary to develop cobalt-induced cardiomyopathy.[12] Suspected cofactors include inadequate protein

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and vitamin (thiamine) intake, zinc depletion, and alcohol-induced heart damage.[13] Several case studies have associated exposure to cobalt dust with the development of cardiomyopathy, but the frequent lack of an etiology in cases of cardiomyopathy limits conclusions about causation.[14]

PHYSICOCHEMICAL PROPERTIES

Cobalt is a relatively rare (i.e., 33rd most abundant) metal that is a gray, ductile, brittle, magnetic element. This relatively unreactive metal does not oxidize in dry or moist air at normal environmental temperatures. The two common valence states are divalent cobaltous (Co^{2+}) and trivalent cobaltic (Co^{3+}). The trivalent forms are strong oxidizing agents. Table 10.1 lists the identifying information and physical properties of metallic cobalt and cobaltous salts. These properties are similar to the physical properties of iron and nickel; cobalt and nickel may substitute for ionic iron or zinc in various biomolecules, resulting in alteration of iron and oxygen homeostasis. Cobaltic oxide (CAS RN: 1308-04-9) is a black-gray trivalent salt that is water-insoluble. Other poorly soluble cobalt compounds include hydroxides, other oxides, sulfides, and some organic cobalt compounds (carbonate, cobaltous oxalate, propionate, stearate, naphthenate, 2-ethyl-hexanoate); inorganic chloride, nitrate, and sulfate salts of cobalt are usually water-soluble. Cobaltous acetate is also water-soluble.

Cobalt is stable in normal atmospheric oxygen, whereas heating produces mixed oxides at temperatures of <900°C and divalent cobaltous oxide above 900°C.[16] When heated, cobalt also combines with carbon, phosphorus, and sulfur, but not with hydrogen or nitrogen. Cobalt is the only element capable of increasing the saturation magnetization of iron; thus, cobalt is an important constituent of permanent magnets. Trivalent cobalt is thermodynamically unstable at typical redox conditions including the pH of the human body. The water solubility of cobalt compounds is pH dependent with the mobility of cobalt greater in acidic than alkaline conditions. Acidic conditions increase divalent cobalt concentrations, whereas alkaline conditions favor the formation of poorly soluble cobalt carbonate complexes.[17] ^{59}Co is the only stable cobalt isotope.

EXPOSURE

Commercial Processes

Mining and production

Cobalt exists in nature primarily as arsenides, oxides, and sulfides. The abundance of cobalt in the earth's crust is similar to the presence of silver; important mineral ores containing substantial amounts of cobalt include cobaltite (CoAsS) in high-temperature hydrothermal deposits and contact metamorphic rocks (Canada, Norway, Australia), erythrite [$Co_3(AsO_4)_2$] Co- and As-bearing sulfide assemblages (Canada, Morocco),

TABLE 10.1. Identifying information and physical properties of metallic cobalt and cobaltous compounds. (Based on Alessio et al.).[15]

Physical Characteristic	Cobalt	Cobaltous Acetate	Cobaltous Carbonate	Cobaltous Chloride	Cobaltous Hydroxide	Cobaltous Oxide	Cobaltous Sulfate
Molecular formula	Co	$Co(C_2H_4O_2)_2$	$CoCO_3$	$CoCl_2$	$Co(OH)_2$	CoO	$CoSO_4$
Synonym	Metallic cobalt	Cobalt diacetate		Cobalt dichloride	Cobalt dihydroxide	Cobalt monoxide	Cobalt sulfate
CAS RN	7440-48-4	71-48-7	513-79-1	7646-79-9	21041-93-0	1307-96-6	10124-43-3
Valence	0	+2	+2	+2	+2	+2	+2
Molecular weight (g/mol)	58.93	177.03	118.94	129.84	92.95	74.93	154.99
Color	Silvery gray	Light pink	Red	Blue	Rose red or green/blue	Pink	Dark blue
Physical state	Solid	Solid	Solid	Solid	Solid	Solid	Solid
Melting point (°C)	1,495	140	Decomposes	724	168	1,795	735[a]
Density (g/mL)	8.9 (20°C)	1.70	4.13	3.356 (36°C)	3.597 (15°C)	6.45	3.71
Water solubility (g/L)[b]	Insoluble (0.0029)	Soluble (348)	Poorly soluble (0.01)	Soluble (450, 7°C)	Poorly soluble (0.0032)	Insoluble	Soluble (38.3, 25°C)

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number.
[a] Decomposes. [b] Soluble defined as >0.1 g/L.

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and smaltite ($CoAs_2$) in Canada and Morocco.[18] The new Idaho Cobalt Project is scheduled to produce >1,500 tons of high-purity cobalt metal annually near Salmon, Idaho. Cobalt is commonly found with copper, iron, lead, nickel, and silver ores in concentrations of <1%; most current cobalt production is a by-product of copper or nickel production.[19] The first stage in the recovery of cobalt from ores is the physical separation of cobalt from other metals either by froth flotation (sulfide ores) or by gravity (arsenide ores). Roasting or acid leaching is necessary to concentrate cobalt in the ores. Refined cobalt is available primarily as broken or cut cathodes.

Hard Metals

Hard metal results from the sintering (compacting) of powdered tungsten carbide with cobalt and some other agents to form a diamond-like, polycrystalline material (sintered carbides). These cemented carbides possess important physical properties, including heat resistance, hardness, and extreme strength, making them suitable for cutting tools and wear-resistant machine parts. This powdered metallurgic process forms hard metal using cobalt as a binder. The cemented carbides primarily contain tungsten carbide (80–95%) and cobalt (5–20%). Occasionally, small amounts (<5%) of nickel and other metals are added to the cobalt. The tungsten powder frequently consists of smaller amounts of titanium, tantalum, and vanadium oxides. The heating of fine particles of tungsten with carbon produces tungsten carbide. The resulting compound is mixed with powered cobalt and small amounts of other metals (chromium, nickel, niobium, molybdenum, titanium, tantalum) based on the desired properties of the final product. The powder is poured into steel or rubber frames, pressed into appropriate shapes, and attached to the backing material. Pre-sintering of this material produces a chalk-like material that is shaped into the final configuration. The final mixture is heated to 1,550°C; the hardness of the resulting material is similar to the hardness of diamonds. The aerosol created from the cutting and polishing of hard metal bathed in coolants and lubricants contains respirable particles of dissolved or ionized cobalt. Analysis of air in a hard metal tool production plant revealed that the highest exposure (range, up to 0.032 mg Co/m^3) occurred in the powder preparation, rubber press, and shaping areas.[20]

Uses

Categories of cobalt alloys include the following: high-temperature, corrosion-resistant superalloys (aluminum, chromium, nickel, tantalum, titanium, tungsten, zirconium) for gas turbines in aircraft engines, magnetic alloys (aluminum, copper, nickel, titanium), high-strength steels, electro-deposited alloys, and alloys with special properties. Technically, hard metals are not cobalt alloys because the cobalt acts as a binding agent for the metal carbides. Superalloys combine high-temperature mechanical properties with a resistance to creep and oxidize at these high temperatures. The base of these superalloys may be cobalt, nickel, or iron, and applications of these alloys include the production of jet engines and magnetic materials. In 1987, the approximate end-use of cobalt in the United States was as follows: superalloys, 41%; drier in paint, 13%; magnetic alloy, 11%; cutting and wear-resistant alloys, 8%; catalyst, 7%; ground coat or frit for porcelain enameling of steel fixtures and kitchen appliances, 5%; and pigment manufacture, 4%.[21] Increasing cobalt uses include high-capacity rechargeable batteries, recycling electronic waste, magnets, and clean energy applications (clean coal, gas-to-liquid and oil desulfurization, solar panels, wind and gas turbines, fuel cells).

Most of the production of cobalt involves the metallic form. For example, heat-resisting steels contain 25–65% cobalt and Vitallium® alloys in prostheses that comprise ~65% cobalt along with chromium, nickel, and molybdenum. The powder metallurgy sector uses cobalt as a binding agent for tungsten carbide. Typically, the hard metals in grinders and cutting tools contain 6–9% cobalt with an upper limit of ~30% cobalt. Electro-deposited cobalt alloys (iron, nickel, platinum, phosphorus) have magnetic properties that are important in computer applications and the recording industry.

Cobalt is a major constituent of cobalt (>34%)-chromium (>19%) metal alloy used in the manufacture of surgical devices, particularly joint replacements.[22] Particles (i.e., typically <50 nm) of bulk metal alloy and corrosion products may appear in cells and synovial fluids surrounding the joint replacements.[23] By the end of the first decade of the 21st century, an estimated 400,000 hip arthroplasties were performed annually in the United States with metal-on-metal (MoM) implants accounting for ~35% of the prostheses; however, that percentage has subsequently declined rapidly worldwide.[24] Other metals (nickel, molybdenum, tungsten) may be added to this alloy to improve its physical characteristics. Stainless steel implants contain little cobalt.

With the exception of mixed divalent and trivalent oxides, the most important cobalt-containing chemicals in the industry are divalent cobaltous salts. Some diamond polishers work with polishing disks composed of a half-hard steel frame (98% iron) and a polishing surface consisting of 10–20% microdiamonds cemented into

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ultrafine cobalt metal powder. Less common uses of cobalt include catalysts (cobalt molybdate oxide, cobalt sulfides, cobalt carbonyl) in the chemical and oil refining industry, drying agents in paints (cobalt naphthenate), electroplating, radiology (^{60}Co), and an additive in fertilizers and animal feed. The latter use involves the addition of small amounts of cobalt to prevent cobalt deficiency in sheep and cattle. Fluomine is a cobaltous chelate (bis(3-fluorosalicylaldehyde) ethylenediimine cobalt] used as part of the oxygen recovery system in high-altitude aircraft.[25] Table 10.2 lists the industrial applications of a variety of cobalt compounds. Cobalt nanoparticles are relatively common in the electronics, medical (e.g., diagnostic testing, therapy), and textile industries.

Sources

For the general population, diet is the main source of cobalt exposure. The cobalt concentration in drinking water is low (<5 μg/L). In the occupational setting, cobalt exposure occurs primarily during the production of cobalt powders. In other industries (e.g., hard metal industry), cobalt exposure involves other compounds that modulate the effect of cobalt; tungsten carbide exposure increases the retention of cobalt in the lungs.[26]

Air

Sources of cobalt in the air are both natural (erosion, volcanic eruptions, forest fires, seawater spray) and anthropogenic (fossil fuel burning, engine emissions, sewage sludge, phosphate fertilizers, processing of cobalt-containing alloys).[21] The cobalt concentration in ambient air depends on the dispersion of particles into the soil by the wind.[16] Typically, the mean cobalt concentration in air is small (~1–2 ng/m^3) in urban areas and somewhat lower in remote areas.[21,27] Cobalt concentrations in ambient air may exceed 10 ng/m^3 near point sources with cobalt concentrations ranging up to 600 ng/m^3 near industrial sources in heavily industrialized areas.[21,28]

Soil

Cobalt is a relatively rare trace element with an average concentration in the earth's crust of 25 mg/kg. Basic and ultrabasic rocks contain cobalt concentrations of ~100 ppm, whereas mantle-type rocks (basalt) contain 40–50 ppm and acidic rocks (granite) contain 1–10 ppm.[3] Soils that contain <0.5–3 mg Co/kg have insufficient cobalt to meet the nutritional needs of grazing animals; therefore, these soils are considered cobalt-deficient. Examples of soils frequently deficient in cobalt include those composed of sand, sandstone, limestone, some types of acidic rocks (e.g., granite), and shale. Cobalt is a frequent addition to fertilizers (commercial, compost, manure, sewage sludge) used on agricultural soils; however, the soil is not a significant route of exposure for the general population. Co concentrations in the soil range from 1–40 mg/kg with an average in the United States of 7.2 mg/kg.[21,29] Cobalt-containing minerals typically exist in relatively small quantities in commercial ores (e.g., arsenides, oxides, sulfides). An important source of cobalt in the United States is smaltite ($CoAs_2$, 25% cobalt).

Water

Cobalt is detected rarely in drinking water with cobalt concentrations ranging from 0.1–5 μg/L when detectable; median Co concentrations in US drinking water are <2 μg/L.[30] Trace amounts of cobalt occur in rivers, lakes, and groundwater.[3] Coastal seawater generally contains more cobalt compared with open ocean waters as a result of the transport of cobalt dissolved with natural organic substances in river waters. Average concentrations in open ocean waters are ~0.3 μg/L. Mining activities and industrial use do not significantly affect the natural transport of cobalt in water because most of the cobalt resides in the sediment.

Diet

The diet accounts for a majority of the cobalt intake with relatively small contributions from drinking water and air. The average daily cobalt intake from the diet is highly variable, ranging from 5–45 μg/day; fish and vegetables contain relatively high Co concentrations.[31] The estimated average daily cobalt intake in samples from the Canadian population was 11 μg (range 4–15 μg).[32] In an evaluation of Canadian foods, the Co concentration was low in most foods with the highest concentration in waffles (76 ng/g), corn cereal (74 ng/g), and potato chips (70 ng/g). The estimated average daily cobalt intake in a standard French diet was 29 μg [33] compared with ~40 μg in an Australian study.[34] In the latter study, the mean cobalt intake in lacto-ovo vegetarians and vegans consuming normal amounts of potatoes was ~20 μg. The cobalt uptake by plants is species-dependent. Green leafy vegetables (broccoli, spinach), seafood, and fresh cereals are the richest sources of cobalt (0.2–0.6 μg Co/g dry weight), but meat is also an important source of cobalt for the general population, depending on the dietary preferences.[16,35] Animal livers also contain high

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TABLE 10.2. Commercial uses of cobalt compounds. (IARC).[16]

Cobalt Compound	Formula	Uses
Acetate(III)	$Co(C_2H_2O_2)_3$	Catalyst
Acetate(II)	$Co(C_2H_2O_2)_2{\cdot}4H_2O$	Driers for lacquers and varnishes, invisible inks, catalysts, pigment for oil-cloth, mineral supplement, anodizer, stabilizer for malt beverages
Acetylacetonate	$Co(C_5H_7O_2)_3$	Vapor plating of cobalt
Aluminate	$CoAl_2O_4$	Pigment, catalysts, grain refining
Ammonium sulfate	$CoSO_4(NH_4)_2SO_4{\cdot}6H_2O$	Catalysts, plating solutions
Arsenate	$Co_3\ (AsO_4)_2{\cdot}8H_2O$	Pigment for paint, glass and porcelain
Bromide	$CoBr_2$	Catalyst, hydrometers
Carbonate	$CoCO_3$	Pigment, ceramics, feed supplements, catalyst
Carbonate (basic)	$2CoCO_3{\cdot}Co(OH)_2{\cdot}H_2O$	Chemicals
Carbonyl	$Co_2(CO)_8$	Catalyst
Chloride	$CoCl_2{\cdot}6H_2O$	Chemicals, sympathetic inks, hydrometers, plating baths, metal refining, pigment, catalyst
Chromate	$CoCrO_4$	Pigment
Citrate	$Co_3(C_6H_5O_7)_2{\cdot}2H_2O$	Therapeutic agents, vitamin preparations
Dicobalt manganese tetroxide	$MnCO_2O_4$	Catalyst
Dicobalt nickel tetroxide	$NiCO_2O_4$	Catalyst, anode
Dilanthanum tetroxide	La_2CoO_4	Catalyst, anode
2-Ethylhexanoate	$Co(C_8H_{15}O_2)_2$	Paint and varnish drier
Ferrate	$CoFe_2O_4$	Catalyst, pigment
Fluoride(II)	CoF_2	Fluorinating agent
Fluoride(III)	CoF_3	Fluorinating agent
Fluoride	$CoF_2{\cdot}4H_2O$	Catalyst
Fluorosilicate	$CoSiF_6{\cdot}6H_2O$	Ceramics
Formate	$Co(CHO_2)_2$-$2H_2O$	Catalyst
Hydroxide	$Co(OH)_2$	Paints, chemicals, catalysts, printing inks
Iodide	CoI_2	Moisture indicator
Lanthanum trioxide	$LaCoO_3$	Electrode
Linoleate	$Co(C_{18}H_{31}O_2)_2$	Paint and varnish drier
Lithium oxide	$LiCoO_2$	Battery electrode
Manganate	$CoMn_2O_4$	Catalyst; electro-catalyst
Naphthenate	$Co(C_{11}H_{10}O_2)_2$	Catalyst, paint and varnish drier
Nitrate	$Co(NO_3)_2{\cdot}6H_2O$	Pigments, chemicals, ceramics, feed supplements, catalyst
Oleate	$Co(C_{18}H_{33}O_2)_2$	Paint and varnish drier
Oxalate	CoC_2O_4	Catalysts, cobalt powders
Oxide(II)	CoO	Chemicals, catalysts, pigments
Oxide(II, III)	Co_3O_4	Enamels, semiconductors
Oxides	Mixed metal	Pigments
Phosphate	$Co_3(PO_4)_2{\cdot}8H_2O$	Glazes, enamels, pigments, steel pretreatment
Potassium nitrite	$K_3Co(NO_2)_6{\cdot}1.5H_2O$	Pigment
Resinate	$Co(C_{44}H_{62}O_4)_2$	Paint and varnish drier, catalyst
Sodium oxide	$NaCoO_2$	Battery electrode
Stearate	$Co(C_{18}H_{35}O_2)_2$	Paint and varnish drier, tire cord adhesives
Succinate	$Co(C_4H_4O_4){\cdot}4H_2O$	Therapeutic agents, vitamin preparations
Sulfamate	$Co(NH_2SO_3){\cdot}3H_2O$	Plating baths
Sulfate	$CoSO_4{\cdot}xH_2O$	Chemicals, ceramics, pigments
Sulfide	CoS	Catalysts
Tricobalt tetralanthanum decaoxide	$La_4Co_3O_{10}$	Catalyst
Tungstate	$CoWO_4$	Drier for paints and varnishes

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concentrations of cobalt. Dairy products, refined cereals, and sugar contain the least cobalt (0.1–0.3 μg Co/g dry weight).

Lifestyle

Tobacco contains <0.3–2.3 mg Co/kg dry weight;[36] ~0.5% of the cobalt in cigarettes appears in the mainstream smoke.[37] The exact bioavailability of cobalt in tobacco is unknown. The contribution of beer to the current total cobalt intake is relatively small, even for heavy beer drinkers. In a Spanish study, the cobalt concentration in beer ranged from 0.16–0.56 μg/L (median, 0.39 μg/L).[38]

ENVIRONMENTAL FATE

Air

Cobalt compounds are nonvolatile; therefore, cobalt enters the ambient air in particulate form with a typical mass median diameter of 2.6 μm (range, <2–12 μm).[39] Cobalt from anthropogenic sources probably exists primarily as oxides with the exception of mining and ore processing facilities (arsenides, sulfides).[40] The fate of cobalt in the atmosphere depends on the size and density of the particles as well as the type of speciation. From sources of combustion, cobalt exists primarily as an oxide, whereas cobalt arsenide and cobalt sulfide complexes occur near extraction processes.

Water

Wet and dry deposition deposits cobalt on surface waters and soil. Sediment is the primary repository for cobalt in contaminated water. Precipitation and adsorption to suspended particles account for >98% of the cobalt present in freshwaters, whereas the remainder exists in the dissolved state. Acidic pH (hydrogen ions compete with metal binding sites), excess chloride anions, and chelating agents enhance the mobility of cobalt from sediment to water. Most of the cobalt released into water reaches the coastal zones of the oceans through transport as suspended matter in rivers. In the deep sea, cobalt precipitates iron and manganese oxides and crystalline sediments (e.g., aluminosilicate, goethite); similar to manganese and aluminum profiles, removal of cobalt involves the interaction of cobalt with MnO and the formation of nodules.[21] Cobalt also precipitates as carbonate or hydroxide in water. Cobalt strongly binds to humic substances naturally present in aquatic environments depending on pH, the metal-to-humic substance ratio, and the nature of the humic material. Cobalt mobility decreases as pH increases (i.e., pH >7), as a result of the formation of insoluble hydroxides or carbonates.

Soil

In most soils, cobalt exhibits lower mobility than cadmium, but higher than that of lead, tin, copper, nickel, and zinc.[41] At higher soil pH, the formation of hydroxide and carbonate complexes with cobalt limits cobalt mobility in soil. The translocation of cobalt from roots to the parts of the plant above ground is limited in most soils by limited Co mobility depending on pH, the concentration of organic matter (e.g., humus), and Fe/MnO_2 concentrations. Consequently, most terrestrial plant species do not accumulate cobalt with the exception of a few hyper-accumulators (Asteraceae, Cyperaceae, Lamiaceae, Scrophulariaceae families; *Alyssum corsicum*, *Berkheya coddii*); plants (e.g., barley, oats, wheat) grown in high-cobalt-containing soils do not translocate much cobalt from the soil.[18] In Saskatchewan where surface soil cobalt concentrations ranged from 3.7–16.4 mg/kg, 10 samples of durum wheat grain contained cobalt concentrations ranging from 0.01–0.02 mg/kg.[42] Significantly higher cobalt concentrations may occur in ryegrass foliage, oats, or barley grown in highly acidic soil (pH 3.3–5).[43] The relatively low cobalt concentrations in fish reflect the strong binding of cobalt to particles and sediment. Little biomagnification of cobalt occurs in animals, whereas the bioaccumulation factor for freshwater fish and marine fish ranges from 40–1,000 and 100–4,000, respectively.[21]

DOSE EFFECT

Acute Toxicity

A 19-month-old male died ~6 hours after the estimated ingestion of ~30 mL of a cobalt chloride solution.[44] The mother induced vomiting several times and then brought the child to the emergency, where he developed altered mental status and cyanosis after gastric lavage. The autopsy did not report any abnormalities in the respiratory tract. A 14-year-old girl presented to the emergency department ~12 hours after the ingestion of an estimated elemental cobalt dose of 96 mg from a chemistry set.[45] Although she vomited spontaneously several times before admission, she remained asymptomatic in the emergency department with stable vital signs and no evidence of hepatorenal dysfunction. She recovered without sequelae after receiving supportive care and three doses of $CaNa_2EDTA$. A 6-year-old boy

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drank a solution containing an estimated 2.5 g cobalt chloride; he developed abdominal pain and vomiting prior to admission; he remained stable in the emergency department with a normal physical examination.[46] He was released 48 hours after admission without sequelae.

Chronic Toxicity

The most common adverse effect associated with cobalt chloride use in patients with anemia during the 1950s was gastrointestinal irritation. Nausea and vomiting were occasional with daily cobalt chloride doses of 100 mg and common with doses of 300–500 mg.[47,48] Hematological and thyroid changes are sensitive endpoints of cobalt toxicity.

Hematological

Roncovite® was a cobalt-iron medication previously used to treat refractory anemia. The erythrocyte count increased by 16–20% in six healthy volunteers receiving 1 mg Co/kg; within 9–15 days after cessation of therapy, the erythrocyte count returned to baseline.[49] In a study of 23 infants aged 1–24 months receiving an aqueous solution of 40 mg $CoCl_2$ (9.9 mg elemental cobalt) and 75 mg ferrous sulfate for iron deficiency anemia, mild nausea, vomiting, and anorexia developed in three subjects.[50] A significant increase in eosinophils (i.e., >6%) occurred in 16 of 23 subjects. The daily administration of this preparation at doses of 50–100 mg cobalt chloride (18.5–37 mg Co/day) was tolerated for long periods of time without significant toxicity. Cobalt chloride without iron supplementation does not prevent the decrease in the hematocrit and hemoglobin concentration typically associated with pregnancy. The ingestion of 75–100 mg cobalt chloride (~0.53 mg Co/kg) daily by 20 pregnant women was associated with a slight decrease in the hemoglobin concentration; no other effects were reported.[51]

Thyroid

In a study of four patients receiving 150 mg cobalt chloride (37.5 mg elemental cobalt) daily for over 10 days, 2 of the subjects had depressed 24-hour thyroid^{131} I uptake.[52] The most common complaint was nausea and vomiting. There were no reported blood cobalt concentrations. The oral administration of 3–4 mg cobalt chloride/kg body weight to children with sickle cell resulted in goitrogenic effects that resolved after cessation of therapy.[53]

Cardiovascular

The estimated daily intake of beer drinkers developing cardiomyopathy was 6–8 mg Co as the chloride or sulfate salt;[54] this dose is relatively small and substantially less than patients treated with cobalt salts for refractory anemia. A 5-year follow-up cohort study of 24 Belgian patients with beer drinkers' cardiomyopathy indicated that the progression of this disease required reduced protein intake and a poor diet, suggesting that factors other than cobalt are necessary for the expression of the disease.[55] The mean daily beer consumption at the time of initial evaluation was ~18 beers. The cobalt salt added to this beer was cobalt chloride in typical doses of 0.5–1.5 ppm with a range up to 5.5 ppm; however, the development of the cardiomyopathy was not dose-related as some brands were not associated with cardiomyopathies despite high cobalt concentrations.

Pulmonary

The risk of pulmonary fibrosis in hard metal workers increases when the cobalt concentration in the air exceeds 100 μg/m^3.[56]

Neurological

Several case reports associate neurological symptoms (hearing loss, visual deficits, tinnitus) with cobalt exposure; however, a causal relationship between these symptoms and specific cobalt concentrations is not well established. Evidence of peripheral neuropathy including eighth-nerve dysfunction as measured by the Weber and Rinne tests was not demonstrated in four anephric patients on hemodialysis receiving 50 mg $CoCl_2$ daily for 12 weeks.[57] Slight high-tone deafness developed in one patient after an additional 40 weeks of therapy. The mean serum cobalt concentration in six anephric patients ranged from 340–1,490 μg/L during therapy, with concentrations declining within several months of cessation of treatment as measured by atomic absorption spectrometry. Transient hearing loss as measured by elevated thresholds on audiometry developed in 3 of 14 dialysis patients receiving consecutive 4-week courses of 25 mg and 50 mg $CoCl_2$.[58] The audiograms returned to baseline values within 1 month in two patients (the third was lost to follow-up). The serum cobalt concentrations at the end of the study ranged from 220–600 μg/L with 1 outlier at 2,100 μg/L. Animal studies suggest the possibility of cochlear damage following the infusion of high Co concentrations. In a study of rabbits receiving daily intravenous infusions of cobalt chloride (1,354 μg over 42 days and 2,708 μg

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over 53 days), histological examination revealed signs of degeneration of the organ of Corti with loss of sensory hair cells (outer hair cells > inner hair cells), reduction in the size of the spiral ganglia, and alterations of the ganglion cells (i.e., shrinking eosinophilic cytoplasm).[59] No pathological abnormalities were detected in vestibular structures.

TOXICOKINETICS

Absorption

Ingestion

The mechanism of the gastrointestinal absorption of cobalt is similar to that of iron with iron deficiency causing an increase in gastrointestinal cobalt absorption ranging from 18–44% in controls compared with 31–71% in iron-deficient subjects.[60] Other factors affecting cobalt bioavailability following ingestion include water solubility of the cobalt compound (soluble ≫ insoluble), the amount of co-ingested material, interindividual variation, and possibly sex (i.e., up to ~2-fold higher in women compared with men depending on iron status).[61] Studies of volunteers ingesting $^{60}CoCl_2$ suggested that the absorption of cobalt from the gastrointestinal tract depends on the dose and timing of the last meal. Absorption ranged from 1–5% ($n = 5$) for a dose of <1 μg ^{60}Co ingested between normal meals compared with 20–28% ($n = 3$) for 1,200 μg ^{60}Co administered between normal meals.[62] In a 70-day study of a worker accidentally swallowing $^{60}CoCl_2$, the estimated uptake of ^{60}Co from the gastrointestinal tract was ~4–5%.[63]

Volunteer studies indicate that low iron stores increase the absorption based on increased cobalt concentrations in subjects with low serum ferritin concentrations. In a study of 448 pregnant Norwegian women, the mean whole blood cobalt concentration in 257 women with low iron stores (serum ferritin <12 μg/L) was 0.61 ± 0.16 μg/L compared with 0.42 ± 0.10 μg/L ($P < 0.001$) in 191 women with adequate iron stores.[64] The average whole blood cobalt concentration in women on oral contraceptives was ~20% lower than nonusers; multiple regression models did not detect any correlation between iron stores and the use of oral contraceptives. The absorption of cobalt in the small intestine probably involves the same transport mechanism (divalent metal transporter 1) as iron; however, the exact role of the common transporter in cobalt absorption is not well defined.[65]

Inhalation

Variables affecting pulmonary absorption of cobalt compounds include water solubility, particle size, and breathing pattern. Inhaled cobalt particles deposit in upper and lower airways depending on particle diameter; mucociliary action removes particles of >2 μm impacting in the upper airways with subsequent ingestion or expectoration. Smaller particles enter the lower airways. In a study of cobalt oxide particles, the fractional deposition of particles with a geometric mean of 0.8 μm was ~50% compared with ~75% for particles with a mean geometric diameter of 1.7 μm.[66] At least ½ of these particles remain in the lung for 6 months.[67] Although limited data are available in humans, animal studies suggest that substantial uptake of cobalt occurs through the lungs. A study in hamsters demonstrated that the lungs absorb ~30% of an inhaled aerosolized dose of the poorly soluble cobalt oxide.[68] Generally, the amount of cobalt in the lungs is low in patients with hard metal pneumoconiosis.[69]

Dermal

Experimental studies suggest that some absorption of cobalt may occur following emersion of the hand in cobalt solution for 1 hour based on elevated urinary Co excretion compared with baseline (24 hours prior to exposure).[70] The mean permeation flux of cobalt in a Franz diffusion cell was 0.0123 ± 0.0054 μg/cm^2/hour with a lag time of 1.55 ± 0.71 hours (permeation coefficient, 0.00037 cm/hour).[71] *In vitro* studies using donor skin and simulated sweat suggest some systemic absorption of cobalt may occur following application to abraded skin by up to 400-fold.[72] *In vitro* studies with diffusion cell systems (Franz cells) suggest Co nanoparticles can penetrate the human skin.[73]

Distribution

Absorbed inorganic cobalt is distributed to the kidney, liver, heart, and spleen with lower concentrations occurring in bone, brain, hair, and the lymphatic system.[62] Divalent cobalt salts bind to albumin in the blood with a relatively small free fraction (<8–12%) based on the intravenous administration of ^{55}Co in two healthy volunteers [74] and $^{60}CoCl_2$ in rabbits.[75] Multiple observations in a 57-year-old woman with very high blood cobalt concentrations from corroded hip prostheses suggested reduced cobalt binding to albumin (whole blood 549 μg/L; plasma 260 μg/L) and increased free cobalt ions;[76] the whole blood/plasma ratio returned to ~1 after replacement of the corroded hip implant. The clinical

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significance of changes to cobalt-albumin binding and other factors (oxidative stress, genetic polymorphism) to individual hypersensitivity to cobalt toxicity remains unclear. An observational study of 37 patients with MoM hip prostheses attending the Rizzoli Orthopedic Institute's Orthopedic Traumatology and Prosthetic Surgery and Revisions of Hip and Knee Implants clinic found no correlation between whole blood, serum, or urine Co concentrations and serum total albumin or ischemia-modified albumin.[77] Although the serum total albumin concentrations were within the reference range, most patients had serum ischemia-modified albumin concentrations above the upper limits of the reference range. Genetic screening for *known* proalbumin and albumin variants was negative for all patients; none of the patients complained of symptoms consistent with cobalt toxicity.

No specific organ accumulates cobalt with the exception of distribution of insoluble cobalt salts (e.g., cobalt oxides) to the lower airways after inhalation of insoluble cobalt particles (e.g., 45% for 0.8 μm particles and 56% for 1.7 μm particles after 180 days).[67] The highest concentrations of cobalt in normal subjects occur in the liver (median, 30 μg Co/kg with a range 6–151 μg Co/kg) and lesser amounts in the kidney, adipose tissue, and heart.[16] Following the intravenous administration of cobalt, the liver accumulates about 20% of the administered dose of radioactive cobalt chloride.[62] Divalent cobalt salts (Co^{2+}) cross the red cell membrane slowly via Ca-dependent pathways; this uptake is practically irreversible as the Ca-pump does not extrude cobalt from the cell as a result of cobalt binding to the globin moiety of hemoglobin.[78] In the cytosol, Co^{2+} also binds to the globulin moiety of hemoglobin with little free cobalt (1%) remaining in the cytosol. The binding is initially reversible; however, the cobalt is more tightly bound with time. Unlike lead and cadmium, significant accumulation of cobalt does not occur in the body with age; the body lacks long-term storage sites for cobalt.[19] Most cobalt in the body resides in the vitamin B_{12} organometallic complex.

Elimination

Cobalt excretion occurs rapidly with the majority of the administered dose eliminated within a few days after exposure ceases. Cobalt elimination is triphasic with the vast majority of the absorbed cobalt dose excreted renally; biliary excretion is small (i.e., <10%) based on volunteer studies receiving radiolabeled Co.[62] Iron deficiency anemia increases the renal excretion of cobalt. In a study of 17 volunteers with normal iron stores, the mean renal excretion of radiolabeled $CoCl_2$ in urine samples collected during the first 24 hours after ingestion was 18% of the administered dose (range, 9–23%).[79] The mean urinary excretion of cobalt in 10 subjects with iron deficiency anemia was 31% of the administered dose (range, 23–42%).

In a whole-body retention study of eight volunteers receiving intravenous chloride salts of ^{57}Co and ^{58}Co, the short-term biological half-time was 0.71 ± 0.03 day compared with 32 ± 8.5 days for the intermediate component and 80–720 days for the long-term component (n = 2).[80] Following accidental inhalation of insoluble radioactive cobalt (^{60}Co), most of the absorbed dose (i.e., 80–90%) has a biological half-life of several days, but a small portion of this dose has a half-life of years.[81] In a study of 12 hard metal workers exposed to cobalt during stone cutting diamond wheel production, the urinary excretion of cobalt was multiphasic with a rapid first phase ($t_{1/2}$ = ~44 hours), a second phase of slower elimination ($t_{1/2}$ = 10 days), and a prolonged terminal phase (years).[82] The first phase of urinary elimination was faster (i.e., ~20 hours) in four control subjects with occupational exposure to cobalt. In an 11-year follow-up study of five workers following the accidental inhalation of the insoluble metal and oxide forms of ^{60}Co, the estimated clearance half-time for systemic cobalt was ~7 years.[83] Little accumulation of cobalt occurs in other organs.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

Prior to the development of recombinant human erythropoietin and related analogs, cobalt salts were stimulants for the production of erythropoietin in patients with anemias of chronic disease (e.g., renal failure, malignancy). Cobalt induces hypoxia-like responses mediated by hypoxia-inducible factor-1α (HIF-α) and the upregulation of associated proteins including atrial natriuretic peptide. The primary physiological stimulus for erythropoietin production is hypoxia; the administration of cobalt salts (Co^{2+}) mimics the effect of hypoxia on erythropoietin-producing cells in the kidney and liver by stabilizing hypoxia inducible factor-1α (HIF-α) and preventing the docking of von Hippel–Lindau tumor suppressor protein. *In vitro* studies suggest that cobalt salts induce erythropoietin transcription by inhibiting the degradation of the transcriptional activator hypoxia-inducible factors, a family of proteins that regulate the cellular response to oxygen deficit.[84,85]

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Mechanism of Toxicity

Classic cobalt toxicity primarily involves increased hemoglobin production (polycythemia), metabolic acidosis (disruption of Krebs cycle, inhibition of pyruvate conversion to acetyl CoA), hypothyroidism (TSH stimulation from blockade of iodine uptake), and cardiomyopathy (impaired myocardial contractility).

Hard metal disease

Hard metal lung disease is a pathological process of the pulmonary parenchyma that ranges from intense alveolitis to end-stage pulmonary fibrosis. This disease is called hard metal lung disease because it rarely, if ever, occurs following exposure to cobalt or tungsten carbide alone.[87] Hard metal contains tungsten and cobalt with small amounts of titanium, tantalum, and vanadium oxides. Because tungsten is relatively inert and the inhalation of cobalt in animal studies produces pulmonary lesions, some authors believe the respiratory effects of exposure to dust from hard metal result from cobalt.[87,88] However, the lesions in animals are not identical to the pathological changes in humans with hard metal lung disease; additionally, the dose of cobalt required to produce the lesions in animal studies is much higher compared with occupational exposure to cobalt. Epidemiological data indicate that interstitial lung disease occurs only among hard metal and diamond workers where exposure involves both cobalt dust and other components (e.g., diamond, iron, silica, titanium, tungsten).[89] A cross-sectional study of workers exposed only to cobalt suggests that exposure to other dust (e.g., tungsten, titanium, iron, silica, diamond) in the hard metal process is necessary to produce the clinical picture of pulmonary fibrosis.[90]

The low incidence of fibrosing alveolitis in cobalt-exposed workers along with similarities to extrinsic allergic alveolitis (positive lymphocyte transformation test, reduced helper/suppressor T cell ratios)[91] suggest that hypersensitivity is the etiology of these effects rather than direct toxicity.[88] A study of Italian workers with hard metal lung disease suggested a genetic predisposition (residue Glu-69 of the HLA-DP β-chain) to the development of hard metal disease.[92] However, specific precipitins have not been demonstrated in exposed workers or patients with hard metal diseases.

The exact cause of these effects remains to be determined as alternate mechanisms include the formation of reactive oxygen species from electrons migrating from cobalt to the tungsten carbide surface.[93] Several histological features of fibrosing alveolitis argue against delayed-hypersensitivity as an etiology. For example, epithelioid cell granulomas and lymphocytic infiltration typically are absent in cobalt-induced fibrosing alveolitis, whereas unusual multinucleated giant cells commonly are present. An alternative hypothesis is the non-immunological activation of macrophages and macrophage-derived mediators (interleukin-1, leukotrienes, prostaglandins) by cobalt that generates toxic oxygen radicals.

Hard metal asthma

Cobalt is a known allergen that produces contact dermatitis [94] as well as asthma in workers exposed to cobalt alone (e.g., cobalt powder, cobalt salts)[95] or cobalt in association with other metals (e.g., hard metal dust) or irritant gases.[96] The etiology of this disease probably is a Type I allergic reaction based on the demonstration of specific IgE antibodies against a complex of cobalt and albumin in workers with hard metal asthma.[97] Cobalt is considered the primary causal agent, although specific IgE antibodies to nickel may be present and may contribute to the etiology of hard metal asthma in some individuals.[98] Both environmental factors and individual susceptibility contribute to the development of hard metal asthma. An epidemiological study of hard metal workers demonstrated that age and atopy were risk factors for hard metal asthma.[99] Multilogistic analysis of the data indicated that the development of hard metal asthma was not dose-related because exposure to cobalt concentrations of $<50\ \mu g/m^3$ was a significant risk factor, but exposure to higher cobalt concentrations was not.

Contact Dermatitis

Cobalt, chromium, and nickel are important skin sensitizers; simultaneous reactivity to these metals occurs frequently. Animal studies indicate that simultaneous reactivity to cobalt and nickel results from multiple sensitizations rather than cross-reactivity.[100,101] *In vivo* studies indicate that cobalt, chromium, and nickel leach from hard metal alloys after sustained contact with sweat; the release of cobalt is sufficient to cause allergic contact dermatitis in cobalt-sensitized patients.[102] The release of cobalt ions and patch test reactivity do not directly correlate to the Co concentration in the alloy. *In vitro* tests suggest that cobalt is released in sufficient quantities from some inexpensive earrings to cause contact dermatitis.[103]

Beer drinkers' cardiomyopathy

This syndrome developed in a small fraction of the beer-drinking population exposed to cobalt during the

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1960s.[55] The etiology of beer drinkers' cardiomyopathy is probably multifactorial because of the inability to replicate the cardiomyopathy in animal models and the absence of similar cardiovascular effects at similar cobalt sulfate doses in other Co exposures. Potential cofactors in this cardiomyopathy include alcoholism, hypothyroidism, thiamine deficiency, genetic susceptibility, and/or a low-protein diet. The cobalt concentration in the beer averaged 1.1–1.2 ppm.[104] Beer drinkers' cardiomyopathy shares many clinical features of hypothyroidism including fatigue, anorexia, pericardial effusions, dilated cardiomyopathy, and elevated hepatic enzymes.[105] The estimated cobalt dose (0.04–0.14 mg/kg/day) in these patients was substantially below Co doses typically associated with adverse effects; the estimated cobalt dose (0.6–1 mg/kg/day) in pregnant women and renal failure patients treated with cobalt chloride for 90 days did not produce evidence of cardiac abnormalities.[10,51] Despite the development of cobalt-induced hypothyroidism and goiter for >40 years from cobalt chloride doses at substantially higher concentrations than the estimated dose in beer drinkers' cardiomyopathy, very little published medical evidence supports a causal relationship with cobalt and cardiomyopathies in these patients.[106]

The mechanism of cardiotoxicity in these beer drinkers is unclear. A suggested mechanism of action is cobalt-induced depression of oxygen uptake in the myocardial mitochondria.[107] This action may result from inhibition of the sulfhydryl groups of α-lipoic acid in the citric acid cycle and the subsequent inhibition of the oxidation of α-ketoglutarate and pyruvate to succinyl CoA and acetyl CoA, respectively. Because cobalt has a high affinity for sulfhydryl (SH) groups, the protective effect of proteins and amino acids probably results from the sequestration of free cobalt in the cell. Other proposed mechanisms of toxicity include the following: 1) cobalt-induced damage to the transmembrane transport system resulting in increased intracellular calcium concentrations[108] and 2) chronic inhibition of sympathetic tone.[109]

Carcinogenesis

Although data are lacking in humans, *in vitro* and *in vivo* experimental studies suggest that cobaltous ions (Co^{2+}) exert potential genotoxic properties. Several potentially carcinogenic mechanisms including the inhibition of DNA repair mechanisms by soluble cobalt(Cr^{2+}) cations (cobalt chloride, cobalt sulfate) and the damage to DNA bases by the production of hydroxyl radicals (i.e., oxidative stress) from interactions with cobalt particles, particularly hard metal particles.[110,111]

Cobalt salts are only weakly genotoxic in bacterial systems. Direct implantation of cobalt-chromium alloy and cobalt salts produced tumors (primarily rhabdomyosarcomas) in rats, but not in mice.[2] In an experiment in rats, the intratracheal instillation of cobalt oxide produced a slight excess of benign and malignant lung tumors.[112]

Pathological Changes

Hard metal lung disease

An interstitial lung disease that ranges from focal peribronchiolar inflammation to diffuse interstitial fibrosis and honeycombing develops after prolonged exposure to high dust concentrations from tungsten carbide-based hard metals that contain cobalt or from cobalt in association with other metals or dust (diamond polishers). Diamond polisher's lung (i.e., cobalt lung) is the name given to the interstitial disease that occurs in diamond polishers using a high-speed polishing disk consisting of a diamond-cobalt surface without tungsten carbide.[113,114] These polishing discs contain 10–20% microdiamonds cemented with cobalt metal powder (80–90%). Depending on the disc type, other components (carbon, iron, manganese, nickel, silicon, sulfur) may be present.

The two histological patterns of hard metal lung disease are the following: 1) an acute or subacute desquamative pneumonitis, and 2) a more latent fibrotic form characterized by progressive interstitial fibrosis. Histological features of the acute or subacute desquamative pneumonitis primarily involve intra-alveolar desquamation of large vacuolated mononuclear cells and limited interstitial fibrosis. The pulmonary changes are relatively uniform. The filling of alveoli with macrophages is significant enough to resemble desquamative interstitial pneumonitis. The presence of unusual, multinucleated giant cells on lung biopsy or bronchoalveolar lavage is a distinctive giant cell interstitial pneumonia,[115] but not invariable feature of hard metal lung disease.[116] Giant cells become less prominent as fibrosis and honeycombing develop. Electron microscopy indicates that these giant cells are both pneumocytes and macrophages.[117] Some evidence associates susceptibility to cobalt-related interstitial lung disease with the *HLA-DPB1* allele (i.e., glutamate substitution at position 69), similar to hypersusceptibility associated with the same allele in chronic beryllium disease.[118] The absence of epithelioid granulomas helps differentiate hypersensitivity pneumonitis from hard metal lung disease.

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The more chronic form is characterized by diffuse mural pulmonary fibrosis with few intra-alveolar cells. Peribronchial and perivascular fibrosis may be present. The extent of fibrosis depends on the duration of the inflammatory process, but substantial variation in the amount of inflammation and fibrosis occurs in different areas of the lung. Hard metal particles in the lung frequently contain high concentrations of tungsten and tantalum, but the concentration of cobalt is usually, but not always, low because cobalt dissolves rapidly in the lung.[119] Transmission electron microscopy detects cobalt in pulmonary particles more effectively than scanning electron microscopy.[113]

Beer drinkers' cardiomyopathy

Postmortem histological changes in patients dying of beer drinkers' cardiomyopathy involve myocardial fiber degeneration, increased vacuolation, and interstitial edema without histological evidence of acute inflammation.[120] Typically, the pericardium contains fluid but not inflammatory exudate. The heart is enlarged, dilated, and flabby; the chambers may contain mural thrombi.[10] Electron microscopy demonstrates extensive intracellular changes involving glycogen, lipid, mitochondria, and myofibrils. The mitochondria are swollen with alterations in the cristae. Myofibrils, Z lines, and A bands demonstrate little detail after staining.

The histological changes associated with beer drinkers' cardiomyopathy are not unique; these changes also occur in patients with ischemia. Myofibrillar loss and atrophy are more prominent in cobalt-induced cardiomyopathy compared with idiopathic forms of cardiomyopathy.[121] In animal experiments, cobalt-induced cardiomyopathy is similar to alcoholic cardiomyopathy with vacuolation and loss of myofibrils along with randomly scattered areas of coagulation necrosis.[109,122] Postmortem examination of thyroid glands from 14 of these patients demonstrated no gross abnormalities; however, histological examination demonstrated distortion of the follicles with depletion of colloid and atypical hyperplasia.[123] There were no clinical features of goiter or hypothyroidism reported in these patients.

The mean concentration of cobalt in the cardiac tissue from postmortem examination of eight patients with fatal beer drinkers' cardiomyopathy was $0.48 \pm 0.24\,\mu g/g$ wet cardiac tissue (range, 0.027–0.77 μg/g weight) as measured by neutron activation analysis.[124] This value was ~10 times higher ($P < 0.005$) than controls (non-alcoholics). The myocardial cobalt concentration in a patient dying 3 months after stopping cobalt chloride treatment was 1.65 μg/g wet weight compared with ≤0.06 μg/g wet weight in control samples (dialysis patients without cobalt therapy and subjects without renal dysfunction).[125] Concentrations of cobalt in normal cardiac tissue range from 0.05–0.4 μg/g dry weight tissue.[14]

Metallic hip prostheses

All materials used for hip implant wear. For metal-on-plastic (MoP), wear produces particle debris in the tens of microns range (i.e., >0.1 μm, primarily polythene) that causes aseptic osteolysis and prosthesis failure, complicating the use of traditional metal-on-polyethylene hip prostheses. These particles are usually seen in surrounding tissue by light microscopy. Subsequently, the second generation of metal-on-metal (MoM) hip prostheses was introduced to reduce wear (i.e., ~100 times) and increase the size of the femoral component; wear of these prostheses produces wear particles primarily in the nanometer range (<100 nm) with relatively larger surface area/volume that is susceptible to corrosion and ion release.[126] The amount of cobalt ions generated from wear and electrochemical corrosion depends on a complex interaction of implant and patient factors. Systemic toxicity potentially results from the transport of soluble cobalt ions and wear particles generated in the periarticular space through the lymphatic and vascular systems to remote sites. Cobalt also mimics hypoxia by interfering with the sensing of oxygen deficiency and stabilization of transcriptional activator hypoxia-inducible factor (HIF), resulting in stimulation of erythropoietin production and upregulation of the response to hypoxia.[127]

The typical alloy composition (ASTM F75) is 60% cobalt, 30% chromium (trivalent), and 7% molybdenum. Particulate wear and corrosion debris also occur following implantation of these prostheses including The following: 1) free metallic ions; 2) inorganic metal (Cr^{3+}, Co^{2+}, Ni^{2+}, Fe^{3+}, Ti^{4+}) salts or oxides (Cr^{3+}, Co^{2+}, Ni^{2+}, Fe^{3+}, Ti^{4+}); 3) metal–protein complexes; and/or 4) organic storage forms (e.g., hemosiderin).[128] Metal-on-metal (MoM) hip replacement involves the use of a stemmed (femoral) component. In younger patients, hip resurfacing is often preferred to conventional MoM hip replacement; the former refers to the capping or resurfacing of the femoral head rather than removal.

Following implantation of cobalt-chromium alloy inside the synovial fluid, a passive oxide layer forms over the implant; *in vitro* studies suggest the composition of this spontaneously-formed biolayer includes ~90% trivalent chromium (oxide, hydroxide, phosphate) with ~5% cobalt (oxide, hydroxide, phosphate) and no detectable hexavalent chromium.[129,130] Factors affecting

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the physiochemical characteristics of MoM wear debris include implant position, implant type, cycle number, loading vectors, fluid chemistry, wear process, and extraction techniques.[131,132] Compared with polyethylene wear particles (>100 nm), the wear particles from MoM hip prostheses are much more numerous (i.e., ~13,000-fold), much smaller (average, 40 nm; range, 30–80 nm), and undetected by light microscopy.[133] In a study of metal wear particles from 13 patients undergoing revision of MoM total hip replacements with cobalt–chromium–molybdenum bearing couples, most wear particles were <50 nm (range, 6–834 nm).[134] The common type of corrosion involves crevice corrosion at tight junctions and pitting corrosion from acidic conditions.

For the typical metallic femoral component of the total hip prosthesis, the estimated rate of total alloy release is 11–22 mg/year (0.15–0.3 μg/cm^2/day); however, excess wear may increase these rates 10-fold.[135,136] Volumetric wear rate is relatively low for well-functioning MoM hip implants (<5 mm^3/10^6 cycles or year), whereas malpositioned implants produce much higher volumetric wear rates (i.e., up to 100 mm^3/10^6 cycles or year) with larger debris particles (up to 1 μm) and higher cobalt content.[132] Both particle size and chemistry contribute to subsequent tissue reactions. Under suboptimal conditions resulting from the absence of the tribolayers (i.e., the fine-grained layer that incorporates the organic material in the joint fluid with the bulk material in the implant), larger wear particles may form (100–500 nm) with the highest concentration of wear particles in the superficial zone of the peri-implant tissue membrane.[137] These conditions develop during abnormal loading (e.g., edge loading, sliding wear conditions) of the implant. The larger particles usually contain more cobalt than chromium as a result of the greater solubility of cobalt; *in vitro* studies suggest that cobalt nanoparticles are more toxic to macrophages than chromium nanoparticles at similar intracellular concentrations.[138] The form of chromium in hip prostheses at neutral pH is predominately trivalent based on analysis of implant debris from hip capsules obtained during MoM hip explantation. Oxidation of the trivalent chromium to the hexavalent form in the body is unlikely physiologically.[139] The majority of nanoparticles from wear debris that enter the systemic circulation probably are chromium rather than cobalt because of the relatively high solubility of cobalt; hence, the primary form of cobalt in the circulation is ionic rather than metallic.[140]

Pathological studies have not detected clinically significant amounts of hexavalent chromium with most chromium existing as trivalent chromium phosphate.[141] Scanning transmission electron microscopic examination of wear debris from a patient undergoing hip resurfacing arthroplasty (DePuy Articular Surface replacement made from ASTM F75 alloy) demonstrated the following two types of wear debris: 1) a diffuse phase containing primarily trivalent chromium with trace amounts of divalent cobalt, and 2) dense core-shell particles containing metallic cobalt, chromium, and molybdenum surrounded by trivalent chromium.[142] The small amounts of cobalt in the majority of debris suggest cobalt particles undergo rapid corrosion in the tissues. In areas of high chromium concentrations from tissue in another study, cobalt (i.e., mixture of metallic Co and divalent Co) and molybdenum oxide were present;[143] hexavalent chromium was not detected in the debris. Macrophages and giant cells phagocytize the wear debris; in the acidic environment of lysosomes, corrosion of the metallic fragments occurs. Corrosion products include metal oxides (CoO, Cr_2O_3, TiO_2) and hydroxides [$Cr(OH)_3$], whereas chromium phosphates ($CrPO_4$) form in extra-synovial environments and metal phosphates [$Co_3(PO_4)_2$, $CrPO_4$] deposit in other extra-synovial sites. The shape, morphology, and physical properties (e.g., agglomeration, surface area) influence the cellular uptake and toxicity of the nanoparticles. Postmortem examinations of patients with revised MoM hip arthroplasties indicate a majority of the livers and spleens in these cases had macrophages with submicron metal particles; however, these macrophages formed focal aggregates without obvious toxicity.[144]

Pathological characteristics of pseudotumors include neo-synovial proliferation with or without fluid and/or tissue necrosis; they typically occur in soft tissues and less often in bone. The formation of pseudotumors is probably a persistent cytotoxic and/or hypersensitivity response to wear debris including cobalt and chromium nanoparticles and microparticles;[145] however, the biological pathway of pseudotumor formation remains unclear and variable (i.e., unpredictable) between patients. The process of pseudotumor formation is neither infectious nor malignant. The extent of tissue destruction seen during revision surgery does not correlate directly (i.e., not dose-related) to the volumetric wear rate suggesting other factors contribute to pseudotumor formation.[146] Proposed mechanisms of toxicity include the following: 1) cytotoxic reaction from macrophage-induced necrosis; 2) cell-mediated, T-cell-mediated, Type IV hypersensitivity reaction (ALVAL); or 3) some combination of these two reactions depending on individual sensitivity.[147] ALVAL is the lymphocyte-dominated immunological response in periprosthetic tissues that correlates the cellular reaction with the presence of wear debris; the ALVAL score is typically higher in low-wear than high-wear

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components suggesting the lymphocyte reaction results from subtoxic corrosion.[148] The distinguishing features of ALVAL in patients with MoM include variable, often extensive surface necrosis, metallic debris-laden macrophages, and loss of architecture; however, these pathological findings also occur in other inflammatory arthropathies.[149] Although up to ½ of the patients with MoM hip implants develop lymphocyte reactivity (i.e., positive lymphocyte transformation test) to Co and Cr within 1–4 years after implant, symptoms in these patients are not related to the metal reactivity.[150] Some patients with MoM hip arthroplasties develop pseudotumors without evidence of hypersensitivity to metals (i.e., negative lymphocyte transformation test).[151] Macrophages and T cells produce cytokines (IL-1β, IL-2, IL-6, TNF-α, IFN, RANKL) and/or upregulation of costimulatory molecules (CD80, CD86, ICAM-1) that initiate an aseptic inflammatory response and tissue destruction (pseudotumor). *In vitro* studies suggest that ionic metal implant debris induces this monocyte/macrophage response more than metallic particles.[152] The presence of robust lymphocytic infiltration in periprosthetic tissue suggests a hypersensitivity reaction.

Postmortem Examination

The autopsy of a 19-month-old child dying ~6 hours after the ingestion of cobalt chloride revealed few specific findings.[44] The stomach mucosa was congested with a thin layer of coagulative necrosis involving the inner 1/3 of the stomach mucosa. The esophageal mucosa demonstrated a few small bullae. Microscopic examination of the brain revealed only edema. The postmortem examination did not report any abnormalities of the respiratory tract (the mother induced vomiting several times, and gastric lavage was performed in the emergency department). A 17-year-old adolescent with renal failure requiring hemodialysis developed a fatal biventricular heart failure after receiving 50 mg cobaltous chloride daily for the preceding 8 months.[153] Analysis of cardiac tissue by neutron activation analysis demonstrated cobalt concentration of 8.9 μg/g dry tissue compared with 0.2 μg/g dry tissue in two patients with renal dysfunction.[154] The case report did not include antemortem or postmortem blood cobalt concentrations.

CLINICAL RESPONSE

The classic presentation of cobalt toxicity involves polycythemia, metabolic acidosis, thyroid hyperplasia, and cardiomyopathy.[155]

Adverse Medical Effects

Past therapeutic use

In the 1950s and 1960s, cobalt chloride was a treatment for refractory anemia (sickle cell disease, renal failure) as well as nephritis and infections. A variety of adverse effects were associated with the use of cobaltous chloride for these conditions including polycythemia and hypothyroidism in a child with lipid nephrosis,[156] congestive heart failure, goiter with dry skin, thin hair, and anorexia,[157] myxedema in a child with goiter and congestive heart failure,[158] hearing/visual impairment, and polyneuropathy. Hypothyroidism, thyroid hyperplasia, and goiter are recognized side effects of the use of cobaltous chloride to treat anemia.[159] Rare case reports associated the use of cobalt chloride with tinnitus (50–150 mg daily),[160] vertigo, transient hearing loss in 3 of 14 dialysis patients receiving consecutive 4-week courses of 25 mg and 50 mg $CoCl_2$,[58] optic atrophy,[161] reduced vibratory sense,[162] and unsteady gait. These case reports involved patients with serious chronic diseases (e.g., chronic renal failure, sickle cell disease, blood dyscrasias); additionally, biomarkers of cobalt exposure were not included in the reports. Consequently, the contribution of cobalt to the development of these neurological effects is unclear.

Metallic Prostheses

A total hip arthroplasty (THA) consists of the following: 1) a femoral head attached to a stem inserted into the femur (metal or ceramic), and 2) a cup anchored in the pelvis (metal, ceramic, or polyethylene). In MoM implants, both surfaces are metal with cobalt-chromium-molybdenum alloy being the predominant metal alloy, whereas other types of implants use polyethylene on metal or metal-on-ceramic surfaces. An MoM-resurfacing hip prosthesis consists of a femoral head capped with a metal covering. The bearing surfaces of hip prostheses contain cobalt and chromium, ceramic, polyethylene, or stainless steel, whereas the nonmoving parts include titanium alloys with small amounts of aluminum and vanadium, cobalt and chromium with trace nickel and molybdenum, or stainless steel. Total knee replacement implants consist of the following: 1) a metallic femoral component attached to the distal femur; 2) a plastic articulating layer; and 3) a tibial component that binds the articulating layer to the proximal tibia. In contrast to MoM total hip prostheses, the design of total knee implants avoids direct metal-to-metal contact.

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Friction between bearing surfaces and corrosion of nonmoving parts produce elevated local and systemic metal concentrations, typically <7 μg/L. Very rare case reports associate systemic cobalt toxicity with hip arthroplasties compared with >1 million total hip implants performed worldwide to date. These case reports typically involve fractured ceramic hip prostheses and excessive wear of metal-on-metal hip arthroplasties. A 2014 review of the English medical literature identified 26 papers describing 18 individual cases of systemic toxicity associated with hip prostheses involving 10 cases of the replacement of fractured ceramic prostheses with metal surfaces and 8 cases of MoM hip implants with excessive wear.[163] The authors proposed the following criteria for assessing patients with hip implants and elevated blood cobalt/chromium concentrations:

(1) History – The patient has an MoM or fractured ceramic-containing prosthesis replaced by a metal component for local pain and symptoms consistent with systemic cobalt toxicity (cardiac, neurological, and thyroid effects). Other explanations for these symptoms are less likely than cobalt toxicity.
(2) Clinical findings – Local abnormalities (corrosion, metallosis) are documented by pathological or imaging studies along with objective evidence of cardiac, neurological, and thyroidal changes consistent with cobalt toxicity. Other explanations for these changes are less likely than cobalt toxicity.
(3) Temporal relationships – Clinical features develop months to years after substantially increasing blood cobalt concentrations.
(4) Blood cobalt concentrations – Blood cobalt concentrations in symptomatic patients are substantially higher than in patients with well-functioning prostheses.
(5) Response to removal and debridement of worn prosthesis – Blood cobalt concentrations decrease after the removal of the prosthesis usually along with improving clinical symptoms.

Using these criteria, the authors attributed 10 of the 18 identified cases to systemic cobalt toxicity; all the attributed cases had very elevated blood cobalt concentrations (i.e., >250 μg/L). A 2016 review of the English medical literature also identified 18 cases of systemic cobalt toxicity associated with hip arthroplasties; MoM articulations accounted for 10 cases.[164] In a retrospective case series of 31 patients referred to outpatient toxicology clinics for evaluation of MoM THA, the median peak cobalt and chromium concentrations were 10 μg/L (IQR = 3.8–32.8 μg/L) and 6.9 μg (IQR = 3.7–18.7 μg/L), respectively. Two patients diagnosed with systemic cobalt toxicity were a 56-year-old man 7 years post-bilateral MoM THA with extreme lethargy and hip pain (peak serum cobalt = 164.8 μg/L, peak serum chromium 100.2 μg/L) and a 60-year-old man 16 years post-right sided MoM THA with optic neuropathy, peripheral axonal neuropathy, polycythemia, and hypothyroidism (peak serum cobalt = 1,096 μg/L).[165] Polycythemia and hepatorenal dysfunction do not usually occur following cobalt exposure except in symptomatic patients with multisystemic diseases and highly elevated serum cobalt concentrations.[166]

Local tissue reactions

The deposition of cobalt-chromium wear particles from wear and corrosion around the MoM hip prostheses may produce inflammatory and necrotic changes, resulting in soft tissue and bone lesions that contribute to loosening of the implant and implant failure. Adverse reactions to metal debris include the following histological changes: 1) metallosis (macroscopic staining of periprosthetic soft tissues); 2) aseptic lymphocytic vasculitis-associated lesions (ALVALs); 3) and 4) pseudotumors (cystic, solid, or mixed peri prosthetic soft tissue mass).[167] The umbrella term, adverse reactions to metal debris (ARMD), refers to large sterile hip effusions, and/or tissue metallosis/necrosis ranging from small pseudocysts to large soft tissue masses (pseudotumors) that ultimately lead to osteolysis and painful joint failures. ARMD also refers to secondary inflammatory cellular reactions and host immune reactions.[168] The cause–effect relationship between hypersensitivity and implant failure remains uncertain. Although the prevalence of hypersensitivity is substantially higher in patients with implant failures than well-functioning arthroplasties, many patients with positive tests have good clinical outcomes.[169]

Symptomatic pseudotumors with ALVAL, extensive tissue necrosis, bone loss around the hip implant, and loosening/failure of the prosthesis requiring revision develop in a relatively small number of total hip replacements (i.e., <5%);[170,171] however, thin-walled cystic lesions on MRI also occur in asymptomatic hip implant patients.[172] The clinical course of pseudotumors is difficult to predict (i.e., expansion, contraction, unchanged).[173] In a study of 1,419 metal-on-metal hip resurfacings implanted by a British orthopedic service in 1,224 patients, 1.8% of the patients had a revision for pseudotumor.[174] Solid pseudotumors almost exclusively occur with resurfacing procedures, particularly with

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acetabular malposition in women under 40 years of age.[175] Case reports associate pseudotumor formation with lower extremity edema (vascular compression)[176] and impairment of the femoral or lateral cutaneous nerve.[177]

Cardiovascular System

Several case reports attribute serious cardiac abnormalities (i.e., impaired diastolic function, dilated cardiomyopathy, pericardial effusion) with excess wear/corrosion of hip prostheses and extremely high blood cobalt concentrations (≫200–300 μg/L), often with comorbidities (e.g., alcoholism, renal dysfunction, diabetes).[178] An otherwise healthy 46-year-old man sustained a fracture of the polyethylene-ceramic sandwich acetabular liner of the left total hip replacement.[166,179] Within 6 months of revision surgery with metal-on-polyethylene (MoP) bearing, he developed severe fatigue, anorexia, weight loss, hypothyroidism, and left hip pain. One year after surgery, he complained of worsening fatigue and dyspnea despite thyroid replacement. He developed left ventricular failure (LV ejection fraction <10%), pericardial effusion, and cardiogenic shock. Despite 2 weeks of chelation therapy, he developed multisystem failure and died. His peak whole blood cobalt and chromium concentrations during this hospitalization were 6,532 μg/L and 23.6 μg/L, respectively. There was severe wear (secondary to embedded ceramic particles) on his implanted Co–Cr alloy femoral head with an estimated 23.3 g loss of mass from the implant. A 60-year-old woman with a history of MoP replacement for a fractured ceramic-on-ceramic right total hip arthroplasty developed right hip pain, dyspnea, increased hearing loss, metallic taste, and weight loss.[180] A whole blood cobalt concentration following the reduction of dislocation of her right hip was 817 μg/L. Prior to succimer initiation and prosthesis removal, she developed hypotension and cardiorespiratory failure. Autopsy demonstrated extensive metallic effusion surrounding the right hip prosthesis.

Moderately reduced systolic left ventricular function, hypothyroidism, headache, muscle loss, peripheral paresthesias, and hearing loss developed in a 55-year-old man after the replacement of fractured ceramic head.[181] On revision, he had severe metallosis from retained ceramic debris; his serum cobalt concentration at revision was 625 μg/L. His symptoms resolved 6 months after the last revision. A 59-year-old woman developed biventricular cardiac failure requiring cardiac transplant and hypothyroidism several years after receiving bilateral MoM ASR™ hip prostheses; cough, exertional dyspnea, and pedal edema began while vacationing in Denmark.[182] There was no documented fever, rash, or new arthralgias. The complete blood count was normal. Deterioration of cardiac function continued posttransplant; 8 months after the transplant, imaging of the hip demonstrated metallosis and the serum cobalt concentration was 399 μg/L. Resection of the hip implants resulted in improved cardiac function and rapid reduction in the serum cobalt concentration. A 55-year-old man developed progressive heart failure, hypothyroidism, fever, and increasing visual loss and deafness after replacing a MoP prosthesis for a fractured ceramic hip implant.[183] Imaging demonstrated myositis ossificans-like changes and blood cobalt concentrations of 885 μg/L. Improvement in cardiac function occurred after removal of the MoP prosthesis and reduction in the blood cobalt concentration (85 μg/L).

Other case reports provide less convincing evidence of an association between cobalt-induced cardiac changes and hip prostheses as a result of preexisting illnesses, renal dysfunction, and nutritional deficiencies. A case report documented normalization of LV systolic function and improvement of cardiomyopathy in a 75-year-old farmer after removal of his MoM hip prosthesis and reduction of his plasma cobalt concentration (pre-op, 13.6 μg/L; 1-month post-op, 4.5 μg/L).[184] Multiple cardiac risk factors including Type 2 diabetes mellitus, single-vessel moderate coronary artery disease, Class I obesity, mild renal impairment, and hypercholesterolemia suggested alternate explanations for his cardiac disease. A 49-year-old man complained of exertional dyspnea 1 year after implant when his serum cobalt concentration was 23 μg/L.[185,186] Six months later, echocardiography indicated diastolic dysfunction; he reported symptomatic improvement 7 months after revision; however, there was no echocardiographic confirmation.

In a retrospective review of 39 patients consulting medical toxicologists about the toxicological effects of hip implants, none of the patients were diagnosed with cobalt-related heart disease.[187] The maximum whole blood cobalt concentration was 254 μg/L. In a cross-sectional study of 35 pairs of asymptomatic patients with metal-on-metal hip resurfacing MoMHR and conventional hip replacement matched for age, sex, and time since surgery (mean = 8 years), transthoracic echocardiography demonstrated a 7.7% reduction in the mean ejection fraction and a 6% increase in left ventricular end-diastolic diameter in the MoM group.[188] These differences did not result in any function impairment. Although the authors recommended monitoring of cardiovascular function, they did not ascribe the cardiovascular effects to cobalt toxicity. The mean whole blood cobalt concentrations were 1.75 μg/L (range,

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1.11–6.11 μg/L) and 0.38 μg/L (range, 0.33–0.55 μg/L), respectively.

Central nervous system

Toxicological data associating cobalt exposure with central nervous system effects in patients with failing hip prostheses primarily involve rare case reports of impaired vision (bilateral optic atrophy and retinopathy), sensorineural hearing loss (bilateral nerve deafness), and peripheral neuropathy (primarily sensory and mixed sensorimotor) without a clear pathophysiological mechanism; frequently, these cases lack sufficient details to exclude comorbidities as causal factors.[189] A longitudinal analysis of the Medicare database 2005–2012 identified 29,483 MoM total hip arthroplasties and 23,587 age- and gender-matched MoP total hip arthroplasties; these groups were also matched in the prevalence of 26 of 30 Elixhauser-measure comorbidities.[190] Using ICD ninth revision procedure codes, the study compared new diagnoses of six neurological side effects (paresthesias, peripheral neuropathy, sensorineural hearing loss, tinnitus, vertigo, visual impairment) over 5 years. The new diagnoses of neurological side effects in the hip replacement were not statistically different than the control group.

Case reports associate substantially elevated cobalt and chromium concentrations with optic atrophy,[191] tinnitus, hearing and visual loss,[192,193] sensorimotor neuropathy (severe metallosis with ceramic debris),[181] and retinopathy with impaired visual acuity and color loss.[194] An 18-month follow-up of the latter case demonstrated improved visual acuity and color vision after hip revision, but electroretinogram abnormalities persisted with the development of optic nerve dysfunction; concurrent blood cobalt and chromium concentrations remained elevated (27.26 μg/L and 31.36 μg/L, respectively) after revision.[195] This 65-year-old man had multiple comorbidities including diabetes, hypertension, hypercholesterolemia, pulmonary embolism, atrial fibrillation, obesity, and cataracts. Other case reports associated additional neurological effects (cognitive decline, poor coordination) with elevated blood cobalt/chromium in hip implant patients;[185,186] however, the lack of data on the toxicokinetics of cobalt with specific types of cobalt biological binders, exposure to multiple metals, confounding illness (stroke, anxiety, depression age), absence of objective data, and the small number of patients affected compared with the number exposed limit conclusions regarding the causal role of cobalt in the development of the latter central nervous system effects. In a retrospective review of 39 patients consulting medical toxicologists about the toxicological effects of hip implants, 1 patient had a demyelinating peripheral neuropathy; her symptoms improved significantly with revision surgery and the decrease in her whole blood cobalt concentration from 254 μg/L to 10 μg/L (serum).[187] Two other patients had symptoms suggestive of demyelinating neuropathy. Nine patients sought consultation for fatigue; tinnitus was a frequent (n = 10) associated complaint, but the primary complaint was in only one patient. Two of the three patients with complaints of hearing loss also had tinnitus.

Thyroid Dysfunction

Large cobalt chloride doses (5–10 mg/day) may cause transient thyroid dysfunction based on the use of this compound to treat anemia in the 1950s.[196] A few case reports of patients with multisystem illnesses associated very high plasma cobalt concentrations (e.g., >400–4,000 μg/L) with malfunctioning hip implants;[179] however, the thyroid dysfunction and goiter in surviving patients typically resolve within several weeks after hip revision.[194]

Acute Toxicity

Pediatric case reports associate cobalt toxicity with exposure to cobalt chloride in chemistry sets.[197] These case reports document gastrointestinal irritation (nausea, vomiting, abdominal pain, erosion of the gastric mucosa). A 19-month-old child died after the ingestion of cobalt chloride; however, the cause of death was unclear.[44] This case report did not include serum cobalt concentrations.

Environmental Exposure

A Quebec case series of 48 alcoholics, mostly malnourished patients (46 M, 2 F) associated the development of cardiomyopathy (beer drinkers' cardiomyopathy) with very high consumption of beer containing relatively large cobalt concentrations (i.e., ~1 ppm as a foam-stabilizing agent) compared with other beers.[8] A majority of these patients drank >12 pints/day for ≥10 years. The clinical presentation included nausea, vomiting, diarrhea, abdominal pain, occasional hematemesis, and progressive heart failure characterized by hypotension, cough, chest pain, pericardial effusion, and progressive dyspnea.[198] These patients also demonstrated peculiar cyanosis limited to the face and trunk along with increased deposition of melanin on skin biopsy.[12] Twenty of the 48 patients died with many of the deaths occurring within 24 hours of the onset of cardiogenic shock. Cofactors (mineral

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and protein deficiencies, alcoholic cardiomyopathy) probably were involved in the development of beer-drinkers' cardiomyopathy because of the low dose of cobalt consumed by these patients and the rare occurrence of cardiomyopathy in subjects drinking cobalt sulfate-containing beer.

Occupational Exposure

Hard metal lung disease

Hard metal lung disease (AKA, giant cell interstitial pneumonia, cobalt lung, tungsten carbide pneumoconiosis, hard metal pneumoconiosis) is a rare giant cell interstitial pulmonary disease that occurs following chronic hard metal dust exposure (e.g., grinder, sharpener). The main pulmonary effects involve the following: 1) reversible airway obstruction; 2) subacute fibrosing alveolitis with intra-alveolar desquamation that includes interstitial, multinucleated giant cells; and 3) chronic, diffuse interstitial pulmonary fibrosis.[199] Although cobalt exposure alone causes occupational asthma, the development of the interstitial fibrosis associated with the hard metal lung disease usually requires exposure to other hard metals (e.g., diamond, iron, silica, titanium, or tungsten).[90] Clinically, this rare disease resembles hypersensitivity pneumonitis with a variable clinical course ranging from a subacute presentation to occasionally rapid progression to pulmonary fibrosis; the correlation between disease occurrence and length of occupational exposure is poor.[200] Pulmonary changes occur in workers using high-speed diamond-cobalt grinding tools with exposure to cobalt-diamond dust rather than hard metal (i.e., tungsten carbide) dust. These polishing disks possess a cutting surface consisting of microdiamonds cemented into a fine cobalt mesh and placed over a frame of half-hard steel that contains mostly iron. The epithet cobalt lung is an older term given to the pulmonary changes in these workers because of the absence of suspected effects from other metals present in the hard metal; however, the hard metal lung disease is a more accurate term because of the necessity for the presence of other metals or diamond dust for the expression of the disease. In addition, exposure to cobalt-containing particles may produce inflammation of the upper respiratory tract, either through direct inflammation or an immunological reaction.

The manifestations of interstitial lung disease following exposure to hard metal dust probably result from a continuous process. This disease process varies from acute alveolitis to chronic pulmonary fibrosis depending on the individual's susceptibility and the duration/severity of the exposure. The abrupt development of fever, anorexia, cough, and dyspnea with exertion indicates the presence of alveolitis, which typically begins months to several years after the initial hard metal dust exposure. Chronic forms of hard metal lung disease or bronchitis usually require prolonged exposure to dust composed of multiple metals. Typically, evidence of interstitial lung disease appears after 10–12 years of exposure to hard metal dust;[201] however, the appearance of symptoms or signs may be shorter (2–7 years) depending on the intensity of exposure.[118] Symptoms may improve following removal from the workplace, but symptoms may recur following reexposure. Repeat episodes of alveolitis may produce interstitial fibrosis.

The most common early symptoms of interstitial fibrosis involve exertional dyspnea and dry cough with the occasional production of scant, mucoid sputum. The fibrotic form of this disease is more progressive and insidious than the alveolar form. Tachypnea at rest, weight loss, and clubbing are late manifestations of pulmonary fibrosis. Inspiratory rales may occur either as a result of active alveolitis or diffuse pulmonary fibrosis. As the extent of pulmonary fibrosis progresses, pulmonary hypertension and cor pulmonale supervenes. Individuals with increased susceptibility may develop interstitial lung disease at lower concentrations and shorter durations of exposure compared with the general population of workers.[202] Pulmonary abnormalities usually improve considerably upon removal of the worker from exposure to hard metal dust;[203,204] continued exposure to high concentrations of hard metal may produce a rapid progression of the pulmonary fibrosis [114] and death.[205]

The presence of interstitial fibrosis in populations of active diamond polishers and tungsten carbide production workers is relatively rare (<1%). A cross-sectional study of tungsten carbide production workers with prolonged exposure to high concentrations of hard metal dust resulting in cobalt concentrations above current occupational standards revealed a 3.8% prevalence of interstitial infiltrates and a 5% prevalence of obstructive defects in nonsmoking workers.[206] The differential diagnosis of hard metal lung disease includes pneumoconioses, hypersensitivity pneumonitis, sarcoidosis, and other granulomatous lung diseases, interstitial pneumonia, and drug-induced lung disease.

Hypersensitivity

Asthma

Occupational asthma characterized by wheezing, coughing, and dyspnea occurs in hard metal workers with

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cobalt-specific IgE-albumin complexes[98] and a positive bronchoprovocation test with cobalt chloride.[207] Occupational asthma is more frequent than interstitial lung disease; occasionally, the two diseases may coexist.[199] These tests demonstrate early, late, and dual reactions to cobalt inhalation. A retrospective study of occupational asthma in a Finnish cobalt production plant reported 22 cases, who were diagnosed an average of 7.4 years after the onset of symptoms. Bronchial challenge tests demonstrated the following types of reactions: immediate, 16%; delayed, 61%, and dual, 19%.[97] One in 14 patients retested for bronchial hyperreactivity improved, whereas half the patient's reactivity remained unchanged on retesting. In contrast to hard metal lung disease, exposure to only cobalt is sufficient to produce asthma.[87] Clinically, asthmatic symptoms usually appear about 4–6 hours after exposure; often, the symptoms worsen in the early evening.[208] Characteristic improvement occurs on the weekend and holidays; however, the presence of late reactions to inhaled cobalt indicates that asthma symptoms may appear up to 48 hours after exposure.

The prevalence of occupational asthma in hard metal workers depends on the population studied (i.e., healthy worker effect) as well as the intensity of exposure. A cross-sectional study of hard metal workers revealed a prevalence of 5.6% for asthma in active workers.[209] The presence of concurrent sensitivity to nickel indicates that nickel may contribute to the development of hard metal asthma.[210] Although there is no evidence that workers with cobalt-induced occupational asthma develop interstitial fibrosis, rarely workers with asthma may develop hypersensitivity pneumonitis.

Dermatitis

Cobalt is one of the three most common metallic sources of occupational contact dermatitis along with nickel and chromium.[211] A meta-analysis of all publications between 1966–2000 using standardized patch testing demonstrated the presence of cobalt hypersensitivity in 4.8% of the patients.[212] Men and women have similar rates of cobalt hypersensitivity with the highest prevalence rates in hairdressers, barbers, building contractors, retail cashiers, machine operators, and domestic cleaners.[213] Products associated with this dermatitis include metal alloys, catalysts, electroplating materials, dyeing agents, and potter/glass colorants. In the occupational setting, cobalt-induced contact dermatitis characterized by erythematous papules occurs commonly on the hands of workers in the hard metal industries, cleaning industries, and textile and leatherwork. The prevalence of hand eczema and irritant reactions in a group of 776 workers in a hard metal factory was ~10% and 15%, respectively.[214] The majority of these rashes begin within the first year of employment. Risk factors for the development of severe eczema include prior nickel sensitization and irritative dermatitis.[95] In a study of 853 hard metal workers, 25% of the nickel-sensitive individuals developed cobalt allergies compared with 5% of the total population tested.[215] Almost all (88%) of the nickel-sensitive individuals were women who developed nickel sensitivity from the use of ear piercings.

Sensitization to these metals results from co-exposure to these metals rather than cross-reactivity among these metals.[216] The incidence of contact dermatitis from chromium, cobalt, and nickel in a group of 1,782 workers exposed to cement, waste fly ash, and asbestos cement was 8.6%, 3.1%, and 1.1%, respectively.[217] The diagnosis was based on definitely positive patch tests for these metals. This diagnosis of cobalt sensitivity is complicated by the fact that nickel contamination of cobalt patch tests may produce false-positive skin tests for cobalt in patients who are highly sensitive to nickel.[218]

Cardiovascular System

Several case reports associate the abrupt development of cardiomyopathy in workers with cobalt exposure based on elevated cobalt concentrations in tissues or blood and no other discernable cause;[14,154,219] however, the lack of exposure data, the absence of a unique marker of cobalt cardiomyopathy, the presence of coexisting illness (e.g., polycythemia),[154] and incomplete epidemiological data supporting a causal connection limit definite conclusions about causal relationships between cobalt exposure and clinically significant heart disease.[220] A Finnish study of 203 cobalt production workers did not detect any clinically significant cardiovascular disease in the exposed workers; however, echocardiography suggested altered left ventricular relaxation and early filling in the exposed workers.[221] In a Belgian study of 256 cobalt production workers, no evidence of dilated cardiomyopathy was detected in the workers as evaluated by echocardiogram and electrocardiogram.[222] The median urinary cobalt concentration was ~4 μg/g creatinine with a median cumulative estimated exposure of 100 μg/g creatinine; the interquartile range was 2.0–8.0 μg/g creatinine with a maximum value of 426 μg/g creatinine. There was no dose-effect suggesting a relationship between incipient dilated cardiomyopathy and cobalt exposure. Recent cobalt exposure was associated with a reduction in the left ventricular internal cavity. The exposure of most of these workers was below current workplace standards (e.g., 15 μg/g creatinine).

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Central nervous system

Although a few case reports associate transient hearing and/or visual impairment with the use of cobalt chloride to stimulate erythropoiesis in chronically sick patients,[160,161] there are few data associating occupational cobalt exposure with impairment of the central nervous system. A 48-year-old smoker presented 4 months after leaving a job involving exposure to high concentrations of raw cobalt powder.[223] He had a 7-month history of progressive bilateral deafness, tinnitus, occasional vertigo, and optic atrophy; his whole blood cobalt concentration was 234 μg/L, and he had elevated CSF protein with oligoclonal IgG banding. Following cessation of cobalt exposure, his bilateral optic atrophy and nerve deafness improved over the next 7 months.

Reproductive Abnormalities

Humans

There are few data on the human reproductive effects of cobalt exposure; existing evidence does not associate cobalt exposure with teratogenesis based on case reports. A woman diagnosed with severe pulmonary fibrosis secondary to the hard metal lung disease before her pregnancy delivered a healthy full-term infant.[224] A 34-year-old woman with a Co concentration of 103 μg/L before her pregnancy delivered a healthy infant with hypospadias at 41 weeks; the maternal blood Co at delivery was 51 μg/L.[225] Blood chromium concentrations were also elevated. The infant was breastfed and developed normally; the infant's blood Co concentrations at 3 weeks and 9 weeks were 20 μg/L and 10 μg/L, respectively. A 41-year-old woman with a metal-on-metal hip implant developed a recurrent pseudotumor and elevated cobalt/chromium concentrations during her pregnancy.[226] The maternal whole blood cobalt concentration at delivery of a healthy full-term infant was 143 μg/L; the cobalt concentration in cord blood was 75 μg/L (52% of maternal blood), indicating that cobalt diffused across the placental barrier. No adverse maternal or neonatal effects were observed 14 months after birth. In a case series of 10 pregnant women with MoM hip arthroplasties, the maternal whole blood cobalt concentration at delivery was 1.39 ± 0.36 μg/L compared with 0.839 ± 0.26 μg/L in cord blood; however, the difference was not statistically significant ($P > 0.05$).[227] In a case study of three women with metallic hip implants during their pregnancy, no abnormalities were detected in the infants at birth.[228] A clinical study of 78 pregnant women receiving 60–100 mg cobalt chloride daily for pregnancy-related anemia detected no adverse effects in the mother or neonate.[51,229] The women received cobalt for a minimum of 3 months and a maximum of 6 months; the number of women receiving cobalt in the first trimester was not reported. Twenty of these patients received cobalt alone, whereas the other women received cobalt chloride and ferrous sulfate.

Animals

In bacterial systems, cobaltous salts are not mutagenic, but studies in mammalian cultures indicate that cobaltous salts inhibit DNA repair and thus may enhance the genotoxicity of other mutagenic agents.[230] Cobaltous chloride induced a low frequency of cleft palate in mice.[231] No fetotoxic or teratogenic effects occurred in rats gavaged with daily doses of 100 mg cobaltous chloride/kg body weight.[232]

Carcinogenesis

The genotoxicity and carcinogenicity of cobalt compounds depend on the type of cobalt compound. The US National Toxicology Program (NTP) lists cobalt-tungsten carbide powders and hard metals as reasonably anticipated to be human carcinogens based on limited evidence of carcinogenicity in human studies and supporting evidence in *in vitro* studies. Although epidemiological data are limited to a few independent populations, the basis for the NTP classification includes the following: 1) a consistent excess lung cancer mortality among cobalt–tungsten carbide hard-metal manufacturing workers, and 2) higher risks among workers with higher exposure levels after adjustment for tobacco smoking. The NTP also lists cobalt and cobalt compounds that release cobalt ions *in vivo* as reasonably anticipated to be human carcinogens based on sufficient evidence from studies in experimental animals and supporting plausible mechanisms (e.g., genotoxicity, oxidative damage from the generation of reactive oxygen species, stabilization of hypoxia-inducible factor resulting in enhanced cancer cell survival in oxygen-deficient environments, inhibition of DNA repair).[233] These experimental data include the development of tumors in the following: 1) two rodent species at several different tissue sites, and 2) experimental animals exposed to metallic cobalt or cobalt compounds via several different exposure routes. The evidence from human studies was inadequate to evaluate the association between cancer and exposure to cobalt and cobalt compounds that release cobalt ions *in vivo* including a lack of sufficient evidence to quantitate the cancer risk in patients with cobalt alloy-containing joint implants.

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The IARC classifies cobalt metal with tungsten carbide as probably carcinogenic to humans (Group 2A) based on limited evidence in humans for the carcinogenicity of cobalt metal with tungsten carbide and sufficient evidence in experimental animals for the carcinogenicity of cobalt metal powder.[234] Cobalt metal, cobalt sulfate, and other soluble divalent cobalt salts without tungsten carbide are listed as possibly carcinogenic to humans (Group 2B) based on inadequate evidence in humans for the carcinogenicity of cobalt metal without tungsten carbide, limited evidence in experimental animals for the carcinogenicity of metal alloys containing cobalt, and sufficient evidence in experimental animals for the carcinogenicity of cobalt sulfate. *In vitro* studies suggest the carcinogenic potential of insoluble Co compounds (e.g., metallic Co) is less than that of soluble Co compounds (e.g., cobalt sulfate).[235,236] A 2-year whole-body inhalation study in rats and mice exposed to cobalt sulfate and insoluble metallic cobalt produced inflammation of the respiratory tract (hyperplasia, squamous metaplasia) and an increased incidence of alveolar/bronchiolar carcinoma, primarily at exposure levels of >10 times the current occupational exposure limits (100 $\mu g/m^3$).[111] The occurrence of pancreatic neoplasms in male rats and leukemias in female rats suggested these substances may be multisite rodent carcinogens at the airborne concentrations tested. In 1999, the IARC listed implanted foreign bodies of metallic chromium or titanium and cobalt-based, chromium-based, and titanium-based alloys as not classifiable as to their carcinogenicity to humans (Group 3).[237] Epidemiology studies of hip implants and cancer at that time were inconsistent with inadequate control of confounders and short follow-up periods compared with latency times for solid tumors.

Occupational Exposure

A cohort study of all hard metal-producing (i.e., cobalt and tungsten carbide) plants in France detected ~30% excess in lung cancer mortality SMR = 1.3, 95% CI: 1.00–1.66, 63 deaths when comparing 7,459 French hard-metal workers with national death rates.[238] A nested case-control study from this study comparing lung cancer risks in workers exposed to cobalt–tungsten carbide with minimally or unexposed workers demonstrated higher risks in the exposed workers (OR = 1.93, 95% CI: 1.03–3.62, 35 cases) based on a job-exposure matrix (0–7). The risk of lung cancer increased significantly with duration of exposure ($P = 0.03$) and cumulative dose (unweighted, $P = 0.01$); however, the increased risk with exposure level ($P = 0.08$) and cumulative dose (frequency weighted, $P = 0.08$) was not statistically significant. Adjustment for smoking and the presence of suspected carcinogens did not alter the odds ratios. In a mortality study of workers at the largest French hard metal production facilities included in the previous French study, the lung cancer risk was increased by ~2-fold for the duration of exposure to hard metal dust before sintering, after adjustment for smoking and known or suspected carcinogens.[239] The SMR for hard metal production workers was 2.42 (95% CI: 1.10–4.59) based on nine deaths. Although exposure misclassification probably would reduce the likelihood of detecting a true effect, these studies are limited by the lack of quantitative exposure assessment and potential confounding (e.g., other carcinogenic metals).

Analysis of data from an international study of 32,354 hard metal production workers from 3 companies and 17 manufacturing sites in 5 countries (Austria, 1970–2014; Germany, 1975–2012; Sweden, 1952–2012; United Kingdom, 1980–2014; United States, 1952–2012) was not consistent with the earlier French and Swedish studies.[240] Although the SMR for bronchus, trachea, and lung cancer in the pooled cohort using regional rates was statistically significant (1.20, 95% CI: 1.09–1.31; $n = 459$), the SMR for workers with >5 years of employment was 1.02 (95% CI: 0.88–1.17) after using regional comparisons and adjusting for age, calendar time, race, and sex. The study found no evidence of an exposure-response relationship for lung cancer or evidence that duration or average intensity of cumulative exposure to individual metals (cobalt, nickel, tungsten) increased the lung cancer mortality risk based on a job-exposure matrix composed of eight job classes.[241]

Some of these studies suggest the possibility of excess risk of other cancers (e.g., leukemia, esophagus, pleura);[242] however, there is no clear association of these cancers with hard metal workers because of the lack of clear dose-response relationships or statistically significant differences between exposed and unexposed workers.

Epidemiological evidence of cancer in humans is stronger following exposure to cobalt with cobalt-tungsten carbide than cobalt without tungsten carbide. A cohort mortality study of 1,143 French workers exposed to cobalt during the production of cobalt at an electrochemical plant revealed an excess of lung cancer.[243] The small number of lung cancer cases (4) and the lack of control of confounding variables (smoking, arsenic, nickel) prevent the establishment of a definite causal relationship between exposure to cobalt and the development of lung cancer. A follow-up study of this cohort of cobalt production workers for an additional 7 years revealed no excess mortality (SMR = 0.85, 95%

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CI: 0.18–2.50, 3 deaths) from lung cancer.[244] A retrospective cohort study of 874 women exposed to cobalt in 2 Danish porcelain factories did not demonstrate a significantly increased relative risk of developing lung cancer (RR = 1.2, 95% CI: 0.4–3.8, $n = 8$ cases).[245] Direct measurements of cobalt concentrations were not available.

Metallic Prostheses

Case reports of sarcomas at the site of hip implants and the induction of carcinomas in animal models by cobalt and chromium wear particles raised concern about the carcinogenic potential of MoM prostheses;[246,247] however, there is no clear epidemiological relationship between implanted cobalt material and specific cancer based on follow-up of total hip or knee arthroplasties ranging from 6 months to 17 years (mean = 7.5 years).[248] Initial data from population-based studies using standardized mortality rates,[249] United Kingdom National Joint Registry data,[250] and standardized incidence ratios,[251] do not suggest an increased incidence of cancer or cancer mortality in patients with total hip arthroplasties containing cobalt. Although local metal concentrations in some patients with unstable hip replacements are substantially higher than normal values, the occurrence of adjacent tumors (e.g., sarcomas) remains rare.[252] The risk of these tumors is not significantly elevated in patients with MoM hip implants when compared with standardized rates.[253] Biochemical studies of patients with loose or worn prostheses indicate some increased chromosomal aberrations and clonal expansion of lymphocytes may develop within 10 years of these implants, but no cellular transformation indicative of cancer occur.[254]

Limitations of existing epidemiological data on hip implants and cancer include insufficient follow-up period, lack of dose-response information, and the presence of confounding comorbidities (e.g., bone infarctions, hereditary bone dysplasia, osteomyelitis, rheumatoid arthritis). Although these epidemiological studies have not detected an increased risk of cancer in patients with MoM total hip arthroplasties, the follow-up periods are relatively short compared with the latency periods for solid tumors.[255] In a Finnish population-based study of 10,728 patients with metal-on-metal total hip arthroplasty and a non-metal-on-metal cohort (conventional metal-on-polyethylene, ceramic-on-polyethylene, ceramic-on-ceramic total hip arthroplasty) of 18,235 patients, there was no association of MoM hip arthroplasty with an increased overall risk of cancer during a mean follow-up of 4 years.[251] The standardized incidence ratio of the MoM cohort was 0.95 (95% CI: 0.85–1.04). A UK observational study of 40,576 patients with MoM hip replacements and 248,995 with alternative bearing surfaces detected no statistically significant increased incidence of all cancers, malignant melanoma, hematological cancer, prostate cancer, or renal tract cancer in the study population compared with the general UK population or patients with alternate bearing surfaces.[256] The mean follow-up period was 3 years with 23% of the cohort followed for 5–8 years.

DIAGNOSTIC TESTING

SI Conversion Units

1 μg/L = 0.017 μmol/L = 16.97 nmol/L
1 nmol/L = 0.059 μg/L
1 nmol/mmol creatinine ≈ 0.59 μg/g creatinine
1 ppm = 2.4 mg/m^3

Analytical Methods

Techniques used to analyze cobalt concentrations in samples include atomic fluorescence spectrometry, voltammetry, liquid chromatography, gas chromatography, neutron activation analysis,[257] and flameless atomic absorption spectrophotometry.[258] Although neutron activation analysis demonstrates good sensitivity and specificity, the procedure is costly and time-consuming. Graphite furnace (electrothermal or flameless) atomic absorption spectrophotometry (GF/AAA) was previously a common method to determine cobalt concentrations in serum and urine as a result of low detection limits (i.e., ~1 μg/L) and ease of use;[259,260] the LOD with Zeeman or deuterium background correction in urine samples is ~0.1 μg/L with an analytical precision of 13%.[261] In this method, the sample is heated to 2,000 °C in the graphite furnace to form an atomic vapor; the atoms cross a light beam that is specific to the element. Absorption of energy during ionization of the element reduces the intensity of the beam in proportion to the concentrations of the element.

Inductively coupled plasma/mass spectrometry (high-resolution or collision/reaction cell quadrupole ICP/MS) has the advantage of lower sensitivity than GF/AAS and the ability to process multiple elements simultaneously.[262] In this method, the sample is nebulized in a changer containing argon and high temperatures to dissociate and atomize the elements; a collection of electrostatic discs extracts the positively charged ions and transports them to a quadrupole mass filter that selects the ions based on mass and charge. The

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LOD for cobalt measured in urine samples by inductively coupled plasma/mass spectrometry is ~0.01 μg/L; however, the presence of polyatomic interferences from $^{42}Ca^{2+}$ and $^{43}Ca^{2+}$ isotopes occurs at very low cobalt concentrations.[261] Results from different laboratories using ICP/MS may vary significantly. In a study of 2 laboratories receiving 45 duplicate whole blood samples for cobalt analysis using ICP/MS, the mean difference between the results was 0.52 ± 1.35 μg/L ($P = 0.012$).[263] Differential pulse cathodic stripping voltammetry is an alternate method for the determination of cobalt in blood and urine with LODs of 0.8 μg/L and 0.2 μg/L, respectively.[264] The most commonly used method for quantification of cobalt in environmental samples is GF/AAS (LOD = 0.02–0.5 μg/L).[265,266] Gamma-ray spectrometry allows the determination of radioisotopes of cobalt in environmental samples.[267]

Sample preparation (e.g., wet ashing) and/or pre-concentration may be necessary for the determination of cobalt in environmental samples. Wet extraction with dilute nitric acid is most suitable for analyzing cobalt in dust samples. The use of filtered and unfiltered samples allows the quantification of soluble and insoluble cobalt. Similar to biological samples, the use of polyethylene containers and acidification of the solution to the appropriate pH reduce cobalt loss. Trace element-certified collection tubes are the best method to store biological media for analysis; preferably, the collection tubes have no additives, heparin, or EDTA with the first draw used for another routine testing. Cobalt contamination in blood samples may occur from the use of disposable syringes or technical-grade anticoagulants.[21]

Biomarkers

A progressive reduction in the reported range of cobalt concentrations in the general population resulted from the improvement in analytical methods.[16] Significant exposure to cobalt occurs primarily in occupational settings because cobalt concentrations in the environment are usually low.

Blood

Most cobalt in the blood occurs in the serum with a relatively small amount in the erythrocytes. Substantial variability occurs in serum, plasma, and whole blood cobalt concentrations in the same sample; consequently, the values for the different types of blood samples are not interchangeable. The serum is usually preferred to plasma because the use of serum avoids the potential complications of using anticoagulants (e.g., red cell lysis during prolonged storage). In general, the cobalt concentrations in plasma and serum are higher than those in erythrocytes as a result of rate-limited uptake of cobalt into the erythrocyte. In a study of 246 concurrent specimens from patients with metal-on-metal (MoM) hip replacements analyzed by high-resolution/inductively coupled/plasma mass spectrometry, the mean difference between serum and whole blood cobalt concentrations was 0.84 μg/L with relatively greater variation at lower concentrations; the difference was statistically significant ($P < 0.0001$).[268] Regression analysis estimated a serum/whole blood cobalt ratio of ~1.4, but excessive interindividual variation and substantial variation with different Co concentrations (i.e., ±65%) limit the usefulness of this conversion factor. In a study of 29 patients with normal functioning unilateral hip prostheses (54-mm femoral Birmingham Hip, Smith & Nephew, London, UK) followed 5–29 months after implantation, most of the cobalt appeared in the serum and plasma fractions with lower cobalt concentrations in erythrocytes.[269] The mean cobalt serum/whole blood ratio was ~1.2 with serum containing about ~5 times higher cobalt concentration than erythrocytes with median cobalt concentration of ~1 μg/L. In 34 paired samples of whole blood and serum from patients with high carbon content Cr–Co alloy in their hip implants, the mean serum/whole blood ratio was 1.37 (range, 0.72–1.80) with the mean serum Co concentration ~2 times higher than erythrocytes.[270] The plasma and whole blood cobalt concentrations were similar in a study of 202 patients with MoM hip prostheses; the median whole blood cobalt concentration was 2.71 μg/L with a range of 0.18–145.73 μg/L compared with 2.31 μg/L with a range of 1.00–158.65 μg/L for plasma.[271]

General Population

The average serum and whole blood cobalt concentrations in the general population without occupational cobalt exposure is ~0.2–0.5 μg/L. In a study of urban adolescents in Sweden, the cobalt concentration in whole blood and serum averaged 0.31 μg/L (range, <0.2–0.9 μg/L) and 0.48 μg/L (range, <0.2–1.1 μg/L), respectively.[272] In a Swedish study of 25 volunteers without occupational exposure to cobalt, the mean whole blood cobalt concentration was 0.50 μg/L (range, 0.10–1.20 μg/L); there was no difference in the whole blood Co concentration between smokers and nonsmokers.[273] In a study of trace metals in a representative sample of 441 urban, suburban, and rural northern Italian residents, the mean whole blood cobalt concentration was 0.39 μg/L with a range of 0.01–0.91 μg/L compared with 0.21 ± 0.008 μg/L (range, 0.008–0.4 μg/L)

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in serum as measured by atomic absorption spectroscopy and neutron activation analysis.[274] The mean whole blood cobalt concentration in 110 healthy urban residents in Rome was 0.12 ± 0.08 μg/L with a 95% CI 0.03–0.25 μg/L as measured by sector field/inductively coupled plasma/mass spectrometry.[275] The corresponding mean serum concentration was 0.19 ± 0.11 μg/L with a 95% CI 0.06–0.42 μg/L.

Therapeutic Use

In a study of four volunteers ingesting a liquid supplement containing 400 μg cobalt daily for 15–16 days, the whole blood cobalt concentrations at the end of the study were 1.8, 2.6, 4.7, and 5.1 μg/L (mean = 3.6 μg/L) as measured by inductively coupled plasma/mass spectrometry.[276] No adverse effects were reported. In a follow-up study of five women and five men receiving 1 mg Co in the form of liquid $CoCl_2$, the mean whole blood cobalt in men was 20 μg/L (range, 12–33 μg/L) compared with 53 μg/L (range, 6–117 μg/L) in women.[277] The mean serum Co concentrations were 25 μg/L (range, 15–46 μg/L) and 71 μg/L (range, 9–149 μg/L), respectively, in men and women. There were no clinically significant changes in biochemical or hematological tests; the T_4, TSH, hemoglobin, creatinine, and liver enzymes remained within normal ranges. The administration of 500 μg soluble $CoCl_2$ to 12 male volunteers produced a mean whole blood cobalt concentration of 2.0 ± 1.6 μg/L (90% range, 0.5–3.0 μg/L) at the end of the 10-day study compared with 7.55 ± 7.48 μg/L (90% range, 1.12–10.77 μg/L) in 11 female volunteers.[62] For 12 men receiving the 500 μg insoluble CoO, the mean whole blood Co concentrations were 0.20 ± 0.18 (90% range, 0.10–0.30) compared with 0.67 ± 0.3 μg/L (90% range, 0.20–1.01 μg/L) in 11 female volunteers. Fourteen hemodialysis patients received 25 mg cobaltous chloride daily for 4 weeks, then 50 mg daily for 4 weeks.[59] At the end of the clinical trial, the pre-dialysis serum cobalt concentrations ranged from 220–2,100 μg/L as measured by atomic absorption spectrometry. Three of the patients developed transient hearing loss detected by audiometry; there was no deafness, tinnitus, or hypothyroidism (i.e., baseline TSH concentration unchanged). Elevated whole blood cobalt concentrations may persist in hemodialysis patients treated with cobalt chloride. In a series of seven dialysis patients treated 13–20 months earlier with cobalt chloride, the whole blood cobalt concentration ranged from 3.1–138 μg/L (median, 6.7 μg/L) as measured by neutron activation analysis.[126] The median whole cobalt concentration in seven dialysis patients without cobalt treatment was 1.4 μg/L with a range of 0.9–3.9 μg/L.

Acute Toxicity

A 6-year-old boy drank a solution containing an estimated 2.5 g cobalt chloride; he developed abdominal pain and vomiting, but he was released 48 hours after admission without sequelae.[46] His serum cobalt concentration ~7 hours after ingestion was 426.6 μg/L (whole blood, 237.2 μg/L; method not reported). Two weeks later, the serum cobalt concentration decreased to 12.7 μg/L (whole blood, 8.9 μg/L). Approximately 4 weeks after the ingestion, the serum and whole blood cobalt concentrations remained ~5-fold above the upper reference range at ~5 μg/L. A 14-year-old girl presented to the emergency department ~12 hours after the ingestion of cobalt chloride from a chemistry set; she had vomited spontaneously several times before admission. Her serum cobalt concentration on admission was 77.9 μg/L as measured by atomic absorption spectrometry.[45] Her vital signs remained stable and asymptomatic; she recovered without sequelae after receiving supportive care and three doses of $CaNa_2EDTA$.

Metallic Prostheses

A variety of factors influence the metallic ion concentrations in patients with prostheses including implant material/design, position of implant, diameter of the bearings, and implant type. No single biomarker is specific for the development of adverse local tissue reactions following metal-on-metal (MoM) total hip arthroplasty; similarly, the blood cobalt/chromium ratio does not correlate closely with adverse effects.[278] The cobalt and chromium (but not molybdenum) concentrations in blood samples from patients with long-term MoM total hip prostheses substantially exceed values for the general population; however, correlating these values to the prevalence of adverse effects in patients with hip prostheses is a complex process including the determination of the existence of a threshold.[279] Some patients with high initial serum cobalt concentrations (e.g., 49 μg/L) during the running-in period may remain asymptomatic, and their serum cobalt concentrations return to more normal concentrations (e.g., 1.6 μg/L) after several years.[280] Postoperative cobalt concentrations usually stabilize over 6 months after a period of variability. An observational, non-randomized cross-sectional study analyzed intraoperative plasma, synovial, and CSF samples from 461 patients undergoing primary (controls) or revision hip/knee arthroplasty.[281] The cobalt concentration was quantifiable (>0.3 μg/L) in 42% of controls (range, 0.30–6.79 μg/L, $n = 106$), 76% of well-functioning implants (range, 0.30–27.67 μg/L, $n = 107$), and 98.5% of hip revisions (0.34–32.21 μg/L, $n = 64$). The reported CSF cobalt concentrations

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were <1% of the synovial fluid adjacent to the joint replacements and <15% of plasma.

Total plasma or serum cobalt concentrations probably reflect both metallic cobalt wear nanoparticles along with free and protein-bound soluble cobalt ions, whereas erythrocyte cobalt reflects the free ionized cobalt (e.g., Co^{2+}) entering the erythrocytes during the lifespan of the red blood cells. Current data suggests that serum cobalt and chromium concentrations are useful biomarkers of excessive wear, localized tissue effects, and potential failure of hip implants when correlated to imaging (plain radiographs, metal artifact reduction sequence MRI, ultrasound) and clinical symptoms (localized pain, grinding sensation with activity, clicking with ambulation).[282]

Metal Concentrations Cobalt toxicity in patients with hip prostheses is a clinical diagnosis based on a constellation of clinical features including hip pain; there are no pathognomonic signs/symptoms of cobalt toxicity. The blood cobalt values must be interpreted in relation to the clinical presentation as the blood cobalt concentration alone is not pathognomonic of cobalt toxicity. Most patients have well-functioning joint implants with serum cobalt concentrations in the range of 2–3 μg/L; however, electrochemical corrosion and wear occur in all metallic joint replacements, resulting in the release of chemically active metallic ions and oxidative stresses on the prosthetic joint. The extent of elevated blood cobalt concentrations depends on a variety of factors including wear and alignment, corrosion, alloy composition, type of implant, renal function, analyticic method, type of sample (serum, whole blood), and femoral head size.[283] Although blood cobalt concentrations are usually elevated in the presence of adverse local tissue reactions (pseudotumors, necrosis, inflammation) and most of these patients demonstrate excessive wear on their implants, the high degree of variability of blood cobalt concentrations between these patients limits determination of a dose-response between wear, blood cobalt concentrations, and local tissue reactions.[284] In a study of 156 consecutive patients with a unilateral ASR XL total hip replacement and plasma cobalt concentration of >5 μg/L, the plasma cobalt concentration correlated to the presence of periprosthetic lucency on radiographs and pseudotumor on magnetic resonance imaging ($P < 0.05$), but not to the patients' symptoms.[285] All patients with high blood cobalt concentrations and high wear do not develop adverse reactions;[286] blood cobalt concentrations may be very elevated (e.g., >300 μg/L) in the absence of systemic toxicity.

In patients with well-functioning hip implants, an initial rise in metallic ion concentrations occurs during the first 1–2 years (i.e., "running-in" or "bedding-in" phase), followed by a steady-state phase with much-reduced wear rates and some reduction in blood cobalt concentrations.[175,287] In a 10-year prospective follow-up study of 10 patients with well-functioning metal-on-polyethylene total hip replacements, the mean serum cobalt concentration was ~3 times higher than baseline as measured by high-resolution sector field/inductively coupled/plasma mass spectrometry.[288] An analysis of 43 studies representing 16 different MoM implants with at least a mean follow-up of 1 year demonstrated average (mean or median) total cobalt concentrations in whole blood of 0.7–3.4 μg/L compared with 0.3–7.5 μg/L in serum.[289] This study did not detect any clear difference in chromium concentrations between the different implants; exclusion criteria included single case reports and bilateral implants.

Studies of patients with MoM implants undergoing revision of hip arthroplasties mostly for malposition of the hip replacement indicate that serum cobalt concentrations are an order of magnitude above reference values in these patients, whereas the elevation of serum chromium concentrations is significantly less. Most blood cobalt concentrations in patients with well-functioning MoM hip prostheses are 1–10 μg/L. After substantial increases (e.g., up to 1–7 Co μg/L) during the running-in period during the first 6–12 months after implant,[280] the cobalt concentration stabilizes without evidence of continuing accumulation as long as the implant remains well-aligned without excessive wear.[290] In a 5-year prospective study of 50 patients with Metasul® MoM total hip arthroplasty (Zimmer Biomet Warsaw, IN), the median serum cobalt concentration at 1 year was 1 μg/L compared with 0.7 μg/L at 5 years.[291] The highest serum cobalt concentration in 10 patients with a minimum of 5-year follow-up after metal-on-metal total hip replacement was 7.93 μg/L (median, 1.55 μg/L)[292] compared with 50.1 μg/L (median, 0.75 μg/L) in 22 patients followed a minimum of 10 years as measured by atomic absorption spectrometry.[293] The patient with maximum serum cobalt concentration of 50.1 μg/L had groin pain and an osteolytic lesion behind the acetabular component; she underwent implant head and liner exchange with the serum cobalt decreasing to 0.8 μg/L 5 months postoperatively.

The blood cobalt concentrations are typically lower in patients undergoing knee or ceramic-on-ceramic hip replacements than with MoM hip implants having similar length of the implant and wear. In a study of 41 patients with cemented unconstrained unilateral total knee arthroplasty without patellar resurfacing

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implanted a median of 66 months prior to analysis, the median serum cobalt and chromium concentrations were 3.28 μg/L (maximum <8 μg/L) and 0.92 μg/L (maximum ~9 μg/L), respectively.[294] The implants had no evidence of excessive wear or osteolysis. The serum cobalt concentrations in the study group were ~10-fold higher than the control group. By comparison, the mean serum cobalt concentration in 28 patients followed for an average of 27 months (range, 16–49 months) after unilateral ceramic-on-ceramic (Co–Cr stem, short Ti modular-neck) total hip replacement was 1.21 μg/L (range, 0.8–2.0 μg/L).[295] All hip replacements were well-functioning.

The concentration of these metals in joint fluid is 1–2 orders of magnitude above serum concentrations. In a study of 26 patients undergoing revisions of hip replacement, the median serum cobalt and chromium concentrations were 5.8 μg/L and 13.2 μg/L, respectively.[296] The median ratio of joint fluid/serum concentration for cobalt was 36.5 (range, 8.3–699.1) and for chromium was 47.4 (range, 10.5–394.4). In this study, serum cobalt concentrations exceeding 19 μg/L (and serum chromium concentrations >17 μg/L) suggested the presence of metallosis. The serum cobalt concentration was below the limit of detection (0.3 μg/L) in all 50 patients with ceramic-on-polyethylene articulations. In this series, a patient with end-stage renal disease had a serum cobalt concentration of 119.2 μg/L compared with a mean serum Co concentration of 12.5 μg/L (range, <0.1–51.6 μg/L) in five patients with renal failure and no evidence of excessive wear or osteolysis.[297]

In a study of 132 patients with MoM implants followed for a mean of 7 years (range, 5–11 years), the median whole blood Co concentration remained relatively stable 4–5 years after implant near 2 μg/L (range up to ~4 μg/L).[298] Long-term studies (i.e., up to 36 years) indicate that these elevated values persist throughout implantation with the whole blood cobalt concentration becoming grossly elevated when excessive wear and osteolysis of the loosened implant occurs.[299,300] The whole blood cobalt concentration in 15 patients implanted with the Metasul® MoM prosthesis with a mean of 2.8 years (range, 2–4 years) prior to analysis, the mean cobalt concentration was 4.1 ± 1.5 μg/L (range, 1.3–6.3 μg/L) compared with 0.3 ± 0.1 μg/L in individuals with similar ages and without implants, as measured by electrothermal/atomic absorption spectrometry with Zeeman background correction.[301] The whole blood chromium concentration was similar between the two groups.

Clinical Correlation Clinical data correlating cobalt concentrations in the blood primarily involve case reports; therefore, the relationship between the prevalence of adverse effects in patients with MoM implants and elevated serum cobalt concentrations is not well-defined. Furthermore, existing serum cobalt data do not correlate closely with patient complaints because symptoms vary significantly between individuals. The UK Medicines and Healthcare Products and Regulatory Authority recommended whole blood cobalt and chromium concentrations of 7 μg/L as a value of concern for the potential development of local reactions and excessive wear from MoM hip prostheses;[302] this cutoff has moderate sensitivity and specificity. Blood ion concentrations alone are not the sole indirect screening test for the surveillance of symptomatic patients with MoM prostheses; reducing the cutoff increases sensitivity while decreasing specificity. In a retrospective review of 209 symptomatic patients with unilateral MoM hip arthroplasties, the median plasma cobalt concentration was 4.2 μg/L (range, 0.4–335.4 μg/L).[303] Using metal artifact reduction sequence MRI scans as the gold standard, the cutoff of 7 μg/L had a sensitivity of 57% (positive predictive value, 52%) and specificity of 65% (negative predictive value, 69%). Although the plasma cobalt concentration helps discriminate well-functioning from failed hip replacements, the plasma cobalt concentration does not reliably predict periarticular soft-tissue damage at the time of revision surgery. In a pair-matched, case-control study of 88 cases with a pre-revision, unexplained failed unilateral MoM hip implant and 88 matched controls with well-functioning unilateral MoM hip replacements, the sensitivity of a 7 μg/L cutoff for detecting a preoperative, unexplained failed MoM hip replacement was 52% with a specificity of 89%.[304] Lowering the cutoff to 5 μg/L increased the sensitivity to 63% while lowering the specificity to 86%.

Many patients with elevated serum cobalt concentrations and excessive wear of hip MoM implants have no or minimal (myalgias, fatigue) symptoms. In a retrospective review of 39 patients consulting medical toxicologists about the toxicological effects of hip implants, 11 patients had elevated cobalt and chromium concentrations without complaints; the maximum serum cobalt concentrations in this group were 132 μg/L.[187] The serum concentrations of these metals do not correlate well with systemic symptoms including neurological effects. The contribution of cobalt to these symptoms remains unclear because of the lack of symptoms in other arthroplasty patients with similar cobalt concentrations; however, cobalt toxicity is unlikely to occur in patients with well-functioning hip prostheses and low blood cobalt concentrations (<4 μg/L).[305]

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Classic features of severe cobalt toxicity include hypothyroidism, polycythemia, cardiomyopathy, hearing/visual impairment, and polymyopathy. Rare case reports associate cardiac (e.g., dyspnea, heart failure) and neurological symptoms (e.g., myalgias, weakness, fatigue, metallic taste, cognitive decline) with dramatically elevated serum cobalt and chromium concentrations in patients with MoM total hip arthroplasty and periprosthetic inflammation.[184,306] These case reports typically occur following the revision of fractured ceramic prostheses with metal implants and the development of extremely high blood cobalt concentrations (i.e., >250–300 μg/L). Revision with MoP implants usually does not result in significantly elevated blood cobalt concentrations unless complicated by the retention of ceramic fragments and excessive wear. Rarely, corrosion of the modular head-neck junction of the MoP results in local pain and modestly elevated cobalt concentrations. In a series of 10 patients with adverse local reactions to the MoP prostheses, the mean serum cobalt concentration was 9.55 ± 12.73 μg/L (range, 1.60–42.45 μg/L).[307]

The serum cobalt concentrations in patients with hip arthroplasties and classic cobalt toxicity typically are very elevated (i.e., >250–300 μg/L).[179,181] A Czech case described the development of weight loss, distal paresthesias, hyporeflexia, gait disturbances, pericardial effusion, left ventricular hypertrophy, and subclinical hypothyroidism 20 months after replacing a fractured ceramic-on-ceramic hip prosthesis with a metal-on-metal prosthesis.[308] At that time, his serum cobalt and chromium concentrations were 506 μg/L and 14.3 μg/L, respectively. With the exception of the hearing impairment, the symptoms improved during chelation therapy despite persistently high serum cobalt and chromium concentrations (i.e., 40-fold above reference values). The improvement in symptoms occurred before the replacement of the metal prosthesis with a ceramic endoprosthesis 21 months after chelation began. Retained ceramic fragments were found during the revision. Severe cobalt toxicity also occurred following excessive wear from retained ceramic fragments in a patient with a metal-on-polyethylene implant. An otherwise healthy 46-year-old man developed severe wear on a metal-on-polyethylene hip implant as a result of retained fragments from a fracture of the polyethylene-ceramic sandwich acetabular liner of his left total hip replacement; he subsequently developed hypothyroidism, pericardial effusion, and fatal cardiomyopathy despite 2 weeks of chelation therapy.[166,179] His peak whole blood cobalt and chromium concentrations during his hospitalization were 6,532 μg/L and 23.6 μg/L, respectively.

Alternate explanations (e.g., diabetes, advanced age, recent stroke, morbid obesity) potentially account for some of the symptoms (e.g., cognitive decline) in case reports of elevated blood cobalt concentrations and systemic complaints. In a case report of a 73-year-old woman with a history of MoM implant 5 years previously, her declining cognitive function and memory loss occurred with a blood cobalt concentration of 24 μg/L.[306] Her age, depression, and a stroke 7 months prior to evaluation are alternate causes of her cognitive decline. A 49-year-old flight surgeon developed neuropsychiatric symptoms (mood swings, anxiety, irritability, loss of libido, depression, tinnitus, hearing loss, tremor).[185,186] His serum cobalt concentration 36 months after MoM hip arthroplasty was 122 μg/L. Subsequently, visual flashes and diastolic dysfunction occurred within 6 months before explantation; progressive improvement in mood, neurological symptoms, and cognition followed post-explantation, but fatigue and subtle visual field deficits persisted for 2 years after explantation. A review of systemic toxicity related to metal hip prostheses indicated the systemic features of this case report were unlikely to be associated with cobalt toxicity.[163]

Hard Metal lung Disease

This disease is not usually associated with any specific blood abnormalities; however, high serum immunoglobulins or autoantibodies occasionally may develop concurrently. *Ex vivo* lymphocyte transformation tests and patch testing for delayed hypersensitivity do not reliably diagnose cobalt-associated lung disease.

Urine

General Population

In a Swedish study of 25 volunteers without occupational cobalt exposure, the mean urine cobalt concentration was 0.41 μg/L (range, 0.10–2.24 μg/L).[273] The concentration of cobalt in urine was higher in smokers (mean = 0.6 μg Co/L) than nonsmokers (mean = 0.3 μg Co/L). In the US National Health and Nutrition Examination Survey NHANES III) study, the upper 95th percentile cobalt concentration was 8.3 μg/L urine as measured by inductively coupled argon plasma mass spectrometry.[309] In the 2009–2010 NHANES IV involving a representative sample of 2,848 individuals aged 6 years and older, the upper 95% was 1.40 μg/dL with a geometric mean Co concentration of 0.37 μg/L (95% CI: 0.341–0.398 μg/L).[310] The estimated upper 95% of Co in urine samples from 189 adult male and female Danish subjects was 1.38 μg/L (23 nmol/L) and 1.86 μg/L (31 nmol/L), respectively.[311]

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Toxicity

Toxic cobalt concentrations in the urine are not well defined. The urinary Co excretion increases rapidly during the first 24 hours after exposure to large amounts of cobalt followed by a slower phase. A 33-year-old metal refinery worker sustained 40% burns from a hot, acidic mixture of nickel and cobalt salts.[312] The patient received a 5-day course of ethylene-diaminetetra-acetic acid (EDTA) beginning 24 hours after the injury; the urine cobalt concentration at the end of the first chelation was 175 µg/L. No obvious signs or symptoms of cobalt toxicity developed.

Abnormalities

Hard metal lung disease

Hard metal lung disease demonstrates the same radiographical and physiological features as other forms of interstitial lung disease except for small multiple nodules in the middle and lower lung zones that may appear initially on the chest X-ray.[199] Diffuse reticulonodular opacities or ground-glass infiltrates usually occur, particularly in the lower lung fields. In a case series of 23 patients with a pathological pattern of hard metal pneumoconiosis, the most common radiographic findings were ground-glass opacities (93%) and small pulmonary nodules (64%).[313,314] Histological features of giant cell interstitial pneumonia appeared in 17 of 20 (85%) surgical biopsies. Although giant cell interstitial pneumonia occurs in other diseases (hypersensitivity pneumonitis, usual interstitial pneumonia, sarcoidosis, nonspecific interstitial pneumonia), the presence of cannibalistic, multinucleated giant cells with a history of hard metal exposure and consistent imaging studies is characteristic of hard metal lung disease.[315] Fibrosis and honeycombing develop in advanced stages of the disease. Abnormalities on high-resolution CT scans of patients with hard metal lung disease include patchy lobular ground-glass opacities, reticulation, consolidation, centrilobular nodularity, and, in advanced disease, honeycombing.[316] Magnetic resonance imaging may reveal residual parenchymal activity before the presence of an abnormal chest X-ray.[317] Abnormalities on bronchoalveolar lavage (BAL) and transbronchial biopsy demonstrate diverse changes related to inflammation including multinucleated giant cells, fibrosis, excessive mast cells and eosinophils, and increased T cells with abnormal helper/suppressor ratios.[318] Although the presence of multinucleated giant cells is pathognomonic for hard metal lung disease, the absence of these cells in BAL does not exclude the diagnosis of hard metal lung disease.

The pulmonary changes associated with hard metal lung disease are not pathognomonic because these common abnormalities occur with other diseases including restrictive impairment, decreased diffusing capacity, resting hypoxemia, and oxygen desaturation with exercise; obstructive changes also may occur. Additionally, evidence of a restrictive impairment on pulmonary function tests may precede changes on the chest X-ray. A reduction in PaO_2 may also occur during exercise.

Neuropsychological testing of retired workers with hard metal lung disease suggests deficits may occur in encoding (allocation of attentional resources, short-term verbal memory) rather than retrieval (long-term memory) when compared with solvent and asbestos workers.[319] The presence of multiple confounders, potential selection bias, and the lack of exposure data limit conclusions regarding the effect of cobalt exposure on these neuropsychological parameters.

Hard metal asthma

Broncho-provocation tests with cobaltous chloride are the gold standard for determining the presence of hard metal asthma.[99] Positive reactions to bronchoprovocation challenges include early, late, and dual reactions. Patch and intradermal skin tests do not discriminate patients with hard metal asthma from controls in the general population.

Beer drinkers' cardiomyopathy

Hemodynamic studies of patients with beer drinkers' cardiomyopathy demonstrated low cardiac output, reduced myocardial compliance, and normal peripheral vascular resistance.[12] Elevated systolic pressure occurred in the right ventricle as a result of increased pulmonary resistance and increased left end-diastolic pressure. Although the patients frequently had sinus tachycardia, dysrhythmias were uncommon. The electrocardiograms demonstrated low voltage in the QRS segment and broad-peaked P waves with right axis deviation in the limb leads along with some nonspecific ST-T wave changes, whereas intraventricular conduction defects were rare. During the acute stages of illness, the serum bilirubin and hepatic aminotransferases were strikingly elevated along with the prothrombin time, suggesting concurrent liver disease.

Metallic hip prostheses

Elevated blood cobalt and chromium concentrations have not been associated with markers of renal dysfunction. In a cross-section study of 31 patients receiving

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MoM implants 10 years earlier, median serum creatinine concentrations, creatinine clearance, and markers of tubular (retinol-binding protein, β_2-microglobulin), glomerular function (albumin), and microtissue damage (Brush Border antigen, *N*-acetyl-β-D-glucosaminidase) were similar to controls.[320] There was no dose-effect relationship between metallic ions and renal markers. In a retrospective Mayo Clinic review of 59 blood samples with serum cobalt concentration of >4.0 ng/mL, statistical analysis indicated no correlation between serum cobalt concentrations and erythrocyte counts.[321] The median serum cobalt concentration was 8.0 ng/mL with a maximum of 108 ng/mL. Almost all these samples were drawn from patients scheduled for total hip arthroplasty revisions.

HEALTH SURVEILLANCE

Risk Assessment

The US EPA has not published a chronic oral reference concentration (RfC) or a reference dose (RfD) for cobalt; however, with the last update in 2000, the EPA is currently evaluating this metal. Based on the development of decreased iodine uptake in a 10-week, multiple-dose study in children at 0.9 mg/kg/day,[322] a calculated chronic oral RfD of 30 μg/kg/day based on uncertainty factors of 10 for human variability and 3 for database adequacy.[323] The European Food Safety Authority guidance value for cobalt in food supplements is 600 μg daily,[324] whereas the United Kingdom Expert Group on Vitamins and Minerals recommends an upper limit of 1,400 μg daily to prevent adverse effects.[325]

The ATSDR MRL (minimal risk level) chronic-duration inhalation exposure is 0.1 μg Co/m^3 based on a NOAEL of 5.3 μg Co/m^3 for decreased respiratory function (FEV_1, FVC) in a cross-sectional study of 194 diamond polishing workers.[326] The MRL for intermediate-duration oral exposure is 10 μg/kg-day based on a LOAEL of 1 mg/kg-day for the development of polycythemia in human volunteers ingesting cobalt chloride.[49]

Environmental Monitoring

Typical ambient air cobalt concentrations in occupational settings vary widely; prior to the mid-1980s, these concentrations ranged from 10–1,700 μg/m^3.[19] The current US OSHA PEL–TWA is 50 μg Co/m^3 for cobalt metal dust and fumes compared with the ACGIH recommendation for the TLV–TWA of 20 μg Co/m^3. The TLV–TWA for cobalt carbonyl and cobalt hydrocarbonyl (C_4CoO_4) is 100 μg Co/m^3. The US NIOSH established an IDLH value of 20,000 μg Co/m^3. Although exposure to cobalt dust exceeding current workplace standards may cause restrictive or obstructive (asthma) disease, exposure to cobalt dust within current guidelines does not usually produce a significant reduction in pulmonary function. In a retrospective follow-up study of 582 Swedish hard metal workers, the age-related decline in FEV_1 was within the expected range of 20–30 mL/year in healthy nonsmoking adults.[327] The exposure to cobalt was below 50 μg/m^3 with the exception of the powder production unit 8 years before the study. A preliminary cross-sectional study of active workers, who volunteered for the study in a plant producing diamond-cobalt tools, demonstrated a moderate restrictive defect in the workers exposed >5 years to cobalt concentrations exceeding 50 μg Co/m^3.[328] Data associating cobalt exposure with obstructive lung disease are less convincing. A statistically significant reduction in FEV_1 occurred in hard metal workers exposed to an average concentration of 126 μg Co/m^3, suggesting that this concentration of cobalt exposure can produce chronic obstructive disease.[329] A cross-sectional study of 46 female Danish porcelain workers associated exposure to cobalt blue dyes with small airway obstruction ($\downarrow MEF_{50}$, $\downarrow MEF_{25}$), when compared with values during a plant shutdown.[220] However, there was no clear dose-response with intensity or duration of exposure. The post-shutdown pulmonary function tests obtained a median of 29 days after the shutdown also demonstrated a statistically significant increase in PEF and FEV_1 during cobalt exposure. These changes were not responsive to salbutamol. Table 10.3 lists regulatory and recommended limits for cobalt exposure.

Biological Monitoring

The exact concentration of cobalt in the urine and serum at which the risk of adverse effects is negligible is not well defined. Biological monitoring of cobalt provides objective data for the evaluation of changes in workplace practices and personal hygiene based on the amount of cobalt absorbed by workers.

Urine

The kidneys initially eliminate cobalt rapidly, but the urinary cobalt concentration gradually rises during the workweek as a result of a slower secondary elimination phase. In high-exposure groups, other routes of

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TABLE 10.3. Guideline and regulatory limits for exposures to metallic cobalt and inorganic cobalt compounds.

Exposure Limit	Value
	OSHA
PEL–TWA[a]	100 μg Co/m^3 (metal, dust, fumes)
PEL-ceiling	None
PEL-acceptable maximum concentration (30-minute maximum during 8-hour shift)	None
	NIOSH
REL–TWA (10-hour)	50 μg Co/m^3 (metal, dust, fumes)
REL–STEL (15-minute)	None
IDLH (30 minute)	20,000 μg/m^3
	ACGIH
TLV–TWA (8-hour)	20 μg/m^3 (Co and Co salts as Co)
REL–STEL (15-minute)	None
BEI	Blood: 1 μg/mL[b] Urine: 15 μg/mL[b]
	US FDA
Bottled water allowable limit	None
	US EPA
RfC (chronic inhalation exposure)	None
RfD (chronic oral exposure)	0.3 μg Co/kg-day (Provisional)
EPA carcinogenic unit risk (oral, daily)	4.3/(mg/kg)
EPA carcinogenic unit risk (inhalation, daily)	2.4×10^{-3}/(mg/kg)[c]
MCL	None
	ATSDR
Oral intermediate (15–364 days)	10 μg/kg/day
Inhalation chronic (≥365 days)	0.1 μg/m^3

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; BEI = biological exposure indices; IDLH = immediately dangerous to life and health; MCL = maximum contaminate level; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency; US FDA = US Food and Drug Administration.

[a] Acceptable maximum 30-minute TWA during an 8-hour shift; [b] End of shift, end of work week; [c] Based on chronic inhalation study of soluble cobalt sulfate heptahydrate.

exposure (gastrointestinal, dermal) to cobalt reduce the correlation of urinary cobalt to cobalt concentration in the air.[330,331] After cessation of exposure to high cobalt doses in the work environment, the reduction of urine cobalt concentrations to values present in the general population may require weeks to months.[332] The use of multivitamins containing vitamin B_{12} may substantially increase the urinary cobalt concentration. Limited data suggest that a substantial portion of the total cobalt in urine is organic Co. Analysis of urine from five controls without occupational Co exposure demonstrated an inorganic/organic cobalt ratio of 1.3 compared with mean ratios of 2.05–2.8 in four groups of four hard metal workers with varying occupational Co exposures.[333] The analytical technique involved Chelex 100 resin chromatography with neutron activation analysis.

The correlation of urine cobalt concentration to the ambient air concentration of cobalt is variable depending on the solubility of the cobalt compound. Total urine cobalt concentration is a better measure of exposure to soluble cobalt compounds (metal, salts, hard metals) than insoluble cobalt compounds (e.g., cobalt oxides).[334] At low ambient air cobalt concentrations (<100 μg/m^3), the correlation between ambient air cobalt concentrations and urinary or blood cobalt concentrations is relatively good.[335] Studies of hard metal workers indicate that urine cobalt concentrations correlate to airborne Co concentrations. Based on the regression equations from these studies, end-of-shift, mid-week urinary cobalt concentrations of 7–15 μg/L occurred following exposure to airborne Co concentration of 20 μg/m^3, whereas airborne cobalt concentrations of 100 μg/m^3 correlated to an upper 95% cobalt concentration of 59–78 μg/L in end-of-shift, mid-week urine samples.[336] The use of dust respirators by 25 of the hard metal workers reduced the urine cobalt concentration by ~85%. Exposure of 26 hard metal manufacturing workers to a TLV–TWA of 100 mg Co/m^3 resulted in an average, end-of-week urine Co concentration of ~60 μg/L.[337] Smoking and alcohol consumption did not significantly affect the urine concentration of cobalt.[71]

A study of 122 cobalt refinery workers and 10 cemented tungsten carbide production workers exposed to the maximum PEL–TWA (50 μg Co/m^3) suggests ~32 μg Co/g creatinine post-shift Monday urine correlates to a soluble cobalt exposure at the maximum PEL–TWA.[334] The types of exposure were as follows: metallic cobalt, 35; cobalt salts, 2; and cobalt oxides, 15. In a review of data on workers exposed to soluble cobalt salts, the average urine cobalt concentration in post-shift-end-of-the-week samples following exposure to cobalt TWA airborne concentrations of 20 μg/m^3

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and 50 μg/m^3 were 18 μg Co/g creatinine and 32 μg Co/g creatinine, respectively.[338]

The ACGIH recommends a BEI of 15 μg Co/L urine at the end of shift at the end of the workweek. Workers sensitized to cobalt may react to concentrations of cobalt much lower than non-sensitized workers. A cross-sectional study of 249 Belgian cobalt production workers did not detect any abnormal thyroid (serum TSH, free T_3, or T_4) or red cell parameters; the median urine cobalt concentration during the end of the fourth or fifth workday was 39 μg/g creatinine with a range up to 204.3 μg/g creatinine.[339]

Blood

Studies of hard metal workers suggest some correlation between blood cobalt concentrations and airborne Co concentrations. Based on the regression equations from these studies, airborne cobalt concentrations of 100 μg/m^3 correlate to an estimated upper 95% limit of whole blood cobalt concentrations of 5.7–7.9 μg/L.[336] The use of dust respirators by 25 of the hard metal workers reduced the whole blood cobalt concentrations by ~60%. A study of 40 cobalt foundry workers suggested that cobalt exposure to 50 μg/m^3 was associated with a mean serum concentration of ~2.5 μg Co/L.[340] The study did not report the solubility of the cobalt salts. A cross-sectional study of 249 Belgian cobalt production workers did not detect any abnormal thyroid (serum TSH, free T_3, or T_4) or red cell parameters; the median blood cobalt concentration during the workday was 1 μg/L with a range up to 32 μg/L.[339]

Medical Screening

The preplacement examination should focus on the evaluation of the respiratory tract (interstitial disease, asthma), skin, blood (polycythemia), and thyroid (thyromegaly). Laboratory examination should include chest X-ray and complete pulmonary function tests. Table 10.4 lists guidelines for the surveillance of hard metal workers. The specific guidelines necessary to monitor workers depend on the amount of exposure to dust from hard metals. Workers should be observed for the development of skin sensitization, hypersensitivity pneumonitis, and occupational asthma. Such workers should be referred to appropriate specialists for allergy testing. The development of interstitial lung disease (e.g., progressive reduction in pulmonary diffusion) in a worker exposed to cobalt indicates the need to terminate the exposure.

TABLE 10.4. Suggested guidelines for health surveillance of hard metal workers. (Adapted from Sabbioni et al.).[318]

Guideline	Examination
Pre-exposure clinical assessment	History/physical examination
	Clinical Lab: (CBC with differential, renal function)
	Lung function: spirometry, carbon monoxide diffusing capacity
	Methacholine challenge, if indicated
	Electrocardiogram
	Chest X-ray
	Urine cobalt concentrations (spot sample)
	Symptom questionnaire
Periodic assessment	History/physical examination (yearly)
	Lung function tests (yearly)
	Chest X-ray (every 3 years)
	Urine cobalt concentration (post-shift, end-week sample every 6 months)
	Symptom questionnaire (yearly)
Symptom questionnaire	Within the last year, have you had the following persistent symptoms:
	Nonproductive cough (during/after work)
	Sudden shortness of breath (during/after work)
	Shortness of breath with exercise
	Repeated episodes of mild fever or night sweats
	Unintentional weight loss
	Fatigue
	Skin rash
	Do you relate any of these symptoms to the workplace

TREATMENT

Treatment is primarily supportive. Cobalt chloride is a gastrointestinal irritant; most significant ingestions produce vomiting, and decontamination measures are usually unnecessary.

Chelation

Acute Toxicity

Clinical data on the efficacy of specific chelation agents are inadequate to determine guidelines for the use of

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these agents in acute cobalt intoxication.[341] Although the administration of $CaNa_2EDTA$ or NAC has reduced blood cobalt concentrations in single case reports, the use of these chelators depends on a careful analysis of risk, benefit, and the expected clinical course. A 14-year-old adolescent presented to the emergency department 12 hours after ingesting cobalt chloride and vomiting several times. Her serum cobalt concentration at admission was 7.8 μg/L.[45] After three intravenous doses of 1 g $CaNa_2EDTA$ during the next 10 hours, her serum cobalt concentrations decreased to 0.7 μg/L. She remained asymptomatic with stable vital signs. The case report included no clearance data. An experimental study of seven patients on chronic bimonthly EDTA chelation therapy and nine patients recently receiving EDTA chelation therapy reported no increased urinary cobalt excretion within the first 4 days after an infusion containing 89 μg Co.[342] Methodological flaws in the design of this study (e.g., no controls, lack of reporting on statistical analysis/kidney function/limits of quantitation, self-collection of urine samples) prevent determination of the influence of EDTA chelation of renal Co excretion.

Rat experiments suggest five daily chelation doses increase cobalt excretion following the administration of *N*-acetylcysteine (↑urine/fecal), EDTA (↑fecal), diethylenetriaminepentaacetic acid (↑urine, DTPA), and DMSA (↑fecal).[343] However, few human data confirm the clinical efficacy of these chelation agents. In a study of cobalt chloride intoxication in Sprague-Dawley rats, *N*-acetylcysteine administered immediately after the oral administration of an LD_{50} dose of cobalt chloride did not reduce mortality in the rats compared with controls (no antidote).[344] There are inadequate data to suggest any other regimen than standard doses of these chelating agents.

Hip Prostheses

There is no consensus on the treatment of elevated blood cobalt concentrations in patients with cobalt-containing hip prostheses including the use of chelation.[345] The UK Medicines and Healthcare Products and Regulatory Authority recommends a whole blood concentration of 7 μg/L as the level of concern for potential local reactions to metal-on-metal (MoM) cobalt-containing hip prostheses.[302] Actions recommended for patients above this value include whole blood cobalt analysis every 3 months and consideration for revision if the whole blood cobalt concentrations continue to rise. The US FDA does not recommend actions at a specific cobalt concentration in blood. The decision to replace the MoM prosthesis depends on clinical judgment based on symptoms, clinical course, cobalt concentrations, imaging (metal artifact reduction sequence magnetic resonance imaging, ultrasound), and orthopedic consultation.[346]

Asymptomatic Patients

Elevated blood cobalt concentrations in asymptomatic patients should be evaluated to exclude contamination and the ingestion of cobalt-containing compounds (supplements, medications). The specimens should be collected in metal-free collection tubes, analyzed by laboratories with substantial experience with metals, and serial analyses performed using the same laboratory and collection methods. Two asymptomatic patients with total hip replacements and elevated blood cobalt concentrations (i.e., 16.06 μg/L, 20.24 μg/L) received 100 mg *N*-acetylcysteine/kg/day for 10 days without complications.[347] The blood cobalt concentrations decreased by 86 and 45% from pre-chelation concentrations; however, the blood cobalt concentration rebounded in the latter patient and both patients were chelated after the cobalt concentrations were significantly declining from peak concentrations. The report did not document clearance rates.

Symptomatic Patients

Symptomatic patients with elevated blood cobalt concentrations should be referred to their orthopedist for evaluation of excessive wear with orthogonal plain-film radiographs of the hip; ultrasound and metal artifact reduction sequence MRI are indicated if the orthopedist suspects a malfunctioning hip prosthesis. Clinical laboratory examination in symptomatic patients includes complete blood count with differential, C-reactive protein, erythrocyte sedimentation rate, serum creatinine, blood urea, serum electrolytes, liver enzymes, total bilirubin, serum albumin, pro-time, and thyroid-stimulating hormone.

As in acute cobalt intoxication, there are inadequate data to recommend a specific chelator and when to administer the chelating agent to patients with hip prostheses and elevated blood cobalt concentrations. The decision to use chelation (NAC, $CaNa_2EDTA$, DMPS) depends on clinical judgment and a careful evaluation of the risks, benefits, the severity of symptoms, and the expected clinical course.

A 58-year-old woman developed visual loss, hearing impairment, generalized weakness, and sensory loss after replacement of her broken ceramic–ceramic coupling with a Co–Cr head.[348] She received weekly EDTA chelation during the 2 months before replacement of the hip prosthesis. Some rebound in plasma and whole blood Co concentrations occurred between chelations.

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The plasma cobalt concentration decreased from ~280 to ~100 μg/L during this time, whereas the whole blood cobalt concentration decreased from ~600 μg/L to slightly <200 μg/L. The case report did not discuss the clinical course of the neurological symptoms or provide pharmacokinetic data to determine the amount of cobalt removed by EDTA chelation. Other case reports suggest the potential use of *N*-acetylcysteine[349,350] and DMPS;[308] however, results are variable and difficult to compare with the natural course of blood and urinary cobalt concentrations post-explantation, particularly when the blood and urinary cobalt concentrations remain extremely high despite chelation therapy. The definitive treatment for symptomatic patients with high blood cobalt concentrations is a revision of the hip prosthesis.

Supportive Care

Management of hard metal lung disease is also supportive following removal from exposure. Although several case reports document improvement following steroid therapy,[199] there is no proven pharmacological treatment for hard metal lung disease. Improvement in patients with hard metal lung disease occurred following the administration of corticosteroids (40–60 mg prednisone daily)[199] and cyclophosphamide (25 mg twice daily),[224] but these case reports do not confirm the effectiveness of these agents. Several patients with hard metal lung disease received lung transplants;[205] however, one patient developed recurrent lung disease in the transplanted lung.[351]

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Chapter 11

COPPER

HISTORY

The cold working of native copper existed during the 9–7th millennia BC in western Iran and Anatolia.[1] Smelting became common by 3,500 BC with the production of relatively pure copper from oxidized low arsenic-containing copper ores. Although copper sulfide-containing minerals contain naturally high arsenic concentrations, the roasting process releases most arsenic into the air. Even though there are only marginal differences between tin bronzes and arsenical copper, tin bronzes dominated the commercial trade throughout the European and Middle Eastern world within 300–400 years. The reappearance of arsenic-copper artifacts occurred primarily during periods of trade disruption.[2] Presumably, the preference for tin bronzes (copper/tin ratio, 9:1) reflected the prominence of chronic arsenic toxicity and the subsequent ease in establishing a causal relationship between signs of arsenic toxicity and exposure to arsenic during the smelting of copper. Near the time of Christ, Assyrian, Egyptian, and Hindu alchemists prescribed copper compounds for a variety of human aliments.[3] In the past, copper sulfate was an anthelmintic agent, an astringent, and an emetic. Currently, rare cases of copper toxicity result from the use of "spiritual green water" for religious purposes.[4] In a Spanish study of human bones from different historical epochs, the peak copper concentrations occurred in bones from the Byzantine Period, whereas the copper concentrations in bones from the Neolithic Period and present-day samples were similar.[5]

Copper contamination of food and beverages may cause an acute gastrointestinal illness. Potential sources of copper poisoning include copper or brass vessels and rarely drinking water.[6] In India, copper is a popular suicidal agent. Discontinuation of the medicinal use of copper as an emetic resulted from case reports associating copper toxicity (hemolysis, acute hemorrhagic necrosis of the small bowel, hepatorenal failure) with the use of copper sulfate as an emetic.[7]

PHYSIOCHEMICAL PROPERTIES

Copper is a member of the third transition series (chromium, iron, cobalt, manganese, nickel, zinc) that occupies a position between nickel and zinc in Group 11 (Group Ib) of the periodic table; copper is a noble metal similar to gold and silver. There are two stable copper isotopes, ^{63}Cu and ^{65}Cu with natural abundances of 69.2% and 30.8%, respectively. Radioactive isotopes include ^{64}Cu and ^{67}Cu, but these isotopes have very short half-lives (12.7 hours and 61.9 hours, respectively). Useful physical properties of copper for industrial applications include appearance, alloying ability, low corrosion, malleability, and high thermal and electrical conductivity. Copper does not dissolve in acidic environments unless an oxidizing agent is present; the formation of a green layer of copper carbonate over the metal limits further oxidation. Copper sulfate forms bright blue crystals that contain five molecules of water (bluestone). Table 11.1 lists the identifying information and the physical properties of copper and copper sulfate.

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TABLE 11.1. Identifying factors and physical properties of copper and copper sulfate.

	Copper	Copper Sulfate
Synonyms	Metallic copper	Copper sulfate; blue, Salzburg, or Roman vitriol; blue copperas
Chemical formula	Cu	$CuSO_4$
Molecular weight (g/mol)	63.546	159.61
Valence	0	+2
CAS RN	7440-50-8	7758-98-7
Color	Reddish	Blue
Physical state	Solid	Solid (crystals)
Odor	Odorless	Odorless
Boiling point (°C)	2567	650 (decomposes to CuO)
Melting point (°C)	1083.4	>200 (decomposes slightly)
Density (g/mL)	8.92	3.603 2.284 (pentahydrate)
Water solubility (g/dL)	Insoluble	320 (20°C)

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.

In the environment, copper usually occurs in the cupric (Cu^{2+}) state as well as in the 0, +1, +2, and rarely +3 valence states.[8] Cuprous ions (Cu^{+}) oxidize rapidly in aqueous solutions to cupric (Cu^{2+}) compounds and disassociate to metallic copper (Cu^{0}). Only insoluble cuprous compounds (e.g., CuCl) are stable in water. Divalent cupric oxide (Cu^{0}) is also insoluble in water; however, many other cupric compounds are soluble in water. Dissolution of these compounds in water frequently causes a blue or green discoloration of the water. The taste threshold of copper in water ranges ~1–5 mg/L; a slight blue-green color appears in the water when copper concentrations exceed 5 mg/L.[9]

Copper binds to metallothionein in the cuprous (Cu^{+}) state; cupric ions (Cu^{2+}) require reduction to cuprous ions prior to transport on metallothionein. Metallic copper is sparingly soluble in water, salt, and mildly acidic solutions, but strong acids (nitric, sulfuric) and basic solutions (ammonium hydroxide) dissolve this metal easily. Acidification of water increases the amount of copper leached from copper piping.[10] Copper sulfate is a strong oxidizing agent with an acidic pH (i.e., ~4) in concentrated solutions. Copper ions can oxidize hemoglobin to methemoglobin. Cupric ions bind easily to oxygen in organic ligands; organic compounds complex almost all copper present in the environment.[11] Cu^{3+} is a strong oxidizing agent that is not important industrially or environmentally.[12] Copper comprises about 40% of the mass of copper sulfate. Copper naphthenate is poorly water soluble, but highly lipophilic with moderately low volatility.

EXPOSURE

Production Process

The most important copper ores are chalcocite (Cu_2S), chalcopyrite ($CuFeS_2$), and malachite [$CuCO_3 \cdot Cu(OH)_2$]. Copper content of ore deposits ranges from 0.5–5% Cu by weight, whereas igneous and crystalline rock typically contain 0.01% and 0.0055% Cu by weight, respectively.[8] Other copper ores include azurite and bornite. Following the mining of the ore, the material is concentrated by crushing and flotation. Leaching of the remaining ore occurs followed by extraction of the remaining copper with ion exchange or solvent extraction. The smelting of chalcopyrite produces metallic copper via a two-stage process: 1) slag-forming stage – formation of iron oxides by oxidation of FeS and the subsequent combination of iron oxides with silica flux to form a slag and 2) copper-producing stage – oxidation of CuS_2 to form SO_2 and Cu^{0}. Copper sulfate is a by-product of copper production during the leaching of the ore with sulfuric acid. Metallic copper is the basis for most industrially important copper compounds; most copper metal is recycled.

Uses

Commercial

The primary use of copper is as a metal or as an alloy (brass, bronze, gun metal, Monel metal). Most metallic copper appears in electrical applications in construction, machinery, transportation, and ordnance, accounting for ~25% of Cu production. Agricultural uses (fungicides, algicides, nutritional supplements) account for the majority of copper sulfate production. Copper naphthenate is a constituent of fungicides and wood preservatives. Industrial uses include azo dye manufacturing, engraving, lithography, petroleum refining, water treatment, metal finishing, wood preservatives, and mineral froth flotation. Copper is a catalyst in the chemical industry and an important constituent of white gold and the newer nickel-tin and palladium alloys used for imitation jewelry.[13]

Medical

Dental applications of copper-based alloys (aluminum, cobalt, manganese, nickel, zinc) include the fabrication of dental bridges and crowns.[14] The addition of small amounts of platinum or palladium to high-copper amalgams reduces tarnish and increases durability.[15]

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Corrosion products of the copper amalgam following exposure to saliva include copper oxides, chloride oxides or hydroxides, chlorides, and sulfides.[16] These high-copper amalgams are less susceptible to corrosion compared with low-copper amalgams.

Copper is a constituent of intrauterine contraceptive devices; the release of copper from these devices is necessary for their contraceptive effects.[17] These devices contain about 100–150 mg Cu, which is approximately equivalent to the average total body burden of copper. The wearing of copper bracelets is a folk remedy for arthritis; currently, data do not support the efficacy of this remedy.[18,19,20] Spiritual water (green water) is an African cathartic used in rituals; the ingestion of this solution may cause hemolysis, renal failure, and death.[4] Samples of spiritual water contained copper concentrations of ~13 g/L.[21]

Copper oxide nanoparticles possess physical properties capable of improving energy conservation by enhancing fluid viscosities and increasing thermal conductivity. Industrial applications include use in high-temperature superconductors, batteries, gas sensors, solar energy converters, catalytic reactions, and lubrication.[22] Potential biomedical uses for copper nanoparticles include applications as antimicrobials, biocides, and nanocomposite coatings; however, evidence of injury to the liver, kidney, and spleen in rodents following ingestion of these nanoparticles and formation of reactive oxygen species in cell lines have limited their use.[23,24]

Sources

Copper is the third most prevalent trace element in animals and plants behind iron and zinc. However, acute copper toxicity is uncommon with the development of acute copper toxicity usually resulting from the contamination of food, water, or other beverages. Chronic copper toxicity (Wilson's disease, Indian Childhood Cirrhosis, idiopathic copper toxicosis) apparently results from a combination of genetic susceptibility and high copper intake. Experimental data suggest that these infants received a mean of 900 μg Cu/kg/day when their milk was boiled in brass vessels.[25] However, these diseases may develop in breast-fed infants without obvious sources of high copper intake.[26]

Air

Average copper concentrations in the atmosphere range ~5–50 ng Cu/m^3 in rural areas and ~30–200 ng Cu/m^3 in urban areas, depending on proximity to point sources (incinerators, power plants, smelters) of copper emissions.[12] A study of the air in several US industrial cities demonstrated fine (<1–2.5 μm) and coarse (2.5–10 μm) copper concentrations ranging <0.1–1,610 ng/m^3 and <0.1–224 ng/m^3, respectively.[27] Emission of copper into the air represents only a small fraction (i.e., ~0.4%) of the copper released into the environment; [28] these emissions result from both natural (windblown dust, volcanoes, forest fires, sea spray) and anthropogenic (nonferrous metal production, copper smelters, iron and steel production, municipal incinerators) sources.[29] In general, combustion processes produce copper in the form of fine particles (<1 μm) of oxides and elemental copper, whereas copper released from particulate matter (windblown dust) exists primarily as large particles (<10 μm) of copper compounds (carbonate, oxide, sulfate).[30] Airborne sampling at a distance of 13 km from a copper smelter in Chile demonstrated average copper concentrations for fine (<2.5 μm) and coarse (2.5–15 μm) copper particles of 66 ng/m^3 and 131 ng/m^3, respectively.[31] During the suspension of operations during a strike, the mean copper concentrations were 22 ng/m^3 and 50 ng/m^3, respectively.

Soil

The natural concentration in soil is ~6–80 ppm Cu (median ~25–30 ppm) by dry weight with higher concentrations near point sources.[8] Copper in tailings from copper mines and mills usually exists in the form of insoluble sulfides and silicates. Most of this copper is incorporated into mineral lattices; therefore, this copper is biologically inert. Accumulation of copper in soil may result from the application of copper-containing fertilizers or fungicides. An analysis of copper in US agricultural soil ranged from 0.3–495 mg/kg with the highest samples reflecting the use of copper fungicides and fertilizers.[32]

Water

The copper concentration in aqueous solutions depends on several factors including pH, the presence of competing cations, concentrations of compounds that complex organic and inorganic copper substances, and concentration of anions in insoluble cupric salts. The most important determinates of copper concentrations in drinking water from copper pipes are pH, the age of the system, and the standing time prior to water collection.[33] The presence of insoluble organic and inorganic copper compounds reduces the bioavailability of copper in drinking water. The median copper concentration in natural

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water is ~4–10 μg/L with most of copper tightly bound to organic matter and not readily exchangeable.[12] Cuprous (Cu^+) ions are unstable in aqueous solutions unless the cuprous ion is present as an insoluble salt (e.g., Cu_2S, CuCN, CuF, CuCl). Most ionizable copper in aqueous solutions exists in divalent form.[34]

The average copper concentration in a study of runoff from 19 cities in the United States ranged from 1–100 μg/L with a geometric mean of 18.7 μg/L.[35] The majority of copper in water results from the natural run-off of copper from soil.[12] Municipal treatment facilities remove ~80% of the total copper in pre-treatment water; the copper concentration in effluent is usually <100 μg/L.[36] Dissolved and total copper concentrations in the water from 11 tributaries feeding Lake Michigan ranged 0.2–2.0 μg/L and 0.4–5.5 μg/L, respectively.[37] The acidity of the water affects the concentrations of copper leaching from point sources. In water discharged from a mine with large sulfide deposits, the copper concentration was below detection limits at pH >5.[38] Dissolved copper concentrations ranged from 0.12–13.5 μg/L at pH 3–4; the copper concentration at pH 2.4 was 190 μg/L. Sediment is an important reservoir for copper.

Diet

Food is the major source of copper for the general population; however, copper in drinking water may contribute significantly to the daily copper intake depending on the composition of the distribution lines and natural sources. The estimated mean daily intake of copper in the US population is <2 mg[39,40] compared with 0.8–1.8 mg with the estimated upper 90 percentile ranging from 1.1–2.2 mg in European populations.[33] A study of 11 healthy adult men demonstrated that the ingestion of slightly less than 0.8 mg Cu daily was sufficient to maintain copper balance during the 42 days of the study.[41] The copper concentrations in food and beverages vary widely depending on the type of processing (i.e., use of copper vessels), growing conditions (soil, use of copper-containing chemicals), and the food product. Copper concentrations in food range from 0.2–44 ppm by wet weight.[9] Foods relatively high in copper content include cereals, mushrooms, dried fruits, legumes, whole-cereal-grain products, peanut butter, nuts, organ meats (liver), and shellfish (crustaceans, oysters). Copper concentrations in freshwater typically are low compared with seawater, where fish and shellfish harvested from the ocean floor contain higher copper concentrations than fish inhabiting shallow waters.[42] In a study of eight species of freshwater fish collected in the US National Contaminant Biomonitoring Program in 1978–1979, the copper concentration in whole fish ranged 0.25–38.75 ppm by wet weight with an average of 0.68–0.86 ppm by wet weight.[43] Meat and dairy products generally contain low copper concentrations; however, boiling milk in a copper vessel results in the binding of copper to the main milk protein (casein).[25] The acidic environment of the stomach liberates copper from the casein; this process allows the rapid absorption of copper present in milk. The acute ingestion of liquid containing concentrations >30 ppm Cu produces gastrointestinal irritation (nausea, vomiting, abdominal pain).[44]

Copper in drinking water is a relatively minor source of copper for the general population.[33] At an average concentration (0.13 mg Cu/L drinking water), drinking water contributes about 6–13% of the average daily intake of copper.[39] Copper from pipes in the water distribution system may contribute up to 1 mg Cu daily to copper intake depending on the acidity of the water, softness of the water, and the extent of copper pipes and brass faucets. The biological significance of this amount of copper depends on its bioavailability. A mail survey suggested that copper-contaminated water caused a gastrointestinal illness among residents of recently remodeled homes in an area where the water supplies were naturally corrosive.[45] However, there was no clear dose-response relationship between the copper concentration in "first draw" tap water and the presence of gastrointestinal symptoms. Water left overnight in these fixtures may contain up to 60 mg Cu/L.

Lifestyle

Alcoholic beverages typically contain low copper concentrations, and the contribution of alcoholic beverages to the total copper intake is minor.[33] A rare case reports associated copper toxicity mimicking Wilson's disease (fulminant hepatic failure, encephalopathy, rhabdomyolysis) with the chronic ingestion of multiple nutritional, weight-loss, and performance-enhancing supplements by a 32-year-old bodybuilder.[46]

Medical Use

The rate of copper loss from copper-containing intrauterine devices (IUDs) depends on the time in the body as well as the weight and surface area of the IUD.[47] Oxidation of the copper and the deposit of calcium limit the amount of copper released from the IUD. During the first month following insertion, mean doses of copper released from IUDs with a surface area of 100–400 mm^2 ranged from 26–74 μg/day.[48] Over the course of 10 years, the loss of copper from a Copper T averages ~8 μg/day for IUDs covered with calcareous deposits and 23 μg/day for devices without visible coating.[49]

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ENVIRONMENTAL FATE

Air

In the air, copper exists as particulate matter or a complex of copper and particulate matter. The fate of copper released into the atmosphere depends on particle size, wind velocity, and source characteristics. Dry disposition, rain, snow, and gravitational settling remove copper from the air. Generally, gravitational settling governs the dispersion of large particles (>5 μm), whereas dry and wet deposition remove smaller particles. Combustion produces sub-micron particles containing copper oxides that may remain in the troposphere for up to 30 days, traveling far from the source of the particles.[12]

Soil

Copper deposited in soil adsorbs strongly to clay minerals, iron and manganese oxides, and organic material. Copper usually remains in the upper few centimeters of soil. Factors that influence the fate of copper in the soil include soil composition (clay, silt, sand), distribution of organic matter, pH, oxidation-reduction potential, presence of bases in the soil, and cation exchange capacity.[8] The binding of copper to ligands in the soil is stronger than that of other metals; therefore, the movement of copper in soil is less influenced by pH compared with other metals.[50] Sandy soils with low pH possess the greatest potential for leaching copper.[51]

Water

The fate and bioavailability of copper in water depend on a variety of factors including pH, oxidation-reduction potentials, oxygen concentrations, bioaccumulation, adsorption to water contaminants (clays, metal oxides, particulate organic matter), and the presence of complexing agents (inorganic and organic ligands). The physiochemical form of copper influences these processes, particularly speciation.[8] Soluble cuprous ions are unstable in water; these ions form cupric compounds and metallic copper complexes, whereas insoluble cuprous compounds (cyanides, fluorides, sulfides) are stable in water. The divalent state (cupric) is the most common valence of copper in water; this ion commonly forms complexes with ammonia, chloride, carbonate, and hydroxide ions. The following species predominate at the following pH: cupric ion below 6; $CuCO_3$, between 6–9.3; and aqueous $[Cu(CO_3)_2]^{2-}$, ion between 9.3–10.7.[52] Copper also forms stable complexes with organic ligands (e.g., humic acids). Near the surface of sea water, almost all (i.e., up to 98%) copper appears in the form of complexes with organic compounds.[53] Sediment is an important reservoir for copper with relatively clean sediment containing <50 ppm Cu and polluted sediment containing several thousand ppm Cu.[12] Iron oxides and humic substances most frequently bind copper in sediment, and such tightly bound copper exerts little biological effects.

Bioaccumulation refers to the net uptake of copper by microorganisms, plants, or animals from sediment, soil, and water in their environment, as well as from their diet. The bioaccumulation of copper from the environment depends on the species of copper and the variety of factors listed above that affect the physiochemical form of copper.[54] The bioaccumulation of copper varies widely between different organisms and between various organs within an organism.[55] High copper concentrations may develop in certain animals and terrestrial plants that are exposed to copper with high bioavailability. However, many organisms are capable of regulating their body burden with copper. Bioconcentration within aquatic organisms refers specifically to the uptake from water. The bioconcentration factor (10–100) of copper in fish is low, but filter feeders (e.g., molluscs) possess high factors (i.e., up to 30,000).

Biomagnification of copper implies that the copper concentration increases in animals at progressively higher levels in the food chain. To date, there is no evidence of biomagnification of copper in the food chain.[56] A study of bottom-feeding fish (white suckers, brown bullheads) from two acidic New York lakes that received elevated loads of copper did not detect elevated copper concentrations in muscle tissues from these fish.[57] The average copper concentration in their muscles was 0.85 and 1.2 ppm. The ratio of copper in the food to the copper concentration in tissue (i.e., the biomagnification ratio) was <1. Similarly, evidence of bioaccumulation was not apparent in a study of fish from copper-contaminated lakes in Canada[58] or in a study of rabbits grazing on land contaminated with sewage sludge from a copper mine.[59]

DOSE EFFECT

Acute Toxicity

Humans

The adult emetic dose of copper sulfate is 0.25–0.5 g copper sulfate, expressed as Cu. Toxic copper concentrations may occur after the ingestion of doses exceeding 1 g Cu.[7] The ingestion of beverages or foods containing ≥25 mg Cu/L has been associated with acute

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gastroenteritis.[60,61] An 18-month-old child developed hemolytic anemia (Hgb = 5.6 gm/dL) and renal tubular damage (hematuria, glycosuria, proteinuria with a normal serum creatinine level) after the estimated ingestion of 3 g cupric sulfate (~120 mg elemental Cu/kg).[62] Copper sulfate is ~40% Cu by weight. Massive hemolysis and renal dysfunction developed in an adult ingesting an estimated dose of 175 g copper sulfate (70 g Cu).[63] Transient hepatic dysfunction and rhabdomyolysis occurred in an adult after ingesting an estimated 250 g copper sulfate despite chelation.[64]

Animal

In animals, the maximum tolerated dose is ~250 mg Cu/kg/day.[65] Copper ingestion exceeding this dose produces extensive hepatic centrilobular necrosis. The toxicity of copper is dependent on the animal species and the type of copper compound. Sheep are the most sensitive species,[66] whereas mice are more resistant to the toxic effects of cupric sulfate compared with rats.[67] Dogs are more susceptible to copper overload compared with humans as a result of differences in copper metabolism.[68]

Chronic Toxicity

Adults tolerate daily Cu doses of 8–10 mg for up to 12 weeks without significant toxicity including normal serum hepatic aminotransferases and biomarkers of oxidative stress.[69,70] The estimated absorption of 7.7 mg Cu after an explosion of copper azide causing multiple lacerations did not produce evidence of copper toxicity in a 55-year-old chemist.[71] The peak serum copper concentration 4 days after the explosion was 1.23 mg/L. The chronic consumption of drinking water containing excessive copper concentrations based on an early morning sample demonstrating 7.8 mg Cu/L was associated with the development of acute gastrointestinal symptoms (nausea, vomiting, abdominal pain) that resolved after cessation of drinking the contaminated water.[6]

TOXICOKINETICS

Absorption

Ingestion

The absorption of copper from the intestines depends on a number of factors including the following: 1) chemical form of copper (e.g., acetate, gluconate, and sulfate salts of copper are more easily absorbed than copper oxides);[8] 2) dietary components (fiber, fats, organic acids); 3) interaction with other metals, particularly zinc and cadmium; 4) pH; and 5) inversely proportional to the amount of copper in the stomach.[72,73] Metabolic studies suggest that copper retention is small (0.06 mg/day) following copper intake of 1.6 mg daily, whereas the retention increased (0.67 mg/day) following copper ingestion of 7.1 mg daily.[74] These values are based on evaluation of nine men on a metabolic research unit. The gastrointestinal tract absorbs ~60% of an ingested dose of ^{64}Cu as the acetate salt, but interindividual variation was large (15–97%).[75] The absorption of copper from the diet was ~65–70% of the dietary intake (~1 mg Cu/day) as measured by flame atomic absorption spectrophotometry.[76]

Animal studies indicate that most absorption of copper from the diet occurs in the small intestine where metallothionein compounds bind most Cu in the cytosol of the mucosal cells.[72] Metallothionein compounds are small, cysteine-rich proteins that store divalent metal ions (e.g., Cu^{2+}, Zn^{2+}, Cd^{2+}, Mn^{2+}). Elevated zinc concentrations enhance the formation of intestinal metallothionein, which blocks copper absorption by the formation of complexes with copper in the intestinal cells.[77] This mechanism and the potential re-distribution of copper in the liver account for the use of zinc in the treatment of Wilson's disease.[78] The amount of copper stored in the body does not affect the absorption of copper; a clinically significant reduction in copper absorption does not occur following the ingestion of zinc concentrations (<15 mg/day) near the Recommended Dietary Allowance.[79] Animal studies suggest that high dietary levels of ascorbic acid may reduce the amount of copper absorbed from the diet.[80] Metallic copper is insoluble; therefore, the absorption of metallic copper from the gastrointestinal tract is probably small. The absorption of copper from the ingestion of 275 US coins (174 pennies) was sufficient to cause fatal copper poisoning.[81]

Inhalation

Little data are available on the absorption of copper from the lungs. The occurrence of metal fume fever during the volatilization of copper metal indicates that the lung absorbs some copper, but the incidence of copper-induced metal fume fever is low because of the high temperatures required to volatilize copper.[82]

Dermal

Little data are available on the dermal absorption of copper compounds; however, case reports indicate that

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copper sulfate[83] and copper azide[71] can be absorbed through damaged skin after prolonged exposure.

Distribution

The body tightly controls copper homeostasis through a complex system of chaperone proteins and copper transporters. Following copper absorption from the stomach and duodenum, albumin and amino acids loosely bind copper during transport in portal blood. The liver releases copper attached mostly to ceruloplasmin. This α_2-globulin binds ~95% of the serum copper, whereas the remainder forms complexes with albumin and certain amino acids (e.g., histidine) in the serum.[84] The copper-albumin complex represents the toxicologically active ("free") portion of the serum copper.[85] Membrane-bound proteins (copper transporters) mediate the cellular uptake and export of copper. Within the cells, copper binds to cytoplasmic transport proteins (copper chaperones) that deliver the copper to specific cytoplasmic compartments and target proteins. Consequently, very little unbound ionic copper exists in man except in the stomach. In acute poisoning, excess copper binds to albumin rather than ceruloplasmin. The liver is the major site of deposition of copper following a large ingestion with most of the copper bound to metallothionein.

The estimated total body burden of copper is ~70 mg with ~1/3 of this amount in the liver and brain.[86] Under normal conditions, the highest copper concentrations occur in the bile, liver, brain, heart, and kidneys. However, ~50% of the total body burden of copper resides in bone and muscle because of their large mass.[87] The mean copper concentration in 35 postmortem sternum samples was 0.59 μg/g wet weight with a range of 0.18–5.17 μg/g wet weight.[88] In samples of ribs from autopsies of 19 individuals, the copper concentration was 5.1 ± 2.6 μg/g dry weight.[89] The copper content in normal adult livers ranges from ~18–45 mg/g dry weight. The liver releases large quantities of copper in the blood at concentrations exceeding 50 mg/g dry weight when liver necrosis occurs.[81] This release of large amounts of copper by the liver causes the rapid accumulation of copper in erythrocytes, resulting in the subsequent production of oxidative damage to the red blood cell. The average total body burden of copper in men ranges from ~50–120 mg.[90]

Elimination

Figure 11.1 outlines the elimination of copper from the human body. Biliary excretion is the major route of elimination for copper; animal studies indicate that little resorption of biliary copper occurs.[42,92] In volunteer studies, urinary excretion of copper accounts only for ~3% of copper absorbed from normal diets.[85] The biological half-life of copper in the blood after the ingestion of 0.29 mg ^{67}Cu ranged from 13–33 days as measured by flame atomic absorption spectrophotometry.[76]

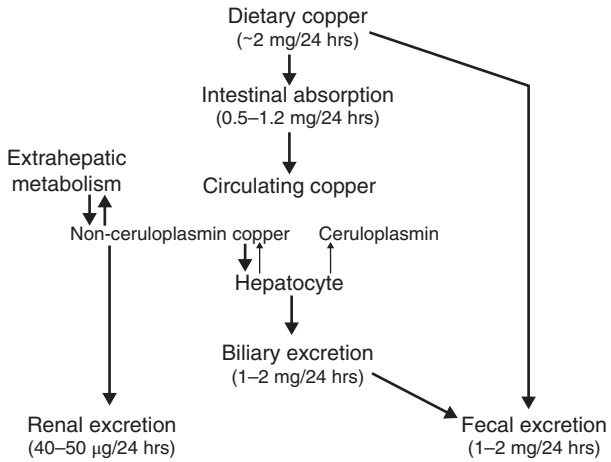


FIGURE 11.1. Elimination of copper from the human body. (Data from Schilsky).[91]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

Copper is an essential trace metal for all biological organisms from bacteria to mammalian species, where copper content ranges from parts per billion (ppb) to parts per million (ppm).[93,94] In humans, copper catalyzes processes in heme synthesis and iron absorption. After iron and zinc, copper is the third-most abundant trace element in the body. The liver is the main organ responsible for copper homeostasis with uptake of copper into the hepatocytes via copper transporter 1. Redox reactions involving copper occur in the synthesis of melanin, cross-linking of collagen, and mitochondrial respiration. A class of proteins called copper chaperones facilitates the intracellular transport of copper to copper-dependent enzymes. The copper chaperone, ATOX1 delivers copper to ATP7B (Wilson's disease protein). ATP7B facilitates the transport of copper into the trans-Golgi and holo-ceruloplasmin as well as into vesicles for export of copper into bile under conditions of copper excess. Copper is a cofactor in the redox function of a variety of cellular enzymes involved in growth and development as a result of the

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property of copper to be an electron donor or acceptor. Copper-dependent enzymes include Cu/Zn superoxide dismutase, ceruloplasmin, amine oxidase, cytochrome-c oxidase, dopamine-β-hydroxylase, tyrosinase, lysyl oxidase, peptidyl-β-amidase, *S*-adenosylhomocysteine hydrolase, and protein-lysine-6-oxidase. These enzymes regulate numerous cellular functions including oxidative phosphorylation, electron transport in the mitochondria, bioactivation of peptide hormones, melanin production, cross-linking of collagen and elastin, formation and maintenance of myelin, detoxification of free radicals, iron transport, blood clotting, and biosynthesis of catecholamines as displayed in Table 11.2.[95] Clinical manifestations of copper deficiency occur primarily in low-birth-weight infants and young children on diets with inadequate copper content; these patients have hypochromic anemia unresponsive to iron and boney abnormalities (osteoporosis, impaired/abnormal bone growth, pathological fractures) similar to scurvy.[12] Other clinical features of copper deficiency include cardiac dysfunction, increased low-density lipoprotein and decreased high-density lipoprotein cholesterol, decreased methionine and leucine enkephalins, decreased erythrocyte copper-zinc superoxide dismutase, decreased glucose clearance, and posterior cord syndrome.[96]

TABLE 11.2. Copper-containing enzymes and their functions. (Adapted from Stern).[93]

Enzyme	Function
Amine oxidases	Group of enzymes oxidizing primary amines (e.g., tyramine, histidine)
Ceruloplasmin (ferroxidase I)	Multi-copper oxidase in plasma, essential for iron transport and copper transport
Cytochrome c oxidase	Terminal oxidase enzyme in mitochondria respiratory chain, involved in electron transport
Dopamine β-hydroxylase	Involved in catecholamine metabolism, catalyzes conversion of dopamine to norepinephrine
Hephaestin	Multi-copper ferroxidase, involved in iron transport across intestinal mucosa into portal circulation
Lysyl oxidase	Cross-linking of collagen and elastin
Peptidylglycine *n*-amidating monooxygenase (PAM)	Multifunctional enzyme involved in maturation and modification of key neuropeptides (e.g., neurotransmitters, neuroendocrine peptides)
Superoxide dismutase (Cu, Zn)	Intracellular and extracellular enzyme involved in defense against reactive oxygen species (e.g., destruction of superoxide radicals)
Tyrosinase	Enzyme-catalyzing melanin and other pigment production

Mechanism of Toxicity

Under conditions of excess copper, redox cycling potentially generates unbound ionic copper, hydroxyl radicals, and oxidative damage along with the displacement of other essential metal cofactors from metalloenzymes.[97] These reactions are similar to the production of oxidative stress and cellular damage (DNA, lipid, protein) from the generation of hydroxyl radicals by the effect of Fe^{2+} on H_2O_2 (Fenton and Haber–Weiss reactions). The copper excess inhibits sulfhydryl groups on enzymes (glucose-6-phosphatase, glutathione reductase), which protect cells from damage by scavenging free radicals. Inhibition of glucose-6-phosphatase leads to hemolysis by the oxidation of the sulfhydryl groups in hemoglobin; increased cellular permeability also results from the inhibition of the Na^+/K^+ ATPase pump. Although copper toxicity is usually associated with the initiation of oxidative damage from free copper-induced reactive oxygen species, other cellular events may contribute to toxicity including alteration of cellular processes (e.g., gene expression, neuronal Cu-protein interactions, hepatic Cu distribution, ceramide release following activation of acidic sphingomyelinase, α-synuclein aggregation).[98] Case reports associate hemolysis and methemoglobinemia with the increased generation of reactive oxygen species.[99]

During acute copper poisoning, erosion of the epithelial lining of the gastrointestinal tract occurs along with centrilobular necrosis of the liver and acute tubular necrosis in the kidney. Copper causes direct damage to the proximal renal tubules, and acute tubular necrosis occurs following copper poisoning in the absence of hypotension or severe hemolysis.[100] Detoxification mechanisms for copper include reduction of copper uptake, enhancement of copper excretion, and sequestration of copper in the body. In mammals, sequestration by copper-binding metallothionein proteins and export via copper-translocating ATPases contribute to copper detoxification.[101] Metallothionein is a cysteine-rich, low-molecular-weight protein that binds to copper and provides some protection against copper toxicity. In acute copper toxicity, formation of metallothionein occurs early in the liver and kidney.[102]

Pathological Changes

Copper Poisoning

Cupric sulfate is a gastrointestinal irritant that causes erosion of the lining of the gastrointestinal tract, a striking blue-green discoloration of the mucosa, and hepatorenal failure.[103] Histological changes in acute

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copper poisoning are nonspecific. Glycogen accumulates in the nucleus and cytoplasm, resulting in fatty degeneration of the liver.[62] Hepatocellular necrosis is the predominant pathological change in the liver following copper toxicity. Copper may also accumulate in periportal hepatocytes following chronic cholestasis drug therapy (e.g., chlorpromazine).[104] Severe chronic copper poisoning has been associated with fatty metamorphosis and portal fibrosis with intralobular extension.[81] The primary changes in the kidney involve necrosis of the tubular epithelium, edema of the medulla, and occasionally the appearance of eosinophilic casts.[102] Histological changes associated with copper toxicity and intravascular hemolysis include anisocytosis, echinocytosis, poikilocytosis, pyknocytosis, intracellular precipitation of hemoglobin, microspherocytosis, and basophilic stippling.[105]

Wilson's Disease

Ceruloplasmin is a copper-containing glycoprotein synthesized primarily in the liver; the main function of this glycoprotein is a ferroxidase for the mobilization of tissue iron. Ceruloplasmin binds ~90% of serum copper. Wilson's disease is a rare autosomal recessive, inherited metabolic disease of copper metabolism that results from alterations in the gene designated *ATP7B* on chromosome 13.[106] *ATP7B* encodes a transmembrane copper-dependent ATPase located intracellularly; the ATP7B protein transports copper into the trans-Golgi network prior to incorporation into ceruloplasmin and into vesicles that merge with bile canaliculus, resulting in biliary copper excretion. A rare genetic abnormality in *ATP7B* produces chronic copper toxicity by causing a defect in a copper-transporting, adenosine triphosphatase. Low ceruloplasmin concentrations allow the accumulation of large amounts of copper first in the liver and then in the brain and other organs. Normally, the liver excretes most excess copper in the bile with very little urinary copper excretion. The incorporation of copper into the six binding domains of ceruloplasmin and the excretion of copper in the bile require the action of Wilson Cu-ATPase (ATP7B). The *ATP7B* gene resides in the trans-Golgi network of hepatocytes and contains a transduction domain (ATP hydrolysis to cation transport), a cation channel, and a phosphorylation domain, in addition to the six copper-binding domains. The accumulation of copper in the liver, brain, and other organs results from the inability of the liver to excrete copper in the bile, resulting in a progressive neurological and hepatic degenerative disorder. Low plasma ceruloplasmin concentrations and increased urinary excretion of copper characterize Wilson's disease.

Pathological changes in Wilson's disease involve cellular injury, apoptosis, and fibrosis that rarely present before age 6 years and progress to advanced stages of the disease.[107] Early changes of Wilson disease include microsteatosis, macrosteatosis, and glycogenated nuclei, along with diffuse cytoplasmic copper accumulation that is detectable only with special immunohistochemical stains for copper. Ultrastructural abnormalities include enlargement and separation of the mitochondrial inner and outer membranes, increased density and granularity of the matrix, widening of the intercristal spaces, and the presence of large vacuoles. These ultrastructural changes are characteristic of Wilson's disease in the absence of cholestasis; these changes are usually present only during the early stages of fatty infiltration.[108] Wilson's disease progresses to an intermediate stage characterized by mononuclear infiltrates, periportal inflammation, lobular necrosis, and bridging fibrosis similar to autoimmune hepatitis.[109] Mallory bodies may be present in areas of cirrhosis. Nonspecific mitochondrial abnormalities produce dense copper-containing lysosomes; however, the absence of histochemical evidence of copper excess does not exclude the diagnosis of Wilson's disease. The intermediate changes of Wilson's disease invariably progress to a micronodular or a mixed macronodular–micronodular cirrhosis in untreated patients.[91] Later, neuronal cell death occurs in the basal ganglia, cerebellum, and spinal cord.[110] Kayser–Fleischer rings are the only clinical sign unique to Wilson's disease.

Menkes Disease

Menkes disease is an X-linked disorder of copper deficiency that results from the intracellular entrapment of copper in the intestinal wall. This rare disease (1/200,000 live births) affects mostly boys and includes the following three clinically distinct copper deficiency disorders: 1) Menkes disease 2) occipital horn syndrome and 3) mild Menkes disease. Male children with Menkes disease are profoundly deficient in copper; these patients rarely live beyond the age of 3–4 years as a result of rapid central nervous system degeneration.[111] Clinical features of this disease (also known as kinky hair disease) include 1) impaired synthesis of collagen and elastin from reduced lysyl oxidase activity 2) coarse, kinky hypopigmented hair secondary to tyrosinase deficiency and poor cross-linking of keratin; 3) diffuse brain atrophy; and 4) severe mental retardation. These patients have loose skin, pathological fractures, and aortic aneurysms. The Menkes disease gene (*ATP7A*) encodes the copper-transporting P-type ATPase (Menkes disease protein).[112] This enzyme regulates the extrusion

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of copper from the cell and the transport of copper from the cytosol to copper-dependent enzymes. The relative copper deficiency associated with the inherited alteration of this gene causes mental retardation, poor temperature control, severe developmental delays, anemia, spontaneous fractures, poor bone development, and disruption of connective tissue.[113]

Indian Childhood Cirrhosis

This disease affects children living primarily in rural India who are between the ages of 6 months and 5 years. Until the 1970s, Indian Childhood Cirrhosis was a common cause of death in children in India, but now this disease is rare.[114] The reduction in the incidence of this disease was associated with a reduction in the use of brass vessels to store food and milk.[115] The disease produces elevated copper concentrations without the reduction in ceruloplasmin concentrations that accompanies Wilson's disease.[116] Typical histological changes in Indian Childhood Cirrhosis include marked degenerative ballooning of the hepatocytes, diffuse Mallory bodies, predominant neutrophilic infiltrate in acini, and a severe micronodular (pericellular) fibrosis.[117] The presence of coarse dark-brown orcein staining and intralobular pericellular fibrosis distinguishes Indian Childhood Cirrhosis from Wilson's disease.[118] The absence of steatosis and appearance of cholestasis late in the course of the disease characterize Indian Childhood Cirrhosis.

These changes probably result from the massive accumulation of copper in hepatic nuclei along with a reduction in catalase activity.[119] Unlike the treatment of Wilson's disease, lifelong treatment with D-penicillamine is unnecessary and chelation with D-penicillamine may be stopped after recovery from Indian Childhood Cirrhosis.[120] The most plausible explanation of the etiology of this disease is the excessive ingestion of copper. Indian Childhood Cirrhosis probably is a specific form of copper-associated childhood cirrhosis, which requires high concentrations of copper in the environment for full expression.[115] This disease may also represent an inherited metabolic disorder because of reports of similar cases outside the geographical area of India.[121,122,123] Rare case reports associate liver pathology (idiopathic copper toxicosis) similar to the hepatic changes reported in Indian Childhood Cirrhosis with infants residing outside India (non-Indian Childhood Cirrhosis).[124,125]

Postmortem Examination

In a postmortem examination of a 58-year-old psychiatric patient dying after the massive ingestion of US coins, extensive disruption of the liver architecture was present with ballooning degeneration, infiltration of polymorphonuclear leukocytes around necrotic cells, Mallory hyalin, and portal fibrosis with intralobular extension.[81] All hepatocytes contained cytoplasmic granules that stained positive for copper (Timm's silver sulfate, rhodamine stain), whereas the bile duct epithelium contained no copper granules. The proximal and distal convoluted renal tubules also contained copper granules. Examination of other organs was unremarkable. Postmortem examination of the liver of a 46-year-old intellectually disabled male, who died after chronically ingesting >700 copper coins, revealed extensive portal fibrosis and portal tract-central vein bridging without cirrhosis.[126] Extensive deposition of granular golden-brown pigment (copper-associated protein) appeared throughout the hepatic parenchyma. Additional findings included patchy lymphocytic infiltration, proliferation of bile ductules, and intracanalicular bile plugs. Following ingestion of copper sulfate, blue staining of the upper lips, gums, and mucous lining of the esophagus may occur.[127]

CLINICAL RESPONSE

Acute Toxicity

The clinical features of copper toxicity depend on the specific copper salt. Copper sulfate is a gastrointestinal irritant that potentially may cause gastrointestinal ulceration, liver or renal dysfunction, intravascular hemolysis, and coma.[128] Case reports of the intentional ingestion of copper sulfate document lethargy, coma, rhabdomyolysis, hemolysis, refractory hypotension, and multi-organ failure.[129] In a retrospective case series of 35 patients presenting to a tertiary care hospital with severe copper sulfate toxicity, vomiting was the most common symptom (85%), followed by diarrhea (46%), epigastric pain (43%), and melena (31%).[130] Major complications included hemolysis (69%), renal failure (51%), acute hepatitis (46%), and upper gastrointestinal bleeding (40%) with hepatic failure accounting for a majority of the deaths. Sepsis may complicate ulceration of the gastrointestinal tract.

Hepatic injury usually develops within several days after massive copper sulfate ingestion with resolution within 1 week unless hepatic failure complicates the clinical course.[64] Hemolysis typically occurs ~12–24 hours after ingestion. A 11-year-old girl died several hours after the accidental ingestion of a saturated solution of copper sulfate despite immediate transfer to medical care; her postmortem blood copper concentration of

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66 mg/L confirmed a large copper sulfate overdose.[131] A 62-year-old man with underlying myocardial disease developed hemorrhagic gastroenteritis, hemolytic anemia, and refractory hypotension after the surreptitious ingestion of copper sulfate; he died on hospital day 2 from cardiovascular failure despite intensive care.[132] Following the subcutaneous injection of copper glycinate, a 41-year-old woman developed nausea, vomiting, renal failure, and hemolytic anemia requiring multiple transfusions.[133] Despite venovenous hemodiafiltration and fresh frozen plasma, hepatic dysfunction with coagulopathy and respiratory failure with bibasilar pneumonia occurred. She survived with intensive care and intubation.

Gastrointestinal Tract

Copper sulfate is a gastric irritant that produces a metallic taste, nausea, vomiting, epigastric burning, and hematemesis beginning soon after ingestion. Nausea, vomiting, diarrhea, hematemesis, and melena also occur following subcutaneous and intravenous administration of copper sulfate.[134] Severe gastrointestinal irritation may cause perforated pyloric ulcers and diffuse bleeding from the duodenal mucosa.[135] A 2-year-old boy developed hemolytic anemia, renal failure, arrhythmias, and central nervous system depression after the occurrence of *Escherichia coli* septicemia secondary to the penetration of the intestinal wall by the bacteria.[136] The greenish-blue vomitus may discolor contaminated skin. Diarrhea is less common with melena or hematemesis occurring primarily in severe cases.[128] The liver is the initial site of copper deposition; severe acute copper toxicity may cause jaundice and centrilobular necrosis of the liver along with hemolytic anemia, hemoglobinuria, and acute renal failure.[133] In patients with chronic renal failure patients receiving excess intravenous copper from dialysis through copper tubing, an acute necrotizing hemorrhagic pancreatitis developed.[137]

Skin

The increased adsorption of copper by hair shafts causes a green hue, particularly in damaged portions of the hair. Additional changes include the loss of the cuticle and the presence of scattered micropits.[138] Corrosion of copper rings and glasses by sweat may cause greenish discoloration of the skin along with localized irritation as a result of a primary irritant reaction.[139,140] Allergic reactions to copper intrauterine devices and metallic copper are uncommon.[141] Sensitization to copper usually occurs from the leaching of copper-containing material in corrosive environments (e.g., dental amalgams, intrauterine devices).[142] Typically, these exposures produce delayed (Type IV) allergic contact dermatitis or systemic contact dermatitis. Rarely, case reports associate an allergic contact dermatitis with copper-containing jewelry[143] and urticaria with the use of a copper intrauterine device.[144] There are inadequate data in the medical literature to associate dermal exposure to copper with systemic toxicity,[93] except following the application of copper-containing liquids to yellow phosphorus burn areas.[145]

Kidney

Anuria or oliguria may develop following acute copper sulfate intoxication, but renal dysfunction is usually mild. Damage to the proximal renal tubules results from the direct effect of copper sulfate, hypotension, and/or hemoglobinuria released from massive hemolysis. Rarely, myoglobinuria is a complication of acute copper poisoning. A 37-year-old Nigerian man developed hemolysis and renal failure requiring hemodialysis after the ingestion of spiritual (green) water containing ~13 mg Cu/L as a home remedy for mid-epigastric pain.[21]

Environmental Exposure

There are few data on copper toxicity associated with environmental copper exposure. A case report temporally associated intermittent vomiting and abdominal pain with drinking water from a copper line; the symptoms resolved after the family ceased using drinking water from the copper line.[6] Although water samples contained copper concentrations exceeding 1.0 mg/L, the report lacked a thorough medical evaluation of the family and an extensive evaluation of comparison families in the area drinking water from the same main line. The median blood copper concentration of the family was below the median concentration of one other neighborhood family. A case report associated the ingestion of royal jelly (honey bee extract) and large doses of copper supplements (30–60 mg copper daily for 3 years in mineral supplements plus zinc and selenium) with the development of cirrhosis and liver failure, resulting in an orthotropic liver transplant.[146] The patient had Kayser–Fleischer rings and elevated copper concentrations in the explanted liver; however, the serum copper and ceruloplasmin were within normal values at presentation. A 20-month-old Australian child developed liver failure that required liver transplantation; histological examination demonstrated findings consistent with Indian Childhood Cirrhosis; the explanted liver

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had a 10-fold increase in copper content.[117] The authors attributed the source of excess copper to copper conduits used to transport the child's milk; these authors suggested the term copper-associated liver disease in childhood for similar cases occurring outside India.

Occupational Exposure

Although copper may act as an irritant to the respiratory and gastrointestinal tracts, there are no well-designed epidemiological studies of workers exposed primarily to copper that demonstrate chronic toxicity including fibrotic interstitial lung disease.[147] Case reports associate occupational exposure to copper dust with mucosal irritation of the mouth, eyes, and nose along with perforation of the nasal septum following heavy exposure.[148,149] In a case report of 26 workers cutting brass pipes with electric cutting torches, metal fume fever (fever, chills, myalgias, headache, malaise, dry throat) was attributed to the inhalation of copper fumes from copper-welding operations;[150] however, only 5 of 12 workers tested had elevated urinary copper concentrations. Inadequate documentation of copper exposure, atypical complaints, and the lack of consistent symptoms from specific work practices limit conclusions regarding the association between copper dust and metal fume fever.[151] The high temperature required to produce copper fumes relative to the temperature of copper in most industrial applications also limits the pulmonary effects of copper dust.

Vineyard sprayer's lung is an occupational disease associated with the use of Bordeaux mixture (~1–2% copper sulfate in hydrated lime) by European vineyard workers.[152] The abnormalities resemble silicosis with early micronodular changes that progress to massive pulmonary fibrosis and respiratory failure. Lung biopsies typically demonstrate three histological stages including alveoli filled with macrophages, granulomas in the alveolar septa, and fibro-hyaline nodules similar to silicotic nodules in areas previously containing granulomas.[153] The granulomas, desquamated macrophages, and fibrohyaline scars usually contain copper. Case series suggest that lung cancer occurs commonly in vine growers diagnosed with vineyard sprayer's disease, but the cause of these tumors remains unclear as a result of the presence of multiple confounding factors (arsenic, smoking) and selection bias.[154]

Wilson's Disease

This rare genetic disorder of copper metabolism causes progressive hepatic and neurological damage that usually manifests during the second or third decade of life; late-onset Wilson's disease (i.e., >40 years of age) is unusual.[108] There are over 300 different mutations distributed across the *ATP7B* gene, resulting in complex genotypes and a wide range of symptoms varying from asymptomatic patients to end-stage liver disease with cirrhosis, portal hypertension, and acute liver failure.[108] Acute liver failure occurs in ~12% of patients with Wilson's disease, predominately in young females.[155] Clinical manifestations include cognitive impairment, behavioral changes (emotional lability, depression, insomnia, loss of concentration), motor abnormalities (dysarthria, tremor, dysphagia, ataxia, difficulty writing), Coombs-negative hemolytic anemia, renal tubular dysfunction (uricosuria, hypercalciuria), renal stones, and fulminant hepatic failure with encephalopathy.[156,157] The liver is the primary organ affected by copper excess; hepatic disease usually occurs before the appearance of extra-hepatic signs and symptoms with the exception of elderly patients, who often present with neurological and psychiatric features. Symptomatic patients, particularly those with neurologic manifestations, often present with Kayser–Fleischer rings (i.e., peripheral golden-brown corneal deposits of copper within Descent's membrane); other ophthalmic findings include sunflower cataracts, night blindness, optic neuritis, pallor of the optic disk, and exotropic strabismus. The ophthalmic changes are usually reversible with medical treatment or liver transplantation. The classification of neurological abnormalities in Wilson's disease includes 1) Parkinson-like akinetic-rigid syndrome, 2) multiple sclerosis-like degeneration dominated by tremor, 3) ataxia, and 4) dystonia.[108] Depression, anxiety, and psychosis may also occur. In the absence of lifelong chelation with D-penicillamine or trientine, progressive anatomical and physiological changes develop, primarily in the liver and brain.[158] The diagnosis of Wilson's disease is based on the presence of a typical history and physical examination including slit lamp evaluation along with elevated copper concentrations in the urine and serum. There is no one definitive test for the diagnosis of Wilson's disease.

Reproductive Abnormalities

Copper is an essential metal that is not a recognized animal or human teratogen. Data on the reproductive effects of copper exposure are limited. Analysis of questionnaires from a group of workers exposed to 111–434 mg/m^3 copper dust during grinding and sieving operations revealed complaints of sexual impotence in 16% of the sample; the lack of a control group and multiple confounding factors limit conclusions regarding causation.[159]

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Carcinogenicity

Neither the International Agency for Research on Cancer nor the US Toxicology Program lists metallic copper or copper compounds as suspected human or animal carcinogens. Epidemiological studies have not established a positive correlation between copper exposure and an increased incidence of cancer. The increased incidence of lung cancer in workers in copper refineries probably results from contamination of copper ore with arsenic or co-exposure to nickel sulfate. Preliminary studies suggest that squamous and small cell lung cancers predominate in pulmonary tumors from copper smelter workers,[160] whereas adenocarcinomas are more common in lung cancer patients without occupational exposure to carcinogens. In a Finnish study of 1,388 workers employed for at least 3 months at a copper/nickel smelter and nickel refinery, the elevated risks of nasal and lung cancer were limited to the nickel refinery and attributed to insoluble nickel compounds rather than copper exposure.[161] A Chinese mortality study of 7,088 copper miners detected increased mortality from lung cancer (SMR = 147, 95% CI: 112–189, $P < 0.01$);[162] however, lack of control of confounding (arsenic, radon, smoking) limits conclusions regarding causation. In a case-control study of four rural Arizona towns near copper smelters, there was little evidence of a positive association between copper smelter emissions and lung cancer incidence based on historical estimates (i.e., interviews and diffusion modeling) of residential exposures.[163]

DIAGNOSTIC TESTING

SI Conversion Units

1 mmol = 63.54 mg
1 mg = 15.74 μmol

Analytic Methods

The most common methods used to determine copper levels in biological or environmental samples are atomic absorption spectrometry (flame or graphite) and inductively coupled plasma/atomic emission spectrometry. The later technique is highly sensitive. These methods determine total copper concentrations. Depending on sample preparation procedures, the detection limits of graphite furnace/atomic absorption spectrometry are about 1 μg/L water compared with 10–20 μg/L water for the less sensitive flame atomic absorption spectrophotometry.[8,164] The major problems with these methods are contamination from impurities in the environment and loss of copper during sample preparation.[12] For laboratories without atomic absorption spectrophotometers, rapid colorimetric assays are available with detection ranges near 0.1 mg Cu/L.[165] Electrochemical and equilibration techniques are available to determine the species of copper present in environmental[166] and biological samples.[167]

Biomarkers

Blood

The whole blood/serum Cu ratio is typically slightly <1; in a study of healthy Italians, the mean whole blood/serum Cu ratio was 0.86.[168] Whole blood copper concentrations may substantially exceed serum copper concentrations during the first few days after intravenous copper exposure.[137]

General Population

The upper range of serum copper concentrations in the general population is ~1.5–1.6 mg/L as measured by ICP/MS.[169] The median serum copper concentration of 122 Czechoslovakian volunteers was ~1.06 mg/L with a range of 0.7–1.53 mg/L.[170] A Spanish study of 15 healthy adults demonstrated a mean serum copper concentration of 0.86 mg (14.4 μmol/L).[171] In a sample of 36 healthy adults[172] and 372 Swedish adolescents,[173] the mean whole blood and serum concentrations were similar (i.e., ~1 mg/L). In a French study of 106 volunteers, the median whole blood copper concentration was 0.937 mg/L (95th percentile, 1.51 mg/L) compared with 0.952 mg/L (95th percentile, 1.66 mg/L) in plasma as measured by ICP/MS.[174] Serum copper concentrations do not significantly increase with age. In a study of 66 Greek children (mean, 7.53 ± 3.31 years; range, 3–14 years) and their parents, the mean serum copper concentrations were 1.67 ± 0.35 mg/L and 1.47 ± 0.33 mg/L, respectively ($P < 0.001$) as measured by flame atomic absorption spectrometry.[175] Renal failure does not significantly increase plasma copper concentrations based on comparisons of healthy adults and hemodialysis patients.[176] The use of oral contraceptives is associated with a moderate, asymptomatic increase in the plasma and whole blood copper concentrations above normal ranges, but erythrocyte copper concentrations usually remain within the normal reference range.[177,178] The increase probably reflects estrogen-associated increased ceruloplasmin production. Serum copper concentrations return to normal values within 2 months of cessation of oral contraceptive use.

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Wilson's Disease

Almost 95% of patients with Wilson's disease have reduced serum concentrations of oxidase-active ceruloplasmin (<20 mg/dL).[179] Reduced concentrations of serum ceruloplasmin alone are not diagnostic of Wilson's disease because ~20% of heterozygotes have decreased ceruloplasmin concentrations. Other conditions with low concentrations of ceruloplasmin include protein-losing enteropathies and nephropathies, as well as defective production of ceruloplasmin peptide. Healthy infants <6 months of age frequently have low serum ceruloplasmin concentrations. A variety of conditions are associated with elevated serum copper concentrations beside Wilson's disease including iron deficiency anemia, leukemia, lymphoma, biliary cirrhosis, hemochromatosis, thyroid disease, pregnancy, infection, and collagen vascular diseases. The use of the penicillamine challenge test for the diagnosis of Wilson's disease remains controversial, in part because penicillamine increases urinary copper secretion in patients without Wilson's disease.[180,181]

Toxicity

The correlation between clinical outcome and blood copper concentrations is limited, in part because of the complexity of copper kinetics and few data comparing whole blood, serum, and unbound copper during copper intoxication. Although serum ceruloplasmin concentrations increase during the first 3 days after acute copper toxicity as a result of increased hepatic synthesis,[182] severity of copper toxicity does not correlate to plasma ceruloplasmin concentrations. Unbound or free copper accumulates rapidly following saturation of metallothionein binding sites, resulting in the rapid intracellular accumulation of free copper and the generation of reactive oxygen species along with liver necrosis. In this situation, serum copper concentrations are low despite serious toxicity. As a result of rapid uptake by the liver and erythrocytes, serum copper concentrations increase rapidly within a few hours after ingestion and then decline rapidly over the next 24–48 hours, typically returning to normal values within 1 week.[135] Although serum ceruloplasmin concentrations increase during acute copper toxicity as a result of increased hepatic synthesis, severity of copper toxicity does not correlate to plasma ceruloplasmin concentrations.[182]

In an Indian case series of 10 patients sent to a referral hospital with renal failure, the mean serum copper was 1.98 mg/L (range, 1.2–3.9 mg/L). The report did not document the time between ingestion and blood sampling, but the time to referral of almost all patients was substantially delayed (3–8 days).[183] Four patients died. On admission to the hospital ~1 hour after ingesting a solution of copper sulfate, the serum from an 18-month-old child contained 16.5 mg Cu/L; within 24 hours, the serum copper decreased to 2.3 mg/L.[62] He developed hemolytic anemia and renal tubular dysfunction but no hepatorenal failure, and he survived without sequelae. A 42-year-old man developed jaundice, 100-fold elevation of his serum transaminases, and rhabdomyolysis after the intentional ingestion of copper sulfate; he survived without sequelae.[64] His serum copper concentration the day after ingestion was 14.2 mg/L.

In an Indian case series of copper sulfate intoxication in 48 adult patients presenting during the 1960s, the mean whole blood copper concentration in patients with mild gastrointestinal symptoms was 2.87 ± 1.27 mg/L compared with 7.98 ± 3.96 mg/L in patients with hepatorenal dysfunction and/or shock as measured by spectrophotometric methods;[184] mean serum copper concentrations were similar between the two groups.[128] The case report did not document the time between ingestion and blood sampling. An Indian case series of four cases of fatal acute copper intoxication documented whole blood copper concentrations ranging from 2.12–2.83 mg/L within 24 hours after ingestion.[185] This study from the 1970s did not report the analytic method. A 55-year-old chemist remained asymptomatic after sustaining multiple lacerations following an explosion involving copper azide.[71] His peak serum copper concentration 4 days after the explosion was 1.23 mg/L.

Postmortem

The rapid uptake of copper by erythrocytes and the prolonged course of acute copper sulfate toxicity prior to death complicate the interpretation of most copper concentrations in postmortem blood. An 11-year-old female died 2 hours after accidentally ingesting an estimated one mouthful of a saturated solution of copper sulfate; her postmortem blood sample contained 66 mg Cu/L.[127] The antemortem copper concentrations in whole blood and serum samples drawn 1 hour after ingestion were 16 mg/L and 25 mg/L, respectively. A 30-year-old woman became comatose and died 48 hours after receiving a concoction of copper sulfate and other substances by an *inyanga* (traditional African herbalist); the autopsy demonstrated aspiration pneumonia and centrilobular congestions of the liver.[186] The copper concentration in her postmortem blood was 42 mg/L.

Urine

Copper concentrations in urine samples are usually relatively low because copper elimination occurs primarily via the bile. In studies of the general population, urine

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copper concentrations range up to 0.05 mg/L.[187] In a French study of 100 healthy volunteers, the median urine copper concentration was 0.007 mg/L with an upper 95% CI of 0.012 mg/L as measured by ICP/MS.[188] The mean urine copper concentration in convenience sample of 507 urban and rural Italian residents without occupational copper exposure was 0.023 ± 007 mg/L with a range of 0.004–0.05 mg/L.[189] The urine copper concentration in patients with symptomatic Wilson's disease usually exceeds 0.1 mg/24-hour urine collection;[190] however, increased copper excretion also occurs from other causes of severe liver disease. One day after ingestion of copper sulfate, the copper concentration in a 2-hour urine sample was 0.5 mg/L; the peak urine concentration of 3 mg/L occurred 11 days after ingestion.[62]

Hair

Limited data are available on copper concentrations in hair. A study of 41 adults undergoing minor surgical procedures demonstrated mean copper concentration of 17.7 ppm (range, 9.5–33.1 ppm) in the proximal 2–3 cm of occipital scalp hair samples and 11.9 ppm (range, 7.2–19.9 ppm) in pubic hair as measured by flameless atomic absorption spectrometry (LOD, 0.6 ppm).[191] In a study of menstruating Polish women, the mean copper concentration in the proximal 1 cm of occipital scalp hair from 28 women aged 19–30 years was 25.8 ± 19.4 ppm (range, 7.6–67.7 ppm) compared with 12.9 ± 5.43 ppm (range, 7.12–17.9 ppm) in 25 women aged 31–40 years.[192] The mean copper concentration in hair from 24 menstruating women aged 41–50 years was intermediate between the former two groups. A study of 39 children aged 1–12 years living in and around a large Australian port city demonstrated copper concentrations in proximal neck hair samples ($n = 22$) from 7–415 ppm with a median of 56.27 ppm; first morning void urine copper concentrations in 37 samples were <0.085 mg/L with a median of 0.012 mg/L.[193] Examination of house dust and drinking water did not suggest the presence of significant copper contamination in their home environment. In a German study of proximal scalp hair samples from 474 preschool children, the geometric mean copper concentration was 10.6 ppm with a range of 5.4–20.7 ppm.[194] Stepwise regression analysis did not detect any significant association between hair copper concentrations and a variety of factors (e.g., place of residence, season, sex, age, hair color). Analysis of metal concentrations in hair of children with autism including copper, cadmium, lithium, mercury, and selenium indicates that these metals are not associated with autism.[195]

Abnormalities

Overdose

Abnormalities resulting from severe copper sulfate poisoning include intravascular hemolysis (anemia, increased plasma hemoglobin, reticulocytosis, hemoglobinuria, hyperbilirubinemia, crenated and fragmented erythrocytes, Heinz body formation), acute proximal renal tubular dysfunction (aminoaciduria, hypercalciuria, phosphaturia, proteinuria, uricosuria), hematuria, elevated serum hepatic transaminases/total bilirubin, oliguria, rhabdomyolysis, and methemoglobinemia.[196,197] Serum hepatic aminotransferase concentrations peak within 3 days of ingestion and resolve by 1 week. A retrospective Indian study of 35 patients with copper sulfate poisoning suggested that elevation of peak serum alanine aminotransferase (ALT) concentrations substantially increases the risk of mortality.[130] All patients dying in this series had peak serum ALT concentrations exceeding 55 IU/L. Massive hemolysis may complicate the analysis of hepatorenal function, blood compatibility, and arterial blood gases.[198] Copper salts, but not metallic copper, are radiolucent.

Wilson's Disease

In Wilson's disease, the free fraction of copper in the plasma is elevated along with subsequent increased urinary copper excretion. Severe liver disease from other causes also produces similar increases; however, the extent of these changes is much more severe in Wilson's disease. Laboratory testing typically demonstrates persistently elevated serum hepatic transaminases with disease progression characterized by reduced albumin, elevated international normalized albumin, elevated international normalized, ratio, hyperbilirubinemia (mostly indirect), and marked Coombs-negative hemolytic anemia.[199] CT imaging demonstrates hypodense nonenhancing foci in the thalami and basal ganglia with dilation of the frontal horns secondary to brainstem and caudate atrophy. MR imaging typically displays increased bilateral, symmetric T2-weighted images in the deep gray areas, commonly in the globus pallidus and putamen.[200] Other abnormalities in these patients include scattered high-signal-intensity foci in white matter and scattered hypo-intensities in the pons, midbrain thalami, and lentiform nucleus.

Serum ceruloplasmin concentrations <0.2 g/L are consistent with Wilson's disease with concentrations <0.14 g/L demonstrating 100% positive predictive values;[201] however, low ceruloplasmin is not specific for Wilson's disease. Although ~95% of patients with

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Wilson's disease will have low serum ceruloplasmin concentrations, other causes of low serum ceruloplasmin concentrations include malnutrition, malabsorption, and cachexia. Low serum ceruloplasmin concentrations also occur in Menkes disease; this protein is an acute-phase reactant that decreases in acute liver failure. Diagnostic criteria for Wilson's disease include 1) the presence of Kayser–Fleischer rings (granular, golden-green corneal copper deposits within Descemet membrane) and low ceruloplasmin, 2) low serum ceruloplasmin and hepatic copper concentrations >75 μg/g dry weight with appropriate histology, and 3) evidence of two mutations of *ATP7B*.[202] In acute hepatic failure, the presence of serum alkaline phosphatase/total bilirubin ratio <4 and serum aspartate aminotransferase/alanine aminotransferase ratio >2.2 is highly suggestive of Wilson's disease.[203] Kayser–Fleischer rings almost always occur in patients with psychiatric or neurological complications of Wilson's disease, whereas only 40–66% of patients with the hepatic form have this sign. These deposits are uncommon in young, asymptomatic patients with the disease.[180] The normal copper content of the liver is <55 μg/g dry weight, whereas hepatic copper concentrations in homozygous Wilson's disease is typically >250 μg/g dry weight; however, values <250 μg/g dry weight do not exclude the possibility of Wilson's disease, particularly in the presence of severe hepatic fibrosis.[108] Urine copper concentrations may exceed 100 μg/24 hours in acute liver failure secondary to Wilson's disease and >40 μg/24 hours; however, asymptomatic patients with this disease may not have elevated urinary copper concentrations.[204]

HEALTH SURVEILLANCE

Risk Assessment

The acute-duration oral minimal risk level (MRL) for copper is 10 μg/kg/day based on the lack of adverse effects (NOAEL) in women ingesting 27.2 μg/kg/day in drinking water for 2 weeks; the uncertainty factor for human variability was 3.[205] Gastrointestinal distress developed in women ingesting drinking water containing 73.1 μg Cu/kg/day. An intermediate-duration oral MRL for copper is 10 μg/kg/day based on the lack of adverse effects (NOAEL) in volunteers ingesting 42 μg/kg/day in drinking water for 2 months; the uncertainty factor was 3.[206] Gastrointestinal effects (i.e., nausea) occurred in volunteers ingesting 91 μg Cu/kg/day in drinking water for 2 months.

Health-based guidelines for copper in drinking water in many countries range from 1–2 mg/L. The World Health Organization guideline for copper in drinking water is 2 mg/L.[52] Blue-green discoloration of laundry and plumbing fixtures occurs at copper concentrations of 1 mg/L, whereas a bitter taste develops in water at copper concentrations of 1–5 mg/L. The US EPA maximum contaminant level (MCL) is 1.3 mg Cu/L based on taste and, to a lesser extent, on limited toxicity data. This drinking water regulation was calculated by Equation 11.1

$$\begin{aligned}\text{MCL} &= \text{LOAEL} \div \text{Safety factor} \\ &\quad \times \text{Daily water consumption.} \\ &= 5.3\ \text{mg} \div 2 \times 2\ \text{L/day} = 1.3\ \text{mg/L/day}\end{aligned} \qquad \text{(Equation 11.1)}$$

where:

lowest-observable-adverse-effect level (LOAEL) = 5.3 mg
Safety factor = 2
Daily water consumption (adult) = 2 L/day

The LOAEL was based on a reconstruction of an incident in 1957 when a group of nurses developed acute gastrointestinal symptoms after ingesting alcoholic beverages from a copper cocktail shaker.[207] The actual amount of copper ingested during the incident was not measured. The estimated amount ingested by these nurses ranged from 5.3–32 mg Cu. Although the data are incomplete, not all nurses became ill; hence, the 5.3 mg dose may represent a NOAEL rather than a LOAEL.[208] Such a change would reduce the safety factor used to calculate the health-based guidelines. Sidhu et al. proposed a reduction in the drinking water standard to 0.3 mg Cu/L as a means to increase the uncertainty factor to account for the sensitivity of children under the age of 10 to copper toxicity. However, currently there are little data to support such a revision.[209] A prospective study of healthy infants aged 3–12 months measured changes in serum concentrations of copper, ceruloplasmin, bilirubin, transaminases, γ-glutamyl transferase, superoxide dismutase, and erythrocyte metallothionein.[210] There were no adverse effects and no statistical differences detected between the group receiving drinking water with 2 mg Cu/L and the control group (<0.1 mg Cu/L). The development of liver disease has not been associated with water supplies that contain concentrations >2 mg Cu/L.[26] A study of 60 women volunteers demonstrated a statistically significant increase ($P < 0.01$) in the incidence of nausea, vomiting, and abdominal pain in the women ingesting drinking water over 2 weeks that contained ≥3 mg Cu/L.[205] The serum copper, ceruloplasmin, and liver enzymes of these women did not change significantly

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from baseline concentrations. A mortality study of Massachusetts residents consuming drinking water with concentrations ranging up to 8.8 mg Cu/L in 1969–1991 did not detect any excess deaths from liver disease.[211] In a Swedish cohort study of 430 children, 43 developed diarrhea and 95 developed vomiting; the mean intake of copper for all children was estimated from the analysis of drinking water.[212] The median copper concentration of the mean drinking water values for the children was 0.61 mg/L (10–90th percentile, 0.04–1.57 mg/L). Comparison of the children with and without gastrointestinal illness indicated no association between copper intake or maximal drinking water copper concentrations and gastrointestinal illness.

Environmental Monitoring

The ACGIH recommends a TLV–TWA for workers exposed to copper fumes of 0.2 mg Cu/m^3 and copper dusts and mists of 1 mg Cu/m^3. Table 11.3 lists the guidelines and regulations formulated for copper exposure.

TABLE 11.3. Copper regulations and guidelines.

Exposure Limit	Value
OSHA	
PEL–TWA (8-hour)	0.1 mg/m^3 (fumes as Cu)
	1 mg/m^3 (dusts/mists as Cu)
NIOSH	
REL–TWA (10-hour)	0.1 mg/m^3 (fumes as Cu)
	1 mg/m^3 (dusts/mists as Cu)
IDLH	100 mg/m^3
ACGIH	
TLV–TWA (8-hour)	0.2 mg/m^3 (fumes as Cu)
	1 mg/m^3 (dusts/mists as Cu)
US FDA	
Bottled water allowable limit	1.0 µg/L
US EPA	
Action level	1.3 mg/L
MCLG	1.3 mg/L
ATSDR	
MRL (oral, acute ≤14 days)	0.01 mg/kg/day
MRL (oral, intermediate >15 days)	0.01 mg/kg/day

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; EPA = (US) Environmental Protection Agency; FDA = (US) Food and Drug Administration; IDLH = immediately dangerous to life and health; MCLG = maximum contaminate level goal; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; TLV = threshold limit value; TWA = time–weighted average.

Workers with potentially increased susceptibility to copper exposure include the following diseases: Wilson's disease, glucose-6-phosphate dehydrogenase deficiency, and possibly liver disease.[12] The preemployment physical examination should concentrate on detecting the following diseases: liver disease, kidney dysfunction, anemia, and the other preexisting diseases listed above.

Biological Monitoring

Copper concentrations in the blood reflect recent exposure; whole blood copper concentrations average 1.2 mg/L (range, 0.8–1.6 mg/L) in workers without copper exposure;[189] however, there are insufficient data to establish biological exposure limits for workers exposed to copper.

TREATMENT

Overdose

Gastrointestinal Decontamination

The induction of emesis or gastric lavage is usually unnecessary following acute copper sulfate ingestions because of persistent vomiting. Copper sulfate is a corrosive that should be treated with early dilution with a glass of water rather than emetics as reexposure of the esophagus to this corrosive substance could worsen gastrointestinal irritation. There are no *in vitro* or *in vivo* data on the efficacy of activated charcoal following an acute ingestion of copper sulfate.

Enhancement of Elimination

Copper is not effectively removed by hemodialysis. Analysis of copper concentrations in serum and dialysate before and after hemodialysis on day 1 and day 3 of hospitalization following the intravenous and subcutaneous injection of copper sulfate did not demonstrate significant differences before and after hemodialysis.[134] The removal of copper by peritoneal dialysis is small, even with the use of salt-poor albumin. Following the ingestion of saturated copper sulfate crystals by a 2-year-old boy, albumin-enriched peritoneal dialysis removed 9.1 mg Cu over 60 hours compared with 0.7 mg Cu over 40 hours of peritoneal dialysis without albumin.[136] Case reports suggest therapeutic plasma exchanges (plasmapheresis) may be effective adjunctive therapy for acute copper overload during acute Wilson's disease while initiating preparations for liver transplantation;[213] however, the amount of copper eliminated by plasmapheresis was not documented and serum copper concentrations remained unchanged.

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Chelation

Chelating agents are often recommended for severe poisoning, but little pharmacokinetic data on humans exist to guide their use or support their efficacy.

BAL and $CaNa_2EDTA$

Either intravenous $CaNa_2EDTA$ or intramuscular BAL are the agents most frequently recommended for severe copper sulfate ingestions;[196] however, availability of these chelating agents is limited, and there is no consensus on the most effective chelating agent.[135] Typically, the duration of chelation is based on reduction of serum copper concentrations to normal or resolution of clinical symptoms (i.e., usually ~5–7 days).

D-Penicillamine

D-Penicillamine may be administered orally, if tolerated, to non-penicillin-allergic patients. A 42-year-old man intentionally ingested ~250 g copper sulfate (serum copper ~24 hours after ingestion = 1,423 μg/dL); he received 4 gm/kg dimercaprol intramuscularly and oral D-penicillamine within several hours of ingestion.[64] Despite developing rhabdomyolysis (CPK 5,620 IU/L), liver dysfunction (bilirubin = 7.0 mg/dL), and hemolysis, he recovered; however, the efficacy of these chelating agents following the ingestion of large doses of copper sulfate was not well documented.[214]

Pharmacokinetics Good absorption of D-penicillamine occurs in the gastrointestinal tract (40–70%); some ingestants (antacids, iron, food) may reduce the efficiency of D-penicillamine absorption.[215] Gastric mucosal injury and subsequent GI distress may limit the oral administration of D-penicillamine. Peak D-penicillamine concentrations appear within several hours following ingestion. Elimination of D-penicillamine is rapid (elimination half-life ~3 hours), almost exclusively by excretion of metabolites into the bile.

Dosage D-Penicillamine is available in 125 mg and 250 mg capsules that may be sprinkled on a more palatable vehicle; the daily adult dose is 1,000–1,500 mg in four divided doses. Limited pediatric experience suggests a dose of 20 mg/kg twice daily up to a maximum of 1,000 mg. Side effects are reduced by beginning with $1/4^{th}$ of the full daily dose and increasing to the full dose over 3–4 weeks. D-Penicillamine is administered orally in four divided doses 2 hours before meals, usually for 4–12 weeks, depending on the occurrence of adverse reactions. The use of D-penicillamine is contraindicated in the presence of penicillin allergy. Complete blood counts and urinalyses should be obtained on days 1, day 14, day 28, and monthly thereafter. If the absolute neutrophil count falls to <1,500 neutrophils/μL, the blood count should be repeated at least daily and D-penicillamine therapy stopped, if the blood count falls below 1,200 neutrophils/μL.[216]

Adverse Effects Side effects resemble penicillin hypersensitivity and appear immune-related rather than dose-related. Adverse reactions occur in up to 33% of patients given D-penicillamine for lead poisoning;[217] these reactions include rash, transient leukopenia and thrombocytopenia, anorexia, eosinophilia, proteinuria, fever, hyporeflexia, and rarely autoimmune hemolytic anemia, Stevens-Johnson syndrome, and nephrotoxicity.[218] Nausea, vomiting, and abdominal pain occur at high D-penicillamine doses; the onset of these symptoms is usually dose-related. The eosinophilia occurs in ~20% of children given D-penicillamine for lead poisoning; often resolution appears spontaneously.[217] Proteinuria and microscopic hematuria may respond to a reduction in dosage or resolve spontaneously.[218] Follow complete blood count with differential counts and urinalysis weekly during therapy. The use of D-penicillamine is questionable during pregnancy because this chelator crosses the placental barrier and is a potential teratogen.

DMSA/DMPS

Although experimental studies in rodents suggest that DMSA and 2,3-dimercaptopropane-1-sulfonate (DMPS) are effective chelating agents for copper and reducing serum copper concentrations,[219,220] human data are inadequate to determine efficacy. A 33-year-old woman intentionally ingested an unknown amount of copper sulfate; she developed gastritis, methemoglobinemia, severe hemolysis, and hepatorenal failure.[221] She survived with supportive care and the intravenous administration of DMPS within ~8 hours after poisoning. The serum copper concentration was within normal limits after admission; serial copper concentrations and copper elimination were not reported.

Supportive Care

Serious complications of copper sulfate ingestions include ulceration and perforation of the gastrointestinal tract with resulting sepsis, rhabdomyolysis, hepatorenal failure, methemoglobinemia, intravascular hemolysis, and subsequent anemia. These complications typically appear within the first few days after ingestion; patients should be monitored for the development of these complications with serial CBC, serum chemistries (electrolytes, creatinine, hepatic transaminases, haptoglobin, creatine phosphokinase), and methemoglobin

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as indicated in the clinical course. Hypotension may result from fluid loss, hemolysis, or sepsis.

Treatment of copper sulfate ingestion is primarily supportive. Endoscopy may be necessary to evaluate the severity of gastrointestinal injury following copper sulfate ingestion in symptomatic patients (hematemesis, gastrointestinal pain). Similar to other corrosive ingestions, endoscopy should be performed within 24–48 hours to minimize adverse effects. Methemoglobinemia usually does not require treatment with methylene blue unless the patient is symptomatic with methemoglobin concentrations above 25–30%; patients with anemia or cardiopulmonary disease may develop symptoms below these concentrations. Patients should be evaluated for the presence of preexisting glucose-6-phosphate dehydrogenase (G6PD) or NADPH-dependent methemoglobin reductase deficiencies. Patients with rhabdomyolysis or hemolysis should be adequately hydrated and observed for the development of renal dysfunction.

Wilson's Disease

FDA-approved drugs for the treatment of Wilson's disease include D-penicillamine, trientine, and zinc acetate. The initial treatment for symptomatic neurological, psychiatric, and liver diseases is chelation with D-penicillamine (initial daily adult dose, 1–1.5 g orally in 2–4 divided doses 1 hour before or 2 hours after meals).[91] Neurological symptoms may initially worsen during the first few weeks to months of chelation therapy, requiring reduction in the chelation dose.[222] Symptoms usually resolve, but neurological deterioration or adverse reactions (fever, rash, lymphadenopathy, neutropenia, thrombocytopenia, proteinuria, aphthous stomatitis) may require the use of other therapies (e.g., trientine). Penicillamine may affect pyridoxine metabolism; vitamin B_6 supplementation (50 mg weekly) should be given to susceptible patients (children, pregnant women, malnourished patients). Trientine is an acceptable alternative to penicillamine for the initial treatment of Wilson's disease.[108] The initial adult dose is 1,200–1,800 mg divided in two to three doses with daily maintenance therapy of 900–1,200 mg and similar restrictions on food as penicillamine. Pancytopenia may occur, but hypersensitivity reactions and renal dysfunction do not usually occur. Tetrathiomolybdate (up to 2 mg/kg orally in divided doses) is an investigational drug, which avidly chelates copper in sheep. Data on humans are limited with relatively few adverse reactions.[223,224] Zinc induces intestinal metallothionein; thus, reduces copper absorption by binding copper within the duodenal enterocytes. A negative copper balance results from the shedding of copper during normal cell turnover. The daily adult dose of elemental zinc is 150 mg; food interferes with the absorption of zinc; dyspepsia may interfere with compliance.

Dietary therapy alone is not effective treatment for Wilson's disease, but foods with high copper concentrations (shellfish, nuts, liver, mushrooms, chocolate) should be avoided. Zinc acetate (50 mg tid) is effective maintenance therapy with relatively minor adverse effects; the US FDA approved the use of this agent in Wilson's disease in 1997.[225] Zinc induces the formation of intestinal metallothionein, which blocks the absorption of copper by inhibiting the transfer of copper from the intestinal mucosa to the blood.[226] The use of hemodialysis in patients with fulminant Wilson's disease (hemolysis, renal failure) was associated with increased clearance of copper, but the serum copper concentrations increased and clinical deterioration occurred.[227] Liver transplantation is an option for patients who are unresponsive to medical therapy. The molecular adsorbent recirculating system (MARS) is an investigational method of treatment in Wilson's disease patients with little data to guide us in acute copper toxicity.

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Chapter 12

GERMANIUM

HISTORY

Germanium is a rare element that always occurs naturally in combination with other elements. In 1886, Clemens Winkler isolated germanium in Germany, naming the element after his native country.[1] Widespread use of germanium did not begin until World War II with the application of germanium in electronics and the initial development of semiconductors. The ability of germanium to convert alternating current into direct current is a desirable physical property to use in simple radio signal detectors as well as in sophisticated semiconductor devices in computers. William Shockley created the first transistor in 1948 based on this metalloid. Germanium tetrahydride is a doping agent for solid-state electronic components; silicon–germanium alloys appeared in the mid-1950s. The use of germanium in diodes, rectifiers, and transistors continued until the early 1970s when high-purity silicon began replacing germanium as a semiconductor.

The use of germanium compounds in the early 20th century as anti-tuberculosis agents and erythrocyte-stimulating drug was ineffective. Uncontrolled animal and human studies suggest that germanium compounds possess analgesic,[2] antihypertensive,[3] erythropoietic,[4] immune modulating,[5,6] and tumor-inhibiting properties.[7,8] Germanium compounds generally produce low toxicity. Although animal studies of germanium compounds in the 1950s demonstrated adverse neurological effects (nystagmus, tremors, seizures),[9] germanium compounds became popular diet supplements in the 1970s for Japanese people with chronic diseases and in the mid-1980s in the United Kingdom. A clinical study using organic germanium compounds (spirogermanium) in the 1980s revealed neurological dysfunction (e.g., ataxia, dizziness) associated with the intravenous administration of these compounds.[10] Case reports also appeared at the same time associating the use of inorganic germanium supplements with the development of acute tubulointerstitial nephritis that progressed to renal failure and permanent renal damage.[11] In the United States, the US Food and Drug Administration (US FDA) does not list germanium as a substance generally recognized as safe (GRAS) to ingest; however, germanium supplements are available over the internet. Suppliers in Europe market germanium compounds as nonprescription drugs for the treatment of AIDS and metastatic cancer.

PHYSICOCHEMICAL PROPERTIES

Germanium (atomic mass, 72.61 g/mol; CAS RN: 7440-56-4) is a member of Group 14 (Group IVa) of the periodic table along with carbon, lead, tin, and silicon. The five natural germanium isotopes are ^{70}Ge (20.55%), ^{72}Ge (27.37%), ^{73}Ge (7.67%), ^{74}Ge (36.74%), and ^{76}Ge (7.67%). Similar to other members of this group, germanium possesses both metallic and nonmetallic properties. This grayish-white, brittle, lustrous metalloid melts at ~972°C. Germanium conducts heat and electricity intermediate between nonmetals and metals similar to other metalloids (antimony, arsenic, astatine, boron, germanium, polonium, silicon, tellurium).[12]

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The semiconducting capacity of germanium is similar to the physical properties of silicon; these properties resulted in the widespread use of germanium in the initial development of electronics. Crystalline germanium is a true semiconductor ("n" or "p" type), but in industrial applications, germanium frequently exists as an alloy with antimony, arsenic, gallium, or indium.[13] A unique property of germanium is the ability to pass electricity only in one direction. The high transparency of germanium to infrared light coupled with its high index of refraction is a desirable property for specialized optical instruments. Germanium can act either as a donor or as a receiver in the formation of chemical bonds, but the valence of germanium is usually +2 to +4. The quadrivalent form of germanium is the most common. Germanium tetrahydride (germane, CAS RN: 7782-65-2, MW: 76.63 g/mol) is a colorless gas that is insoluble in water and is reasonably stable at temperatures below 130°C.

EXPOSURE

Production Processes

Germanium never occurs in its pure metallic state. The most common germanium commercial ores are argyrodite (Ag_8GeS_6, 5–7% Ge) and germanite ($7CuSFeSGeS_2$, 8.7% Ge); however, production of Ge primarily involves the recovery of residues from the metallurgical treatment of zinc or copper–lead–zinc ores. Zinc–cadmium and copper–lead–zinc sulfide ores are readily available sources of germanium. Germanium is present in small quantities in many types of coal.

Uses

The use of germanium in the semiconductor industry has decreased with the improvement in the technology of silicon semiconductors. The major use of metallic germanium now is in the production of infrared sensing, infrared optics, γ-ray spectroscopy detectors, and identification systems.[14] Less common applications involve catalysts, metallurgy, and phosphors. Germanium tetrahydride is a doping agent for electronics, whereas germanium tetrachloride is an intermediate in the production of germanium dioxide and organic germanium compounds. Although a number of medicinal uses of germanium compounds have been proposed (e.g., arthritis, cancer, osteoporosis),[15] the efficacy of these compounds remains unproven.[16]

Sources

Environment

Ge is a relatively common metal in the Earth's crust with similar to those of lead and zinc. Soils contain an average Ge concentration of ~1.5–7 mg Ge/kg. The amount of germanium in air varies widely (0.01–1,700 ng Ge/m^3), depending on the presence of point sources (e.g., coal-burning plants).[17] Similar to other metalloids, Ge generally forms oxides in the environment. Combustion of coal releases substantial amounts of germanium into the air; flue gas and coal ash may contain up to 280 mg Ge/kg.[14] Soil germanium concentrations range from 0.6–1.0 ppm. In a study of waters in and around Tampa Bay, Florida, germanium concentrations in seawater averaged ~79 ng/L compared with 16 ng/L (maximum, 600 μg/L) in fresh water as measured by hydride generation/atomic emission spectrometry.[17] The study found little methyl germanium in the environment.

Diet

Despite relatively low Ge concentrations in food, the diet is the main source of Ge for the general population. Dietary studies from the 1960s and 1970s estimated the average adult ingested ~1.5 mg germanium daily with a range of 0.4–3.5 mg Ge.[18,19] In the 2006 UK Total Diet Study, the estimated mean daily Ge intake for adults was 0.001–0.018 mg/kg (upper 97.5%: 0.002–0.033 mg/kg) as measured by inductively coupled plasma/high resolution/mass spectrometry (LOD, 0.0003–0.002 mg/kg).[20] The primary sources of germanium in this diet were offal and meat products. The latter estimated daily intake values are substantially less than earlier estimates using older analytical methods (e.g., atomic absorption spectometry). Germanium occurs in most food sources. A spectrophotometric study of food sources revealed the highest Ge concentrations (>2 mg/kg wet weight) of germanium existed in raw clams, fish, tomato juice, and canned baked beans.[18] Cereals (e.g., barley, oats), garlic, ginseng, tomato juice, and seafood also contain relatively high Ge concentrations.

ENVIRONMENTAL FATE

The geochemical behavior of germanium in fresh water and seawater is similar to that of silicon. The weathering of continental rocks releases germanium into rivers, which transport this metal to the oceans. Siliceous organisms absorb germanium and deposit the germanium in biogenic opal.[21] Methylated germanium species

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are highly stable in ocean waters. The estimated residence time of monomethyl and dimethyl germanium in oceans is hundreds of thousands of years compared with thousands of years for inorganic germanium.[22] Unlike all other metals, the concentrations of methylated germanium species in the ocean are much higher than inorganic species. The most important environmental form of germanium in aqueous solution is germanic acid (H_4GeO_4).[12] The high first and second dissociation constants (pH 9 and 11.5) are too high to affect germanic acid under normal environmental conditions. Although polymeric forms of Ge exist, these species are probably unstable in the environment.

DOSE EFFECT

Acute Toxicity

There are few data on the effects of large, single ingestions of germanium. Generally, the acute toxicity of germanium compounds is low. Germanium tetrahydride is a moderately toxic gas that causes hemolytic anemia similar to arsine gas based on German data from the 1920s.[23] Animal studies suggest a 1-hour germanium tetrahydride exposure to 100 ppm may cause hemolytic anemia and exposures exceeding 185 ppm may cause death.[24]

Chronic Toxicity

Some suggested therapeutic doses of daily germanium supplements include the following: germanium dioxide, spirogermanium, 120 mg (22 mg Ge); carboxyethylgermanium sesquioxide, 150–500 mg (Ge-132, 32–107 mg Ge); and germanium lactate-citrate, 250 mg (45 mg Ge). There are inadequate data to determine a safe or effective dose. Estimating toxic doses based on data from case reports is limited by the lack of analytical confirmation, poor labeling, confounding illnesses, and reporting bias. In a review of 31 case reports of germanium toxicity (as dioxide, carboxyethylgermanium sesquioxide, germanium lactate-citrate, unspecified forms), the total Ge dose varied from 15–>300 g over a duration of 2–36 months.[25] This review estimated the LOAEL for these cases as 1–4 mg/kg/day. Cumulative germanium dioxide doses of 30 g (~21 g Ge)[26] over 2 months and ~110 g germanium lactate-citrate (~76 g Ge)[27] over 8 months were associated with the development of chronic tubulointerstitial nephritis. The latter case was associated with severe necrotizing pancreatitis, localized peritonitis with negative blood cultures, elevated serum CK, lactic acidosis, and intractable hypotension in a patient with breast cancer on tamoxifen. She ingested nine times the supplier's recommended dose. A case series of five patents ingesting a cumulative dose of 27–250 g GeO_2 (19–174 g Ge) developed tubulointerstitial nephritis that progressed slowly and improved (but did not resolve) 10–40 months after cessation.[28] The ingestion of ~80 g inorganic Ge over 6 years (36 mg daily) as a dietary supplement by a 63-year-old woman was associated with the development of anorexia, nausea, vomiting, peripheral neuropathy (difficulty in writing, gait disturbance), and mild renal dysfunction.[29] The neuropathy and renal dysfunction did not improve after cessation of germanium supplements; she later died after developing pneumonia and sepsis. The lack of improvement following cessation of Ge use limits conclusions regarding causation.

TOXICOKINETICS

Very few human data are available on germanium kinetics. In a study of eight different healthy adult volunteers receiving liquid oral preparations containing organic Ge (Ge-132) in doses of 1 g/m^2 BSA, 2.5 g/m^2 BSA, or 4 g/m^2 BSA, the mean C_{max} was 5.3 ± 2.2 mg/L, 13 ± 5 mg/L, and 18 ± 8 mg/L, respectively.[30] The T_{max} (time to C_{max}) ranged from 0.7–2.0 hours. The terminal elimination half-life based on a two-compartment model was 5–6 hours. Renal elimination accounted for <11% of the administered dose. In a study of seven workers exposed to metallic germanium ($n = 3$) and germanium oxide ($n = 4$), the urinary elimination half-life of germanium averaged ~13 hours with a range of 8–13 hours.[31]

In animals, the lung and gastrointestinal tract absorb inorganic and organic germanium compounds rapidly with absorption almost complete within several hours. These studies indicate that germanium compounds are fairly evenly distributed throughout the body with the highest concentrations occurring in the kidney, liver, spleen, and, to a lesser extent, in bone.[32] Plasma and erythrocyte Ge concentrations are similar. Elimination of germanium occurs primarily by excretion in the urine with most of the dose eliminated within 4–7 days.[9] In these animal studies, the body does not accumulate germanium; the biological half-life is ~1.5 days.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

The role of germanium in the body is unclear; there are inadequate data to determine if germanium is an

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essential trace element. Similarly, the mechanism of toxicity is unknown, but other heavy metals (cadmium, copper, lead) produce similar kidney damage.

Kidney

The kidney is the most sensitive organ to the effects of the chronic ingestion of inorganic germanium; the classical pathological abnormalities associated with renal damage include interstitial changes (focal interstitial infiltrates) and vacuolar degeneration of the tubular epithelium with relative sparing of the glomeruli.[33] In a fatal germanium intoxication, electron microscopy of the renal tissue demonstrated mild mesangial proliferation with foamy cell transformation of the glomerular epithelium.[11] Permanent sequelae may occur. The chronic ingestion of a high dose of germanium lactate citrate by a patient with stage II HIV infection produced focal distal tubular atrophy and slight interstitial fibrosis on renal biopsy 20 months after discontinuation of germanium supplements.[34] In animal studies, the administration of inorganic germanium induces degenerative changes in the epithelium of the proximal and distal convoluted tubules; however, markers of proximal tubular dysfunction (*N*-acetyl-β-D-glucosaminidase) are usually normal.[28]

Liver/Muscle

Histological features of germanium toxicity other than renal pathology include marked liver steatosis and vacuolar degeneration of skeletal muscle and myocardium.[35] In animal models, long-term administration of germanium dioxide produces a myopathy characterized by the formation of ragged-red fibers.[36] The associated decrease in cytochrome *c* oxidase activity and the accumulation of high electron-dense material in the mitochondria suggest mitochondrial dysfunction is an important mechanism in the development of germanium-induced myopathy.

CLINICAL RESPONSE

Adverse Medicinal Effects

Case reports associated chronic ingestion of inorganic (germanium dioxide, germanium lactate-citrate) and organic (carboxyethylgermanium sesquioxide, spirogermanium) germanium compounds as diet supplements with the insidious onset of renal failure, primarily involving the renal tubules and interstitial tissue with little glomerular damage.[37] Some of these patients had neurological (hyperesthesias, paresthesias, hyporeflexia, hypotonia) and myopathic (muscle weakness) symptoms as well as chronic illnesses (diabetes mellitus, malnutrition, unexplained weight loss).[38] The cessation of germanium therapy stops the progression of the renal disease, but renal dysfunction may persist.[39] Transient neurological dysfunction (ataxia, dizziness, nystagmus, paresthesias, vertigo) and interstitial pneumonia occurred in Phase I and Phase II clinical trials of an azaspiran organic germanium compound (2-aza-8-germanspiro[4,5] decane-2-propamine-8,8-diethyl-*N*,*N*-dimethyl dichloride, spirogermanium) used for the treatment of advanced stages of cancer.[8,40,41,42] These clinical trials did not report adverse renal effects. Case reports also associate the chronic ingestion of inorganic Ge as a dietary supplement with the development of gait disturbances and sensory ataxia, resulting in difficulty with fine motor movements (writing), paresthesias, and weakness.[29,43] Germanium tetrachloride is a strong irritant of the skin, mucous membranes, and upper respiratory tract as a result of the hydrolysis of this compound to HCl.[44] Germanium tetrahydride is probably a hemolytic agent with toxic properties similar to arsine and stibine based on guinea pig studies;[45] however, there are few human data to determine the toxicity of this gas.

Carcinogenesis

Germanium exposure has not been associated with a significantly increased risk of reproductive abnormalities, mutagenic activity, or increased prevalence of cancer.[46] Neither the International Agency on Cancer nor the US National Toxicology Program list Ge as a suspected carcinogen. Although there are limited data, germanium compounds do not demonstrate significant mutagenic activity; however, under certain conditions, the administration of Ge compounds may inhibit the mutagenic activity of other substances.[47] Studies of patients with cancer suggest that organic germanium compounds possess some anti-tumor activity.[34,48] Examination of these properties has not progressed beyond Phase II clinical trials.

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DIAGNOSTIC TESTING

Analytical Methods

Techniques for analyzing total Ge in biological samples include graphite furnace/atomic absorption spectrometry (GFAAS), various applications of inductively coupled plasma/mass spectrometry (ICP/MS), and microwave-induced plasma/mass spectrometry (MP/MS). In standard solutions of Ge, the LOD for GFAAS and MP/MS were 3 μg/L and 0.05 μg/L, respectively.[49] The use of high-performance liquid chromatography with quadrupole/ICP/MS allows speciation of organic and inorganic germanium.[50]

Biomarkers

In a study of 100 healthy French volunteers, the median plasma germanium concentration was 5.06 μg/L with a 95% CI of 3.70–6.17 μg/L as measured by ICP/MS (LLOQ, 0.09 μg/L).[51] The median whole blood Ge concentration in this group was 16 μg/L (95% CI: 10.8–19.5 μg/L) with an LLOQ of 0.17 μg/L. The urine germanium concentration in the general population is often below the limits of detection (<0.25 μg Ge/L).[31] In this French study, the median urine Ge concentration was 2.0 μg/L (95% CI: 1.17–3.37 μg/L) with an LLOQ of 0.08 μg/L.

Abnormalities

Proteinuria and hematuria are uncommon in patients with germanium-induced renal disease because the disease process primarily involves the interstitial renal parenchyma and tubules. Additionally, markers of proximal renal function are frequently normal and the physiological dysfunction involves the distal tubules (i.e., defect in concentrating ability).[28] Consequently, laboratory studies demonstrate disturbances in water and electrolyte balance. Animal studies demonstrate myopathies following the chronic ingestion of germanium compounds.[36] Therefore, the elevation of serum creatinine phosphokinase and hyperuricemia theoretically may occur in germanium toxicity, although no human data are available to confirm animal studies. Other abnormalities reported in association with the chronic ingestion of germanium compounds include elevated liver serum hepatic aminotransferases and lactic acidosis.[27] Evidence of hemolysis (anemia, hemoglobinuria, free plasma hemoglobin) may occur following exposure to germanium tetrahydride.

HEALTH SURVEILLANCE

The ACGIH recommends an 8-hour TLV–TWA for germanium tetrahydride of 0.2 ppm (0.6 mg/m^3) with no TLV–STEL.[24] The United Kingdom has a 10-minute STEL of 0.6 ppm germanium tetrahydride. The US OSHA PEL is the same as the ACGIH-recommended standards. There are few data on the use of urine germanium concentration to monitor occupational exposures to germanium. Exposure to inorganic germanium compounds (e.g., GeO_2) in occupational settings typically is greater (i.e., 7–10-fold) than exposure to metallic Ge. Using a hydride generation-based method coupled with flow-injection graphite furnace atomic absorption spectrometry (limit of detection, 0.25 μg Ge/L urine), germanium was not detectable in urine samples from Belgian control male subjects without occupational Ge exposure.[31] The urine samples of workers exposed to metallic Ge had a mean Ge concentration of 3.4 μg/g creatinine compared with 23.4 μg/g creatinine for workers exposed to inorganic germanium. In a cross-sectional study of 75 workers exposed to airborne inorganic Ge concentrations ranging from 0.03–300 μg/m^3, the exposed workers had a slightly higher urinary concentration of high-molecular-weight proteins (albumin, transferrin) when compared with 79 matched referents.[52] Although this finding suggests the presence of subclinical glomerular changes, the lack of a relationship between these changes and the intensity of exposure does not support a causal association. Renal and tubular function as measured by serum creatinine and low-molecular-weight proteins (retinol binding protein, *N*-acetyl-β-D-glucosaminidase, β_2- and α_1-microglobulin) were similar between the two groups. Because of the relatively rapid urinary elimination of germanium, post-shift urine specimens are the preferable samples for monitoring inorganic germanium exposure in the occupational setting.

TREATMENT

Because there are few human data on the treatment of germanium toxicity, treatment is primarily supportive. Theoretically, the treatment of an exposure to germanium tetrahydride would be similar to the treatment of arsine poisoning (see "Arsenic" chapter).

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Chapter 13

GOLD

HISTORY

Gold has been a precious metal since antiquity. The Chinese, Egyptians, and Greeks admired the luster and corrosion resistance of this metal, especially as a constituent of jewelry and adornments. Some alchemists during the Dark Ages considered gold a panacea for all diseases and an elixir for eternal youth. In the 16th century, Paracelsus considered the combination of mercury and gold the "elixir of life."[1] Following Robert Koch's 1890 report that gold cyanide inhibited the tubercle bacilli *in vitro* but not *in vivo* (guinea pigs), gold monovalent salts (sanocrysin, sodium aurothiosulfate) were administered as nonspecific antiseptics for various infections including bacterial endocarditis, gonococcal arthritis, lupus vulgaris, rheumatic fever, and syphilis.[2] In 1927, Lande introduced the parenteral use of the gold thio salt, aurothioglucose (Solganal-B-Oleosum), for rheumatoid conditions believing these conditions resulted from nonspecific, low-grade infections (e.g., tubercle bacilli).[3] Also believing in an infectious etiology, Jacques Forrestier and later TA Kean promoted the use of gold for the management of rheumatoid arthritis during the 1930s.[4,5] Gold therapy (also known as chrysotherapy) flourished during 1925–1935 as the period became known as the Gold Decade in tuberculosis treatment; however, the recognition of serious adverse effects and questionable efficacy limited the overall use of gold therapy by the end of the 1930s.[6] During this period, bluish discoloration of the skin (chrysiasis) became a recognized complication of parental chrysotherapy. In 1945, Thomas Fraser reported that parenteral sodium aurothiomalate (Myocrisin® or Myocrisin®) was effective for the treatment of rheumatoid arthritis in the first controlled clinical trial based on clinical improvement in 82% of the Myocrisin® patients and 45% of the controls.[7] However, 75% developed mostly mild toxic reactions (headache, shivering, skin rash, oral lesions, albuminuria, reduced white blood cell count, colitis) when using the high gold doses associated with treating tuberculosis. In 1961, the Empire Rheumatism Council concluded multicenter trials that documented the efficacy of monovalent gold (aurothioglucose, gold sodium thiomalate).[8] The oral gold phosphine compound, auranofin, was approved for the treatment of rheumatoid arthritis in 1985; however, this drug is rarely used now because subsequent clinical studies reported injectable gold drugs are more effective than auranofin.[9] Despite the introduction of therapeutic drugs for rheumatoid arthritis with fewer adverse effects and greater overall efficacy, chrysotherapy remains an option for patients with poor responses to other antiarthritic drugs. Currently, gold nanoparticles (i.e., engineered nanoparticles with all three dimensions < 100 nm) are constituents of automobile parts, beverages, cosmetics, food packaging, lubricants, toothpaste, and medical diagnostics.[10,11]

PHYSIOCHEMICAL PROPERTIES

Gold is a soft, malleable, lustrous yellow, water insoluble, and corrosion-resistant member of Group 11 (Group Ib) in the periodic table with several oxidation states (1−, 0, 1+, 2+, 3+, 5+). This tasteless and odorless metal does not oxidize in air. Metallic gold (0) is relatively inert, resulting in low toxicity and

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immunogenicity. This metal shares similar electronic configuration as other transition metals (e.g., copper, silver). Although gold has at least 70 isotopes, only ^{197}Au is stable. The high chemical affinity of mercury for gold results in the common formation of mercury–gold amalgams.

Gold nanoparticles possess unique optical and physiochemical properties useful in biological and pharmaceutical fields (e.g., drug delivery, imaging, phototherapy), particularly the property of surface plasmon resonance. The absorption and scattering of light in response to the resonance of gold electrons produce localized heating and color changes. As a result of coherent oscillations by conduction-band electrons *plasmons* during irradiation with light, gold nanoparticles appear in different colors (e.g., red, blue) depending on the wavelength and size/shape of the nanoparticles.

Therapeutic use of gold involves the use of complex, monovalent gold. Parenteral monovalent gold compounds include gold sodium thiomalate, gold thioglucose, and gold sodium thiosulfate. Auranofin (triethylphosphine gold) is a lipid-soluble oral gold preparation that differs structurally from parenteral compounds by the presence of gold–phosphine and gold–thiol bonds. The gold content of auranofin is ~29% w/w, whereas the injectable formulations contain ~50% gold w/w. Figure 13.1 displays the chemical structures of three gold preparations previously used to treat rheumatoid arthritis, including auranofin.

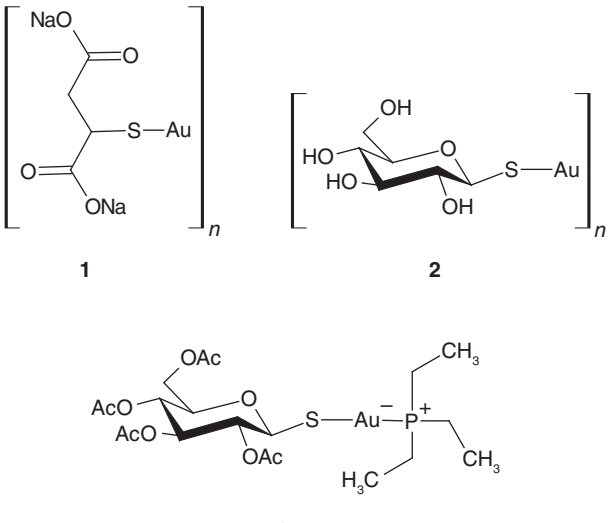


FIGURE 13.1. Therapeutic gold compounds. **1**. Sodium aurothiomalate (Myocrisin®), **2**. Aurothioglucose (Solganol), **3**. Tetraacetyl-β-D-thioglucose gold(I) triethylphosphine (auranofin). (Adapted from Berners-Price).[12]

EXPOSURE

Uses

The uses of this rare metal include components of jewelry and medical devices (prostheses, acupuncture needles), chrysotherapy (soluble gold salts) for rheumatoid arthritis, and restorative dentistry (prosthetic alloys containing copper, silver, and platinum).[13] The ductility, high malleability, and ease of conduction of heat and electricity favor industrial uses in telecommunication (semiconductors, integrated circuits, cable termination) and electrical contacts as well as an antiglare agent in space helmets to protect astronauts from intense solar radiation.[14] Newer uses of this metal involve the production of gold nanoparticles to deliver drug and gene therapy, noninvasive whole-body imaging, and hyperthermic cancer therapy. Properties useful for biomedical applications include the high biocompatibility of bulk gold, easy surface functionalization with amine and thiol compounds, narrow size control during synthesis, and good chemical stability.[15]

Production Processes

Gold exists naturally in its elemental state typically in pyrites, quartz, or gold telluride ores. Pure metallic gold is reddish-yellow; however, the presence of other metals (e.g., copper, nickel, palladium, platinum, silver, tellurium) in ores or alloys produces multiple colors from silver-white to orange and red/purple. White gold is a gold-based alloy containing nickel, palladium, platinum, silver, and zinc that produce the white color. Extraction and purification of gold involve the following: 1) amalgamation with mercury and 2) MacArthur-Forrest Process (cyanide), flotation procedures (telluride ores), Miller Process (chlorination), and Wohlwill Process (electrolytic).[14] Adverse effects associated with these processes usually result from by-products or contaminants (e.g., arsenic, free cyanide, mercury vapor, radon, silica dust) rather than gold.

Sources

The earth's crust contains an average of ~5 ppb Au (5 μg/kg) dry weight. A review of gold concentrations in the environment reported maximum gold concentrations of 0.001 ppb (0.001 μg/L) in rainwater and 0.0015 ppb in seawater.[16] Fallout from atmospheric dust accounts for most of the gold in ocean surface waters. Commercial ventures mining gold from the ocean have been unsuccessful; during the 1920s, German

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scientists failed to recover sufficient gold from seawater to help reduce the German debt from World War I.[17] Comparisons of gold concentrations in preconcentrated samples from various sites are complicated by the use of various analytical techniques with different limits of quantitation. Gold is detectable in vegetable and animal sources, including food. In a cross-sectional study of 84 German children aged 14–83 months, the median *weekly* dietary gold intake was 1.1 μg with an upper 95% of 4.9 μg as measured by sector-field inductively coupled plasma mass spectrometry.[18] The weekly arithmetic mean was 2.07 ± 4.33 μg with a maximum weekly Au intake of 35 μg.

DOSE EFFECT

The usual dosage schedule for parenteral gold involves weekly injections of 1, 5, or 10 mg, followed by 50 mg each week up to a total dose of 1 g Au. The typical oral dose of auranofin (triethylphosphine gold) for rheumatoid arthritis is 6 mg daily for 6 months and 9 mg daily for an additional 3 months if initial therapy was ineffective. In dose-establishment studies, the efficacy of 2, 3, and 6 mg auranofin is similar.[19] Although higher doses are more frequently associated with more rapid clinical improvement, more frequent or severe lower gastrointestinal complaints occur at higher doses. Most overdoses of parenteral compounds involve the iatrogenic administration of 10 times the daily dose. Patients have tolerated 500 mg aurothioglucose without significant toxicity or deterioration in their disease.[20] There are no data in humans on the fatal dose of gold.

TOXICOKINETICS

Absorption

The pharmacokinetics of gold depends on the oxidation state and the route of exposure. In general, absorption of elemental gold from the gastrointestinal tract is low.[18] The absorption of auranofin following ingestion is relatively low (i.e., ~25%) compared with the parenteral route.[21] A 50-mg intramuscular injection of gold sodium thiomalate produces peak serum gold concentrations of 6–8 mg/L within 2 hours.[22] These values decline over 7 days to the range of 3 mg/L. Oral daily doses of auranofin of 2–9 mg produce serum Au concentrations of 0.3–1 mg/L; these values do not vary significantly during the day while on chronic therapy.[23]

Distribution

Gold distributes widely throughout the body with the highest concentrations occurring in the liver, kidneys, adrenals, and spleen during therapeutic use. In the blood, gold is ~80–90% protein-bound, primarily to metallothionein,[24] albumin,[25] and γ-globulin.[26,27] Parenteral gold preparations produce higher gold concentrations in the tissues compared with the oral gold preparation, auranofin. Gold concentrates in red blood cells, particularly in smokers,[28] whereas little accumulation of gold occurs in the hair, nails, or skin.

Elimination

Following intramuscular administration of gold sodium thiomalate (Myochrysine®), excretion accounts for ~40% of the dose within the first week as measured by neutron activation analysis. During this period, ~70% appeared in the urine and ~30% in the feces.[29] The initial elimination half-life of gold in the blood after parenteral gold therapy is ~6 days compared with a half-life of 17–26 days after daily oral administration of 6 mg auranofin.[30] However, the body retains parenteral gold (sodium thiomalate) longer than auranofin. After 250 days, ~25% of a parenteral dose of gold remains in the body compared with 1% of an auranofin 180 days after administration.[31]

Maternal–Fetal Kinetics

Gold crosses the placenta and diffuses into fetal tissue. Umbilical blood and maternal blood contain similar concentrations of gold after the maternal administration of sodium aurothiomalate throughout pregnancy.[32]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Although a few plants accumulate gold while growing in gold-rich soils, living organisms do not use metallic gold in chemical processes reflecting the stability and rarity of elemental gold. The mechanism of action for the anti-inflammatory effects on the joints of rheumatoid arthritis patients remains unclear. *In vitro* studies suggest gold has an affinity for thiol-containing proteins, selenoproteins, cysteine proteases, mitochondrial isoforms, and transcription factors.[12] Potentially, the difference in binding accounts for the difference in toxicity between the two main types of gold compounds. Gold compounds also inhibit mononuclear function as well as pinocytosis and phagocytosis *in vitro*. Pathological changes associated with gold therapy include acute

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tubular necrosis, tubular degeneration, and immune complex glomerulonephritis; proximal tubular epithelial cells may contain gold inclusions (aurosomes) on pathological examination.[33]

CLINICAL PRESENTATION

Adverse Medicinal Effects

Adverse reactions develop in approximately one-third of patients undergoing treatment with gold salts for rheumatoid arthritis, primarily dermatological (dermatitis, pruritus, stomatitis), and gastrointestinal (diarrhea).[21] Bluish-gray discoloration of the skin (chrysiasis) has been a recognized complication of gold therapy since the late 1920s. In a case series of five patients receiving 4–10 g elemental gold parentally as an aurothiopolypeptide over many years, skin biopsies demonstrated crystalline, amorphous, and spherical auriferous deposits in the upper dermis.[34] Most adverse reactions are mild (anemia, thrombocytopenia), but life-threatening complications may involve kidney failure, agranulocytosis, or aplastic anemia depending on the type of gold compound and dose.[35] Proteinuria develops more commonly in patients receiving parenteral therapy than other types of exposure or other second-line drugs for rheumatoid arthritis;[9] the proteinuria usually resolves within 1–3 years after cessation of therapy.[36] Some of these patients progress to nephrotic syndrome and reversible renal failure.[37] Rarely, an enterocolitis characterized by profuse diarrhea and vomiting along with abdominal pain, fever, and eosinophilia develops, typically during parenteral gold therapy.[38] Pulmonary complications (bronchiolitis, fibrosis) are also rare. Case reports associate the development of diffuse pulmonary infiltrates and a restrictive ventilatory defect with gold therapy.[39,40] Studies in animals suggest high gold concentrations may produce acute renal failure.[41]

Acute Toxicity

Most overdoses to date involve the inadvertent administration of 500 mg gold salt as an intramuscular injection (10 times the therapeutic dose). Typically, these patients remain asymptomatic; occasionally, mild elevations in serum hepatic aminotransferase concentrations[42] and thrombocytopenia[43] develop. Rarely, case reports associate cardiac dysthymias with gold toxicity. Three hours after the intramuscular injection of 500 mg of aurothiomalate, a 32-year-old patient developed ventricular tachycardia along with weakness, palpitations, and dizziness.[44] The dysrhythmia resolved within a few hours of treatment with lidocaine and BAL.

Environmental Exposure

Eczema of the head and neck is the most common hypersensitivity reaction to gold, particularly gold-containing body-piercing jewelry containing other metal sensitizers (white gold);[45] however, hypersensitivity to pure gold is very rare.[46] A 24-year-old woman developed a contact hypersensitivity reaction to her 18-carat gold wedding ring.[47] Patch testing with pure gold leaf was negative. Patch testing with 0.2% gold chloride was positive at 72 hours, whereas the response with 0.02% gold chloride was equivocal.

Occupational Exposure

Gold is a rare skin allergen that may produce allergic contact dermatitis or pigmented papular eruption. A 32-year-old man developed discrete dark-brown macular pigmentation 30 minutes after direct contact with gold trichloride crystals; he subsequently developed pigmented papules at the contact site.[48] Patch tests and intradermal injections with gold salts confirmed hypersensitivity to gold. In a cross-sectional study of 1,197 active South African gold miners, 139 (12%) had evidence of reactive airways as defined by >10% increase in FEV_1 following inhalation of salbutamol.[49] A history of wheezing in these miners did not predict the presence of reactive airway disease. Of the 272 miners (i.e., 23% of the cohort) with a history of wheezing, only 40 miners had objective evidence of reactive airways as defined above. The study detected no correlation between the duration of mining and airway reactivity with the authors concluding that the evidence did not support an association between gold exposure and airway reactivity. Silicosis was prevalent in the gold miners; a subsequent study reported that emphysema accounted for the pulmonary changes in this cohort.[50]

Reproductive Abnormalities

Gold compounds demonstrate dose-related teratogenic effects in rabbits and rats;[51] however, gold doses in these experiments far exceed currently recommended doses. Limited human data on the use of gold therapy do not suggest an increased risk of reproductive abnormalities.[52] A follow-up study of six offspring of mothers who received parenteral gold from the second to ninth week of gestation did not detect any congenital abnormalities.[53]

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Carcinogenesis

The International Agency for Research on Cancer and the US National Toxicology Program do not recognize gold or gold compounds as potential human carcinogens. A mortality study of 13,603 Canadian gold miners revealed an increased risk of cancer (SMR = 129, 95% CI: 115–145) in gold miners with >5 years of gold mining experience before 1945.[54] The minimum latency period between initial employment in the gold mine and the discovery of cancer was 15 years. Lung cancer mortality was not increased in workers employed after 1945. A follow-up study of these gold miners demonstrated a number of respirable carcinogens in the mines including radon, arsenic, and asbestos.[55]

DIAGNOSTIC TESTING

Analytical Methods

Typical analytical procedures for the determination of picogram ranges (μg/L) involve pretreatment (e.g., dry ashing, microwave-assisted decomposition, wet digestion) followed by separation from interferents/complex matrices and multielement instrumental techniques.[56] Sensitive, reliable analytical techniques for quantitation of gold in environmental samples include inductively coupled plasma/mass spectrometry and inductively coupled plasma/optical emission Spectrometry.[57] Electrothermal atomic spectrometry (graphite furnace/atomic absorption spectrometry) and neutron activation analysis provided low limits of detection. High-performance liquid chromatography/inductively coupled plasma/mass spectrometry can identify oxidation state and gold complexation in aqueous environments with detection limits in the range of 0.05–0.30 μg/L.[58]

Biomarkers

The weekly administration of 50 mg of soluble salt produces steady-state serum gold concentrations of 4–8 mg/L by the eighth week; however, adverse reactions were not correlated to serum gold concentrations. The peak serum gold concentration after an injection of 500 mg gold aurothiomalate was 50 mg/L.[43] In the cross-sectional German Environmental Survey of 1,080 inhabitants aged 18–69 years, the geometric mean urine gold concentrations were 45.5 ng/L with an upper 95% of 239 ng/L and a maximum of 2,120 ng/L.[59] The number of bridges, crowns, and dental inlays strongly influenced the urinary gold concentration.

TREATMENT

Treatment is primarily supportive. Individual case reports document the use of steroids (pneumonitis),[60] peritoneal dialysis,[61,62] and BAL chelation;[63] however, few clinical data are available to confirm efficacy or guide treatment. The reports of the successful use of dimercaprol,[64] penicillamine,[65] and *N*-acetylcysteine[66] as chelating agents for gold toxicity are largely anecdotal without good clearance data. Technically, anti-rheumatoid arthritis drugs are monovalent gold compounds that do not contain the four atoms in a square-planar four-coordinate necessary for the formation of a chelate ring; trivalent gold compounds are able to form chelate rings.[67] A study in mice receiving 3 mol antidote/mol gold intraperitoneally 20 minutes after the intraperitoneal administration of monovalent gold indicated that survival was greater in the mice administered 2-dimercaptosuccinic acid (DMSA) or sodium 2,3-dimercpatopropane-1-sulfonate (DMPS) than *D*-penicillamine or *N*-acetyl-L-cysteine.[68] There are inadequate human data on DMSA or DMPS to determine the efficacy of these agents for gold intoxication. A patient who received two 500-mg gold aurothioglucose injections within 1 week remained asymptomatic without chelation therapy.[42] Consequently, the decision to use chelation therapy (e.g., BAL) for gold toxicity depends on clinical judgment, the degree of expected toxicity, and the adequacy of treatment alternatives.

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Chapter 14

INDIUM

HISTORY

In 1863, Theodore Richter and Ferdinand Reich isolated indium from zinc ores using spectroscopy. The name indium derives from the indigo flame created by the ignition of indium. Until the early 1990s, indium production was small with uses limited to dental alloys, nuclear reactor rods, and semiconductor research. The development of transparent conductive coatings for liquid crystal displays and plasma televisions with fine, poorly water-soluble indium compounds (indium oxide, indium hydroxide, indium tin oxide) substantially increased the exposure of workers to indium compounds. In 2001, a worker exposed to indium dust during the polishing of indium tin oxide targets died after developing bilateral pneumothoraces from interstitial pulmonary disease.[1] Subsequently, several cases of pulmonary alveolar proteoses, interstitial fibrosis, and emphysema ("indium lung") have been associated with occupational exposure to indium compounds in Japan, the United States, and China.

PHYSIOCHEMICAL PROPERTIES

Indium is a rare, soft, ductile, silvery-white nonferrous metal in Group 13 (Group IIIa) of the periodic table with boron, aluminum, gallium, and thallium; indium phosphide is a black cubic crystalline powder. As a malleable and ductile metal, indium easily forms alloys, particularly low-melting-point alloys. Indium tin oxide is a sintered ceramic material consisting of 90% trivalent, water-insoluble indium oxide (In_2O_3, CAS RN: 1312-43-2) and 10% tin oxide (SnO_2). In aqueous solutions, only the trivalent form of indium is stable. The most common indium salts are trivalent; monovalent and divalent indium salts also exist. Table 14.1 lists the identifying information and physical properties of indium and indium phosphide.

TABLE 14.1. Physical and chemical characteristics of indium and indium phosphide.

Physical Characteristic	Indium	Indium Phosphide
CAS RN	7440-74-6	22398-80-7
Molecular formula	In	InP
Molecular weight (g/mol)	114.82	145.79
Melting point/boiling point (°C)	156.6/2080	1062
Density (g/mL)	7.31	4.81
Water solubility (25 °C)	Insoluble	Low

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number.

EXPOSURE

Uses

The use of indium is limited by the low rate of recovering indium as a by-product of zinc and lead–zinc smelting; trace amounts of indium exist in sphalerite (ZnS). Occupational exposure to indium occurs primarily in the microelectronics industries. The leading end use of indium is the production of indium tin oxide for electronics. Thin-film coatings of indium tin oxide are

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used primarily for their electrical conduction properties as transparent conductive films on a variety of flat-panel devices (e.g., liquid crystal displays, light-emitting diodes, plasma display panels). Optoelectronics (e.g., photovoltaic, light-emitting diodes) uses a variety of indium compounds besides indium tin oxide, including indium phosphide, indium arsenide, indium sulfide, copper indium diselenide, and copper indium gallium diselenide. Indium phosphide is an excellent semiconductor with high operating efficiency and power; the relatively high refractive indices of indium phosphide and ternary (InGaAs) and quaternary (InGaAsP) derivatives allow sharp, small bends for the fabrication of very small devices. Indium phosphide is used for the production of nanowires and quantum dots.[2,3] Other uses of indium include semiconductors, electrical components, low-melting point solders and alloys (fuses, temperature indicators, infrared detectors, high-speed transistors, high-efficiency photovoltaic devices), and medical research (indium radioisotopes). Medical uses of organoiridium complexes include electrodes for stimulation, brachytherapy in gynecological oncology, catalysts, and anticancer agents.[4]

Production Processes

Zinc ores are the most common sources of commercial indium including christophite (FeS:ZnS) and sphalerite (ZnS). Methods to recover indium from the acid leachate of crude zinc liquors during zinc smelting include precipitation as a phosphate or on metallic zinc rods. The primary source of indium is a by-product of smelting zinc ores and, to a lesser extent, sulfide ores of copper, tin, iron, and lead. Indium combines with phosphorus under controlled conditions (high temperature, pressure) to form indium phosphide; alternately, the thermal decomposition of trialkyl indium and phosphine gas (PH_3) produces indium phosphide. This compound does not occur naturally. Disposal and recycling of component materials in liquid crystal displays may result in exposure to indium compounds.

Sources

Air

Ambient air concentrations of indium are very low. In a study of ambient air in the relatively unpolluted Lake District of the United Kingdom, the average indium concentration in air samples collected during the calendar year was ~0.3 ng/m^3 as measured by neutron activation analysis.[5] This value was similar to analyses of indium in ambient air samples collected at six other UK nonurban sites. The mean indium concentration in high-volume air particulate filters collected in downtown Kellogg, Idaho, during a calendar year was 5.79 ng/m^3 (range, 0.06–43.3 ng/m^3).[6] This town is located in the Kellogg Valley near a lead smelter that began operations in 1916.

Soil

Indium is a rare element with soil concentrations typically of <0.01 ppm. In a study of soil samples near an Idaho lead smelter, the mean indium concentration was ~2 ppm as measured by neutron activation analysis.[6]

Water

In a Taiwanese study of 30 groundwater samples from an industrial district containing a large industrial park with semiconductor manufacturers, the mean indium concentration was 9.25 μg/L (range, 0.95–20.05 μg/L) compared with 0.01 μg/L (range, <0.005–0.05 μg/L) in a distant district (control).[7] The samples were collected from well water 10 m below the surface and analyzed by inductively coupled/mass spectrometry. The mean indium concentration in 229 dissolved river water samples from a summary of 4 Japanese studies was 1.9 ± 4.4 ng/L compared with 9.1 ± 35.5 ng/L in 179 particulate samples from the same area, as measured by ICP/MS.[8] For 25 dissolved and particulate lake water samples, the mean indium concentrations were 1.4 ± 1.8 ng/L and 4.8 ± 14.8 ng/L, respectively. The mean indium concentrations in 38 dissolved and 24 particulate water samples from coastal seawater were 3.0 ± 6.4 ng/L and 2.4 ± 1.5 ng/L, respectively. There are few data on the environmental exposure of the general population to indium.

Food

The estimated average daily intake of indium is minimal (i.e., <10 μg/kg body weight) as a result of the poor oral absorption of indium and the low indium concentration in most foods.[9] Beef and ham typically have the highest indium concentrations (<0.01 ppm), although shellfish and fish living near point sources may contain indium concentrations exceeding these concentrations. The estimated body burden is ~50 ppm.

DOSE EFFECT

There are inadequate data to determine dose-effect responses in humans. Pulmonary exposure of rodents

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to indium compounds produces inflammation in the lungs. Intratracheal instillation of 24 mg/kg copper indium diselenide produced pulmonary inflammation within 72 hours characterized by an influx of macrophages, lymphocytes, and polymorphonuclear leukocytes.[10] Some systemic absorption of indium occurred.

TOXICOKINETICS

Tracer studies indicate that indium is poorly absorbed (<2%) through the gastrointestinal tract when administered as the $^{113m}InCl_2$ or ^{113m}In DTPA (diethylene triamine penta acetic acid) complex.[11,12] *In vitro* studies indicate that trivalent indium binds to transferrin in the blood.[13] Rodent studies suggest that most indium is distributed to kidneys, liver, and spleen.[14] In these studies, the kidney excretes ~50% of the indium chloride with an initial elimination half-life of ~2 days followed by a slower elimination half-life of ~2 months.[15,16] An observational study of 465 current and 127 former indium workers suggested the dissolution and clearance of indium from the body are slow.[17] The mean serum indium concentrations were similar in the two groups (8.4 μg/L and 9.6 μg/L, respectively), despite time following cessation of indium exposure of 58.3 months (95% CI: 2–201 months) for the latter group; however, estimates of cumulative exposure parameters for former workers were not reported. In a follow-up study of retired indium workers, the estimated indium biological half-life was ~8 years based on serial serum indium concentrations drawn after retirement.[18] For indium colloidal hydrated indium oxide, the feces account for a majority of the elimination with <10% of the dose eliminated in the urine during the first month. The biological half-lives of indium chloride and indium oxide were similar.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Indium is a rare metal with no known physiological role in humans. Occupational exposure to indium compounds is associated with pulmonary inflammation and interstitial disease in some of the exposed workers. In a case series of 10 workers diagnosed with indium lung, a granular, eosinophilic intraalveolar exudate consistent with alveolar proteinosis was present in all but one worker.[19] Other histological changes included cholesterol clefts (acicular spaces resulting from the dissolution of cholesterol esters during histological processing), granulomas associated with the cholesterol clefts, fibrosis, and occasionally honeycombing and emphysema. Occasional macrophages and lymphocytes occur in alveolar wall cellular infiltrates. Fibrotic foci may occur in areas without cholesterol clefts. The pathogenesis of these indium-associated changes remains unclear.

CLINICAL RESPONSE

Acute Toxicity

The medical literature contains little documentation of the acute effects of indium exposure.

Environmental Exposure

Indium is a rare metal with minimal exposure to the general population.

Occupational Exposure

There are few epidemiological data on the toxicity of indium compounds. Case reports of indium-exposed workers suggest that occupational exposure to indium compounds may cause pulmonary disease beginning as pulmonary alveolar proteinosis and progressing to interstitial lung disease ("indium lung") with fibrosis and emphysema.[20] Follow-up studies of indium workers suggest interstitial lesions regress partially with reduction in ambient air indium concentrations; however, emphysematous lesions continue to progress.[18] Two case reports from a Japanese factor associate wet surface grinding of indium tin oxide during production of liquid crystal displays with the development of pulmonary toxicity (subpleural emphysema, cholesterol granulomas).[1,21] Symptoms included dry cough, dyspnea, sputum production, weight loss, and exertional dyspnea. Both patients had elevated serum indium concentrations (51 μg/L, 290 μg/L) compared with controls; lung biopsies demonstrated the presence of submicron particles in the alveolar spaces, alveolar septum, and bronchiolar lumens that contained indium and tin based on X-ray energy spectrometry. One of these patients died after developing bilateral pneumothoraces. The exact etiology remains unclear as there was no exposure data on indium or tin concentrations in the workplace; other disease processes (e.g., lipoid pneumonia) may have contributed to the pulmonary effects. A cross-sectional study of 108 workers in this plant revealed 18 workers (83% smokers) with chronic cough and/or sputum production with the geometric mean indium concentrations in working areas of 0.01–0.05 mg/m^3 up to a

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maximum of 0.36 mg/m^3 as measured by inductively coupled plasma/mass spectrometry (ICP/MS).[22,23] Four workers had clubbed fingers; however, none of the workers complained of exertional dyspnea or peripheral cyanosis. There was evidence of subclinical pulmonary disease (fine reticulonodular shadows, reduced diffusing capacity, DL_{CO}, and vital capacity, VC) in some of the workers; 79% of the workers were former or current workers. The DL_{CO} decreased with each quartile of serum indium concentrations, with the fourth quartile statistically significantly lower than the first quartile.

Two workers (hydrogen furnace operator, indium tin oxide department) developed pulmonary alveolar proteinosis while working at a US facility producing indium tin oxide.[24] Both workers had symptoms of impaired gas exchange including dyspnea on exertion. Lung biopsies demonstrated intraalveolar proteinaceous material and globules positive for periodic acid-Schiff (PAS) stain and the presence of indium in the lung material. One worker died of progressive pulmonary failure, whereas the other worker improved after treatment (albeit with some respiratory impairment). The latter worker had positive antibodies to granulocyte macrophage-colony stimulating factor. Pulmonary alveolar proteinosis is a rare, usually idiopathic disease that classically involves the alveoli rather than the interstitial infiltration and fibrosis seen in Japanese workers. Four months before developing pulmonary symptoms, the surviving worker had an undetectable plasma indium concentration following an acute ammonium hydroxide exposure.

A cross-sectional study of 93 Japanese workers in 2 indium tin oxide manufacturing and 2 recycling plants and 93 controls without indium exposure did not detect differences in spirometry, subjective symptoms, or the prevalence of interstitial or emphysematous changes on lung high-resolution computerized tomography between exposed and nonexposed workers.[25] About half the workers were exposed to airborne concentrations of indium tin oxide compared with 40% to indium trioxide and/or indium hydroxide dust and ~10% to metallic indium dust. The study did demonstrate an exposure-response relationship between serum indium concentrations and markers of lung inflammation (Krebs von den Lungen-6 or KL-6, surfactant protein-A or SP-A, SP-D); however, the clinical significance of these serum markers remains unclear.

Reproductive Abnormalities

There are few data in humans; animal studies suggest that the teratogenic potential of indium and indium compounds is relatively low.[26,27]

Carcinogenicity

There are few data on the carcinogenicity of elemental indium in humans that focus specifically on indium. Despite the limited human data, the IARC lists indium phosphide as probably carcinogenic to humans (Group 2A) based on extraordinarily high incidence of malignant pulmonary, hepatic, and adrenal (pheochromocytoma) neoplasms in rodents following inhalation exposure to indium phosphide.[28] One case of lung cancer was reported in a nonsmoking Japanese worker exposed to indium tin oxide;[29] however, the IARC lists these substances as a possible human carcinogen (Group 2B) based on sufficient evidence in animals (i.e., ↑ bronchioloalveolar carcinoma in rats, but not mice)[30] and inadequate data in humans.[31]

DIAGNOSTIC TESTING

Analytical Methods

Techniques for the determination of indium in biological samples include spectrophotometry, voltammetry, neutron activation analysis, electrothermal atomic absorption spectrometry,[32] graphite furnace atomic absorption spectrometry (GF/AAS), and inductively coupled plasma/mass spectrometry (ICP/MS). The latter technique has good sensitivity (LOD, 0.17 μg/g; LLOQ, 0.57 μg/g) with small sample sizes, minimal elemental interference, and capability for multi-elemental analysis.[33] The use of GF/AAS after precipitation of chitosan at pH 7–9 allows the determination of indium in water samples with a limit of detection (LOD) of 0.04 μg/L with a relative standard deviation of <5%.[34] Using flame atomic absorption spectrometry with slotted quartz tube or slotted quartz tube atom trap, the LOD was 3.63 ng/mL and 2.60 ng/mL, respectively.[35] The low indium concentration in environmental samples and the matrix effects of interfering species complicate indium analysis; consequently, a separation enrichment procedure is necessary prior to spectrometry. Techniques for preparation of samples containing indium include solvent extraction, coprecipitation, electrochemical methods, and solid-phase extraction with

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various absorbants (e.g., Chromosorb 108 resin).[36] Current analytical methods typically measure total indium without speciation. The use of selective sequential extractions combined with inductively coupled plasma/mass spectrometry allows the determination of elemental indium, soluble trivalent salts, and insoluble trivalent salts.[37]

Biomarkers

Indium is not typically quantifiable in the blood of persons without occupational exposure to indium depending on the sensitivity of the analytical method.[38] In a study of occupational indium exposure, 19 of the 24 controls (management jobs in the same factory) had whole blood indium concentrations below the limit of detection (<0.7 ng/mL); 23 of the 24 controls had serum indium concentrations below the limit of detection (<0.4 ng/mL) as measured by graphite furnace atomic absorption spectrophotometry after wet digestion.[39] The single regression coefficient for whole blood and serum indium concentration was 0.94, suggesting that indium is relatively evenly distributed between serum and erythrocytes. However, the uptake of indium by erythrocytes is relatively small, resulting in the distribution of indium primarily in the plasma of partially hepatectomized rats.[40] There are inadequate data to quantitate the plasma/erythrocyte indium ratio.

Abnormalities

Indium lung disease is an interstitial illness characterized by pulmonary alveolar proteinosis that may progress to fibrosis with or without emphysema. Spirometric abnormalities include reduced diffusing capacity, FEV_1, and FVC. Additionally, biomarkers of interstitial lung disease (e.g., Krebs von den Lungen-6, surfactant protein-D) are typically elevated.[41]

HEALTH SURVEILLANCE

Environmental Monitoring

There are no established regulatory limits for exposure to indium phosphide. The ACGIH recommends a threshold limit value/time-weighted average (TLV–TWA) of 100 μg/m^3 for inhalation of indium. Table 14.2 lists regulatory and suggested guidelines for exposure to indium and indium compounds. In a study of a Japanese ingot production plant, the indium concentration in air varied between ~10–1,030 μg/m^3 with a mean of 190 μg/m^3 and a median of 55 μg/m^3.[38] There was substantial interindividual and intraindividual variation. The study did not detect a correlation between ambient air indium concentrations and the indium concentration in the blood or urine of the workers.

TABLE 14.2. Regulations and guidelines for exposure to indium and indium compounds.

Exposure Limit	Value
OSHA	
PEL–TWA (8-hour)	NE
PEL-Ceiling	None
PEL-Acceptable Maximum Concentration (30 minute maximum during 8-hour shift)	None
NIOSH	
REL–TWA (10-hour)	100 μg/m^3
REL–STEL (15-minute)	None
IDLH	None
ACGIH	
TLV–TWA (8-hour)	100 μg/m^3
Indium and indium compounds	100 μg/m^3 (as In)
Indium tin oxide	0.1 μg/m^3 (as In)
TLV–STEL (15-minute TWA)	None

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; IDLH = immediately dangerous to life and health; NE= not established; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average.

Biological Monitoring

Urine

The mean indium concentration in end-of-shift, end-of-work week urine samples from nine indium ingot production workers exposed primarily to In_2O_3 was 1.58 μg/L (1.54 μg/g creatinine) with a range in workweek samples of 0.13–8.68 μg/L (0.22–3.50 μg/g creatinine).[38] In a study of 72 production workers and 72 engineers exposed to unspecified indium compounds, the 2 exposed groups had mean inhalable air indium concentrations of 8.4 μg/m^3 (range, 0.34–101.26 μg/m^3) and 7.4 μg/m^3 (range, 0.25–100.27 μg/m^3), respectively, compared with a mean of 2.1 μg/m^3 (range, 0.14–18.00 μg/m^3) for 72 administrative workers as measured by ICP/MS.[42] The mean indium concentrations in spot end-of-shift urine samples were 7.0 ng/mL (range, 3.05–35.89 ng/mL), 5.9 ng/mL (range, 3.02–34.09 ng/mL), and 1.2 ng/mL (range, 0.05–7.27 ng/mL), respectively.

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Measurements of inhalable gallium and arsenic in this study indicated that exposure to these two metals in this semiconductor plant was higher than indium.

Blood

Although plasma or serum indium concentrations are commonly used as biomarkers of indium exposure, limited data are available to determine the best biomarker. In a study of 87 current ITO facility workers with median duration of indium exposure of 1.9 years, current and cumulative exposures ranged from 0.4–108 μg/m^3 and 0.4–923 μg-year/m^3, respectively.[43] For participants with duration of indium exposure of <1.9 years, current ($r_s = 0.74$) and cumulative ($r_s = 0.72$) were similar; however, the correlation between indium exposure and health effects was better for cumulative indium exposure than the current plasma indium concentration. Cumulative indium exposure is correlated with dyspnea, ↓FEV_1, ↓FVC, and elevated biomarkers of interstitial lung disease (KL-6, SP-D). An observational study of an indium-tin oxide production facility with a medical surveillance program to prevent the occurrence of indium lung detected more spirometric changes (restriction, excessive decline in FEV_1, low TLC, low DL_{CO}) and abnormal chest X-rays in workers with serum indium concentrations exceeding 5 μg/L than workers with lower indium concentrations.[44] However, the difference between the two groups was not statistically significant ($P = 0.07$).

In a study of 93 workers in indium-tin oxide manufacturing and recycling plants, the geometric mean serum indium concentration was 8.25 ± 4.55 ng/mL (maximum, 116.9 ng/mL) in the exposed workers compared with 0.25 ± 2.64 ng/mL in 93 nonexposed workers.[25] For comparison, the geometric mean indium concentration in 107 workers exposed to water-insoluble, partially respirable particles of unspecified indium compounds was 4.09 ± 7.15 ng/mL (90th percentile: 42.7 ng/mL) in whole blood and 2.86 ± 8.81 ng/mL (90th percentile: 36.1 ng/mL) in serum.[39] The whole blood and serum indium concentrations were below the limit of detection in 34 and 37 workers, respectively. The mean whole blood indium concentration in 103 Taiwanese workers exposed to unspecified indium compounds was 0.22 ± 0.17 ng/mL compared with 0.14 ± 0.12 ng/mL in blood samples from unexposed controls (office workers), as measured by inductively coupled plasma/mass spectrometry after microwave dissolution.[45] There was no difference in the mean urine indium concentrations between the two groups. The mean plasma indium concentration in nine current indium ingot production workers in Friday post-shift blood samples was 5.59 μg/L with a workweek range of 0.32–12.61 μg/L (0.22–3.50 μg/g creatinine) compared with a mean of 0.71 μg/L and median of 0.17 μg/L in plasma samples from five retired workers.[38] These workers were exposed primarily to In_2O_3 along with $In(OH)_3$ and elemental indium. The persistence of indium in former workers limits the correlation of plasma or serum indium concentrations with current indium exposure.

The Japan Society for Occupational Health proposed a serum indium concentration of 3 ng/mL as a biological monitoring limit based on reducing pulmonary inflammation as defined by elevated serum KL-6 concentrations.[22] In a Korean study of 50 indium workers, workers with serum indium levels of ≥3 μg/L had longer exposure durations and a higher prevalence of HRCT-detected interstitial lung changes; the KL-6 and surfactant protein-D (SP-D) concentrations were significantly higher in the highest serum indium quartile than the lowest quartile.[46] In a cross-sectional study of 87 indium-tin oxide production and reclamation facility workers, the median duration of exposure was 2 years (range, 0.1–5.5 years); the median plasma indium concentration was 1.0 ng/mL (interquartile range, 0.2–2.3 ng/mL with maximum value, 37 ng/mL).[41] The majority of the workers (56%) were asymptomatic. Spirometric abnormalities (i.e., emphysema ($n = 4$), fibrosis ($n = 2$), alveolar proteinosis ($n = 0$)) were similar to the general population; however, statistically significant differences occurred in the subset with plasma indium concentrations of ≥1 ng/mL when compared with workers with plasma indium concentrations <1 ng/mL. These differences included dyspnea (but not chronic cough, wheezing, sputum production, or chest tightness), predicted FEV_1 and FVC (92% ± 2.6%), and increased serum inflammatory markers (Krebs von den Lugen-6, surfactant protein-D).

TREATMENT

Treatment is supportive. There are no human data to recommend specific antidotes or methods to enhance elimination of indium.

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Chapter 15

IRON

HISTORY

Iron is an essential element for body function that has been used for many centuries in commercial processes. The production of steel is one of the cornerstones of the development of the industrialized world. For thousands of years, man used steel to build a variety of structures. In contrast to other cases of heavy metal poisoning involving the workplace and environment, most cases of iron toxicity result from the ingestion of iron-containing products by children. A dramatic increase in iron poisoning appeared during the middle of the 20th century. In the 1980s, ~5,000 cases of poisoning with iron preparations occurred annually in the United States, with the vast majority of these poisonings occurring in children of <6 years of age. Although the introduction of deferoxamine in the 1960s substantially reduced the mortality of patients hospitalized for iron poisoning, fatalities from iron ingestion remained a leading cause of death in young children ingesting adult iron medications.[1] Between 1983–1998, 44 reported pediatric deaths occurred in the United States from iron toxicity.[2] A US federal packaging regulation in 1997 required unit-dose packaging for all pharmaceutical products containing ≥30 mg elemental iron/dose. Pediatric deaths consequently decreased to <1/year. According to American Association of Poison Control Centers (AAPCC) data, exposure to iron salts accounts for <15% of the reported exposure to minerals and electrolytes (e.g., fluoride, calcium, potassium), whereas iron salts produce a majority of the moderate and major adverse outcomes following exposure to iron salts.[3] Among the electrolytes/minerals or vitamins with iron categories during 2013, the AAPCC reported no pediatric or adult fatalities from iron or iron salts.

Prolonged iron exposure from iron overload disorders increases intestinal iron absorption and causes hemochromatosis. This disease produces excessive iron deposition in tissues along with progressive fibrosis and organ failure (i.e., liver, heart, pancreas). During the mining and/or refining of iron ore, the protracted inhalation of iron or iron oxide dust may cause siderosis, particularly following heavy iron dust exposures in the 1940s and 1950s.[4] This condition describes the presence of stainable iron in lung tissue, but siderosis is usually benign and does not result in pulmonary dysfunction.

PHYSIOCHEMICAL PROPERTIES

Iron (CAS RN: 7439-89-6, atomic weight 55.85 g/mol) is a silver-white transition metal that is the primary constituent of the earth's molten core. The specific gravity of iron is 7.86. The magnetic properties of iron exceed similar properties of other metals; however, elemental iron loses its magnetic properties when heated to >770°C. The physical properties of iron change significantly with the addition of impurities (i.e., in ferroalloys) or temperature changes. The melting point of iron is 1,535°C, whereas the boiling point is 2,750°C. Fumes of iron oxide are red-brown in color. Iron pentacarbonyl (CAS RN: 13463-40-6) is a yellow, highly flammable, viscous, water-insoluble liquid that is a strong reducing agent. This compound forms in the presence of high partial pressures of carbon monoxide (e.g., steel cylinders containing carbon monoxide, steel pipes containing

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illuminating gases). The vapor pressure of iron pentacarbonyl at 25°C is 35 torr. Reduced iron is a high-density, amorphous powder formed by the reduction of iron oxide. The oxidation of reduced iron is an exothermic reaction.

Iron combines with many compounds including carbonates, carbonyls, chlorides, disulfides, oxides, and sulfates. The most stable oxidation states of iron compounds are ferrous (2+) and ferric (3+). While ferrous chloride, ferrous sulfate, ferric chloride, ferric nitrate, and ferric sulfate are water-soluble, the water solubility of the following iron salts is limited: carbonates, fluorides, hydroxides, oxides, phosphates, and sulfides. The strong tendency of iron to combine with oxygen results in the formation of stable hydroxyl groups (chelates). In the body, iron compounds promote (catalyze) oxidation reactions for many important functions. Iron binds to carbon forming a variety of commercial ferroalloys including wrought iron (0.035% C), cast iron (2–4% C), and steel (~0.2–1.5% C). Mild steel contains ~0.25% carbon, whereas high-carbon steel contains carbon concentrations exceeding 0.6%.

EXPOSURE

Production Processes

Steel is the main refinery product for processing iron ore; besides iron, steel may contain other metals including chromium, manganese, molybdenum, or nickel to improve the characteristics of the steel. Most iron ores are oxides; the most common iron ores are the orange-red hematite (Fe_2O_3, 40–70% Fe) and silver-gray magnetite (Fe_3O_4, ~70% Fe) ores; taconite is a lower-grade magnetite ore (i.e., 25–30% Fe, silicates, quartz) found in North America (e.g., Minnesota, Labrador). Steelmaking consumes almost all of the mining of hematite ores. Less common iron ores include limonite ($Fe_2O_3 \cdot H_2O$) and siderite ($FeCO_3$). Occupational exposure to iron occurs primarily following the inhalation of iron oxide during mining, steel refining, or the use of iron products (arc welding, metal polishing). Limited data from the 1960s suggest that airborne iron oxide concentration in some steel manufacturing plants in those years may have averaged 20–30 mg/m^3 (i.e., substantially above current workplace standards) ranging up to 60–70 mg/m^3.[5] Depending on the specific processes used, iron and steel foundry workers may be exposed to a variety of air contaminants in addition to iron oxides including silica, metal dust, carbonyl sulfide, hydrogen sulfide, sulfur dioxide, phenols, benzene, formaldehyde, acrolein, aldehydes, nitrogen oxides, ammonia, aromatic amines, and diisocyanate.[6] The latter chemical is associated with occupational asthma in iron and steel foundry workers. Processing iron containing arsenic or phosphorus may liberate arsine or phosphine gases, respectively. The reduction of iron oxide by hydrogen produces reduced iron.

Uses

The vast majority of iron is used to construct arms, bridges, buildings, highways, railroads, ships, and vehicles. Steel is an iron product that contains up to 1.5–2% carbon. The tensile strength of steel increases with increasing carbon content; hence, mild steel is suitable for fabricating wire, pipes, and sheets, whereas tools and cutting instruments require high-carbon steel. Structural steel typically uses medium steels. The addition of silicon, tungsten, or manganese to ferroalloys increases the hardness of steel, whereas nickel and chromium improve resistance to corrosion (i.e., stainless steel).

Iron compounds (e.g., iron oxides) account for <1% of the total consumption of iron; these compounds appear in magnetic tapes, pigments, polishing compounds, and plastics. In Europe, iron pentacarbonyl is an antiknock agent in gasoline. Reduced iron is the main ingredient in instant hand warmers and disposable heating pads that produces heat when exposed to oxygen. Superparamagnetic iron oxide nanoparticles contain maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4); these nanomaterials are typically considered biocompatible with numerous biomedical applications including enhanced MRI contrast agents for early detection of metastatic lesions and receptor-specific targeted drug delivery to cancerous tissues.[7,8]

Pharmaceutical Formulations

Indications for the medical use of iron salts include primarily iron deficiency and mineral supplementation during pregnancy. The relative toxicity of iron depends on the amount of elemental iron ingested, which varies according to the type of iron salt involved. Many iron poisonings result from the ingestion of ferrous sulfate. The percentages of elemental iron contained within various ferrous salts are listed in Table 15.1.

In general, the ingestion of nonionic forms of iron (carbonyl, iron polysaccharide complex) produces less severe toxicity than ionic ferrous salts. Carbonyl iron contains uncharged submicroscopic spheres of elemental iron crystals that require solubilization to ionized iron in the stomach prior to absorption. Consequently, the toxicity of carbonyl iron does not correlate to ionic

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TABLE 15.1. Elemental iron content in various iron salts.

Compound	Salt	Elemental Iron (%)
Ferrous sulfate	Anhydrous	36.8
	Crystalline	20.1
Ferrous chloride	Anhydrous	44.1
	Crystalline	28.1
Ferrous gluconate	Anhydrous	12.5
	Dihydrate	11.6
Ferrous fumarate		33.0
Ferric chloride	Anhydrous	34.3
	Hexahydrous	20.7
Ferric ammonium citrate		14.0–18.0

ferrous salts on a weight basis, despite the presence of 98% elemental iron in carbonyl iron products.[9] Similarly, iron polysaccharide complex contains 46% elemental iron by weight, but the effect of this product depends on the rate-limiting step of gastrointestinal absorption. Typically, chewable children's multivitamins contain up to 20 mg elemental iron/tablet compared with 50 mg elemental iron/tablet adult multivitamins and 100 mg elemental iron/tablet prenatal multivitamins. Table 15.2 lists the approximate elemental iron concentrations in representative iron products.

Sources

Environment

Iron is the fourth most abundant atomic element comprising ~5% of the earth's crust; iron-containing ores include hematite, magnetite, limonite, and siderate. The iron concentrations in freshwater and drinking water supplies vary widely with concentrations ranging from 0.01–1 mg/L,[10] whereas seawater contains much lower iron concentrations (<60 µg/L). Sampling of ambient air iron concentrations in the United States indicates that rural air contains 0.08–0.7 µg Fe/m_3 compared with 0.3–4.2 µg Fe/m^3 in air surrounding urban areas.[11] The average concentration of iron in the soil is ~5% (50 mg Fe/kg); some iron ores contain >50% Fe.

Diet

The average daily American diet contains about 15–40 mg Fe with approximately half of the iron in soluble form.[12,13] The concentration of iron is relatively high (30 mg Fe/kg) in beef, egg yolk, kidney, liver, and soybeans, whereas iron concentrations in grains, milk, and fruits are usually low (1–20 mg/kg).

TABLE 15.2. Elemental iron content of representative iron products. (Manoguerra et al.).[9]

Iron Product	Dosage Forms	Elemental Iron/Unit Dose
Ferrous sulfate		
	250 mg tablets	50 mg/tablet
	325 mg tablets	65 mg/tablet
	Timed-release tablets	65–105 mg/tablet
	Elixir 220 mg/5 mL	44 mg/5 mL
Ferrous gluconate		
	Drops (75 mg/0.6 mL)	9 mg/0.6 mL
	240 mg tablets	28 mg tablet
	300 mg tablets	36 mg/tablet
	325 mg tablets	40 mg/tablet
Ferrous fumarate		
	100 mg chewable tablets	33 mg/tablet
	Time-release tablets	50–110 mg/tablet
	200 mg tablets	65 mg/tablet
	325 mg tablets	107 mg/tablet
	350 mg tablets	115 mg/tablet
	Suspension (350 mg/5 mL)	33 mg/5 mL
Multivitamin hematinic products		
	Tablet or capsule	65–150 mg/tablet
Prenatal vitamins with iron		
	Tablet or capsule	9–106 mg/tablet
Adult multiple vitamin plus iron		
	Tablet or capsule	3–110 mg/tablet
Pediatric multiple vitamin plus iron		
	Chewable tablet	10–18 mg/tablet
	Drops	10 mg/mL
	Liquid	10 mg/5 mL
Carbonyl iron		
	Tablets and capsules	50–66 mg/tablet or capsule
	Liquid	15 mg/1.25 mL
Polysaccharide-iron complex		
	Tablets	50–150 mg/tablet
	Capsules	150 mg/capsule
	Elixir	100 mg/5 mL

The consumption of iron-rich staples combined with heavy iron contamination during the preparation process significantly increases the average daily iron intake in the diet of people in rural Ethiopia (i.e., 450 mg);[14] however, the clinical effects of high iron load is limited by the poor solubility of most iron forms. The local

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brewing of kaffir (corn beer) in South Africa produces high iron concentrations (50–250 mg/L) in the beer as a result of the acidity and the presence of iron-binding ligands (e.g., fructose).[15] Consequently, beer-drinking Bantu men ingest an average of 50–100 mg Fe/day. The relatively high prevalence of hemosiderin deposits and liver cirrhosis probably results at least partly from genetic influences, apart from HLA-linked hemochromatosis.[16,17]

DOSE EFFECT

Acute Ingestion

Reduced iron is an amorphous powder that has low toxicity as a result of limited gastrointestinal absorption;[18] however, case reports suggest that mild gastrointestinal irritation and slight elevation of serum iron may occur after ingestion of the contents of disposable heating pads.[19] An accurate estimation of the number of iron tablets ingested depends on the reliability of the history. Consequently, the onset and severity of symptoms are a more reliable way to determine the seriousness of iron poisoning than an estimation of the iron dose. Early onset of gastrointestinal symptoms may limit the amount of iron absorption, reducing toxicity.[20] Children's multivitamins with iron do not usually contain sufficient iron amounts or bioavailability to produce serious iron intoxication.[21,22] Based on the quantity of iron tablets ingested, the following amounts of elemental iron indicate the severity of toxicity:

Minimal risk of toxicity: <10–20 mg of elemental iron ingested per kilogram (e.g., 3 tablets of ferrous sulfate in a 10-kg child = 3 × (0.20) (325 mg)/10 kg = 19.5 mg/kg) produces little risk of toxicity.

Toxic range: At 40 mg elemental iron/kg (7 ferrous sulfate tablets in a 10-kg child = 7 × (0.2) (325 mg)/10 kg = 45.5 mg/kg), the risk of iron toxicity is moderate and referral to a health care facility is recommended.[9] Pediatric or adult patients with severe or persistent symptoms and patients with stated or suspected self-harm should also be referred to a health care facility. The risk of iron toxicity becomes high as iron concentrations exceed 60 mg Fe/kg. At this level, referral to a physician is necessary and chelation may be required.[9,23]

Lethal range: 180–300 mg elemental iron/kg (30–45 tablets in a 10-kg child). Death has been associated with the ingestion of 2.7 g (542 mg elemental iron/kg) and survival after the ingestion of 19.5 g of ferrous sulfate (3,900 mg elemental iron/kg). Solutions of ferric chloride are corrosive (pH 1.0). Death occurred 4 hours after the ingestion of 200 mL ferric chloride (230 mg Fe/kg) in a patient with aspiration pneumonia and hypoxemia.[24]

Chronic Iron Overload

As a result of the limited ability to excrete excess iron, chronic overload occurs from enhanced absorption (e.g., hemochromatosis) or excessive exposure (e.g., multiple transfusions in aplastic anemia, myelodysplastic syndrome, thalassemia). Hemochromatosis is an autosomal-recessive disorder (i.e., mutation in homeostatic iron regulator (*HFE*) gene in chromosome 6) that results from the inability to down-regulate intestinal iron absorption in the presence of high iron loads.

TOXICOKINETICS

Absorption

Following typical iron doses, iron absorption is a capacity-regulated process that depends on several factors including the iron formulation, the presence of polyanionic iron-binding compounds (e.g., phosphates, phytic acid, tannins), rate of erythropoiesis, total body iron stores, and genetic status. The diet contains iron primarily in the ferric state (3+), but cell membranes essentially are impermeable to iron in this form.[25] Gastric secretions facilitate the conversion of ferric iron to the ferrous state (2+), as does the presence of ascorbic acid and other reducing agents. The presence of different types of food in the stomach has a variable effect on the bioavailability of iron.[26] Iron absorption occurs primarily in the duodenum and the proximal jejunum, where iron penetrates the mucosal barrier in the ferrous (2+) form. The absorption of iron by the cells of the mucosal lining of the gastrointestinal tract exhibits the following two phases: 1) the uptake of iron by the enterocyte from the gastrointestinal lumen, and 2) the active transfer of iron across the cell and into the circulation where iron attaches to the storage protein, ferritin.[27] Brush border membranes in the epithelial lining of the proximal intestines contain saturable iron receptors for inorganic iron and duodenal cytochrome B (DCYTB, iron-regulated ferric reductase). The latter enzyme promotes the formation of ferrous iron before being transported into the enterocyte by the apical transporter, DMT1/NRAMP2.[28] The basolateral transporter (ferroprotein1) transfers the ferrous ion from the enterocyte to the plasma; this process requires the ferroxidase activity of a ceruloplasmin-like molecule

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(hephaestin).[29] Even after a massive ingestion of iron, first-order kinetics describes the absorption of iron with the intestines controlling the amount of iron absorbed.[30] Control of iron stores depends on variations in absorption because there is no specific mechanism for iron excretion.

The ingestion of large iron doses overwhelms the normal gastrointestinal regulatory mechanism, resulting in massive iron absorption.[31] Saturable transport systems probably are not involved in the absorption of high iron doses. There are few data regarding the amount of iron absorbed after a toxic dose, but the percentage of the absorbed dose is probably near 10%.[32] The absorption of nonchewable iron tablets is somewhat erratic and slow compared with chewable iron tablets, which reach peak concentrations 4.2–4.5 hours following the ingestion of 5–10 mg Fe/kg.[33] Peak serum iron concentrations occur ~4–6 hours after ingestion in pharmacokinetic studies.[34] At a given iron dose, the chewable tablets in multivitamin preparations tend to produce higher and earlier peak levels of iron than regular adult preparations. A fatal case of iron toxicity developed in a worker who fell into a vat of ferrous chloride as a result of iron absorption through aspiration, ingestion, and burned skin.[35]

Distribution

The average adult body contains about 3–4 g Fe; hemoglobin attaches ~70% in the ferrous state, whereas apoferritin binds ~25% of the iron in the ferric state as ferritin. Ferritin releases the iron in the plasma to a glycoprotein β-1-globulin, transferrin. This transporter tightly binds iron in the blood while transferring the iron to the blood-forming sites for incorporation into hemoglobin. Free iron is not typically present in the blood.

The body stores iron as ferritin (70%) and to a lesser extent as hemosiderin (30%).[34] The liver is the primary site for the storage of ferritin. In an acute iron overdose, plasma transferrin becomes saturated and free iron appears in the circulation. Greater than 99% of the iron present in whole blood appears in the erythrocyte bound to hemoglobin; therefore, the whole blood iron concentration is directly proportional to the hemoglobin concentration.

Elimination

No adequate mechanism for iron excretion exists. Consequently, the natural elimination of iron by the body is extremely limited with the loss occurring primarily by bleeding or desquamation of gastrointestinal mucosa. Adults lose up to 2 mg of iron daily. The half-life of transferrin in the blood is ~8 days compared with a plasma iron half-life of ~2–3 hours after therapeutic doses[36,37] and 4–6 hours after an overdose.[38]

Maternal–Fetal Kinetics

Transplacental transfer of iron is an active, saturable process; thus, the risk to the fetus is maternal toxicity rather than a direct effect of excessive maternal iron on the fetal tissues.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

Iron is an essential biological catalyst involved with electron transport, oxygen transport, cell proliferation, and DNA synthesis.[39] Every cell in the body acquires iron in the heme and nonheme forms, except differentiated lens epithelium and mature red cells. Although iron is essential for growth and survival, specialized mechanisms and molecules are necessary for the transport and storage of iron in a soluble, nontoxic form that prevents the development of oxygen radicals and oxidative damage to cell structures. At pH 7.4 and normal oxygen tension, the relatively soluble ferrous ions easily oxidize to the ferric ion followed by hydrolysis to insoluble ferric hydroxides. The most common proteins involved with these protective functions are transferrin, transferrin receptor, and ferritin; however, a variety of proteins participate in iron metabolism and transport including ceruloplasmin, ferrochelatase, frataxin, heme oxygenase-1, hepcidin, hephaestin, lactoferrin, mitoferrin, sideroflexin 1, and STEAP3 metalloreductase.

Mechanism of Toxicity

The mechanism of iron toxicity involves a direct local corrosive effect on gastrointestinal mucosa and the physiological effects of free iron in tissues. The presence of free iron results in the formation of highly reactive hydroxyl radicals via the iron-catalyzed Haber–Weiss reaction using Fenton chemistry.[40] Although other transition metal ions can catalyze this reaction, the major mechanism for the formation of hydroxyl radicals from superoxide and hydrogen peroxide involves free iron.[41] A number of reactive species occur in biological systems beside hydroxyl radicals including other reactive oxygen species (peroxyl radical, superoxide anion, alkoxyl

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radical). These reactive oxygen species contribute to various pathological conditions being prominent toxicological intermediates involved with oxidation stress. These processes produce depolymerization of polysaccharides, inactivation of enzymes, DNA damage (strand breaks, oxidative base modifications, DNA-protein cross-links), and initiation of lipid peroxidation, particularly in the mitochondrion.[42,43] Superoxide radical anion also reacts with nitric oxide to produce the strong oxidant, peroxynitrite.

In severe iron overdose, coagulative necrosis with platelet aggregation appears similar to the damage caused by corrosive agents. Major toxicity occurs when serum iron concentrations exceed the iron-binding capacity of transferrin. Free-circulating iron damages systemic blood vessels. The iron-induced release of the potent vasodilator, nitric oxide, and, possibly, the release of serotonin and histamine potentiate the vascular damage caused by free serum iron. Cellular damage from iron overload occurs in a wide range of tissues with a high rate of superoxide radical anion ($O_2^{\bullet -}$) formation, particularly the liver, heart, and pancreatic beta cells.

Gastrointestinal Tract

The corrosive effect of iron produces congestion, edema, hemorrhage, ulceration, coagulative necrosis, and infarction of the stomach and proximal intestine (i.e., hemorrhagic gastritis, peritonitis, perforation); however, there is a lack of correlation between the severity of intestinal damage and death. An empty stomach increases iron-induced gastrointestinal damage.[44] Pyloric obstruction and intestinal scarring are rare, late complications of an iron overdose. The ingestion of enteric-coated iron tablets results in damage to the more distal portions of the small intestine.[45] The mechanism of the erosion of the lining of the gastrointestinal tract includes direct corrosive effect, local ischemia secondary to the formation of thrombi, disruption of the cell membrane as a result of ATP depletion, and the formation of hydroxyl radicals. Masses of iron-containing granules accumulate in the capsular space and lumen of the renal tubules; however, tubular degeneration is rare.

Liver

Acute Toxicity

Circulating free iron initially accumulates in the Kupffer's cells and later in the mitochondrial crista of hepatic parenchymal cells when free iron exceeds the storage capacity of ferritin. Ferrous ions catalyze the lipid peroxidation of mitochondrial membranes, leading to the increased intra-mitochondrial accumulation of iron. The effects of excess iron on the liver are highly variable, ranging from no abnormalities to cloudy swelling of the hepatocytes, mitochondrial injury, portal iron disposition, fatty metamorphosis, and massive periportal necrosis.[46] Free iron inhibits the thrombin-induced conversion of fibrinogen to fibrin, and free iron also directly affects coagulation. Therefore, a coagulopathy potentially may appear before iron-induced liver dysfunction occurs.[47]

Chronic Toxicity

The liver is a major site of iron storage that is susceptible to damage from the chronic accumulation of iron, particularly from hemochromatosis. The major pathological effects of chronic iron overload include cirrhosis, porphyria cutanea tarda, and hepatocellular carcinoma.[48] Current data do not suggest that chronic iron overload occurs following exposure to iron compounds in the work environment.

Cardiovascular System

Direct myocardial injury (e.g., fatty degeneration of the myocardium) may occur in fatal cases of iron poisoning. Histopathological changes in hearts from fatal iron overdose cases include stainable iron in the myofibrils, contraction bands, myocytolysis, and frank necrosis.[49] In animal models of iron poisoning, depletion of intravascular volume is the single most important hemodynamic effect; however, other factors influence the development of hypotension because the maintenance of cardiac filling (pulmonary artery wedge pressure) does not prevent a reduction of cardiac output in this model.[50] Iron acts on the vascular system to increase venous pooling (increased capillary permeability) and to decrease cardiac output (reduced post-arteriolar and venous tone). Proposed etiologies for post-arteriolar dilation include a direct iron effect, ferritin release, and serotonin/histamine release.

Blood

The release of free iron inhibits the oxidative phosphorylation pathway. This interference with oxidative enzymes in the Krebs cycle along with the release of hydrogen from the conversion of ferric ion to the ferrous state and anaerobic metabolism may produce severe metabolic acidosis with hyperlactatemia.[51] Ferrous ions catalyze lipid peroxidation that can cause disruption of mitochondrial membranes and the Krebs cycle. Iron

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also shunts electrons from the electron transport system by acting as an electron sink.[52] The result is impaired reconstitution of adenosine triphosphate (ATP), that produces metabolic acidosis.

CLINICAL RESPONSE

Acute Ingestion

Classically, severe iron toxicity presents in five distinct but sometimes overlapping phases and not necessarily related to the time since ingestion.[53,54] Symptoms in the first phase result primarily from the corrosive effects of iron on the gastrointestinal mucosa; the initial phase also may involve the early (<6 hours) onset of metabolic abnormalities (e.g., acidosis, hyperglycemia) following severe overdoses. Ferric chloride is a corrosive acid that produces nausea, vomiting, sore throat, abdominal pain, and oral ulcers.[55] In severe cases of exposure to ferric chloride, metabolic acidosis, hypotension, aspiration pneumonia, and respiratory failure develop. Maroon or reddish-colored, nonbloody stools may occur after the ingestion of cefdinir (third-generation cephalosporin) with iron or iron-containing products (e.g., infant formula).[56,57] The stools return to normal color after cessation of cefdinir with no recognized adverse effects.

Initial Period (Gastrointestinal Phase)

Irritation of the gastric mucosa (phase 1) characterizes the initial period during the first 1/2–2 hours and up to 6 hours postingestion; a severe hemorrhagic gastritis (i.e., protracted vomiting, hematemesis, diarrhea, hematochezia) may develop depending on the iron dose. Vomiting is the most sensitive indicator of iron ingestion with 94% sensitivity but only 25% specificity; however, the presence of vomiting does not necessarily indicate severe iron ingestion.[58] Diarrhea is a less sensitive, but more specific indicator, of iron ingestion. Most patients do not progress beyond this stage, and symptoms resolve within 6–8 hours.[20] The early appearance of central nervous system (lethargy, coma) or cardiovascular (pallor, tachycardia, hypotension) effects are the most reliable signs of a severe ingestion. The absence of symptoms in children within the first 6 hours after ingestion indicates that further sequelae are highly unlikely.[2,9]

Quiescent Period (Latent Phase)

Most patients appear well during phase 2, and the majority of patients will recover uneventfully. However, during this variable period (6–24 hours postingestion), a deceptive improvement and stabilization occur in severely poisoned patients that may result in the premature discharge of the patient from the health care facility. Alternating periods of lethargy may emerge during this stage. During severe overdoses, this quiescent period may be very brief and evidence of multi-organ failure develops quickly. Although gastrointestinal symptoms often resolve during this period, progressive cellular damage continues during serious intoxication with the development of metabolic acidosis.

Recurrent Period (Metabolic/Cardiovascular and Hepatic Phases)

Systemic symptoms (phase 3) that appear during this phase (12–48 hours postingestion) are life-threatening (hemodynamic instability, shock, coagulopathy) with multi-system organ failure. Vasomotor collapse, cyanosis, and pulmonary edema may develop as a result of myocardial depression. Intractable shock appeared in three cases of iron intoxication at 1 day, 2 days, and 5 days postingestion; the patients died in spite of aggressive fluid management and catecholamine infusions.[49] The etiology of shock in this phase is multifactorial and includes fluid and blood loss, metabolic acidosis, and primary cardiac dysfunction.

Acute hepatic failure (phase 4) occurs only in those patients with severe iron poisoning, usually within the first 24–48 hours.[59,60] Hepatic damage may progress to hepatic failure with hypoprothrombinemia, hypoglycemia, and the hepatorenal syndrome. Coagulopathy may occur without hepatic failure as a result of the inhibition of thrombin by free iron.[61] Complications include hematemesis, melena, and gastrointestinal perforation. Hepatorenal failure develops usually toward the end of this phase with coagulation defects and acute renal tubular necrosis.[62] Most authors consider hepatic necrosis a separate phase from the recurrent phase. Increasing lethargy, coma, and convulsions develop, depending on the severity of the overdose.

Late Period (Delayed Phase)

Gastric scarring, strictures, fistulas, and pyloric or jejunal obstruction may appear during phase 5 (4–6 weeks post-ingestion).[63] These obstructions develop in the area of initial damage to the gastrointestinal mucosa, causing abdominal pain.

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Occupational Exposure

Iron Oxides

Exposure to iron (i.e., primarily iron oxides) occurs in iron mining, iron refining, and the welding or polishing of iron or steel. Concurrent exposure to other toxic substances (e.g., welding, diesel fumes, silica, radon) complicates the interpretation of the health effects of iron oxides on these workers. In a 17-year follow-up study of 167 miners (80 active workers, 58 retired) from the original cohort of 240 Swedish iron ore miners, the prevalence of chronic bronchitis was 9.6% with no excess chronic obstructive pulmonary disease based on a structured interview and pulmonary function testing.[64] Smoking, but not working in the mine, correlated to the prevalence of chronic bronchitis; spirometry values were similar between surface and underground workers. The study could not exclude selection bias (i.e., healthy worker effect).

The inhalation of iron oxide fumes for 6–10 years produces radiographic changes in the lungs characteristic of a benign pneumoconiosis (siderosis) that probably does not progress to pulmonary fibrosis.[65] In a study of 14 iron oxide production workers with total particulate exposures of 10–15 mg/m^3 for a mean of 10 years, chest radiographs demonstrated some nodular opacities; however, the pulmonary function tests did not demonstrate evidence of obstructive or restrictive disease.[66] The deposition of iron oxide in the lung (i.e., siderosis) usually causes little physical disability.[67] Studies of workers with siderosis generally demonstrate minimal or no clinical changes.[68] Siderosis occurs in arc welders, oxyacetylene cutters, and silver finishers as a result of the prolonged inhalation of ferric oxide fumes and dust, but hematite iron ore workers rarely develop siderosis unless they are exposed to arc welding fumes.[69] The prevalence of siderosis among iron workers (electric arc and powder-burning operations) exposed to levels exceeding 10 mg Fe/m^3 for periods of >5 years was 5–15%.[5] Pulmonary siderosis following occupational exposure is not associated with superficial siderosis of the central nervous system (hearing loss, cerebellar ataxia, myelopathy) secondary to the deposition of breakdown products of hemoglobin (hemosiderin) in the brainstem, cerebellum, and spinal cord.[70]

Iron Pentacarbonyl

There are limited human data on the clinical effects of iron pentacarbonyl. Based on animal studies,[71,72] the clinical effects of a single large exposure to iron pentacarbonyl vapors clinically resemble those of an exposure to nickel carbonyl with the exception that iron pentacarbonyl is a less potent toxin.[73] Clinical symptoms include the immediate onset of headache, vomiting, and lightheadedness followed in 12–36 hours by cough, cyanosis, dyspnea, and fever. Exposure to high concentrations of iron pentacarbonyl may cause pulmonary consolidation, degeneration of the central nervous system, and death within 4–11 days.[74] Short-term studies in animals do not indicate that iron carbonyl possesses significant fibrogenic properties after chronic exposure.[72]

Carcinogenicity

Iron Oxides

Neither the International Agency for Research on Cancer (IARC) nor the US National Toxicology Program lists iron oxide as a potential carcinogen. Most studies of iron foundry workers demonstrate an excess of lung cancer; however, potential carcinogens (silica, polycyclic aromatic hydrocarbons) contaminate the work environment in the foundries. A nested case-control study of lung cancer mortality from 1950–1989 in a cohort of 8147 foundry men did not detect an increased incidence of lung cancer, even among workers exposed to formaldehyde and silica.[75] Based on conditional logistic regression analyses, cigarette smoking was strongly associated with lung cancer mortality; however, there was no significant association between lung cancer mortality and work at any of the six major work areas of the foundry.

Underground hematite miners have ~10-fold increase in the risk of developing lung cancer compared with surface hematite workers, probably as a result of exposure to radon. A retrospective mortality study of workers in a hematite mine did not demonstrate an excess incidence of lung cancer in workers with low-grade exposure to radon, diesel exhaust, and silica and work rules prohibiting smoking underground.[76] The standardized mortality ratios based on standard US rates were similar between underground (SMR = 100) and above-ground (SMR = 88) miners. In a mortality study of 3,444 men employed for at least 3 months in Minnesota taconite mining operations from 1947–1958 and followed until 1983, the standardized mortality ratio for all deaths was 88 using rates for US Caucasian males.[77] There were 41 respiratory cancer deaths compared with 67 expected (SMR = 61, $P \leq 0.01$). The study did not demonstrate evidence of a significant exposure-response with 25 respiratory cancers (SMR = 57, $P \leq 0.01$) in workers employed at least 20 years. A 5-year follow-up study of this cohort updating deaths to 1988 did not detect a significant increase

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in the SMR for respiratory cancer.[78] Studies of workers exposed to iron oxides are complicated by the presence of other potential carcinogens (e.g., soot, crystalline silica, asbestos). There is no conclusive evidence that the inhalation of iron oxide in mice, hamsters, or guinea pigs produces carcinogenic effects.[79]

Iron Dextran

Both the IARC and the US National Toxicology Program[80] list iron-dextran complex as a probable carcinogen based on sufficient evidence of carcinogenicity in animals. The repeated subcutaneous and intramuscular injection of iron dextran complex in rodents produces local sarcomas. The evidence for the carcinogenicity of iron-dextran complex in humans is inadequate. An uncontrolled study of 196 cases of sarcoma of the buttock revealed that 4 cases had received intramuscular injections of iron-dextran complex with an interval of at least 2 years occurring between the injection and the development of the sarcoma in 3 cases.[81] Selection bias limits the interpretation of this study regarding the issue of causation.

Reproductive Abnormalities

The risk of spontaneous abortion is low following an acute iron overdose in a pregnant woman, but some risk may exist. A study of 49 pregnancies involving iron poisoning did not reveal an excess incidence of malformations or premature births at follow-up 2 months postdelivery.[82] When treated with deferoxamine, the majority of the women ingesting large doses of iron in the second or third trimester ultimately deliver a normal infant. The primary risk to the fetus during maternal iron toxicity is metabolic acidosis and hypotension.

DIAGNOSTIC TESTING

SI Conversion Units

1 μmol/L = 5.5845 μg/dL
1 μg/dL = 0.1791 μmol/L

Analytical Methods

Iron

The colorimetric method using both liquid reagents and dry agents is the most common technique in clinical laboratories for the determination of small amounts of iron. Atomic absorption spectrometry (AAS) correlates well to colorimetric methods, but AAS is more specific than colorimetric techniques. For example, the administration of deferoxamine interferes with colorimetric methods of iron determination (i.e., falsely lowers the serum iron); however, this antidote does not interfere with assays that rely on atomic absorption spectrophotometry.[83] The addition of sodium hydrosulfite reduces the effect of deferoxamine on the colorimetric assays of iron.

Total Iron-Binding Capacity

The lack of sensitivity and specificity of the serum total iron-binding capacity (TIBC) seriously limits the usefulness of this laboratory test in the diagnosis and treatment of iron poisoning. The use of the TIBC is generally not recommended because of issues about the reliability of this test and the lack of clinical evidence that this test separates toxic from nontoxic, iron-exposed patients. Case reports document serious iron toxicity in infants with the TIBC exceeding the serum iron concentrations.[23] Most clinical laboratories use colorimetric methods to determine the TIBC. Experimental studies indicate that procedures measuring TIBC by the addition of excess iron followed by adsorption with alumina are not suitable for estimating TIBC. The homogeneous TIBC method is more reliable only when the serum iron is <500 μg/dL; however, this test yields falsely elevated results in the presence of free deferoxamine.[84] Consequently, unpredictable variability in test results complicates the interpretation of test results in patients with serious iron toxicity or in patients receiving deferoxamine. A study of six healthy volunteers receiving 20 mg elemental Fe/kg demonstrated that the serum TIBC level remained elevated for 6 hours postingestion compared with the TIBC level before ingestion, even though the serum iron level rose to 300 μg Fe/dL.[85] In this study, the TIBC after the iron ingestion increased to the upper limits of normal for the TIBC level. Occasionally, TIBC levels increase above the reference range and then return to normal as the serum iron level returns to normal. The temporary elevation of the TIBC during iron intoxication probably represents a laboratory aberration rather than a true increase.[86] Additionally, this study noted a substantial variation in the measurement of the TIBC as reflected in a mean coefficient of variation of 16% for a TIBC of 60 μmol/L (333 μg/dL). Deferoxamine contributes to the iron-binding capacity of the serum; therefore, the administration of deferoxamine falsely elevates the TIBC without interfering directly with the colorimetric assay.[87] The normal TIBC level in a healthy child is ~300–350 μg/dL.

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Biomarkers

Theoretically, systemic iron toxicity occurs when free iron appears in the plasma (i.e., the serum iron concentrations exceed the total iron-binding capacity). The serum iron concentration is the most useful laboratory test for the diagnosis and management of acute iron poisoning. The TIBC level is not recommended because of the highly variable correlation of this test to iron toxicity. Gastrointestinal toxicity results from local corrosive effects of iron rather than the systemic effects of serum iron; therefore, gastrointestinal symptoms do not necessarily correlate to serum iron concentrations. Peak serum iron concentrations occur 2–4 hours after ingestion depending on the type of iron preparation; peak serum iron concentrations correlate best with potential toxicity. Serum iron concentrations drawn >6 hours postingestion may underestimate toxicity because of the binding of iron to ferritin and the distribution of iron into the tissues.

Indications

All symptomatic patients and those patients with a history of ingestion of >40 mg of elemental Fe/kg should have blood drawn for serum iron. Heparinized samples of whole blood should be drawn 3–5 hours postingestion. Because of rapid iron clearance, low serum iron concentrations after this period may underestimate the seriousness of iron poisoning. Fatal iron toxicity may occur in patients with normal serum iron concentrations 24 hours after ingestion as a result of the intracellular redistribution of iron 6–12 hours after ingestion.[88] Deferoxamine interferes with the analysis of the serum iron and the TIBC; therefore, blood samples should be drawn at least 4 hours after the last dose of deferoxamine to minimize this interference.[84]

Interpretation

Because of the variability of the TIBC and the interference of deferoxamine with the analytical procedure, the serum iron is the best laboratory measure of potential toxicity.[89] Fewer than 10% of patients with peak serum iron concentrations of <500 μg/dL will develop cardiovascular collapse or coma. Between 500–700 μg/dL, the percentage increases to 25% with the majority of patients developing hepatotoxicity. Above 700 μg/dL, ~50% of the patients have severe symptoms.[90] In a retrospective study of 77 patients with peak serum iron concentrations of >300 μg/dL *within* 12 hours of ingestion, 12 patients had hepatotoxicity (serum ALT or AST >150 U/L).[91] The nine patients with severe liver toxicity (serum ALT or AST >1,000 U/L) had peak serum iron concentrations of >1,000 μg/dL; clinically significant liver injury was unlikely in patients with peak serum iron concentrations of <700 μg/dL within 12 hours of ingestion. Case reports suggest that severe neurologic, hepatic, metabolic, or cardiovascular complications may not occur in the presence of high initial serum iron concentrations (2,260 and 6,798 μg/dL 1.5–2 hours postingestion) following prompt administration of deferoxamine.[92,93] Coma, radiopaque iron tablets in the gut, leukocytosis, and an elevated anion gap suggest serum iron concentrations of >500 μg Fe/dL.[94] The absence of any of these indicators suggests a serum iron level of <500 μg Fe/dL; however, the lack of these indicators does not exclude serum iron concentrations of >300 μg/dL or significant toxicity.[95] The clinical presentation is a more important determinate of appropriate therapy than either the serum iron concentrations or the history of ingestion. When inconsistencies occur between these measures of potential toxicity, the clinical presentation should be given preference over the history and laboratory values. Table 15.3 correlates the peak serum iron concentrations (i.e., 3-5 hours postingestion) with expected clinical effects.

Serum iron concentrations decline rapidly 12 hours postingestion; consequently, serum iron concentrations are not good biomarkers during the clinical course of iron poisoning. The presence of persistent metabolic acidosis during this interval indicates serious toxicity.

TABLE 15.3. Peak serum iron concentrations and expected clinical effects.

Peak Serum Iron (μg/dL)	Clinical Effect
0–150	Normal range.
150–350	Possible poisoning. Signs of gastrointestinal toxicity may appear, but systemic toxicity is unlikely.
350–500	Potentially serious toxicity. Chelation may be required depending on clinical features and history.
500–1,000	Definite serious toxicity. Chelation is necessary.
>1,000	Potentially fatal. Case reports document survival[63,96] and death[59] in severely poisoned infants with peak serum iron concentrations near 14,000–16,000 μg/dL.

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Abnormalities

Abdominal X-Rays

The appearance of iron tablets on the abdominal radiograph depends on several variables, including time since ingestion, content of elemental iron, and type of formulation (e.g., vitamins with iron and sugar-coated candy tablets are not radiopaque). Ferrous sulfate tablets remain radiopaque longer than ferrous gluconate tablets because ferrous sulfate tablets contain higher elemental iron concentrations than ferrous gluconate. Negative abdominal radiographs do not exclude iron overdose, particularly >2 hours after ingestion;[97] however, the presence of iron tablets indicates the need for gut decontamination and whole bowel irrigation should be considered. Although chewable vitamins with iron are radiopaque, visualization of these tablets clinically is unlikely.[98] Within several hours of ingestion, the abdominal X-ray is a useful measure of the efficiency of any gastric emptying procedure except following minor ingestions.

Blood

Potential indicators of elevated serum iron concentrations include the white blood cell count and blood glucose concentration. A leukocytosis of > 15,000/mm^3 and hyperglycemia of >150 mg/dL correlated with elevated serum iron concentration (>300 μg/dL) in a retrospective study;[58] however, these tests are *not* sensitive predicators of severe iron intoxication. These values have poor negative predictive power for serious iron intoxication if there are <15,000 WBC/mm^3 or the serum glucose is <150 mg/dL. When serum iron concentrations are not immediately available, the presence of hyperglycemia and leukocytosis suggests serious iron intoxication. However, decisions for the management of iron overdose should be based on clinical history and physical examination rather than the presence of these values alone. Severe metabolic acidosis and hypoglycemia may develop as a result of hepatic and pancreatic damage.

Ancillary Tests

Supportive studies in patients with a potentially serious iron ingestion (i.e., serum iron concentrations > 350 μg/dL) include guaiac tests of the stool and gastric aspirate, serum hepatic aminotransferase levels, coagulation studies, complete blood count, hemoglobin, hematocrit, electrolytes, glucose, arterial blood gases, blood type, and antibody screen. Iron ingestion does not cause false-positive guaiac test results. Hepatic injury is unusual when peak serum Fe concentrations are < 500 μg/dL.

Rapid Screening Tests

Fischer developed a rapid *qualitative* method for determining the presence of iron using the chromogen 2,4,6-tripyridyl-*s*-triazine (TPTZ).[99] McGuigan et al. described a qualitative deferoxamine color test for gastric aspirate as an adjunctive screening method for iron within 2 hours of ingestion.[100] Two milligrams of gastric fluid and two drops of 30% H_2O_2 are placed in each of two plastic tubes. One-half milliliter of a deferoxamine solution (composed of one 500-mg ampule of deferoxamine and 4 mL of distilled water) is added to one tube. An immediate change of color (light orange to dark red) in that tube compared with the control indicates the presence of iron. Negative results from these tests >2 hours postingestion do not reliably exclude iron poisoning because of the possibility of absorption. This test does not distinguish between toxic and nontoxic ingestion.

HEALTH SURVEILLANCE

Table 15.4 lists guidelines and regulatory values for exposure to iron and iron compounds. The US OSHA PEL–TWA for iron oxide dust and fumes is 10 mg Fe/m^3 measured as total particulate, whereas the ACGIH recommends a TLV–TWA of 5 mg Fe/m^3 to minimize the potential for the occurrence of radiographic changes of siderosis after long-term exposure.[73] European regulations for the TWA–TLV range from 3.5 mg Fe/m^3 in Sweden to 6 mg Fe/m^3 in Germany. The 10-minute STEL in the United Kingdom is 10 mg Fe/m^3, but there is no US OSHA recommendation for a STEL. The US OSHA PEL–TWA for iron pentacarbonyl is 0.1 ppm (0.23 mg/m^3), while the TLV-STEL is 0.2 ppm (0.45 mg/m^3) measured as Fe.

TREATMENT

Decontamination

The American Association of Poison Control Centers (AAPCC) recommends evaluation of pediatric

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TABLE 15.4. Regulations and guidelines for exposure to iron and iron compounds.

Exposure Limit	Value
	OSHA
PEL–TWA (8-hour)	10 mg/m^3 iron oxide as total particulate
	NIOSH
REL–TWA (10-hour)	5 mg/m^3 as iron oxide fumes 1 mg/m^3 as iron salts 0.23 mg/m^3 as $Fe(CO)_5$
REL–STEL (15-minute)	0.45 mg/m^3 as $Fe(CO)_5$
IDLH	2,500 mg/m^3 as Fe
	ACGIH
TLV–TWA (8-hour)	5 mg/m^3 as respirable mass 1 mgFe/m^3 as soluble iron salts[a] 0.23 mg/m^3 (0.1 ppm) as $Fe(CO)_5$
TLV–STEL (15-minute)	0.45 mg/m^3 (0.2 ppm) as $Fe(CO)_5$

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; IDLH = immediately dangerous to life and health; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average.
[a] $FeCl_3$, $FeCl_2$, $Fe(NO)_3$, $Fe_2(SO_4)_3$, $FeSO_4$.

patients at a health care facility when the estimated accidental ingestion exceeds 40 mg elemental Fe/kg; all intentional ingestions should be evaluated at a health care facility regardless of the estimated dose. The appropriate measures for decontamination of the gut following the ingestion of iron tablets are controversial. The ingestion of children's vitamins, carbonyl ions, or polysaccharide-iron complex formulations typically can be observed at home with follow-up. Any ingestion with persistent nausea or vomiting, altered consciousness, or gastrointestinal bleeding should be referred immediately to a medical facility. Acute ingestions without symptoms in the first 6 hours postingestion do not usually require referral or observation.

Emesis

Induced-emesis is usually unnecessary because early vomiting commonly occurs during iron toxicity. Syrup of ipecac should not be administered unless the benefits clearly outweigh the risks. The induction of emesis with syrup of ipecac is an option early in the course of iron poisoning if the history indicates a very large ingestion of iron presenting 1–2 hours after ingestion to the health care facility and there are a substantial number of iron tablets in the stomach on abdominal radiograph. A definite risk of aspiration within the expected duration of action contraindicates the use of syrup of ipecac. Abdominal X-rays should be repeated after decontamination measures to assess the effectiveness of these measures. The disappearance of iron tablets from the X-ray does not necessarily indicate that the decontamination measures were successful because of the natural tendency of the tablets to dissolve. The use of syrup of ipecac delays the use of whole bowel irrigation for at least several hours after the administration of syrup of ipecac.

Lavage

The use of gastric lavage is not routinely recommended. Mechanical removal by lavage may be difficult because of tablet size and cohesiveness; therefore, large bore (32–40 F) lavage tubes are necessary to remove iron tablets efficiently. The type of lavage fluid used to complex iron is controversial. Although there are theoretical advantages to the use of bicarbonate and deferoxamine in lavage solutions, there are insufficient data to conclude that either lavage solution is superior to saline. Consequently, the routine use of these solutions as decontamination measures is *not* recommended due to a lack of proven efficacy, unless the physician determines that specific conditions exist to indicate that these solutions will improve the clinical outcome. All patients with potentially serious iron ingestions should receive an abdominal X-ray. Decontamination procedures should be repeated if the upright abdominal film shows retained tablets in the stomach. Otherwise, whole bowel irrigation should be considered. Volunteer studies do not support the administration of magnesium hydroxide (Milk of Magnesia) as a measure to reduce iron absorption.[101]

Bicarbonate

A 1–4% sodium bicarbonate solution (add one 50 mEq ampule to 1 L D_5W/0.45% NaCl) complexes some of the free ferrous ion into the relatively insoluble ferrous carbonate form. The actual amount of ferrous carbonate formed has not been well studied *in vivo*; factors affecting the formation of ferrous carbonate include gastric pH, contact time, and relative concentrations. *In vitro* studies of the effect of lavage solutions of bicarbonate and phosphate indicate that these solutions retard the dissolution of the iron tablets,[102] but ~83–86% of the iron remains in the soluble form.[103] Furthermore, these insoluble complexes of iron appear labile and may dissociate into soluble complexes when the pH decreases in

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the gastrointestinal tract.[104] Whether this solution significantly decreases iron absorption remains controversial; conventional antacids probably are an equally safe alternative to the administration of the standard solution of bicarbonate (1 mEq/kg).

Deferoxamine

The role of oral deferoxamine solution is limited, in part because of the lack of sufficient data to support the efficacy of this treatment.[105,106] This complex requires an alkaline solution; hence, bicarbonate must be added. A major problem is the large amount (and high cost) of deferoxamine required to complex the intestinal iron (100 mg deferoxamine complexes 8.5 mg iron). An animal study of oral deferoxamine revealed that the use of lavage solution of deferoxamine reduced the absorption of iron, but serum iron concentrations were not significantly decreased.[107] The methodology (colorimetric assay) used in this study did not reliably measure serum iron absorbed as ferrioxamine. In a group of seven adults administered 5 mg elemental iron/kg, the concurrent ingestion of equimolar doses (59 mg/kg) of buffered deferoxamine did not significantly alter the plasma iron concentrations over 8 hours when compared with the control (iron alone).[108] Large oral doses of deferoxamine may produce hypotension.[106] Additionally, volunteer studies do not support the oral administration of $CaNa_2EDTA$ as a method to reduce iron absorption following ingestion of iron.[109]

Bezoar Formation

Iron tablets may form concretions or adherent masses that are resistant to decontamination measures and endoscopic removal. Continued release of iron from large bezoars may produce delayed elevation of serum iron concentrations, gastrointestinal inflammation, hemorrhage, and scarring.[110] Endoscopy and gastrotomy are therapeutic modalities to reduce complications (e.g., perforations) when serum iron concentrations increase and the concretions fail to progress down the gastrointestinal tract.[111,112] Emergency gastrotomy should be considered only after endoscopy, and decontamination measures including whole bowel irrigation fail to remove the iron tablets.

Activated Charcoal

Animal studies do not support the use of activated charcoal to reduce the absorption of iron compounds (e.g., iron sulfate).[113] Activated charcoal binds relatively small amounts of iron; however, the iron-deferoxamine complex does adsorb onto charcoal with an affinity similar to that of salicylates.[114] A prospective, crossover, controlled volunteer study evaluated the effect of the simultaneous administration of 5 mg ferrous sulfate/kg and a slurry of 8 g DFO and 25 g of 20% (weight/volume) activated charcoal on the absorption of iron.[115] The area under the curve (AUC) and peak serum iron concentration in the DFO/activated charcoal limb was significantly different compared with the two control limbs. The clinical relevance of this study is unclear; there are no clinical trials to support the use of the combination of DFO and activated charcoal.

Whole Bowel Irrigation (WBI)

Whole bowel irrigation is the enteral decontamination method of choice for iron based on case reports; however, randomized clinical studies are not available to confirm efficacy. If the abdominal radiograph reveals iron tablets beyond the pylorus, neither emesis, activated charcoal, nor lavage will reduce the absorption of these tablets. Whole bowel irrigation with a polyethylene glycol electrolyte lavage solution (Colyte, GoLYTELY) is a safe and rapid method for the removal of iron tablets from the intestines that is preferable to the use of saline cathartics (sodium sulfate or magnesium sulfate).[116] Over 44 L of lavage fluid were administered to a 33-month-old child over 5 days without complications.[117] The major indication for WBI is massive iron ingestion in which the usual decontamination measures fail to remove iron tablets from the gastrointestinal tract (stomach and small bowel) in adults or children.[118] Further studies are necessary to define the use of WBI as a routine part of decontamination measures. Case reports indicate that iron bezoars may remain in the gut after prolonged WBI, despite the presence of a clear rectal effluent.[119]

The rate of fluid administration for WBI is 20–35 mL/kg/hour in infants, 0.5 L/hour in children, and 2 L/hour in adolescents and adults via a nasogastric or orogastric tube until the rectal effluent is clear. Oral administration of this solution is an alternative to the use of the nasogastric tube if the patient can tolerate oral fluids. Adverse effects associated with WBI include vomiting and, less often, abdominal pain.[120] Slowing the infusion and the use of IV metoclopramide help reduce the amount of vomiting associated with the use of WBI in the setting of an iron intoxication.[121] Contraindications to the use of WBI include hemorrhage, obstruction, and ileus. Ipecac should not be administered within several hours of the initiation of WBI.

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Cation Exchange Resin

Studies in volunteers indicate that sodium polystyrene sulfonate does not reduce the absorption of iron when administered 45 minutes after the administration of a 10 mg/kg iron dose.[122]

Elimination Enhancement

Exchange Transfusion

Exchange transfusion offers the greatest potential for iron removal. In animal models, this procedure removes more iron than intravenous deferoxamine;[123] however, the clinical efficacy of such removal is uncertain because deferoxamine chelates only the important toxic component (i.e., *free* iron), whereas exchange transfusion removes both *free* and *bound* iron. The rapid cellular uptake of free iron limits the effectiveness of exchange transfusion; the use of exchange transfusion to remove the iron-deferoxamine complex is primarily useful in massive iron overdose when the patient continues to deteriorate despite high-dose deferoxamine.[63]

Hemodialysis

Hemodialysis removes the iron-deferoxamine complex, but this procedure does not increase the elimination of iron. Hence, its use is limited to patients with impaired renal function. Methods to enhance elimination probably do not alter clinical outcome as a result of the minimal removal of absorbed iron. Animal studies suggest that continuous arteriovenous hemofiltration (CAVH) is an alternative to hemodialysis for patients with renal failure following iron intoxication;[124] however, there are inadequate human data to recommend the routine use of CAVH to remove absorbed iron.

Antidotes

Mechanism of Action

Deferoxamine is the chelating agent of choice for acute iron poisoning;[125] this compound is a specific chelator in a 1:1 molar ratio of ferric iron that is produced by the bacteria *Streptomyces pilosus*. Ferrioxamine is the chelated iron-deferoxamine complex. Potential alternative chelating agents for iron based on preliminary studies include ethylenediamine-*N*,*N*′-bis(2-hydroxyphenylacetic acid[126] and calcium salts of diethylene triamine pentaacetic acid (DTPA);[127] however, inadequate clinical data are available to assess the effectiveness of these agents compared with or in addition to deferoxamine. Newer oral iron chelating agents are available in the United States for patients with chronic iron overload from conditions requiring multiple transfusions including deferasirox[128] and deferiprone.[129] The latter is a bidentate chelator that binds iron in a 3:1 ratio. Although studies of patients with thalassemia major indicate the administration of deferiprone is efficacious in reducing their iron load, risks include neutropenia, arthropathy, and rarely agranulocytosis.[130] Deferasirox is a tridentate molecule that binds iron in a 2:1 ratio. At low doses, adverse effects are mild and usually limited to transient skin rashes and gastrointestinal upset. At high chronic doses (>40 mg/kg/day), potential complications include hypophosphatemia (Fanconi-like syndrome), cataracts, and hepatorenal dysfunction.[131]

In vivo, 100 mg of deferoxamine binds ~9 mg of free circulating elemental iron. Additionally, deferoxamine removes iron to a limited extent from ferritin, hemosiderin, and transferrin; deferoxamine does not remove iron from hemoglobin.[132] Deferoxamine may operate on the labile iron pool in the intracellular portion of hepatocytes, where deferoxamine preferentially removes ferritin iron over hemosiderin iron.[133]

Increasing iron elimination is not necessarily the main mechanism involved with the reduction of iron toxicity.[20] Because the volume of distribution of the iron-deferoxamine (ferrioxamine) is relatively small, free iron is kept in the extracellular space. The binding of cytoplasmic free iron reduces the free iron-induced disruption of mitochondrial cell membranes and enzyme systems. The iron-deferoxamine complex (ferrioxamine) is highly stable at physiological pH.[106]

Pharmacokinetics

Deferoxamine is poorly absorbed from the gastrointestinal tract; therefore, this agent should be given parenterally for maximum effect. Although orally administered deferoxamine blocks the uptake of only a small amount of iron by the small intestine, parenteral deferoxamine inhibits the uptake of inorganic iron and transferrin-bound iron, perhaps by limiting the chelatable pool of iron in the epithelial cells of the small intestine.[134] Animal studies indicate that deferoxamine has a volume of distribution of about 60% of body weight corresponding to total body water.[135] The plasma elimination half-life of deferoxamine is short (i.e., <1 hour).[136] Steady-state concentrations occur after ~90 minutes of a constant deferoxamine infusion.[137] Renal clearance accounts for ~30% of the total body clearance of a pharmacological dose of deferoxamine, whereas the liver detoxifies the rest of the absorbed deferoxamine dose.[138] The kidney excretes the deferoxamine iron complex (ferrioxamine)

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unchanged. The volume of distribution of ferrioxamine is ~20% of body weight based on animal studies.[111]

Adverse Effects

Acute Administration

Cardiorespiratory Hypotension is the most serious side effect of an infusion of deferoxamine; the blood pressure usually returns to normal within 1 hour.[139] Doses of 45 mg/kg/hour produce hypotension that usually responds to a reduction in the infusion rates and increasing fluid administration. Vasopressors may be necessary. Typically, hypotension associated with a deferoxamine infusion occurs during a rapid infusion; however, there is no specific threshold infusion rate for the development of hypotension during a deferoxamine infusion. The infusion of 425 mg deferoxamine/kg intravenously over 24 hours (i.e., 16 g) to thalassemia patients and 50 mg deferoxamine/kg/hour to dialysis patients did not cause clinically significant complications.[140,141] Hypotension in a patient with iron poisoning on deferoxamine may occur when the infusion rate exceeds 20–45 mg deferoxamine/kg/hour and other causes of hypotension (inadequate filling pressure, vasodilation) have been excluded. The lower limit of deferoxamine-induced hypotension below this infusion rate remains a possibility.

Acute respiratory distress syndrome (ARDS) may develop in iron overdose patients receiving large deferoxamine doses for >1 day. Tenenbein et al. reported four fatal cases of ARDS in adults receiving deferoxamine infusions of 15 mg/kg/hour for 32–72 hours.[142] However, studies from the 1950s before the use of deferoxamine indicate that pulmonary toxicity similar to ARDS may develop in patients poisoned by iron.[143] Consequently, the contribution of deferoxamine to the development of ARDS remains unclear. Several case reports associate the use of deferoxamine with the development of *Yersinia enterocolitica* O:9 sepsis.[144,145] This organism displays low virulence in the absence of free iron because of the lack of yersiniabactin, the iron-binding siderophore of *Yersinia pestis* (plague). In the presence of free iron, *Y. enterocolitica* develops an invasive phenotype capable of causing sepsis.

Systemic Reactions Flushing, erythema, urticaria, and rare cases of anaphylactoid reactions may occur; although histamine release is a suspected etiology, pretreatment with diphenhydramine does not prevent these reactions.[105] Rapid desensitization protocols have been developed for sensitive patients with serious iron toxicity.[146] The initial dose is 0.015 mg deferoxamine over 30 minutes; if no symptoms develop, the dose increases by 10-fold during each 30-minute interval until achieving the maximum infusion rate. Other adverse effects of deferoxamine include abdominal discomfort, diarrhea, fever, leg cramps, and dysuria.

Ocular and Auditory The major risk factors for ototoxicity or ocular toxicity include dose and duration of deferoxamine therapy, low serum ferritin, and low iron stores. Almost all reported cases of ocular or ototoxicity involve the chronic administration of deferoxamine. A single case report associated short-term administration of deferoxamine with visual impairment.[147] Ocular toxicity is usually reversible.

Kidney Renal impairment limits the excretion of the deferoxamine-iron complex (ferrioxamine); therefore, deferoxamine should be used cautiously in patients with compromised renal function. Some case reports suggest acute kidney injury may occur following deferoxamine use in renal dialysis patients.[148] Hemodialysis may be necessary in cases requiring high deferoxamine doses. Preliminary animal studies suggest the development of high-molecular-weight derivatives of deferoxamine may reduce the toxicity associated with high-dose deferoxamine, allowing the use of higher doses of this chelator during massive iron overdose.[149]

Chronic Administration

A small number of patients treated with deferoxamine for chronic iron overload (e.g., thalassemia, Diamond-Blackfan syndrome) develop neurotoxicity (visual impairment, hearing loss). Risk factors for the development of neurological complications include the presence of renal failure, the maximum deferoxamine dose, low serum ferritin levels (<2,000 μg/L), and young age. Risk factors for ototoxicity may be somewhat different than ocular toxicity because ototoxicity may occur at low deferoxamine doses when the iron overload is minimal as defined by the serum ferritin.[150] Lens opacities usually improve with cessation of therapy; these opacities are rare following the subcutaneous administration of deferoxamine.[151]

Case reports of prolonged daily administration of large intravenous doses (125 mg deferoxamine/kg) associated night blindness and visual field defects that improved on withdrawal.[152] Reported ocular complications of long-term, high-dose deferoxamine therapy include reduced visual acuity and peripheral vision, retinal stippling, defective dark adaptation, abnormal visual evoked responses, thinning of the retinal vessels, cataracts, and dyschromatopsia.[153] Recovery from retinal pigmentary changes, optic atrophy, and

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abnormal visual evoked responses may be incomplete.[154] Rheumatoid arthritis patients treated with deferoxamine doses as low as 15 g over a week have developed retinal damage.[155] Auditory abnormalities at doses up to 126 mg deferoxamine/kg/day involve bilateral, high-frequency sensorineural hearing loss.[156] The development of hypersensitivity pneumonitis (cough, dyspnea, pulmonary infiltrate, a restrictive defect on pulmonary function tests) appeared within 4–9 days of the initiation of a continuous deferoxamine infusion.[157]

Indications

Acute Overdose

The severity of symptoms and the serum iron concentrations determine appropriate therapy. Treatment of moderately to severely symptomatic patients (e.g., altered consciousness, metabolic acidosis, shock, hepatotoxicity) should begin as soon as possible because of the rapid distribution of iron from blood into tissue; confirmation with serum iron concentrations in these patients is not necessary to begin intravenous deferoxamine. Seriously symptomatic patients should be given IV deferoxamine regardless of the relationship of the serum TIBC to the serum iron concentrations. The interpretation of serum iron concentrations drawn during deferoxamine therapy should be discussed with laboratory personnel because deferoxamine interferes with colorimetric assays of iron, resulting in falsely low (25–50%) serum iron concentrations. The presence of a normal abdominal radiograph, a normal serum leukocyte count, and/or a normal serum glucose concentration does not obviate the need to administer deferoxamine unless confirmed by nontoxic serum iron concentrations and a benign clinical presentation.

Peak Serum Iron Levels <350 μg/dL The value of deferoxamine at this concentration is minimal, if any, because significant toxicity does not usually occur. The presence of significant symptoms of iron poisoning indicates the need to repeat the serum iron concentration and begin deferoxamine.

Peak Serum Iron Levels 350–500 μg/dL Any symptomatic patient (excluding nausea or vomiting) with serum iron concentrations in this range should receive deferoxamine. No clear, well-documented guidelines exist to decide which asymptomatic patients in this range will develop subsequent toxicity.[158] Some patients with self-limited, non-bloody vomiting and diarrhea and peak serum iron concentrations in this range within 3–5 hours after ingestion will not develop sequelae when deferoxamine treatment is withheld.[159] Hence, the use of deferoxamine in this range requires clinical judgment. The presence of persistent or worsening metabolic acidosis indicates serious toxicity and the need for immediate chelation.

Peak Serum Iron Levels >500 μg/dL Almost all patients should receive intravenous deferoxamine therapy promptly. Patients with serum iron levels exceeding 1,000 μg/dL almost always develop serious toxicity, whereas asymptomatic patients rarely present with serum iron concentrations of >500 μg/dL.

Significantly Symptomatic Patients All patients with altered mental status (after checking for hypoglycemia), hypotension, bleeding, or protracted vomiting that suggest severe poisoning should receive prompt intravenous deferoxamine therapy without waiting for the results of the serum iron concentration. The correlation between reported iron dose or clinical symptoms is less clear in mild to moderate iron toxicity. In a retrospective analysis of UK poison control data on mild to moderate iron intoxication in 475 adults/teenagers and 86 children ≤12 years of age, the reported iron dose and clinical symptoms did not correlate to 4–6-hour iron concentrations.[160] The total series of 1,839 single-agent iron ingestions reported to the UK National Poisons Information Service did not contain any patients developing organ failure or fatalities.

Pregnancy Pregnancy is not a contraindication to the use of deferoxamine; intravenous deferoxamine should be administered promptly based on the serum iron concentrations and the clinical presentation.[161,162] Limited human data and data from the ovine model of maternal iron poisoning do not indicate that deferoxamine crosses the placenta in the last trimester.[163] Deferoxamine has been administered to pregnant women without adverse effects to the developing child;[164] conversely, a pregnant mother died of iron poisoning (serum iron, 1,700 mg/dL) after deferoxamine was withheld.[165]

Chronic Iron Overload

Factors to consider for the treatment of chronic iron overload include the degree of iron overload, the expected course of transfusions, age, psychosocial background, and medical history. Patients with clinical signs of iron intoxication or total iron stores of >0.7 g/kg probably require aggressive treatment.[166] Because serum ferritin and serum iron concentrations are not specific for iron overload, biopsies of the liver or bone marrow may be necessary to confirm or estimate total body iron stores. The most frequent choice for chelation in chronic iron overload is oral deferasirox,

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although there are no long-term studies on the efficacy of deferasirox or deferoxamine.[167]

Dosage Recommendations (Acute Overdose)

Intravenous Deferoxamine

Intravenous deferoxamine is the preferable route of administration for any serious iron ingestion.[141] Very little dose-response data are available to determine the appropriate deferoxamine dose for iron-poisoned patients. Consequently, the choice of a deferoxamine dose is empirical. A dose of 15 mg deferoxamine/kg/hour does not usually produce hypotension while probably chelating the most free circulating iron.[106] The exact dose required to prevent serious sequelae from massive iron ingestion has not been defined; higher infusion levels (20–35 mg deferoxamine/kg/h our) have been used anecdotally. However, these higher levels may require hemodynamic monitoring to ensure the optimization of cardiovascular parameters (e.g., pre-load, systemic vascular resistance).[168] Deferoxamine degrades quickly in alkaline (pH >10) and acidic (pH <2) solutions; at pH 4–6, deferoxamine retains 90% of the original concentration when stored at room temperature (<23°C).[169] A bolus of saline prior to deferoxamine therapy reduces the risk of acute renal failure in patients with contracted intravascular volumes during iron poisoning.[170]

Intramuscular Deferoxamine

The intravenous route is probably more effective because of the short half-life of deferoxamine (<1 hour) and the constant exposure to free circulating iron during the redistribution phase. The intramuscular deferoxamine dose is 40–90 mg/kg as a deep intramuscular injection up to a maximum of 2 g deferoxamine per injection. The maximum recommended deferoxamine daily dose is 6 g.

Deferoxamine Challenge

Previously, this procedure was administered to identify patients with free, circulating iron and the need for chelation therapy, when serum iron was unavailable or the history suggested toxic ingestion by an asymptomatic patient. The deferoxamine challenge has very limited use currently because of the reliability of the serum iron concentration and the importance of avoiding a delay in the administration of intravenous deferoxamine during serious iron poisoning. The appearance of the iron-deferoxamine complex turns the urine a reddish-orange (vin rose) color at ferrioxamine concentrations of >10 μg/mL urine.[171] The intensity of this color is dose-dependent with the color changes appearing within ~3 hours of administration.[172] Because chelation occurs optimally at a urine pH of 7–8, check the urine pH periodically. Rarely, high iron concentrations occur in the absence of colored urine, particularly when the urine pH level is <6. The deferoxamine dose is 40 mg/kg as a deep intramuscular injection (dilute 500 mg deferoxamine in 2 mL sterile water).

Duration of Treatment

Although little human data exist, the maximum recommended daily deferoxamine dose is 360 mg/kg up to a limit of 6 g deferoxamine. An infusion of 15 mg deferoxamine/kg/hour can be administered safely for 24–48 hours; most seriously poisoned patients require chelation therapy for 1–2 days. Deferoxamine infusion rates of >45 mg/kg/hour are often associated with hypotension secondary to vasodilation. Reducing the deferoxamine infusion rate to 5–6 mg/kg/hour following stabilization (typically 4–6 hours after initiation of the infusion) helps limit the total deferoxamine dose to 6 g. Empirically, deferoxamine doses of >6 g over 24 hours have been administered without complications; however, the use of *high* rates of deferoxamine infusions over several days has been associated with rapidly progressive acute respiratory distress syndrome. The decision to discontinue therapy depends on the clinical condition, the clearance of the reddish-orange color of ferrioxamine from the urine, and the return of serum iron concentrations to <100–150 μg/dL as measured by methods unaffected by deferoxamine interference.

The return of the urine to normal color after the appearance of the reddish-orange ferrioxamine complex is an indication that chelation may be discontinued after 24 hours of therapy assuming symptoms resolve. In the absence of color changes in the urine, normal serum iron concentrations help confirm the decision to stop chelation therapy. Ferrioxamine interferes with the colorimetric assay of iron; the laboratory performing these assays should be aware of the use of deferoxamine because the administration of deferoxamine may falsely decrease the serum iron concentration up to 30–50% when analyzed by colorimetric methods.[173] Deferoxamine does not interfere with the measurement of serum iron when analyzed by atomic absorption spectrometry. The exact length of therapy for iron poisoning necessary to eliminate systemic toxicity requires a better understanding of iron-induced mitochondrial toxicity and the effects of deferoxamine at these sites.[110] The deferoxamine infusion can be safely discontinued when the serum iron concentration is within the normal range and no clinical or laboratory evidence of iron toxicity (i.e., acidosis) remains.

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Supplemental Care

1) Watch vital signs carefully for signs of hypovolemia.
2) Replace fluid loss aggressively.
3) Watch for signs of blood loss (guaiac-positive stool) and send type/screen and cross-match when appropriate (e.g., evidence of bleeding).
4) Follow serum creatinine, prothrombin time, and serum aminotransferases concentrations as measures of renal and hepatic function.
5) In seriously poisoned patients, invasive or noninvasive monitoring may be necessary for dynamic cardiovascular monitoring to maximize cardiac output (i.e., preload, systemic vascular resistance) while administering high-dose deferoxamine infusions.[63]

Admission Criteria

All patients requiring chelation should be hospitalized. Patients remaining asymptomatic 6 hours after ingestion may be discharged if the following conditions are met: no vomiting/diarrhea/epigastric pain/lethargy; negative upright abdomen film for iron pills; and serum iron concentrations of <350 μg/dL.[51] Significantly symptomatic cases should receive chelation, as noted above.

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Chapter 16

LEAD

ELEMENTAL AND INORGANIC LEAD

HISTORY

Lead is the fifth most abundant metal in the earth's crust after iron, zinc, copper, and aluminum. Although lead is not essential to any know biological process in humans, this metal is a common constituent of the human body that results from the ubiquitous presence of lead in the environment.[1] Since the earliest recorded times, lead has been a constituent of homeopathic medicines, cosmetics,[2] building paints, and ceramic glazes. Lead-based ocher paints were part of Neanderthal artifacts recovered from the Middle Paleolithic age (~40,000 BC);[3] by the third millennium BC, Mesopotamia, predynastic Egypt, and Troy developed lead-smelting techniques. During the Neolithic age (6,200 BC), mines in Turkey contained leaded beads and slag. The Chinese Shang dynasty (1,555–1,145 BC) fabricated bronze alloys with soft metallic lead; studies suggest that aristocrats of that dynasty[4] may have ingested substantial amounts of lead while drinking rice wine stored in bronze vessels.[5]

Lead is an ancient chemical toxin.[6] Hippocrates described lead colic in 370 BC and Nicander of Colophon documented lead palsy in the 2nd century BC, both without recognizing the cause, whereas Pliny was the first writer to suspect lead toxicity as a cause of illness in Roman shipbuilders during the 1st century AD.[7] The Greek botanist–physician, Dioscorides, also described occupational lead poisoning in his book (*De Materia Medica*) during the time of Nero. The Romans discovered that the storage of wine in leaded vessels produced sweeter, more visually appealing wine and improved storage by reducing the conversion of wine to vinegar. Additionally, the grape syrup was commonly boiled down in a lead pot or lead-lined copper kettle before being added to the wine. In reality, the lead acetate in these vessels had a sweet taste and acted as a fungicide. Replication of Roman recipes suggests the wines may have contained up to 80 µg Pb/L accounting for ~50–60% of the daily Pb intake for the free Rome population.[8]

The contamination of wine by lead and the high prevalence of gout, colic, infertility, and neurological symptoms in the Roman aristocracy suggested the possibility that lead poisoning may have contributed to the downfall of the Roman Empire.[9] By the time of the fall of the Roman Empire, the estimated lead production was 40 million tons, primarily as a by-product of silver mining.[10] The use of lead pipes for water distribution was widespread in ancient Rome; analysis of lead isotopes from the harbor of Imperial Rome suggests these pipes increased the lead content by two orders of magnitude above natural lead concentrations.[11]

Examination of lake bed sentiment in Sweden indicated that the cumulative deposition of lead from anthropogenic sources in the preindustrial period (i.e., 600 BC–1800 AD) was at least as large as the cumulative lead deposition after 1800 AD (i.e., the industrial period).[12] Lead in pigments are suspected causes of illnesses suffered by Michelangelo (gout, melancholy) and the Spanish Grand Master, Francisco de Goya; wine stored in lead containers may also have contributed to

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the lead exposure of Michelangelo.[13] During the 17th and 18th centuries, lead poisoning (Devonshire Colic,[14] Colic of Poitier) occurred in the English aristocracy as a result of the consumption of lead-tainted Portuguese wine transported in containers containing lead bars to enhance flavor and prevent spoilage, particularly after the Treaty of Methuen ending the War of Spanish Succession (1701–1714) increased importation of inexpensive Portuguese wine.[15]

Benjamin Franklin associated lead poisoning with a disease (dry-gripes) that affected Europe and British colonies during the early 1700s.[16] In 1723, the Massachusetts colonial legislature banned lead in heads and coils of rum stills to reduce lead-contaminated rum distribution. Franklin's subsequent discussions on lead poisoning helped Dr. George Baker discover the association of lead toxicity with Devonshire Colic (muscle weakness, weight loss, pallor) in Dr. Baker's native Devonshire. Despite the absence of evidence of motor neuropathy, chronic consumption of lead-tainted wine is a suspected cause of the deafness of Ludwig von Beethoven (1770–1827). This theory is consistent with autopsy findings of shrunken cochlear nerves and inadequate evidence for otosclerosis (his temporal bones were lost).[17] Other suspected causes of Beethoven's deafness include autoimmune disease and cochlear otosclerosis.[18] In the United States during the 20th century, consumption of lead-contaminated moonshine caused an epidemic of gout and renal disease in the southern United States.[19] Lead was administered as an abortifacient in the early 1900s with subsequent reports of fatal lead poisoning.[20]

The estimated blood lead level of preindustrial humans was 0.5 μg/dL,[21] whereas the average blood lead level in the contemporary population in the Himalayas is ~3–4 μg/dL.[22] Lead use and environmental lead pollution increased dramatically during the first part of this century, as demonstrated in sequential layers of ice in Greenland. At the beginning of the Industrial Revolution in 1780, 1 g of ice contained 10 pg Pb. Two hundred years later, the lead content in 1 g ice increased to 200 pg (i.e., 20-fold) with the largest increases occurring since 1940.[23] During the 1970s, the United States consumed 1.3 million tons of lead, releasing an estimated 100,000 tons into the air and water.[24] Beginning in the 1950s, paint manufacturers began replacing lead in white pigment with the less expensive titanium. Lead exposure in the US population decreased substantially as a result of the elimination of lead from paint in 1977 and the phaseout of leaded gasoline. Analysis of $^{207}Pb/^{206}Pb$ ratios in permanent teeth formed between 1936 and 1993 in urban African-Americans from Cleveland, Ohio, indicated that about 2/3 of the total lead uptake into their enamel was attributable to leaded gasoline.[25] In blood samples from women living in lightly populated areas of Wales, blood lead levels decreased 30% during 1972–1982, despite little change in the total amount of lead used in gasoline.[26] The changes in blood lead levels in these two studies were similar. Vehicle exhaust contributed an average of up to 24–27% of total blood lead during this time, reflecting different sources in rural and urban areas;[27] the mean blood lead level in most countries averaged ~10–20 μg/dL.[28] The last reported death from lead encephalopathy in the United States occurred in 2006 (the last preceding death was in 1990).[29]

Humans accumulate lead based on past exposure to lead in the environment; average blood lead concentrations in the US population continue to decline as lead exposure in the environment decreases. The average US blood lead level declined 37% as leaded gasoline consumption declined 55% during 1976–1980.[30] For the US population, the geometric mean for the blood lead level during 1988–1991 in Phase 1 of the NHANES III study was 2.8 μg/dL (95% CI: 2.7–3.0 μg/dL). This mean represents a 78% decline since 1976–1980.[31,32] Overall, 8.9% of children 1–5 years of age in this study had blood lead levels >10 μg/dL. Variation in the blood lead level depends on geographic area and age. In Chicago, the median blood lead levels among children declined from 30 μg/dL in 1968 to 12 μg/dL in 1988, while air lead levels decreased ~20-fold.[33] Blood lead levels continue to decline. The geometric mean blood lead level in the US population during 1991–1994 was 2.3 μg Pb/dL with 4.4% of the children aged 1–5 years having blood lead levels exceeding 10 μg/dL.[34] The geometric mean declined to 1.66 μg/dL (95% CI: 1.60–1.72 μg/dL) in 1999–2000 (NHANES III), then to 1.12 μg/dL (95% CI: 1.08–1.16 μg/dL) in 2009–2010 (NHANES IV).[35] The blood lead level in children aged 1–5 years in the National Health Nutrition and Examination Survey continued to decline in the 2010s with an estimated 97.5% BLL of 3.48 μg/dL in 2011–2014.

As blood lead levels declined, classic lead poisoning (peripheral neuropathy, kidney disease, encephalopathy) became rare and mortality from lead intoxication decreased dramatically. Within the past 40 years, epidemiological studies have provided evidence of health effects at low blood Pb levels. Research work on the clinical effects of lead now focuses on the subtle neuropsychological (reduced IQ, behavioral abnormalities), cardiovascular, reproductive, and developmental effects of chronic low-dose lead exposure. The US National Toxicology Program review of epidemiology studies raised concern about the effects of blood lead levels <10 μg/dL in several domains in children

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(reduced academic achievement/IQ, attention-related behavior problems, reduced postnatal growth, delayed puberty) and adults (decreased glomerular filtration rate, increased blood pressure, essential tremor).[36]

Children are particularly susceptible to lead-induced impairment of neuropsychological development because of their reduced ability to excrete lead and enhanced lead absorption compared with adults. Difficulty controlling confounding variables (maternal and paternal IQ, prenatal care, educational interventions) and the relatively small effect of lead exposure compared with the effect of these confounding variables complicate the interpretation of the effect of lead on cognitive development. Because the efficacy of chelation in patients with blood lead levels <45 μg Pb/dL is unproven, treatment involves prevention and modification of the environment. In 1991, the Centers for Disease Control and Prevention (CDC) reduced the blood lead "level of concern" at which intervention is desirable from 25 to 10 μg/L. In 2012, the CDC shifted its focus to the primary prevention of lead exposure to expedite the identification of children at risk of serious lead exposure (e.g., cognitive abnormalities, behavioral development). Consequently, the CDC replaced the level of concern (i.e., >10 μg/dL) with the 97.5th percentile of the NHANES distribution of lead in US children (>5 μg/dL). The effect of low-level lead exposure is less clear in adults than children, particularly subclinical effects (e.g., inhibition of heme biosynthesis enzymes, impairment of renal tubular function, reduction of sperm formation, diminished conduction of motor nerve impulses, elevated blood pressure). The difficulty of detecting the extent of chronic lead exposure over a lifetime confounds epidemiological studies.

PHYSIOCHEMICAL PROPERTIES

Metallic lead is a relatively rare element in the natural environment. Lead occurs naturally as a mixture of the following four stable isotopes: ^{208}Pb (51–53%), ^{206}Pb (23.5–27%), ^{207}Pb (20.5–23%), and ^{204}Pb (1.35–1.5%).[37] Although lead exists in three oxidation states (0, 2+, 4+), lead exposure primarily involves the divalent inorganic salt. The excellent corrosion resistance of lead results from the formation of lead salts (carbonates, oxides, sulfates) following exposure to air or water. Most of the lead salts (e.g., sulfide, oxide) are poorly water-soluble with the exception of chlorate and nitrate. The solubility of lead chloride is intermediate between the solubility of nitrate and oxide salts. Tetravalent lead compounds occur only under extreme oxidizing conditions; consequently, inorganic tetravalent compounds do not usually exist under normal environmental conditions. Table 16.1 lists the identifying information and physical properties of lead and divalent lead salts.

EXPOSURE

The blood lead level in an individual depends on several risk factors including age, gender, menopausal status, trimester of pregnancy, smoking, and alcohol consumption.[38,39] The segment of the population with the highest risk from lead toxicity includes preschool children, pregnant women and their fetuses, and older workers (e.g., 40–59 years old) with chronic lead exposure. Despite the potentially increased release of lead from bone stores as the population ages, analysis of NHANES data and evaluation of inner-city populations over the age of 80 years indicate elevated blood lead levels as defined by >10 μg/dL were rare in this group.[40] Specific risk factors include habitation or renovation of older homes (pre-1950–1960), occupational or para-occupational exposure, smoking, and illicit wine or whiskey consumption. The overwhelming majority of serious lead exposure in adults occurs in the work environment via inhalation; lack of proper hygiene in lead-contaminated environments (e.g., eating or smoking in areas containing lead dust) increases the risk of lead toxicity.[41] In a subset of the Normative Aging Study established in 1963 to study men from Greater Boston, the highest mean bone lead concentrations occurred in protective service workers (police, firefighters, guards) and construction/extractive workers (foremen, carpenters, electricians, painters, plumbers).[42]

Other than a lead-contaminated point source (e.g., lead smelter, leaded gas fumes), the most important sources of lead exposure for young children include direct or indirect contact with lead-based paint and, to a lesser extent, house dust, contaminated soil, drinking water, formula in contaminated milk containers,[43] paint chips,[44] ceramics, and medications.[45,46] A review of the lead toxicology program in Massachusetts indicated that the most common sources of lead exposure in infants up to 12 months were the following: household renovation, direct ingestion of paint chips, infant formula preparations with lead-contaminated water, lead dust importation, and congenital exposure to an elevated maternal lead level.[43] In this study, paint chips were a more important source of elevated lead concentrations than a household renovation in the group of children aged 18–30 months. A pooled analysis of 12 epidemiological studies on children aged 6–36 months with

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TABLE 16.1. Identifying characteristics and physical properties of lead and divalent lead salts.

Physical Characteristic	Lead	Lead Acetate	Lead Bromide	Lead Carbonate	Lead Chloride	Lead Chromate
Synonym	Metallic lead, plumbum	Lead acetic acid, plumbous acetate		Cerussite, carbonic acid lead salt	Plumbous chloride	Chromic acid lead salt, Yellow 34
CAS RN	7439-92-1	301-04-2	10031-22-8	598-63-0	7758-95-4	7758-97-6
Molecular formula	Pb	$PbC_4H_6O_4$	$PbBr_2$	$PbCO_3$	$PbCl_2$	$PbCrO_4$
Molecular weight (g/mol)	207.2	325.28	367.04	267.2	278.11	323.19
Valence	0	+2	+2	+2	+2	+2
Color	Bluish-silver gray	White	White	Colorless rhomboid crystals	White	Yellow, yellow-orange
Physical state	Solid	Solid	Crystalline powder	Solid	Solid	Solid
Odor	Odorless	Slightly vinegary	None	Odorless	Odorless	Odorless to slight
Melting/boiling points (°C)	327.4/1,740	280/>200[a]	373/916	315[a]	501/950	844[b]
Density (g/mL, 20°C)	11.34	3.25	6.66	6.6	5.85	6.12
Water solubility (mg/L, 25°C)	Insoluble	443,000 (520°C)	8,441 (20°C)	1.1	9,900 (20°C)	0.2
Vapor pressure (mmHg)	1.77 (100°C)	NA	1 (513°C)	NA	1 (547°C)	NA

Physical Characteristic	Lead Iodide	Lead Nitrate	Lead Oxide	Lead Phosphate	Lead Sulfate	Lead Sulfide
Synonym	Lead diiodide, plumbous iodide	Lead dinitrate, plumbous nitrite	Yellow lead monoxide, litharge, massicot	Phosphoric acid lead salt	Sulfuric acid lead salt	Lead monosulfide, plumbous sulfide, natural galena
CAS RN	10101-63-0	10099-74-8	1317-36-8	7446-27-7	7446-14-2	1314-87-0
Molecular formula	PbI_2	PbN_2O_6	PbO	$Pb_3P_2O_8$	$PbSO_4$	PbS
Molecular weight (g/mol)	461.01	331.21	223.20	811.54	303.26	239.27
Valence	+2	+2	+2	+2	+2	+2
Color	Golden yellow	Colorless to white	Red–yellow[c]	White	White	Blue, black, or silver
Physical state	Powder/crystals	Solid	Solid	Solid	Solid	Crystals or powder
Odor	Odorless	Odorless	Odorless	NA	NA	NA
Melting/boiling points (°C)	402/872[a]	470[a]	888/1,472[a]	1,014	1,170	1,114/1,281[d]
Density (g/mL, 20°C)	6.16	4.53	9.3 (litharge, 8.0 (Massicot)	6.9	6.2	7.58
Water solubility (mg/L, 25°C)	630 (20°C)	565,000 (20°C)	17 (20°C)	0.14 (20°C)	42.5	0.86 (13°C)
Vapor pressure (mmHg)	1 (479°C)	NA	NA	NA	NA	10 (975°C)

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.
[a] Decomposes; [b] Decomposes at higher temperatures; [c] Yellow above 489°C; [d] Sublimes.

blood lead concentrations of 10–25 µg/dL demonstrated lead-contaminated house dust as the major source of lead exposure.[47] Major factors affecting the blood lead concentration in these children included age, race, mouthing behaviors, and site-specific factors (e.g., heavy contamination of soil by lead mining wastes[48]). The ingestion of >5 µg inorganic lead/kg of body weight in children contributes to an increasing blood lead concentration by producing a positive lead balance.

Uses

The physical properties of lead include high density, ease of fabrication, low melting point, chemical stability,

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TABLE 16.2. Current and previous lead uses. (Adapted from Centers for Disease Control and Prevention).[35]

Lead Salt	Uses
Acetate	Dyeing of textiles, waterproofing, varnishes, lead driers, chrome pigments, gold-cyanide process, insecticides, anti-fouling paints, analytical reagents, hair dye
Arsenite/arsenate	Insecticide, herbicide, rodenticide
Azide	Primary detonating compound for high explosives
Bromide	Photopolymerization catalyst, inorganic filler in fire-retardant plastics, general-purpose welding flux
Carbonate	Polymerization catalyst, high-pressure lubricating grease constituent, vinyl chloride polymer coating
Chloride	Preparation of lead salts, lead chromate pigments, analytic reagents
Chromate	Pigment in industrial paints, rubber, plastics, ceramic coatings; organic analysis
Tetrafluoroborate	Salt for electroplating lead; can be mixed with stannous fluoroborate to electroplate any composition of tin and lead as an alloy
Iodide	Bronzing, printing, photography, cloud seeding
Molybdeum chromate	Analytical chemistry, pigments
Nitrate	Lead salts, mordant in dyeing and printing calico, matches, mordant for staining mother of pearl, oxidizer in the dye industry, sensitizer in photography, explosives, tanning, process engraving, lithography
Oxide (black)	Storage batteries, ceramic cements and fluxes, pottery and glazes, glass, chromium pigments, oil refining, varnishes, paints, enamels, assay of precious metal ores, manufacture of red lead, cement (with glycerol), acid-resisting compositions, match-head compositions, other lead compounds, rubber accelerator
Phosphate	Stabilizing agents in plastics
Styphnate	Primary explosive, firing Pb-based ammunition storage batteries, paints, ceramics, pigments, electrical and other vinyl compounds requiring high heat stability
Silicate	Ceramics
Tetraethyl lead	Anti-knock agent in 100 low-lead (100LL) aviation gasoline

and corrosion resistance; these desirable characteristics are useful in storage batteries, weights, solder, and pipes.[49] Occupations associated with potential lead exposure include the following: plumbers, pipefitters, construction workers, bridge reconstruction workers, steel welders and cutters, firing range instructors, shipbuilders, battery manufacturers and recyclers, printers, automobile painters, printers, glass manufacturers, lead miners and refiners, rubber product manufacturers, and plastic manufacturers. The most common worldwide uses of lead include manufacturing of storage batteries, production of leaded fuel, and formation of lead-containing alloys with the former accounting for most of the lead consumed in the United States. The US EPA banned lead arsenate and lead arsenite as insecticides in 1988. Although the US EPA banned gasoline fuel containing >0.05 g Pb/gallon for motor vehicles in 1996, other engine types can use gasoline with lead additives including farm equipment, marine craft, airplanes, and race cars.

Lead-antimony alloys insulate cables from moisture and form grids in storage batteries, whereas lead-arsenic-bismuth-tin alloys are constituents of power cables. Solders and bullets may contain lead. The chemical industry uses lead, particularly in the manufacture of sulfuric acid. The excellent sound and radiation attenuating properties of lead are favorable for use in construction and X-ray machines. Lead chromate and lead molybdate form paint pigments with excellent protective properties for bridges, pipelines, and ships. Table 16.2 lists the current and former uses of lead compounds.

Production Processes

Mined ores are the primary source of lead. Galena (PbS) is the most important lead ore; the weathering of galena produces other lead-containing minerals (cerussite, $PbCO_3$; anglesite, $PbSO_4$). Zinc and silver ores also may contain lead. Production of primary lead involves the concentration of lead in a sulfide concentrate (crushing, grinding, froth floatation, dense medium separation), followed by the removal of sulfur and the formation of lead oxide by oxidative roasting.[37] Then blast furnace reduction converts the lead oxide to lead. Secondary lead results from the recycling of lead scraps, primarily storage batteries.

Sources

The estimated daily intake of lead from the environment at the end of the 20th century was ~5–11 µg.[50] Food is usually the major source of lead intake for the general population with small contributions from

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drinking water and air.[51] The impact of each pathway on blood lead levels depends on a variety of circumstances and behaviors. Lead toxicity in children usually results from oral exploration of a contaminated environment with certain sociological-demographic factors and housing characteristics increasing the risk of lead toxicity.[52] Sources of lead exposure in children include old lead-based house or bridge paints, take-home lead from father's workplace,[53,54,55] lead-glazed pottery, lead in dust or topsoil (e.g., near smelter dumps, burning battery casings, freeways), and traditional remedies including Hispanic, Hmong, and Indian folk medicine (e.g., pay-loo-ah, ghasard, Azarcon, Greta).[56,57,58] Table 16.3 lists potential sources of lead toxicity in children. Severe acute lead poisoning in children may occur from the ingestion of lead-containing objects (e.g., curtain weights, clothing accessories, live lead-based ammunition).[59,60] Current predictors of elevated blood lead levels in US children include air lead, residence in pre-1950 housing, African-American ethnicity, and poverty.[61]

The intentional ingestion of nonfood substances (pica) is the most important route of lead poisoning in toddlers and older preschool children, whereas the ingestion of lead-contaminated formula and exposure to lead during renovation are more important sources of lead exposure in infants.[43] Children can potentially ingest up to 20–50 mg soil/day; this amount correlates to an intake of 25 μg Pb assuming the soil contains 100 μg Pb/g.[62] Pica as a source of lead poisoning is exceedingly rare in the adult population with cases typically involving psychiatric disorders (e.g., schizophrenia, dementia)[63,64] or pregnant immigrant women.[65]

High-precision lead isotope measurements (isotope ratio, IR) help determine the sources of lead exposure.[67,68] This method identifies unique isotope ratios for each source and compares the ratio of the source to the isotope ratio in the blood. In the United States, measurements of the $^{206}Pb/^{204}Pb$ IR in natural lead sources ranged from 16.3 in the Coeur d'Alene mining district in Idaho to 22.54 in Mississippi Valley lead deposits, whereas the $^{206}Pb/^{207}Pb$ IR was 1.05 and 1.4, respectively, in these two locations.[69] Lead dust in residences is probably a composite of many sources of lead over time; lead paint chips under areas where the samples are collected may contaminate the dust sample. Two studies in the northeastern and central United States suggest that a $^{206}Pb/^{207}Pb$ IR in blood outside 1.185–1.215 indicates a geological point source for the lead.[70] The ratio is geographically specific with ratios in other areas (e.g., the western United States) varying as a result of different point sources for lead. The potential

TABLE 16.3. Potential sources of childhood lead toxicity. (Adapted from Woolf et al.).[66]

Area	Source	Examples
Environment	Antique or foreign toys, cribs, furniture	Toy soldiers, necklaces
	Contaminated foodstuffs	Homegrown vegetables, imported spices, calcium supplements, flour
	Cosmetics	Kohl, surma, ceruse,
	Crafts	Ceramic glazes, paints, stained glass material
	Exterior home material	Pewter-like fencing
	Drinking water	Leachate from leaded pipes
	Dust contamination, soil	Lead smelters, leaded gasoline sources
	Folk remedies	Pay-loo-ah, ghasard, azarcon, greta, litarigio, bali bali, coral, liga, reuda
	Herbal products	Ayurvedic medicine and supplements
	Imported material	Toys, crayons, ceramics, pewter, pots, kettles
	Methamphetamine	Lead acetate process (prior to 1970s), ephedrine or pseudoephedrine process, and lead-contaminated adulterating (cutting) agents
	Moonshine whiskey	Processes using lead containers
	Paint	Primarily houses built before the 1970s
	Plaster, putty	
Activities	Burning painted wood	Pre-1950 homes
	Hobbies	Target shooting, stained glass, glazing pottery, toy soldiers, fishing weights
	Home renovation	Primarily houses built before the 1970s
	Occupations	Auto repair, mining, smelting, demolition, battery manufacture, construction, painting, pipe fitting, plumbing, shipbuilding, welding, bridge reconstruction, firing ranges
Pregnancy (*in utero*)	Dietary supplements/herbal products	
	Hobbies	
	Lead-related jobs	

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TABLE 16.4. Some historical average and upper range concentrations of lead contamination in selected sources 1970s–1980s. (Adapted from Nyhan et al.).[23]

Source	Item	Estimated Lead Concentration
Food	Baby food in tin can	202 μg/L (M)
	Drink in glazed pottery mug	2,000 μg/L (UR)
	Bone meal	60–190 μg/g
Water	Drinking water	640–1,850 μg/L (UR)
Air	Smelter within 1.6 km	8–10 $\mu g/m^3$
	Smelter within 4.0 km	14–16 $\mu g/m^3$
Soil	Smelter within 1.6 km	7,600 μg/g (M)
	Urban residential	9–7,890 μg/g (M = 585 μg/g)
	Urban park	194–3,357 μg/g
House dust	New inner-city homes	2–24 $\mu g/ft^2$
	Old inner city homes	33–486 $\mu g/ft^2$ floor
	Lead smelter workers' homes	2,687 μg/g (M)
	Homes within 1.6 km from smelter	22,191 μg/g (M)
	Homes 1.7–3.2 km from smelter	2,124 μg/g (M)
	Paint chips	100,000 μg/g (UR)

Abbreviations: M = mean; UR = upper range.

sources of lead must be few in number and isotopically distinct in order for this method to identify effectively the pathway of lead exposure.[71] Table 16.4 lists lead contamination in selected sources based on data prior to the banning of leaded gasoline in the United States; data must be interpreted cautiously when extrapolating lead concentrations from various sources because of the historical reductions in lead concentrations over the later decades of the 20th and 21st centuries.

Air

The major natural sources of lead include emissions from sea spray, volcanic eruptions, and the weathering of the earth's surface. The contribution of natural lead sources to lead exposure in the general population is relatively small compared with anthropogenic sources.[72] An estimated 19,000 tons Pb/year is released from these natural sources throughout the world with volcanic eruptions accounting for about 6,400 tons Pb/year.[73] Lead concentrations in ambient air range from 0.000076 $\mu g/m^3$ in Antarctica[74] to >10 μg Pb/m^3 near smelters, with average annual urban levels <1 μg Pb/m^3. In 1925, leaded gasoline was introduced into the United States with mandatory reductions in lead content beginning in 1973 culminating in a ban on most uses by 1996. Lead has not been completely removed from aviation gasoline because damage from engine knocks may cause sudden engine failure. Prior to the restriction of leaded gasoline by the US EPA, the combustion of alkyl-leaded fuel was the major (80–90%) source of airborne lead in the United States. High lead concentrations may contaminate soils surrounding major highways as a result of the previous use of leaded gasoline. Currently, industrial processes are the major sources of lead emissions into the atmosphere with the highest lead concentrations found around smelters and battery manufacturers. In 1982, the ambient air in urban areas of Mexico contained 0.6–5.7 μg Pb/m^3 compared with <0.07 μg Pb/m^3 in US urban air after the restriction of leaded gasoline use.[75] In 1988, auto emissions accounted for only 34% of the annual amount of lead released into the air.[76] By the early 2000s, US EPA National Air Quality Monitoring Program data indicated a 94% reduction in the average air quality lead concentration since the early 1980s based on a mean atmospheric lead concentration of <0.05 $\mu g/m^3$.[77] The lead concentrations in indoor air range from 30–80% (mean ~50%) of the outdoor lead concentrations. The lead level in ambient indoor air depends primarily on the presence of lead-painted surfaces. In a study of 213 residences in the Midwestern United States during the 1990s, the mean lead concentration in indoor ambient air was 0.015 ± 0.038 $\mu g/m^3$ with a median of 0.006 $\mu g/m^3$ and a maximum value of 0.293 $\mu g/m^3$.[78] Analysis of this data indicated that the difference between the mean lead concentration in indoor ambient air from homes built before 1940 (0.046 ± 0.002 $\mu g/m^3$) was significantly different (P = 0.036) than homes built from 1960–1979 (0.013 ± 0.002 $\mu g/m^3$). However, the differences between homes built from 1940–1959 (0.022 ± 0.005 $\mu g/m^3$) or 1980–1995 (0.023 ± 0.005 $\mu g/m^3$) and pre-1940 homes were not statistically significant.[79]

Except for near-point sources (e.g., smelters,[80] battery manufacturing or disposal), airborne lead is a minor pathway of exposure in countries that limit the use of leaded fuel.[81] Lead concentrations are usually highest within 3 km of these sources; concentrations near these sites may exceed 10 μg Pb/m^3.[72] Ambient air concentrations >2 μg Pb/m^3 as a monthly average are associated with increased blood lead levels in children.[82] For each 1 μg Pb/m^3 of ambient air, the blood lead of an exposed person increases by 1–2 μg Pb/dL.[83] Global distribution of lead occurs as a result of anthropogenic sources, primarily as a result of the continued use of leaded fuel additives.

Soil

The average lead concentration in the crust of the earth is ~10–30 mg Pb/kg with the major geological sources

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being metamorphic and igneous rocks, mostly galena (PbS). Studies of lead speciation indicate that the form of lead changes during the smelting process. Galena is the major constituent in samples obtained during ore handling, whereas lead oxide is the dominant species associated with the smelter operation.[84]

Domestic ore production and ammunition use produce most of the lead-containing solid waste. For lead contamination from anthropogenic sources, the soil is the most important repository. Soil and sediment are important sinks for lead in the environment with sources typically containing higher lead concentrations than adjacent surface waters. Both wet and dry deposition are important routes of contamination of the soil. Because lead does not dissipate, degrade, or decay in soil, lead deposited in the soil or dust represents a potential long-term source of lead exposure. Lead exposure from soil results from surface dust and the actual content of lead in soil. Background lead concentrations in soil range from 10–70 mg/kg with concentrations near point sources (e.g., highways) up to several times higher depending on proximity.[72] Local point sources of lead may increase the lead content in sediments significantly. In a study of sediment in surface waters near mines located in the old lead belt of Missouri, lead concentrations in sediment near the mines ranged from 10,550–12,400 mg/kg dry weight compared with 72–400 mg/kg in sediment from areas without lead-contaminated mine tailings.[85]

Exclusive of lead-contaminated paint sources, the lead concentration in soil largely reflects the deposition of lead from the atmosphere. The predominant species emitted from lead smelters are lead sulfur compounds.[86] Lead deposited from the air resides in the top 2–5 cm of undisturbed soil. The major chemical factors that affect the bioavailability of lead from the soil include the species of lead, the matrix attached to lead, and the size of the lead-containing particles.[87] Lead sulfide is less bioavailable compared with lead carbonate and lead oxide. Although the reduction of leaded fuel has dramatically reduced the lead concentration in air, soils within 25 m of roadways typically contain 30–2,000 ppm of lead above natural levels depending on the amount of vehicular traffic.[72] In less developed countries, cottage and conventional smelters are potential hazards for nearby residents, particularly children aged 1–2 years old.[88] In areas surrounding lead sources, the blood lead level of children correlates to soil lead concentrations, whereas the blood lead level of pregnant women does not.[89] Releases of lead from lead-based paints are usually limited to the immediate vicinity of painted surfaces; however, deterioration or removal of lead-containing paint can produce high localized lead concentrations in house dust, particularly following the use of power sanders or sandblasting. In a case series of 31 New Orleans houses, paint chips contained a median lead concentration of 35,000 μg/g with a range up to 257,000 μg/g.[90] Power sanding one of these houses (exterior paint, 130,000 μg Pb/g) resulted in blood lead concentrations in house dust from the living area and soil from the front entrance porch of 23,300 μg/g and 27,600 μg/g, respectively.

Water

Analysis of data from ocean water indicates very low lead concentrations (i.e., 0.005 μg/L) in seawater not directly affected by anthropogenic sources.[91] Lead concentrations in the ground or surface water are variable, rarely exceeding 5–10 μg/L depending on point sources, sediment contamination, and soil/water conditions (e.g., pH, temperature, humus content). The component of lead in water attributed to natural sources accounts for ~0.02 μg/L.[92] The major sources of lead in drinking water are lead pipes and leaded solder in lead service lines connecting the house to the main water lines, faucets, and fixtures, particularly in houses built before 1986. The presence of leaded water pipes may increase these concentrations substantially (i.e., 100 μg/L). Surveys of drinking-water supplies leaving treatment plants indicate lead concentrations averaging 2–3 μg/L; however, concentrations in households with corroded lead plumbing may range 10–30 μg/L, particularly in systems installed prior to 1930 or connected to main lines with lead piping. In a study of 381 water samples from 73 residences obtained during the mid-1990s throughout Maryland, the median lead concentration was 0.33 μg/L with a mean of 1.08 ± 2.01 μg/L (maximum, 13.40 μg/L).[93] Prior to the collection of the water samples, the tap was flushed for 2 minutes. First-draw water samples from a study of 2,146 private drinking water systems in Virginia exceeded 15 μg/L (US EPA standard) with brass as the likely lead source.[94]

Aquatic releases from industrial sources primarily involve leachates from steel/iron industries and lead production/processing operations with the lead primarily suspended in solids or adsorbed into the sediment. Urban runoff and atmospheric deposition are indirect lead sources. Lead concentrations typically are low in ground and surface water averaging <4 μg/L; contamination of water with lead usually occurs in the distribution system. Common areas of lead contamination in the water distribution system include 1) lead connectors (goosenecks, pigtails), 2) lead service lines or pipes, 3) lead-soldered joints in copper plumbing, 4) lead-containing water fountains and coolers, and 5)

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lead-containing brass faucets and other fixtures. The latter accounts for up to 1/3 of the lead present in the first-draw sample. Currently, installation of residential plumbing systems involves the use of lead-free solder and copper piping; the solder and flux must contain <0.2% lead, whereas pipes, pipe fittings, and well pumps must contain <8% lead based on the 1986 Safe Drinking Water Act Amendments.

The contamination of drinking water by lead occurs during the leaching of lead from lead-laden pipes and/or lead-containing solder on copper pipes, primarily in areas with soft (low calcium, low magnesium, acidic pH) water. In April 2014, the city of Flint, Michigan, switched their drinking water source from the low corrosivity of Detroit Water and Sewage Department water (↓ chloride, ↓ chloride/sulfate mass ratio, orthophosphate corrosion inhibitor) to Flint River water (↑ chloride, ↑ chloride/sulfate mass ratio, no orthophosphate corrosion inhibitor); this change resulted in lead leaching into the drinking water from some homes with leaded water pipes (e.g., 104 μg/L, 397 μg/L, 707 μg/L).[95,96] Before the issuance of boiling water advisory in October 2014 and reduced drinking water consumption, the estimated likelihood of a child presenting with blood lead level (BLL) >5 μg/L increased by a factor of 1.91–3.5 depending on the season and neighborhood studied within Flint; however, retrospective analysis of BLL of Flint children did not support a global increase in the BLL of young children in Flint during the 18-month period of Flint River water use.[97] The geometric mean BLL of affected children decreased in blood samples during the period immediately before the switch from 1.47 ± 0.02 (n = 1,834 samples) to 1.32 ± 0.02 (n = 1,734 samples) during the 18 months of Flint River water use. Some of the increased BLL during this period may have resulted from seasonal variation in BLL (e.g., resuspension of lead-contaminated soils during the summer).[98] The city of Flint switched back to the Detroit Water District in November 2015.

Grounding of electrical systems to pipes may increase the lead content in water by increasing corrosion. Acidity increases the amount of lead in water with higher lead concentrations occurring in drinking water with pH <8.[99] Detectable lead concentrations may occur in "first draw" water from plastic or galvanized pipes despite the absence of lead-containing material. In a study of >1,000 water samples from regulated facilities throughout the United States during the 1980s, the mean lead concentration in 1-L samples of "first draw" water was 4.5 μg/L from plastic piping and 4.2 μg/L from galvanized piping without lead solder.[99] Brass faucet fixtures accounted for most of the lead content. Significant lead contamination of tap water is unusual. A follow-up study of elderly men in Boston indicated that measures of cumulative lead exposure (tibia and patella bone lead levels) correlated to first-morning tap water lead concentrations ≥50 μg/L and the daily consumption of ≥1 glass of tap water; however, there was no correlation in men to lower lead exposure.[100]

The highest lead concentrations in tap water occur in the "first-draw" water from seldom-used faucets following extended periods of disuse.[101] This "first draw" water may contain up to 10 times the lead concentration present in fully flushed water.[102] Within 3–5 hours of a 10-minute flush, the lead level in drinking water is similar to lead concentrations prior to the 10-minute flush.[103] The effectiveness of many point-of-use devices (e.g., water taps) in reducing the lead content in water depends on the location of the device in relation to the source of lead and compliance with maintenance/use requirements. Reverse osmosis and distillation units usually remove lead more effectively from water than carbon, sand, or cartridge filters.

Diet

The major source of lead exposure for the general adult population is water and food with lead intake decreasing significantly during the last part of the 20th century. The average daily dietary lead intake of a 2-year-old child decreased from 30 μg in 1980 to 5 μg in 1988.[81] The estimated daily total lead intake for all age groups (n = 176) in the NHEXAS Arizona study during the mid-1990s was 36 μg with a range of 11–107 μg.[104] The 90th percentile of lead in food analyzed in this study was 0.016 μg/g. Isolated epidemics of lead poisoning occur as a result of lead contamination in dietary sources (e.g., paprika).[105] Acidic foods (e.g., fruit/vegetable juice, salsa) can release lead from improperly fired ceramic glazes or lead-soldered cans;[106] however, the impact of the latter is decreasing as the use of lead solder decreases. Although the acidic pH of alcoholic beverages favors the leaching of lead, alcoholic beverages probably are not a significant lead source for the general population.[72] The leaching of lead from lead-containing containers is higher for some foods (e.g., corn, beans) than others with similar pH.

The quantity of lead in food decreased substantially with reductions in the use of leaded gasoline and lead-containing solder in food containers. The use of food containers with leaded solder was reduced substantially in the US markets in 1979–1989 with elimination by 1995. In the US FDA Total Diet Study (TDS) 1991–1996, analysis of lead concentrations in a market basket of 260 foods from four geographic regions of the United States detected lead below 0.03–0.05 mg/kg

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(lower level of quantitation) in 255 foods; samples included cereal and grain products, desserts, eggs, infant and junior foods, fish, legumes, meat, milk and cheese, poultry, snacks, and vegetables.[107] Quantifiable lead concentrations occurred in canned peaches (0.032 mg/kg), canned pineapple (0.013 mg/kg), canned fruit cocktail (0.031 mg/kg), dry table wine (0.023 mg/kg), and sweet cucumber pickles (0.036 mg/kg). In a Canadian study of retail foods in five cities during 1986–1988, the median lead concentrations in food categories other than miscellaneous ranged from <0.003 mg/kg (maximum, 0.089 mg/kg) for beverages to 0.016 mg/kg (maximum, 0.37 mg/kg) for fruits and fruit juices.[108] The mean lead concentration for all categories was 0.023 mg/kg with a maximum of 0.52 mg/kg. During this 3-year period, the mean lead concentration in canned foods decreased by 60% with the increased use of lead-free containers. Rarely, chickens raised in urban gardens contaminated by lead (e.g., peeling lead paint) produce eggs containing lead concentrations in edible portions exceeding current recommended lead thresholds.[109]

Lifestyle

Common nonoccupational exposures to lead include shooting firearms, renovating, painting, lead casting, and retained bullets.[110] Potentially hazardous hobbies involving lead contamination include stained glass production, casting ammunition, assembling fishing weights and toy soldiers, painting, and furniture refinishing. Lead toxicity occurred in a family as a result of exposure to lead fumes from the extraction of gold and silver from jeweler's waste.[111] Smoking increases the risk of lead toxicity in smokers residing in lead-contaminated houses.[112] Lead content in tobacco varies from 2.5–12.2 μg/cigarette with ~2–6% inhaled by the smoker.[113] A study of filter-tip Finnish cigarettes in the 1970s detected a mean lead concentration of ~2.4 μg/g.[114] The estimated amount inhaled was ~5% with the remaining lead in side-stream smoke and ash. In 320 samples from participants in the 2009 International Tobacco Control United States Survey, the mean lead content was 0.44 ± 0.24 μg/g dry weight (range, <0.19–2.40 μg/g),[115] whereas the reference range for lead in a study of major US cigarette brands was 0.6–1.2 μg/g (dry weight).[116]

Housing

Structure Since 1978, federal US statutes restrict the manufacture of paint with lead content >0.06% (600 ppm) by weight in its final, dry solid form. The use of lead-based paint was common in older homes built before 1940, where lead content from lead carbonate and lead oxide typically ranged 5–40%. These dwellings may also contain leaded pipes that produce lead-contaminated leachate in household water. During this time interval, lead oxide was the main constituent of white pigment in paint.[117] Renovation of these homes can result in significant lead contamination.[118] The use of interior lead-based paint declined dramatically during the 1950s, but the use of exterior lead-based paint continued until the mid-1970s. A 1990s study analyzing the isotope ratios of Pb in house dust samples from an urban New Jersey environment demonstrated that outside sources of lead contribute as much Pb to the house dust wipe samples as interior lead-based paint.[119] Soil and paint in modern and well-maintained homes probably contribute little to the lead exposure of children.[120]

A temporary exacerbation of lead toxicity may occur in children following the removal of lead from old, lead-contaminated homes.[121,122] The renovation of older homes (e.g., sandblasting, sanding, heating with torches) can produce serious lead toxicity in children[123] and adults.[124] Adults performing the restoration work and the youngest children in the dwelling are at the greatest risk of developing lead toxicity. Although a typical (25–50% lead by weight) 1 cm^2 chip of paint contains ~0.5 gm Pb, most lead is not absorbed because of the lamination of the lead in the chip and the ingestion of the chip as a whole. Windows are a common source of house dust with high lead concentrations, particularly during restoration work on older homes;[125] some vinyl mini blinds contribute to the lead burden as a result of the deterioration of lead-containing material and deposition of lead-contaminated dust. In a study of 92 children with elevated blood lead concentrations in North Carolina,[126] the median lead concentration of dust on the mini blinds was 590 μg Pb/ft^2 with a range up to 73,302 μg Pb/ft^2. However, the contribution of the lead-containing mini blinds to the development of lead toxicity was not established because the study was based on a convenience sample of lead-exposed children rather than a controlled study involving a comparison group of children without lead poisoning.

Para-occupational Exposure Case series and cross-sectional studies indicate that para-occupational exposure of children may elevate blood lead levels as a result of lead-contamination of the home, cars, work shoes, and work clothes from fine-particulates transferred from severely contaminated workplaces.[127,128,129,130] However, not all studies of children in lead-contaminated environments demonstrate evidence of neurotoxicity.[131] In a study of 227 persons from 78 families of lead

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battery recycling workers, 57% of the children aged <6 years had BLL exceeding 5 μg/dL and 16% had BLL >10 μg/dL.[132] Dust wipe and vacuum sampling detected lead concentrations exceeding 40 μg/ft^2 (US EPA lead level of concern, 3.7 μg/m^2) in 85% of vehicle dust samples and 49% of home dust samples.

Parental occupational sources for these lead exposures include the following: cottage industries (belt buckles, awards, type printing), pottery manufacturing, battery repair shops, lead or copper smelters, radiator mechanics, capacitor and resister plants, and electric cable splicing.[133] In a study of blood lead levels in families of workers from a plant manufacturing ceramic-coated capacitors from leaded glass, the mean blood lead level of family members of exposed workers was 10.2 μg/dL compared with 6.2 μg/dL in family members of unexposed workers.[129] The lead contamination of exposed workers was severe (i.e., ambient air, 61–1,700 μg Pb/m^3).

A study of construction workers with elevated blood lead levels demonstrated that these workers carried lead from construction sites on their skin; the pathway of lead contamination was workplace to worker, car, then home.[134] The highest levels occurred on the driver's and passenger's armrest with a geometric mean (GM) of 2000 μg Pb/m^2 and 1200 μg Pb/m^2, respectively. The study reported a statistically significant difference (P = 0.005) in the surface lead concentration (GM = 370 μg/m^2) in the rooms where clothing was changed compared with neighborhood controls (GM = 120 μg/m^2). Poor hygiene practices of these workers contributed to the increased lead contamination in their homes. Compared with controls, the odds ratio for workers' children with blood lead levels >10 μg Pb/dL was 6.1; however, the 95% confidence interval was large (0.9–147).

Leaded Substance Use

Drug Abuse Sniffing leaded gasoline increases blood lead levels as a result of the conversion of tetraethyl lead to inorganic lead.[135] The elimination of tetraethyl lead from gasoline has reduced significantly the hospitalizations associated with gasoline sniffing;[136] however, abuse of other lead-containing substances (e.g., lead-contaminated heroin) is a potential source of lead exposure in substance abusers.[137,138] Rare case reports associate chronic ingestion of opium containing ~3.5% lead with a blood lead level of 50 μg/dL and lead toxicity (abdominal colic, constipation, gingival discoloration, basophilic stippling).[139] Lead contamination may occur from use of lead acetate as a reagent during methamphetamine production or distribution phase from Pb-contaminated adulterating agents. A case series documented blood lead levels ranging from 49–513 μg/dL in 14 intravenous drug users using lead-contaminated methamphetamine;[140] however, a cross-sectional study of intravenous drug users presenting to an emergency department did not detect evidence of subclinical lead poisoning.[141]

Moonshine Whiskey Although lead poisoning-related deaths continue to decline dramatically in the United States, moonshine whiskey remains a source of serious lead toxicity, particularly among rural African-American men in the southeastern and midwestern United States.[142,143] Lead commonly contaminates moonshine whiskey at high concentrations as a result of the distillation of whiskey in containers (e.g., automobile radiators) with lead-soldered parts.[144] The maximum lead concentration in an analysis of 12 samples of Georgia moonshine was 5.3 mg/L; 7 of the samples contained detectable amounts of lead. Of 115 samples of suspected moonshine confiscated by local law enforcement in 1995–2001 and analyzed by the Bureau of Alcohol, Tobacco, and Firearms, 28.7% contained lead concentrations >3 mg/L (median, 0.44 mg/L; maximum, 532 mg/L).[145] In a cross-section study of emergency department patients in Atlanta, Georgia, the median blood lead level in 50 moonshine drinkers was 11.0 μg/dL (range, 1.0–107.0 μg/dL) compared with 2.5 μg/dL (range, 0.5–22.1 μg/dL) in 581 non-moonshine drinking patients.[146] Other sources of these epidemics include wine stored in leaded crystal, lead-colored glass, lead-glazed ceramic tile containers.[147]

Consumer Products Some consumer products may contain substantial amounts of lead including herbal supplements, inexpensive costume jewelry,[148] cosmetics, and folk remedies.[149,150] In a study of traditional Asian remedies sold in eastern US Asian grocery and health food stores during the early 2000s, lead was the most common heavy contaminate of these products.[151] Case reports documented the presence of lead in Chinese herbal preparations (e.g., contaminated clam shell powder producing BLL = 76 μg/dL),[152] Chinese baby powder (e.g., ~22% lead tetroxide),[153] Chinese anticonvulsants,[154] and traditional Ayurveda analgesic (3.6% lead).[155] In a study of 95 dietary supplements (i.e., primarily herbal or botanical products), the median lead concentration was 0.40 μg/g with a range of <0.02–0.49 μg/g; the highest lead concentration occurred in a sample of pseudoginseng root.[156] Analysis of Brazilian herbal medicine samples suggested that some of these products (e.g., horse chestnut, *Aesculus hippocastanum*) may contain lead concentrations exceeding guidelines for oral lead intake as measured

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by atomic absorption spectrophotometry.[157] Lead may contaminate calcium supplements, particularly natural supplements (bonemeal, dolomite, oyster shells). In a California study of 136 calcium supplements purchased during 1996, the mean lead concentration (μg/g dry weight) for bonemeal ($n = 9$) was 0.60 ± 0.39 (range, 0.21–1.38) compared with 0.97 ± 0.49 for dolomite ($n = 5$; range, 0.39–1.56) and 0.88 ± 0.51 for oyster shells ($n = 26$; range, 0.12–2.10).[158] Refined calcium (chelated and non-chelated) also contained relatively high lead concentrations (mean = 0.73 ± 1.60; range, <0.6–10.05); $n = 37$.

Litargirio is a yellow-peach-colored antiperspirant/deodorant and a folk remedy from the Dominican Republic that contains up to 79% lead oxide.[159] Lead sulfide is a component of black eye makeup, particularly in Nigeria (tiro), India (Surma), and the Arab world (kohl, kajal).[160,161] The maximum allowable content of lead in US cosmetics is 0.6% w/v.[51]

Occasionally, case reports document lead contamination in traditional herbal medicine following consumption of ayurvedic medicines for diabetes,[162] fertility (deshi dewa),[163] psoriasis,[164] and malaise (mineral tonics).[165] In a review of published cases concerning 76 patients with lead encephalopathy, 87% of the cases were associated with Middle Eastern traditional medicines (surma or kohl, saoott or cebagin, bint al dahab, santrinj, bokhoor), 7% with Ayurvedic medicines, and 7% with other traditional medicines from Latin America (azarcon, greta) and China (ba-baw san, po ying tan).[166] Two lead-containing Mexican remedies (azarcon, lead tetraoxide; greta, lead oxide) were folk remedies for the treatment of colic (empacho).[167] Other names for these remedies include liga, alarcon, coral, Maria Luisa, and rueda.

Hobbies

General Hobbies associated with potential lead exposure include pottery glazing, stained glass construction or repair, lead soldering, car or boat repainting, fishing or hunting with lead sinkers or shot, target shooting, reloading lead bullets, and remodeling older homes. Lead-containing products include casting fishing weights or toy soldiers (molten lead), pottery making (frits, leaded glazes), paintings (lead paint), glass blowing (coloring agents), and screen or platinum printing material.[168]

Pottery Rare case reports attribute lead poisoning to the use of lead-contaminated ceramics[169,170] including cocktail glasses glazed with lead sulfide.[171] Lead is a common component of earthenware glazes, particularly low-fired glazes. Some lead compounds (e.g., carbonate, monosilicate, oxide) are highly soluble. The addition of various oxides to lead-bearing glazes increases the solubility, even in glazes formulated to yield small amounts of lead. Frits are glassy materials that fuse various glaze components, imparting a smooth, glossy finish to the fired earthenware. The use of frits reduces the solubility of lead glazes, but their use does not guarantee a glaze of low lead solubility.[170] The use of an airbrush to apply fritted lead glazes produced lead poisoning in a potter.[172] Concentrations of lead oxides in ceramic glazes range up to 25–30%; the ingestion of ceramic glazes by mentally impaired residents of a nursing home resulted in serious, acute lead toxicity.[173] Both heat and the storage of acidic food increase the leaching of lead from earthenware;[174,175] however, the clinical relevance of the use of lead-containing ceramics to the total lead burden remains unclear because of variability and complexity in determining the amount of lead absorbed from lead-containing ceramics.[176]

Retained Lead

Wounds Lead intoxication from retained bullets is rare compared with the incidence of gunshot wounds as a result of the encapsulation of the bullets in soft tissue. In a convenience sample of 451 patients presenting to an urban emergency department with retained projectiles (typically, copper-clad lead bullets), the prevalence of whole blood lead levels >20 μg/dL at 3 months and 6 months was 11.8% and 2.6%, respectively.[177] Although ~60,000–75,000 nonfatal firearm-related injuries occur each year in the United States, there are only ~100 case reports of lead toxicity from retained bullets, primarily as a result of retained lead bullets near or in joints.[178] These injuries usually occurred before the mid-1990 when steel shot replaced most lead shot. Risk factors for the development of lead intoxication in these cases include bullet fragmentation within the joint space,[179] embedding of the fragments in fractures (thorax, long bones) with cyst formation surrounding the lead,[180] bullet composition, total lead load, and contact with cerebrospinal, synovial, or pleural fluid. The retention of large numbers of lead pellets from shotgun wounds can produce substantially elevated blood lead concentrations and lead toxicity as a result of the larger surface area of many small pellets.[181,182] Bullets lodged in joints or in other relatively acidic environments degrade more easily than environments with neutral pH, increasing lead absorption.[183,184] Although retained lead bullets represent a potential risk of lead intoxication, neither the exact risk of intoxication nor the length of the latency period can be predicted accurately because existing data is based on case reports.[185] Lead toxicity from retained lead bullets may occur within

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a few days to many years after the bullet enters the wound in patients with substantial risk factors.[186,187] Case reports indicate that lead bullets may remain in nonarticular tissues for 50 years without the development of lead toxicity.[188] Fatal lead toxicity from retained bullet fragments is extremely rare; typically, these lead fragments lodge near bone and toxicity may occur many years after the gunshot wound.[188] A variety of factors may precipitate lead toxicity in these patients including metabolic stress (infection, substance abuse, thyrotoxicosis, sepsis, shock, multiple fragments, recent trauma or fracture, long duration of retention) and pregnancy. Rapid bone growth may precipitate lead toxicity in patients with retained bullets long after the wound.

Analysis of lead fragments removed from patients with lead toxicity secondary to retained lead bullets suggests that lead hydroxide carbonate ($C_2H_2O_8Pb_3$, CAS RN: 1319-46-6) is the main form of lead on the surface of these fragments.[189] Pseudocysts may form from bullet fragments outside of synovial cavities as a result of redistribution of lead from the bullet fragments; these pseudocysts contain large amounts of soluble lead, friable lead dioxide, and fine, insoluble, black, radiopaque material lining the cyst.[190]

The amount of lead in air rifle pellets has changed over the years; the popular mushroom-shaped *Diablo* pellets contain soft lead, whereas the newer *Prometheus* pellets contain steel and nylon.[191] Ball bearings and *Prometheus* pellets are often ferromagnetic, resulting in strong deflections in magnetic fields that limit the use of MR imaging.[192]

Ingestion The ingestion of lead foreign bodies poses little risk of lead poisoning when the foreign body passes through the GI tract. Occasional case reports document the development of lead-induced encephalopathy from retained lead (i.e., fishing weight) in the stomach[193] or mild lead poisoning from a lead shot pellet retained in the ascending colon or appendix.[194,195,196]

ENVIRONMENTAL FATE

Air

Inorganic lead exists primarily as particulates in the atmosphere with median particle size in lead released from smelters of ~1.5 μm; high-temperature combustion processes produce relatively small particles.[37] Although the wide distribution of lead from point sources occurs via the atmosphere, ~80% of the lead discharged to air typically deposits near the source (i.e., <10 km).[197,198] The remaining 20% is dispersed widely to remote locations up to several thousand kilometers away. The actual distance lead travels depends on particle size with most particles >2 μm depositing close to the source. An estimated 20–60% of the lead particles from auto exhaust (i.e., primarily lead halides) fall into the soil within 25 m of the road. The average residence time of inorganic lead in the atmosphere is ~10 days.[199]

Soil

Chemical and biotic processes in soil transform most forms of lead released from anthropogenic sources into adsorbable lead salts (i.e., PbClBr, $PbCO_3$, $PbCrO_4$, $Pb(OH)_2$, PbS, $PbSO_4$).[87] Most of the lead halides present in automobile exhaust are converted to lead carbonates or lead sulfates within 24 hours.[200] Some transformation of inorganic lead to tetramethyl lead may occur in the soil, but the significance and source (i.e., abiotic transformation, biomethylation) are unclear. Lead complexes typically precipitate in soil, particularly in soil containing high amounts of organic matter and pH 6–8; subsequently, most lead is bound in the upper 5 cm of soil.[201] At pH 6–8, lead complexes with insoluble organic compounds. These processes substantially limit the mobility of lead in soil. Except under very acidic soil conditions, the leaching of lead into groundwater is very slow. The presence of lead carbonate in the soil and soil pH 8–10 minimizes the penetration of lead into groundwater.[202]

Lead persists in soil. The soil around houses built after 1978 does not usually contain elevated lead concentrations, whereas the soil near a house built before 1950 may contain substantial lead concentrations.[203] Although lead is an element that is not subject to degradation, transformation of inorganic species and/or particle size may occur in soil. In the soil, the bioavailability of lead depends on several factors including mineral content, temperature, pH, the presence of organic material, and the subsequent speciation of lead. These factors cause adsorption of lead at the mineral interfaces, formation of lead complexes with organic matter, and precipitation of poorly soluble lead salts. The processes that reduce lead mobility in the soil also reduce lead uptake by plants. The bioavailable lead in a vegetable plant depends on cation exchange capacity, pH, soil moisture, and the concentration of organic matter or other soil amendments.[37] In a pilot study of plants grown in an urban setting, lead concentrations in the edible portion of the plant did not correlate to soil lead concentrations.[204] Despite high lead concentration in the soil (27–4,580 mg/kg), only 1 (i.e., cucumber, 81 μg

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Pb/g) of 52 fruiting vegetables contained detectable lead concentrations (>10 μg/g); however, after washing, 12 of 31 samples of the leafy vegetables had detectable lead concentrations in the edible portions with a range of 11–60 μg/g. Plants and animals may bioconcentrate lead from aquatic or terrestrial food chains, but these organisms do not biomagnify lead.[37,205]

Water

Following the deposition of lead in water, rapid partition into sediment occurs. Lead exists in water either as soluble lead or undissolved particles in suspension or on surface coatings. In contaminated aquatic systems, most lead is bound to sediment with little lead dissolved in water.[72] The tendency of lead to complex with common anions to produce compounds of low solubility significantly limits the ability of lead to contaminate natural water. The amount of lead in the solution depends on pH and dissolved salt content. At pH >5.4, the maximum solubility of lead is ~30 μg/L in hard water compared with ~500 μg/L in soft water. Precipitation of lead sulfate limits lead concentrations in soft water (pH <5.4), whereas lead carbonates reduce the solubility of lead in hard water (pH >5.4). Typically, benthic organisms and algae contain the highest lead concentrations in aquatic environments, whereas carnivorous fish (i.e., upper trophic level predators) contain much lower lead concentrations.

DOSE EFFECT

Blood Lead Levels >25 μg/dL

The effect of confounding factors complicates the association of specific blood lead levels with neurological abnormalities including age, gender, diet, disease, parental IQ/educational level and home environment,[206] socioeconomic status, and co-exposure to neurotoxins, particularly determining the magnitude of the effect of lead. The developing brain of a young child is more susceptible to the neurotoxic effects of lead than the mature brain of an adult, resulting in a reduction in neuropsychological function (IQ, sustained attention)[207,208] and behavioral abnormalities.[209] Table 16.5 summarizes observed approximate threshold blood lead levels associated with specific adverse health effects.[210] Substantial variability in response to a specific blood lead level may occur between children and adults. Examination of 55 chronically lead-intoxicated (mean = 48 μg/dL, range 9.2–119.1 μg/dL) Andean children revealed a relatively normal neurological examination in most children.[211]

Neurological impairment may occur following exposure to blood lead levels <25 μg/dL including decreased intelligence, behavioral and learning disorders, and reduced neuropsychiatric testing scores (e.g., visuomotor function, perceptual integration, verbal abstraction).[212] Observed deficits on neuropsychological testing based on standardized norms included the following: reduced tendon reflexes, finger tapping,

TABLE 16.5. Observed lower thresholds of blood lead levels associated with specific health effects. Subclinical effects may occur at lower blood levels than noted. The table does not indicate when the effect will probably occur. (Based on Centers for Disease Control, CDC).[210]

BLL (μg/dL)	Children	Adults
>10–15	↑ Zinc protoporphyrin	
>15–25	↓ Vitamin D	↑ Erythrocyte protoporphyrin (women)
>25–30		Elevated erythrocyte protoporphyrin levels; zinc protoporphyrin[a]
>30–40	↓ Peripheral nerve conduction	↑ Urinary tubular enzymes, proteins
>40	↓ Hemoglobin synthesis	↓ Peripheral nerve conduction (subclinical), ↑ blood pressure, chronic nephropathy, ↓ fertility
>50	Peripheral neuropathy	↓ Hemoglobin production, impaired neuropsychiatric testing scores, ↓ testicular function, gastrointestinal distress (abdominal pain, nausea, diarrhea, constipation, anorexia)
>60	Colic	Female reproductive effects, central nervous system symptoms (sleep disturbances, headaches, mood changes, impaired memory/concentrations)
>70	Colic, gastrointestinal distress	Clinical peripheral neuropathy
>80	Encephalopathy, chronic nephropathy (e.g., aminoaciduria)	Anemia
>100		Encephalopathy

Abbreviations: BLL = Blood Lead Level

[a] May occur at 10–15 μg/dL in women.

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impaired visual pursuit, math calculation skills, and visuomotor integration.[213] The lack of consistent normative data for the specific population tested complicates the interpretation of abnormalities on neuropsychological testing. Abnormalities in gross motor movements were rare.

Blood Lead Levels <10 μg/dL

Although the ancient Greeks and Romans recognized the toxicity associated with high lead levels, recognition of the adverse health effects associated with low-level Pb exposure did not occur until the second half of the 20th century. The US Centers for Disease Control and Prevention lowered the recommended blood lead level limit for children from 30 μg/dL to 25 μg/dL in 1985. In 1986, the World Health Organization reduced the upper acceptable limit for blood lead to 20 μg/dL based on studies that indicated that lead exposure *in utero* was associated with preterm delivery, decreased birth weight, and increased stillbirths. In 1991, the CDC revised the recommended blood lead limit from 25 to 10 μg/dL as a result of studies that suggested impaired cognitive and behavioral development at blood lead levels of 10–15 μg/dL. Concern persists that chronic exposure to blood lead levels <10 μg/dL causes adverse neurological, developmental, reproductive, renal, and blood pressure effects. In 2012, the CDC shifted focus to the primary prevention of lead exposure to expedite the identification of children at risk of serious lead exposure (e.g., cognitive abnormalities, behavioral development); the CDC replaced the lead level of concern (i.e., >10 μg/dL) with the 97.5th percentile of the NHANES distribution of lead in US children (>5 μg/dL). The medical literature contains many thousands of studies on the effects of lead levels in humans. The 2012 US National Toxicology Program Review of Epidemiology studies identified several effects concerning the effects of chronic blood lead levels <10 μg/dL including reduced academic achievement/IQ, attention-related behavior problems, reduced postnatal growth, and delayed puberty in children, as well as decreased glomerular filtration rate, increased blood pressure, and essential tremor in adults.[36]

Table 16.6 summarizes the conclusions of the US NTP regarding the effects of chronic exposure to blood lead levels <5 and <10 μg/dL. The duration of lead exposure and the lead concentration to probably cause these effects are not well defined. Measuring a single blood lead reflects an equilibrium between current and past exposure (half-life of lead in blood ≈1 month), whereas bone lead represents long-term lead stores (half-life Pb bone ≈10–30 years).

TABLE 16.6. Summary of National Toxicology Program conclusions on the health effects of low-level lead exposure. (National Toxicology Program).[36]

Life Stage (BLL μg/dL)	NTP Conclusion	Principal Health Effects	Bone Lead Evidence
Children <5	Sufficient	↓ Academic achievement, IQ, specific cognitive measures; ↑ attention deficits/behavioral problems.	Tibia/dentin Pb associated with behavioral/attention problems, cognition.
	Limited	Delayed puberty/↓ renal function in ≥12 years of age.	Single available study does not support association with postnatal growth.
<10	Sufficient	Delayed puberty, ↓ postnatal growth, ↓ hearing, ↓ IQ.	No data.
	Limited	↑ Hypersensitivity/allergy by skin prick test, ↑ IgE[a].	No data.
	Inadequate	Asthma, eczema, non-allergy immune function, cardiovascular effects, ↓ renal function <12 years of age.	No data.
Adults <5	Sufficient	↓ Glomerular filtration rate, ↓ fetal growth for maternal blood <5 μg/dL.	Single available study supports ↑ bone Pb/↓ renal function.
	Limited	↑ Essential tremor.	No data.
<10	Sufficient	↑ blood pressure, ↑ risk of hypertension, ↑ incidence essential tremor.	↑ Bone Pb more consistently associated with cardiovascular effects than blood Pb.
	Limited	Psychologic effects, ↓ cognitive function, ↓ hearing, ↑ incidence ALS, ↑ cardiovascular mortality, ↑ incidence of spontaneous abortion/preterm birth for maternal blood Pb <10 μg/dL.	↑ Bone Pb more consistently associated with ↓ cognition than blood Pb.
	Inadequate	Immune function, stillbirth, endocrine effects, birth defects, fertility/time to pregnancy,[b] sperm parameters[b].	No data.

Abbreviations: ALS = amyotrophic lateral sclerosis; BLL = Blood Lead Level; IgE = immunoglobulin E; IQ = intelligence quotient; Pb = lead.
[a] Not necessarily related to disease; [b] Reproductive and developmental effects may be associated with Pb >10 μg/dL.

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TOXICOKINETICS

Absorption

Gastrointestinal Tract

The absorption of metals in humans depends on several factors including chemical species, environmental matrix that surrounds the metal, particle size, contents of the gastrointestinal tract, diet, age, nutritional status, and characteristics of the media containing the lead.[214] Gastric acid solubilizes lead salts, whereas alkalinization and calcium reduce solubilization. Serious elevations in blood lead concentrations may occur following the ingestion of large amounts of small lead pellets because the large total surface area promotes lead dissolution.[215] The ingestion of lead accounts for the vast majority of the lead body burden. Lead absorption occurs in the small bowel by active and passive transport. A recently fed adult absorbs ~5–10% of an ingested lead dose, primarily in the duodenum by saturable mechanisms as suggested by the curvilinear relationship between blood lead and lead in drinking water.[216,217] Tracer studies suggest that lead absorption increases substantially (40–50%) in a fasting individual.[218] In a study of 23 adults ingesting ^{203}Pb during the fasting state, the whole-body counter indicated the retention of ~60% of the ingested dose.[219] The retention rate after eating a balanced meal and ingesting the lead tracer was ~4% of the dose, probably as a result of the lead complexion of calcium and phosphate salts in the meal.

Lead bioavailability is substantially less in lead-contaminated soil than in solutions of water-soluble lead salts commonly used in experimental studies with similar differences in the fasted and fed states. An *in vivo* study of volunteers ingesting 250 μg Pb/70 kg body weight from soil collected in the Bunker Hill Mining & Metallurgical Complex demonstrated average lead absorption of 26 and 2.5% in the fasted and fed states, respectively, based on isotopic analyses.[220] The particle size of the lead in the soil from the Superfund site was <250 μm. In small, nonfasting children, gastrointestinal absorption of water-soluble lead is higher than that of nonfasting adults, approaching 40%.[221] Decreased iron, protein, calcium, and zinc concentrations increase lead absorption.[222,223] In a prospective study of Nigerian children 12–18 months old followed by 18 months, the addition of calcium supplementation (400 mg elemental calcium daily) to 2,500 IU vitamin A did not alter the blood lead concentration as determined by a multiple linear regression model.[224] During this study, the mean blood lead level decreased from 11.1 ± 7.8 to 8.1 ± 6.3 μg/dL.

Lungs

The bioavailability of lead is greater following inhalation than ingestion. The amount of lead absorbed from ambient air depends on a variety of factors including the ambient lead concentration, duration of exposure, respiratory rate, and physical characteristics of the lead species (i.e., particle size, solubility, chemical form).[225] The average estimated rate of deposition of particulate airborne lead in an adult is ~30–50%.[37,226] In an experimental study of volunteers inhaling inorganic lead aerosol through a standard respiratory mouthpiece for 5 minutes, ~25% of inhaled lead chloride or lead hydroxide was deposited in the respiratory tract. The mass median aerodynamic diameters (MMAD) of the two lead salts were 0.26 μm and 0.24 μm, respectively.[227] In a study of three volunteers inhaling $^{203}PbCl_2$, the lungs retained ~40% of the dose, whereas ~60% was exhaled.[228] Once deposited, lead absorption depends primarily on particle size and solubility. The absorption of submicron particles (<1 μm) of lead is almost complete when these particles reach the alveoli. Significant differences occur in the size distribution of lead aerosols as a result of variation in the production process and chemical form.[229] Approximately 14% of an inhaled dose of 0.05 μm mean-diameter particles of lead sesquioxide cross the alveolar epithelium.[230] In an industrial spray painting operation that used lead salts as drying agents in oil-based paints, the maximum airborne lead concentration was 2–3 mg/m^3; however, only 2% of the particles were in the respirable range (10 μm).[231] Ciliary action (i.e., mucociliary transport) removes particles >2.5 μm impacting the ciliated portions of the airway either by swallowing or expectoration. The gastrointestinal tract absorbs <10% of the amount of lead swallowed compared with ~95% absorption of submicron particles in the gas exchange areas of the lung.[232]

Skin

Although data are limited, available evidence indicates that inorganic lead does not pass easily through the skin with an absorption rate of <1% of the dose. Studies of human skin indicate the dermal absorption of lead acetate is poor based on *in vitro* studies.[233] Following skin application of ^{203}Pb-labeled lead acetate in cosmetic preparations (1.2 mg Pb/mL) to eight volunteers for 12 hours, the estimated lead absorption from the solution was ≤0.3% based on whole-body counts and tracer concentrations in urine and blood.[234] The estimated lead absorption from similar solutions during normal use of cosmetics was 0.06%. *In vitro* and *in vivo* studies of lead oxide suggest that some dermal

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absorption of lead oxide can occur, but the clinical relevance of this route of exposure compared with pulmonary absorptions remains unclear.[235,236] A case report associated the subdermal injection of lead-based red vinyl paint in the hand of a ship painter with lead toxicity.[237] Although ~90% of the injected paint was removed during surgery 24 hours after the incident, the patient developed headaches, nausea, dizziness, abdominal discomfort, weakness, insomnia, tremor, and hyperreflexia. The blood lead level 19 days after the incident was 82 μg/dL; subsequently, the blood lead level increased to 94 μg/dL 1 week later prior to chelation.

Distribution

The distribution of absorbed lead is similar regardless of the route of exposure.[238] Kinetic studies of volunteers on metabolic wards using enriched $^{204}PbNO_4$ indicate lead distributes into three compartments as outlined in Figure 16.1. The blood and soft tissue represent the active pool and bones the storage pool. Following acute ingestion of lead, steady-state concentrations in the tissue occur after several days. In the blood, 95–99% of the lead exists in the red blood cells (RBCs). Most intracellular lead binds to δ-aminolevulinic acid dehydratase (i.e., ~80%), primarily on zinc-binding sites on this molecule; lesser amounts of lead are bound to other intracellular proteins (e.g., pyrimidine-5-nucleotidase).[239] Genetic polymorphism in the enzyme δ-aminolevulinic acid dehydratase (ALAD) affects the toxicokinetics of lead as a result of the associated anemia and reduction in red cell mass. When not excreted (bile, urine), plasma lead redistributes to soft tissue or bone. Hence, blood lead levels may not reflect the total body burden.

Animal studies suggest that lead distributes from the blood initially to soft tissues and then to repositories in the bone.[37] About 2–5% of the total body lead burden distributes in soft tissue (kidney, liver, pancreas, spleen, lungs, thyroid, brain) with a half-life of ~1–2 months based on stable isotope tracer studies in healthy volunteers.[240] Although data are limited, lead probably does not accumulate in the soft tissues of adults including the brain with age.[241,242] In a postmortem study of adults without documented lead exposure, calcified tissues (bones, aorta) contained the highest lead concentrations, whereas nonglandular tissues (adipose, fascial and dermal collagen) and muscular tissues (heart, bladder, muscle) contained the lowest lead concentrations on a wet weight basis.[243] In postmortem examination of 32 long-term, lead-exposed smelter workers, the major soft tissue organs containing were, in decreasing order, liver > kidney > lungs > brain.[244]

Bones are the major depository for lead in the body containing ~90–95% of the total body lead burden in the adult skeleton, primarily in dense bone (i.e., cortical bone).[245] The body burden of lead (i.e., ~70%) in the skeleton of children is somewhat smaller than that of adults. Lead deposits in the bones increase steadily during life; these deposits exist as insoluble lead phosphate that does not produce toxicity unless the chemical form of lead changes.[246] In a study of 14 retired lead workers followed for 18 years, the half-life of lead in finger bone based on an *in vivo* X-ray fluorescence method followed a tri-exponential model with group half-times of 34 days (95% CI: 29–41 days), 1.2 years (95% CI: 0.9–1.8), and

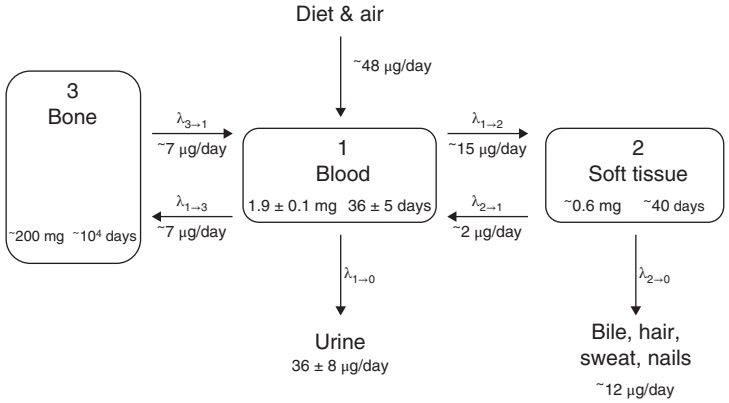


FIGURE 16.1. Three-compartment model of lead distribution based on tracer and balance data. The figure displays the lead distribution in three compartments with the estimated lead content and mean life of each pool along with rates of lead movement between pools (λ) based on mean intake of 48 μg Pb/day by five volunteers. Pool 0 represents the excretion of lead from the body including urinary and fecal elimination. Loss of lead from pool 2 (soft tissue) includes lead elimination in integumentary structures (hair, nails, sweat) and secretions from the alimentary tract (bile, stomach, pancreas, saliva). (Rabinowitz et al.).[240]

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13 years (95% CI: 10–18 years).[247] The turnover of lead in bone is slow; the high body burdens in bone from prior occupational lead exposures contribute significant amounts of lead to the blood lead level in lead workers, primarily from the surface layers of the bones.[232] The calculated turnover rates for compact bone in the tibia and skull average ~2%/year in healthy adults compared with ~8% for the spine.[248] These rates vary with age; higher turnover rates occur at the beginning and toward the end of life. Bone and blood lead stores exist in equilibration. Up to 70% of steady-state blood lead concentrations may derive from the bones of adults without occupational lead exposure. In a study of five adults with low blood lead levels (<6 μg/dL) and no occupational lead exposure, stable lead isotope studies indicated that bone lead stores contributed ~40–70% of the blood lead.[249]

Elimination

Urine

The kidney filters absorb lead unchanged, although at high concentrations some active tubular transport occurs. Following lead absorption, urinary lead concentrations increase within several hours with steady-state concentrations occurring within several days. The urinary excretion rate depends on the glomerular filtration rate and renal plasma flow. The elimination of lead through the kidney is slow because relatively small amounts of lead appear in the plasma compared with erythrocytes. Most ingested lead appears in the feces. The kidney accounts for 75% of daily lead loss; integumentary (nails, sweat, hair) and alimentary losses account for the remainder. Humans maintain a positive lead balance with a total body burden of ~165 mg Pb in subjects without occupational exposure.[241]

Whole Blood/Plasma

The half-life of lead in blood follows a three-compartment model with a fast phase, an intermediate phase (soft tissues, trabecular bone), and a slow pool (cortical bone). The average half-lives of these three compartments are ~30 days, 1 year, and 13 years, respectively.[247,250] The half-life of lead in whole blood varies with age, body lead burden, lead concentration, hematocrit, and the presence of more than one biokinetic compartment. Retrospective analysis of venous blood lead data suggests the lead elimination rate from the body is slow. In a study of 573 children without chelation therapy, the time required for the whole blood lead concentration to decrease from 25–29 to <10 μg/dL was ~24 months compared with 9 months for children with an initial blood lead concentration of 10–14 μg/dL.[251]

The relationship between plasma and whole blood lead concentrations is curvilinear (i.e., concave downward). Analysis of case series of lead poisoning suggests that saturation of lead binding sites in the erythrocytes occurs with increasing blood lead levels, particularly at lead concentrations >40–70 μg/dL.[252] Additionally, anemia associated with chronic lead toxicity further reduces the volume of erythrocytes and lead binding sites. In a study of plasma and whole blood lead concentrations in five adults exposed to lead for 1–144 months and followed for 21–316 months, the average plasma elimination half-life was ~1 month (range, 23–69 days).[253] The whole blood elimination half-life could not be calculated within the duration of the study, but the value was much slower than the plasma elimination half-life.

Maternal–Fetal Kinetics

Blood

Lead easily crosses the placenta;[254] cord blood lead levels are typically 85–90% of maternal blood lead levels.[255] Lead follows a U-shaped course during pregnancy; a significant drop occurs from the first to second trimesters, followed by a gradual rise until delivery. In the blood, lead occurs mostly inside red blood cells; therefore, the whole blood lead concentrations vary with changes in blood volume during pregnancy. Blood lead levels in the mother initially increase during pregnancy and then decrease after delivery. Observational studies indicate that blood lead falls more than expected from hemodilution during early pregnancy, probably as a result of the resorption of trabecular bone with presumably lower lead content compared with the cortical bone.[256] In later pregnancy, increasing resorption of cortical bone increases whole blood lead concentrations. In a study of 98 pregnant women with a geometric mean BLL of 0.42 μg/L in the second trimester, the median change in BLL from second to third trimester was 0.015 μg/L (P = 0.08) compared with 0.06 μg/L (P = <0.01).[257] Without further exposure to lead, maternal blood lead levels increase by 6–8 months postpartum.[258]

Breast Milk

Maternal diet and release of lead from bone loss are the major sources of lead in breast-milk-fed infants aged <3 months. In a study of mothers (n = 21) and their

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breastfed infants ($n = 24$) 2–3 months postpartum, the contribution of breast milk to blood lead levels in the infants ranged 36–80% based on lead isotope ratios ($^{207}Pb/^{206}Pb$, $^{206}Pb/^{204}Pb$).[259] The mean lead concentration in breast milk for participants in the study was 0.73 ± 0.70 μg/kg. The infant can substantially reduce the body burden of lead during the first months of life in the absence of postnatal lead exposure.[260]

There are few data to indicate that lead is preferentially excreted in breast milk; breastfeeding probably does not increase the risk of lead toxicity in infants from mothers with normal blood lead concentrations.[261] The concentration of lead in breast milk is relatively low with typical maternal milk/whole blood ratios <3%,[262] even among women with relatively high lifetime exposure to lead. In a review of 11 studies analyzing lead in breast milk, the mean lead concentrations in mature milk samples ranged from 0.15–6.1 and from 0.48–14.6 ng/mL in colostrum samples. Some samples were below the limit of detection (0.1–2 ng/mL). The milk/whole blood lead ratio ranged 0.01–0.48; the heterogeneity of the data and analytic methods indicate a wide variation in study design and sample collection. In a study of the four stages of breast milk production (colostrums, transitional milk, early mature milk, mature milk), the concentrations of microelements decreased with advancing lactation stages.[263] The mean lead concentration in samples from 45 lactating women in each lactation stage ranged from 13.22 ± 3.58 ng/mL (range, 6.70–22.36 ng/mL) in colostrum samples to 2.93 ± 1.70 ng/mL (range, 0.45–7.80 ng/mL) in mature breast milk samples.

In a study of 310 lactating women in Mexico City at 1 month postpartum, the geometric mean lead concentration in breast milk was 1.1 ng/mL (range, 0.21–8.02 ng/mL).[264] The primary determinants of lead in breast milk were current lead exposure and redistribution of bone lead from past environmental exposures. In a study of mothers living in Andean Ecuadorian villages with high lead contamination, the lead concentration in breast milk from five nursing mothers ranged from 1–49 ng/mL (ppb).[265] The median lead concentration in breast milk from 37 lactating mothers living near Brazilian tin ore smelters was 11.3 ng/mL (range, 0.9–29.4 ng/mL) with 79% of the samples above the WHO limit of 5.0 ng/mL; the limit of detection for graphite furnace atomic absorption spectrometry was 0.9 ng/mL.[266] In comparison, the median lead concentration in milk samples from 45 lactating women from fishing villages was 3.5 ng/mL (range, 0.9–16.2 ng/mL). Maternal milk/plasma ratios are significantly higher than milk/whole blood ratios. In a Mexico City study of 81 lactating women providing breast milk samples 1 month postpartum, the mean milk/plasma lead ratio was 7.7 (range, 0.6–39.8).[267] The mean infant blood lead level of 60 infants at 3 months of age was 3.4 ± 2.2 μg/dL with the blood lead level increasing 1.8 μg/dL for each 1 μg/L increase in maternal milk lead.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Effects

Over 90% of absorbed lead resides in erythrocytes. Inorganic lead inhibits a number of intracellular biochemical processes that generally reduce cellular growth and disrupt cellular processes. A review of lead-interacting proteins identified 23 proteins bound by lead involving a variety of cellular processes including heme biosynthesis (e.g., δ-aminolevulinic acid dehydratase), oxidative stress/lipid peroxidation (e.g., glutathione peroxidase), calcium metabolism/pathways (e.g., calmodulin-mediated pathways, synaptotagmin, voltage-gated calcium channels), nuclear function (e.g., apurinic/apyrimidinic endonuclease 1), lead chelation (↑ metallothionein), nervous system metabolism, and receptor function (acetylcholine, NMDA).[268] The uptake of lead by the mitochondria inhibits cellular respiration, resulting in swelling, loss of crista, and disruption of oxidative phosphorylation and ion transport.[269] The precise mechanism of action of lead on cellular metabolism remains unclear despite the recognized effects of lead on porphyrin and heme biosynthesis from the inhibition of δ-aminolevulinic acid dehydratase (ALAD), δ-aminolevulinic acid synthetase (ALAS), coproporphyrinogen III oxidase, and ferrochelatase. Lead complexes with ligands (sulfhydryl groups most prominently) of enzyme systems throughout the body, leading to diffuse effects. The chemical similarity between lead and calcium suggests that lead may compete with calcium to alter critical intracellular processes (e.g., ion transport, energy production, heme-containing enzymes),[270,271] intracellular messenger systems (calmodulin, protein kinase C),[272] neurodevelopment (altered neuron migration, reduced neural cell adhesion, disruption of cellular communication, decreased synaptic plasticity from disruption of *N*-methyl-D-aspartate type of excitatory amino acid receptor-mediated calcium signaling in glutamatergic synapses),[273] and neurotransmission (blockage of calcium into nerve terminals, impaired uptake by calcium channels, reduced calcium-binding sites, impaired

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mitochondria calcium uptake, alteration of glutamatergic, dopaminergic, and cholinergic pathways).[274]

Susceptibility

Children are more susceptible to lead toxicity than adults because of several factors including 1) increased bioavailability of lead in children, 2) increased distribution of lead to soft tissues rather than bones, 3) increased penetration of lead into the brain as a result of an immature blood–brain barrier, and 4) the presence of developing body systems.[66]

ALAD (aminolevulinate dehydratase) polymorphism may alter the susceptibility of workers to the effects of lead exposure as a result of the relative tighter binding of the ALAD2 protein to lead compared with the ALAD1 protein.[275] The ALAD2 allele is present in about 7–10% of the population. The *ALAD* genotypes do not affect heme synthesis at whole blood lead concentrations <20 μg/dL.[276] Blood samples from ALAD1 homozygotes contained increased ZPP concentrations at whole lead concentrations ranging 20–59 μg/dL and increased plasma aminolevulinic acid (ALA) concentrations at whole blood concentrations ranging 40–59 μg/dL compared with blood samples from ALAD2 homozygotes.[277] Theoretically, the relatively stronger binding of ALAD2 protein to lead may reduce the amount of biologically active lead in ALAD homozygotes, but there are few data on the clinical effect of these differences in lead workers. A cross-sectional study of middle-aged and elderly men in the Department of Veterans Affairs Normative Aging Study did not detect a significant difference in serum uric acid, serum creatinine, or estimated creatinine clearance by *ALAD* genotype; the study suggested *ALAD* genotype may modify the effect of lead on the renal excretion of uric acid after control of confounding variables.[278]

Pathological Changes

Hematopoietic System

Impaired heme biosynthesis is the most sensitive reaction to increasing blood lead levels. Lead alters the activity of at least four heme enzymes (ALAS, ALAD, coproporphyrinogen III oxidase, ferrochelatase) resulting in reduced heme production and increased urinary porphyrins, coproporphyrins, δ-aminolevulinic acid, erythrocyte protoporphyrin (EP), free erythrocyte protoporphyrin (FEP), and zinc protoporphyrin (ZPP) as outlined in Figure 16.2. The most sensitive reaction in humans occurs when lead inhibits the conversion of δ-aminolevulinic acid to porphobilinogen by forming

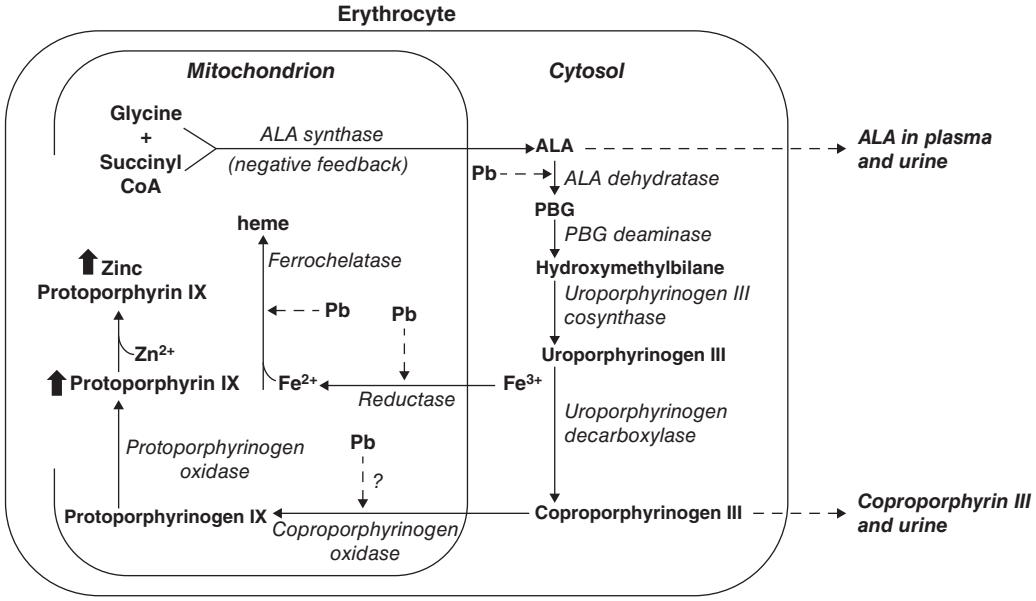


FIGURE 16.2. Schematic representation of the effects of lead on three lead-sensitive heme enzymes and resultant changes in urinary aminolevulinic acid, porphyrins, coproporphyrins, and heme production (anemia). Inhibition of ALA synthases increases plasma/urinary ALA and urinary coproporphyrin, whereas increased intracellular protoporphyrin IX increases free erythrocyte protoporphyrin and zinc protoporphyrin in the erythrocyte. *Abbreviations:* ALA = δ-aminolevulinic acid; PGB = porphobilinogen. (Redrawn from Sakai).[283]

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a mercaptide from δ-aminolevulinate dehydratase.[279] Some animals are less sensitive to the hematological effects of lead. In a rodent study, lead exposure caused a transcription-dependent induction of ALA dehydratase that potentially compensated for the lead-induced inhibition of this enzyme.[280] Porphyrinogen is the intermediate in heme biosynthesis, and coproporphyrin is a by-product of the nonenzymatic oxidation of coproporphyrinogen. Lead-induced inhibition of ferrochelatase causes an accumulation of protoporphyrin IX in bone marrow normoblasts;[281] in circulating erythrocytes, the replacement of iron by zinc in the porphyrin moiety produces ZPP. The binding of ZPP in the heme pockets of hemoglobin remains throughout the life of the erythrocyte. Zinc protoporphyrin accumulates when inadequate supplies of iron substrate limit the chelation of iron by protoporphyrin to form heme.[282] The accumulation of ZPP occurs only in erythrocytes formed primarily in the bone marrow normoblasts when lead exists during erythrocyte formation. Consequently, the erythrocyte maturation process produces a lag time between lead exposure and elevated ZPP concentration, whereas the steady state only occurs after the turnover of the entire red cell population (i.e., 120 days).

Anemia is the most common *hematological* manifestation of lead exposure. Decreased hemoglobin production and increased erythrocyte destruction cause hypochromic, normocytic anemia with associated reticulocytosis. Lead-induced anemia increases in frequency and severity with increasing blood lead levels; however, the anemia is rarely severe. The common hematological abnormalities involve the erythroid series (erythroid hyperplasia with ring sideroblasts) and include reticulocytosis and basophilic stippling. The latter results from aggregated RNA material from the inhibition of pyrimidine 5′-nucleotidase. In one study of children living near a smelter, 17% of children with blood lead levels >80 μg/dL had hematocrit levels <33% compared with 1.6% of children with lead levels <80 μg/dL.[284] Neither anemia nor basophilic stippling is a sensitive indicator of lead intoxication because concurrent congenital defects in heme synthesis may be required to express the anemia. A study of lead-exposed workers suggests that lead may affect erythrocyte glycolysis at the hexokinase step; however, the clinical significance of this effect is unclear.[285]

Nervous System

Peripheral Nervous System

The motor axons are the principal target of lead in the peripheral nervous system. Primary segmental demyelination followed by axonal degeneration of peripheral nerves leads to decreased motor nerve conduction velocity. In adults, peripheral neuropathy is the most common neurological manifestation of lead toxicity, whereas encephalopathy appears more frequently than peripheral neuropathy in children. Although lead affects the peripheral nervous system in several ways, a primary mechanism of toxicity involves disruption of calcium homeostasis and cell-signaling pathways including activation of protein kinase C. Many peripheral and central nervous system processes rely on the calcium-dependent protein kinase C isoenzyme family for synaptic transmission (e.g., ion channel conduction, ligand-receptor interactions, neurotransmitter synthesis, dendritic branching).[37] Lead also displaces zinc in zinc-finger proteins found in enzymes, channels, and receptors.

Central Nervous System

The encephalopathy produced by inorganic lead depends on the route of exposure, dose, and age with young children (1–4 years) particularly vulnerable. Lead appears to pass the blood–brain barrier more easily in children, resulting in disruption of mitochondrial function leading to the onset of coma and convulsions at lower blood lead levels than adults.[23] Acute cerebral and cerebellar edema with hemorrhage occurs in neonates following acute, high-dose lead exposure. Pathological findings probably result from increased microvascular permeability that causes erythrocyte leakage, microthrombosis, endothelial cell necrosis, perivascular exudation of periodic acid-Schiff (PAS) positive material and erythrocytes, and subacute endothelial proliferation.[286]

A direct neurotoxic effect of lead on neurons is equivocal,[287] but lead-induced premature activation of protein kinase C (PKC) may impair brain microvascular formation. High lead levels also produce alterations in the astrocytes and endothelial cells in the blood–brain barrier (BBB), resulting in diffusion of albumin, ions, and water intracellularly along with disruption of the BBB. As a result of the slow clearance of plasma constituents, intracranial edema and hypertension develop contributing to acute lead encephalopathy. Other pathological changes associated with lead toxicity include inflammatory changes (perivascular cuffing, granuloma formation) in the cerebral cortex and diffuse cerebral edema. Cerebral edema is a late complication of lead encephalopathy, and coma may appear in the absence of cerebral edema. Rodent studies suggest that vascular endothelial growth factor mediates the vasogenic edema associated with acute lead encephalopathy.[288]

The difference in the incidence of encephalopathy between small children and adults may result from

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the maturation of the choroid plexus sink.[289] Potential mechanisms for the increased susceptibility of young children to lead neurotoxicity include the disruption of cellular migration during critical periods of CNS development secondary to interference with synaptic neurotransmission and cell adhesion molecules.[66] Lead inhibits *N*-methyl-D-aspartate receptor function, enhances background transmitter release, and stimulates background levels of the intracellular messenger protein kinase C.[290] The subsequent reduction in the synaptic signal-to-noise ratio may permanently disrupt the refinement of synaptic connections during a critical early period of postnatal development. Well-defined neuropathological findings have not been described in humans exposed to low lead levels; animal models demonstrate conflicting results.[287] Abnormalities in spatial learning and memory may result from abnormalities in dopamine, γ-aminobutyric acid, and glutamate kinetics (uptake, efflux, metabolism) in the brain, particularly long-term potentiation related to the latter neurotransmitter.[291]

Kidney

In animal models, chronic lead toxicity produces lesions in the S3 segment of the straight proximal tubule, interstitium, and loops of Henle characterized by round, eosinophilic, or acid-fast intra-nuclear inclusion bodies.[292] Lead-induced renal disease occurs in the following principal stages: 1) acute, reversible changes that produce an alteration of mitochondrial function and proximal renal tubular dysfunction, and 2) irreversible, chronic changes characterized by tubular atrophy and dilation, arteriosclerosis, and interstitial fibrosis.[293] The latter stage represents the kidney's nonspecific response to chronic disease that occurs following many types of nephrotoxins. The physiological consequences of these anatomic changes include enzymuria (e.g., ↑ urinary *N*-acetyl-β-D-glucosaminidase, retinol-binding protein), low-molecular-weight proteinuria (e.g., ↑ urinary β_2-microglobulin), high-molecular-weight proteinuria (e.g., ↑ albumin), impaired transport of organic anions and glucose, and depressed glomerular filtration rate (↑ serum creatinine, ↓ urine creatinine clearance). These changes are particularly evident following chronic lead exposure exceeding 50 μg/dL.[37,294] Although hyperuricemia is common during renal failure, gout is rare except in these patients. Lead decreases tubular secretion of uric acid, causing a higher incidence of gout,[295] but factors other than lead exposure account for most cases of end-stage renal disease in patients with gout and renal failure.[296]

Acute Toxicity

Severe, acute lead poisoning produces proximal tubular dysfunction that results in a Fanconi-like syndrome (aminoaciduria, phosphaturia, glycosuria, renal tubular acidosis). These acute tubular changes are usually reversible; the proximal tubular defects do not typically progress to interstitial nephritis following cessation of acute lead exposure.[297] Pathological changes in the proximal tubules include epithelial cell proliferation, mitochondrial swelling, loss of basilar infolding and crista, and lysosomal-like structures with dense inclusion bodies. The intranuclear inclusion bodies contain sulfhydryl-rich lead-protein complexes that probably form in the cytoplasm and migrate to the nucleus.[298] These inclusion bodies disappear after chelation and sloughing of the tubule.

Chronic Toxicity

Renal biopsies of patients with chronic lead-induced nephropathy demonstrate a chronic nephropathy that may progress to contracted kidneys with arteriosclerotic changes, interstitial and peritubular fibrosis, glomerular sclerosis, tubular atrophy, and hyaline degeneration of the renal vasculature.[299,300] Florescent microscopy of seven of eight renal specimens demonstrated glomerular and tubular immunoglobulin deposition, suggesting an autoimmune process. End-stage lead nephropathy is characterized more by chronic interstitial disease than glomerular disease. Histological changes in the kidneys are not invariably present in patients with excessive body burdens of lead. Structural mitochondrial abnormalities in renal proximal tubule cells are a consistent feature of lead-induced nephropathy.[301] The formation of intranuclear inclusion bodies in the renal proximal tubule frequently develops in patients with lead nephrotoxicity; these bodies represent a shift in lead from the cytosol to nuclear material. These inclusion bodies are not specifically associated with tubular injuries. In rodent studies, inclusion bodies were more frequent in the less severely affected S2 segment than the more severely affected S3 segment of the proximal tubule.[302] Although intranuclear eosinophilic inclusion bodies (i.e., lead–protein complexes) usually occur in the proximal tubular cells following acute renal toxicity, these pathological abnormalities may or may not occur in chronic lead-induced kidney disease.[83] In a study of 12 lead workers with reduced glomerular filtration rates, only about ½ of the renal biopsies demonstrated changes consistent with lead nephropathy including focal tubular atrophy and interstitial disease.[303] Age- and hypertension-related changes may confound the interpretation of the causal role of lead in these changes.

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Endocrine

Occupational studies suggest an association between high blood lead levels (≥40–60 μg/dL) and alteration of thyroid (↓ serum thyroxine, T4; ↑ thyroid-stimulating hormone),[304] pituitary, and testicular hormones (follicle-stimulating hormone, luteinizing hormone, testosterone); however, the results are inconsistent secondary to potential confounding (e.g., age, tobacco use), design issues (e.g., small sample sizes), and differences in laboratory methods/outcomes.[305] In some occupational studies, the thyroid effects (i.e., ↓ T4 with inappropriately low TSH or poor thyrotropin-releasing hormone response) were consistent with a primary pituitary or hypothalamic insufficiency.[304,306] Positive studies reported alterations of thyroid changes following high chronic lead exposure (≥40–60 μg/dL).[307] Limited data in children does not indicate an association between lead exposure and altered thyroid hormone concentrations; these children typically have BLL lower than adults with occupational lead exposure. In a study of 68 inner city children with mean blood lead of 25 μg/dL (range, 2.0–77 μg/dL), linear regression analysis demonstrated no association between blood lead levels and either serum T4 or free T4.[308]

Disturbances of vitamin D metabolism occur both in animal models and children with moderate to marked elevations of blood lead (30–60 μg/dL). In a study of 177 children age 1–16 years with BLL ranging 12–120 μg/dL, the active form of vitamin D (1,25-dihydroxycholecalciferol, 1,25-CC, 1,25-dihydroxyvitamin D_3), was negatively associated with BLL ($r = -0.88$).[309] Sex and season were not associated with serum, 1,25-CC concentrations, whereas the serum 1,25-CC concentration was higher in children aged 11–16 than ≤10 years of age. A Midwestern US study of 105 children at ages 1 and 3 years detected no significant alterations in vitamin D metabolism or calcium and phosphorus homeostasis in children with normal nutritional status and low–moderate blood lead levels (<25 μg/dL).[310] An increase in the serum level of 1,25-dihydroxyvitamin D_3, a potent vitamin D metabolite formed in the proximal renal tubules, was detected in workers exposed to lead, primarily in those workers with blood lead levels >60 μg/dL.[311] A study of lead-exposed workers did not detect a statistically significant increase in the excretion of major catecholamine metabolites (homovanillic acid, vanillylmandelic acid).[312]

Reproductive System

Occupational studies suggest some association between high lead exposure and stillbirths, spontaneous abortions, and decreased sperm counts. In a study of lead concentrations in umbilical cord blood from 5,183 consecutive deliveries of at least 20 weeks gestation, stepwise logistic regression suggested a dose-related association between minor congenital abnormalities and cord blood lead.[313] Occupational studies suggest an association between high blood lead levels (≥30–40 μg/dL) and alteration of testicular hormones (follicle stimulating hormone, luteinizing hormone, testosterone). Although changes occurred in the serum FSH, LH, and testosterone concentrations in highly lead-exposed workers (↑ LH, ↓ testosterone),[314] there was no consistent pattern of exposure-response.[315] Potential mechanisms for the observed lead-induced reduction of stature include diminished human growth hormone secretion and inhibition of insulin-like growth factor I formation.[316]

Liver

Transient elevations in serum hepatic aminotransferase concentration occur rarely in severe lead poisoning, but impairment of liver function is not well documented in workers exposed to lead.

Cardiovascular System

Meta-analyses suggest a persistent but weak association between blood lead levels and hypertension.[317] Lead affects several hormonal and neural systems that alter heart rate, cardiac output, and regulation of peripheral vascular resistance. The mechanisms of action include the direct effect on end-arterioles by alteration of intracellular calcium and the indirect effect of renal dysfunction.[318] Potential mechanisms of toxicity are multifactorial including 1) deficiency of nitric oxide from direct (inactivation of endogenous nitric oxide) and indirect actions (downregulation of soluble guanylate cyclase by reactive oxygen species); 2) increased sympathetic activity and plasma norepinephrine with depressed vascular and elevated renal β-adrenergic receptor density; 3) elevated plasma angiotensin-converting enzyme activity, plasma renin activity, angiotensin II, and aldosterone concentrations; 4) increased kininase I and kininase II activity; 5) lead-induced increased intracellular sodium and calcium by inhibition of vascular smooth muscle Na^+-K^+ ATPase; and 6) increased endothelin and thromboxane generation.[319] Subjects from the general population with hypertensive nephropathy and nephropathy from other causes have similar body lead burdens. In a study of 40 adults with hypertensive nephropathy and 24 controls with a similar degree

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of renal dysfunction from causes other than hypertension, chelatable lead and blood lead levels were statistically similar (7.2 ± 4.7 μg/dL and 7.2 ± 4.1 μg/dL, respectively).[320]

Postmortem Examination

Diffuse cerebral edema and dilated ventricles are common pathological findings in autopsies of fatal pediatric poisoning cases.[321] In a postmortem study of 20 children with fatal lead encephalopathy, the most common histological finding following examination of the brain was dilation of the capillaries with swollen endothelial nuclei protruding into the lumen and diffuse astrocytic proliferation.[322] A 2-month-old infant developed vomiting, tonic-clonic seizures, anorexia, demyelinating neuropathy, and tarry stool from lead poisoning; she died despite chelation therapy from sepsis (organism not reported).[323] Postmortem examination demonstrated cerebral edema with subarachnoid hemorrhage, acute renal tubular necrosis, and massive liver necrosis. Histological examination revealed mild perineurial edema and focal segmental demyelination of the median nerve, focal necrosis of neurons in the cerebral cortex with reactive astrocytosis and microgliosis, and dilation of the perivascular spaces with PAS-positive exudate. A 41-year-old man died of lead oxide poisoning that was recognized posthumously.[324] On exhumation 6 months after the death, forensic analysis demonstrated the following lead concentrations (μg/g): liver, 47.6; kidney, 4.75; femur, 20.4; sacral vertebra, 103; pubic hair, 33.7; and nails, 13.6.

CLINICAL RESPONSE

The clinical presentation of lead poisoning (plumbism, saturnism) is typically nonspecific with the signs and symptoms of lead poisoning depending on blood lead concentration, age, and duration of exposure. The presence of clinical features of lead intoxication requires a careful evaluation of the potential sources of lead in the environment of the patient. High risk of lead toxicity may occur in children residing in houses, daycare centers, or preschools with old (pre-1960) chipping paint; frequent visitations to pre-1960 houses undergoing renovation; living or playing with children diagnosed with elevated lead levels; residing with adults exposed to lead (job, hobby); or living near a point source of lead (factory, hazardous waste site). Case reports associated the intravenous injections of lead and opium with the development of elevated serum hepatic aminotransferases, symptoms of acute hepatitis (general malaise, vomiting, constipation), musculoskeletal pain, and anemia.[325,326]

Acute Ingestion

Acute lead poisoning in adults is rare, typically resulting from very large intentional ingestions of lead salts, surreptitious lead salt ingestions by mentally impaired patients,[173,327] ingestion of lead objects, or intravenous administration of lead salts or lead-contaminated drugs of abuse.[328] Clinical features of acute lead poisoning typically involve abdominal pain with gastrointestinal distress, peripheral neuropathy, and less often encephalopathy (delirium, hallucinations), hepatorenal dysfunction, low-grade fever, and acute hemolytic anemia.[173,329] An acute encephalopathy following single, large ingestions of inorganic lead is relatively rare in adults; high whole blood lead concentrations may occur without clinical evidence of an acute encephalopathy that commonly develops in children at similar high blood lead concentrations.[330] In a study of 32 adults presenting with acute lead poisoning after ingesting lead-contaminated flour over ~2 weeks, clinical features involved systemic symptoms, gastrointestinal distress, anemia, and musculoskeletal complaints.[331] A few patients with the highest blood lead concentrations developed hemolytic anemia, high-output congestive heart failure with severe anemia, transient proximal renal tubular dysfunction (glucosuria, aminoaciduria, hypoproteinemia), prerenal azotemia (renal vasoconstriction, volume depletion), toxic hepatitis, gouty arthritis with hyperuricemia, and encephalopathy. The mean whole blood lead level in the 13 most severely affected patients was 102 ± 26 μg/dL. Following acute lead arsenate exposure, nausea, constipation, metallic taste, and abdominal pain occur along with vomiting of milky material resulting from the formation of lead chloride. Although lead arsenate is an acid-soluble compound, absorption is considerably slower for lead than arsenic. These patients typically present with signs of arsenic toxicity.[332]

Occupational Exposure

The vast majority of excessive chronic lead exposures in adults occur in the work environment; common sources of occupational lead exposure include the use of acetylene torches to demolish lead-containing pipes, paint, or tanks.[333] Neurasthenic symptoms (headache, generalized weakness, fatigue, lightheadedness, anorexia, arthralgias) are frequent complaints among these workers.[334,335] A case series of 47 demolition workers developed elevated BLL (mean = 59 μg/dL; range 15–99 μg/dL) following the removal of leaded tanks and pipes over 2 weeks.[336] The most common symptoms in

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the group were fatigue (83%), headache (45%), sleep disturbances (40%), abdominal cramps (40%), constipation (40%), dizziness (38%), and anorexia (34%). Following improved hygiene, symptoms diminished with declining BLL. Determination of the causal relationship between specific symptoms and lead exposure is complicated by a variety of factors that contribute to the reporting of symptoms including work conditions, job satisfaction, overall health, social support, selection bias, and test conditions. Prospective studies of lead workers demonstrate a high percentage of central nervous system and musculoskeletal symptoms in both chronic lead-exposed workers and control groups (e.g., 75% vs. 60% and 65% vs. 40%, respectively).[337] Many studies use the measure of recent lead exposure (i.e., blood lead level) rather than measures of cumulative lead exposure, including bone lead, of the cumulative blood lead index (area of the BLL curve over time). The latter two cumulative measures probably better reflect chronic lead exposure in an individual than the blood lead level alone, particularly at low-dose lead exposure.[338] Burton's line is the bluish-purple discoloration of gums associated with high blood lead levels and the deposition of lead sulfide in the gum line.[339,340] Although these discolorations often occur in patients with poor oral hygiene, the condition and color of the gum are not affected directly by lead.

Gastrointestinal Tract

Clinically significant gastrointestinal symptoms typically occur at high whole blood lead levels (>70–80 μg/dL). Abdominal colic characterized by a combination of abdominal pain, constipation, cramps, nausea and vomiting, anorexia, and weight loss is a consistent, early symptom of acute and chronic lead poisoning. Diarrhea occurs less often than other gastrointestinal complaints. Histopathological evidence of lead-induced gastrointestinal damage does not usually occur;[37] therefore, gastrointestinal symptoms often resolve following decreases in the blood lead level. Case reports indicate that the gastrointestinal symptoms following the absorption of high lead dose (e.g., blood lead level >100 μg/dL) rapidly improve after chelation.[285]

Peripheral Nervous System

Currently, lead neuropathy is an infrequent form of lead toxicity that usually develops after long-term exposure to high lead levels (>70 μg Pb/dL).[341] Rarely, this abnormality results from very high blood lead levels during acute lead toxicity. The peripheral neuropathy associated with chronic lead toxicity is classically a symmetrical, painless polyneuropathy with motor weakness, particularly in the extensor muscles of the most active extremity (i.e., dominant upper extremity) with minimal sensory changes (e.g., paresthesias). The peripheral motor neuropathy is characterized by segmental demyelination and axonal degeneration that cause wrist and ankle drops in severe cases. Although weakness can occur as the only symptom of lead toxicity, most patients with lead neuropathy have other clinical evidence (e.g., abdominal colic, constipation) of lead poisoning.[342] Weakness usually develops first in the finger and wrist extensors. Muscular wasting is a conspicuous finding in early, severe lead poisoning.[343] Although an acute myopathy may occur following gasoline sniffing (organic and inorganic lead exposure), little evidence supports an association between chronic lead exposure and myopathy (acute muscle necrosis, tender muscles, myalgias, limb weakness).[344]

Some abnormalities in nerve conduction studies occur following chronic exposure to blood lead concentrations <40 μg/dL; however, the clinical significance of mild reductions in nerve conduction velocity remains unclear, especially when the findings are not consistent with the specific nerve (median, ulnar, peroneal, posterior tibial) or type of measurement (maximum nerve conduction velocity, amplitude, latency). If segmental demyelination develops, only partial improvement in the peripheral neuropathy may occur following cessation of lead exposure.

Central Nervous System

Case series associated a wide variety of neurological effects with acute onset of lead encephalopathy ranging from confusion, disorientation, irritability, and memory loss to seizures, obtundation, cerebral edema, papilledema, coma, and death.[345] Headache, nausea, vomiting, tremor, and optical neuritis occur less frequently. Dramatic neurological symptoms of inorganic lead encephalopathy are uncommon in adults. Tremor may occur in workers with blood lead concentrations >70 μg/dL.[346]

Nonspecific symptoms reported by lead-exposed workers include fatigue, arthralgias, headache, irritability, insomnia, and diminished libido, but the exact contribution of lead toxicity to these symptoms remains difficult to define because of the high prevalence of these symptoms in control groups. The evidence for subtle changes in neurological function without evidence of an encephalopathy remains somewhat controversial because of the difficulty controlling confounding variables and the validity of measures of chronic exposure. A study of 466 elderly US men (67.4 ± 6.6 years) in

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the Normative Aging Study compared scores on the Mini-Mental State Examination (MMSE) at an average of 3.5 ± 1.1 years apart. A 1-interquartile range (20 μg/g bone mineral) higher patella bone lead concentration measured with K-shell X-ray was associated with a decrement of 0.24 (95% CI: −0.44 to −0.05) in the mean score after adjustment for age, smoking, education, alcohol consumption, and years between testing.[347] This difference was equivalent to ~5 years of age-related cognitive decline from the baseline MMSE score. There was no difference in the quartiles of the whole blood lead level based on 2 μg/dL increments for this cohort with lead-exposed groups similar to the general population; the association between tibial lead and MMSE scores was weak.

There are few prospective data on the effect of chronic lead exposure on adult cognitive function. A 2-year longitudinal study of 803 current and former lead workers in South Korea suggested some decrement in neurological function based on linear regression models, primarily in the domains of executive abilities and manual dexterity. These decrements were correlated to blood lead levels but not to tibial lead concentrations. Further studies are necessary to elucidate the effect of chronic lead exposure on neurological functions. A study of this South Korean cohort indicated that patellar lead did not add significant information to the study of neurobehavioral function when compared with blood lead and tibial lead.[348] A meta-analysis of nine epidemiology studies suggested an association between chronic occupational lead exposure and amyotrophic lateral sclerosis (ALS).[349] The odds ratio was 1.81 (95% CI: 1.39–2.36) with relatively low heterogeneity ($I^2 = 0.14$). Adjusting for age and sex reduced the estimated odd ratio to 1.41 (95% CI: 1.21–1.65). Because of the rarity of ALS, only two cohort studies were included in the analysis; consequently, recall bias is an unresolved issue. The estimated attributable risk of ALS resulting from occupational lead exposure was 5%.

Kidney

The chronic form of lead-induced nephropathy is a slowly progressive, clinically silent nephropathy that may progress to renal impairment following long-term, high-dose lead exposure (>50–80 μg/dL). The clinical presentation often manifests as chronically reduced glomerular filtration and interstitial fibrosis of the kidney; gout and hypertension also may occur as a result of the decreased secretion of urate.[350] Renal failure does not usually develop in workers with chronic, long-term lead exposures defined by blood lead levels <60 μg/dL.[351,352] Some population-based studies suggest that environmental lead exposure may produce slight renal impairment,[353] but the epidemiological studies to date cannot exclude the possibility that renal impairment itself may increase the body lead burden or that the small changes in renal function are clinically relevant.[354,355] A cross-sectional study of 652 Korean lead workers with mean blood lead levels of ~31 ± 17 μg/dL and mean duration of lead exposure of 10 ± 6.5 years suggested patella lead levels correlated to *N*-acetyl-β-D-glucosaminidase concentrations blood lead, and tibial lead levels.[356] The association between these lead biomarkers and measures of renal function (serum creatinine, creatinine clearance) was not statistically significant.

Hypertension

An increased incidence of hypertension and cerebrovascular disease occurred in lead workers exposed chronically to lead doses during the early 1900s.[357] A review of epidemiological studies (occupational and general population) up to the mid-1990s suggested a small dose-response (~1–2 mm Hg systolic/doubling of BLL) for BLL <30–40 μg/dL.[358] A cross-sectional study of 222 lead battery manufacturing workers with a mean blood lead level of 56.9 ± 25.5 μg/dL did not demonstrate a correlation between current blood lead levels and blood pressure based on multivariate regression analyses.[359] A meta-analysis of 12 occupational studies detected a weak association between blood lead concentrations and hypertension.[317] In this study, a 2-fold increase in the blood lead concentration was associated with a mean elevation of the systolic and diastolic blood pressure of 1.0 mm Hg and 0.6 mm Hg, respectively. Observed associations between lead exposure and blood pressure may reflect an immediate response to blood lead concentration or a persistent effect of the cumulative lead dose. A cross-sectional study of 632 current and former lead workers (BLL mean = 31.9 μg/dL) demonstrated a relationship between blood lead concentration and systolic blood pressure, but not to patellar lead, diastolic blood pressure, or hypertensive status based on linear regression analysis.[360] For BLL and patella lead, the Spearman correlation coefficient is 0.66 ($P < 0.0001$).

Environmental Exposure

Lead toxicity should be considered in the differential diagnosis of the following disorders: recurrent abdominal pain or vomiting, autism, learning disabilities or behavior disorders, developmental delay, speech and hearing deficits, encephalopathy, and convulsions.[361]

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Acute Toxicity

Irritability, lethargy, and ataxia may be early signs of acute encephalopathy, whereas convulsions, cerebral edema, and coma are the hallmarks of acute encephalopathy; however, irritability, lethargy, and ataxia may precede the onset of frank encephalopathy.[362] Other symptoms of lead-induced encephalopathy may include bizarre behavior, ataxia, apathy, and memory loss. About 30% of children with encephalopathy from acute lead exposure have permanent neurological deficits.

Central Nervous System

The most severe form of pediatric lead poisoning is an acute encephalopathy in children <30 months of age characterized by increased intracranial pressure, protracted vomiting, abdominal colic, behavioral abnormalities, ataxia, seizures, and altered mental status ranging from disorientation to coma. Vomiting and lethargy frequently occur in the week preceding the development of acute encephalopathy.

Kidney

Acute lead nephropathy manifests as a reversible, proximal renal tubular damage characterized by epithelial degenerative changes and one or more elements of the Fanconi syndrome. This form of high lead exposure causes proximal renal tubular impairment including aminoaciduria, glycosuria, and hyperphosphaturia that usually resolves after lead exposure ceases.[294] This form of lead nephropathy occurs primarily in children. Some,[363] but not all studies,[364] of children chelated for severe lead poisoning demonstrate an increased incidence of chronic nephropathy during adulthood. The positive studies suggested the persistence of a partial Fanconi syndrome (↑ aminoaciduria, ↑ glucosuria) when compared with historic controls; however, renal function as measured by serum creatinine and blood pressure remained normal.[365] A 50-year follow-up of 35 survivors of childhood lead poisoning occurring primarily in the 1930s and 22 matched (age, sex, race) controls demonstrated an increased risk of hypertension (RR = 7, 95% CI = 1.2–42.3) in the exposed cohort; however, the creatinine clearance rates in the exposed cohort were above normal.[366]

Musculoskeletal

In contrast to primary gout, the most commonly affected joint in saturnine gout is the knee rather than the first metatarsophalangeal joint; polyarthritis occurs in a minority of cases of saturnine gout.[367] The onset of saturnine gout typically occurs after other features of lead toxicity (e.g., abdominal pain, constipation, radial/peroneal nerve palsies) in a patient with high BLL (e.g., 80 μg/dL).[368]

Chronic Toxicity

Symptoms associated with chronically elevated lead levels (i.e., >15–20 μg/dL) include colic, headache, myalgias, dizziness, and paresthesias.[369] Anorexia, lethargy, vomiting, and colicky abdominal pain are the most common symptoms of lead intoxication in children. Cross-sectional studies using dentine lead levels as a surrogate for excessive lead exposure associated high dentine (>18–20 ppm Pb) levels with higher school absenteeism and drop-out rates,[370] small decrements in verbal and full IQ,[371] and school performance.[372] Some,[373,374,375] but not all,[376,377] epidemiological studies using prenatal and postnatal blood lead levels suggest low-level lead exposure has a small mean (1–3 IQ points) negative effect on intellectual performance as well as some behavioral abnormalities.[378,379] Continual exposure to lead risks permanent central nervous system damage; therefore, the lead source requires elimination.

Substantial numbers of children with elevated total body lead burdens do not display overt symptoms of lead toxicity. Subclinical lead toxicity in these children produces subtle effects on behavior, cognitive development, growth, and hearing; these effects may occur at relatively low blood lead levels (5–10 μg/dL) by historical standards. In general, the contribution of lead at blood lead levels <10 μg/dL is relatively less than other factors.[380,381] These confounding factors (e.g., environment, socioeconomic status, maternal and paternal IQ/education, genetics) complicate the quantitation of lead effects on measured outcomes (e.g., IQ) because of the relatively large effect of these confounders compared with the effect of lead.

Cognitive Deficits

There is no single neurobehavioral abnormality or a unique group of neurobehavioral abnormalities that identify lead exposure in children with no consistent effects on individual cognitive domains.[382] Confounding the effects of lead on cognitive and behavioral development include iron deficiency and permissive parenting styles.[383] Although elevated body lead burden and mild iron efficiency states often occur concurrently, the effect of iron deficiency on lead toxicity has not been well studied. Despite the effects of lead neurodevelopment and behavior problems, the presence of elevated lead concentrations does not necessarily imply that impairment will occur.

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Intelligence

In the early 1990s, the US Centers for Disease Control and Prevention[81] and the US EPA[384] concluded that blood lead levels of 10–15 μg/dL present risks of developmental abnormalities in children; therefore, these agencies recommended screening children for blood lead to reduce blood lead levels below 10 μg/dL. Recently, some analyses suggest lead effects on cognition may extend below blood lead concentrations of 10 μg/dL.[36] Despite many studies on the cognitive effects of lead, a number of methodological issues complicate the interpretation of many positive studies including ascertainment bias, specificity of outcome variables (neuropsychological and development testing), multiplicity of outcome measures, control of confounding variables having a greater effect on development than blood lead, and the lack of consistency in the outcome. Most of these studies use blood lead (i.e., a measure of recent lead exposure) rather than long-term lead exposure (cumulative blood lead index, K X-ray fluorescence). Most epidemiological studies indicate a modest inverse association between lead exposure and cognitive function in children; there is general, but not unanimous, consensus that this association is causal.[385,386]

Deficit Initial studies during the 1980s and 1990s linking the effect of biomarkers of lead exposure (blood, teeth, bone) on cognitive development primarily involved intelligence testing. Several,[387,388,389] but not all,[390] epidemiological studies associated blood and bone lead concentrations with decrements in intelligence testing during childhood; some of the positive studies[387] developed hypotheses after the study outcomes were known, resulting in selected choices of statistics, models, and result reporting (i.e., harking). The effect of blood lead in these studies on cognitive development is relatively small (e.g., ~1–3 point decrease in WISC-R Full-Scale IQ with an increase in average lifetime blood lead from 10–20 μg/dL) compared with confounding variables (e.g., social factors, serum folate concentrations, home environment, family income).[391,392] Needleman et al. reported a 4-point reduction in Intelligence Quotient scores; significantly fewer children with superior Intelligence Quotient scores in a study of asymptomatic children with elevated total body lead stores as measured by lead dentine concentrations.[393] A study of nonverbal intelligence in 188 children of Ecuadorian Andean lead-glazing workers suggested a dose-related decline in visual-spatial intelligence and nonverbal reasoning of ~2 IQ points per 10 μg/dL increase in blood lead levels as measured by the Raven Colored Progressive Matrices (RCPM).[394] The mean blood lead level of the children was 29.3 μg/dL with a range of 3.5–94.3 μg/dL. Of the 47 children with blood lead levels <10 μg/dL, 30 children had RCPM standard scores $\leq 25^{th}$ percentile, whereas 97 of 141 children with blood lead levels >10 μg/dL had abnormal RCPM scores. Although lead exposure may affect performance on neurodevelopment measures, lead concentrations in children account for a relatively small portion (i.e., ~4–8% of the explained variance) compared with the child's family and personal psychosocial experiences.[395] In a study of 68 children aged 12–36 months presenting to a large urban public hospital clinic, children with capillary blood concentrations between 10–24.9 μg/dL had a mean Mental Developmental Index (Bayley Scales of Infant Development) score of 6.2 points (95% CI: 1.7–10.8) lower than children with blood lead concentrations <10 μg/dL after adjustment for confounders.[396] Regression analysis indicated that blood lead accounted for 5% of the variance in the Mental Development Index compared with 13% for cognitive stimulation in the home environment.

Cross-sectional and prospective studies associating blood lead levels of 10–25 μg/dL with a reduction in IQ (i.e., primarily verbal IQ) provide the strongest evidence available on the neurotoxicity of low-level lead exposure. Most studies show an inverse relationship between blood lead levels in this range and measures of IQ. At these lead concentrations, perceptuomotor skills appear significantly more sensitive to the effects of lead than the language-related measures of intelligence.[397] A meta-analysis of available studies indicated that the magnitude of the reduction is 0–5 points for every 10 μg/dL increment in blood lead level. Controlling for socioeconomic factors (maternal education, child-rearing environment, maternal depression) reduces the most likely range to ~1–3 points.[72] These studies adjusted for maternal IQ but not for paternal IQ.

The shape of the exposure-response curve below 10 μg/L remains controversial. Several cross-sectional observational studies suggest an inverse association between intelligence and blood lead levels at concentrations <10 μg/L;[398] this nonclassical exposure-response curve implies increasing impact of the blood lead level at concentrations <10 μg/L. Confounding factors (i.e., covariates) that vary from study to study may account for some of the differences in deficits including prenatal lead exposure, particularly in the third trimester.[399] As the blood lead level decreased over the last several decades, the frequency distribution changed from normal to exponential.[400] Several authors suggest the shape of the curve at low blood lead concentrations may reflect a statistical artifact rather than a biological effect.[401,402]

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Threshold The threshold for the effect of lead on neurodevelopment is not well defined; risk models (e.g., benchmark dose analysis) suggest reductions in IQ may occur at prenatal and postnatal lead exposures <10 μg/dL.[403] To date, there is no clearly defined blood lead concentration below which cognitive performance does not decline, including blood lead concentrations <10 μg/dL based on a pooled analysis of seven cohort studies of the association between blood lead concentrations and intelligence measures.[398] Reanalysis of the Lanphear pooled-analysis data supported a nonlinear exposure-response; however, the exposure-response for decrements in IQ and blood lead concentrations <10 μg/L was linear.[404] The effects of confounding variables (maternal/paternal education, homeownership, employment status, residential mobility, insurance status, child health, maternal smoking) and the lack of precision in the neuropsychological measures limit the ability of these studies to detect a threshold effect of lead on IQ. The exact temporal relationship is unclear. Some studies suggest that blood lead levels <10 μg/dL are associated with decrements in achievement tests and IQ scores when compared with children with very low blood lead levels (i.e., 1–2 μg/L). In an analysis of data from the New England Children's Amalgam Trial, school-age children (mean age = 8 years, range 6–11.5 years) with blood lead levels of 5–10 μg/dL had lower adjusted scores in overall intelligence (Wechsler Intelligence Scale for Children), visual-spatial skills, executive function, and IQ-adjusted academic achievement when compared with children with blood lead levels <2 μg/dL.[405] The former group had adjusted scores 7.8 ± 2.4 and 6.9 ± 2.2 points lower on reading and math composite scores, respectively, compared with the low lead group ($P < 0.01$). Higher lead levels were associated with more negative effects on verbal IQ (e.g., vocabulary) than performance IQ. These scores were adjusted for age, race, socioeconomic status, and primary caregiver IQ, but there was no information on lead concentrations prior to the initiation of the study. This study did not detect cognitive effects at blood lead levels <5 μg/dL. The prospective Port Pirie study demonstrated a linear association between blood lead and developmental outcomes without definite evidence of a threshold; however, the magnitude of the effects was sufficiently small to define this curve only at a group rather than individual level.[406] The effect of lead on IQ at low lead levels is also relatively small compared with other factors. In a Swedish study of 3,176 primary school children aged 7–12 and followed to ages 16–19 years (mean BLL = 3.4 μg/dL; 90th percentile = 6.0 μg/dL), univariate analysis indicated the BLL accounted for 1.5% of the variance in IQ.[407] Other factors accounted for 19.3% of the variance; socioeconomic status did not correlate to BLL in this study.

Persistence There are limited data on the critical periods of lead exposure and the persistence of these neurobehavioral effects. The effect of lead *in utero* and the first year of life does not appear to persist into the grammar school year when lead exposure ceases and blood levels return to normal by the age of 2 years.[408,409] During preschool years, several factors are associated with the persistence of neuropsychological deficits including high prenatal exposure to lead, high postnatal lead exposure with elevated blood lead levels at the age of 2 years, and lower socioeconomic characteristics.[410] Ruff et al. reported an improvement in cognitive skills in children aged 13–87 months when blood lead concentrations were reduced.[411] The initial blood lead concentrations ranged from 25–55 μg/dL. The Port Pirie study followed children with mean blood lead levels of 21.2 μg/dL at 2 years of age; the mean lead level declined to 7.9 μg/dL at age 11–13 years.[412] The cognitive deficits associated with lead exposure in early childhood were only partially reversible after a subsequent decline in blood lead levels. Within this cohort, the cognitive skills of children with higher lead exposures changed little with age compared with children with lower exposure levels. Because very early lead exposure (i.e., perinatal period) is not correlated well to school-age IQ, the issue of reverse causality remains (i.e., do children with lower IQ eat more lead?). This prospective study indicated cumulative lead exposure across childhood and early adolescence rather than prenatal blood lead best predicted developmental outcomes, suggesting persistent rather than transient effects. The Dunedin cohort study followed 565 participants (56% participation rate) with BLL at age 11 of 10.99 ± 4.63 μg/dL until age 38 years.[413] Each 5 μg/dL increase in BLL was associated with 1.61 (95% CI: −2.48 to −0.74) decline in adult IQ driven primarily by lower scores in perceptual reasoning (IQ = −2.07, 95% CI: −3.14 to −1.01) and working memory (IQ = −1.26, 95% CI: −2.38 to −0.14). The associations were not statistically significant between BLL and verbal comprehension or processing speed. Each 5 μg/dL increased in BLL was also associated with lower socioeconomic status (IQ = −1.79, 95% CI: −3.17 to −0.40).

School Performance An observational study comparing school examination performance in Wisconsin children with moderately elevated blood lead levels (10–<20 μg/dL) before age 3 years and control children (<5 μg/dL) indicated the highest association with lead and proficiency category was language arts (OR = 1.70,

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95% CI: 1.31–2.21) and lowest for math (OR = 1.40, 95% CI: 1.08–1.81).[414] Household social status and childhood health partially explained the decreased examination scores. A study of 855 children aged 6–9 years found a 5.8-point difference on the British Ability Scales between the groups with the highest and lowest blood levels (range, 3–34 μg/dL).[415] Although there was a dose-response relationship between blood lead level and test scores, there was no evidence of a threshold effect. Retrospective cohort studies of children with early lead exposure suggest effects on academic achievement persist into elementary and junior high school, particularly for children with blood lead concentrations >10 μg/dL based on a convenience sample extracted from databases and multivariate logistic regression analysis of Michigan Educational Assessment Program scores.[416] These scores were analyzed by two categories rather than a continuous variable. Additionally, some epidemiology data suggest decrements (i.e., 10–15%) in math/reading achievement when comparing third-grade children with current BLL 5–9 and 0–4 μg/dL.[417]

Behavior Abnormalities

Although some neurobehavioral abilities appear more vulnerable to early lead exposure, current studies have not clearly identified a neurobehavioral phenotype characteristic of early lead exposure.[418] Early studies suggested an association between elevated lead levels and signs of inattention, hyperactivity, and disruptive behavior.[419] A retrospective cohort study of 850 first grade boys years as the exposure measure associated high bone lead levels as measured by tibial K X-ray fluorescence spectroscopy at age 12 with an increased clinical score for attention deficits, delinquency, and aggression as assessed by teachers and parents.[420] The study compared groups with scores in the upper 30th percentile on a self-reported antisocial behavior scale with controls matched by an equal number drawn randomly from the group with scores in the lower 70% of the distribution. A case-control study from the same group compared 194 youths aged 12–18 years, arrested and adjudicated as delinquent by a Pennsylvania Juvenile Court with 146 controls from high schools in Pittsburgh without juvenile records.[421] After adjusting for covariates (parental education/occupation, single-parent home, race, children in the home, neighborhood crime rate), bone lead concentrations >25 ppm were four times higher in adjudicated delinquent controls using logistic regression models. The study did not report blood lead levels or establish a dose-response relationship between bone lead and adjudicated delinquency. A prospective longitudinal birth cohort study of 195 urban, inner-city adolescents recruited from the Cincinnati Prospective Lead Study between 1979–1985 analyzed the relationships between prenatal/postnatal lead exposure and antisocial/delinquent behaviors.[422] The mean maternal blood lead level was 8.9 μg/dL with 35% of the cohort exceeding 25 μg/dL between birth and 5 years of age. After adjustment for co-variables, prenatal and postnatal blood lead concentrations were significantly associated with an increased frequency of parent-reported delinquent and antisocial behaviors. The study reported total scores without individual covariate analysis; maternal blood lead levels were surrogates for cord blood lead concentrations. Subsequent studies demonstrated inconsistent findings, in part because of the difficulty controlling confounding social and demographic variables (e.g., poverty, parenting practices) and design issues (lack of simple measures of neurobehavioral function, substantial individual variation, strong multifactorial causes).[423] The true associations between BLL and behavioral outcomes including criminal behavior are difficult to separate from low socioeconomic status. In a study of 553 New Zealand participants (56% participation rate) in the Dunedin Multidisciplinary Health and Development Study followed 15–38 years of age, the BLL at age 11 (10.99 ± 4.63 μg/dL) did not correlate to self-reported offenses, recidivism, convictions, or violence.[424] Although the BLL and socioeconomic status of participants in this study were similar to children in New Zealand,[425] the BLL was a poor discriminator between any conviction and no convictions (AUC = 0.58). The study did not support a dose-response relationship between BLL and criminal behavior, despite the lack of confounding of poor socioeconomic status.

Private structured interviews assessed psychopathology symptoms in the New Zealand Dunedin cohort using the Diagnostic Interview Schedule five times between ages 18–38 years evaluating 11 disorders scaled to 100 ± 15.[426] Each 5 μg/dL increase in childhood BLL at age 11 years was associated with a 1.34 (95% CI: 0.11–2.57, $P = 0.03$) increase in general psychopathology driven primarily by internalizing (depression, anxiety, fears, phobias) and thought disorders (manic, obsessive-compulsive, psychotic). As with IQ, the effect sizes associated with childhood lead exposures and adult psychopathology/personality difficulties are small ($r = 0.08$) compared with childhood maltreatment ($r = 0.21$) and family mental health illness ($r = 0.23$), suggesting childhood lead exposure is not a major etiological factor in adult psychiatric disease. In childhood, psychopathological symptoms are more often externalizing (e.g., hyperactivity) than internalizing symptoms.

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Well-controlled studies demonstrate small, but significant, associations between blood lead and symptoms of hyperactivity, but evidence that lead causes attention-deficit hyperactivity disorder is inconclusive.[66,427] A study of 579 New Zealand 11-year-old children detected a statistically significant association between teacher-reported general behavioral problems and the log blood lead level after adjustment for social, background, and environmental factors. The impact of blood lead levels was small with a 10-fold increase in blood lead associated with an increase in behavioral scores of ~0.1 points. From birth, Wasserman et al. followed 379 3-year-old Yugoslavian children born in two towns, one with a smelter and one without a point source of lead.[428] The children were evaluated by the Child Behavior Checklist; the results were controlled for social and demographic factors as well as for difficult infant temperament. Multiple regression analysis demonstrated that the concurrent blood lead level explained ~1–4% of the variance on the Destructive and Withdrawn subscales. An increase in the blood lead level from 10–20 μg/dL was associated with an increase of 0.5 points on the subscale scores. A prospective observational study followed 780 urban 12–33-month-old children with blood lead concentrations of 20–44 μg/dL. The blood lead concentration at 2 years old was not associated with Conners' Parent Rating Scale-Revised scores at 5 years old or the Behavioral Assessment for Children scores at 7 years of age.[429] However, the concurrent blood lead concentration was associated with externalizing and school problems scales at 7 years of age.

Hearing

Although the exact mechanism is unclear, a cross-sectional study of children over the age of 6 years indicated an increased blood lead level of 6–18 μg/dL was associated with a 2 dB loss in hearing at all frequencies.[430] A prospective study of children in Mexico City demonstrated a significant association between maternal blood lead levels at 20 weeks gestation (GM = 7.7 μg/dL; range, 1–31 μg/dL) and brainstem auditory evoked responses in neonates, 3-month-old infants, and 5½-year-old children.[431,432] The I–V and III–V interpeak intervals data were concave upward, decreasing between BLL 1–8 μg/dL and increasing with a rise in the BLL 8–31 μg/dL. However, a cross-sectional study of 112 Andean children with high blood lead concentrations (mean = 49.25 μg/dL; range, 4.4–119.1 μg/dL) did not detect a significant correlation between blood lead concentration and the brainstem auditory evoked responses including BAEP interpeak conduction.[433]

Kidney

The proximal tubule is the most sensitive renal tissue with inhibition of the activation of vitamin D synthesis occurring near blood lead levels of 25 μg/dL.[434] Intense, short-term lead exposure in children may cause proximal renal tubular dysfunction (i.e., Fanconi syndrome) characterized by aminoaciduria, hypophosphatemia, glycosuria, renal tubular acidosis, and hyperphosphaturia. A case series of 151 young children with elevated blood lead levels (mean = 34.2 ± 22.4 μg/dL), demonstrated elevated urinary concentrations of *N*-acetyl-β-D-glucosaminidase compared with standardized control values.[435] Blood lead concentrations did not correlate to abnormalities of albumin, α-1 microglobulin, retinol-binding protein, or alanine aminopeptidase in urine samples. The study did not report measures of kidney function for children.

In a study of 744 men from the Normative Aging Study initially enrolled in Boston 1963–1968 and evaluated in 1988–1991, multivariate linear regression analysis with log-transformed BLL demonstrated a statistically significant ($P = 0.04$) association between covariant-adjusted creatinine clearance and blood lead levels.[436] The mean age of the study group was 64 years (range, 43–90 years) with a mean baseline BLL of 8.1 μg/dL (range, <4–26 μg/dL). In a similar longitudinal study of 459 enrollees, multivariate linear regression (with log-transformed BLL) demonstrated a statistically significant increase in serum creatinine after adjustment for covariates (hypertension, alcohol consumption/tobacco smoking, age, body mass index, education). The adjusted serum creatinine increased 0.08 mg/dL (95% CI: 0.02–0.13) for a 10-fold increase in BLL. In the cross-sectional Belgian Cadmibel Study of 965 males (mean = 48 years) and 1,016 females (mean = 48 years), multivariate linear regression analysis (with log-transformed BLL) demonstrated 10–13 mL/minute reduction in co-variant-adjusted creatinine clearance for a 10-fold increase in the BLL; the co-variants included diabetes mellitus, analgesic/diuretic therapy, age, body mass index, and urinary γ-glutamyltransferase activity.[437] The mean BLL in men and women were 11.4 μg/dL (range, 2.3–72.5) and 7.4 μg/dL (range, 1.7–6.0), respectively. Issues remain controversial regarding the clinical significance and reversibility of renal abnormalities as well as the contribution of renal impairment to elevated blood lead levels.

Hypertension

Collective evidence from studies of the general population indicates the association between blood lead and hypertension is relatively weak (i.e., 1–2 mm Hg elevation in systolic blood pressure/doubling of BLL)

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and inconsistent.[438,439] The British Regional Heart Study demonstrated lead exposure was a minor contribution to the development of hypertension,[438] but the exact strength of the association and the dose-response characteristics were less clear. In a multivariate analysis of NHANES IV data, slight increases in systolic (+0.76 mm Hg, 95% CI: 0.38–1.13 mm Hg) and diastolic (+0.43 mm Hg, 95% CI: 0.18–0.68 mm Hg) blood pressures occurred with doubling of the BLL; however, the odds of developing hypertension were not elevated (0.95, 95% CI: 0.90–1.01; $P = 0.11$).[440] Systolic blood pressure correlated significantly with ethnicity and sex. Several epidemiological studies suggest that the effect of lead on blood pressure in the general population is modest (adjusted regression coefficient, 2–4 mm Hg/ln (μg Pb/dL)).[441] Confounding factors interacting with the effect of lead on hypertension include caffeine use, ethnicity, and amount of lead accumulation. Concern exists over the possibility that soft acid water increases lead solubility and the incidence of hypertension/cardiovascular mortality in areas with soft water supplies. Consequently, the importance of lead-induced changes in blood pressure remains controversial.

In a study of participants in NHANES II, linear regression analysis indicated an independent relationship between blood pressure and blood lead level in middle-aged men, but not women.[442] The cross-sectional study of 7,731 men (range, 40–59 years) from 24 British towns in the British Regional Heart Study demonstrated a covariate-adjusted blood pressure increase per 2-fold increased BLL of 1.45 mm Hg (95% CI: 0.47–2.43 mm Hg) systolic and 1.25 mm Hg (95% CI: 0.65–1.85 mm Hg) diastolic based on multiple regression analysis.[443] Covariates included alcohol consumption, cigarette smoking, age, body mass index, and socioeconomic factors. The median BLL was 13–16 μg/dL with 8% ≥25 μg/dL.

A meta-analysis of 58,518 subjects from the general population and 12 occupational studies detected a weak association between blood lead concentrations and hypertension.[317] In this study, a 2-fold increase in the blood lead concentration was associated with a mean increase of 1.0 mm Hg systolic and 0.6 mm Hg diastolic blood pressure. A logical regression model of hypertensive patients in a group of US veterans from the Normative Aging Study suggested that long-term accumulation of lead as measured by K X-ray fluorescence was an independent risk factor for the development of hypertension.[444] The mean BLL was 6.3 ± 4.1 μg/dL.

The relationship between blood lead and the development of hypertension in women is suggestive, but the association in epidemiological studies is weaker than with men; this relationship varies more with other factors (e.g., alcohol consumption, age).[445] A case-control study evaluated lead concentrations from 93 middle-aged (mean = 61 years) self-referred patients with hypertension chosen from the National Nurses' Health Study and 204 controls matched for age and smoking.[446] The combined (cases and controls) mean BLL was 3 μg/dL (range, <1–14 μg/dL). Although there was no statistically significant association between hypertension and mean blood or tibial lead concentrations, the odds ratio of developing hypertension was ~2 for women in the 90th percentile of patella lead values compared with women in the 10th percentile.

In an analysis of 2,563 males (mean = 47.5 years) and 2,394 females (mean = 47.7) without a history of treated hypertension from the Health Survey for England, HSE, the covariate-adjusted diastolic blood pressure increased with increasing BLL in men but not in women based on multivariate linear regression (with log-transformed BLL).[447] Systolic blood pressure was not correlated to the BLL in men or women. Covariates included in the above model were region of residence, socioeconomic status, alcohol consumption, tobacco smoking, age, and body mass index. The geometric mean BLLs in men and women were 3.7 μg/dL and 2.6 μg/dL, respectively. An 8-year prospective cohort study of 728 people aged 20–82 found no consistent association between change in blood pressure and blood lead levels <30 μg/dL.[448] The risk ratio for developing hypertension given a doubling of the initial blood lead level was 1.2 (95% confidence interval, 0.7–2.0). The blood lead level did not predict the development of hypertension in the 47 patients in this study.

Reproductive Abnormalities

Increased fetal mortality in the offspring of women exposed to high lead concentrations (>40–60 μg/dL) is an unfortunate part of the Industrial Revolution.[449] Sterility, miscarriages, stillbirths, premature births, and low birth weight were recognized complications of high lead exposure in female workers and wives of husbands working in the lead industry.[450] Current data do not suggest lead causes major congenital abnormalities. Pica increases the risk of maternal blood lead concentrations >45 μg/dL. In a study of New York City Health Department data on 491 cases of lead-poisoned pregnant women, the odds ratio for BLL >45 μg/dL was 3.3 (95% CI: 1.25–8.68) in women with pica compared with women without reported pica.[65] The mean BLL for pregnant women with pica was 29.5 μg/dL.

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Pregnancy Outcomes

Issues regarding the timing and maternal BLL necessary to cause adverse effects of lead on pregnancy outcomes (low birth weight, preterm delivery, small-for-gestational-age) at maternal BLL <25 μg/dL complicate the interpretation of limited data on the possibility of a specific no-adverse-effect threshold.[451] Some, but not all, epidemiological studies reveal a dose-response effect of preterm delivery and maternal blood lead concentrations >10–15 μg/dL. Lead exposure at this concentration probably does not cause an increased risk of premature rupture of membranes, miscarriages, or stillbirths.[451,452] In a study of 262 mother–infant pairs reported to California lead surveillance agencies for elevated BLL from various clinical laboratories, an increased risk of adverse pregnancy outcomes (preterm delivery, small-for-gestational-age) was associated with maximum maternal BLL >10 μg/dL when compared with maximum maternal BLL <10 μg/dL.[453] The reason for the referrals was not available, limiting the extrapolation of the data to all pregnant women. Additionally, women with maximum BLL <5 μg/dL tended to deliver smaller infants (mean = 3401 g) than women in the range of 6–9 μg/dL (mean = 3571 g), suggesting the presence of confounding variables.

In a nested case-control study of 668 Mexican women seeking prenatal care in Mexico City, the odds ratio for spontaneous abortion after multivariant adjustment was 1.8 (95% CI: 1.1–3.1) for every 5 μg/dL increase in blood lead level.[454] The mean BLLs in cases and controls were 12.0 μg/dL and 10.1 μg/dL, respectively. A study of 304 Yugoslavian women living near a lead smelter (mid-pregnancy mean BLL = ~16 μg/dL) did not detect a positive association between low lead levels and the rate of spontaneous abortion when compared with 335 pregnant women living >25 km away (mid-pregnancy mean BLL = ~5 μg/dL).[455] A higher incidence of premature delivery (13% vs. 3%, respectively) and early membrane rupture (17% vs. 0.41%, respectively) occurred in 253 women living near Missouri mines compared with 249 women from a different area of Missouri.[456] The prospective Australian Port Pirie study compared women in a lead smelter community in South Australia with women in surrounding rural areas and neighboring towns; the mean mid-pregnancy maternal blood lead levels in 851 pregnant women from Port Pirie and surrounding community controls were 10.6 μg/dL (n = 531) and 7.6 μg/dL (n = 171), respectively.[457,458] The study demonstrated no association between spontaneous abortions and BLL, whereas preterm delivery correlated to maternal lead levels at delivery. The risk of preterm delivery at maternal blood lead levels of 14 μg/dL was 8.7 times greater than maternal blood levels <8 μg/dL. Other investigators have not detected a statistically significant relationship between maternal or fetal lead levels and preterm delivery.[459,460,461] In a convenient sample of 121 Finnish women occupationally exposed to lead and categorized with BLL <10 μg/dL, 10–19 μg/dL, and ≥20 μg/dL, time-to-pregnancy was not associated with BLL when compared with low lead exposure.[462]

A review of nine studies on lead exposure and gestational hypertension or preeclampsia indicated a positive association in six of the studies.[463] The mean whole blood lead concentration in most of the studies was <10 μg/L as measured during a range of time from the last trimester to the postpartum period. Interpretation of these studies and the association between gestational hypertension is complicated by a lack of control of confounding variables (e.g., calcium supplementation, body mass index) and inadequate exposure measures (e.g., plasma lead is probably a better measure of the lead available to diffuse into the placenta than whole blood lead).

Congenital Abnormalities

Currently, few data associate increased blood lead levels and major malformations following exposure to low lead levels; the data on the pattern of minor congenital abnormalities and BLL is inconsistent. A case report associated the VACTERL association (*V*ertebral anomalies, *A*nal atresia with/without fistula, *C*ardiac defect commonly with ventricular septal defect, *T*racheoesophageal fistula, *R*enal anomalies, *L*imb anomalies) with a maternal blood lead level of 62 μg/dL at 8 weeks gestation.[464] In a retrospective study, Needleman et al. found a statistically significant association between cord blood lead levels and the occurrence of minor malformations (e.g., hemangiomas, hydrocele, undescended testes, lymphangiomas) as a whole; however, no single malformation demonstrated a statistically significant correlation with cord blood lead levels.[313] Other studies (Port Pirie,[458] Cleveland[465]) found no association between congenital anomalies and lead exposure at the blood lead concentrations present in the women. The mean venous blood lead concentration at delivery for 248 Port Pirie women was 11.2 ± 0.21 μg/dL compared with 6.48 ± 1.88 μg/dL (2.7–11.8 μg/dL) in whole blood at delivery for 185 Cleveland women.

Fetal/Infant Physical Development

The association between lead levels <25 μg/dL and early development is less clear; data on physical development

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are conflicting. A study of 305 lower socioeconomic status women residing in predesignated lead-hazardous areas of Cincinnati reported a statistically significant association between maternal blood lead levels between 6–28 weeks of gestation and birth weight; all maternal blood lead levels were <30 μg/dL.[379] Infant development rather than birth weight was the primary outcome of this study. A cross-sectional study of 165 pregnant women living in a rural area and 19 pregnant women living in an urban area demonstrated no association between maternal blood lead levels in early pregnancy and fetal development at 6 days of age (Guthrie test).[466]

Some, but not all, epidemiological studies reveal a dose–response effect of maternal blood lead concentrations >15 μg/dL on some measures of fetal growth and development. An analysis of the National Health and Nutrition Examination Survey 1976–1980 data on ~2,700 children aged 0.5–7 years suggested that blood lead levels of 10–35 μg/dL were inversely correlated to stature (height, weight, chest circumference).[467] In a prospective study of 260 infants followed from birth, covariate-adjusted growth rates in stature were negatively correlated to the mean infant BLL at 3–15 months only when prenatal (maternal) blood lead levels were >7.7 μg/dL.[468] An increase in the postnatal blood lead concentration of 10 μg/dL was associated with a 2 cm decrease in height compared with an infant having a stable blood lead concentration.

Male Reproduction

In male workers, very high chronic lead exposure may produce decreased libido, impotence, abnormalities in the formation of sperm, and reduced fertility. Chronic lead exposure (blood lead levels >45–55 μg/dL) results in a progressive decline of the total sperm counts along with abnormal sperm motility and morphology, particularly when the blood lead levels exceed 60–70 μg/dL.[469,470,471] European cross-sectional studies of lead-exposed workers indicate adverse lead effects on sperm concentration and susceptibility to acid-induced denaturation of sperm chromatin are unlikely following chronic lead exposure below whole blood lead levels of 45 μg/dL.[472] Total sperm count and sperm concentration are the most sensitive measures of semen quality in men exposed to lead.[473] Follow-up studies on cohorts of lead-exposed workers suggest that lead-related changes in sperm quality are at least partially reversible following a reduction in lead exposure.[474] Although these studies indicate chronically high lead exposures adversely affect sperm quality, a cohort of 229 French battery workers aged 20–60 years with mean annual BLL of 46.3 ± 15.2 μg/dL and followed a mean of 4.1 years did not demonstrate a consistent association between measures of lead exposure or a dose-related reduction in fertility based on the annual occurrence of live births.[475] The 125 non-lead exposed workers were not evaluated for BLL. Similarly, a cross-sectional study of 97 South African lead battery workers with mean whole blood lead levels of 53.8 ± 11.2 μg/dL reported no consistent association between lead exposure and measures of fertility or procreation.[476] The study did not include a control population. Together, these studies suggest the reduction in semen quality at these blood lead levels is not sufficient (i.e., sperm concentration $<5 \times 10^{-6}$/mL) to cause a reduction in the fertility rate of these workers.

Although the evidence for reduced fertility is inconclusive, current data suggest the threshold for fertility in men begins in the BLL range of 30–40 μg/dL. A study of Taiwanese lead workers indicated that increasing the whole blood lead concentration by 1 μg/dL increased the time to pregnancy by 0.15 cycles in workers with BLL ≥30 μg/dL; there were no statistically significant reductions in fertility below these lead concentrations.[477] A retrospective study of Finnish lead workers did not detect reduced time to pregnancy or decreased fecundability in workers exposed to whole blood lead levels up to 50 μg/dL.[478] In a group of 74 Belgian lead battery workers with a mean BLL of 46.3 μg/dL, the logistic regression model demonstrated a significant reduction in fertility (OR = 0.65, 95% CI: 0.43–0.98) during the period of exposure to lead, cadmium, and manganese when compared with 138 controls (mean BLL = 10.4 μg/dL). The mean duration of lead exposure was 10.7 years; the duration of lead exposure correlated to the decrease in fertility.

Studies on the effects of lead on male endocrine function are conflicting. A study of 122 current lead workers (mean BLL = 35 μg/dL, range 9.6–77.4 μg/dL) demonstrated a moderate increase in plasma luteinizing hormone and plasma follicle stimulating hormone at blood concentrations 10–40 μg Pb/dL; however, these hormone levels reached a plateau or decline at higher blood lead levels.[315] Another study of lead workers with BLL 17–77 μg/dL demonstrated a subclinical increase in follicle-stimulating hormone only at blood lead levels >47 μg/dL.[479] Neither study detected a change in plasma testosterone levels. A case-control study of Finnish lead workers did not demonstrate a statistically significant relationship between the incidence of spontaneous abortions and paternal lead exposure.[480] None of the adjusted odds ratios for the categories of paternal lead exposure during spermatogenesis (i.e., 80 days before conception) reached statistical significance including the highest category (BLL = ≥39.3 μg/dL; OR = 1.6, 95%

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CI: 0.6–4.2). Adjusted confounders included maternal organic solvent/mercury exposure, parity, contraception, previous spontaneous abortion, paternal cadmium/mercury exposure, and alcohol use. A retrospective case-control study of estimated paternal lead exposure and strabismus suggested a weak but statistically nonsignificant association (RR = 2.6, 95% CI: 0.4–27) between paternal lead exposure and strabismus.[481] Three industrial hygienists estimated the blood lead exposure during conception through infant age of 9 months or age at diagnosis; no blood lead levels were available for confirmation of estimated lead exposure. The unadjusted odds ratio for the highest paternal lead exposure category was 1.2 (95% CI: 0.4–3.3). Multivariate adjustments did not affect the exposure odds ratios.

Carcinogenesis

The National Toxicology Program lists lead and lead compounds as reasonably anticipated to be human carcinogens; the International Agency for Research on Cancer determined inorganic lead was Group 2A carcinogen (probably carcinogenic to humans) and organic lead was Group 3 (not classifiable). Overall, there is small, but consistent increased incidence of some cancers following long-term inorganic lead exposure in occupational cohorts. The strongest epidemiological evidence involves stomach and lung cancers.[482] The IARC determined inorganic lead was a Group 2A (probable) human carcinogen based on limited epidemiological data in workers and an excess of renal tumors and gliomas in rodents administered lead acetate and lead subacetate. The US National Toxicology Program lists lead and lead compounds as substances reasonably anticipated to be carcinogens with limited epidemiological evidence of carcinogenicity in humans.[483] Almost all epidemiological studies of lead workers have design flaws that limit the validity of conclusions regarding the carcinogenicity of lead.[37] Several cohort studies suggest small excesses (i.e., RR = 1.3–1.5) of stomach cancer, but the effect of confounding variables (dietary habits, ethnicity, *Helicobacter pylori* infection, socioeconomic status) could not be excluded; a nested case-control study of stomach cancer suggested causes other than lead for the elevated SMR of stomach cancer.[484] The risk of lung cancer appears relatively small with possible confounding by exposure to arsenic and smoking. The association between occupational lead exposure and other cancers (e.g., brain, bladder, kidney) is equivocal. There are few data on the carcinogenic effect of metallic lead in animals, in part because of the difficulty of administering these relatively less soluble lead compounds compared with lead acetate.

Occupational Exposure

The results of cancer mortality studies of lead workers are inconsistent. Some mortality studies of lead workers suggest the possibility of an association between respiratory or stomach cancers and lead exposure,[485,486] but the small size of the studies, potential confounding factors, and the lack of a clear trend between exposure (duration, intensity) and the incidence of cancer limit conclusions about a definite causal relationship. In a cohort study of 4,518 lead battery workers and 2,300 lead smelter workers, there was a statistically significant increased mortality from lung cancer (SMR = 116, 95% CI: 104–130), stomach cancer (SMR = 147, 95% CI: 112–190), and cancer of the thyroid and other endocrine glands (SMR = 308, 95% CI: 133–607).[484] Except in some lung cancer studies, the lack of an exposure-response relationship suggested that the increased incidence of cancer was not related to lead exposure. A review of the blood lead concentrations of these workers suggested that the lead exposure exceeded current biological exposure limits. About 69% of the lead battery workers and ~39% of the lead smelter workers were employed for at least 20 years. The lack of exposure data and the presence of confounding variables (arsenic, nickel, smoking) complicate the interpretation of the data on lead and cancer.

A meta-analysis of cancer studies of workers exposed to lead suggested increased relative risk ratios for developing lung cancer (RR = 1.29, 95% CI: 1.2–1.5), stomach cancer (RR = 1.33, 95% CI: 1.18–1.49), and bladder cancer (RR = 1.41, 95% CI: 1.16–1.71).[487] However, the authors noted that most of the studies did not account for confounding variables (e.g., smoking). A mortality study of 1,388 Italian workers at a lead-smelting plant did not demonstrate an elevated rate of digestive, nervous system, or lung cancer using standardized mortality ratios.[488] Although Poisson regression analysis indicated the risks of kidney and genitourinary cancers increased with the duration of employment, the SMR of these cancers was not elevated when compared with national mortality rates. There were no data on exposure, smoking, or the histological type of these cancers. A study of 3,979 Swedish workers at a lead smelter revealed an increased mortality rate (SIR = 2.8, 95% CI: 2.1–3.8) from lung cancer for the group of long-term lead workers when compared with cancer rates of the general population in the surrounding county.[489] The cancer rates of all other malignancies were comparable to those of the general population. Several factors suggested a possible interaction between lead and other carcinogens including the lack of a significant relationship between cumulative lead exposure index and lung cancer rates.

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The small number of cases and the presence of several confounding variables (smoking, arsenic, nickel) limited definitive conclusions about the carcinogenicity of lead. A subsequent nested case-referent study of this Swedish cohort of primary smelter workers did not support a causal relationship between occupational exposure to inorganic lead or lead compounds and lung cancer.[490] A Canadian case-control study of histologically confirmed cases of lung cancer did not find an excess risk of lung cancer associated with occupational exposure to inorganic lead (engine emissions or other sources) based on a blinded expert-based assessment of lifetime occupational exposure and adjustment for smoking and sociodemographic characteristics.[491] Comparing ever- to never-exposed subjects, the odds ratios were 0.89 (95% CI: 0.72–1.09) for inorganic lead from engine emissions and 0.99 (95% CI: 0.76–1.29) for inorganic lead from other sources.

Some,[492,493] but not all,[484,494] hypothesis-generating studies of workers exposed to inorganic lead suggest an association between brain cancer and lead exposure. A nested case-referent study of neurological cancers revealed a 2-fold increase in the odds ratio of nervous system cancer in workers with blood lead >30 μg Pb/dL compared with workers with BLL <15 μg Pb/dL.[495] The small number of cases and the wide confidence interval limit any conclusions. All the confidence intervals included 1; therefore, the increased ratios were not statistically significant. A meta-analysis of six occupational cohorts provided little evidence of an association between occupational lead exposure and brain cancer.[482] The overall relative risk of brain cancer in these cohorts was 1.06 (95% CI: 0.8–1.4, 69 cases observed), using meta-analysis techniques.

Environmental Exposure

In a study of the US general population, there was no clear relationship between blood lead concentrations and all cancer mortality using data from the National Health and Nutrition Examination Survey II (NHANES II 1976–1980) Mortality Study.[496] The median blood lead level for the highest quartile of the US population in this study was ~20 μg/dL compared with ~7 μg/dL for the lowest quartile of lead exposure. Blood lead levels declined dramatically from NHANES II to NHANES III (1988–1994), when few adults had BLL exceeding 20 μg/dL. Statistical analysis of mortality data from NHANES III suggests BLL as low as 5 μg/dL is associated with an increased risk of death from all causes. In a study of 9,757 participants ≥40 years of age followed a median of 8.55 years with a single BLL measurement at the time of examination, the participants were divided into the following three groups: BLL <5 μg/dL (referent), BLL 5–9 μg/dL, and BLL ≥10 μg/dL.[497] Table 16.7 lists the relative risk of all cause, cancer, and major cardiovascular disease mortality as identified by ICD-10 codes in these two groups compared with the referent group.

Another statistical study of mortality rates in participants in NHANES III also detected a slight increase in mortality rates in the highest tertile (BLL ≥3.62 μg/dL), when compared to the lowest tertile (BLL <1.94 μg/dL).[498] In contrast to the former study, the increased mortality resulted from increased mortality rates from cardiovascular disease; the mortality rates for cancer were similar in both groups. In general, the hazard ratios were <2; therefore, inadequate control of confounding and exposure misclassification (i.e., single BLL) can account for the statistical differences between these groups. In a prospective cohort study of 533 women aged 65–87 years enrolled in the Study of Osteoporotic Fractures from 1986–1988, the risk of multivariate-adjusted all-cause mortality increased 59% (hazard ratio = 1.59, 95% CI: 1.02–2.49, $P = 0.041$) based on the a priori categorization of women into blood lead concentrations above and below 8 μg/dL, respectively.[499] Coronary heart disease accounted for

TABLE 16.7. Relative risk of mortality in NHANES III participants categorized by blood lead level (BLL). (Data from Schober et al.).[497]

	BLL <5 μg/dL (Referent Group)	BLL 5–9 μg/dL	BLL ≥10 μg/dL
Participants	6,608	2,532	617
Deaths	1,402	828	255
All-cause mortality	1	1.24 (1.05–1.48)[a]	1.59 (1.28–1.98)[a]
Cancer mortality	1	1.44 (1.12–1.86)[a]	1.69 (1.14–2.52)[a]
Major cardiovascular disease mortality	1	1.20 (0.93–1.55)[a]	1.55 (1.16–2.07)[a]

Abbreviation: BLL = blood lead level.

[a] Relative risk (95% confidence limit) compared with referent group (BLL <5 μg/dL).

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most of the increased mortality (HR = 3.08, 95% CI: 1.23–7.70, $P = 0.016$) in the women with blood lead concentrations ≥8 μg/dL; there was no association between blood lead and cancer, stroke, or non-cardiovascular deaths. In the population-based Shanghai Women's (n = 73,363) and Men's (n = 61,379) Health Studies, lead exposure was estimated for each participant based on a job-exposure matrix as developed by expert analysis of self-reported job history; the referents were the participants with no reported lead exposure. The cohort-specific relative hazard rate ratios were elevated for meningioma (RR = 2.4, 95% CI: 1.1–5.0) for women ever exposed; no meningiomas occurred in men ever exposed to lead.[500] The rate ratios were above 1 for kidney (RR = 1.4, 95% CI: 0.9–2.3) and brain (RR = 1.8, 95% CI: 0.7–4.8) cancers in the ever-exposed group, but the value was not statistically significant. There was no association between ever-exposed to lead and lung or stomach cancers.

DIAGNOSTIC TESTING

SI Conversion Units

1 μg/dL = 0.0483 μmol/L = 48.3 nmol/L
1 μmol/L = 20.7 μg/dL = 207 μg/L
1 nmol/L = 0.207 μg/L
1.77 μmol ZPP/L = 110.81 μg ZPP/dL

Analytic Methods

Biological Samples

Techniques for the analysis of lead in biological media include anode stripping voltammetry (ASV), flame atomic absorption spectrometry (AAS), graphite furnace atomic absorption spectrometry (GFAAS),[501] inductively coupled plasma/atomic emission spectrometry (ICP/AES),[502] and inductively coupled plasma/mass spectrometry (ICP/MS). The latter allows the analysis of multiple trace metals from a single sample with low detection limits; however, the cost is substantially higher than GFAAS. Limits of detection for flameless/atomic absorption spectrometry and graphite furnace/atomic absorption spectrometry are ~0.1 μg/dL and 0.005 μg/dL, respectively.[503] Comparison of lead results from samples of blood and food by GFAAS and ICP/MS indicates the latter results are ~10–20% lower than GFAAS results.[504] Specialized methods for analyzing lead in biological samples include neutron activation analysis, X-ray fluorescence spectroscopy, and isotope dilution mass spectrometry. The latter method is highly sensitive for the detection of lead. Some, but not all, methods involve digestion of the sample by wet ashing with strong acid and heat, followed by the conversion of all lead species to the same lead compound by redissolving the residue in dilute acid.

US proficiency standards allow blood lead testing to operate within a total allowable error of ±4 μg/dL or ±10% whichever is greater; however, the evaluation of blood lead concentration <10 μg/dL requires better precision (i.e., ±2 μg/dL).[395] Most common commercial laboratories lack sufficient accuracy to distinguish between a BLL of 3.5 and 5.0 μg/dL. Common clinical laboratory tests reliably detect the biological effects of lead including coproporphyrin, δ-aminolevulinic acid (ALA), ALA dehydratase activity, and erythrocyte protoporphyrin concentrations; however, these tests are not specific for lead.

Protoporphyrins

Measurement of free erythrocyte protoporphyrin and erythrocyte zinc protoporphyrin are less susceptible to environmental contamination than whole blood lead analysis. Older extraction techniques did not separate protoporphyrins including zinc protoporphyrin, but contemporary technology directly measures zinc protoporphyrin concentrations in whole blood using liquid chromatography. The normal ratio between free erythrocyte protoporphyrin and zinc protoporphyrin is ~10/9.[505] ZPP concentrations vary depending on the specific analytical technique. The ZPP concentrations measured by hemato-fluorometer are consistently higher (i.e., ~1/3) compared with analysis by HPLC.[506] Contemporary assays directly measure ZPP concentrations, whereas older extraction methods converted ZPP to FEP by removing the zinc.

Bone Lead

Methods for the determination of lead in bone include ^{57}Co K X-rays in the second phalanx of the index finger (primarily cortical bone) using a germanium silicon detector,[507] ^{109}Cd K X-rays of the tibia (midshaft cortical bone) and calcaneus/patella (trabecular bone),[508] L X-rays of the tibia produced using an X-ray generator, and *in vivo* bone K X-ray fluorescence.[509] The most reliable technique is K X-rays as a result of deeper penetration (i.e., 2 cm) into cortical bone than the lower energy L X-rays; the latter technique penetrates the outer 0.5 cm of periosteal bone, detecting high bone lead concentration only at the surface.[510] Thus, K X-rays better analyze the average lead content over the entire bone thickness (i.e., cumulative lead dose) than L

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X-ray methods.[511,512] Precision of X-ray fluorescence techniques depends on bone mass; therefore, greater measurement errors occur during the analysis of relatively thin pediatric bones compared with the mature bones of adults.

K-shell X-ray Fluorescence

Although K-shell X-ray fluorescence (K-XRF) determines the average lead concentrations in the first 2–4 cm of cortical bone, the measurement is weighted primarily at the surface. The clinical application of K-XRF is limited by its restricted availability and experimental imprecision at low bone lead concentrations. The minimum detectable bone lead level is 3–15 μg/g bone mineral; uncertainty in bone lead measurements ranges from ~3–30 μg Pb/g bone mineral.[513] Because of photon scattering by overlying tissue, imprecision is problematic in obese patients and young children. Bone lead levels based on K-XRF correlate well with age. A little increase in bone lead concentration occurs before the age of 20 years; then, the bone lead level increases linearly in persons without definite exposure to lead.[514] The lead level correlates better with the intensity and chronicity of exposure to lead in the tibia than in the phalanx, calcaneus, ulna, or sternum.[515] Although this technique is reliable, lead contamination may cause inaccurate results in samples from active lead workers.[516] The maximum skin dose of radiation to the tibia from K-XRF is small (0.45 mSv) compared with a chest X-ray.[517]

Bone lead levels measured by K-XRF correlate to cumulative blood lead levels rather than recent blood levels in both workers and children. A cross-sectional study of members of a construction trade union with relatively low exposure (mean = 8.3 μg Pb/dL blood) found a negative correlation between patellar lead levels using K-XRF and the hemoglobin levels;[518] however, the explanatory power of the final model after adjustment for confounding variables was relatively weak ($R^2 < 0.1$). At these low lead levels, no correlation was found between bone lead levels and blood pressure or serum creatinine.

L-shell X-ray Fluorescence

L-shell X-ray (L-XRF) fluorescence detects lead in the first 1–2 mm of bone just below the periosteum using ^{125}I. Unlike K-XRF, L-XRF is sensitive to slight variations in the thickness of skin overlying the bone and movement. These two types of techniques sample different lead pools with L X-ray fluorescence and EDTA-chelatable lead correlating well to recently deposited lead, whereas K X-ray fluorescence techniques sample a much larger lead pool more reflective of chronic lead exposure.[519] The detection limit on L-XRF is 7 μg Pb/g tissue, but the K-XRF technique has several methodological advantages over the L-XRF technique in studying the chronic effects of lead in epidemiological studies.[520] A 3–5-day course of EDTA chelation does not affect the measured bone lead level.[521,522] The effective dose equivalent of L-XRF is small (2.5 μSv).[523] K-XRF is a more widely accepted technique because of the requirements for minimal movement during the L-XRF procedure.

Environmental Samples

The most common methods to determine the content of lead in inanimate objects (dust, soil, paint chips) are inductively coupled plasma/atomic emission spectrometry (ICP/AES), graphite furnace/atomic absorption spectrometry (GFAAS), flame atomic absorption spectrometry, anode stripping voltammetry (ASV), and inductively coupled plasma/mass spectrometry (ICP/MS).[503] These methods detect lead concentrations in the range of 0.24–1.5 μg/dL (2.4–15 ppb) with sensitivity in air in the low μg/m^3 range (0.1–20 μg/m^3).[37] Analysis of environmental samples for lead by ICP/MS displays high sensitivity and easy sample preparation. Although the cost is relatively high compared with ICP/AES, the sensitivity of ICP/MS is many times greater (i.e., three orders of magnitude) than that of ICP/AES. Similar to biological matrices, isotope dilution mass spectrometry is the definitive technique for determining lead with precision, sensitivity, and accuracy; however, technical expertise and high costs limit the availability of this method.

The use of X-ray dispersive electron microscopy allows the determination of metal composition in tissues and powder residues on the skin including lead; these results help establish the distance of the gun from the surface of the skin.[524] Measurements of lead isotope ratios by ICP/MS allow the identification of specific sources of childhood lead poisoning and the relative importance of various environmental sources (soil, water, air).[525,526] Common methods for sample preparation involve microwave and hot plate techniques. For lead concentrations commonly present in the environment, interlaboratory variability ranges up to ~10–15%.[527] Because lead is ubiquitous in the environment, contamination of biological samples may produce false-positive values. Special collection tubes designed for the analysis of trace metals are the preferred containers for the collection of biological samples.

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Storage

Whole venous blood lead testing requires careful skin preparation, stainless-steel needles, and special lead-free (tan top) or trace element-free (dark blue top) containers (e.g., Vacutainer, Becton Dickinson Co.). The lead-free Vacutainer tubes should be used unless the batch of Vacutainer tubes is tested for lead contamination. Accurate measures of blood lead levels are labor-intensive and expensive. An alternative is rapid microblood lead method,[528] but the accuracy of this method as a screening procedure remains unclear because of its high false-positive rates (>50%).[529] Contamination of capillary specimens may result from lead-soiled fingertips; falsely low values also may occur. Compared with venous blood samples, capillary lead sampling is usually slightly less sensitive but comparably specific when standard techniques prevent contamination.[530] The difference between venous blood lead levels and capillary-venous lead levels is typically relatively small (<1 μg/dL);[531] however, elevated capillary-venous lead concentrations should be confirmed with an analysis of a venous blood sample.[395] The preferred anticoagulant is EDTA rather than heparin. Urine should be collected in acid-washed (nitric acid) propylene bottles washed thoroughly in ultrapure water.

Biomarkers

Blood

Whole blood lead level is the principal biomarker of lead exposure available in clinical laboratories. Whole blood remains the best practical biomarker to discriminate between individuals with different mean lead concentrations.[532] Blood lead is a biomarker of recent exposure (i.e., the last few months); the elimination half-life of lead in whole blood is ~1 month.[72] Time-integrated blood lead concentrations and K X-ray fluorescence are better measures of lead accumulation in the body compared with the blood lead level.[533] Blood lead does not necessarily distinguish between high acute lead exposure and low-level intermediate or chronic high-level lead exposure as a result of the variation of blood lead in response to recent lead exposure. Epidemiological studies document the release of lead from the skeleton and elevations of the blood lead levels in several physiological states including pregnancy, postmenopause, osteoporosis, and lactation.[534]

Erythrocytes contain ~95% of the lead in whole blood.[535] Venous blood is preferable to fingerstick blood because of potential contamination by environmental lead during the latter procedure. Although the whole blood lead concentration is a sensitive index of absolute changes in lead exposure at low blood lead concentrations, the relationship between whole blood lead and lead uptake by the lungs and gastrointestinal tract at high lead concentrations is nonlinear probably as a result of the saturation of lead binding in erythrocytes.[536] The relationship between serum and whole blood lead concentrations is also nonlinear. Basophilic stippling occurs in acute and chronic lead poisoning.

Whole Blood

Whole blood lead is a biomarker of recent exposure (i.e., the last few months), reflecting the exchangeable lead pool, primarily between blood and soft tissues; in the very young, a small, highly mobile bone lead compartment links blood lead and soft tissue lead concentrations.[537] There is substantial interindividual variation in the mobilization of lead from these compartments. Whole blood is an indirect marker of body lead burden in adults as a result of the storage of >90–95% of the total lead body burden in bones and teeth.[538] The slow release of long-term lead stores from the bones and saturation of erythrocytes lead binding sites by increasing blood lead levels produce a curvilinear relationship between bone lead stores and whole blood lead levels.

General Population Whole blood lead concentrations in infants begin increasing in late infancy with a peak of 18–36 months; blood lead levels decline as the age of the child increases.[395,539] Substantial elevations of blood lead levels may occur in children following immobilization as a result of the release of lead from stores in bone.[540,541] The blood lead concentration is relatively labile in young children compared with adults. In a hospital-based study of routine lead screening in Washington, DC, during 2001–2002, the upper limit (97.5%) of lead concentrations in blood samples from female and male infants aged 0–12 months was 4.7 μg/dL and 4.9 μg/dL, respectively, compared with 5.2 μg/dL and 5.6 μg/dL, respectively, for female and male children aged 1–2 years.[542] The mean blood lead concentration decreased in this study for children >10 years of age (4.4 μg/dL) compared with young children <2 years of age. Part of the stabilization with age results from the larger bone stores in adults that contribute relatively larger portions of the blood lead than external

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sources.[543,544] In urban children, the blood lead concentration is ~1–2 μg/dL higher in summer than winter, depending on the amount of lead in the environment.[545] The peak blood lead levels in the summer months usually result from outdoor activity linked to the ingestion of soil contaminated with flaking exterior paint.[546]

Blood lead concentrations in the general population including children have declined exponentially over the last several decades including the prevalence of elevated blood lead concentrations that exceed current recommendations (i.e., ≥5 μg/dL) for reducing the risk of neurobehavioral, cognitive, and developmental effects. The geometric median of blood lead concentrations in children aged 1–5 years based on the NHANES III 1999–2004 data was 1.9 μg/dL (95% CI: 1.8–2.0 μg/dL).[547] The prevalence of children with blood lead concentrations exceeding 10 μg/dL was 1.4%, an 84% decline since 1988–1991. In the United States NHANES IV study, the geometric mean lead concentration in the general US population declined from 1.66 μg/dL (95% CI: 1.60–1.72 μg/dL) in 1999–2000 (US NHANES III) to 1.12 μg/dL (95% CI: 1.08–1.16 μg/dL) in 2009–2010 (US NHANES IV).[35] The 95% CI of blood lead in children aged 1–5 years was 3.37 μg/dL (95% CI: 2.63–4.11 μg/dL) in 2009–2010 with 2.6% of the children >5 μg/dL.

In the general population, the whole blood lead concentration is higher in smokers than nonsmokers.[548] The use of alcohol is associated with blood lead concentrations above the mean concentration in the general population. Case reports suggest lead mobilization during periods of increased bone turnover may increase blood lead levels in adults with thyrotoxicosis[549] and women during menopause[550] or pregnancy.[534,551] A 12-year-old girl developed a peak blood lead level of 32 μg/dL during a period of rapid growth (10.42 cm over preceding 15 months).[552] Her BLL at the beginning of that growth spurt was 10 μg/dL. The bone turnover biomarker, osteocalcin, was elevated at 212 ng/mL (reference, 9–42 ng/mL) at presentation. No external lead source was discovered with all family members having normal BLL. She had a prior history of a BLL of 36 μg/dL at age 6 when she lived in a dwelling built in 1910.

Toxicity Biochemical effects usually occur sooner in children (e.g., ↓ δ-ALAD activity BLL <5–10 μg/dL) than adults with children more susceptible to lead encephalopathy at lower blood lead concentrations (e.g., BLL >80 μg/dL) than adults (BLL >100–150 μg/dL). Obvious clinical symptoms do not usually occur until blood lead concentrations exceed 60 μg/dL in children and 80 μg/dL in adults. Table 16.8 demonstrates the acute clinical effects commonly associated with specific blood lead concentrations in children; the correlation between blood lead levels and symptoms is approximate.

Table 16.9 lists adult symptoms frequently associated with chronic lead poisoning correlated to ranges of whole blood lead concentrations. Nonspecific subjective symptoms (e.g., fatigue, headache, sleep disturbances, constipation, abdominal pain) do not correlate well to elevated blood lead levels in workers.[553] The dominant clinical pattern of adults with chronic lead intoxication and whole blood lead levels >75–80 μg/dL involves gastrointestinal and musculoskeletal effects, whereas whole blood lead levels >100–120 μg/dL are associated with neurological dysfunction (depression, personality changes, confusion, seizures, mental status changes). Acute lead ingestion by adults may produce extremely high lead concentrations with primarily gastrointestinal symptoms. The acute onset of encephalopathy following chronic lead exposure does not usually occur in adults unless the blood lead concentration exceeds 100–120 μg/dL, primarily following blood lead levels >150 μg/dL.[37]

A 45-year-old schizophrenic developed abdominal pain, anemia, and gastrointestinal bleeding after ingestion of over 200 lead bullets.[63] The first serum blood lead concentration drawn 8 days after ingestion and before chelation was 391 μg/dL. A 23-month-old child died from acute lead encephalopathy and cerebral edema ~1 month after ingesting a leaded curtain weight; the BLL shortly before her death was 283 μg/dL.[362] A

TABLE 16.8. Clinical features associated with grades of acute lead toxicity in children.

Severity	BLL (μg/dL)	Age	Clinical Features
Mild	<50		Lethargy, irritability, behavioral changes, impaired cognition, mild fatigue, abdominal discomfort, anorexia, myalgias, paresthesias, poor coordination, reduced hearing
Moderate	50–70	1–5 years	Fatigue, decreased focus headache, tremor, arthralgias, muscle weakness, apathy, abdominal pain, nausea/vomiting, constipation, weight loss
Severe	>70–100	12–30 months	Altered consciousness (encephalopathy), seizures, coma, paresis, paralysis, colic (severe, intermittent abdominal cramps), blue-black discoloration of gingiva (lead lines)

Abbreviation: BLL = blood lead level.

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TABLE 16.9. Clinical manifestations of chronic lead toxicity in adults correlated to blood lead levels. Although most studies use the blood lead level, this test measures recent exposure; therefore, the ranges are approximate. Better measures of cumulative lead exposure include bone lead and cumulative blood lead index.

Clinical Severity	Adverse Effects	Blood Lead Level (μg/dL)
Mild	Mild fatigue, lethargy, irritability, moodiness, abdominal discomfort, sleep disturbances, apathy, decreased interest in leisure activities, reduced sperm count, myalgias, subclinical reduction in nerve conduction	>40–50
Moderate	Headache, insomnia, memory disturbances, metallic taste, abdominal pain, anorexia, constipation, anorexia, weight loss, myalgias/arthralgias, muscle weakness, decreased libido, mild anemia, nephropathy (↓ glomerular filtration rate)	>70–80
Severe	Encephalopathy – obtundation, delirium, seizures, coma, headaches, papilledema, cerebral edema, focal motor signs; peripheral neuropathy (foot/wrist drop), abdominal colic; anemia, renal dysfunction, sterility, impotence, depression, blue-black discoloration of gingiva (Burton's lead lines)	>100–150

47-year-old man developed arthritis and gastrointestinal symptoms (constipation, abdominal pain, weight loss) 8 years after sustaining a gunshot to his knee.[554] The serum lead concentration in a blood sample drawn during hospitalization was 148 μg/dL.

Postmortem Limited postmortem data suggest little postmortem redistribution of lead. In a cross-sectional study of 66 adults dying without evidence of lead contamination, the geometric means of the lead concentration in femoral and cardiac blood were 1.78 μg/dL and 1.87 μg/dL, respectively.[555] The mean postmortem interval was 13.3 hours with a maximum of 24.5 hours. Case reports associate fatal lead intoxication with the following postmortem blood lead levels: 95 μg/dL in a 17-year-old girl chronically ingesting lead-contaminated flour;[556] 92 μg/dL in 4¾-year-old girl with pica and fatal lead encephalopathy (111 μg/dL 4 days prior to death and chelation);[557] and 530 μg/dL in a 54-year-old woman dying of lead encephalopathy from a retained bullet.[558] In the latter case, the antemortem blood collected 5 days before death contained 510 μg Pb/dL. These case reports did not list the source of postmortem blood.

Plasma/Serum

The concentration of plasma lead is ~0.5% of the whole blood lead concentration. In a study of 959 healthy Italians, the mean whole blood (BLL) was 15.8 ± 1 μg/dL compared with 0.03 ± 0.002 μg/dL in plasma (PLL) from 228 healthy Italians; the mean BLL/PLL ratio was ~500.[559] However, the ratio is variable because the association between BLL/PLL ratio is curvilinear depending on the lead concentration; this ratio decreases with increasing PLL as the lead-binding sites in the erythrocytes become saturated, particularly at BLL >40–70 μg/dL.[252,560] Additionally, the plasma lead concentration may vary 2–4-fold at a specific whole blood lead concentration.[561] In a group of 20 active lead smelter workers, the plasma lead concentration ranged 0.02–3.7 μg/dL, whereas the whole blood lead concentration ranged from 0.9–93 μg/dL.[562] As measured in these studies by inductively coupled plasma/mass spectrometry, a whole blood concentration of 40 μg/dL was correlated to plasma lead concentrations of ~0.2 μg/dL (BLL/PLL = ~200). In a study of healthy adults exposed to environmental lead, the whole blood/plasma/ ratio ranged ~140–370.[563] Plasma lead concentrations are somewhat less than serum lead concentrations.[564] The whole blood/serum lead ratio in samples from 49 active lead workers ranged from 40–125[565] compared with 30 in healthy adults[566] and 45 in healthy adolescents.[567]

At high lead concentrations, the relationship between plasma lead and exposure/effect is more rectilinear than whole blood because the latter reflects erythrocyte lead concentrations more than bioavailable lead in tissues.[568] Additionally, the lead exposure/whole blood lead relationship becomes curvilinear at high lead concentrations, whereas the lead exposure/plasma lead concentration probably does not.

Lead within the red cell does not diffuse readily into the plasma, whereas plasma lead equilibrates easily with soft tissue and bone lead stores. Consequently, plasma lead concentrations reflect very recent exposure (i.e., few hours).[569] Plasma lead concentrations must be interpreted cautiously because hemolysis elevates plasma lead concentrations. Hemolysis can cause a 15–30% elevation of plasma lead concentrations without any visible signs of hemolysis.[570] Consequently, plasma lead concentrations should not be used as biomarkers of lead exposure in the general population where lead concentrations are low.[532]

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Erythrocyte Protoporphyrin (FEP, ZPP)

Several factors limit the usefulness of ZPP and FEP for lead screening including individual variability, poor specificity, low sensitivity at lower blood lead levels, and delayed response to changing blood lead levels.[571] Under steady-state conditions, whole blood lead levels >30–40 μg/dL correlate roughly to the ZPP and FEP concentrations; however, erythrocyte protoporphyrins are not sensitive screening tests below these levels. Neither the FEP nor ZPP offers a significant advantage over the BLL as a screening tool for lead toxicity; hence, whole blood lead levels remain the preferred screening test for excessive lead exposure. Predicting the whole blood lead concentration from the ZPP or FEP is difficult because of large individual variations and fluctuations in lead exposure.[572,573] Although the blood lead level is the most reliable measure of recent lead exposure, the FEP and the ZPP are better measures of soft tissue lead levels than whole blood lead because the FEP and ZPP depend on the lead concentration at the time of erythrocyte formation.[574] Consequently, these tests provide insight into the chronicity of current lead exposure and remain helpful to distinguish acute and chronic lead exposure, evaluate response to chelation therapy, diagnose lead re-exposure or false positive lead elevations, and aid in the diagnosis of lead poisoning in the absence of blood lead results. Both blood lead levels and either the FEP or ZPP are required to assess the body's lead burden because iron deficiency anemia causes an elevation of the FEP and ZPP. The ideal ratio of FEP to ZPP is 1:1.11 on a molecular formula weight basis, but this ideal ratio is altered by methodology, reagent purity, and extraction inefficiencies.

Following chronic lead exposure, the ZPP peaks after the whole blood lead levels; the ZPP concentration remains above reference values after whole blood lead levels decrease.[575] The ZPP and FEP help distinguish recent exposure (elevate whole blood lead, normal FEP and ZPP) from exposure more than several months in the past (normal whole blood lead, elevated ZPP and FEP). Elevations of the FEP and ZPP lag after an acute increase in the blood lead level by several weeks, up to 6–10 weeks, based on a study of lead workers returning to lead-contaminated environments after a strike.[576] Under conditions of continuing lead exposure, peak blood ZPP concentrations develop ~120 days after an acute increase in lead exposure; the ZPP returns to baseline levels ~3–4 months after an acute lead exposure ceased. Therefore, an elevation of blood lead with normal FEP or ZPP indicates recent lead exposure.

Free Erythrocyte Protoporphyrin (FEP) Lead inhibits the reduction of iron during the last step in the heme pathway by binding to sulfhydryl groups on heme synthetase (ferrochelatase), resulting in an accumulation of protoporphyrin in the erythrocyte. The FEP concentration correlates to lead exposure over the last 3–4 months based on an average erythrocyte survival time of 120 days. The FEP is not a sensitive test for acute lead intoxication; however, the presence of extremely high whole blood lead levels with normal FEP concentrations suggests acute lead poisoning. The FEP does not detect subjects with whole blood lead concentrations <25 μg/dL; an FEP concentration >35 μg Pb/dL demonstrated 73% sensitivity for detecting whole blood lead concentrations >25 μg/dL, but the sensitivity dropped to 8% for subjects with blood lead concentrations >15 μg/dL.[577] The Centers for Disease Control (CDC) recommends all children between 9 months and 6 years of age be tested for whole blood lead rather than FEP because of the insensitivity of FEP at whole blood lead concentrations <25 μg Pb/dL.[81] Therefore, the FEP is useful primarily to help determine the timing of acute lead exposure within the last 2–3 months and suggest false positive lead elevation.[578] However, a normal FEP does not exclude acute lead exposure and should be interpreted with other factors (e.g., time of exposure, source, clinical course). The FEP concentration rises exponentially at blood lead levels >40 μg/dL.[579]

Although iron deficiency and lead toxicity produce similar effects on the hematological system (microcytosis, anemia), lead intoxication can occur at high lead concentrations (>60 μg/dL) without the development of anemia.[580] At whole blood lead concentrations of 30 μg/dL, 60% of females, but only 10% of males, have an elevated FEP level. Following acute lead exposure, the peak elevation of the FEP in blood samples occurs several months after peak lead levels, despite the cessation of lead exposure.[581] A FEP concentration >35 μg/dL and a blood lead level >25 μg Pb/dL indicate excess lead exposure as well as the need for further medical evaluation and investigation of the lead source. Table 16.10 suggests the possible diagnoses associated with blood FEP >35 μg/dL and blood lead levels >25 μg/dL.

Zinc Protoporphyrin (ZPP) Zinc protoporphyrin is a metabolic product formed instead of heme under certain conditions (e.g., lead exposure, anemia). The final step in the heme pathway is the insertion of ferrous ion (Fe^{2+}) into the protoporphyrin XI molecule by ferrochelatase (heme synthetase). Lead inhibits ferrochelatase (acutely) and blocks the intracellular transfer of iron (chronically), resulting in the decreased

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TABLE 16.10. General interpretation of free erythrocyte protoporphyrin (FEP) and blood lead level (BLL). The clinical significance of these concentrations should be validated by symptoms, physical examination, and laboratory testing. (Adapted from Piomelli).[582]

BLL (μg/dL)	FEP <35 (μg/dL)	FEP 35–220 (μg/dL)	FEP >220 (μg/dL)
<25	Insensitive	Iron deficiency	Erythropoietic protoporphyria
25–59	Mild ↑ lead body burden	↑ Lead body burden	↑↑ Lead body burden
≥60	False +	↑↑ Lead body burden	Clinical lead toxicity

Abbreviation: BLL = blood lead level; FEP = free erythrocyte protoporphyrin.

transportation of ferrous ions into the mitochondria and the accumulation of protoporphyrin XI in the erythrocyte. Zinc chelates the free protoporphyrin to form zinc protoporphyrin *(*ZPP*)* in the red cell during the formation of the RBC in the marrow. Because the accumulation of ZPP occurs only in erythrocytes formed during the presence of lead in erythropoietic tissue, a lag occurs between excessive lead exposure and elevation of the ZPP, reflecting the maturation of erythrocytes.[583] Mean ZPP concentrations in whole blood are slightly higher (i.e., 10–15%) in women compared with men, and smoking does not affect the whole blood ZPP concentrations.[573]

During steady-state exposure to excessive amounts of lead, the ZPP does not reach steady-state values until the turnover of the entire population of erythrocytes (i.e., ~90–120 days). Consequently, this blood test measures the effects of lead on bone marrow averaged over the preceding 90–120 days.[584] Compared with whole blood lead levels, the ZPP requires more time to reach elevated concentrations after excessive lead exposure and longer to return to normal after cessation of lead exposure. Because chronic lead exposure causes higher bone lead stores and persistent increases in the blood lead level, the ZPP remains elevated longer compared with acute lead exposure. In a nonrandom clinical series of lead workers chelated with calcium disodium edetate for chronic lead intoxication (blood lead >60 μg/dL), the half-life of ZPP in whole blood was ~60–70 days following cessation of lead exposure.[585] The mean time for the ZPP to return to normal baseline concentrations was ~167 days.

Zinc protoporphyrin levels begin to increase at blood lead concentrations of 15–25 μg/dL in children, 20–25 μg/dL in women, and 30–40 μg/dL in men. In a study of 30 male lead-acid storage battery workers and 24 assembly workers during their initial year of occupational lead exposure, elevated ZPP concentrations (>40 μg/dL) were associated with steady-state BLL of ~30 μg/dL.[575] For blood lead concentrations <30 μg/dL, single ZPP concentrations do not predict the risk to an individual worker because of the presence of numerous confounding variables at blood lead concentrations <25–40 μg/dL.[586,587] An exponential increase in the ZPP concentration begins at blood lead levels of 40 μg/dL; almost all workers with blood lead levels >50 μg Pb/dL will have increased ZPP concentrations at steady state. The elevation of the blood ZPP begins later (i.e., several weeks >30–40 μg Pb/dL) than the increase in blood lead level following increased lead absorption; the ZPP is slower (e.g., several months) to return to normal after lead exposure ceases. Because the effect of lead on hemoglobin formation occurs before the classical symptoms of acute lead toxicity, the ZPP is a good biomarker for detecting elevated blood lead absorption before the effects of acute lead toxicity occur. Zinc protoporphyrin levels are more sensitive to the presence of high blood levels (>60 μg Pb/dL) in the presence of iron deficiency compared with the FEP.[580]

Delta-Aminolevulinic Acid Dehydratase Inhibition

Delta-aminolevulinic acid dehydratase (porphobilinogen synthase, ALAD) is the second enzyme in the heme biosynthetic pathway; this enzyme catalyzes the condensation of two aminolevulinic acid molecules to form porphobilinogen as displayed in Figure 16.2. The lead-induced reduction in ALAD activity and the activation of aminolevulinic acid synthetase by negative feedback cause an increase in δ-aminolevulinic acid in plasma, urine, and tissues. The inhibition of δ-aminolevulinic acid dehydratase is the most sensitive indicator of the lead effect with changes initially detected in plasma δ-aminolevulinic acid concentrations at blood lead levels near 5–10 μg/dL.[588]

The concentration of ALA in the plasma or whole blood is a more direct measure of the lead effects on the bone marrow than the urinary ALA. Plasma is a more practical sampling site for blood ALA compared with whole blood because ALA distributes primarily into plasma; additionally, plasma samples are more stable than whole blood in storage at 4°C (6 days vs. 3 days, respectively).[279,589] The plasma ALA concentration increases slowly at whole blood lead concentrations up to 40 μg/dL; then, plasma ALA concentrations increase

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rapidly up to whole blood lead concentrations up to 100 μg/dL.[588] The instability of δ-aminolevulinic acid dehydratase requires analysis within 24 hours of blood sampling, depending on storage conditions and temperature. This instability and the inability to separate moderate and severe lead exposures at blood lead concentrations >40 μg/dL limit the usefulness of the ALA as a screening measure of lead exposure.[574]

Urine

Lead

Analysis of urine lead concentrations is a less reliable biomarker of lead exposure than whole blood lead levels because of the technical difficulties with 24-hour samples, substantial individual variability in urinary lead excretion rates, variation in urine volume, and potential lead contamination of the urine containers. Urine lead concentrations do not correlate well to blood lead concentrations on an individual basis.[590] None of the specific correction methods (specific gravity, creatinine) for adjusting urine volume completely normalize the urine lead concentration for volume differences between urine samples.[591] Although urine lead concentrations reflect recent lead exposure, urine lead concentrations are not routine measures of lead exposure or a substitute for whole blood lead levels.[279] The amount of lead excreted in the urine depends on the total body burden of lead, urine volume, and renal function, as well as the extent of lead exposure. Daily adult lead excretion can range up to 500 μg (average, 300 μg) Pb, but the lead excretion by children is substantially less (i.e., 30 μg Pb daily).[23] The lead in a 24-hour urine sample from an individual without occupational or excessive environmental lead exposure is usually <85 μg/24-hour total urine volume.[592]

Delta-Aminolevulinic Acid Dehydratase Inhibition

Lead poisoning mimics the clinical features of acute intermittent porphyria with abnormal urinary porphyrin concentrations. Screening for the latter disease involves measuring urinary porphobilinogen and total porphyrin concentrations normalized to urinary creatinine during an acute intermittent porphyria attack. ALA dehydratase-deficiency porphyria is an extremely rare disease.

Urine aminolevulinic acid concentrations in adults initially increase near whole blood lead concentrations of 30–40 μg/dL.[593] At that concentration, 20% of patients have 70% inhibition of δ-aminolevulinic acid dehydratase activity. The use of the ratio of ALA/log urine creatinine concentration improves the screening efficiency of the urinary ALA.[594] Smoking is a confounding variable for the interpretation of urinary ALA. The urinary δ-aminolevulinic acid level in smokers is higher than in nonsmokers with similar blood lead levels in the range that produces enzyme inhibition.[595] Impairment of heme synthesis also develops in this range; however, the whole blood lead concentration is a more practical screening method. Although the measurement of ALAD activity is a sensitive hematological marker of lead exposure, the extensive inhibition of the enzyme at blood lead levels >30 μg/dL significantly limits the ability of this test to distinguish between moderate and severe lead exposure. Thus, the need for 24-hour urine collections and the urinary excretion of excessive amounts of ALA restrict the usefulness of urine ALA as a screening measure at whole blood lead levels >40 μg/dL.

Coproporphyrin

Coproporphyrinogen I and III are intermediate metabolites of the heme pathway that easily oxidize to their respective coproporphyrins (CP). Increased excretion of CP III occurs at least 2 weeks after lead exposure begins. Urinary CP concentrations are relatively insensitive biomarkers of lead effects because significant changes in the urinary concentration of CP begin at whole blood lead concentrations of 70–80 μg/dL.[279] Increased urinary CP excretion occurs in certain disorders of porphyrin metabolism (e.g., hereditary coproporphyria (CP III), congenital erythropoietic porphyria (CP I)).

Urinary measurements of lead, aminolevulinic acid, and coproporphyrins are either too insensitive or too variable to use as a screening technique for excessive lead exposure in children or adults.[285] The use of erythrocyte or urinary aminolevulinic acid synthetase is also too sensitive to small changes in lead concentrations and ethanol. Urinary coproporphyrin III concentrations do not correlate to whole blood lead levels, whole blood ZPP, or urinary δ-aminolevulinic acid concentrations.

Bone

Bone lead is a reliable measure of lead accumulation in the body because the skeleton stores the vast majority of the absorbed lead; however, there is substantial variation in the lead content and turnover of different bones. Cortical bone accounts for 80% of the bone mass, but turnover rates of lead are lower in cortical bone (tibia) than trabecular (calcaneus, patellar) bone. The half-life of lead in cortical bone averages ~10–20 years, whereas the half-life of trabecular bone averages ~5–10 years. In a study of active lead smelter workers, the estimated mean biological half-lives of lead in the calcaneus and

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tibia were 16 years (95% CI: 11–29 years) and 27 years (95% CI: 16–98 years), respectively, as measured by ^{109}Cd K X-ray fluorescence.[596] This study concluded that the precision of bone lead concentrations measured by X-ray fluorescence was greater in tibia than calcaneus bone. Lead has a stronger affinity for the organic portion of the bone matrix than the mineral component.[597] The lead concentration of active smelter workers was higher in the calcaneus (trabecular bone) than the tibia (cortical bone), suggesting more rapid lead absorption in trabecular bone.

Bone lead is a source of internal lead exposure during periods of increased bone activity (e.g., prolonged bed rest, pregnancy, lactation,[229] cisplatin chemotherapy, postmenopausal osteoporosis).[598] Some redistribution of lead from trabecular bone (patella, calcaneus) to cortical (tibia) bone may occur during chelation. Lead levels in trabecular bone tend to decrease more rapidly than in cortical bone following chelation probably as a result of greater turnover of lead in trabecular bone.[521] Case reports suggest that postmortem absorption of lead by skeletal bones may occur when the skeleton remains in contact with lead-containing coffins.[599] Analysis of bone lead in tibias from cadavers indicates higher bone lead concentrations in the mid-shaft than at the proximal and distal ends. In a series of nine cadavers (lead exposure history unknown), the tibial lead concentration ranged 3.1–27.9 μg/g bone *dry weight* with surface lead concentrations averaging ~5–8 μg/g higher than core lead concentration as measured by electrothermal atomization/atomic absorption spectrometry.[600]

The relationship between bone lead and blood lead varies depending on several factors including the analytic method, current employment status, and type of bone analyzed.[247,515] In general, models of lead transfer from bone to blood are limited by a lack of human data on transfer rates. A study of 776 participants in the US Normative Ageing Study indicated a significant but nonlinear association between bone lead and blood lead.[601] This nonlinear association was not modified by age or bone turnover as measured by urinary *N*-telopeptide. In a study of 81 lead smelter workers, bone lead was measured in the mid-tibia using K-X-ray fluorescence.[602] The slope of the blood lead compared with the tibial lead was 0.178 μg Pb/dL blood per μg Pb/g bone mineral. In a study of 77 male workers from a secondary lead smelter founded in 1942, linear regression analysis indicated that both trabecular lead concentrations (calcaneus, R^2 (proportion of variance explained) = 0.78) and cortical lead (tibia, R^2 = 0.80) measurements correlated to cumulative blood lead determinations.[603] Blood lead concentrations were available from 1968; the bone lead measurements were done in 1986 by *in vivo* K X-ray fluorescence.

Table 16.11 estimates the approximate correlation between bone and blood lead concentrations in adults based on K X-ray fluorescence and bone biopsies based on *wet weight*.

Hair

Hair lead concentrations are relatively poor predictors of blood lead concentrations, particularly at low hair lead concentrations (i.e., <12 μg/g). Case studies indicate that symptoms of lead toxicity do not correlate to the lead concentrations in hair;[604] additionally, hair lead concentrations are not sensitive screening tests for lead toxicity in children when compared with whole blood lead concentrations.[605] Properly washed and segmented hair samples give an approximate estimate of the history of lead absorption during the life of the hair shaft based on the average growth rate of 1 cm/month. However, interpretation of hair lead concentrations is difficult because of external lead contamination (e.g., hair dye/bleaches/permanents, lead water pipes), interindividual variability (hair type and texture), age,[606] washing and analytical technique,[607] source of the hair sample (e.g., proximal lead < distal lead), and residence.[72,608,609] In general, lead concentrations are higher in hair samples from urban residents than those from rural inhabitants unless a local source of lead exists.[610] Based on lead tracer studies, the appearance of lead in the hair shaft is delayed by ~35 days; however, the lead pattern in hair does not represent a simple

TABLE 16.11. Approximate correlation of blood and tibial lead levels in an adult. (Adapted from Wedeen).[510]

Exposure	Blood Lead Level (μg/dL)	Tibial Lead (μg/g wet weight)[a]	Tibial Lead/Calcium (μg/g wet weight)[b]
Low, continuous	<20	<20	<160
Moderate, occasional	20–50	20–60	260–480
High, persistent	>50	>60	>480
Massive, acute	>60	Time dependent	Time dependent

[a] *In vivo* tibial K X-ray fluorescence; [b] Transiliac bone biopsy.

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delay in the deposition of blood lead in hair.[611] Consequently, the lead pattern in the hair shaft is part of an intermediate pool in equilibrium with the blood.

Hair lead content varies substantially between various studies of the general population. The mean Pb concentration in hair samples from male and female patrons of a local barbershop in Port Arthur, Texas, was 26.7 μg/g (range, 10.6–191 μg/g) and 24.1 μg/g (range, 7.6–61 μg/g), respectively, as measured by flameless atomic absorption spectrophotometry.[612] In a study of hair samples from residents of New York City, the mean lead concentration was 12.2 μg/g (range, 2–155 μg/g).[613] Analysis of distal scalp hair from 126 male and 55 female customers of a Northeastern US barbershop demonstrated a mean lead concentration of 17.8 ± 2.17 μg/g and 19.0 ± 2.95 μg/g, respectively.[614] The samples were washed with carbon tetrachloride; bleached or dyed hair was excluded. The exact location of the residents (urban vs. rural) was not reported. The 90th percentile of lead concentrations in hair samples from a reference population of US residents without known lead exposure was 10.8 μg/g.[615] The median lead concentration in washed hair samples from 45 residents of Toronto was 16.9 μg/g with a range of 0.5–35 μg/g as measured by instrumental photon activation analysis.[616] In a study of distal hair samples from 250 subjects representing a cross-section of residents from a New Zealand city and surrounding rural areas, the geometric mean lead concentration was 128 μg/g hair (range, 2–360 μg/g hair).[617]

The precise relationship between blood lead and hair lead concentrations is not clearly defined. In a study of lead workers, a hair lead concentration of 70 μg/g (3 ng/cm) in the first 1-cm segment of hair samples corresponded to a whole blood lead concentration of ~60 μg/dL.[618] In another occupational study, 4 ng Pb/cm single hair corresponded to a blood lead concentration of ~60 μg/dL, whereas 3 ng Pb/cm single hair from a worker approximated a whole blood lead concentration of 40 μg/dL.[619] In a study of 21 children living with lead workers, the mean lead concentration in hair samples was 17 ± 14 μg/g with a range of 0.4–58.3 μg/g.[620] In a patient accidentally ingesting a lead-contaminated solution, the maximum blood lead concentration was 41.3 μg/dL 9.5 hours after ingestion.[621] Chelation with DMPS began 6 hours after ingestion. Hair samples analyzed for lead content on the day of admission and 3 months later were similar (2–5 ng/mg hair).

Teeth

Although the lead concentration in teeth is a potential biomarker for long-term lead exposure as a result of accumulation in the dentin and enamel,[622] the use of teeth as a biomarker requires validation of this biomarker against other biological and environmental matrices. Deciduous teeth are typically shed between 6–12 years of age; hence, this biomarker does not necessarily apply to ages outside this range. Determining the exact age is complicated, requiring sophisticated analytical methods and histological analysis.[623] Different sources of lead have unique isotopic signatures (e.g., relative short-lived ^{204}Pb and long-lived ^{206}Pb, ^{207}Pb, and ^{208}Pb); hence, isotopic lead concentrations vary with different populations. The application of stable isotope geochemical analysis to deciduous teeth allows the identification of lead sources during tooth formation.[25] Experimental studies in rodents indicate that the distribution of lead is not uniform as a result of the heterogenous distribution of lead between enamel and dentine depending in part on the time of lead exposure in relation to tooth formation.[624] In general, dentine contains 4–6-fold higher lead concentrations than enamel.[625,626] The circumpulpal dentine has particularly high lead concentrations compared with other areas of dentine. Some studies have not confirmed higher lead concentrations in the dentine of permanent teeth compared with enamel. In a study of 89 permanent teeth from rural Finnish subjects aged 8–67 years, lead concentration increased with age in the dentin (3.1 μg/g/10 years), but not in enamel; the mean Pb concentration in the enamel and dentine were similar in these subjects.[627] Table 16.12 displays the mean differences in lead concentrations between the 21 shed deciduous teeth of children living near heavy industries (i.e., oil refineries, fertilizer plants) and the 38 teeth of children living near light (i.e., hospital) industries in South Africa.[628]

Chemical concentrations in teeth are not necessarily stable over time; some exchange may occur between dentine lead and environmental exposures.[629] Lead concentrations are more stable in enamel than dentine; however, postmortem changes occur in enamel as a result of contact with lead in the burial site, particularly in the first 30 μm of enamel from ancient and modern teeth.[630] Isotopic lead patterns in teeth help identify the geographic origins of bones because of the incorporation of lead isotopes from ores specific to a geographic region; the isotopic lead patterns of teeth from US residents are unique in the world.[631]

EDTA Mobilization Test

In general, urine mobilization (challenge) tests are not reliable measures of metallic body burden or provide dependable data to determine appropriate therapy. These tests are rarely, if ever, clinically useful. Direct,

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TABLE 16.12. Mean lead concentrations in shed deciduous teeth from children residing near heavy and light industrial sources in Cape Peninsula, South Africa. (Data from van Wyuk and Grobler).[628]

Sample	Heavy Industry (ppm)	Light Industry (ppm)	Statistical Significance
Whole teeth	20,419	16,556	$P > 0.01$
Enamel	10,952	2,919	$P > 0.01$
Dentine	22,733	19,926	$P > 0.05$

noninvasive procedures (K X-ray fluorescence) rather than calcium disodium EDTA mobilization (provocation) tests are preferable measures of bone lead stores. Reasons for lack of provocation test utility include difficulty collecting 24-hour urine samples after administering intravenous tests, poorly established post-chelation reference ranges, concern over possible redistribution of lead stores, concerns regarding patient safety, and questionable efficacy of chelating patients with blood lead levels <45 μg/dL.[632] Calcium disodium EDTA mobilization tests increase urine lead concentrations in healthy patients without symptoms or suspected lead poisoning.[633] This test is unnecessary for a patient with high blood lead concentrations (>70 μg/dL in adults, >45 μg/dL in children) or a symptomatic patient requiring chelation.[634] Mobilization tests probably reflect the lead in soft tissues and, to a lesser extent, in the trabecular bone pool. Most of the body burden of lead resides in cortical bone; this pool equilibrates very slowly with blood, and little transfer of lead to the blood occurs following the mobilization test.[635]

Little diuresis of lead occurs in children with blood lead levels <25–30 μg/dL.[636] In a study of 178 $CaNa_2EDTA$ mobilization tests, a positive test was rare in children <3 years of age with a blood lead <35 μg/dL and children >3 years of age with a blood lead <30 μg/dL.[637] The amount of lead removed by chelation with $CaNa_2$ EDTA from children with blood levels between 25–45 μg Pb/dL correlates positively with the initial blood lead level; there are inadequate clinical data to confirm the efficacy of administering $CaNa_2$ EDTA to these children.[638] Iron deficiency decreases the response to the lead mobilization test in the moderate toxicity range (25–40 μg Pb/dL).[639] Renal dysfunction alters the pharmacokinetics (e.g., ability to chelate lead, $CaNa_2$ EDTA-lead distribution or excretion, blood-lead distribution) of the $CaNa_2EDTA$-lead complex and lead.[640] The mobilization test may underestimate total body lead stores in patients with lead nephropathy.[641] Acute febrile reactions occur following $CaNa_2EDTA$ therapy, but complications following the single administration of $CaNa_2EDTA$ are very rare.[642]

$CaNa_2EDTA$, 1 g or 500 mg/m^2, is diluted in 5% dextrose in 0.45% NaCl, 250–500 mL, and administered intravenously over 1–2 hours. A painful but practical alternative is to deliver the undiluted dose intramuscularly with procaine. A 24-hour urine specimen is collected for lead concentration in lead-free containers. A 6-hour urine collection has better specificity but less sensitivity than the 24-hour collection.[643] A 3-hour urine test for lead is not an accurate predictor of the 24-hour urine lead level after the administration of $CaNa_2EDTA$.[644] The lead excretion ratio is the total urinary lead excreted in μg Pb/mg $CaNa_2EDTA$ administered. A ratio >1 *suggests* the possibility of chelatable lead. In a study of lead workers given $CaNa_2EDTA$, the plasma lead concentration at 2-hour postinjection correlated well ($r = 0.74$) with the amount of urinary lead excretion over 24 hours.[645] A lead excretion ratio (urine μg Pb/mg $CaNa_2EDTA$) exceeding 0.6[646] or a urinary lead concentration >1.0 μg Pb/mL[647] *suggest* chelatable lead in children. The difficulty of administering $CaNa_2EDTA$ and interpreting results (incomplete urine collection (i.e., creatinine clearance <90 mL/min/1.73 m^2 body surface area), efficacy) seriously limits the use of $CaNa_2EDTA$ mobilization test for the determination of chelatable lead in children.

Abnormalities

Blood

Lead toxicity produces hematological abnormalities primarily in erythrocytes as a result of the inhibition of hemoglobin synthesis and increased erythrocyte destruction. Common laboratory abnormalities during lead poisoning include normocytic or microcytic anemia, basophilic stippling, and renal/liver dysfunction. In adults, anemia is more common during acute lead toxicity than chronic inorganic lead intoxication. The microcytic, hypochromic anemia resembles iron-deficiency anemia; the anemia of lead toxicity is not usually severe, even during severe acute lead intoxication. Less often, normochromic, normocytic anemia occurs with reticulocytosis. The inhibition of

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δ-aminolevulinic acid dehydratase begins at blood lead levels of 10–20 μg Pb/dL; this inhibition is almost complete at 70–90 μg/dL.[648] In lead workers, the hemoglobin level does not correlate well to the blood lead level; most cases of lead-induced anemia occur at blood lead levels chronically exceeding 80 μg/dL.[649] Consequently, lead workers with anemia and blood lead levels <70–80 μg/dL should be carefully screened for causes of anemia unrelated to lead exposure. Basophilic stippling is an uncommon manifestation of chronic lead toxicity except during severe lead toxicity; however, the presence of basophilic stippling along with ringed sideroblasts and reticulocytosis is highly suggestive of lead intoxication. Other causes of basophilic stippling include sideroblastic anemia, arsenic or benzene poisoning, aniline toxicity, and various thalassemias.[650]

Changes in uric acid concentrations are usually subclinical. Hyperuricemia occurs primarily in patients with severe lead toxicity and lead-induced nephropathy. Although uric acid levels increase with increasing lead accumulation, there is no direct correlation between low-level lead exposure and gouty arthritis based on a retrospective cohort study of 777 middle-aged and elderly men with only environmental lead exposure.[651] There was a positive association ($P = 0.02$) between patellar bone lead and uric acid concentrations, but the association between blood lead and gouty arthritis was not statistically significant. The lead exposure of this male cohort was comparable to that of the general population as determined by a mean current blood lead concentration of 5.9 μg/dL.

Little data are available in humans on the effect of chronic low lead levels on the immune system. *In vitro* data suggest that exposure to lead exceeding 60 μg/dL may depress phagocytosis and chemotaxis of human neutrophils.[652,653] A study of lead-exposed workers revealed a statistically significant decrease in chemotaxis but not in phagocytosis.[654] The clinical significance of these changes remains unclear.

Imaging Studies

Conventional Radiography

Potential radiographic abnormalities associated with lead poisoning include metaphyseal densities at the ends of long bones, paint chips, and lead foreign bodies. The flat plate (plain film) of the abdomen is significant only if positive, reflecting recent lead ingestion (24–36 hours). Of 90 children in St. Louis, Missouri, with moderate to severe lead toxicity, 26% of the children with BLL >55 μg/dL had radiographic evidence of paint chips, whereas only 1% of children with BLL <55 μg/dL had positive abdominal X-rays for lead.[44] The width and density of lead lines on long-bone radiographs (wrist, knee) reflect a chronic exposure. These opacities represent dense zones of calcium rather than actual lead deposition, most commonly appearing in children aged 9 months to 5 years during the age of rapid bone growth. The development of long-bone opacities requires 4–8 weeks of heavy exposure (BLL >40–50 μg/dL).[646] Radiographs are insensitive screening tests for lead toxicity because the tests are helpful only in rare circumstances when they are positive. Radiographs demonstrate lead lines in metaphyseal ends of fast-growing bones of children (knees, wrists) with chronic plumbism typically at blood lead levels >70 μg/dL; however, these boney abnormalities may occur at BLL <50 μg/dL.[655] These bands represent failed remodeling of calcified cartilage in the zone of provisional calcification and primary trabeculae of bone rather than lead deposition. Radiographic findings in neonates exposed to lead *in utero* include dense cranial vault, delayed skeletal and deciduous dental development, and lead lines.[656]

Computerized Tomography

Classic findings of lead arthropathy include joint space narrowing, intact bone density, and intraarticular speckled lead deposits occasionally creating a lead arthrogram. Nonenhanced CT imaging and plain radiographs demonstrate intraarticular metallic material; however, CT is superior to plain radiographs for evaluating joint effusions, synovitis, and other soft tissue abnormalities.[657] Post-gadolinium MRI is an alternative to detect synovial inflammation and bone marrow edema. Several case reports[658,659] and case series[660] suggest an association between intracranial calcification and chronic lead poisoning, particularly in the cerebellum; however, many of these patients had multisystemic diseases and the etiology of the calcifications is unclear.

Magnetic Resonance Imaging

There are limited data on the MR scans in patients with lead encephalopathy with varying lesions in the deep gray matter, subcortical white matter, insula, pons, and cerebellum.[661] A 41-year-old man with short-term memory loss, poor balance, apathy, and a blood lead level of 161 μg/dL had bilateral symmetric hyperintensities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images in the occipital lobes; these lesions affected primarily the gray matter, gray-white matter junction, and the subcortical white matter.[662] Similar lesions occurred in the frontal, temporal, and parietal regions. T1-weighted images were hypointense. After chelation, these lesions mostly resolved with the exception of some focal subcortical white matter

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lesions in the occipital lobe. Diffusion tensor imaging may be more sensitive than T2-weighted images for the detection of early changes in axonal integrity and myelination in the white matter of the cerebral cortex, hippocampus, occipital lobe, and cerebellum.[663]

Nerve Conduction

Lead toxicity produces a classical motor neuropathy characterized by reduction in the conduction velocity of the fast, large, myelinated fibers in the motor nerves of the upper (median, ulnar, radial) and lower extremities (peroneal). These effects are reversible following short-term lead exposure (several months), but continuous exposure for 6–23 months to high lead levels may produce irreversible changes.[664] In a case-control study of battery workers and referents, mild asymptomatic slowing of median motor/sensory nerve conduction, distal latency, and amplitude occurred in the group chronically exposed to 40–50 μg/dL; ulnar nerve conduction was minimally affected.[665] In contrast to sensory nerve changes, asymptomatic slowing of the maximal motor nerve conduction velocity (large myelinated fibers) occurred in lead storage battery workers with blood lead concentrations >60–70 μg/dL.[666,667] Motor conduction velocities and distal latency may be significantly prolonged or delayed without clinical evidence of lead toxicity at blood lead concentrations <70 μg/dL; sensory conduction velocities are usually normal or slightly reduced.[668,669] Some,[668,670,671] but not all,[672] studies of asymptomatic, lead-exposed workers suggest decreased nerve conduction in the small motor fibers (e.g., ulnar nerve, peroneal) is a sensitive measure of lead-induced peripheral neuropathy at blood lead concentrations ~50 μg/dL.[673] Lead exposure does not usually affect the amplitudes of the sensory compound nerve action potential (CNAP) or the motor compound muscle action potential (CMAP).[674]

The threshold for the lead-induced changes in peripheral nerve conduction occurs in the range of 30–50 μg/dL in some,[675,676] but not all,[666,677] studies of workers developing blood lead levels in this range following chronic lead exposure. In a group of asymptomatic lead smelting workers with a geometric mean blood lead concentration of ~40 μg/dL, no consistent abnormalities of nerve conduction were detected.[678] Although there were statistically significant differences between the control and the exposed groups for measures of motor and sensory nerve conduction as well as distal latency, the individual differences were within the normal range; the study detected no consistent correlation between blood lead concentrations and the neurophysiological measurements. A 2-year prospective study of lead battery workers suggested some reduction in median motor nerve velocity occurs in workers with blood lead concentrations >30 μg/dL, when compared with workers with blood lead concentrations <30 μg/dL.[679] However, there was a high dropout rate. The study contained an inadequate number of workers with a duration of employment >2 years and blood lead concentrations >30 μg/dL to determine the long-term effect of chronic lead exposure exceeding this value. A study of children exposed to lead near a smelter suggested the threshold for changes in the maximal motor nerve conduction velocity in children begins near blood lead concentrations ~30 μg Pb/dL.[680] For the detection of early changes in the peripheral nervous system, alternate electrophysiological tests to detect slowed nerve conduction include electromyography (neurogenic polyphasic waves, spontaneous activities) and prolonged distal motor latencies (e.g., median nerve).[681] However, there are few data to determine the clinical significance of changes in these electrophysiological tests.

Limited data suggest asymptomatic reduction in somatosensory evoked potentials, brainstem evoked potentials, visual evoked potentials, and event-related potential (i.e., P300) in workers with blood lead levels ~30–50 μg/dL;[682,683] however, the clinical significance of these changes remains unclear. A study of lead battery workers detected a threshold effect for vibration perception threshold ~30 μg Pb/dL based on 5-year cumulative measures of blood lead concentrations but not on current blood lead concentrations.[684] Case-control studies suggest that lead exposure may cause sensory-neural hearing loss[685] and asymptomatic reduction in neural transmission;[686] environmental noise probably contributes significantly to this loss.[687]

Neuropsychological Tests

Adults

Although exposure of workers to lead frequently is associated with abnormalities on neuropsychological testing, interpretation of the meaning of these changes is complicated by the complexity (confounding variables, selection and examiner bias, multiple tests, standardization of tests, large intersubject variability in test scores, pre-exposure test values, publication bias) created by comparing published test results between different groups. Most neuropsychological tests measure multiple, complex functions; furthermore, most studies use current blood lead (i.e., half-life ~1 month) rather than cumulative measures of chronic lead exposure (e.g., tibial lead, cumulative blood lead index). The Digit Symbol measures visuospatial processing, processing speed, working memory, and attention, whereas

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the Stroop test assesses selective attention. The most common domains potentially associated with blood lead concentrations are manual dexterity (e.g., Pursuit Aiming, Purdue Pegboard), visuomotor skills (e.g., Grooved Pegboard, Digit Symbol), psychomotor speed (e.g., simple reaction time), and verbal memory (e.g., Digit Span). To date, cross-sectional studies on lead workers suggest blood lead concentrations are better predictors of neurobehavioral performance than tibial lead concentrations.[688] The lack of correlation between cumulative exposure data and neurobehavioral test performance, the lack of preexposure data, and the inconsistencies between studies limit definitive conclusions regarding the effect of chronic lead exposure on specific neuropsychological functions.[689] A 22-year follow-up study of 83 lead-exposed and 51 nonexposed workers reported a 17% greater loss in total cognitive score than nonexposed workers during this period.[690] The most consistent association was between peak tibia lead levels and spatial ability, learning/memory, and total overall cognitive score. Multiple regression analysis detected a statistically significant difference ($P = <0.01$) for spatial abilities, executive function, and total cognitive score of the exposed workers based on peak tibial lead level after adjustment for age, education, and income; there were significant differences between spatial and general intelligence scores in lead-exposed workers compared with the nonexposed workers.

Reviews of cross-sectional testing of lead workers demonstrate few unequivocal differences in neuropsychological scores between lead workers with blood lead concentrations <70 μg/dL and control groups.[691,692] A meta-analysis of workers with chronic lead exposure resulting in blood lead concentrations 40–70 μg/dL demonstrated reduced scores on Block Design and Logical Memory of the exposed workers.[693,694] There was a tendency for reduced scores on other tests (Similarities, Trail Making A and B, Digit Symbol, simple reaction time) examined in this meta-analysis, but the effects were inconsistent across the studies and the size of the effects was generally small. This meta-analysis excluded 10 of 22 studies published between 1977 and 1997 because of inadequate exposure data or methodological flaws. The meta-analysis scores indicated impairment of central information processing, especially for visuospatial organization and short-term verbal memory. Although the size of these effects was relatively small compared with population norms, the decrement in test scores was relatively large compared with age-related changes in test scores. Not all studies using Block Design detected a significant difference between workers exposed to lead and controls.[695] Block Design is a performance subtest of the Wechsler Adult Intelligence Scale-Revised that uses perceptual organization, visuoconstructive abilities, and visuospatial organization to measure the speed of learning new responses. Studies on lead workers demonstrated an effect of lead exposure as measured by current blood lead concentration on reaction time and dexterity as well as on visuomotor functioning and verbal memory.[696,697] Cross-sectional studies of lead workers suggest reduction of test scores of visuomotor functions (Grooved Pegboard, Digit Symbol) occurs more commonly than deterioration of cognitive function. Measures of psychomotor speed and dexterity (Trail Making A and B) were inversely related to blood lead concentrations in some studies.[698] Overall, intelligence, long-term memory, common sense, and logical reasoning demonstrate minimal decline.[699,700]

Digit Span is a measure of auditory memory. The correlation between Digit Span Forward, a relatively pure measure of attention, and blood lead concentrations is inconsistent.[698] Digit Span Backward is a more complex skill of working memory; this test is usually unaffected by blood lead levels in adults. A cross-sectional study in Andean children suggested an inverse association between blood lead level and Digit Span scores.[701]

Cohort studies and case series associate subclinical effects in some scores on personality, memory, learning, choice reaction time,[702] verbal concept formation, psychomotor or visuomotor function, and motor coordination with chronic occupational exposure to lead defined by blood lead concentrations of 50–69[703,704] and 40–60 μg/dL.[705] The latter occurred in the absence of abnormalities in the peripheral nervous system. Impairment of neuropsychological tests is unusual below blood lead levels of 40 μg/dL;[693] reducing the blood lead below 40 μg/dL is associated with improvement in verbal memory scores in some studies of lead workers.[706] A study of workers with high exposure to lead (blood level 41–80 μg Pb/dL) indicated cognitive impairment primarily involved sensory motor speed and certain aspects of memory, whereas processing function and long-term memory were well preserved.[707] A study of 80 active lead smelter workers (mean BLL = 26 μg/dL; range 13–43 μg/dL; mean bone lead = 41 μg Pb/g bone mineral) measured the effect of lead on measures of verbal memory (Rey Auditory Verbal Learning Test, Verbal Paired Associates).[695] The fundamental processes of verbal memory involve acquisition (memory span, learning increment over time) and retention of information (storage, retrieval). All of the variance in verbal memory resulted from differences in measures of lead dose intensity (blood lead, TWA) rather than measures of cumulative lead dose (bone lead, working lifetime integrated blood lead). In a cross-sectional

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study of 256 English-speaking lead smelter workers, the average age was 41 ± 9.4 years and the duration of employment was 17 ± 8.1 years.[708] The working lifetime weighted average blood lead was 39 ± 12.3 μg/dL; the working lifetime integrated blood lead index was 728 ± 434.4 μg-year/dL. As determined by the Rey Auditory Verbal Learning Test, measures of chronic lead exposure, but not current blood lead levels, were associated with impaired storage and retrieval of verbal information. There was no impairment of immediate memory span or verbal learning.

A small cross-sectional study of 17 gun-metal foundry workers detected a significant reduction only on the picture completion scale of the 5 performance scales of the Wechsler Adult Intelligence Scale at blood levels 40–64 μg/dL; these reductions resolved after chelation.[709] A cross-sectional study of 222 workers exposed to inorganic and organic lead revealed the most common abnormalities in neuropsychological testing occurred in manual dexterity and verbal memory and learning.[710] Although some studies attribute abnormalities on neuropsychological testing to peripheral sensorimotor deficits, no consistent relationship existed in this study between lead exposure and measures of peripheral nervous system function.

Little, if any, decrement in psychomotor performance (e.g., reaction time) occurs at blood lead levels <60 μg/dL.[699] Studies of personality and mood of lead-exposed workers suggest an increased prevalence of depression, fatigue, anxiety, irritability, and interpersonal problems.[704,705,711] Use of common neuropsychological tests (e.g., Profile of Mood States (POMS)) is complicated by the lack of normative data that correlates to groups of workers rather than psychiatric patients. Factor analysis did not support the use of the six separate POMS sub-scales (anger, confusion, depression, fatigue, tension, vigor) in a group of lead-exposed workers (mean current BLL, 28 μg/dL).[712] Although some studies suggest heavy, chronic lead exposure may cause personality changes and alterations of mood, neuropsychological studies of workers exposed to low lead concentrations are not well controlled for confounding variables (age, education, alcohol use, working conditions, motivation). Therefore, a causal relationship between these neuropsychological symptoms and exposure to low-level lead remains unconfirmed.

Children

There is no characteristic lead-induced neurodevelopmental pattern. In a study of 756 Indian children aged 3–7 years, comparisons of outcome Z-scores to assess the relationship between log-blood lead and the different behavioral domains suggested an association with anxiety, social problems, and ADHD, particularly with global executive function ($\beta = 0.42$; $P < 0.001$).[713] In the New Zealand observational and correlational 1972–1973 birth cohort study of 1,037 children, a population-representative sample of 565 children had BLL at age 11 years and were studied at age 38 years; the mean BLL at 11 years was 10.99 ± 4.63 μg/dL (range, 4–31 μg/dL) with 94% above the current lead standard of 5 μg/dL.[413] The mean IQ scores between these two samples were statistically different (tested, 101.01; not tested, 98.91). After adjustment for maternal IQ, childhood IQ, and childhood socioeconomic status, each 5 μg/dL-higher childhood BLL was associated with cognitive decline characterized by lower scores on overall adult IQ (mean = 1.61 IQ points), perceptual reasoning (mean = 2.07 points), and working memory (mean = 1.26 points); verbal comprehension and processing speed were not statistically different.

Renal Function

The serum BUN and creatinine increase only after the loss of ~2/3 of the kidney function. The lysosomal enzyme, *N*-acetyl-β-D-glucosaminidase (NAG), leaks from the brush borders of the proximal renal tubules early after injury to the renal tubules. Retinol-binding protein (a major α_1-microglobulin) is a low-molecular-weight protein that is also a sensitive indicator of early renal injury. This protein does not hydrolyze in the urine like β_2-microglobulins. A study of lead refinery workers indicated significant elevations of urinary NAG in workers with blood lead levels >80 μg/dL.[714] A cross-sectional study of 22 auto mechanics also associated elevated urinary NAG with blood levels of 30–69 μg/dL.[715] In this group, β_2-microglobulin concentrations were not correlated with blood lead levels; there was no significant decrement in creatinine clearance noted in the workers. Increased urinary NAG concentrations may be more closely related to the integrated blood lead level than BLL.[716]

HEALTH SURVEILLANCE

Risk Assessment

The estimated daily intake of lead corresponding to blood lead concentrations of 10 μg/dL in children and pregnant women and 30 μg/dL in adults includes the following: 60 μg for children ≤6 years old, 150 μg for children ≥7 years old, 250 μg for pregnant women, and

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750 µg for adults.[717] In 2012, the CDC lowered the level of concern for lead in the blood of children ≤5 years old to 5 µg/dL. The CDC also introduced the population-based blood lead reference value (BLRV) to identify children with the highest blood lead levels; using the National Health and Nutrition Examination Survey (NHANES) data, this level was based on the 97.5% of the blood lead distribution in US children aged 1–5 years. The BLRV is a guide to prioritize primary prevention of lead exposure and determine the need for medical and/or environmental interventions rather than a toxicity threshold or health-based standard. In 2021, the BLRV was lowered from 5 to 3.5 µg/dL. There is a negligible risk of reproduction or teratogenic effects from the intake of lead at concentrations currently in the general environment.[51]

Children

Available models estimate blood lead concentrations in adults and children. These models are not interchangeable because adults and children differ in exposure pathways and pharmacokinetic parameters that determine the distribution of lead in the body.[718] The Integrated Exposure Uptake Biokinetic (IEUBK) Model was developed by the US EPA to predict the risk of blood lead concentrations >10 µg/dL in children <7 years old as a result of exposure to environmental lead sources.[719] This model was designed to estimate the average blood lead concentration for an entire population rather than a specific child based on assumptions regarding default media concentrations and media intake rates over an exposure period >3 months, as noted in Table 16.13. The recommended default values for lead in air and drinking water are 0.1 µg/m^3 and 4 µg/L, respectively, whereas site-specific data should be used for lead concentrations in soil and dust. This model is not designed to correlate environmental exposure to blood lead concentrations >30 µg/dL.

Adults

Estimation of blood lead concentrations in adults from environmental sources (air, water, soil/dust) involves calculating the biokinetic slope factor relating total uptake of lead in adults to blood lead. Equation 16.1 defines the estimated blood lead concentration (PbB) based on the baseline blood lead concentration ($PbB_{basline}$), the biokinetic slope factor (BSF), and the uptake of lead from sources in air (C_a), soil/dust ($C_s + C_d$), and water (C_w).

TABLE 16.13. Guidelines for the median lead intake when using the EPA integrated exposure uptake biokinetic model. (Based on The Technical Review Workgroup for Lead).[719]

Age	Daily Lead Intake
Soil/dust[a]	
0–1 year	0.085 g
1–4 years	0.135 g
4–5 years	0.100 g
5–6 years	0.090 g
6–7 years	0.085 g
Air[b]	
0–1 year	2 m^3
1–2 years	3 m^3
2–5 years	5 m^3
5–7 years	7 m^3
Drinking water[b]	
0–1 year	0.2 L
1–2 years	0.5 L
2–3 years	0.52 L
3–4 years	0.53 L
4–5 years	0.55 L
5–6 years	0.58 L
6–7 years	0.59 L
Diet[c]	
0–1 year	5.53 µg
1–2 years	5.78 µg
2–3 years	6.49 µg
3–4 years	6.24 µg
4–5 years	6.01 µg
5–6 years	6.34 µg
6–7 years	7.00 µg

[a] Default ratio for soil/dust ingestion is 45:55, default values recommended; [b] Default values recommended; [c] Site-specific data recommended to augment estimates of dietary intake.

$$PbB = PbB_{basline} + (BSF)(Uptake_{air} + Uptake_{water} + Uptake_{soil/dust}) \quad \text{(Equation 16.1)}$$

where:

$$Uptake_{air} = (A_a)\,(V_a)\,(C_a)$$
$$Uptake_{water} = (A_w)\,(I_w)\,(C_w)$$
$$Uptake_{soil/dust} = (A_{s/d})\,(I_{s/d})\,[(t_0)(C_s) + (t_i)(C_d)]$$

The parameters t_0 and t_i represent the relative amount of time spent in contact with soil (exterior) and dust (interior). The sum of t_0 and t_i is up to 1 depending on the fraction of time spent on the site where the soil and dust samples were taken. Table 16.14 defines the parameters used in Equation 16.1. The average absorption factor for lead in adults is ~8%,[720] whereas

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TABLE 16.14. Adult parameters for the calculation of blood lead concentrations from environmental exposure. (Based on The Technical Review Workgroup for Lead).[719]

Symbol	Description	Value
$A_{s/d}$	Soil/dust absorption	0.08
A_w	Water absorption	0.08
A_a	Pulmonary absorption	0.32
$I_{s/d}$	Soil/dust ingestion	0.02 g/day
I_w	Water ingestion	2.0 L/day
V_a	Ventilation rate during waking hours	20.0 m^3/day
BSF	Biokinetic slope factor	0.375 µg/dL per µg/day

the average daytime ventilation rate averaged over all activities except sleep is ~20 m^3 (0.83 m^3/hour) for men and 16 m^3 (0.67 m^3/hour) for women.[721]

Environmental Monitoring

Residential

House dust

House dust is a heterogeneous mixture of mineral and organic components with various sizes, densities, and shapes. In preschool children, lead-contaminated dust is a major determinate of lead exposure that originates primarily from lead-based paints, soil, and street dust. The US Centers for Disease Control and Prevention (CDC) reduced guidelines for blood lead in children from 10 to 5 µg/dL because of lack of evidence for a safe threshold of lead exposure in children.[722] Renovation of older houses with lead-based paint is a major source of residential lead dust.[723] The estimated percentage of older houses built before 1977 with lead hazards is as follows: before 1940, 68%; 1940–1959, 43%; and 1960–1977, 8%.[724] The relative contribution of each of these lead sources depends on local natural and anthropogenic sources, the age and condition of the housing, and the level of urbanization.[725] In 1995, the US EPA and the US Department of Housing and Urban Development issued interim guidelines regarding surface lead concentrations in public housing following remediation work based on lead loading of surface dust as measured by wipe samples.[726] Lead loading is the amount of lead in a given area (weight/surface area); Equation 16.2 calculates the absolute amount of lead available for absorption using the lead concentrations and amount in a specific area.

$$\text{Lead loading } (\mu g/m^2) = \text{lead concentration } (\mu g\ Pb/g\ dust) \times \text{amount of dust in defined area } (g\ dust/m^2) \quad \text{(Equation 16.2)}$$

High lead loading indicates a potential hazard, assuming the area sampled represents a relatively large portion of the living space of the inhabitants. High lead concentrations in dust are hazardous only if the total amount of dust is large. Dust wipe methods that measure lead loading (µg Pb/surface area) correlate more closely to blood lead concentrations of children than dust vacuum methods that measure dust lead concentration (µg Pb/g dust).[727] In general, the fine dust fractions (<10 µm) contain higher lead concentrations than more coarse fractions; there is some variation between wipe sample techniques based on differences in the collection of large lead particles.[728] Window wells are reservoirs for lead in the environment because the lead concentrations of dust are several orders of magnitude higher in window wells than in other accessible household areas.[729] Lead concentrations in dust from inaccessible surfaces (e.g., light fixtures, cabinets) may be significantly higher than in accessible areas in the living space; lead in these inaccessible areas does not correlate well to blood lead concentrations in children.[730]

In 2001, the US EPA issued a final regulation under Section 403 of the Toxic Substances Control Act (TSCA) that established standards for lead-based paint hazards in pre-1978 houses and child-occupied facilities.[731] As defined by US statutes, lead-based paint contains lead concentrations ≥1 mg/cm^2 or 0.5% (5,000 ppm) by weight. The current dust-lead hazard standards are 40 µg/ft^2 for floors (carpeted and uncarpeted), 250 µg/ft^2 for interior window sills, and 400 µg/ft^2 for window troughs based on a weighted average of all wipe samples. The US Consumer Protection Safety Commission's limit on lead in paint is 90 ppm. These standards were formulated to minimize the risk of children with blood lead concentrations >10 µg/dL; analysis of exposure pathways indicates that children's blood lead concentration directly correlates to floor lead concentrations, whereas the effect of sill lead concentrations is indirectly mediated by floor lead concentrations.[732] Carpets and rugs are large potential sources of lead-contaminated dust in the microenvironment of children.[733] The hazard standard for soil is 400 ppm by weight as an average in bare soil samples from play areas and an average of 1,200 ppm in bare soil samples from other areas. The endpoint for the risk analysis used to formulate these standards was a 1–5%

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probability of a 1–2-year-old child having a blood lead concentration >10 μg/dL.

Water

The current WHO European standard for lead in drinking water is 10 μg/L. The Maximum Contaminant Level (MCL) for lead formulated by the US EPA is 15 μg/L. Assuming that contaminated drinking water contributes 7% of the lead burden of an adult and 15% of the lead burden of children, water concentrations of 100 μg Pb/L produce an average blood lead level of 24 μg Pb/dL, whereas the reduction of water lead concentrations to 10 μg/L decreases the population mean <15 μg/L blood.[734] Practical measures to reduce the absorption of lead from drinking water include increasing the pH of the water, using fully flushed water, and drinking from the cold faucet. Treatment technologies for diminishing lead in water distribution systems involve coagulation/filtration, ion exchange, reverse osmosis, and lime softening.

Soil

For each increase of 100 ppm lead in surface soil *above* 500–1,000 ppm lead, the mean whole blood lead level of a child exposed to that soil increases ~1–2 μg/dL.[735,736] The US EPA estimates that the blood lead level of a child increases 3–7 μg/dL for each 1,000 ppm lead increment in surrounding soil; however, the actual increase depends on a number of factors including the chemical form of lead, the particle size, access to soil, behavior patterns, the presence of vegetation (ground cover), personal and household hygiene (handwashing, wet mopping), and other factors.[81] For a soil lead concentration of 1,000 ppm lead, a child is unlikely to have a blood lead level exceeding 24 μg/dL unless the child plays outside and/or lives with a household smoker.[737] Although the abatement of soil containing 1,000 ppm lead or more results in a modest decline of blood lead levels in children with access to the soil, abatement is probably not a useful intervention for most urban children with low lead exposure.[738] The presence of soil concentrations exceeding 5,000 ppm lead indicates the need for abatement.

Occupational

The type of industry most commonly associated with high adult lead exposure depends on the type of industry in a particular region and work practices (e.g., housekeeping, personal hygiene, ventilation). In general, airborne lead levels are potentially high in the following industries: battery manufacturing, steel welding or cutting operations, printing, construction (painting, paper hanging), secondary smelting and refining of nonferrous metal, chemical plants, pigment manufacturing, telephone cable splicing/recycling,[739] and brass/bronze foundries.[740] The prevalence of blood lead levels ≥25 μg/dL declined from 14.0 per 100,000 employed adults in 1994 to 6.3 μg/dL in 2009.[110] Industries with the highest number of lead-exposed workers were battery manufacturing, secondary smelting and refining of nonferrous metals, and painting and paper hanging. Even though blood lead levels correlate to air lead concentrations, the range of blood lead levels is large and correlation between blood lead levels in workers and air lead levels is relatively weak.[741]

In California, workers in lead smelting, battery manufacturing, and brass foundries accounted for 80% of the elevated blood lead (>60 μg Pb/dL) reported in a statewide surveillance program, whereas construction, radiator repair, pottery ceramics manufacturing, and gun firing ranges accounted for the rest of the serious exposures to lead.[742] The demolition or repair of ships[743] and bridges[744] increases airborne lead levels as a result of the use of acetylene torches on leaded paint. The demolition of a steel bridge painted with lead paint (60% by weight) produced lead concentrations of 2–38 mg/m^3 in the breathing zone of the workers.[745] A cross-sectional study of 127 house painters in 5 North Carolina cities did not reveal any painters with whole blood lead levels >40 μg/dL.[746] The geometric mean BLL of this group was 6.8 μg/dL.

The mean air lead levels at indoor firing ranges may range up to 2 mg/m^3 during the firing of lead bullets.[747] In spite of natural ventilation, elevation of blood lead levels also occurs in instructors at uncovered, outdoor shooting ranges.[748] The exclusive use of completely copper-jacketed bullets substantially reduces the exposure of firing-range instructors to lead.[749] Lead naphthenate is a drying agent in paint and a high-pressure lubricant. The use of lead naphthenate as a spray without proper ventilation produced excessive concentrations (i.e., up to 430 $\mu g/m^3$) exceeding the current US occupational standard of 50 μg Pb/m^3 as a time-weighted average.[750]

In 1993, the US Occupational Safety and Health Administration (OSHA) reduced the PEL for lead in an 8-hour shift from 200 to 50 $\mu g/m^3$. In the US, OSHA requires medical surveillance of workers if the ambient air lead concentration exceeds 30 $\mu g/m^3$ air for more than 30 days as an 8-hour TWA or if the blood lead level of workers exceeds 40 μg/dL. The correlation between lead in air and blood lead levels in workers is not strong as a result of a number of confounding factors (e.g., nonoccupational sources of exposure, smoking, personal hygiene). A study of the relationship between

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ambient lead and whole blood lead levels in 219 battery workers exposed to a mean lead concentration in air of ~200 μg Pb/m^3 suggested improvement of personal hygiene practices was as important as lowering the ambient concentration of lead in air.[751] If a combination of changes in administrative, engineering, and work practices (e.g., personal hygiene, smoking and eating habits, laundry procedures, personal protective equipment) fails to reduce the lead concentration in ambient air to <50 μg/m^3, then improvement in these practices must be supplemented with the use of respirators. Table 16.15 lists the regulations and guidelines for exposure to lead.

Biological Monitoring

Children

The issue of mass screening for elevated blood lead levels in children remains controversial because of the

TABLE 16.15. Regulations and guidelines for inorganic lead exposure.

Exposure Limit	Value
OSHA	
PEL–TWA (8-hour)	50 μg/m^3 (toxic/hazardous substances)
	50 μg/m^3 (general/shipyard industry)[a]
Action level	30 μg/m^3[a]
NIOSH	
REL–TWA (10-hour)	50 μg/m^3 (0.006 ppm)
IDLH	100,000 μg/m^3
ACGIH	
TLV–TWA (8-hour)	50 μg/m^3 (0.006 ppm)
US FDA	
Bottled water allowable limit	5 μg/L
Action level (leaching solution)	
Flatware	3.0 mg/L
Small hollowware	2.0 mg/L
Large hollowware	1.0 mg/L
Cups/mugs/pitchers	0.5 mg/L
Silver-plated hollowware (adults)	7.0 mg/L
Silver-plated hollowware (infants)	0.5 mg/L
US EPA	
Ambient air (3-month average)	0.15 μg/m^3[b]
MCL (action level)[c]	15 μg/L
Residential	
Bare soil	1,200 ppm
Bare soil children's play area	400 ppm
Settled dust interior floors	40 μg/ft^2
Settled dust interior window sills	250 μg/ft^2
Settled dust interior window wells	400 μg/ft^2
WHO	
Drinking water	10 μg/L[d]
Air quality	0.5 μg/m^3

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; IDLH = immediately dangerous to life and health; MCL = maximum contaminate level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; TLV = threshold limit value; TWA = time-weighted average; US EPA = United States Environmental Protection Agency; WHO = World Health Organization.

[a] Beginning 1/1/2025, Cal/OSHA lowered the eight-hour time-weighted average lead permissible exposure limit (PEL) in the construction and general industry from 50 μg/m^3 to 10 μg/m^3 and the action level from 30 μg/m^3 to 2 μg/m^3; [b] Not-to-exceed air lead concentration of 0.15 μg/m^3 in total suspended solids for a 3-month rolling average; [c] Treatment technique requires control of water corrosiveness and additional steps (replace lead distribution lines, reduce water sources with elevated lead levels) if >10% of water samples exceed action level. The MCL goal for lead in drinking water is zero; [d] Provisional guideline value on basis of treatment performance and analytical achievability.

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TABLE 16.16. Recommended actions for pediatric screening of confirmed venous blood lead levels from CDC (https://www.cdc.gov/nceh/lead/advisory/acclpp/actions-blls.htm) and AAP. Environmental investigations in the BLL category 3.5–19 vary with jurisdictional requirements and resources. Some healthcare providers may repeat the BLL in this category within 1 month to determine if the BLL is increasing more than anticipated. (Adapted from Henretig).[755]

Blood Lead Level (μg/dL)	Recommend Action	Additional Actions
<3.5	Follow-up blood lead testing at recommended intervals depending on local risks	Routine assessment of developmental milestones and nutritional status (iron, calcium). Guidance regarding lead sources and preventing lead exposure. Correct iron deficiency.
3.5–9	Retest 3 months after BLL declining 6–9 months	Environmental exposure history plus environmental investigation when required. Nutritional counseling and correct deficiencies (iron, calcium) as needed. Assess development per AAP guidelines and refer as needed. Report BLL results to state or local health department.
10–19	Retest 1–3 months, after BLL declining 3–6 months	Actions similar to 3.5–9 category. Referral to supportive services as needed.
20–44	Clinical evaluation, retest 2 weeks–1 month, after BLL declining 1–3 months	Follow recommendations from above plus complete history and physical exam for lead toxicity, environmental investigation of home, and lead hazard reduction; consider abdominal X-ray for evidence of pica or lead foreign bodies, consult with poison control center or Pediatric Environmental Health Specialty Unit (PEHSU).
45–69	Clinical evaluation for symptomatic lead toxicity and need for hospitalization	Follow recommendations above plus case management within 48 hours, chelation, environmental investigation, lead hazard control, education, developmental monitoring. Follow-up BLL during and after documented decreasing BLL as soon as possible. Correct iron deficiency after chelation.
≥70	Hospitalization	Immediate chelation, environmental investigation, lead hazard control, education, developmental monitoring. Follow-up BLL during and after documented decreasing BLL. Correct iron deficiency after chelation.

large variation in the prevalence of elevated lead levels between children in different regions.[752,753,754] Most physicians now target specific populations of children at risk of lead poisoning including Medicaid-eligible, recent immigrants, refugees, international adoptees, and inner city children living in older housing. Many significant lead exposures occur in children living in older housing (pre-1950), where the ingestion of leaded paint and water from lead pipes substantially increases blood lead levels. Recommendations vary within state and local health departments. The American Academy of Pediatrics (AAP) and the CDC recommend screening all poverty assistance program-eligible children, including Medicaid, at ages 1 and 2, as well as children in these programs aged 3-6 years without prior screening and all children immigrating to the United States from foreign countries. Table 16.16 lists recommended guidelines for determining the actions for confirmed venous BLL screening results depending on state and local recommendations and requirements.

Occupational Exposure

The whole blood lead level (BLL) reflects lead exposure over the last few months; this value is the standard test for determining excessive lead exposure. Cross-sectional studies of lead battery workers suggest a number of factors affecting the BLL based on regression analysis of the blood lead concentrations including age, sex, alcohol consumption, personal hygiene practices, and the type of lead exposure.[751] US OSHA standards on initial biological monitoring (i.e., BLL, ZPP) of construction workers begin following any day when the ambient air lead concentration exceeds 30 μg/m^3 as an 8-hour TWA (action level). For all other employees, a biological monitoring program should begin whenever area samples indicate that the ambient air lead concentrations exceed the action level for 30 days or the BLL of a worker exceeds 40 μg/dL. Construction workers must be removed from their work environment if their BLL exceeds 50 μg/dL and the follow-up blood sample drawn within 2 weeks of the elevated BLL confirms a lead concentration >50 μg/dL. For general industry, the removal requirements are slightly different as displayed in Table 16.17.

Removal from airborne lead exposure above 30 μg/m^3 is also required if a medical examination detects the presence of a medical condition in the worker that increases the worker's risk of damage to a target organ of lead toxicity, particularly when the work has a documented blood lead level >50 μg/dL within the preceding 6 months.[756] Workers removed from lead exposure

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TABLE 16.17. Medical actions required by OSHA based on blood lead levels. The physician has the discretion to remove a worker from lead exposure if lead exposure may increase the risk of impairment from a detected medical condition.

Blood Lead Level, µg/dL	Medical Action	Repeat Testing
<40	Below BLL action level (AL).	None
	AL exceeded.	General industry (GI): repeat BLL and ZPP every 6 months.
		Construction industry (CI): repeat BLL and ZPP every 2 months for 6 months, then every 6 months thereafter.
40–49	Annual history/physical examination, BLL, ZPP, complete blood count (CBC) with red cell indices and peripheral smear, routine urinalysis, blood urea nitrogen (BUN), serum creatinine.	Repeat BLL and ZPP every 2 months until 2 consecutive BLL <40 µg/dL.
≥50 (CI)	Removal from lead exposure, complete lab and physical exam.	
≥50–60 (GI)	Removal from lead exposure if mean of three values ≥50 µg/dL or if single value ≥60 µg/dL; complete lab and physical exam.	Repeat BLL and ZPP monthly until 2 consecutive BLL <40 µg/dL.

Abbreviations: air = air concentration of lead; AL = action level (>30 µg Pb/m^3); BLL = blood lead level; CI = construction industry; GI = general industry; ZPP = zinc protoporphyrin.

may return to work when two consecutive blood samples demonstrate a BLL <40 µg/dL. Blood lead levels decline more rapidly in workers with more recent than long-term lead exposure.[757] Exposure to lower lead concentrations (i.e., <30 µg/dL) is recommended for male or female workers intending to have a child in the near future. Some,[751] but not all,[758] epidemiology studies associate elevated BLL with the use of alcohol by lead-exposed workers.

Medical Surveillance

Requirements for medical surveillance depend on the lead concentration in air, the blood lead level of the workers, and, in construction trades, work involving certain high-risk lead exposures (e.g., abrasive blasting, sanding, torch cutting, welding, or demolition where lead is present). The frequency of biological monitoring and medical surveillance of an individual worker also depends on the BLL, as outlined in Table 16.17.

Full medical surveillance (i.e., bimonthly blood lead levels) is required for workers with >30 days of lead exposure and BLL >40 µg/dL. Medical examinations should include the following: 1) detailed work and medical histories with particular attention to personal habits and past lead exposure, 2) a complete medical examination (gums, teeth, skin, gastrointestinal tract, kidney, heart, neurological system including mood, affect, cognitive function, and lung function, 3) blood samples to measure blood lead concentrations collected in lead-free containers, complete blood count, and renal function, and 4) urinalysis as outlined in Table 16.18. Additional air samples and biological monitoring of workers may be necessary in the following situations: 1) employees with symptoms of lead poisoning, 2) an employee requesting medical advice about the effects of lead exposure on plans to conceive children, and 3) an employee with difficulty using a respirator. More frequent (monthly) monitoring of blood lead concentrations of lead-exposed workers may be necessary when lead exposure is not well controlled.[759] The ACGIH-recommended biological exposure index (BEI) for lead is 30 µg/dL. This value represents the lead concentration in blood most likely to be present in samples from workers exposed to the threshold limit value (TLV) for lead. The TLV refers to the airborne lead concentration at which nearly all workers may be repeatedly exposed, day after day, without adverse effects.

Reliable clinical laboratory techniques are available for δ-aminolevulinic acid dehydratase, urinary coproporphyrin, and δ-aminolevulinic acid (plasma, urine);[760] however, these biochemical measures depend on physiological factors other than the blood lead level. Therefore, these indices are not specific to lead poisoning.

TREATMENT

Embedded solid lead objects do not usually produce significant lead toxicity because of the small surface area and the limited dissolution rate of lead objects in physiological pH.[761] Management of ingested lead

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TABLE 16.18. Minimum components for medical evaluation of lead-exposed workers.

Category	Examples
Past lead exposure	
Environmental history	
Social history including hobbies	
Complete work and lead exposure history	
	History
	Review of systems
Constitutional	Anorexia, fatigue, weight loss
Cardiovascular	Dyspnea, cough, chest pain, palpitations, orthopnea, PND
Gastrointestinal	Nausea, vomiting, constipation, diarrhea, abdominal pain, melena
Hematological	Pallor, easy fatigability
Neurological	Weakness of hands/legs, irritability, insomnia, forgetfulness, confusion, hallucinations, gait disturbance, ataxia, seizures, headache.
Renal	Polyuria, polydipsia, frequency, renal disease
Reproductive	Infertility, loss of libido, pregnancy history, impotence
Musculoskeletal	Arthralgias, myalgias
	Complete Medical Examination
Gums/dentition	Lead lines, hyperpigmentation
Cardiovascular	Blood pressure
Gastrointestinal	Organomegaly, diffuse abdominal pain
Hematological	Anemia
Neurological	Mental status exam, behavioral/psychological abnormalities, memory loss, muscle weakness (extensors), gait, coordination, sensation
Renal	
Pulmonary (if symptomatic)	
	Laboratory
Blood lead level	
Complete blood count with smear	Serum iron, RBC indices, serum folate/B_{12} if indicated
Zinc protoporphyrin level	
Serum creatinine	
Urinalysis	Serum uric acid, if indicated.
	24-hour urine collection for creatinine clearance, protein, electrolytes, if indicated.
Pregnancy test or semen evaluation (if requested by employee)	

foreign bodies is similar to the management of an uncomplicated foreign body ingestion; however, the patient should be followed closely with abdominal X-rays to determine the progression of the lead foreign body and the blood lead levels (every 4 days) if the elimination from the gastrointestinal tract is slow (i.e., >1–2 weeks). Unrecognized retention of lead foreign bodies near acidic environments (stomach, joints) can produce severe lead toxicity.[362,762] Parenteral chelation should be considered following a large amount of liquid lead (e.g., lead glaze) ingestion when the material is not removed by whole bowel irrigation and the BLL exceeds 45 μg/dL.[173,763] Although there are inadequate human data, primate studies suggest the initiation of oral succimer does not increase the gastrointestinal absorption of lead.[764]

Gut Decontamination

Activated charcoal does not adsorb lead well, while the presence of activated charcoal obscures endoscopic visualization of the foreign body. The decision to use whole bowel irrigation, endoscopic removal, or surgery to remove lead material depends on clinical judgment regarding the severity of the poisoning (e.g., BLL) and the location of the foreign body. The latter should be removed prior to initiation of chelation if amenable to removal. Elemental lead is relatively insoluble at alkaline pH and more soluble in acidic environments with most lead absorption occurring in the duodenum after passage through the acidic environment of the stomach. The reduction in absorption following alkalinization is time-sensitive. An *in vitro* controlled

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study comparing simulated gastric fluid at pH 1 with gastric fluid alkalinized with calcium carbonate at pH 6 suggested the administration of calcium carbonate (TUMS®) reduced elemental lead absorption.[765] At 4 hours, total lead liberated from the soluble fraction at pH 1 and pH 6 was 850 µg and 12.4 µg, respectively, resulting in a 60-fold difference. Inadequate human data are available to confirm efficacy of alkalinization following lead overdoses.

Remediation

The primary goal of lead screening programs is the identification and elimination of lead from the environment of children, particularly the stabilization or removal of peeling lead paint and cleaning of lead-contaminated house dust.[81] Table 16.19 lists potential sources of excessive lead exposure. Without remediation of lead sources in the environment at an individual level, chelation will have little impact on the total body burden of lead. Community-wide environmental interventions (e.g., widespread removal, replacement of lead-contaminated soil) are less effective than abatement of individual houses for the reduction of BLL among residents;[766] currently, there is inadequate evidence at the *population level* that education or dust control measures reduce blood lead levels in children. Education and dust control do not improve the effectiveness of abatement and cleaning lead-contaminated houses as a *population* health strategy based on a meta-analysis of BLL from 12 studies (n = 2,239 children).[767]

Table 16.20 lists procedures for the reduction of lead absorption by children from environmental sources. A study of 113 urban children with ages ranging from 6–36 months revealed maternal education and biweekly assistance with household cleaning reduced the mean BLL by an average of 17% over ~1 year compared with baseline lead concentrations.[768] The primary methods of cleaning included wet mopping, damp-sponging of walls and horizontal surfaces, and vacuuming with a high-efficiency particle accumulating vacuum. During a pilot study of the cleaning of buildings with highly deteriorated lead-based paint, the wet scrape/high-efficiency particulate air (HEPA) vacuum method produced substantially less lead exposure to workers than the dry scrape/sweep method.[769] However, the addition of portable HEPA-filtered exhaust fans did not reduce the lead exposure of workers using the wet method.

The three methods of lead abatement include replacement, encapsulation, and removal. Replacement is the process whereby lead-painted structures (e.g., windows, doors, frames) are exchanged for non-leaded structures. Encapsulation involves the covering or resurfacing of lead-painted surfaces with durable materials (e.g., Formica®, paneling, tile, gypsum board, canvas-backed vinyl, vinyl flooring, wood stone, plastic, metal). Removal of lead paint from a structure is the most hazardous alternative; this action should be considered only when replacement and encapsulation are not feasible. Safe work practices include 1) relocating families as indicated, 2) minimizing dust creation, 3) containing dust in the work area, 4) completing cleanup, 5) safe waste disposal, and 6) clearance testing to confirm residences comply with EPA lead standards.[395]

X-ray fluorescence is the most accurate method available to detect lead in paint. Lead abatement performed by legal standards reduces the blood lead level of children by ~30% over 6 months.[122] Deleading should be performed by trained and certified crews with experience in lead removal. Cleanup of the contaminated house dust (>1,000 µg Pb/ft^2) involves vacuuming with a high-efficiency particulate accumulator (HEPA vacuum) and wet mopping with a high-phosphate detergent. Household members should leave the house

TABLE 16.19. Potential sources of lead exposure. (Based on Roper).[81]

Category	Source
Para-occupational exposure	Home production of belt buckles, awards, and type printing, pottery manufacturing, battery repair shops, lead or copper smelters, radiator mechanics, capacitor and resister plants, electric cable manufacturing
Lead-containing materials	Folk medicines, costume jewelry, herbal supplements, cosmetics
Hobbies	Pottery glazing, toy soldiers, stained glass construction or repair, lead soldering, car or boat repainting, fishing or hunting with lead sinkers or shot, target shooting, gold/silver extraction
Residences	Dilapidated condition, pre-1960 buildings, inner-city location, older day care facilities/caretaker residence, preschool
Home remodeling	Pre-1960 construction
Proximity to point sources	Industrial facilities, hazardous waste sites
Diet	Food utensils (imported or glazed ceramics), herbal products
Drinking water	Lead pipes
Drugs	Moonshine whiskey, lead-contaminated illicit drugs

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TABLE 16.20. Simple methods to reduce lead exposure.

Actions	Examples
Keep home as clean and dust-free as possible. Remove or clean shoes before entering house.	Wet mop floors, wipe window ledges, wash surfaces with water and detergent.
Leave lead contamination at work.	Leave work clothes at work; shower at work if lead-exposed.
Lead-contaminated paint.	Never sand, burn or scrape paint with high lead content (pre-1960); X-ray fluorescence is the best method to detect leaded paint; keep furniture away from old, damaged paint.
Encourage good nutrition. Wash children's hands often.	Calcium and iron-rich foods, low-fat diet.
Avoid lead-contaminated objects.	Lead-glazed utensils, toys, hobbies, home remedies, cosmetics. Restrict play in lead-contaminated areas.
Reduce lead consumption from drinking water.	Use only cold water that was flushed prior to consumption until it is as cold as possible. Use only cold water for cooking, and preparing baby formula.

during the deleading and return after inspection of the house confirms that dust-wipe samples meet US EPA clearance standards as defined in the section on Environmental Monitoring.

Nutrition

A review of the nutritional status with emphasis on adequate dietary intake of iron, calcium, and zinc is necessary to ensure the maximum therapeutic benefit from efforts to reduce blood lead levels. Experimental evidence indicates that iron deficiency facilitates the absorption of lead and adequate iron stores improve the efficiency of EDTA chelation.[770] Iron supplements (6 mg elemental iron/kg/day) for 2–4 weeks are recommended in order to reduce lead absorption. Iron therapy during chelation is not recommended. Concomitant administration of iron and BAL is contraindicated because of the formation of a toxic complex that produces protracted vomiting. Observational studies also suggest that a low-fat diet may be beneficial for children at high risk of developing lead toxicity.[771]

Chelation

Chelation is a relatively inefficient form of therapy because a course of treatment removes only ~1–2% of the total body burden of lead depending on the length of exposure, primarily from soft tissue stores.[772] Although chelation therapy produces definite short-term benefits, successful long-term therapy requires a drastic reduction in lead exposure as the first priority. Discharge planning should include 1) identification and remediation of lead exposure hazards, 2) education of parents or guardians regarding compliance and dosing of chelator, and 3) adequate reduction in BLL during inpatient therapy.[773]

Dimercaprol (British Anti-Lewisite Compound, BAL)

Mechanism of Action

The sulfhydryl ligands of BAL attract heavy metals (e.g., lead) to form a stable heterocyclic metal-chelate complex. BAL enhances fecal and urinary lead excretion; this chelating agent diffuses well into erythrocytes and brain cells. The high affinity of BAL for heavy metals reduces the binding of these metals to essential sulfhydryl groups in enzyme systems in the body, thus decreasing toxicity. Disassociation of the complex and oxidation of BAL can occur *in vivo* when the plasma BAL concentrations decrease.

Pharmacokinetics

The onset of action of BAL is ~30 minutes; excretion of the majority of the chelated metal complex occurs within 4–6 hours, primarily in the bile.[774] BAL promotes the renal excretion of lead from the RBC pool within several hours.

Uses

Indications for lead chelation are acute encephalopathy, classic plumbism, and some asymptomatic cases with high BLL.

Adverse Effects

Adverse effects associated with BAL are common and dose-related with ~50% of patients treated with 5 mg/kg developing BAL-related symptoms. Transient hypertension and tachycardia can occur within 30 minutes of administration and last several hours. Reported adverse effects include irritability, anxiety, nausea, vomiting, paresthesias, headache, lacrimation, rhinorrhea, conjunctivitis, salivation, diaphoresis, burning of the throat, lips, and eyes, muscle cramps, abdominal pain, and fever (more common in children). Transient elevation of

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serum hepatic transaminases occurs commonly. Excessive doses may result in coma, stupor, convulsions, and hypotension because of direct capillary damage and relative hypovolemia. Patients should be well-hydrated with intravenous fluids to reduce gastrointestinal distress. Fever occurs in ~30% of children receiving BAL; hemolytic anemia may develop in patients with G-6-PDase deficiency.[770] Because BAL is formulated in peanut oil, an allergic reaction may occur in patients allergic to peanuts.

Contraindications

BAL is contraindicated in the presence of liver failure and glucose-6-phosphate dehydrogenase deficiency (which induces hemolysis). Renal impairment is not an absolute contraindication because BAL excretion occurs primarily in the bile. The concurrent administration of medicinal iron is contraindicated because the BAL–iron complex is toxic. BAL may potentiate the renal toxicity of cadmium and selenium; therefore, BAL is not recommended in patients with cadmium or selenium toxicity.

Dosage

For maximum effect, BAL should be given as soon as possible to prevent irreversible cell damage by metallic cations. The severity of the lead poisoning and the response of the patient determine the amount administered as displayed in Tables 16.21 and 16.22. BAL is available only as a 10% solution in oil for intramuscular injection. The initial daily BAL dose ranges from 18–24 mg/kg (300–450 mg/m^2) in 2–6 divided doses by deep intramuscular injection. Dosage is often reduced on the second day; a full course continues for 5–7 days, followed by a rest period. A repeat course may be necessary. Pre-administration of diphenhydramine may alleviate some of the adverse effects of BAL. The presence of lead encephalopathy indicates the need

TABLE 16.21. Recommendations for chelation of symptomatic and asymptomatic children.

Clinical Presentation (BLL, µg/dL)	Chelating Agent	Dose	Comments
		Symptomatic Children	
Acute encephalopathy	BAL	450 mg/m^2/day	Initially start BAL, 75 mg/m^2 IM every 4 hours for 5 days.[a] Maximum *daily* dose ~24 mg/kg.
	$CaNa_2EDTA$	1,500 mg/m^2/day	Start 4 hours *after* BAL with continuous or 2–4 divided doses/24 hours for 5 days. Repeat 5-day cycles after a 2-day rest may be necessary if BLL remains high or lead rebound occurs. The maximum *daily* dose is ~2–3 g.
Symptomatic without encephalopathy or BLL >69	BAL	300–450 mg/m^2/day	Initially start BAL, 50–75 mg/m^2 IM every 4 hours for 5 days.[a]
	$CaNa_2EDTA$	1,000–1,500 mg/m^2/day	Start 4 hours *after* BAL with continuous or 2–4 divided doses/24 hours for 5 days. Repeat 5-day BAL/$CaNa_2EDTA$ cycles after a 2-day rest may be necessary if BLL remains high or lead rebound occurs depending on duration/severity of symptoms and BLL.
		Asymptomatic Children	
45–69	DMSA[b] (Succimer)	700–1,050 mg/m^2/day	350 mg/m^2/day tid PO for 5 days, then bid PO for 14 days.[c] Remove from lead exposure. $CaNa_2EDTA$ provocation test not recommended. Maximum *single* dose is ~10 mg/kg.
45–69 (option to use DMSA)	$CaNa_2EDTA$[b]	1,000 mg/m^2/day	Continuous or 2–4 divided doses/24 hours for 5 days. Repeat 5-day cycle after rest period depends on BLL, rebound, and duration of lead exposure.[a]
20–44	DMSA (Succimer)	700–1,000 mg/m^2/day	Routine chelation is *not* recommended; however, if clinically indicated 350 mg/m^2/day tid PO for 5 days, then bid PO for 14 days.[c] Emphasis on reduction of lead exposure.
<20	No chelation		Emphasis on reduction of lead exposure.

Abbreviation: BLL = blood lead level.

[a] Baseline labs include CBC, BLL, Ca, Cr/BUN, LFTs, UA with repeat BLL on days 3 and 5; [b] D-Penicillamine is a rare option to DMSA or $CaNa_2EDTA$; [c] Baseline labs include CBC, BLL, LFTs with a repeat on days 7 and 21.

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TABLE 16.22. Recommendations for chelation in lead-exposed adults.

Clinical Presentation (BLL, µg/dL)	Chelating Agent	Dose	Comments
Acute encephalopathy	BAL	450 mg/m^2/day	Initially start BAL, 75 mg/m^2 IM every 4 hours for 5 days.
	$CaNa_2EDTA$	1,500 mg/m^2/day	Start 4 hours *after* BAL with continuous or 2–4 divided doses/24 hours for 5 days. Repeat 5-day cycles after a 2-day rest may be necessary if BLL remains high or lead rebound occurs.[a] Maximum dose ~2–3 g/day.
Encephalopathic symptoms or BLL >100	BAL	300–450 mg/m^2/day	Initially start BAL, 50–75 mg/m^2 IM every 4 hours for 5 days.
	$CaNa_2EDTA$	1,000–1,500 mg/m^2/day	Start 4 hours *after* BAL with continuous or 2–4 divided doses/24 hours for 5 days. Repeat 5-day BAL/$CaNa_2EDTA$ cycles after a 2-day rest may be necessary if BLL remains high or lead rebound occurs depending on duration/severity of symptoms and BLL.[a] Maximum dose ~2–3 g/day.
Mildly symptomatic without evidence of encephalopathy or 70–100	DMSA	700–1,050 mg/m^2/day	350 mg/m^2/day tid PO for 5 days, then bid PO for 14 days.[b] Remove from lead exposure. Maximum dose ~10 mg/kg.
Asymptomatic or <70	—	—	No chelation routinely recommended. $CaNa_2EDTA$ provocation test not recommended.

Abbreviation: BLL = blood lead level.
[a] Baseline labs include CBC, BLL, Ca, Cr/BUN, LFTs, UA with repeat BLL on days 3 and 5; [b] Baseline labs include CBC, BLL, LFTs with a repeat on days 7 and 21.

for coadministration of BAL and the administration of $CaNa_2EDTA$ beginning 4 hours after BAL. The urine specific gravity typically is kept below 1.020 with IV fluids; however, fluid balance and electrolytes should be monitored closely as SIADH and hyponatremia may develop after several days of BAL, particularly in patients with very high BLL and inadequate fluids. Keeping the urine specific gravity below 1.020 decrease the risk of SIADH. Oral iron therapy and parenteral BAL are not recommended concurrently.

$CaNa_2EDTA$

Mechanism of Action

This compound forms a stable, soluble complex with lead drawn from extracellular stores. $CaNa_2EDTA$ does not penetrate cells and removes only extracellular lead; the reduction of lead stores in erythrocytes, soft tissue, and the central nervous system results from equilibration of intracellular lead with lead in the extracellular compartment. The kidneys excrete the complex. At lead levels <40 µg/dL, rodent studies suggest some redistribution of lead following a single dose of CaNa2EDTA.[775] This model demonstrates increased hepatic and central nervous system lead, whereas bone and renal lead concentrations decrease. These effects are probably transient. In a subsequent study in albino rats ingesting drinking water containing 100 µg Pb/L, stable Pb isotope tracer methodology confirmed the reduction of soft tissue lead stores following $CaNa_2EDTA$ chelation.[776] There was no evidence of redistribution of lead to the brain. When used alone, $CaNa_2EDTA$ may worsen an acute encephalopathy in children; however, all symptoms related to acute lead toxicity resolved in adults after the use of intravenous $CaNa_2EDTA$.[744]

Pharmacokinetics

The gastrointestinal tract absorbs small amounts (<5%) of $CaNa_2EDTA$; the plasma half-life is <1 hour. In patients with normal renal function, most excretion of the lead-EDTA complex occurs within 8 hours; elimination results from renal tubular secretion of unchanged lead-$CaNa_2EDTA$ with ~95% excreted within 24 hours.[777] The presence of renal failure may delay the excretion of the lead–EDTA complex for up to several days. The drug appears primarily in extracellular fluid; little of the drug diffuses into erythrocytes or crosses the blood–brain barrier. $CaNa_2EDTA$ does cross the placenta with similar distribution in the fetus and mother.[770]

Adverse Effects

The kidney is the target organ of toxicity for $CaNa_2EDTA$. Proximal tubular damage (hydropic vacuolization, loss of brush borders, degeneration) is unusual in doses below 1,500 mg $CaNa_2EDTA$/m^2; the effects are usually reversible. Maintenance of adequate urinary output before administration of $CaNa_2EDTA$ reduces renal complications. Side effects reported after the administration of $CaNa_2EDTA$ include headache,

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anorexia, nausea, vomiting, chills, fever, myalgias, excessive thirst, malaise, fatigue, and a mucocutaneous reaction similar to vitamin B_6 deficiency.[770] Although urticaria and other rashes may occur, allergic reactions to $CaNa_2EDTA$ are rare.

This compound should not be administered orally because it probably enhances lead absorption by this route. $CaNa_2EDTA$ depletes iron and trace metals (copper, zinc, manganese) stores; therefore, this chelating agent should be used cautiously in any patient with decreased zinc stores. Rest periods of 2–14 days between $CaNa_2EDTA$ doses are necessary to allow equilibration of blood lead and the recovery from zinc depletion.

Dosage

The combination of $CaNa_2EDTA$ (ASD Healthcare, https://www.asdhealthcare.com/, 800-746-6273) and BAL effectively prevents rapid mobilization of lead into the blood for patients requiring chelation with BLL >60–70 μg/dL. When used in combination with BAL, $CaNa_2EDTA$ therapy should begin after the second dose of BAL to prevent elevated blood lead levels from soft tissue stores. $CaNa_2EDTA$ should not be administered alone to treat lead encephalopathy. The precise dose depends on the clinical situation. In children, the standard dose is 50 mg $CaNa_2EDTA$/kg/day (1,500 mg/m^2/day) intravenously as a dilute, continuous infusion (maximum concentration, 0.2–0.5% solution or 2–5 mg $CaNa_2EDTA$/mL in dextrose and water); an alternative is the administration of the daily dose as 2–4 divided doses intravenously over several hours.[778] In severe cases, the daily dose may be increased to 75 mg $CaNa_2EDTA$/kg/day. The maximum daily dose of $CaNa_2EDTA$ in adults is 2–4 g, depending on the severity of the poisoning. Intramuscular injections are painful; the addition of 0.5 mL of 2% procaine or lidocaine reduces the pain of deep intramuscular injection. Adequate renal function must be documented daily. The full course of chelation is 5 days with at least a 2–5 day rest period between courses for equilibration of lead stores and replenishment of zinc stores. Case studies suggest equilibration of lead between blood and bone stores requires at least 2 weeks.[779] The number of courses depends on the clinical response and the severity of symptoms. Initially, lead levels should be monitored weekly after chelation until the blood level no longer rebounds.

The use of disodium edetate (Endrate, sodium versenate, disodium EDTA, Na_2EDTA) for lead chelation is contraindicated because of the potential for fatal hypocalcemia.[780] Iron and zinc supplements should not be administered during chelation because the use of these metals with $CaNa_2EDTA$ decreases the effectiveness of lead chelation. $CaNa_2EDTA$ should be used cautiously in oliguric patients. The addition of $CaNa_2EDTA$ to the peritoneal dialysate of an anuric patient with lead toxicity chelated lead with ~70% of the efficiency of intravenous $CaNa_2EDTA$.[781] During chelation therapy, the blood should be monitored closely for urine output, renal function, complete blood count, and serum hepatic transaminases.

Meso-2,3-dimercaptosuccinic acid (DMSA)

Dimercaptosuccinic acid (DMSA) and 2,3-dimercapto-1-propanesulfonic acid (DMPS) are water-soluble, highly polar chemical analogs of dimercaprol (BAL). In animal models, DMSA and DMPS are less toxic and more effective orally than BAL.[782] Both DMSA and DMPS have much higher LD_{50} values in rats and wider therapeutic indexes than BAL; DMSA appears to be the least toxic of the two analogs.[783] DMPS is used extensively in Europe for mercury poisoning, but practical concerns (smell) and complications with Steven–Johnson syndrome limit the use of DMPS in the United States. Both DMSA and DMPS also chelate arsenic, organic/inorganic mercury, and other heavy metals, whereas these drugs cause minimal effects on iron, calcium, and magnesium. Small increases in urinary zinc and copper excretion may occur.[784]

Indication

DMSA is the preferred chelating agent for mild or asymptomatic cases of lead toxicity with BLL >45 μg/dL; the use of this drug in children with BLL <45 μg/dL remains controversial despite two negative clinical studies.[785] Although short-term courses of DMSA increase the urinary excretion of lead and reduce the blood lead level in children with moderate lead toxicity,[786] insufficient data are available to recommend DMSA chelation of children with lead-related neurotoxicity and BLL <45 μg/dL. Experimental studies suggest that both oral DMSA and parenteral calcium disodium EDTA are effective chelating agents; DMSA is the preferred alternative to calcium disodium EDTA in the United States and the United Kingdom for moderate lead poisoning, particularly when the oral route is preferable for the treatment.[787] Adults are not typically administered chelating agents with BLL <45 μg/dL. The US FDA approved DMSA for the oral chelation of children with blood lead levels >45 μg/dL. A case report of a 66-year-old woman with lead encephalopathy (headache, altered mental status, irritability, BLL = 148.2 μg/dL on hospital day 14) associated rapidly reduced BLL and marked improvement

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in her mental status with the administration of the usual course of DMSA.[788] She received one dose of BAL (BAL was discontinued when DMSA administration began) and no $CaNa_2EDTA$ because of a national shortage.

Mechanism of Action

DMSA efficiently mobilizes lead from soft tissue stores including the brain.[789] The lack of serious side effects allows prolonged therapy; however, blood lead levels rebound (~70% pre-chelation levels) rapidly after chelation ceases.[790] In a study of 10 workers with a mean blood lead concentration of 67.9 µg/dL, the mean blood lead concentration 12 and 72 hours after the last DMSA dose was 38.92 µg/dL (i.e., 53% baseline) and 49.38 µg/dL (i.e., 73% baseline), respectively.[791] A study of Korean lead workers suggests that tibial lead stores are less bioavailable (and contribute less to blood lead concentrations) in older subjects than in younger subjects.[792] Lead chelatable by DMSA represents the currently bioavailable lead burden, whereas tibial lead represents cumulative lead exposure.

DMSA chelates lead and cadmium with a sulfur-oxygen ligand, whereas mercury and nickel attach to two sulfur atoms. At 1,050 mg DMSA/m^2/day (equivalent to 30 mg/kg) in three divided doses, DMSA was more effective at lowering the blood lead levels and restoring erythrocyte delta-aminolevulinic acid dehydratase activity than intravenous $CaNa_2EDTA$. The excretion of urinary lead with these two chelating agents was comparable.[793] DMSA does not enhance the excretion of zinc, copper, iron, or calcium to the same extent as $CaNa_2EDTA$.[794] Furthermore, DMSA does not interfere with the parenteral administration of iron during long-term chelation therapy.[795]

Pharmacokinetics

Absorption of DMSA from the gastrointestinal tract is rapid, but variable with peak plasma DMSA concentrations occurring ~3 hours after ingestion.[796] DMSA probably does not increase the absorption of lead from the gut. The volume of distribution (V_d) is limited mostly to the extracellular space with V_d in the range of ~0.35 L/kg; most (92–95%) of the DMSA is protein-bound, primarily by albumin via a disulfide bond. Minor amounts of free DMSA appear in the plasma.[797] DMSA probably does not cross the blood–brain barrier. The urinary excretion of DMSA is rapid. Maximal renal excretion of DMSA/metabolites occurs on the first day after ingestion with about ¾ of the DMSA appearing in the urine within 24 hours. After the administration of a single 10 mg/kg dose of DMSA to lead workers, the maximum urinary excretion of lead occurred ~2 hours after ingestion.[798] During this study, the administration of intravenous $CaNa_2EDTA$ 2 weeks before DMSA increased DMSA-induced lead excretion. Biotransformation of DMSA primarily involves the formation of mixed disulfides of L-cysteine, probably in the kidney.[799] Elimination of DMSA occurs almost exclusively (90–95%) by the renal excretion of these mixed succimer-cysteine disulfides. Compared with healthy subjects, lead toxicity may slightly reduce DMSA clearance[800] There are few data on the excretion of DMSA in breast milk. Most lead excretion occurs in the first week with excretion rates declining after the first week of therapy. Although the administration of DMSA initially reduces the blood lead concentrations, redistribution of lead from bone stores causes a rebound in the blood lead concentrations beginning within several weeks of the cessation of chelation.[801] The rebound in blood lead concentrations depends on the extent of bone lead stores; however, chelation in some patients with acute and subacute lead toxicity may not produce a rebound in blood lead concentrations.[802]

Dosage

The preferred oral dose of DMSA is ~30 mg/kg/day. A dose of 30 mg DMSA/kg divided into 3 doses daily and administered over 5 days reduced pretreatment blood lead levels in 18 patients by an average of 72.5%; a mild, asymptomatic elevation of serum alanine aminotransferase occurred in two subjects.[803] Data on the bioavailability of DMSA in food and fruit drinks are limited; therefore, DMSA should not be mixed with these agents immediately before administration. The 5-day dose is followed by 20 mg DMSA/kg body weight/day for 14–21 days in two divided doses as a means to blunt the rebound in blood lead concentrations; rebound up to 70% of the pre-chelation level often occurs within weeks to months. Limited clinical data suggest the repeat 5-day 30 mg/kg/day courses may be as effective as the prolonged course as long as a week separates the repeat courses to allow lead redistribution; some benefit may result from extending the 5-day course in severely lead-poisoned patients.[799] $CaNa_2EDTA$ is an alternative to DMSA in the pregnant patient because rodent studies suggest high daily DMSA doses (100, 300, and 1,000 mg/kg) produce maternal toxicity manifested by decreased weight gain without teratogenicity;[804,805] however, there are inadequate clinical data to determine the risk/benefit of DMSA and $CaNa_2EDTA$ chelation in the pregnant female.

Monitoring of blood lead and serum hepatic aminotransferases during chelation therapy involves the analysis of samples at baseline (i.e., pretreatment), 14 and 21 days after initiation of therapy, and 2 weeks after

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chelation ceases (i.e., rebound). A 2-week rest period is recommended between the 19th and 26th days of chelation in order to allow equilibration of lead in blood and bone. In the Treatment of Lead-Exposed Children Trial (1994–2004), DMSA reduced short-term BLL; however, 36-month follow-up cognitive, neuropsychological, and behavioral scores did not improve compared with controls. In the Treatment of Lead-Exposed Children Trial of 12–33-month-old children with blood lead concentrations 20–44 μg/dL, DMSA reduced the blood lead concentration in the short term, but the blood lead concentrations of controls and treated children were statistically similar 1 year after cessation of treatment.[806] There were no detectable improvements in a variety of measurements of cognitive and behavioral functions. DMSA is not indicated for prophylaxis of lead poisoning in a lead-contaminated environment.

Adverse Effects

DMSA lowers blood lead concentrations in children with relatively few side effects, although a rebound occurs following cessation of therapy.[801] Common adverse reactions to DMSA include gastrointestinal symptoms (nausea, vomiting, diarrhea, anorexia), mucocutaneous lesions, and erythematous rash. DMSA administration produces an unpleasant odor to urine, feces, and sweat resulting in compliance issues in some patients. Although DMSA increases copper and zinc elimination, the changes are not usually clinically significant compared with $CaNa_2EDTA$.[807] Transient elevations of serum hepatic transaminases tests may occur at the beginning of therapy, but the continued elevation of these tests is uncommon; the clinical significance of these changes is unclear. Children with both G-6-PD deficiency and sickle cell anemia have been treated with DMSA without complications.[808] The US FDA classifies DMSA as a category C agent based on teratogenicity and fetotoxicity in rodents.[809] There are few data on the human teratogenicity of DMSA.

D-Penicillamine

This compound is a weak oral chelator; prior to the approval of DMSA in the United States, D-penicillamine was the only oral agent available experimentally for the reduction of BLL 25–40 μg/dL. This drug produces less effective enhancement of urinary lead excretion than $CaNa_2EDTA$;[810] the mechanism of its action is unclear. Although D-penicillamine effectively reduces BLL in children in the short term, the high incidence of adverse effects limits the use of this chelating agent.[810] DMSA is generally preferred to D-penicillamine as an oral chelating agent for lead toxicity.

General Chelation Guidelines

Tables 16.21 and 16.22 provide general guidelines for chelation therapy for children and adults, respectively; however, certain areas remain controversial including what is the lowest blood lead concentration to initiate chelation therapy in asymptomatic patients. The EDTA lead mobilization test is rarely used to determine the need for chelation.

Symptomatic Children (Acute Symptomatic Plumbism)

The presence of an acute encephalopathy requires the administration of high-dose combination chelation (BAL, 4 mg/kg every 4 hours for 5–7 days, together with $CaNa_2EDTA$, 12–24 mg/kg every 4 hours beginning with the second dose of BAL). In mildly symptomatic cases without acute encephalopathy, BAL may be discontinued after 3 days when the BLL declines <50 μg/dL. Repeat chelation courses may be necessary after a 2–4-day interval depending on the resolution of symptoms and repeat blood lead levels. An additional course with 7–10 days of treatment is necessary when the BLL rebounds >50 μg/dL.[640]

Asymptomatic Children (Subclinical Plumbism)

Table 16.21 outlines the treatment of symptomatic and asymptomatic children. In asymptomatic children with blood levels <70 μg Pb/dL, the decision to perform chelation should be based on factors in addition to the BLL including the following: 1) age (the brain of children <2–3 years is more susceptible to neurotoxicity), 2) source of poisoning and likelihood of reduction in exposure to lead, 3) duration of poisoning (short-term exposure responds better to chelation), and 4) iron status. Chelation is commonly recommended for children with BLL of 45–69 μg/dL including asymptomatic children.[811] All patients with elevated BLL should have repeat blood samples drawn to exclude the possibility of contamination or laboratory error; the FEP may be helpful if the BLL is >30 μg/dL. Check blood iron levels before chelating because iron deficiency alone causes elevated FEP levels. FEP concentrations <35 μg/dL are normal, whereas concentrations >250 μg/dL are grossly abnormal. Following chelation, the FEP concentration helps distinguish a continuing lead exposure; a rising FEP level indicates reexposure, whereas a steady or declining FEP concentration suggests rebound from bone stores.

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BLL >70 μg/dL

Children with blood levels over 70 μg/dL require hospitalization for chelation therapy and immediate confirmation of the blood lead level to reduce the risk of cerebral edema, coma, and severe neurological damage. They usually receive the combination of BAL and $CaNa_2EDTA$ to prevent a transient rise in lead levels and the precipitation of acute encephalopathy. Children with BLL >70 μg/dL require careful observation during chelation. Fluid administration should be generous (10 cc/kg bolus, 1½ times maintenance therapy). The presence of lead on the KUB indicates the need for decontamination (i.e., whole bowel lavage). There are limited data on DMSA use in developed countries for BLLs in this range. In a retrospective study of severe lead poisoning in rural Zamfara, Northern Nigeria, 1,156 children ≤5 years of age underwent 1–15 courses of DMSA chelation.[812] The study reported no clinically severe adverse drug effects or laboratory findings that required discontinuation of treatment. The authors considered oral DMSA pharmacodynamically effective in a resource-limited setting.

BLL 45–70 μg/dL

Initial blood lead levels in this range should be repeated within 2 days. Asymptomatic children with repeat blood levels between 45–70 μg/dL usually require chelation depending on clinical judgment. Outpatient oral therapy (DMSA) is an adequate treatment regimen *if* the child is discharged to a lead-safe environment. Positive long-bone X-rays for lead lines also indicate the need for chelation. Although D-penicillamine previously was used for mild to moderate lead poisoning, adverse effects of this drug limit its current use to patients unable to tolerate DMSA or $CaNa_2EDTA$ in a clinical situation requiring chelation.

BLL 20–45 μg/dL

Confirmed venous blood lead concentrations in this range should be repeated within 2 weeks to 1 month. Although somewhat controversial, routine chelation is not recommended in this range. The decision to use chelation therapy following confirmation of blood lead concentrations in this range depends on clinical judgment of various factors including the presence of biochemical evidence of toxicity, the persistence of elevated blood lead levels for several months despite the removal of lead from the child's environment, and susceptibility to lead toxicity (<2 years of age). Remediation of the home environment is the most important aspect of clinical management for reducing blood lead exposure in children. A small-scale study of children with blood lead concentrations 30–45 μg/dL randomized to DMSA treatment and placebo did not detect a statistically significant difference in the blood lead concentration between the two groups at 1-month (end of treatment) and 6-month follow-up.[813] Although the blood lead concentrations following treatment were lower than baseline, remediation of the home environment in both groups accounted for the difference in the mean blood lead concentrations.

$CaNa_2EDTA$ provocation test previously was used to decide the necessity of chelation in children with BLL 35–45 μg/dL, particularly when the FEP concentration was elevated. The increasing use of oral chelation with the technical and practical limitations of the lead mobilization test significantly restricts the current use of the $CaNa_2EDTA$ provocation test.[814] Lack of adequate hydration, difficulty obtaining complete urine collection, and iron deficiency can produce false-negative lead mobilization tests, commonly when blood lead levels remain elevated after remediation.

The lack of data to support the effectiveness of chelation in the reversal of neurotoxicity restricts the use of chelation for BLL 20–45 μg/dL. A modest cognitive improvement following $CaNa_2EDTA$ chelation occurred in children treated with $CaNa_2EDTA$, but the nonrandom design of the study prevented adequate evaluation of confounding environmental and genetic variables.[815] In a randomized, placebo-controlled, double-blind (treatment of lead-exposed children) study of 780 children with BLL of 20–44 μg/dL at ages 12–33 months, the use of up to three 26-day courses of DMSA did not improve scores on cognitive, neuropsychological, or behavioral tests when compared with placebo.[806,816] At 7 years of age, 647 subjects remained in the study. Although the use of DMSA did lower the mean blood lead concentration ~4.5 μg/dL (95% CI: 3.7–5.3 μg/dL) during the first 6 months of treatment, the mean scores on cognitive, behavioral, and neuropsychological function at the 36-month follow-up period were similar to placebo. Reanalysis of the control data indicated that improvement in scores in the placebo group (i.e., no chelation) resulted from factors other than declining blood lead levels.[817] The mean blood lead concentration in the study group was 26 μg/mL; the mean maternal IQ was 80.

BLL <20 μg/dL

Confirmed venous blood lead levels <10 μg Pb/dL usually require follow-up BLL within 3 months and then 6–9 months after the BLL declines. Blood lead levels in the range of 10–20 μg Pb/dL should be repeated

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within 1–3 months as displayed in Table 16.16 followed by retesting 3–6 months after the BLL declines. If the blood lead level remains within 10–14 μg/dL, the patient's family should receive additional advice on methods to reduce blood lead exposure (see Table 16.20) and the blood lead test repeated within 1–3 months along with a careful environmental history, advice on nutrition (e.g., iron, calcium), and education to decrease blood lead exposure.[818] There is no clear evidence that chelation alone improves IQ in children with lead levels elevated above population norms.[816]

Adults

The treatment of adults is based primarily on the presence of symptoms of lead intoxication that usually occur at somewhat higher blood lead levels compared with children. Symptomatic patients (usually >70 μg/dL) should be chelated. Chelation based on specific BLL for adults is controversial (see Table 16.22) because of the lack of data documenting the improvement in neurological function in asymptomatic patients.[632] Furthermore, a 5-day course of $CaNa_2EDTA$ does not reduce brain lead concentrations.[819] A prospective, observational study of Taiwan residents with high-normal body lead burdens (EDTA-mobilization test results ≥80 μg to <600 μg over 72 hours) suggested that chelation may slow the progression of chronic renal disease in these patients, but the study did not separate the effects of EDTA chelation from the effects of a reduction of the body lead burden.[820]

There are limited clinical data on the efficacy of DMSA to reduce symptoms during lead intoxication in adults. A case report on a 54-year-old man with chronic lead toxicity associated a dramatic drop in the blood lead concentration following administration of a daily dose of 30 mg DMSA/kg bodyweight for 3 days and 20 mg DMSA/kg for 4 days.[821] Although substantial rebound in the lead concentration occurred within 89% of baseline, he reported improved memory and fewer headaches. Treatment was terminated because of mucocutaneous lesions; the BLL rebounded to 52 μg/dL.

Pregnant Patients

Scientific evidence regarding chelation in pregnant patients is very limited consisting primarily of animal studies and a few case reports mostly on $CaNa_2EDTA$ administration during the second and third trimesters. Calcium disodium edetate is usually the preferred lead chelator during pregnancy.[787] Edetate disodium (Na_2EDTA) should never be administered because of the potential for life-threatening hypocalcemia. Most experts recommend inpatient chelation for pregnant women with BLL >70 μg/dL and particularly with evidence of encephalopathy to reduce maternal and fetal toxicity regardless of the trimester. Rodent studies with calcium edetate suggest chelation therapy during organogenesis potentially increases the risk of congenital abnormalities from the excretion of essential metals.[822] Thus, the CDC recommends considering chelation for maternal BLL >45 and <70 μg/dL after completion of organogenesis in consultation with lead poisoning and high-risk pregnancy experts consistent with the general concern about administering unusual drugs during organogenesis.[823] Rodent studies indicate that DMSA is not teratogenic, but high daily doses (100–1,000 mg/kg) produce maternal toxicity (decreased weight gain) and fetotoxicity. A single case report described the outpatient administration of DMSA to a 38-year-old woman with chronic lead poisoning (BLL = 57 μg/dL in the late third trimester).[824] The maternal blood level did not decline (questionable compliance), and the cord blood lead was 126 μg/dL. The lead source was never identified. The maternal BLL should be confirmed in a second blood sample drawn within 24 hours of the first draw. The CDC recommends pumping and discarding breast milk when the maternal BLL is ≥40 μg/dL and the initiation of breastfeeding when the maternal BLL declines below 40 μg/dL.[823]

Pregnant women with BLL <5 μg/dL do not require follow-up during pregnancy; BLL above this value should be repeated to confirm excessive lead exposure. Repeat BLL should be drawn depending on the extent of BLL elevation and risk factors. Pregnant patients with BLL 15–24 μg/dL may retest every 2–3 months along with evaluation of lead sources, whereas patients with BLL 25–44 μg/dL require monthly blood lead concentrations and examination of their environment for lead sources.[825]

Enhancement of Elimination

Methods to enhance elimination typically do not alter blood lead concentrations. Hemodialysis of a patient following the ingestion of lead oxide reduced the blood lead half-life to 9 hours in combination with EDTA chelation; the blood lead half-life during EDTA infusion alone was 96 hours.[826] The case report provided no assessment of the efficacy of hemodialysis including no data on the amount of lead removed in the dialysate.

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Supplemental Care

Acute Encephalopathy

Laboratory studies during treatment of lead-induced encephalopathy include serum creatinine BUN, and calcium, serum hepatic aminotransferases, urinalysis, 24-hour urine creatinine and protein, peripheral motor nerve conduction velocity, intelligence/personality tests, and sperm counts.

1. Maintain generous daily urine flow (350–500 mL/m^2) to keep the urine specific gravity <1.020.
2. Treat acute encephalopathy promptly.
3. Monitor blood lead levels daily. Stop BAL if BLL decreases <50–60 µg/dL. Stop $CaNa_2EDTA$ if BLL decreases <40 µg/dL or urinary lead decreases <2 mg Pb/24 hours.
4. Usually, three or four 5-day courses are necessary for acute encephalopathy. Obtain a CT head to evaluate cerebral edema if acute changes in neurological status develop.
5. Maintain hydration and watch for deteriorating renal function with daily urinary protein and serum creatinine measurements.
6. After treatment courses, measure blood lead in 10–12 days for rebound from bone stores. The post-chelation lead value is highly variable depending on dose and chelating agent, body burden of lead, continuing lead exposure (e.g., retained lead foreign body near acidic environment), and time since chelation ended. The post-chelation rebound usually does not exceed pre-chelation values.
7. *Always* identify the lead source in the environment to prevent reexposure. Children should be hospitalized until they can be discharged into a lead-safe environment. Focused dust-control programs in contaminated homes can significantly reduce BLL in children.[827]
8. Cerebral edema usually responds to chelation therapy. IV or IM midazolam is the preferred drug of choice for rapid control of seizures. The use of surgical decompression and mannitol to relieve intracranial pressure should be used cautiously.[646]

Retained Lead Bullets

Most retained bullets require no surgical intervention as the *initial* therapy. Surveillance of blood lead levels depends on the assessment of risk. High risk of lead toxicity involves bullets near joints (shoulder, hip, knee), large load of multiple lead fragments (e.g., multiple shotgun pellets), direct contact with bone, and possibly intraabdominal fragments. These patients should have a baseline blood lead level, then repeat BLL within 2 weeks. Depending on the risk, these patients should be followed monthly for several months, then yearly. Lead toxicity may develop long after the initial injury; hence, these patients should be followed long-term. Removal of bullets is usually necessary for patients with high BLL and/or symptoms of lead toxicity. Chelation should be started before surgery to reduce the postoperative elevation of the BLL. Intraarticular lead bullets may produce opacification of the synovium with fine lead particles (lead arthrogram), thinning of the cartilage, proliferative synovitis, and arthritic changes.

ORGANIC LEAD

HISTORY

The research lab of General Motors Corporation in Dayton, Ohio discovered the value of tetraethyl lead as a gasoline additive in 1921; the use of leaded gasoline allowed the development of powerful, high-compression engines. The US Surgeon General temporarily suspended the production and sale of leaded gasoline in 1925 as a result of the occurrence of behavioral abnormalities and fatalities in workers manufacturing tetramethyl lead. Production continued in 1926 after an investigatory committee formed by the US Surgeon General recommended continued use of leaded gasoline as a motor fuel as long as distribution and use were controlled by proper regulation. The Committee warned that widespread use may create more hazardous conditions than their investigation uncovered. Production of tetraethyl lead increased dramatically during World War II with most gasoline containing lead by the 1950s.[828] US peak consumption of tetraethyl lead occurred in 1969.[829] Other organolead compounds used to improve octane in gasoline include tetramethyl lead, ethyltrimethyl lead, triethylmethyl lead, and dimethyldiethyl lead; however, tetraethyl lead was by far the most common gasoline additive. In 1973, the US EPA issued regulations requiring the gradual reduction of lead in all gasoline. US automakers introduced catalytic converters in 1975 in response to the timetable for the reduction of lead in gasoline. Although farm equipment and aviation fuel can still contain alkyl lead additives, the use of lead >0.05 g Pb/gallon was banned in automobile fuel by 1996.

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PHYSIOCHEMICAL PROPERTIES

Tetramethyl lead is highly flammable with a tendency to collect in low areas as a result of a vapor density of 6.5. Table 16.23 lists the identifying information and physical properties of organic lead compounds.

EXPOSURE

Exposure to organic lead occurs almost exclusively as a result of direct contact (e.g., service station, refinery) with leaded fuel because combustion of gasoline oxidizes organic lead to inorganic lead salts. Organolead compounds are fuel additives and antiknock agents in aviation and motor vehicle fuels including tetraethyl lead, tetramethyl lead, diethyldimethyl lead, triethylmethyl lead, and ethyltrimethyl lead.

ENVIRONMENTAL FATE

Air

More than 90% of the lead emitted from automobile exhaust appears in the form of inorganic particulate matter (e.g., lead bromochloride, double salts with ammonia halides), whereas the remainder occurs as organic lead vapors.[37] About 1% of the organolead content of gasoline releases unchanged to the atmosphere from car exhaust.[830] In the atmosphere, tetraethyl and tetramethyl lead compounds exist primarily in the vapor phase.[831] The atmospheric half-life of organic (i.e., tetraethyl, tetramethyl) lead ranges up to ~2 days with the trialkyl and dialkyl lead compounds being more persistent than tetraalkyl compounds.[832] The organic lead vapors are photoreactive; consequently, the residence time of these vapors is limited. Tetraethyl and tetramethyl lead compounds decompose rapidly to trialkyl and dialkyl lead compounds after exposure to sunlight within 12 hours during summer and 36 hours in winter;[829] subsequently, these compounds degrade to inorganic lead oxides as a result of direct photolysis or reactions with hydroxyl radicals and/or ozone. The reaction of tetraethyl lead and hydroxyl radicals during summer has a half-life of ~6 hours, whereas the estimated overall half-life of tetraethyl lead is <2–3 days.[833] Halogenated lead compounds form during combustion by the reaction of halogenated lead scavenger compounds with tetraalkyl lead compounds. Within 1 day, ~75% of the brominated lead compounds and ~30–40% of chlorinated lead compounds undergo conversion to lead carbonates, oxycarbonates, and oxides.[834]

Water

In water, tetraethyl lead and tetramethyl lead rapidly undergo photolysis and volatilization with <1% tetraethyl lead remaining after 2 weeks.[829] In experimental studies, tetraethyl lead compounds decompose within 48 hours to trialkyl lead in rainwater samples exposed to sunlight; trialkyl and dialkyl compounds are stable in rainwater without light.[835] Tetraalkyl lead compounds (e.g., tetraethyl lead) are insoluble in water; consequently, leaching from the soil is unlikely. Trialkyl and tetraalkyl lead compounds can bioconcentrate in aquatic organisms; however, biomagnification of organolead compounds does not occur.[37]

TABLE 16.23. Identifying information and physical properties of some organic lead compounds.

Physical Characteristic	Tetraethyl Lead	Tetramethyl Lead	Diethyldimethyl Lead	Triethylmethyl Lead
Synonym	TEL, tetraethyl-plumbane	Tetramethyl-plumbane	Diethyldimethyl-plumbane	Methyltriethyl-plumbane
CAS RN	78-00-2	75-74-1	1762-27-2	172-28-3
Molecular formula	PbC_8H_{20}	PbC_4H_{12}	PbC_6H_{16}	PbC_7H_{18}
Molecular weight (g/mol)	323.45	267.3	295.4	309.4
Valence	+4	+4	+4	+4
Color	Colorless[a]	Colorless[a]	Colorless	Colorless
Physical state	Oily liquid	Liquid	Liquid	Liquid
Odor	Pleasant, sweet, characteristic	Fruity	NA	NA
Melting point (°C)		−30.2		
Boiling point (°C)	200 (decomposes at 227.7)	110	51 (13 mmHg)	70 (15 mmHg)
Density (g/mL, 20°C)	1.653	1.995	1.79	1.71
Water solubility (mg/L, 25°C)	0.29 (minimal)	15 (slight)	4.6 (slight)	1.9 (slight)
Vapor pressure (mmHg)	0.26 (25°C)	26 (20°C)	2.2 (25°C)	1.3 (25°C)

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.
[a] Usually dyed blue, orange, or red.

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Soil

Although dry deposition is an important process for the removal of lead from the air, the majority (40–70%) of lead partitions from air to soil via wet deposition. Most lead remains in the area of deposition as a result of poor solubility and binding to organic matter. At a pH of 4–6, organic lead complexes become soluble; these compounds leach from the soil, resulting in uptake by plants.

DOSE EFFECT

Organolead compounds are potent neurotoxins. A 13-year-old boy accidentally ingested a mouthful of fuel stabilizer containing 80–90% tetraethyllead along with dibromoethane and dichloroethane.[836] He developed severe neurological symptoms including agitation, visual hallucinations, tremor, muscle weakness, and respiratory insufficiency that required hospitalization for 2 months. Three months after ingestion, he was able to ride his bike; his parents reported some difficulty concentrating. Two adolescents ingested ~15 mL tetraethyllead; within 12 hours, they developed altered consciousness, convulsions, hyperreflexia, and respiratory insufficiency.[837] They ultimately sustained a fatal cardiac arrest (19 hours and 26 days after ingestion) after developing hypotension.

TOXICOKINETICS

The absorption of inhaled aerosols of tetraethyl lead is relatively rapid and almost complete based on experimental radiotracer studies. Dermal absorption of tetraethyl lead is also greater than inorganic lead based primarily on *in vitro* studies.[37] In contrast to inorganic lead, organic alkyl lead (tetraethyl lead, lead naphthenate) may diffuse across the epidermal layer in sufficient quantities to produce toxicity after prolonged, heavy dermal exposure.

Organic lead is distributed primarily to liver, brain, and kidney.[838] The liver metabolizes organic lead compounds by oxidative dealkylation via CYP450 isoenzymes; metabolites appear primarily in the urine and feces. After absorption, tetraethyl lead undergoes biotransformation to triethyl lead (central nervous system toxin), followed by dealkylation to diethyl lead and inorganic lead based on the analysis of urine from patients poisoned with tetraethyl lead. A worker was hospitalized for 2 months for tetraethyl lead poisoning after cleaning an aviation fuel tank; 3 weeks after exposure to tetraethyl lead, his urine contained the following lead species: triethyl lead, 2%; diethyl lead, 50%; and inorganic lead, 48%.[839]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Inhibition of dopamine, γ-aminobutyric acid (GABA), and glutamate uptake and/or metabolism is a suspected cause of the neuromuscular and behavioral abnormalities associated with organic lead toxicity; however, the exact role of these neurotransmitters in the development of triethyl lead neurotoxicity remains unclear.[287] The inhibition of intracellular ATP synthesis and transduction and/or binding of lead to intracellular Ca^{2+}-cytoplasmic proteins (e.g., calmodulin) causes mitochondrial swelling, dysfunction, and cell death. *In vitro*, triethyl lead interacts with two thiol groups of the tubulin dimer, inhibiting microtubule assembly and direct cellular movement (chemotaxis); *in vivo*, interactions with the tubulin/microtubule system cause aneuploidy and subsequently cytotoxicity.[840]

Nonpolar organic lead compounds penetrate the blood–brain barrier more easily than inorganic lead. Animal data and a case report suggest that the toxicity of tetramethyl lead is substantially less than that of tetraethyl lead, consistent with the lack of formation of the toxic metabolite, triethyl lead.

Pathological Changes

Exposure of animals to organic lead produces a limited pattern of neuropathological changes, primarily involving the frontal cortex and the limbic forebrain, particularly the hippocampus and anterior pyriform cortex.[841] The limbic system modulates learning, memory, motivation, and behavioral reactivity; organolead toxicity resembles the neurobehavioral deficits associated with limbic system damage. In rodents exposed to tetraethyl lead and the neurotoxic metabolite (triethyl lead), neurotoxic effects include lethargy followed by hyperexcitability, hypermotility, tremors, aggression, and convulsions consistent with damage to this region of the brain.[842]

Postmortem

The most severe damage following death from tetraethyl lead exposure involves the central nervous system; pathological changes also occur in the kidneys, bone

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marrow, and peripheral nervous systems. The most dramatic histological change in the brain of a 25-year-old male with a 5-year history of sniffing leaded gasoline was cerebellar atrophy manifested by severe loss of Purkinje cells and thinning of the granule cell layer of the superior vermis.[843] Neuropathological abnormalities included chromatolysis of neurons in the reticular formation and cerebral cortex as well as loss of neurons in both the hippocampus (Ammon's horn) and cerebellum. The lead concentration in his brain tissue was 2.1 μg/g compared with 0.1 μg/g in tissue from a man with similar age and no unusual lead exposure.

CLINICAL RESPONSE

Acute Toxicity

A 22-year-old man sustained blast injuries when an angle-valve on an autoclave containing tetramethyl lead blew off; he was doused with material containing ~30% tetramethyl lead and ~70% inorganic lead that also partially blocked his mouth and nose.[844] He remained in the hospital for 58 days recuperating from traumatic injuries; at no time did he develop neurotoxic symptoms suggestive of lead poisoning, despite a blood lead level of 81 μg/dL the day after admission.

Inhalation

Tetraethyl lead is a central nervous system toxin characteristically causing an acute toxic psychosis with early subtle, nonspecific symptoms.[845] This toxic psychosis differs from the motor neuropathy, anemia, and coproporphyrinuria commonly seen with inorganic lead toxicity. Clinical features of acute tetraethyl lead encephalopathy include headache, anxiety, diaphoresis, sialorrhea, weakness, lethargy, tremor, insomnia, euphoria, hallucination, memory disturbances, and ataxia;[846] these symptoms may be delayed 12–24 hours after acute ingestion.[837] Abnormal myoclonic (chorea, facial grimacing) movements, confusion, disorientation, and decreased concentration often develop.[847] In more severe cases, the clinical effects progress to hyperexcitability, hypermotility, aggression, toxic delirium, hallucinations, convulsions, coma, hypotension, and cardiac arrest.

Ingestion

A 13-year-old adolescent developed severe neurological symptoms after the accidental ingestion of a fuel stabilizer containing 80–90% tetraethyl lead.[836] He had vomiting and abdominal pain immediately after ingestion; then, he developed progressive tremors, generalized weakness, hallucinations, and tremors over the next 48 hours. By the third day post-ingestion, he had slurred speech and was unable to stand; he ultimately required high doses of benzodiazepines, prolonged propofol infusion, and several days of intubation to control his severe neuromuscular symptoms. His cardiovascular system remained stable throughout his hospitalization. By 2 months after ingestion, he was able to perform all activities of daily living with mild slurred speech and a slight limp.

Environmental Exposure

Available data on organic (e.g., alkyl) lead compounds suggest these chemicals produce toxicity primarily through metabolism to inorganic lead including the release of inorganic lead from the combustion of gasoline containing alkyl lead.[37] The rapid oxidation of lead alkyl halides in automobile exhausts by sunlight and air significantly limits exposure to these compounds. In cases of chronic gasoline sniffing with tetraethyl lead, most cases of encephalopathy have substantially elevated inorganic blood lead concentrations.[848] Aspiration pneumonia and sepsis are the main causes of death in patients with lead encephalopathy from sniffing organic lead in gasoline.[849] Case reports associate gasoline sniffing with the development of an acute myopathy with myoglobinuria and markedly elevated creatine kinase activity.[850]

Occupational Exposure

The most common symptoms reported by 58 organic lead workers who self-referred to an occupational medicine clinic relate to the central and peripheral nervous systems. Forty-two of these workers participated in an epidemiological study of neurobehavioral performance involving mixed exposure to inorganic and organic lead.[851] The most common reported symptoms were memory loss (74%), joint pain (56%), trouble sleeping (54%), paresthesias (49%), fatigue (49%), nightmares (35%), and moodiness (28%). The co-exposure to inorganic lead complicates the determination of the cause of these symptoms. All workers had current BLL <40 μg/dL (mean = 19.4 ± 6.5 μg/dL).

Carcinogenesis

The IARC lists organic lead as a group 3 (not classifiable to carcinogenicity to humans) compound. The US

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National Toxicology Program lists lead and lead compounds as reasonably anticipated to be carcinogenic; however, the monograph does not specifically comment on cancer risk following exposure to organic lead other than mentioning positive animal studies. A case-control study of occupational exposure to lead compounds suggests an increased risk of stomach cancer (odds ratio = 2.0, 95% CI: 1.1–3.8) for exposure to organic lead compared with cancer controls.[852] Determination of organic lead exposure was based on job history and interpretation by expert chemists. This study did not detect an association between organic lead and other types of cancer or between inorganic lead and cancer. A Canadian case-control study of histologically confirmed cases of lung cancer did not find an excess lung cancer risk associated with occupational exposure to organic lead based on blinded expert-based assessment of lifetime occupational exposure and adjustment for smoking and sociodemographic characteristics.[491] Comparing ever- to never-exposed subjects, the odds ratio for lung cancer and organic lead exposure was 1.39 (95% CI: 0.77–2.52). A case-control study of cancer incidence and tetraethyl lead manufacturing workers exposed to both organic and inorganic lead detected a statistically significant increased incidence of rectal cancer (OR, 3.7, 90% CI: 1.3–10.2).[853] The incidence of rectal and sigmoid cancers increased with increasing exposure to the organolead manufacturing process, particularly with a 10-year latency. The incidence of cancer in exposed workers did not increase at other sites (i.e., bone, brain, kidney, lung, spleen, stomach). There are few data on the carcinogenic effect of tetra-alkyl lead compounds in animals, in part because of the difficulty of administering these relatively less soluble lead compounds compared with lead acetate.

DIAGNOSTIC TESTING

Three days after the ingestion of tetraethyl lead-containing fuel additive, the whole blood of a 13-year-old adolescent contained 62 μg Pb/dL; he was severely symptomatic with agitation, confusion, hallucination, hyperreflexia, severe rhythmic myoclonus, and generalized muscle weakness. The whole blood lead remained at 62 μg/dL 1 month later, despite clinical improvement. By 2 months, his whole blood lead was 51 μg/dL; he recovered with the exception of mild slurred speech and a slight limp. A cross-sectional cohort study of 543 of 2,798 former organic lead workers used X-ray fluorescence of tibial lead as the measure of long-term cumulative exposure to lead.[854] The study detected statistically significant negative correlations between tibial lead concentrations and the following domains during neuropsychological testing: manual dexterity (finger tapping), executive ability (Trail Making Test B), verbal intelligence (Wechsler Adult Intelligence Scale-Revised Vocabulary Subtest), and verbal memory (Rey Auditory-Verbal Learning Test). There were multiple comparisons; pre-lead exposure estimates of premorbid function of these workers were not available. Furthermore, verbal intelligence is usually relatively resistant to neurotoxic effects.

HEALTH SURVEILLANCE

The US OSHA PEL (8-hour TWA) for tetraethyl lead and tetramethyl lead in general industry is 75 $\mu g/m^3$ compared with 100 $\mu g/m^3$ for tetraethyl lead and 150 $\mu g/m^3$ for tetramethyl lead in the construction and shipyards industries. The NIOSH REL (10-hour TWA) and IDLH for tetraethyl lead and tetramethyl lead are 75 $\mu g/m^3$ and 40,000 $\mu g/m^3$, respectively, as lead. Studies of occupational cohorts indicate diethyl lead is the most sensitive and specific biomarker of tetraethyl lead exposure. Urinary concentrations of triethyl lead are relatively low compared with diethyl lead; total urinary lead and the BLL do not correlate to the ambient air concentration of tetraethyl lead.[855] In a study of 26 workers at a petrol plant exposed to tetraethyllead, the BLL (mean = 25.6 μg/dL; range, 19.0–53.5 μg/dL) did not correlate to ambient air concentrations of tetraethyllead;[856] however, the urinary diethyl lead ranged from 0.25–2.7 μg/dL and correlated (r = 0.70) to airborne tetraethyllead concentrations (range up to 810 $\mu g/m^3$).

TREATMENT

Treatment of acute tetraethyl lead toxicity is primarily supportive. The efficacy of chelation for tetraethyl lead toxicity is unproven. Theoretically, chelation provides some utility by chelating the tetraethyl lead converted to inorganic lead; however, rodent studies indicate that none of the alkyl lead forms bind well to traditional chelating agents.[842] Chelation of two patients with severe tetraethyl lead poisoning did not alter their fatal course.[837] In a case series of neurotoxic leaded gasoline sniffers, the use of BAL and $CaNa_2EDTA$ substantially reduced blood lead levels; however, the long-term efficacy remained equivocal. In a case series of 20 males admitted for lead encephalopathy from petrol sniffing and chelated with intramuscular $CaNa_2EDTA$ and BAL, the median blood lead level decreased from 99.5 μg/dL pre-chelation to 39.3 μg/dL post-chelation.[849]

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This study indicates that these patients have a significant pool of inorganic lead similar to heavily lead-exposed workers; however, the study did not evaluate the effect of chelation on the neurotoxicity associated with lead toxicity. Chelation remains an option for severely symptomatic patients with very elevated BLL.

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Chapter 17

LITHIUM

HISTORY

In 1817, Johan August Arfedsson discovered lithium; medical use of lithium began in 1844 when Alexander Ure introduced the use of lithium carbonate for the dissolution of rheumatic nodes and bladder stones.[1] The widespread use of daily doses of 3–26 mmol Li for anti-rheumatic treatment was not commonly associated with reports of toxicity. In 1871, William Hammond recommended the use of relatively high lithium carbonate doses (45 mmol Li every 2–4 hours during the first day or until sleep occurred followed by 3–4 times daily maintenance doses) for the treatment of acute mania and melancholia; however, acute toxicity associated with these large doses limited the widespread use of these recommendations.[2] Kopilinski reported symptoms of lithium toxicity associated with the use of lithium citrate in 1898.[3] During the 19th century, lithium was administered for gout based on the *in vitro* solubility of urate in lithium solutions; however, toxicity occurred with the required lithium dose.[4] Commercial production of lithium began in 1925, but significant production occurred during World War II with the use of lithium to absorb CO_2 in submarines, inflate emergency signal balloons (lithium hydride), and lubricate high-temperature parts.

The use of 25% lithium chloride as a salt substitute in the 1930s and 1940s for patients with hypertension and heart failure caused serious lithium toxicity; in early 1949, the US Food and Drug Administration (US FDA) banned the use of lithium salts as drugs and food supplements including the use of lithium as a flavoring agent in beverages.[5,6] In the same year, John Cade initiated the beginning of the "second lithium era" by recommending the use of lithium carbonate for acute mania;[7] however, high lithium doses (50 mmol Li daily) frequently produce adverse neurological effects. The Danish psychiatrist, Mogens Schou, in collaboration with Paul Christian Baastrup, conducted the first clinical trial on the mood-stabilizing effects of lithium. In 1970, the US FDA approved the administration of lithium carbonate in the treatment of bipolar mental illness. Currently, lithium is an important drug for the treatment of manic–depressive affective disorders. Lithium has a narrow toxic therapeutic index with most accidental poisoning resulting from altered drug kinetics during chronic therapeutic use. During 1995, the database for the American Association of Poison Control Centers recorded ~5,300 cases of potential lithium toxicity.[8] Of these cases, ~3% were considered serious and five deaths were ascribed to lithium intoxication. Twenty years later, lithium exposures reported to AAPCC were ~6,700 with ~2% listed as serious and 3 deaths attributed to lithium toxicity.[9]

PHYSIOCHEMICAL PROPERTIES

Lithium (CAS RN: 7440-73-5) is a soft, silvery-white Group 1 (Group IA) alkali metal with physical properties similar to sodium. This metal is the lightest solid metallic element with a atomic weight of 6.94 g/mol and density of 0.534 g/cm^3; its water solubility is 12.8 g/L. Lithium exists almost exclusively as the ^{6}Li and ^{7}Li isotopes. The melting point of lithium is relatively low (180.5°C). Lithium is a univalent cation that requires administration with an anion (carbonate, citrate).

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Lithium exists naturally in minerals (pegmatite, brines) as stable salts rather than a pure element because of its reactivity. Lithium orotate is an organic lithium compound that provides 3.83 mg elemental lithium/100 mg compared with 18.8 mg/100 mg inorganic lithium carbonate.

Lithium hydride (CAS RN: 7580-67-8; MW: 7.95 g/mol) is an odorless, combustible white-to-gray solid that forms when lithium reacts with hydrogen at ~500°C; the compound darkens after exposure to light. This compound has a melting point of 680°C, specific gravity of ~0.77, and vapor pressure of 0 at 20°C. This compound forms flammable dust clouds and decomposes in water to form lithium hydroxide and explosive hydrogen gas.

EXPOSURE

Uses

Lithium carbonate possesses a wide variety of useful industrial applications including a fluxing agent to reduce the thermal expansion in enamel coatings, the consumption of electricity, and the emissions of fluorine in aluminum pot lines. Lithium carbonate is a constituent of ceramic/glass production and primary aluminum production. Lithium hydroxide is an important compound for the production of lithium grease, which has numerous high-temperature applications. Lithium is a strong fluxing agent in the ceramics and glass industry, particularly in heat-resistant cookware as well as a component of alkaline cells and rechargeable batteries. The uses of lithium hydride include nuclear shielding material, a desiccant, a source of hydrogen, and a condensing agent for chemical synthesis. Although lithium is used in a variety of occupational settings, lithium intoxication in the work environment is rare. Toxicity from lithium compounds in the work environment results primarily from the corrosive actions of lithium hydride.

Sources

Soil

Lithium exists in most soils in trace concentrations. In a study of 180 soil samples from the Jordan Valley, the mean water-soluble lithium concentration from different locations ranged from 950–1,040 ng/mL in top soil (0–20 cm) and from 1,060–2,680 ng/mL in subsoil (20–40 cm).[10] In a study of soil samples from the Piedmont and Coastal Plain regions of Georgia and South Carolina, the total lithium content correlated with clay content ranged from 3.74–59.93 mg/kg.[11] Total exchangeable lithium was insignificant (<0.1%).

Water

Lithium typically occurs in low concentrations (<40 ng/mL) in surface waters with lithium concentrations in major US rivers of <2 ng/mL.[12] Surface waters in the Atacama Desert of northern Chile may contain lithium concentrations up to a few thousand ng/mL as a result of natural sources of lithium.[13] This desert is one of the driest in the world. In a study of maternal and neonatal lithium concentrations in the Atacama Desert and Argentina, water samples contained the following geometric mean of the lithium concentrations (ng/mL): San Antonio del los Cobres (n = 4), 705 (range, 650–740); Arica (n = 9), 60 (range, 25–80); and Santiago (n = 6), 21 (range, 16–34).[14]

Volcanism is a major source of lithium, resulting in relatively high lithium concentrations in thermal sources including natural spas. In a study of soil samples from the Piedmont and Coastal Plain regions of Georgia and South Carolina, the mean dissolved lithium concentrations in surface water from these two regions were 1.16 ng/mL and 0.70 ng/mL, respectively, with an overall range of 0.08–4.62 ng/mL.[11]

Lithium usually exists in drinking water at concentration of <10 ng/mL except in areas of naturally high soil content (northern Chile, northern Argentina, Austria) or anthropogenic sources (e.g., nuclear waste-disposal areas). In a study of 37 imported and US bottled mineral waters purchased in Chicago and Pittsburgh, the lithium concentration ranged from 2–5,240 ng/mL with the majority of bottle water containing <100 ng/mL.[15]

Diet

Lithium occurs in highly variable amounts in foods and drinking water. Limited data on US residents suggest the daily dietary lithium intake ranges from 650–3,100 µg.[16] Although no human diseases are clearly linked to lithium deficiency, animal studies suggest some reproductive and behavioral abnormalities in lithium-deficient animals with resulting recommendations for daily lithium intake of 1 mg.[16,17] The primary sources of lithium in the diet are grains and vegetables, particularly spinach; typically lithium concentrations in these foods range from 0.5–4.6 µg/g (ppm). Preliminary Chilean studies in areas of very high lithium concentrations in drinking water (>1,000 ng/mL) suggest that the diet may contribute substantial amounts of lithium (i.e., up to ~100 mg/day) to daily lithium intake; green vegetables (chard, parsley, lettuce), alfalfa, and milk contained the highest lithium concentrations.[18]

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Pharmaceuticals

Pharmaceutical preparations of lithium include lithium carbonate as a 300-mg tablet (8.12 mEq Li) and lithium citrate as a syrup (8 mEq Li/5 mL). The lithium carbonate capsules are also available as slow-release preparations. Lithium orotate is an organic lithium compound that is available over the Internet as a "dietary supplement." Lithium carbonate contains ~5 times the elemental lithium content as an equivalent amount of lithium orotate.

ENVIRONMENT FATE

Lithium occurs naturally in water and soil, primarily at low concentrations.[19] Representative background concentrations based on limited data include the following values: fresh water, 0.07–40 μg/L; seawater, 170–190 μg/L; sediment, 56 mg/kg; soil, 3–350 mg/kg (ppm); and atmosphere, 2 ng/m^3.[20] Li concentrations in major US rivers are <2 μg/L with some surface waters reaching 40 μg/L.[12] Metallic lithium reacts with water to form hydrogen and lithium hydroxide. High lithium concentrations exist in natural brines including Searle's Lake (Mojave Desert, California), Clayton Valley (Nevada), Salar de Rincon (Argentina), and Salar de Atacama (Chile) as well as certain lakes (Dead Sea, Israel; Great Salt Lake, Utah).

A variety of environmental chemicals have been associated with an increased incidence of autism spectrum disease including lithium in drinking water; however, current epidemiological evidence is insufficient to distinguish spurious from causal associations. Trace amounts of lithium occur in most soils, primarily in the clay fraction from sedimentary rocks. The earth's crust contains an average of 0.006 ppm (27th most abundant element). Although lithium is not an essential element for plant development, low Li concentrations stimulate growth, whereas high concentrations produce chlorosis-like effects.[21] The estimated average daily lithium intake for a 70-kg US adult ranges from 0.65–3.1 mg with grains (e.g., oats) and vegetables being the major sources.[16] Although the data on lithium bioaccumulation are limited, low Li affinity for particles suggests bioaccumulation is not clinically significant. Acidity increases lithium uptake by plants.

DOSE EFFECT

The therapeutic daily dose of lithium carbonate varies widely between individuals. The average daily dose of lithium is 900–1200 mg (62–83 mmol) Li. Before the era of therapeutic drug monitoring, neurological symptoms associated with daily doses of 24–80 mmol Li included asthenia, ataxia, depression, giddiness, myoclonus, and slurred speech.[22] Renal dysfunction reduces lithium clearance; therefore, dose reductions are necessary for patients with renal insufficiency in order to prevent lithium intoxication. Recommendations for patients with renal dysfunction include 50–75% of the maintenance dose for glomerular filtration rates between 10–50 mL/minute and 25–50% of the maintenance dose for glomerular filtration rates of <10 mL/minute.[23] A single ingestion of 40 mg Li/kg by a patient with a history of prior lithium use may produce toxic lithium blood concentrations. Lithium orotate is an organic lithium compound that provides ~1/5 of the elemental lithium present in an equivalent amount of inorganic lithium carbonate. The estimated ingestion of 2.7 g lithium orotate by an 18-year-old woman was associated with the development of mild tremor, nausea, and vomiting; symptoms resolved within 4.5 hours post-ingestion.[24] The serum lithium concentration 2.5 hours after ingestion was 0.41 mEq/L.

TOXICOKINETICS

Absorption

Nearly complete lithium absorption of therapeutic lithium carbonate doses occurs from the gastrointestinal tract with peak therapeutic concentrations developing within ~1–3 hours after the ingestion of standard-release lithium preparations. Average peak plasma lithium concentration of 1.66 mEq/L occurred ~1 hour after the ingestion of 1,500 mg lithium carbonate, standard-release preparation by 3 healthy adult volunteers.[25] Sustained-release preparations produce peak levels ~2–6 hours after ingestion with peak serum concentrations reaching ~50% of the peak concentration after standard formulations.[26] The water solubility of lithium carbonate is low; case reports suggest clinically significant delayed absorption may occur up to 48–72 hours after large ingestions of sustained-release preparations.[27,28]

Distribution

Lithium initially distributes into the extracellular space with an apparent volume of distribution of ~0.7–1.0 L/kg, similar to total body water; lithium does not bind to serum proteins.[29] The distribution of lithium after ingestion is complex with preferential uptake in certain compartments (bone, kidney, thyroid, pituitary

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glands). Lithium concentrations in plasma, lung, heart, and umbilical cord are similar, whereas lithium concentrations in erythrocytes are approximately half of the serum lithium concentration. Although equilibrium between the cerebrospinal fluid and serum is rapid, lithium concentrations in cerebrospinal fluid at equilibrium are ~25–65% of the serum lithium concentrations as a result of the active efflux of lithium from cerebrospinal fluid by arachidonic membranes and capillary endothelium.[30] However, lithium concentrations in cerebrospinal fluid do not accurately reflect brain lithium concentrations.[31] The distribution of lithium into the liver and kidneys is relatively rapid compared with lithium distribution into bone, muscle, and brain. Equilibration of lithium between serum and brain tissue requires ~1 day.[32,33] Complete equilibrium between the serum and deep compartments in the brain, bone, and muscle may require up to ~1 week.[34]

Lithium crosses cellular membranes slowly; this slow re-distribution accounts for the delayed onset of action and the slow clinical response of serum lithium concentrations to hemodialysis. Severe toxicity does not usually develop until the distribution phase is sufficiently complete to allow significant penetration of lithium into the central nervous system. Consequently, a patient with an acute overdose and high initial serum concentrations of lithium may not develop neurological symptoms, if hemodialysis removes the lithium before penetration into the central nervous system. Conversely, symptoms may persist in a chronically intoxicated patient despite the reduction of serum lithium concentrations to the normal therapeutic range.

Persistently high concentrations of lithium in the brain of chronically intoxicated patients may account for slow neurological improvement despite relatively low serum lithium concentrations.

Elimination

There is no significant biotransformation of lithium in the body; lithium clearance occurs almost exclusively through the kidneys with negligible amounts of lithium (i.e., <5%) excreted in the bile, saliva, and feces. The kidneys process lithium similar to potassium, magnesium, and sodium through glomerular filtration.[26] The proximal renal tubules absorb 60–80% of the filtered lithium load, whereas minimal lithium absorption occurs in the distal tubule.[35] Lithium clearance is proportional to the glomerular filtration rate; during impaired renal function, a proportional decrease in the effective renal plasma flow results in a reduction in the clearance of lithium.[36] In patients with chronic nephropathy and reduced glomerular filtration rates, the fraction of lithium excreted into the urine remains normal until the glomerular filtration rate decreases below 25–35 mL/minute.[37] Events that increase the absorption of sodium and water in the proximal tubule will increase serum lithium concentrations including hyponatremia, low-salt diet, volume depletion, cardiac failure, diuretics, and nonsteroidal anti-inflammatory medication. The development of polyuria and diarrhea during long-term lithium therapy enhances the accumulation of lithium in the blood by causing sodium and water depletion.[38] Lithium clearance increases in alkaline urine.

The wide variation in the reported serum lithium elimination half-lives in randomly selected subjects results from differences in renal function and duration of lithium use. In volunteers receiving a single dose of lithium, the serum lithium half-life was ~9–13 hours during the initial elimination phase.[25] A two-compartment model best describes the elimination kinetics of lithium. The terminal β-serum lithium half-life ranges from ~18–36 hours during the beginning of lithium therapy; however, the terminal serum half-life increases up to ~60 hours following chronic therapy. In a study of 30 patients hospitalized for primary affective disorders, the approximate mean serum elimination half-life of lithium in patients receiving chronic lithium therapy recently, <1 year, and >1 year was 31 hours, 40 hours, and 58 hours, respectively.[39] Similarly, the lithium elimination half-life is longer during chronic lithium intoxication than acute or acute-on-chronic lithium intoxication. In a series of lithium intoxications reported to a regional poison control center, the mean elimination half-lives of lithium during acute, acute-on-chronic, and chronic lithium intoxications were ~12 ± 10 hours (range, 6–24 hours), 13 ± 8 hours (range, 3.5–45 hours), and 36 ± 23 hours (range, 11–100 hours), respectively.[40] In a study of 68 patients admitted for lithium intoxication, the approximate mean serum lithium half-lives for acute, acute-on-chronic, and chronic lithium intoxication were 12 hours, 21 ± 1 hours, and 32 ± 3.5 hours, respectively.[41] The mean serum lithium half-life in a cohort of 14 patients admitted to an intensive care unit with lithium toxicity was ~23 ± 9 hours.[42] The cohort contained a mixture of acute, acute-on-chronic, and chronic lithium poisoning with the serum lithium concentrations ranging from 1.4–9.6 mEq/L.

Maternal-Fetal Kinetics

Breast milk contains variable amounts of lithium in mothers receiving therapeutic lithium doses. Serum lithium concentrations in infants breast-fed by mothers on lithium are somewhat lower than maternal serum lithium concentrations. An analysis of case reports of mothers on lithium during breastfeeding suggested

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that lithium concentrations in breast milk are ~40% of the maternal lithium concentrations with a range of ~25–70%.[43,44] Similarly, in a study of lactating mothers from areas in Chile and Argentina, the geometric mean of the breast milk/blood ratios from three cohorts residing in different areas was ~40% despite widely varying blood lithium concentrations.[14] In a study of 11 lactating women receiving lithium doses of 600–1,500 mg/day, the mean neonatal lithium dose ranged from 0–30% (mean = 12.2% ± 8.5%, 95% CI: 6.3–18.0%) of the maternal dose.[45] Although the authors observed no adverse effects in the neonates, they recommended close monitoring of neonatal serum lithium concentrations and adverse effects. There are few data on the clinical consequences of lithium concentrations in these infants; most physicians do not encourage breastfeeding during lithium therapy without close monitoring.

Drug Interactions

Table 17.1 lists numerous drug interactions associated with lithium use. Drug–drug interactions are classified into pharmacokinetic and pharmacodynamic interactions based on pharmacological mechanisms. Pharmacokinetic drug interactions result from alterations in absorption, distribution, or elimination of a drug and/or the metabolites. Lithium is not metabolized; therefore, lithium toxicity from these interactions usually develops from the interaction of drugs on the renal clearance of lithium ions, particularly thiazide diuretics and angiotensin-converting enzyme inhibitors in the elderly.[46,47,48] Pharmacodynamic drug interactions occur directly at the site of action or indirectly from interference by another physiological mechanism.[49] These interactions are subclassified as the following: 1) additive (the sum of individual drug effects); 2) synergistic (greater than additive); and 3) antagonistic (less than additive). The pharmacodynamic interactions of lithium are complex, affecting many biological processes, but not serum lithium concentrations.[50,51] Pharmacodynamic interactions with lithium most commonly involve antipsychotic agents, calcium antagonists, and antiepileptic drugs (e.g., carbamazepine, lamotrigine, valproate).[49,52] The simultaneous ingestion of ethanol and lithium does not significantly alter the pharmacokinetics of therapeutic lithium doses except for a minor increase in peak lithium concentrations.[53] Case reports associate elevated lithium concentrations with the administration of some COX-1 (e.g., ibuprofen) and selective COX-2 (e.g., celecoxib) nonsteroidal anti-inflammatory drugs,[54] particularly in the setting of renal dysfunction.[55]

TABLE 17.1. Drug interactions with lithium. (Adapted from Timmer and Sands).[56]

Drug Classification	Effect on Plasma Lithium Concentration
Diuretics	
Thiazide	Increase
Loop diuretics	Variable (increase/decrease)
Osmotic diuretics	Decrease
Potassium sparing	Variable (increase/decrease)
Acetazolamide	Decrease
Mannitol	Decrease
Angiotensin-converting enzyme inhibitors	Increase
Angiotensin receptor blockers	Increase
Nonsteroidal anti-inflammatory drugs[a]	
Indomethacin	Increase
Ibuprofen	Increase
Mefenamic acid	Increase
Naproxen	Increase
Sulindac	No effect
Aspirin	No effect
Theophylline, caffeine	Decrease
Verapamil	Decrease
Topiramate	Slight decrease
Carbamazepine	Increase

[a] Effects vary between nonsteroidal anti-inflammatory drugs. Sulindac and aspirin do not usually alter the lithium concentration.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

At the neuronal level, lithium inhibits gamma-aminobutyric acid (GABA) neurotransmission, while reducing excitatory dopamine and glutamate neurotransmission. Although the mechanism of action is not well defined, lithium probably acts through multiple pathways as a substitute for body cations (sodium, potassium) on several transport proteins (e.g., sodium channel, sodium-proton exchanger) and as an inhibitor of glycogen synthetase kinase-3β. The latter action reduces phosphorylation of nuclear factors that promote cell growth and protective mechanisms (nuclear factor of activated T cells, Wnt/β-catenin signaling pathway).[57] Lithium also upregulates neurotrophins including nerve growth factor, neurotrophin-3, and brain-derived neurotrophic factor; additionally, lithium alters transduction pathways related to glutamate, decreases noradrenaline and dopamine release, and transiently increases serotonin release.[58] Potential mechanisms for the effectiveness of lithium in bipolar disease include the following: 1) decrease in excitatory glutamatergic activity by modulation of neurotransmitters, and 2) modulation of messenger systems

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including protein kinase C, cAMP-dependent kinase, and glycogen synthetase kinase 3β.[59]

A partial substitution for normal cations causes changes in ion exchange and transfer in cellular processes. The sodium channel is the key transporter for sodium homeostasis in the renal collecting ducts; this channel is equally permeable to lithium and sodium. Under normal physiological conditions, the sodium-proton exchanger is the transport system that is responsible for sodium reabsorption across the proximal tubule. This protein also transports lithium, although the maximal transport rate for lithium is half the rate of sodium transport.[60] Amiloride inhibits both the sodium channel and sodium-proton exchanger transporters. The transport of lithium by Na^+/K^+ ATPase pump is probably small under normal physiological conditions because the affinity of lithium for this protein is at least an order of magnitude less than the affinity of this protein for sodium and potassium. Lithium does not equilibrate passively between intracellular and extracellular compartments; this ion must be actively transported out of most cells by proteins (e.g., the sodium–sodium exchange protein).[56] The exact molecular basis for lithium transport currently is unknown. Incorporation of lithium into membrane structures may alter responses to hormones and the uncoupling of energy processes.

Mechanism of Toxicity

Central Nervous System

The major target organ for lithium toxicity is the central nervous system.[61] Damage to the basal ganglia may produce cerebellar signs;[62] rarely, horizontal down-beating nystagmus occurs following an acute lithium overdose as a result of cytotoxic damage to the nuclear structures in the cervicomedullary region.[63] Other reported ocular disturbances include horizontal gaze-evoked nystagmus, saccadic pursuit, saccadic dysmetria, unilateral gaze palsy, and oculogyric crisis. Electrolyte abnormalities (hypernatremia, hypomagnesemia) may contribute to the development of neurological symptoms; the rapid increase of serum sodium concentrations may cause central pontine myelinolysis. This demyelinating condition occurs in patients with chronic systemic illness (e.g., alcoholism, cancer, liver disease, malnutrition, sepsis) as well as hyperosmotic stress and disruption of the blood–brain barrier from rapidly correcting hyponatremia.[64] Common features of central pontine myelinolysis include dysarthria, dysphagia, mutism, and quadriplegia. Loss of myelin and oligodendrocytes may also occur at extra-pontine locations (e.g., basal ganglia, cerebral gray–white junction, cerebellar cortices, lateral geniculate);[65] furthermore, elevation of the serum sodium concentration above 160 mEq/L can cause parenchymal or subdural hemorrhages as a result of the rapid shrinkage of the brain matter.

Kidney

Acquired Nephrogenic Diabetes Insipidus

Arginine vasopressin-resistant, nephrogenic diabetes insipidus resulting in polyuria is the most common renal side effect of lithium therapy occurring in up to 55% of patients on long-term lithium therapy. Mechanisms of toxicity are multifactorial including the following: 1) inhibition of adenylyl cyclase in the principal cells within the collecting duct, and 2) reduction of medullary interstitial osmolality by decreasing the abundance of AQP2, UT-A1, and UT-B proteins.[66] Downregulation of AQP2 protein decreases vasopressin-induced water reabsorption across the apical membrane in the collecting duct. Reducing UT-A1 protein abundance interferes with vasopressin-induced phosphorylation of UT-A1, whereas a reduction in UT-B abundance in the inner medulla reduces the urinary concentrating ability by decreasing urea recycling and countercurrent exchange efficiency. The slow recovery from lithium-induced renal dysfunction relates to the partial reversal of AQP2 abundance following discontinuation of lithium therapy, desmopressin treatment, and water restriction.[67]

In nephrogenic diabetes insipidus, the renal tubules fail to respond to the antidiuretic action of arginine vasopressin (antidiuretic hormone, ADH), whereas central (neurogenic) diabetes insipidus results from inadequate secretion of ADH from the posterior pituitary. Cellular remodeling of the collecting duct and downregulation of the vasopressin-regulated water channel aquaporin-2 on the apical plasma membrane of the renal collecting ducts produce nephrogenic diabetes insipidus in patients on chronic lithium therapy.[67] Lithium enters the cells of the collecting duct via the luminal apical epithelial sodium channel;[68] the proximal tubule and thick ascending limb proteins are not affected by lithium. In volunteer studies, the epithelial sodium channel inhibitor, amiloride, reduces lithium uptake in the principal cells of the collecting duct and improves responsiveness to vasopressin-stimulated translocation of urinary aquaporin-2 to the apical membrane of the principal cells.[69]

Arginine vasopressin produces fluid retention by increasing the water permeability of the renal collecting ducts. The binding of vasopressin to the V_2 receptor on the basolateral membrane of the collecting duct causes activation of adenyl cyclase via magnesium-dependent

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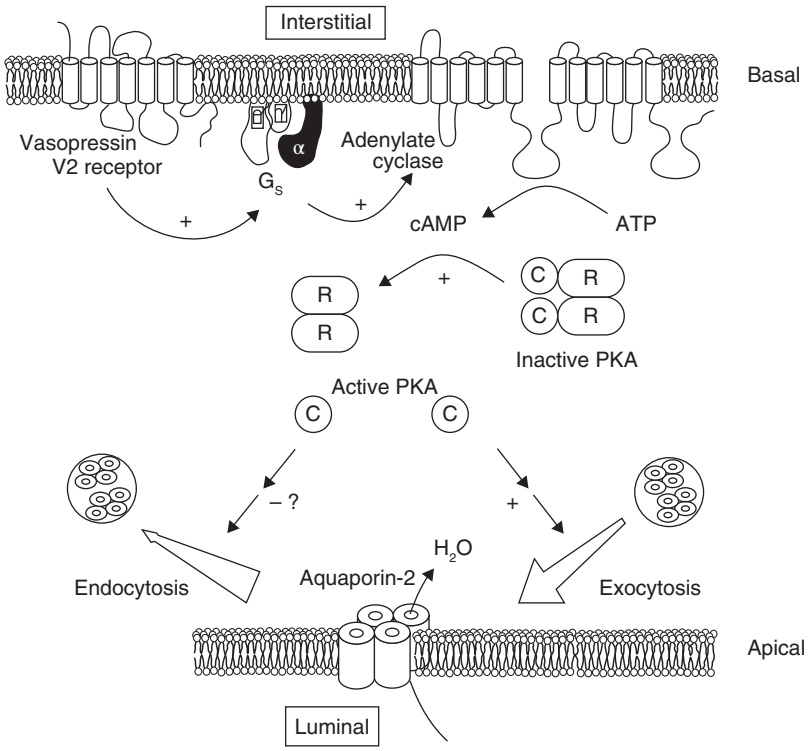


FIGURE 17.1. Schematic representation of the antidiuretic effect of vasopressin on the collecting duct. Catalytic (C) and Regulatory (R) are subunits of Protein Kinase A (PKA). (Modified from Oksche et al.).[70]

protein G_s. Aquaporine-2 channels in the luminal membrane markedly increase water permeability. Under normal circumstances, the increased cAMP and stimulation of protein kinase A fuse vesicles carrying aquaporine-2 leading to reduced water excretion into the collecting ducts as demonstrated by Figure 17.1. Patients with nephrogenic diabetes insipidus are unable to concentrate urine on fluid restriction as reflected by high **serum** osmolalities (>300 mOsmol/kg) compared with relatively low **urine** osmolality (<280 mOsmol/kg, specific gravity <1.010) associated with a normal response to dehydration. Their kidneys do not respond to pharmacological doses of vasopressin. Normal patients and patients with psychogenic polydipsia respond to dehydration by concentrating their urine (>450 mOsmol/kg, specific gravity >1.020).

Lithium accumulates in collecting tubule cells after passage through the sodium channels in the luminal membrane; lithium directly impairs arginine vasopressin-mediated activation of adenylate cyclase in the collecting ducts.[71] This action decreases intracellular cyclic AMP formation and protein kinase A stimulation of the aquaporine-2 channels.[72] The effect of these changes is a reduction of aquaporin-2, the vasopressin-regulated water channels in the collecting ducts, resulting in loss of renal concentrating ability. Lithium also modulates the phosphoinositol pathway by decreasing the metabolism of inositol-1,4,5-trisphosphate (IP_3) and increasing the concentration of inositol-1,4-bisphosphate (IP_2) and IP_3. IP_3 is a common second messenger that mediates the increased concentrations of cytosolic calcium by various cell types. Other potential lithium-induced causes of vasopressin resistance include inhibition of glycogen synthase kinase-3, β-isoform, dysregulation of renal prostaglandins, and altered purinergic signaling.[73]

Chronic Renal Disease

Impairment of renal concentrating capacity is the most consistent renal abnormality detected by cross-sectional and longitudinal studies of patients on long-term lithium therapy. Both retrospective and prospective studies of patients treated chronically with lithium demonstrate that long-term lithium therapy produces urinary concentrating defects, but the effect on glomerular function is relatively small.[74,75] Progression to end-stage renal disease is rare. The histological changes present in renal biopsies from patients on chronic lithium therapy include interstitial fibrosis (increased myofibroblasts, collagen deposition, enhanced transforming growth

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factor-β1 expression), tubular atrophy, and minor glomerulosclerosis.[76] Although studies of patients on long-term lithium therapy suggest that maximum renal concentrating capacity correlates to the degree of tubular atrophy, there is no simple relationship between renal function and structure.[77] These renal changes are nonspecific, and the exact contribution of lithium to these changes remains unclear. Minimal change disease and nephrotic syndrome occur rarely during lithium therapy.[78] Chronic lithium toxicity produces abnormalities in the distal renal tubule, whereas a large, single ingestion of lithium causes proximal tubular damage along with prerenal azotemia.

Cardiovascular System

Bradycardia associated with lithium toxicity probably results from suppression of cardiac muscle automaticity. Lithium alters phase 4 of the pacemaker action potential by attenuating inward Na^+ current by competing with Na^+ for passage through the slow voltage-dependent (f-Na^+) channels and reducing resting membrane voltage/f-Na^+ channel opening during the end of phase 3 repolarization.[79] Similarly, lithium intoxication may produce PR and QRS prolongation by inactivating fast voltage-dependent channels. Other adverse cardiac effects following the treatment of patients with lithium involve T wave changes, QT prolongation, and the appearance of U waves on the ECG, similar to hypokalemia. These changes probably result from cation shifts that produce intracellular lithium accumulation and intracellular potassium depletion; however, human data correlating intracellular potassium concentrations to lithium-induced changes in cardiac conduction or excitability are limited.[80] Conduction and rhythm disturbances are rare during lithium intoxication except for cases of severe overdose, particularly in patients with preexisting cardiovascular disease. In a study of 83 patients on lithium, there was no increased risk (unadjusted odds ratio = 1.0, 95% CI = 0.43–2.4) of prolongation of the QTc interval (i.e., >456 msec) when compared with healthy controls.[81] There was an increased risk of QTc dispersion in the lithium group, but this measurement is not directly correlated to an increased risk of dysrhythmias in patients *without* cardiovascular disease. Animal studies suggest that lithium has some anti-arrhythmic properties in treating digitalis-induced ventricular tachycardia, but the clinical relevance of these effects in humans is unclear.[82] The effect of lithium on cardiac contractile function is less pronounced than cardiac conduction, probably resulting from inhibitory effects on the Na^+/Ca^{2+} exchanger; hypotension usually develops after serious neurological dysfunction (i.e., coma).[83]

Thyroid

Lithium concentrates in the thyroid gland where Li inhibits the uptake of iodine.[84] In addition, lithium inhibits iodotyrosine coupling, alters thyroglobulin structure, and decreases the secretion of thyroid hormones. As a result of increased thyrotropin release secondary to the inhibition of T_4 release from the thyroid gland, a smooth, non-tender goiter develops in ~5% of the patients chronically treated with lithium.[85] Chronic toxicity may present as euthyroid goiter, hypothyroid goiter, subclinical hypothyroidism, and exophthalmos with classical hypothyroidism.[86] Hypothyroidism may contribute to the occurrence of sinus node dysfunction associated with lithium therapy.[87]

Pathological Changes

A small minority of patients on chronic lithium therapy develop a chronic tubulointerstitial nephropathy. Typically, renal biopsies demonstrate interstitial fibrosis, distal renal tubular and collecting duct microcysts, and tubular atrophy out of proportion to the degree of glomerulosclerosis or vascular disease.

CLINICAL RESPONSE

Adverse Medicinal Effects

Adverse effects associated with lithium therapy include gastrointestinal irritation, weight gain, drowsiness, mild essential or postural tremor (i.e., rhythmic with frequency 8–12 Hz), muscle weakness, polyuria, and polydipsia. The tremor associated with lithium is usually regular and rhythmic (i.e., different than the pin-rolling tremor associated with Parkinson's disease). Typically, the prevalence and intensity of these side effects increase when serum lithium concentrations exceed 1.5–2.0 mEq/L, but these adverse effects also develop in the upper therapeutic ranges of lithium. Worsening tremor may occur as the first sign of lithium toxicity.[88] Dermatological side effects following chronic lithium therapy are uncommon. Hair loss and dry skin may occur during lithium therapy, but the presence of these dermatological effects also suggests the presence of hypothyroidism.

Complications of chronic lithium therapy primarily involve the kidney (reduced urinary concentrating ability), thyroid/parathyroid glands (hypothyroidism,

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hyperparathyroidism), central nervous system, and rarely, the cardiovascular system.[89] The risk of end-stage renal failure from chronic lithium therapy is low.[90] Patient factors contributing to the development of lithium toxicity include age of >50 years, renal impairment, nephrogenic diabetes insipidus, thyroid dysfunction, and hyperparathyroidism.[58] Physiological factors (e.g., dehydration, renal insufficiency, heart failure) or drug interactions (thiazide diuretics, angiotensin-converting enzyme inhibitors)[46] increase proximal renal tubule lithium absorption and/or reduced glomerular filtration, resulting in decreased lithium excretion and increased serum lithium concentrations along with the development of toxicity. Although the neurological features of chronic lithium intoxication typically occur in patients with elevated serum lithium concentrations, neurological symptoms may develop in patients with therapeutic concentrations of lithium.[91]

Central Nervous System

Cerebellar dysfunction is the most common chronic neurological complication following acute and chronic lithium intoxication including ataxia, dysarthria, and dysmetria with neuronal loss and gliosis of cerebellar gray matter. In a review of 90 cases of neurological symptoms persisting at least 2 months after lithium cessation described as SILENT (Syndrome of Irreversible Lithium-Effectuated Neurotoxicity), cerebellar dysfunction (e.g., dysarthria, ataxia) was the most common presentation. Atypical presentations of SILENT included extrapyramidal syndrome, brainstem dysfunction, retrobulbar optic neuritis, central pontine myelinolysis, and dementia.[92] A 44-year-old woman developed SILENT after a lithium overdose; eight weeks after the overdose, she had coarse axial tremor, ataxic gait, nystagmus, severe scanning dysarthria, and limb incoordination that was severely disabling.[93] At 1-year follow-up, the severe gait difficulties, ataxia, and tremor continued. The prognosis of patients with SILENT is not well defined.

In a series of 28 patients hospitalized for lithium toxicity primarily after chronic therapeutic use, the most frequent clinical abnormalities in decreasing order of occurrence were hyperreflexia, confusion, tremor, agitation, muscle rigidity (usually cogwheel type), drowsiness, and ataxia.[41] Alterations in mental status may develop despite declining serum lithium concentrations as a result of lithium neurotoxicity or electrolyte imbalance following the development of diabetes insipidus. These mental status changes range from drowsiness, lethargy, and disorientation to paralysis, stupor, seizures, and coma.[94] Although chronic lithium intoxication is usually associated with central nervous system depression, occasionally agitation, disorientation, and confusion similar to a manic episode complicate lithium intoxication.[95] Most neurological effects of lithium toxicity resolve when lithium concentrations return to the normal therapeutic range. Persistent neurological abnormalities following lithium intoxication are unusual;[88] however, some neurological signs of lithium toxicity may persist, particularly cerebellar signs (i.e., truncal ataxia, hyperreflexia, dysarthria, intention tremors).[96] Improvement in these cerebellar effects occurs over 6–12 months; residual effects are usually relatively minor.[97] Case reports also associate chronic lithium intoxication with movement disorders (myoclonus, choreoathetosis), proximal muscle weakness, fasciculations, bilateral horizontal nystagmus, incontinence, and corticospinal tract signs.[88,98]

Cardiovascular System

Serious cardiac complications do not usually occur in patients with chronic lithium intoxication unless severe neurological abnormalities (e.g., coma) are also present. Hypotension typically results from volume depletion rather than cardiotoxicity. A case report associated sinus arrest and asystole requiring a temporary pacemaker with chronic lithium toxicity (serum lithium concentration = 3.49 mEq/L) in a 72-year-old man with preexisting right bundle branch block and left axis deviation.[99] Lethargy, coarse hand tremor, and multiple syncopal episodes developed after he began a starvation diet to lose weight. Case reports suggest that delayed effects of chronic lithium toxicity may occur up to 48 hours after admission. A 72-year-old woman developed severe bradycardia, hypotension, and confusion about 48 hours after admission for chronic lithium toxicity secondary to dehydration.[100] A 54-year-old man with a history of bipolar disorder treated with lithium carbonate developed a sinus arrest with a slow junctional escape rhythm and lightheadedness; he also had renal dysfunction (serum creatinine, 4.15 mg/dL; potassium not reported).[101] He recovered without sequelae after hemodialysis with recovery of a normal sinus rhythm.

Kidney

Partial nephrogenic diabetes insipidus is the most common renal complication of lithium therapy with polyuria (>3 L urine/day) and secondary polydipsia occurring in a substantial portion of patients on chronic lithium therapy.[102] Mild symptoms typically occur following the development of partial nephrogenic diabetes insipidus in patients on lithium therapy that include

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polyuria (3–6 L/day), normal serum sodium and osmolality, and low urine osmolality (<300 mOsmol/kg). Partial nephrogenic diabetes insipidus may develop in patients on chronic lithium therapy, despite the absence of a history of excessive serum lithium concentrations.[103] Rarely lithium-associated nephrogenic diabetes insipidus may persist for several years after cessation of lithium use, despite desmopressin acetate and triamterene-hydrochlorothiazide therapy.[104] Although chronic lithium therapy may contribute to a reduction in glomerular filtration rate, the development of chronic renal failure requiring hemodialysis and the cessation of lithium therapy are rare.[105] Similarly, minimal change disease with nephrotic syndrome and heavy proteinuria is a rare, idiosyncratic effect associated with chronic lithium therapy.[106] Potential complications of the reduction of maximum concentration capacity include increased urinary water loss (i.e., polyuria), polydipsia, nocturia, hypernatremia, hypotension, mental status changes, and hyperosmolar coma. The physiological changes associated with nephrogenic diabetes insipidus and chronic lithium therapy usually resolve after cessation of lithium therapy.[107] The differential diagnosis of lithium-associated nephrogenic diabetes includes hypercalcemia, hypokalemia, excessive water ingestion, and osmotic diuresis (e.g., hyperglycemia).

Case reports indicate that a small group of patients on long-term lithium therapy may develop renal insufficiency without obvious episodes of lithium intoxication. Renal function of 82 patients attending an affective disorders clinic was monitored (mean duration, 4.3 years).[108] Three patients (i.e., 3.7%) initially with normal renal function developed serum creatinine concentrations above 2 mg/dL. One patient developed chronic renal failure requiring dialysis after deciding to continue lithium therapy despite the presence of deteriorating renal function. His renal biopsy demonstrated interstitial fibrosis, focal sclerosis, and renal cysts. A meta-analysis of six case-control studies (cases = 372, controls = 307) demonstrated a small difference in the weighted mean (−6.22 mL/minute, 95% CI: −14.65 to 2.20 mL/minute) in patients on lithium followed a mean of 1 year; however, the difference was not statistically significant ($P = 0.148$).[90] The mean maximum urinary concentrating ability was reduced by ~15% (weighted mean difference = −158.43 mOsm/kg, 95% CI: −229·78 to −87.07 mOsm/kg, $P < 0.0001$) in the treated patients from four of these studies.

The predominant form of chronic renal disease in the small minority of patients with renal insufficiency on long-term lithium therapy is a chronic tubulointerstitial nephropathy. Clinical features of these patients involve the insidious onset of mild renal insufficiency and minimal proteinuria.[109] End-stage renal failure is a rare complication in patients with lithium-associated renal insufficiency that requires about 20 years to develop.[110,111] Although the primary targets of lithium nephrotoxicity are the collecting ducts, proteinuria and hematuria may occur in patients on long-term lithium therapy with moderately severe renal dysfunction.[112] Rare case reports associated the development of nephrotic syndrome with chronic lithium therapy, primarily as a result of minimal change disease.[113] The proteinuria usually resolves within 4 weeks, sometimes without steroid therapy. Even rarer case reports associate proteinuria and hematuria with membranous nephropathy or focal glomerulosclerosis.[114]

Thyroid/Parathyroid

Hypothyroidism most commonly occurs 6–18 months after initiation of lithium therapy. The incidence of clinically significant hypothyroidism is ~5% with rapidly cycling, bipolar women particularly susceptible.[115] In a meta-analysis of case-control studies (cases = 654, controls = 377), the weighted mean difference in TSH concentrations between cases and controls was 4.00 IU (95% CI: 3.90–4.10 IU, $P \leq 0.001$) higher in treated patients.[90] Rarely, hyperthyroidism occurs during the chronic administration of lithium. Hyperparathyroidism may also develop during lithium therapy. The risk of hyperparathyroidism is small (<3%), but hypercalcemia secondary to hyperparathyroidism may increase the risk of lithium toxicity as a result of an osmotic diuresis and volume depletion producing decreased lithium clearance and increased serum lithium concentrations. In a meta-analysis of 13 case-control studies comparing patients receiving lithium with unexposed controls using random effects models, serum calcium concentrations were ~10% higher in treated patients (weighted mean difference = 0.09 mEq/L, 95% CI: 0.02–0.17 mEq/L, $P = 0.009$).[90] The weighted mean difference in serum parathyroid hormone was also higher in patients on lithium (i.e., mean = 7.32 pg/mL, 95% CI: 3.42–11.32 pg/mL, $n = 10$ studies). Both meta-analyses displayed serious heterogeneity ($I^2 = 99.5\%$, $P_{\text{heterogeneity}} \leq 0.0001$ and $I^2 = 89.2\%$, $P_{\text{heterogeneity}} \leq 0.0001$, respectively).

Acute Overdose

Categorization of lithium intoxication involves separation of patients into acute overdose (i.e., no recent lithium use), acute-on-chronic toxicity (i.e., acute overdose in patient currently using lithium), and chronic

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toxicity (i.e., therapeutic use of lithium without history of excessive lithium ingestion).[40] The latter has the highest risk of neurotoxicity secondary to accumulation of lithium in neural tissue and the prolonged elimination half-life of lithium. The basis for this classification is the multicompartmental pharmacokinetic lithium profile and the resulting difference in the course of toxicity; the profile reflects the slow intracellular distribution of lithium to the brain. Factors potentially contributing to lithium toxicity include the following: 1) the amount ingested; 2) time course of treatment (acute, acute-on-chronic, chronic); 3) clinical presentation; and 4) plasma/serum lithium concentrations, lithium formulation (immediate-, controlled-release), and patient profile (age >50 years, concurrent illness, renal function, thyroid dysfunction, volume status/hypercalcemia). Mortality from the three forms of lithium toxicity currently is relatively low (≤1%).[58] Acute exploratory lithium ingestions in children of <6 years of age are usually not associated with serious symptoms. In a retrospective observational study of 1,863 single-substance exploratory lithium ingestions in children of <6 years of age reported to US poison centers, symptoms were described in 184 children.[116] The most common symptoms were vomiting ($n = 76$), drowsiness/lethargy ($n = 58$), and ataxia ($n = 20$). Most of the children remained asymptomatic.

Absent Recent Lithium Use

In general, acute lithium poisoning in patients without recent lithium use produces relatively mild effects. The central nervous system is the primary target organ for acute lithium intoxication. Neurological symptoms (e.g., slurred speech, coarse tremor, ataxia, lethargy, confusion) usually predominate in symptomatic acute lithium ingestions;[117,118] severe neurological complications are unusual during acute lithium poisoning.[119] Gastrointestinal symptoms (nausea, vomiting, diarrhea) occur more commonly during acute rather than chronic lithium intoxication.[61] The ingestion of a single, large dose of lithium frequently produces vomiting within 1 hour of ingestion.[120]

Chronic Lithium Therapy

Potentially, acute-on-therapeutic lithium intoxication produces more serious toxicity compared with the acute ingestion of lithium in drug naïve individuals, primarily from saturation of lithium binding sites following chronic lithium therapy.[121] Serious complications of acute-on-chronic lithium toxicity primarily involve the central nervous and cardiovascular systems; renal dysfunction following acute lithium intoxication is uncommon. Rare case reports associate the acute coingestion of lithium with neuroleptic agents and the neuroleptic malignant syndrome.[122]

Central Nervous System

The presentation of acute-on-chronic lithium toxicity is variable with neurological effects primarily involving ataxia, extrapyramidal symptoms, neuromuscular signs, and behavioral abnormalities (poor memory, disorientation, apathy, incoherent speech).[123] Tremor, extrapyramidal symptoms, drowsiness, and stupor occur more often in acute-on-therapeutic poisonings than chronic lithium poisoning, whereas neurological impairments are more common following ICU discharge than acute-on-therapeutic poisonings.[124] Deterioration in the neurological status may occur 1–2 days after presentation to the emergency department in patients, particularly following the ingestion of large doses of sustained-release preparations by patients on lithium therapy. The presence of seizures, coma, and cardiovascular instability indicates serious lithium toxicity. Status epilepticus is a rare complication of lithium toxicity. Signs of lithium intoxication typically resolve within 2 days of the return of the serum lithium concentrations to the normal therapeutic range (<1.2 mEq/L).

Cardiovascular System

Cardiac abnormalities including rhythm disturbances (sinus node arrest) and conduction delay (reversible 1° A-V block, intraventricular conduction delay, prolonged Q-T interval) typically develop after the appearance of serious neurological symptoms (seizures, mental status alterations).[125] Electrocardiographic abnormalities are relatively uncommon during lithium intoxication. Rarely, monomorphic ventricular tachycardia,[126] hypotension, cardiovascular collapse, and acute myocardial infarction occur during severe, acute-on-chronic lithium intoxication (e.g., admission serum lithium concentration = 14.6 mEq/L).[127] The occurrence of fatal cardiac dysrhythmias is unlikely without the presence of severe CNS manifestations (e.g., coma).[125]

Kidney

Mild renal dysfunction often occurs in association with lithium intoxication, but acute renal failure is a rare complication of lithium poisoning including acute-on-therapeutic lithium intoxication.[128] The acute kidney injury associated with acute lithium toxicity is usually reversible; however, data are insufficient to determine the long-term impact of acute lithium poisoning on kidney function. Fatalities are unusual

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complications of lithium intoxication, occurring primarily following large acute-on-therapeutic ingestions. A 65-year-old woman on lithium therapy for chronic depression developed acute renal failure, hypotension, high-degree atrioventricular block, and confusion 48 hours after a large lithium carbonate overdose (peak serum lithium concentration = 8.5 mEq/L).[129] She died after developing refractory hypotension and ventricular fibrillation.

Occupational Exposure

Lithium hydride is a highly corrosive material. Skin contact with lithium hydride produces a severe chemical burn; exposure to dust from lithium hydride causes inflammation of the eyes and respiratory tract. Corneal scarring and strictures of the lower respiratory tract and of the esophagus developed in a technician following exposure of his eyes and ingestion of a small amount of lithium hydride during an explosion of a lithium hydride cylinder.[130]

Carcinogenesis

Neither the IARC nor the US Toxicology Program lists lithium as a suspected human carcinogen; however, data are limited. Population studies support the lack of increased cancer risk in lithium-treated patients including the absence of an increased incidence of acute or chronic myelogenous leukemia following exposure to elevated lithium concentrations in drinking water.[131]

Reproductive Abnormalities

Lithium is a pregnancy class D drug (i.e., positive evidence of risk) based on the US FDA classification that grades the increasing risk of abnormalities from A–D with class X being contraindicated and class D being the highest intermediate risk of reproductive abnormalities. Lithium crosses the placental barrier; evidence in animals suggests that lithium may cause teratogenesis. Both therapeutic and toxic doses of lithium carbonate produce craniofacial defects in rodents,[132] but studies in primates have not duplicated these abnormalities.[133] Since 1968, the Danish Register of Lithium Babies has collected cases of congenital abnormalities in infants born to mothers on lithium therapy during the first trimester of pregnancy. By 1983, this voluntary, retrospective cohort collected 225 cases with most of the serious cardiac abnormalities consisting of the rare Ebstein's anomaly (severe tricuspid valve insufficiency, right ventricular hypoplasia, varying degrees of septal defects). The relative risk for Ebstein's anomaly in this early study was high (i.e., 400). In a cohort study of 1,325,563 pregnancies in women receiving Medicaid and delivering a live-born infant during 2000–2010, cardiac malformations accounted for 2.41% of the lithium-exposed infants compared with 1.15% for nonexposed infants and 1.39% for lamotrigine-exposed infants.[134] The adjusted risk ratio for cardiac malformation in lithium-exposed compared with nonexposed infants was 1.65 (95% CI: 1.02–2.68) with the risk ratio for right ventricular outflow tract obstruction defects marginally significant (RR = 2.66, 95% CI: 1.00–7.06). The risk ratio was statistically different for these two groups only for daily lithium doses exceeding 900 mg.

Case reports of other congenital heart defects in newborns from mothers treated with lithium during pregnancy included coarctation of the aorta, dextrocardia, mitral and tricuspid valve atresia, tricuspid regurgitation, intraventricular septal defect, patent ductus arteriosus, atrial fluter, and congestive heart failure. A subsequent retrospective cohort study of 59 women with manic-depressive illness in the Swedish birth registry demonstrated a statistically significant increase in the risk for all congenital anomalies (RR = 3.0, 95% CI: 1.2–7.7) and cardiac malformations (RR = 7.7, 95% CI: 1.5–41.2).[135] A later review of the teratogenic risk of lithium treatment during the first trimester indicated that the risk of teratogenesis was less than previously suggested because of the biases associated with retrospective studies.[136] A prospective study of 148 women on lithium therapy during the first trimester of pregnancy revealed a major malformation rate of 2.8% that was not statistically different than the control rate of 2.4%.[137]

Case reports associate a variety of neonatal abnormalities with lithium therapy during pregnancy including poor respiratory effort and cyanosis, rhythm disturbances, thyroid dysfunction, hypoglycemia, hypotonia, and lethargy; however, the role of lithium in the development of these abnormalities remains unclear. The use of lithium in manic-depressive mothers during the first trimester requires careful evaluation of the risks and benefits as well as fetal screening tests (ultrasound, echocardiography) and monitoring of maternal lithium concentrations. In general, lithium remains the safest mood stabilizer for use during pregnancy.[138] Transient neurodevelopmental deficits (e.g., lethargy, poor oral feeding, hypotonia) can occur in neonates born to mothers receiving lithium during pregnancy.[139] Given the high rate of maternal relapse following discontinuation of lithium therapy and the low rate of malformations following fetal exposure to lithium, the

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continuation of lithium therapy during pregnancy is currently recommended with close monitoring. Limited data from cohort studies of children exposed to lithium during the second and third trimesters of pregnancy do not indicate significant behavioral problems during the first 5 years of life.[140] Population-based cohort studies indicate that bipolar disorders are associated with increased risks of adverse pregnancy outcomes, whether or not the mother is treated with lithium during pregnancy.[141]

DIAGNOSTIC TESTING

SI Conversion Units

1 mEq = 1 mmol
1 mg = 0.1441 mmol
1 mmol = 6.941 mg

Analytical Methods

Blood samples for serum lithium concentrations should be collected in red top vacuum tubes. The collection of blood in green top tubes for lithium analysis may result in the factitious elevation of serum lithium concentrations as a result of the presence of the anticoagulant, lithium heparin.[142] Collection of blood samples in these speckled green top tubes caused the false elevation of serum lithium concentrations, particularly when the tube is partially filled with blood.[143] Experimental studies of healthy volunteers and case reports suggest the collection of blood samples in lithium heparin-containing green top tubes may result in factitiously elevated serum lithium concentrations in partially filled vacuum blood tubes up to 4.3 mEq/L.[144,145]

Biomarkers

Blood

The red blood cell actively transports lithium into the cell via the sodium–potassium pump; erythrocyte lithium concentrations are approximately half of the serum lithium concentrations with a mean range of 0.35–0.55.[146] Therefore, whole blood lithium levels average about 20–30% less than serum lithium concentrations. Erythrocyte lithium concentrations do not clearly correlate to clinical effects better than serum or plasma lithium concentration.[147] Lithium is not bound to plasma proteins; therefore, serum and plasma lithium concentrations do not vary significantly. However, serum lithium typically is the preferred medium to avoid contamination of the sample by lithium heparin.

General Population

In a convenience sample of 186 healthy adult Norwegians without known exposure to lithium, the median serum lithium concentration was 0.42 ng/mL as measured by inductively coupled plasma/atomic emission spectrometry.[148] The median plasma lithium concentration in blood samples from 106 healthy French hospital staff volunteers was 0.64 ng/mL (95% CI: <0.06–1.88 ng/mL) as measured by inductively coupled plasma/mass spectrometry.[149] Increased lithium exposure occurs in a few areas (e.g., northern Chile, northern Argentina), where high lithium concentrations in drinking water produce detectable plasma lithium concentrations (e.g., 2–83 ng/mL).[150]

Therapeutic

Peak serum lithium concentrations occur within 3 hours after ingestion of standard-release preparations and within ~6 hours after ingestion of sustained-release preparations. Steady-state lithium concentrations develop within ~5–6 days after the initiation of treatment. On average, the ingestion of an additional 300 mg lithium carbonate (8.1 mEq Li) in a healthy adult raises the serum lithium concentration by 0.2–0.4 mEq/L after equilibration. The daily dose of lithium varies substantially between patients; lithium concentrations in blood samples also vary significantly in relation to time of lithium ingestion during the preceding 24-hour period. Lithium concentrations in plasma or serum typically are <0.2 mEq/L in drug-naïve individuals. The therapeutic concentration of lithium ranges from 0.6–1.2 mEq/L in serum or plasma samples drawn during the morning before the first daily dose of lithium. Recent recommendations suggest that serum lithium concentrations should be maintained in the lower therapeutic range (i.e., 0.6–0.8 mEq/L) to reduce adverse effects.[151] Serum lithium concentrations in the upper therapeutic range may be necessary during the treatment of acute mania.

Toxic

Serum and plasma lithium concentrations should be interpreted as part of the overall clinical evaluation of patients with suspected lithium intoxication because lithium toxicity correlates best to target organ symptoms (i.e., primarily central nervous system and renal effects) and tissue lithium concentrations rather than plasma, erythrocyte, or whole blood lithium concentrations.[58] Factors affecting the correlation of serum lithium concentrations to clinical effects include the following: 1) time since ingestion; 2) drug interactions; 3) coexisting

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disease processes including kidney function; 4) duration of lithium therapy; 5) ingestion of sustained-release lithium preparations; and 6) the delayed transfer of blood lithium to intracellular receptors. Interindividual variability of the brain/serum ratio also complicates the interpretation of the serum lithium concentration.[152] Animal studies suggest neurotoxicity correlates primarily to brain lithium content, which depends more on the pattern of lithium poisoning than serum or RBC lithium concentrations.[153] Although interpretation of serum lithium concentration typically requires analysis of specimens drawn at least 6–12 hours after acute or acute-on-chronic ingestions, earlier determination may aid the toxicologist's determination of the causal effect of lithium or anticipate serious lithium toxicity.

Table 17.2 correlates serum lithium concentrations with toxicity in patients currently on lithium therapy. Fine tremor of the hands and mild nausea may occur at therapeutic concentrations of lithium; the presence of myoclonic or choreoathetosis movements suggests moderate lithium intoxication.[80] In general, mild lithium toxicity is associated with serum concentrations between 1.5 and 2.5 mEq/L, whereas lithium concentrations between 2.5 and 3.5 mEq/L produce moderate lithium intoxication. Serum lithium concentrations above 3.5–4.0 mEq/L are associated with life-threatening toxicity. However, these ranges do not define toxic responses at a given serum lithium concentration in all patients because of the factors listed above. Consequently, interpretation of serum lithium concentrations requires careful correlation to clinical effects.

Case reports suggest that single acute ingestions of lithium by patients without recent use of lithium usually produce less severe toxicity compared with chronic intoxication producing the same serum lithium concentration, primarily because of the slow distribution of lithium and the lack of intracellular lithium stores.[154] Thus, lithium toxicity may occur at lower serum lithium concentrations in patients on chronic lithium therapy than patients without recent lithium use. Typically, the acute ingestion of lithium without recent lithium use produces only mild symptoms independent of the serum lithium concentration.[155,156] Conversely, some features of lithium intoxication may develop in patients concurrently receiving lithium, despite serum lithium concentrations below 1.5 mEq/L. Following the ingestion of sustained-release lithium preparations, delayed peak lithium concentrations may occur up to ~2 days after ingestion.[27]

Urine

In a convenience sample of 87 urban German residents, the mean urine lithium concentration was 35 ng/mL with a range of 4–237 ng/mL (95% CI: 115 ng/mL) as measured by ICP/MS.[157] The mean urine lithium concentration for 72 children from the same region was somewhat higher (mean = 77 ng/mL with range of 7–580 and 95 percentile of 306 ng/mL). Lithium concentrations in the environment and diet were not reported. The median urine lithium concentration in 100 healthy French volunteers was 12 ng/mL (95% CI: 4.6–219 ng/mL).[158] Urine lithium concentrations in residents of areas with very high lithium concentrations (e.g., the Atacama Desert of northern Chile) may range up to 7,000 ng/mL.[14]

Abnormalities

Blood

Leukocytosis commonly occurs following the initiation of lithium therapy, but lithium does not interfere with neutrophil function. Lithium also suppresses T cell production without reducing lymphocyte activity.[57] The leukocytosis and lymphopenia in patients ingesting

TABLE 17.2. Clinical manifestations associated with serum lithium concentrations in patients on lithium therapy. However, the multiple factors that affect serum lithium concentrations should be interpreted cautiously as adjunctive data to the clinical presentation because of the multiple factors that affect them. Toxic effects may occur at serum lithium concentrations lower than indicated in this chart, particularly in acute-on-chronic intoxication, as a result of delayed absorption and distribution of lithium. Patients ingesting lithium without prior recent exposure may exhibit relatively few symptoms despite high serum lithium concentrations. Consequently, interpretation of serum lithium concentrations requires correlation to dosing history and clinical effects. (Adapted from Hansen and Amdisen).[61]

Serum Lithium (mEq/L)	Severity of Intoxication	Clinical Effects
1.5–2.5	Mild	Lethargy, drowsiness, increased hand tremor, nausea, vomiting, diarrhea, polyuria, polydipsia, blurred vision, dizziness
2.5–3.5	Moderate	Confusion, disorientation, ataxia, muscle weakness, fasciculations, nystagmus, dysarthria
>3.5	Severe	Serious alteration of consciousness, syncope, coma, renal insufficiency, seizures, hypotension, dysrhythmias

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lithium do not correlate to lithium dose or serum lithium concentration.[159] Lithium is a cation; the presence of lithium lowers the serum anion gap depending on the lithium concentration. Although therapeutic lithium concentrations may slightly reduce the serum anion gap, substantial reductions in the serum anion gap usually occur only in the presence of high lithium concentrations (>4 mEq/L).[160,161]

Urine

Nephrogenic diabetes insipidus results from the interference of lithium with the ability of the renal tubules to respond to antidiuretic hormone (arginine vasopressin). This defect results in polydipsia, hypotonic polyuria (urine volume >3 L/day, urine hypoosmolality), and the inability to concentrate urine on fluid restriction. Other conditions associated with decreased ability to concentrate urine include hypokalemia (e.g., hyperaldosteronism), hypercalcemia (e.g., hypervitaminosis D, bone cancer), and renal tubular abnormalities (e.g., Fanconi's syndrome). Laboratory abnormalities associated with nephrogenic diabetes insipidus include plasma hyperosmolality (>300 mOsm/kg water), urine hypoosmolality (<280 mOsm/kg water), and low urine specific gravity (<1.010). Restriction of access to water during the polyuria associated with diabetes insipidus causes serum hypernatremia. Polyuria develops from water diuresis (hypotonic polyuria), osmotic or solute diuresis (hypertonic polyuria), or renal tubular dysfunction. The presence of normal or low urine osmolality excludes the diagnosis of osmotic diuresis from the excessive excretion of solutes (e.g., glucose). Typically, patients with water diuresis have urine osmolalities below 250 mOsm/kg, whereas patients with osmotic diuresis have either isoosmotic or hyperosmotic (>300 mOsm/kg) urine. Other causes of the water diuresis in addition to lithium-induced nephrogenic diabetes insipidus include central diabetes insipidus (inadequate ADH secretion), mobilization of "third-space" fluids, and excessive water ingestion (psychogenic polydipsia). In a patient presenting with polyuria/polydipsia and a urine osmolality of <300 mOsm/L, the occurrence of urine osmolality of >300 mOsm/L after a 6-hour water deprivation test indicates psychogenic polydipsia. The normal response to the water-deprivation test is the maintenance of a urine osmolality below 300 mOsm/kg after dehydration with no or minimal (<9%) rise in urine osmolality after the administration of desmopressin. In partial diabetes insipidus, the urine osmolality rises to 300–750 mOsm/kg after dehydration and urine osmolality remains below 750 mOsm/kg after the administration of desmopressin.

Electrophysiological Testing

Electroencephalogram

The most common changes associated with lithium toxicity involve continuous or paroxysmal polymorphic and rhythmic slowing in the theta and delta range along with disorganization of the background and increased response to hyperventilation; the EEG changes may mimic the changes associated with status epilepticus.[162] Diffuse, nonsynchronous slowing (<8/second) of the EEG occurs during lithium intoxication along with increased amplitude and bilateral synchronous bursts of delta activity.[163] Lithium produces a persistent or intermittent generalized slowing of the electroencephalogram, involving the dominant rhythms (e.g., theta (5–7 cps), delta (2–3 cps) activities.)[164] Grouped delta–theta waves may dominate the EEG in severe Li intoxication.[165]

Electrocardiogram

Cardiac complications from lithium toxicity are relatively uncommon compared with adverse neurological effects. In a study of 629 hospitalized lithium overdoses reported to the California Poison Control System, there were 29 cases with adverse cardiovascular effects; the majority of these patients developed isolated bradycardia in the absence of hypotension.[166] Only seven patients (i.e., all with chronic lithium toxicity) required cardiovascular support including two cases of bradycardic arrest. Minor electrocardiographic abnormalities in lithium intoxication included intraventricular conduction defects (first-degree atrioventricular block, intraventricular conduction delay),[125] prolongation of the QT_c interval, T-wave flattening or inversion, the appearance of U waves, and nonspecific ST-T wave changes.[167] Sinus node dysfunction is the most commonly reported, clinically significant conduction defect in patients on lithium, primarily in patients with underlying structural disease.[80] Case reports of lithium toxicity occasionally associate impaired conduction with serious lithium intoxication including sinoatrial block,[168,169] sinus bradycardia,[101,170] and junctional bradycardia.[128]

Lithium therapy may unmask underlying cardiac diseases including sick sinus syndrome,[171] Brugada syndrome (RBBB, ST elevation V_1–V_3),[172,173] and sinoatrial block with slow idioventricular escape rhythm.[174] Type I Brugada Syndrome may occur in patients with therapeutic or toxic lithium concentrations. Lithium-induced, dose-dependent sodium blockade begins at lithium concentrations below therapeutic concentrations.[175] Predisposing factors to the development of type I Bragada in patients receiving lithium include hyponatremia

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and the administration of ACE inhibitors (↓ glomerular filtrations rates from vasoconstriction)[176] or sodium channel blockers (e.g., lamotrigine).[177] Serious ventricular dysrhythmias are uncommon during lithium intoxication in the absence of electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia) or preexisting cardiovascular disease. Rare case reports associate lithium toxicity (Li = 3.0 mEq/L) and hypothyroidism with the development of ventricular fibrillation in a patient with normal serum electrolytes including normal serum magnesium concentrations.[178]

Imaging

Lithium is not radiopaque. The presence of mild, increased echogenicity on renal ultrasound with or without the presence of punctate, hyperechogenic foci suggests the possibility of underlying renal parenchymal injury; MRI is more sensitive and specific for the detection of the parenchymal renal cysts associated with chronic lithium therapy.[179] MR imaging of the kidney may demonstrate fluid-filled microcysts (i.e., 1–2 mm) in the cortex and medulla of patients with moderate-to-severe chronic renal insufficiency and a history of chronic lithium therapy.[180]

Neuropsychological Testing

Neuropsychological testing of patients after chronic lithium intoxication suggests that visuoperceptive, verbal recognition, and constructive abilities are the most sensitive measures of lithium toxicity, whereas orientation, language comprehension, and memory are not significantly impaired.[181] However, the lack of premorbid data and the limited amount of neuropsychological testing after lithium intoxication limit conclusions regarding the permanent cognitive effects of lithium toxicity.

HEALTH SURVEILLANCE

The US OSHA PEL–TWA and the ACGIH TLV–TWA is 0.025 mg lithium hydride/m^3 based on the prevention of nasal, ocular, and skin irritation. Permissible exposure limits for lithium hydride are similar in Australia and the United Kingdom.

TREATMENT

After assessment and stabilization of the airway, breathing, and circulation, the treatment of lithium intoxication primarily involves fluid resuscitation to optimize renal perfusion, routine poisoning treatment (gastrointestinal decontamination, electrocardiogram/cardiac monitoring, pulse oximetry, serum acetaminophen/salicylate concentrations), cessation of drugs contributing to increased serum lithium concentrations (NSAIDS, renin-angiotensin system inhibitors, thiazide diuretics, spirolactones, calcium channel blockers), evaluation of the need for enhanced elimination, and serial lithium concentrations every 4 hours until steady state. Serum lithium concentrations may not reach steady state until 12–24 hours after ingestion depending on the amount, formulation, and renal function. Collection of blood for lithium in a tube containing lithium heparin (light green top) must be avoided.

Decontamination

In vitro studies indicated that activated charcoal does not effectively adsorb lithium.[182] Syrup of ipecac should not be administered to patients following the ingestion of drugs that potentially produce obtundation and seizures. Because of the lack of adsorption of lithium to activated charcoal, other decontamination measures (e.g., lavage) are therapeutic options in patients ingesting >40 mg immediate-release lithium/kg, when the patients present within 1–2 hours of an acute ingestion. Limited data suggest that the use of gastric lavage does not improve clinical outcome.[183] Furthermore, the use of gastric lavage for sustained-release preparations is probably not efficacious because these large capsules usually do not dissolve in the stomach.

Although the absorption of therapeutic lithium doses is rapid, ingestion of sustained-release tablets may delay absorption following an overdose. Whole bowel irrigation is an option to other decontamination measures within the first few hours following the large ingestion of sustained-release preparations (e.g., >80 mg/kg lithium carbonate) based on a volunteer study demonstrating a two-third reduction in area under the lithium serum concentration-versus-time curve.[184,185] However, there are no data to confirm that reduced absorption demonstrated in volunteer studies improves clinical outcome without significant adverse effects (e.g., hypokalemia, fluid depletion). The administration of cathartics is discouraged because of potential exacerbation of lithium toxicity following fluid imbalance caused by cathartic administration.

Elimination Enhancement

Peritoneal dialysis is a relatively inefficient method for removing lithium with case studies suggesting peritoneal dialysis and endogenous clearance are similar.[186] Lithium does not adhere well to charcoal; hence,

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charcoal hemoperfusion does not increase lithium clearance. There is little evidence that the administration of amiloride or furosemide significantly increases lithium elimination.

Sodium Polystyrene Sulfonate

The role of sodium polystyrene sulfonate in reducing the lithium load is not well defined and probably limited because of the limited capacity to bind lithium and the risk of hypokalemia. A study in human volunteers demonstrated that 30 g sodium polystyrene sulfonate administered 1 hour after a dose of 18.5 mg lithium carbonate/kg reduced the absorption of lithium by ~30%.[187] An *in vitro* study indicated that lithium binds more readily to polystyrene sulfonate than activated charcoal; however, potassium also binds to polystyrene sulfonate and hypokalemia potentially may complicate the use of polystyrene sulfonate.[188,189] The use of multiple doses of sodium polystyrene sulfonate (150 g over 24 hours) was associated with a reduction in the serum lithium half-life to 12 hours in a patient with an acute-on-chronic overdose of lithium.[190] A retrospective cohort study of 48 patients with chronic lithium intoxication compared the median serum lithium half-life in 12 patients treated with sodium polystyrene sulfonate with controls (no treatment).[191] The median serum half-lives were 20.5 hours and 43.5 hours, respectively. Adverse effects in the treatment group included mild hypokalemia and constipation. The study did not standardize the group dose, interval between ingestion and presentation, or treatment. The use of multiple doses of sodium polystyrene sulfonate also reduces lithium concentrations in mice, but the clinical significance of these reductions in mice given low doses of lithium is unclear.[192] Although these data suggest a role for polystyrene sulfonate in the decontamination of patients with an overdose of lithium, more clinical data are necessary before the routine use of polystyrene sulfonate can be recommended. The limited binding of sodium polystyrene sulfonate to lithium and the need to use large volumes to significantly increase lithium clearance complicate the use of this modality. The use of forced diuresis during lithium intoxication is not recommended.[61] Correction of fluid and electrolyte imbalances is important to prevent reduced lithium clearance from decreased glomerular filtration rates.

Hemodialysis

Hemodialysis effectively removes lithium from the blood and substantially reduces the elimination half-life of lithium based on case reports.[193] The significant variability in recommendation for extracorporal treatments following lithium intoxication reflects the absence of randomized controlled clinical trials and the heterogeneity of patients with lithium poisoning (e.g., acute, acute-on-chronic, chronic). Intermittent hemodialysis is the usually recommended extracorporeal modality for lithium removal unless the patient is clinically unstable (e.g., hypotensive) or hemodialysis is unavailable. The low molecular weight, small volume of distribution, and the negligible protein binding of lithium favors removal by extracorporal measures. Hemodialysis decreases the serum lithium half-life during acute lithium intoxication to ~3–6 hours with lithium clearance up to 170 mL/minute (i.e., >8 times endogenous clearance);[194] a 6-hour hemodialysis reduces the serum lithium concentration by ~50–60% during the elimination phase.[42,195] In spite of the reduction of serum lithium concentrations following hemodialysis, immediate improvement in clinical status often does not occur as a result of the slow lithium redistribution from intracellular stores. In a case of chronic lithium intoxication, hemodialysis decreased the serum lithium half-life from 54 hours to 25 hours.[34] In these cases, tissue stores of lithium act as a reservoir for the extracellular compartment. About 6–12 hours after hemodialysis, the serum lithium concentration rebounds to 20–100% of pretreatment lithium concentrations from the slow shift of lithium from the intracellular to extracellular compartment. The hemodialysis catheter should remain in place until the serum lithium concentration remains consistently below 1 mEq/L. Newer extracorporeal measures other than standard hemodialysis include sustained low-efficiency dialysis (e.g., blood flow of 200 mL/minute and countercurrent dialysate flow of 300 mL/minute over 8 hours);[196] however, clearance data on these new techniques are limited.

Clearance

Lithium freely diffuses across the glomerulus and reabsorbs into the proximal convoluted tubule with a clearance of 20–30 mL/minute. Consequently, lithium clearance is proportional to the glomerular filtration rate with a fractional excretion rate of ~25%. Hemodialysis significantly increases lithium clearance with lithium plasma dialyzer clearance (dialysance) of ~60–170 mL/minute compared with normal renal clearance of ~20–30 mL/minute.[186,194] A case report documented a lithium clearance of 272 mL/minute with the use of high blood pump speed (300 mL/minute) during severe lithium intoxication.[160] Hemodialysis does not reduce the normal lithium renal excretion.[42] Although the serum lithium concentrations typically

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rebound after cessation of intermittent hemodialysis, case reports suggest cerebral spinal fluid lithium concentration continues to decline despite the rebound in serum lithium concentration.[197]

Indications

In addition to the serum lithium concentration, the decision to institute dialysis depends on clinical judgment regarding the duration of the poisoning, the estimated time to peak serum lithium concentrations, type of poisoning (acute vs. chronic), severity of neurological impairment, renal function, age, and the clinical course of the patient during the first 8–12 hours following admission. A deterioration of the clinical condition (i.e., altered consciousness, seizure, hypotension) during this period indicates the need for hemodialysis. Intermittent hemodialysis is an effective method to increase serum lithium clearance.[198] Increasing muscle rigidity and tremulousness often precedes the development of life-threatening deterioration of the condition of the patient by several hours. Recommended indications for hemodialysis during lithium intoxication based on expert opinions include the following: 1) the presence of serum lithium concentrations exceeding 4 mEq/L with impaired kidney glomerular filtration rate below 45 mL/minute/1.73 m^2 (EXTRIP workgroup criteria, https://www.extrip-workgroup.org/lithium) or ≥5.2 or serum creatinine >2.25 mg/dL (Paris criteria); 2) the appearance of serious central nervous system (↓consciousness, seizure) or cardiovascular symptoms (life-threatening dysrhythmia); and 3) chronic lithium intoxication and signs of neurotoxicity or nephrotoxicity. The use of hemodialysis may be considered in patients with serum lithium concentrations between 2.5 and 4.0 mEq/L, particularly older patients on lithium with renal dysfunction and neurological impairment (e.g., confusion). The lack of randomized clinical trials and the complex pharmacology of lithium limit the development of definitive guidelines.

Patients with normal renal function and no prior use of lithium may tolerate lithium concentrations substantially exceeding 4 mEq/L with supportive care only (i.e., no dialysis), following an acute overdose without developing neurological symptoms.[199] Dialysis is usually unnecessary for patients with lithium concentrations below 2.5 mEq/L unless associated with clinically significant neurological abnormalities or serious renal impairment. A 60-year-old bipolar woman on chronic lithium therapy developed ataxia, myoclonic jerks, irritability, dysphoria, and dementia; her serum lithium concentration was 2.45 mEq/L.[200] Her neurological examination became normal with resolution of the ataxia and dementia after her serum lithium concentrations returned to baseline.

Endpoint

Intermittent hemodialysis can be stopped when clinical improvement occurs or the serum lithium concentration is <1 mEq/L.[201] In the absence of serum or plasma lithium concentrations, hemodialysis should continue for at least 6 or 18 hours for less efficient methods (e.g., CAVH). Because of a slow redistribution phase (6–12 hours) and distant receptor sites, repeat dialysis may be necessary to reduce the tissue stores of lithium manifested by a rebound in serum lithium concentrations following intermittent hemodialysis.[202] For similar reasons, clinical recovery may not closely follow declining serum lithium concentrations. Hence, repeat dialysis should be based both on the clinical response and the serum lithium concentrations with the options of repeat intermittent hemodialysis or the initiation of continuous renal replacement therapy. The latter is associated with a reduced risk of rebound plasma or serum lithium concentrations; however, lithium clearance is lower and few patients exhibit clinical deterioration because of rebound elevations in the serum lithium concentration. Serial serum lithium concentrations should be followed closely after dialysis (e.g., 2, 6, 12 hours post-treatment). Continuing lithium absorption from sustained-release preparations may require the extension of lithium monitoring up to 72 hours after ingestion. The hemodialysis endpoint of <1 mEq Li/L 6–8 hours after the end of hemodialysis is based on a research protocol rather than a study of clinical outcome.[120]

Continuous Arteriovenous Hemofiltration (CAVH)

The main advantages of continuous renal replacement therapies (e.g., CAVH) include the suitability of this technique in unstable, hypotensive patients, ease of operation, and reduction of lithium rebound after cessation of use; however, limited data on the efficacy of these techniques limit conclusions about the role of these therapies in lithium intoxication. The clearance of lithium by CAVH is similar to the lithium clearance by the normal kidney and lower than that of intermittent dialysis.[203] Generally, 24 hours of CAVH and 4 hours of intermittent hemodialysis eliminate similar amounts of lithium. The lithium clearance during 14 hours of continuous venovenous hemodiafiltration in a 45-year-old woman with oliguria and mild hypotension ranged from ~30–35 mL/minute.[204] Although the clearance of lithium by CAVH (i.e., 20–40 mL/minute)

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is slower than the lithium clearance during hemodialysis (60–170 mL/minute),[42,186,205] the continuous use of CAVH allows the clearance of lithium over many hours as long as the patient is hemodynamically stable. The use of CAVH after dialysis substantially reduces the rebound in serum lithium concentrations.[206] Although repeat hemodialysis is often unnecessary following the use of CAVH,[207] repeat sessions may be necessary depending on the duration of the initial session of CAVH. In a 58-year-old woman, 14 hours of CAVH removed an amount of lithium equivalent to the quantity eliminated by 3–5 hours of hemodialysis.[208] Repeat hemofiltration was necessary 17 hours after cessation of the first session when the serum lithium concentration increased to 1.1–2 mEq/L.

Antidotes

There are no antidotes for lithium intoxication.

Supplemental Care

Medications associated with potentiation of lithium toxicity should be discontinued including nonsteroidal anti-inflammatory drugs, rennin–angiotensin system inhibitors, thiazide diuretics, spironolactone, and calcium channel blockers (diltiazem, nifedipine, verapamil) unless their use is expected to improve fluid and/or electrolyte balance. For patients with nephrogenic diabetes insipidus and lithium intoxication, correction of fluid and electrolyte balance along with withdrawal of lithium is the important method of supportive care. Large amounts of fluid may be necessary to prevent hypotension and underperfusion of vital organs. The use of normal saline (0.9% NaCl) has theoretical benefits by reducing lithium tubular reabsorption by providing an additional sodium load; however, the patient should be closely monitored for nephrogenic diabetes insipidus and hypernatremia.[41] Assessment of electrolytes loss during polyuria (e.g., potassium, magnesium) is essential to prevent serious dysrhythmias.

Adjunctive therapy to reduce urine volume for patients with nephrogenic diabetes insipidus *without* lithium toxicity includes indomethacin (50 mg t.i.d.), thiazides (with sodium restriction to enhance sodium depletion), and amiloride (10–20 mg/day) as well as protein- and sodium-restricted diet. Therapy with indomethacin is most useful when immediate reduction in urine volume is necessary, but the chronic use of indomethacin therapy for maintenance of patients with polyuria is not recommended. Thiazide diuretics decrease extracellular fluid volume and increase the resorption of fluid and lithium. Consequently, lithium, magnesium, and potassium concentrations should be monitored closely. The medications of the patient should be reviewed to determine any adverse drug reactions while the lithium dose is reevaluated. Anecdotal reports suggest acetazolamide may reduce daily urine output in patients with nephrogenic diabetes insipidus resistant to treatment with desmopressin, hydrochlorothiazide, amiloride, and sodium restriction.[209]

Evaluation of electrolyte status including serum magnesium concentrations is particularly important during serious lithium intoxication.[178] Severe chronic hyponatremia should be corrected relatively slowly (<0.55 mEq/L/hour) to prevent the development of central pontine myelinolysis. Depending on the initial serum sodium concentration, the serum sodium should not exceed 135 mEq/L with in the first 48 hours of treatment; hypernatremia should be avoided. Diuretics (e.g., furosemide, amiloride) are not typically recommended during acute lithium poisoning.[58]

Admission Criteria

The decision to admit patients with suspected lithium intoxication requires careful evaluation of initial and serial lithium concentrations, estimated lithium dose, concurrent use of lithium, renal function, and the presence of clinical features of lithium intoxication. Because of the delayed equilibration of serum and tissue lithium concentrations, the serum lithium concentration does not always reflect the severity of lithium intoxication, particularly during the first 6 hours after ingestion. Most symptomatic patients should be admitted to a monitored bed for observation and serial lithium concentrations collected in tubes without lithium heparin (q4h or sooner for large recent ingestions), especially following the ingestion of sustained-release preparations until peak lithium concentrations occur (i.e., typically 12–24 hours). Subsequently, serial lithium concentrations every 6–12 hours should be sufficient.

Asymptomatic patients with serum lithium concentrations exceeding 2.0 mEq/L and all patients with substantial ingestion of sustained-release preparations should be considered for admission and monitoring. Asymptomatic or minimally symptomatic patients may be considered for discharge if the serial lithium concentrations obtained at least 4–6 hours apart remain below 1.5–2.0 mEq/L with no evidence of continued lithium absorption. These patients should be evaluated for factors (e.g., dehydration, loop diuretics, drug interactions) contributing to toxicity as well as for psychiatric stability prior to discharge.

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Chapter 18

MAGNESIUM

PHYSIOCHEMICAL PROPERTIES

Magnesium (CAS RN: 7439-95-4, atomic weight 24.31 g/mol) is an abundant silvery-white metal that is part of the Group 1 (Group IIa) alkaline earth metals along with barium, beryllium, calcium, radium, and strontium. Naturally occurring isotopes include ^{24}Mg (78.7%), ^{25}Mg (10.13%), and ^{26}Mg (11.17%).[1] This metal does not occur naturally in its elemental form. In nature, magnesium exists in >50 salts and several minerals including carnallite ($KMgCl_3$), dolomite [$CaMg(CO_3)_2$], epsomite ($MgSO_4$), kieserite ($MgSO_4$), olivine [$(Mg^{2+}, Fe^{2+})_2SiO_4$], and magnesite ($MgCO_3$). This extremely flammable metal is water-insoluble but reacts with water to produce hydrogen gas. Magnesium is the lightest structural metal, displaying 67% of the weight of aluminum and 22% of the weight of steel. The specific gravity of magnesium is 1.74, and the vapor density is 0.84. Magnesite (CAS RN: 546-93-0, MW: 84.3 g/mol) is a white to yellowish-brown solid that is slightly water-soluble (0.01%) and has a specific gravity of 2.96. Magnesium oxide (CAS RN: 1309-48-4) is a fine, white, and slightly soluble (0.009%) powder that occurs naturally as the mineral periclase with a small amount of iron oxide; the molecular weight of MgO is 40.3 g/mol and the specific gravity is 3.58. High temperatures in production processes produce MgO as a fume. In saturated aqueous solutions, MgO combines with water to form $Mg(OH)_2$, producing a solution with a pH of 10.3.

EXPOSURE

Uses

Magnesium is one of the most common industrial metals with widespread applications as structural alloys in aircraft, tools, machines, engines, and office equipment. The reducing properties of magnesium are an important part of the production processes of beryllium, titanium, uranium, and zirconium. Other uses involve fireworks and flares (magnesium nitrate), organic chemical reactions, batteries, desulfurization of steel and iron, and corrosion prevention. Potential applications of magnesium oxide nanoparticles include the removal of contaminants from wastewater and drug delivery.[2] Pharmaceutical magnesium compounds include the administration of antacids (oxide and hydroxide) and cathartics (citrate and sulfate) as well as the treatment of a variety of illnesses (sulfate) including preeclampsia, asthma, migraine, depression, and dysthymias.

Production Processes

The production of magnesium metal is relatively small compared with the production of steel and aluminum; the production process primarily includes electrolytic reduction of magnesium chloride or thermal reduction of magnesium oxide. The most common production

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TABLE 18.1. Average magnesium content of various foods. (Adapted from Gums).[27]

Content (mg/100 mL)	Sources (mg/100 mL)
High (>100)	All bran (420); cashews (267); soybeans (255); peanuts (174); whole wheat (147); chocolate (119); rice (106); shrimp (105).
Moderate (25–100)	Clams (89); coconut (80); apricots (65); dates (60); spinach (55); peaches (54); cheese (45); oysters (40); bananas (37); raisins (34); potatoes (29); liver (26); celery (25).
Low (<25)	Pork (24); broccoli (24); ham (20); chicken (19); mushrooms (16); cherries (14); milk (14); eggs (13); tomatoes (12); oranges (11); apples (10); onions (7); butter (1).

method is the electrolytic process that involves the heating of carbonaceous materials (e.g., coke, coal tar). Magnesium oxide forms from the filtering and burning of magnesium hydroxide, which precipitates from separation tanks containing dolomite and seawater. The heating of a mixture of pulverized coal or coke and magnesium oxide in the presence of chlorine gas produces pellets of magnesium chloride that feed electrolytic cells to form metallic magnesium. Following refining procedures, alloys of magnesium are formed with aluminum, beryllium, manganese, and zinc. During this process, potential chemical exposures include chlorinated aromatic hydrocarbons, chlorine gas, asbestos, carbon monoxide, sulfur dioxide, volatile coal tar products, and dust of magnesium oxide.[3]

Sources

Large natural deposits of magnesium exist in minerals (dolomite, magnesite, olivine), salt deposits, and seawater. Magnesium occurs in animal and plant tissue throughout nature, where chlorophyll a and b are magnesium chelates of porphyrin. An average daily diet contains about 300 mg (25 mEq) of magnesium. Table 18.1 lists the relative magnesium content of common foods in mg/100 mL.

ENVIRONMENTAL FATE

Typically, hard water contains high concentrations of calcium and magnesium ions that increase the capacity of the water (i.e., alkalinity) to neutralize acids by forming carbonate, bicarbonate, hydroxide, and occasionally borate, silicate, or phosphate compounds. Other dissolved divalent or multivalent metal cations also potentially increase water hardness including aluminum, barium, iron, manganese, strontium, and zinc. Monovalent ions (e.g., sodium, potassium) usually do not cause hardness; generally, hardness develops in groundwater as the water percolates through minerals containing calcium (limestone) or magnesium (dolomite). Soft water typically contains <60 mg Mg/L, whereas hard water has 120–180 mg Mg/L, and water containing >180 mg Mg/L is considered very hard. Desalinated water contains little calcium or magnesium.[4] In a Swedish study of 79 water samples from 18 municipalities, the magnesium concentrations ranged from 0 (water filtered) to 44.0 mg/L.[5]

DOSE EFFECT

Magnesium toxicity usually results from increased magnesium load (e.g., Epsom salts or $MgSO_4$) in the presence of renal dysfunction because the kidney effectively excretes moderate Mg excesses.[6] One tablespoon of Epsom salt contains ~35 g magnesium sulfate (3.4 g or 287 mEq elemental magnesium). A positive magnesium balance occurs in healthy patients with normal renal function when the daily Mg intake exceeds 6 g. The inadvertent intravenous infusion of 40 g $MgSO_4$ to a 28-year-old primigravida with preeclampsia caused somnolence, dyspnea, and ventilatory insufficiency.[7] She survived without sequelae following intubation, calcium bolus, and forced diuresis with furosemide.

Impaired Renal Function

Hypermagnesemia peaks during the early diuretic phase of renal failure without exogenous Mg loads. Accumulation of magnesium after exogenous administration occurs when the creatinine clearance falls below 10–30 mL/minute.[8] Iatrogenic hypermagnesemia with respiratory depression has been reported in patients with mild–moderate renal dysfunction who received doses of 10% hemiacidrin (Renacidin; 14.8% magnesium carbonate, 2.5% magnesium acid-citrate, pH = 3.9)[9,10], and magnesium citrate.[11] In an 87-year-old man with a creatinine clearance of 29 mL/minute on admission, the administration of 6.6 g Mg as magnesium citrate over 16 hours produced confusion, somnolence, and diminished deep tendon reflexes; the serum Mg concentration was 4.34 mEq/L (5.3 mg Mg/dL).[12]

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His admission serum creatine was 1.8 mg/dL. Both hypermagnesemia and hypercalcemia developed in two patients with hepatorenal failure after receiving magnesium sulfate enemas.[13,14] A 39-year-old woman presented to the emergency department after a tricyclic antidepressant overdose; the admission serum Mg concentration was 1.9 mEq/L.[15] She received ~58 g (5,017 mEq) Mg citrate via nasogastric tube over 72 hours, resulting in marked hyporeflexia, paralytic ileus, and respiratory arrest. She recovered after intensive supportive care.

Normal Renal Function

Although magnesium toxicity occurs rarely in patients with normal renal function, large Mg doses may produce magnesium toxicity in patients with normal renal function. Single doses of magnesium-containing cathartics usually do not cause statistically significant elevations in the serum magnesium concentrations of in patients with normal renal function.[16] Modest elevations of serum magnesium concentrations occurred in 102 adults with normal renal function treated for overdose with repetitive doses of magnesium citrate (mean = 960 mL (9.22 g Mg) over 24–48 hours).[17] The mean initial and final serum magnesium concentrations were 1.8 ± 0.03 mEq/L and 2.5 ± 0.05 mEq Mg/L, respectively; 12 patients had serum Mg concentrations of >3.0 mEq/L with no value higher than 4.0 mEq/L. The Mg citrate dose did not correlate with the serum Mg concentrations. In a study of 14 overdose patients receiving three 30-g doses of $MgSO_4$ (8.64 g, 720 mEq), 4 patients had peak serum magnesium concentrations of >3 mEq/L with a maximum of 5.0 mEq/L.[16] A patient with normal kidney function developed symptomatic hypermagnesemia (respiratory arrest, bradycardia) after receiving 90 g $MgSO_4$ (7,380 mEq Mg) over 18 hours.[18] Ingestion of 200 g magnesium sulfate by a hypothermic patient did not produce cardiovascular effects despite an admission serum Mg concentration of ~19 mEq Mg/L.[19] The ingestion of 17.5 g (140 mEq Mg) Epsom salt ($MgSO_4$) produced extreme musculoskeletal weakness and altered mentation,[20] whereas the ingestion of 50 g (400 mEq Mg) was associated with hypotension, coma, and cardiopulmonary arrest.[21] Both patients survived without sequelae. Neonates may be susceptible to hypermagnesemia as a result of immature renal function. A dose of ~380 mg Mg/kg/day for 3 days caused hypotonia, lethargy, and an initial serum Mg concentration of 7.6 mEq Mg/L in a 25-day-old neonate.[22]

TOXICOKINETICS

Absorption

Substantial interindividual variation occurs in the absorption of magnesium depending, in part, on the amount of magnesium present. In a metabolic study of eight healthy volunteers fed collards, turnip greens, leaf lettuce, and spinach grown in a nutrient solution containing radiolabeled magnesium, the estimated gastrointestinal absorption of radiolabeled Mg was ~40–60%.[23,24] The natural abundance of ^{26}Mg limits the sensitivity of determining the gastrointestinal absorption of magnesium by isotope studies. The amount of magnesium absorbed into the blood is dose-dependent with relatively less absorption occurring at higher than lower Mg concentrations.[25] Following the oral administration of 13.9 g (56.5 mmol) magnesium sulfate in four equal hourly increments to six healthy volunteers, the mean gastrointestinal absorption of Mg during the first 24 hours was 4.0 ± 2.9% (range: 0.8–8.7%) of the Mg sulfate dose and 6.9 ± 7.0% during a 72-hour interval, based on urinary Mg excretion (corrected for baseline excretion rate).[26] All subjects had mild-to-moderate diarrhea.

Distribution

The total body content of magnesium averages ~24 g.[27] Accumulation of magnesium in the bone accounts for ~60% of the total body content of magnesium in the following two pools: 1) a surface limited exchangeable pool in equilibrium with plasma magnesium (i.e., ~1/3 of the bone stores) and 2) a deep reservoir in the crystal mineral lattice portion of bone. The former, freely exchangeable pool acts as a reserve for maintaining extracellular magnesium concentrations.[28] Another 20% appears in the skeletal muscle with the remaining 20% distributed in a variety of organs including the heart, kidney, and liver. Only 1% of the total content of magnesium exists in the blood with ~30% bound to proteins.

Elimination

Elimination of magnesium occurs almost only by renal excretion. After the glomerulus filters magnesium, the proximal tubule and the ascending loop of Henle reabsorb ~95% of the filtered load. Glomerular filtration rates below 30 mL/minute predispose patients to hypermagnesemia. Both magnesium resorption and calcium resorption in the kidney are closely related because a

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common carrier exists for calcium and magnesium. The fractional excretion of magnesium varies inversely with the serum magnesium concentration and, to a lesser extent, with the effects of diuretics and parathyroid hormone.[29] Hypercalcemia and high sodium intake increase magnesium excretion.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

Magnesium is an essential, primarily intracellular cation with a wide range of functions including channel regulation (potential-dependent L-type calcium channels), membrane and nucleic acid stability, maintenance of the cell cycle, and a cofactor for many enzymes including Na^+/K^+ATPase. Magnesium is also an NMDA-receptor antagonist. This metal ion is the second most abundant intracellular cation after potassium and is involved in >600 enzymatic processes in the brain, heart, and skeletal muscles.[30] Within the cell, magnesium binds to ATP and proteins. Magnesium is an essential component of enzyme processes that involve protein synthesis, energy storage, and utilization (e.g., transfer of phosphate in nucleotide triphosphate reactions, ATP), DNA synthesis, metabolism, and the maintenance of cellular electrolyte balance. As a result of the role of magnesium in these biochemical reactions, magnesium is an important element in the control of neuromuscular transmission, neuronal activity, muscle contraction, and cardiac conduction.

Magnesium homeostasis and blood magnesium are tightly controlled because of the importance of magnesium in the pathogenesis of a variety of diseases including type 2 diabetes mellitus, osteoporosis, asthma, and cardiovascular diseases.[31,32] Although bone and intracellular magnesium are the primary storage areas for magnesium in the body, the kidney is the most important organ involved with magnesium homeostasis. The epithelial Mg channel (Melastatin 6) in the distal convoluted tubule functions as the gatekeeper for controlling Mg balance in the body by matching urinary magnesium excretion and the net entry of magnesium into the extracellular fluid.[33] Several mutations produce hypomagnesemia including mutations in transient receptor potential Melastatin type 6, renal tight junction protein claudin 16 (*CLDN16* gene), and cyclin M2 (*CNNM2*) gene, as well as mutations in Mg^{2+} transporter 1 linked to T cell deficiency and reduced cell viability.[30] Clinical features of hypomagnesemia include nystagmus, tremulous, hyperactive deep tendon reflexes, dysphagia, and dysrhythmias (premature ventricular contractions, multifocal atrial tachycardia, torsades de pointes, ventricular fibrillation). Hypokalemia strongly correlates to hypomagnesemia.

Mechanism of Toxicity

Hypermagnesemia affects primarily the cardiovascular and nervous systems in a dose-dependent relationship, resulting in stabilization of cell membranes, delayed nerve conduction, prolonged refractory period, and compromised muscle contraction. Alterations in extracellular magnesium levels cause impaired nerve conduction and synaptic blockade. Elevated Mg concentrations reduce impulse conduction at the neuromuscular junction by impairing the sensitivity of the postsynaptic junction to acetylcholine, decreasing acetylcholine release from the presynaptic terminals, and reducing the action potential produced by acetylcholine at the postsynaptic junction.[34] Hypermagnesemia probably does not directly slow motor and sensory nerve conduction velocities. Hypermagnesemia produces direct depression of atrioventricular conduction by suppressing the A–H interval. The latter interval approximates the conduction time through the AV node represented on the ECG by the time between the initial rapid deflection of the atrial wave (A) and the bundle of His (H); the typical A–H interval is 50–120 msec. Magnesium is a calcium antagonist that causes systemic and cerebral vasodilation, increases cyclic guanosine monophosphate, and modulates vasomotor tone by increasing nitric oxide and decreasing endothelin-1 concentrations.[35,36]

The kidney has a common transport system for the reabsorption of calcium and magnesium; consequently, hypercalcemia produces a concomitant increase in magnesium excretion.[37] Chronic diseases associated with hypercalcemia (e.g., milk-alkali syndrome, multiple myeloma, primary hyperparathyroidism, vitamin D intoxication) may cause hypomagnesemia.

Postmortem Examination

A 75-year-old woman was found dead in bed after ingesting magnesium-containing milk during the preceding several days.[38] Autopsy performed three days after death demonstrated congestion of the brain and lungs along with advanced arteriosclerosis and calcification of the coronary arteries, thoracic aorta, and abdominal aorta. The mildly enlarged heart weighed 480 g without evidence of myocardial infarction. Histological findings included fibril formations in the left

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ventricular wall, indurated glomeruli, and marked inflammatory cell infiltration in the kidney. The presence of advanced arteriosclerosis suggests the possibility of a fatal dysrhythmia secondary to hypermagnesemia.

After a 40-week gestation, a newborn aspirated meconium during delivery.[39] At 1½ hours after delivery, the newborn received 5 g (416 mEq) magnesium as $MgSO_4$ enema before being transported to a referral hospital. A respiratory arrest occurred 1½ hours after the enema followed by asystole. The Mg concentration was 4.6 mEq/L 4¼ hours after the enema and 7.6 mEq/L before exchange transfusion. An EEG was isoelectric 18 hours after the enema. The infant died 46 hours after delivery, despite resuscitative efforts and treatment for hypermagnesemia. The autopsy demonstrated evidence of moderately severe aspiration, cerebral edema, and hemorrhagic necrosis of the midbrain, pons, and inferior olivary nucleus of the brain stem. The presence of moderate pulmonary disease, pulmonary aspiration, and extensive hypoxic brain damage from her cardiac arrest confounds the interpretation of the clinical effect of hypermagnesemia.

CLINICAL RESPONSE

Acute Toxicity

Hypermagnesemia usually occurs in the setting of large iatrogenic doses or in the presence of renal failure with large magnesium loads (e.g., iatrogenic, rhabdomyolysis).[40,41] Progressive loss of neuromuscular, cardiovascular, and respiratory functions characterizes hypermagnesemia. Symptomatic hypermagnesemia appears rarely in the absence of intestinal or renal disease. Table 18.2 lists the common clinical settings of hypermagnesemia. The main symptoms involve neuromuscular (impaired conduction, synaptic blockade, loss of reflexes, paralysis), cardiac (hypotension, bradycardia, heart block), and respiratory (insufficiency, arrest). These signs and symptoms include central nervous system depression, respiratory depression, hypomotility of the bowel, muscle paralysis, hyporeflexia, and electrocardiographic changes similar to those in hyperkalemia (prolonged QRS, QT, and PR intervals, peaked T waves, interventricular conduction defects, atrioventricular block, and eventually asystole). In severe magnesium intoxication, patients manifest absent deep tendon reflexes, alteration of mental status progressing coma, dysrhythmias, refractory hypotension, and respiratory arrest.

Elevated serum magnesium concentrations may cause hypocalcemia because of decreased parathyroid hormone activity and decreased end-organ responsiveness,[19] especially in neonates born to preeclamptic mothers treated with magnesium sulfate.[42] Both preeclamptic mothers and their unborn children have survived accidental overdoses of magnesium sulfate without immediate evidence of sequelae.[43,44] The clinical presentation of hypermagnesemia is nonspecific; the differential diagnosis of hypermagnesemia includes primary central nervous system lesions, sepsis, bowel obstruction, and ethanol intoxication.

TABLE 18.2. Clinical settings associated with hypermagnesemia.

Frequency	Setting
Common	Acute renal failure, chronic renal failure with exogenous magnesium intake, magnesium sulfate therapy for toxemia.
Occasional	Chronic renal failure without exogenous magnesium intake, rectal administration of Mg-containing solutions.
Unusual	Acute diabetic ketoacidosis, Addison's disease, hyperparathyroidism with renal disease, hypothyroidism, lithium therapy, milk-alkali syndrome, neoplasm with bone metastasis, parasitosis with exogenous Mg intake, perforated viscus with exogenous Mg intake, pituitary dwarfism, viral hepatitis.

Environmental Exposure

There are few data to document the toxicity of excessive magnesium concentrations in the environment; most epidemiology studies examine the risk of cardiovascular disease and hypomagnesemia, calcium concentrations, and water hardness. Currently, there is inadequate evidence to justify the addition of magnesium to drinking water for preventive purposes.[45]

Occupational Exposure

Magnesium and magnesium alloys exhibit low toxicity. Magnesium oxide fumes form during the application of high temperatures to Mg-containing metals; however, experimental studies indicate MgO is substantially less toxic than oxides associated with metal fume fever (e.g., zinc oxide).[46] Exposure to these fumes may cause conjunctivitis, cough, and mild irritation of the nose and throat, but systemic symptoms (e.g., metal fume fever) occur rarely.[47,48] The latter reports do not provide sufficient exposure data to exclude other causes of the systemic complaints (i.e., confounding chemical exposures). Prolonged exposure to high doses of magnesium

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carbonate at a magnesite production facility was associated with a 2.1% incidence of benign pneumoconiosis (cough, sputum, emphysema), but these effects could not be directly attributed to $MgCO_3$ because of the presence of silica and asbestos.[49]

Carcinogenesis

Magnesium is an essential cofactor for the proper functioning of numerous enzyme systems. Neither the International Agency for Research on Cancer (IARC) nor the US National Toxicology Program lists magnesium or magnesium compounds as suspected carcinogens. Magnesium production workers may be exposed to carcinogens (e.g., asbestos, coal tar pitch, chlorinated hydrocarbons). A cohort study of 2,391 male magnesium production workers detected a statistically significant excess of lung cancer with a relative risk of 1.8 (95% CI: 1.2–2.5), but not in the cohort with exposure to magnesium oxide (RR = 1.71, 95% CI: 0.6–3.7). Interpretation of the study is limited by the lack of adjustment for exposure to known carcinogens (e.g., coal tar, asbestos, smoke), crude exposure data, and the small number of cases.[3] A population-based, prospective study of 23,366 Swedish men aged 45–79 years with relatively high intakes of dietary magnesium did not detect an excess all-cause or cancer mortality after comparing the highest tertile of Mg intake (mean = 523 ± 38 mg/day) with the lowest tertile (mean = 387 ± 31 mg/day).[50]

DIAGNOSTIC TESTING

SI Conversion Units

1 mg/dL = 0.4114 mmol/L
1 mmol/L = 2.431 mg/dL
1 mg = 0.0823 mEq
1 mEq = 12.15 mg

Analytical Methods

Serum magnesium concentrations are common analytical measurements in clinical laboratories. In samples containing Mg in the mg/L range, the use of inductively coupled plasma/optical emission spectroscopy allows lower limits of quantitation in serum and whole blood in the range of 0.16 mEq/L and 0.8 mEq/L, respectively.[51] Preanalytic studies indicate magnesium is stable in whole blood, serum, and plasma for 6 hours at 25°C and 24 hours at 4°C.[52]

Biomarkers

Blood

General Population

The serum magnesium concentration does not always correlate well to clinical signs and symptoms because magnesium is primarily an intracellular cation with only ~1% of the body burden of magnesium in the blood.[25] Total serum magnesium concentration reflects the free or ionized form (55%), the protein-bound fraction (33%), and the chelated portion (12%).[53] Alterations in acid-base status and serum protein concentrations affect the active (free) fraction of magnesium similar to calcium.[54] A decrease in the serum albumin concentration lowers the total serum Mg concentrations without affecting the active (free) form of magnesium, whereas acidosis decreases protein binding and increases the active portion of magnesium. The mean serum magnesium concentration in 15 healthy Spanish adults aged 25–40 years was 1.65 mEq/L (0.83 mmol Mg/L).[55] Typical serum magnesium concentrations in the general population range from 1.5–2.5 mEq/L.

Toxic

Patients usually tolerate mildly elevated serum magnesium concentrations (2.5–3.25 mEq/L) without symptoms.[56] A 32-year-old woman with end-stage renal disease and a history of ingestion of magnesium oxide cathartics developed weakness and quadriparesis; her admission serum magnesium was 4.34 mEq/L (10.58 mg/dL).[57] A 56-year-old man developed coma, respiratory failure, and flaccid extremities after the ingestion of three tablespoons of Epsom salts and the iatrogenic administration of 2 g magnesium citrate; he survived with intensive supportive care.[58] His peak serum magnesium concentration was 9.43 mEq/L (23 mg/dL). A 56-year-old woman survived a cardiopulmonary arrest with supportive care after developing severe hypermagnesemia from multiple-dose $MgSO_4$ therapy; the initial serum Mg concentration was 21.3 mEq/L.[59] A 7-year-old boy sustained a cardiac arrest with asystole following the use of an Epsom salt enema earlier in the day.[60] He failed to respond to advanced cardiac life support that included the use of calcium; the admission serum Mg concentration reported after he was declared dead was 33.9 mEq/L. Table 18.3 outlines the clinical effects of hypermagnesemia associated with specific magnesium concentrations.

Postmortem

A 75-year-old woman developed muscle weakness and diarrhea after ingesting a home remedy for weight loss

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TABLE 18.3. Clinical effects of specific serum magnesium levels. The typical serum magnesium concentrations in the general population are 1.5–2.5 mEq/L.

3.25–9.9 mEq/L	Erythema, nausea, vomiting, bradycardia, delayed cardiac conduction (↑ PR interval, ↑ QRS duration), hypotension, decreased reflexes, sedation
≥10–14 mEq/L	Muscle paralysis, respiratory depression, coma, hypotension with decreased ventricular conduction, ventricular arrhythmias
>14–15 mEq/L	Cardiac arrest, asystole

containing milk with magnesium chloride.[38] She was found dead in the morning; her heart blood contained a total magnesium concentration of 10.2 mEq/L. The mean postmortem magnesium concentration in heart blood from three autopsy cases with similar postmortem intervals and without excessive magnesium exposure was 6.6 ± 0.4 mEq/L; the femoral blood contained similar magnesium concentrations without evidence of significant postmortem redistribution.

Urine

Analysis of the 24-hour urinary magnesium is a good measure of total magnesium body burden that avoids the effect of circadian rhythms on magnesium excretion. In a study of 7,664 subjects mostly with a history of albuminuria, the mean urinary magnesium excretion was 4.24 ± 1.64 mmol/24 hours for men and 3.54 ± 1.40 mmol/24 hours for women.[61]

Abnormalities

Numerous factors affect the serum magnesium concentrations, as listed in Table 18.4. Fluid and electrolyte (hypokalemia, hypernatremia) imbalances may occur concurrently in patients with hypermagnesemia, but hypermagnesemia does not directly affect these concentrations. Some reductions in calcium concentrations develop during hypermagnesemia as a result of the effect of elevated magnesium concentrations on the secretion of parathyroid hormone.[62] Alkalosis decreases free magnesium in the serum by increasing protein binding, whereas acidosis increases free serum magnesium. Magnesium is usually an unmeasured cation; hence, in this situation, hypermagnesemia occurs with a low to normal anion gap. Hypermagnesemia causes PR interval widening and transient tachycardia progressing to third-degree heart block, bradycardia, and eventually asystole as the serum magnesium concentration increases.

TABLE 18.4. Factors altering serum magnesium concentrations. (Adapted from Gums).[27]

Serum Magnesium	Factor
Increased	↑ Serum phosphate; ↑ parathyroid hormone secretion
	↓ Serum magnesium (feedback loop); ↓ serum calcium
Decreased	Acute acidosis, acute pancreatitis, alcohol (inhibits Mg resorption), bowel resection, drugs (aldosterone, amphotericin, calcitonin, carbenicillin, cisplatin, digoxin, diuretics, gentamicin, growth hormone, protein pump inhibitors, tobramycin, thyroxine), ↑ sodium intake, hypercalcemia, ↑ extracellular volume, ↑ serum magnesium, malabsorption, osmotic diuresis, thyroid disease

For detection of magnesium-induced diarrhea, 24-hour fecal output of magnesium is the most sensitive indicator. The upper limits of the fecal output of soluble magnesium and fecal magnesium concentrations in a study of normal subjects were 14.6 mmol Mg/day and 45.2 mmol Mg/L/day, respectively.[63]

HEALTH SURVEILLANCE

Table 18.5 lists regulations and guidelines for exposure to magnesium oxide and carbonate. The US OSHA PEL–TWA for MgO fume is 10 mg/m^3 as total particulate in order to protect workers from irritation of the eyes and the throat. Workers with chronic renal disease are more susceptible to the accumulation of magnesium, but systemic symptoms are unlikely unless the exposure to MgO fumes is excessive. The US OSHA PEL–TWA (8-hour) for magnesite ($MgCO_3$) is 15 mg/m^3, total particulate, and 5 mg/m^3 for the respirable fraction. The ACGIH recommends a TLV–TWA of 10 mg/m^3 when the total dust does not contain asbestos and the crystalline silica content is <1% based on the lack of inflammatory effects following MgO exposure of volunteers to 100 mg/m^3.[46,64]

TREATMENT

Stabilization

Hypermagnesemia is potentially life-threatening with severe hypermagnesemia (>10–15 mEq Mg/L) causing sudden respiratory arrest and asystole; these patients should be followed closely with cardiac monitoring

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TABLE 18.5. Regulations and guidelines for exposure to magnesium compounds.

Exposure Limit	Value
	OSHA
PEL–TWA (8-hour)	
MgO	10 mg/m^3 (total particulates)
$MgCO_3$	15 mg/m^3 (total particulates)
	5 mg/m^3 (respirable particulates)
	NIOSH
IDLH (30 minute, MgO)	750 mg/m^3
	ACGIH
TLV–TWA (8-hour)	
MgO	10 mg/m^3 (total particulates)
STEL–TWA (15-minute)	None
	US FDA
Bottled water allowable limit	None
MCL	None
US federal drinking water guidelines	None

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; IDLH = immediately dangerous to life and health; MCL = Maximum contaminate level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average; US FDA = United States Food and Drug Administration.

and pulse oximetry for the development of bradycardia, progressive QRS widening, hypotension, and respiratory insufficiency. Generous saline replacement should precede the use of vasopressors. Frequently, hypotension responds to calcium administration. Serum electrolytes (i.e., potassium, calcium, phosphate) should be evaluated urgently because electrolyte abnormalities commonly occur with hypermagnesemia including hypocalcemia and hypokalemia.[65] With careful attention to fluid and electrolyte balance, the use of loop diuretics (e.g., furosemide) increases the renal excretion of magnesium; adequate hydration is necessary to enhance the renal elimination of magnesium.

Decontamination

Activated charcoal, emetics, and cathartics are not indicated in the treatment of hypermagnesemia.

Elimination Enhancement

Hemodialysis effectively removes magnesium; immediate hemodialysis may be necessary for severely intoxicated patients, particularly if the patient does not respond to calcium. Serum Mg concentrations of >8–10 mEq Mg/L suggest the need for dialysis in patients with renal dysfunction. The decision to institute hemodialysis in patients with normal renal function depends on clinical judgment because patients with normal renal function have survived severe hypermagnesemia without hemodialysis.[18]

Antidotes

Calcium is an antagonist of the membrane effects of hypermagnesemia. The exact mechanism of action is unknown, but calcium may displace magnesium from cell membranes. Treatment with intravenous calcium is indicated in symptomatic patients with serum magnesium concentrations of >5 mEq/L. The adult dose of calcium gluconate is 10–30 mL of a 10% solution (4.5–13.5 mEq elemental Ca^{2+}) over 10 minutes, depending on the severity of the symptoms. This dose may be delivered over 1 minute if the patient is *in extremis*. The dose may be repeated once; then, the serum calcium concentrations should be reevaluated to determine the need for more calcium and to prevent hypomagnesemia. Calcium chloride provides three times more elemental calcium (13.6 mEq/10 mL 10% solution) than the gluconate salt; however, intravenous calcium chloride is much more irritating to the vein and skin than calcium gluconate. The administration of repeat doses of intravenous calcium may require a central line, particularly calcium chloride.

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Chapter 19

MANGANESE

ELEMENTAL AND INORGANIC MANGANESE

HISTORY

Manganese toxicity (manganism) is a rare central nervous system disease that results from chronic, high-dose occupational exposure to manganese dust or to manganese fumes.[1] In 1837, the Scottish physician, John Couper, published the first report of manganism in workers processing pyrolusite (mineral manganese dioxide). These mill workers inhaled manganese oxides while grinding ore at his father-in-law, Charles Tennant's bleach factory near Glasgow.[2] At that time, this factory was the world's largest hypochlorite bleaching powder plant.[3] Later reports documented similar neurological effects in Czechoslovakian manganese workers exposed to manganese-containing dust while pulverizing pyrolusite during the early 1900s.[4] In 1913, the Columbia University physician, Louis Casamajor, reported the first US cases of manganism in workers exposed to manganese-containing dust from the magnetic separation of zinc from ore also containing iron and manganese.[5] As the use of manganese in alloys, armaments, and welding increased manganese demand, other reports of manganism were published including those of Chilean manganese miners during the 1940s[6] and 1950s.[7] The inhalation of high doses of manganese initially produced an acute psychiatric syndrome in these workers called "manganese madness." Characteristic symptoms of this syndrome included compulsive and aberrant behavior, emotional lability, and hallucinations. Later reports associated a syndrome similar to Parkinson's disease (e.g., mask-like face, stooped posture, cogwheel rigidity, tremor, impaired speech, clumsiness) with workers exposed chronically to manganese.[8]

PHYSIOCHEMICAL PROPERTIES

Manganese is a very hard, brittle Group 7 (Group VIIB) transition metal that appears whitish-gray in color. Manganese is a constituent of many alloys because of its favorable physical properties. The outer electron shell of manganese can donate up to 7 electrons; therefore, there are 11 oxidation states (3− to 7+) with the most stable being Mn^{2+}, Mn^{4+}, and Mn^{7+}. Manganese is a cofactor in many enzymatic reactions. The divalent form (+2) is the most common valence state of manganese in biological systems, although the trivalent form (+3) is the oxidative state of manganese in superoxide dismutase and transferrin. Absorption of manganese from the diet occurs in the divalent and tetravalent states. Manganese oxide (tetravalent M_gO_2) is the most important tetravalent manganese compound. Most manganese salts are readily water-soluble, except for the limited water solubility of phosphate and carbonate salts.[9] Manganese oxides (dioxide, tetroxide) are also poorly water-soluble. Table 19.1 displays identifying information and physical properties of manganese and industrially important manganese compounds. At manganese concentration of >0.1 mg/L, this element stains plumbing fixtures, produces an undesirable

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TABLE 19.1. Identifying information and physical properties of elemental manganese inorganic manganese compounds. (Data from International Programme on Chemical Safety).[11]

	Manganese	Manganese Chloride	Manganese Sulfate	Manganese Tetroxide	Manganese Dioxide
Synonyms	Elemental manganese, colloidal manganese, cutaval	Manganous chloride, manganese dichloride	Manganous sulfate, sulfuric acid manganese	Trimanganese tetroxide, mango-manganic oxide, manganese oxide, hausmannite	Manganese peroxide, manganese binoxide, manganese black, battery manganese, pyrolusite
Chemical formula	Mn	$MnCl_2$	$MnSO_4$	Mn_3O_4	MnO_2
CAS RN	7439-96-5	7773-01-5	7785-87-7	1317-35-7	1313-13-9
Mass (g/mol)	54.94	125.85	151.00	228.81	86.94
Color	Gray-white	Pink	Pale rose-red	Black	Black
Physical state	Solid	Solid	Solid	Solid	Solid
Melting point (°C)	1244	650	700	1564	535
Boiling point (°C)	1962	1190	850 (Decomposes)	2847	Insufficient data
Solubility	Dissolves in dilute mineral acids	Very soluble in water (723 g/L at 25°C); soluble in alcohol	Soluble in water (520 g/L at 5°C) and alcohol	Insoluble in water; soluble in hydrochloric acid	Soluble in hydrochloric acid; insoluble in water

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number.

taste in beverages, and discolors laundry.[10] Black precipitate may slough from water pipes coated with manganese.

Manual and gas metal arc welding releases a complex mixture of welding fume particles with a dominant aerodynamic size of 0.1–2 μm;[12] X-ray diffraction of these particles indicates the manganese oxidation state in the aerosols is primarily divalent and trivalent with manganese oxides predominating in particles of <50 nm. Manganese compounds include MnO, Mn_3O_4, $KMnF_3$, and K_2MnO_4. In a study of 137 currently exposed manual and gas metal arc welders, the mean solubility of total Mn mass in welding aerosols collected in 237 personal air samples was 13.8% (range, 1–49%) as measured in the simulated lung lining fluid (Hatch solution).[13]

EXPOSURE

Production Processes

Manganese occurs in the environment combined with a variety of borates, carbonates, phosphates, oxides, sulfides, and silicates. The most important manganese-bearing mineral is pyrolusite (MnO_2, black oxide) with less common manganese ores including rhodanate (manganese silicate) and rodochrosite ($MnCO_3$). The mining of these ores occurs in shallow underground mines or open pits. Most of the uses of manganese ores involve the production of the manganese-iron alloy (ferromanganese) by the smelting of the ore in electric furnaces. For workers in the manganese alloy-producing industries, the predominant oxidation states of manganese in the respirable aerosol fraction are Mn^0 and Mn^{2+}.[14] The main manganese ores are manganese oxides that range in valence from +2 to +4. Fumes from the pouring and casting of molten ferromanganese are primarily manganese tetroxide. Low-purity manganese (97–98%) results from the aluminum reduction of low iron-containing manganese ores or from by-products of ferromanganese alloys.[15] Manganese compounds form from chemical reactions with metallic manganese or manganese ores. In nature, elemental manganese usually exists in an iron ore rather than the elemental form.

Uses

High-grade manganese ores occur in South Africa, the Commonwealth of Independent States (CIS), Gabon, Australia, Brazil, China, India, Mexico, Ghana, and Chile.[16] The principal use of metallic manganese is in the production of carbon and high-temperature steel to improve hardness and strength. Modern steel technology uses less manganese compared with the manganese consumption of older steel technologies. Table 19.2 displays some common uses of manganese compounds.[17]

Sources

Manganese is a ubiquitous constituent of the environment comprising about 0.1% of the earth's crust,

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TABLE 19.2. Common uses of manganese compounds. (Based on Agency for Toxic Substances and Disease Registry).[17]

Manganese Compound	Uses
Manganese chloride	Dry-cell batteries, supplemental trace element in animal feed, catalyst for chlorination of organic compounds, precursor for manganese compounds
Manganese dioxide	Glass production, semiconductors, catalysts, ceramics, incendiaries, dry-cell batteries
Manganese sulfate	Ceramics, fungicides, nutritional supplements

primarily as carbonates, oxides, or silicates. This metal is a normal constituent of the human body. Crustal rock is the major natural source of manganese found in the atmosphere with other sources including vegetation, forest fires, volcanic activity, and ocean spray.[11] Food is the most important source of manganese for the general population, and daily intake ranges from 2–9 mg Mn depending on nutritional habits involving the consumption of high manganese-containing foods (e.g., tea).[17]

Occupational exposures result from metallurgical operations (e.g., ferrous/nonferrous alloys, iron, steel), mining, and ore-crushing. Welding is the most common source of occupational Mn exposure from the inclusion of this metal in steel production and the off-gassing of fumes from the steel welding processes (e.g., arc welding) involving manganese-containing base metal, welding rods, wire, or flux.[18] The extent of manganese exposure varies with the amount of Mn in the base metal, flux, rods, or welding wires, as well as the process and industrial hygiene factors. These processes produce respirable particles, primarily complex oxides that sometimes contain a silicon oxide shell. In contrast, manganese mining and ore milling produce much simpler forms of manganese-containing particles than welding processes. With the exception of cutting arc and hard-facing/burning processes, the manganese percentage in these fumes typically is low (i.e., 2%). Although elemental manganese and manganese oxides in these fumes are water-insoluble, some manganese absorption occurs after alveolar deposition.

Air

The background concentrations of manganese in rural and urban areas without point sources of manganese range from 0.01–0.07 μg Mn/m^3, whereas average ambient air concentrations of manganese near industrial sources range from 0.22–0.3 μg/m^3.[19] The anthropogenic sources of manganese in ambient air include the combustion of fossil fuels (20%) and the emission of manganese from industrial sources (80%).[17] Erosion of soil is the most important natural source of manganese in the ambient air, but little data are available to estimate the contribution of manganese from this source. Indoor and contiguous outdoor respirable Mn concentrations are usually similar. Despite higher respirable Mn concentrations in urban than rural areas, studies suggest that the higher ambient air concentrations do not produce relatively higher whole blood Mn concentrations in urban residents. In a Canadian study comparing Mn concentrations in ambient air and whole blood in five urban residents (Montreal) with five rural residents (Saint-Philippe), the mean whole blood Mn concentrations were similar (8.4 μg/L vs. 7.8 μg/L, respectively) despite differences in Mn concentrations in ambient air.[20] There was no correlation between blood Mn and duration of residence.

Canadian garage mechanics were exposed to a mean of 0.25 μg Mn/m^3 at work compared with a mean of 0.007 μg Mn/m^3 at their homes.[21] For taxi drivers, the mean was 0.024 μg Mn/m^3 compared with 0.011 μg Mn/m^3 at their homes. In general, the exposure of the general population to organic manganese from engine emissions is much lower than most exposures to manganese in the occupational setting.[22] Studies of Canadian subway systems suggest that internal Mn sources do not increase the ambient air concentrations of Mn in the subway above background (outdoor) concentrations.[23]

Water

Concentrations of manganese in seawater average about 2 μg Mn/L with higher Mn concentrations (1–200 μg/L, median ~10 μg Mn/L) occurring in freshwater.[24] A study of water samples from US rivers during 1974–1981 measured dissolved manganese; the median manganese concentration was 24 μg/L.[25] Manganese concentrations in drinking water vary substantially. A study of tap water samples from 278 homes in southwest Quebec demonstrated a mean Mn concentration of 6.4 μg/L (range, <0.1–159 μg/L).[26] Excluding samples from 16 wells, the range of Mn concentrations was 0.5–71.1 μg/L. In a study of drinking water in northwest Peloponnesos, Greece, the manganese concentration ranged from 3.6–14.6 μg/L to 1,800–2,300 μg/L.[27] Total manganese concentrations also reflect the amount of manganese adsorbed to sediment, but the bioavailability of manganese in sediment has not been established. Some manganese compounds ($MnCl_2$, $MnSO_4$) are soluble

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in water; therefore, Mn exposure may result from the ingestion of manganese-containing water. Reducing conditions in lakes and groundwater favor high Mn concentrations. Generally, the contribution to overall daily Mn intake is smaller from drinking water than from food. High Mn concentrations (e.g., 400–800 μg/L) in ground or surface waters may result from industrial pollution. Contamination of well water by waste disposal produced concentrations near 2,000 μg Mn/L.[28]

Soil

Manganese exists in almost all types of soil. Concentrations of manganese in soil average 40–900 mg/kg with a mean of 330 mg/kg and maximum concentrations up to 7,000 mg/kg depending on the extent of mining activities.[24,29] Accumulation of manganese in soil usually occurs in the subsoil rather than the topsoil.[9]

Diet

Food is the most important Mn source in the general population with the daily intake from ambient air (i.e., ~0.04 ng) usually contributing several orders of magnitude less than the diet; homeostatic control mechanisms limit Mn absorption and manganese toxicity from dietary sources.[30] Food contributes ~95% of manganese absorbed from the diet (e.g., grains, tea, green leafy vegetables) with a small contribution from water consumption, except in areas with unusually high manganese concentrations (e.g., industrial pollution, contaminated wells).[31] Vegetarian diets typically contain higher manganese concentrations than animal-derived diets. The average daily intake is ~2–6 mg Mn,[32,33] ranging up to 11 mg Mn in vegetarian diets consisting of large portions of nuts and cereals.[34]

The highest manganese concentrations occur in nuts (18–46 ppm), grains (0.4–40 ppm), legumes (2.2–6.7 ppm), fruits (0.2–10 ppm), and vegetables (0.4–6.6 ppm), particularly avocados, blueberries, egg yolks, dried peas, green leafy vegetables, green tea, and seaweed.[35] Poultry, meat, refined foods, fish, and dairy products contain relatively small amounts (0.2–0.5 ppm Mn). A 1992 survey of bluefin tuna (*Thunnus thynnus*) from the Northwest Atlantic detected Mn concentrations ranging from 0.16–0.31 μg/g dry weight muscle with an average of 0.22 μg/g dry weight muscle.[36] Heavy consumption of green tea can significantly increase the daily Mn intake with the average cup of tea containing ~0.4–1.3 mg Mn.[37] The concentration of Mn in milk is relatively low with typical mean concentrations of ~5 μg/L in human breast milk and 25 μg/L in cow's milk.[38]

ENVIRONMENTAL FATE

Air

Release of manganese into the air occurs primarily as particulate matter with the fate and transport of the particles depending on size, density, and wind speed. Elemental manganese and manganese compounds have little vapor pressure, but transport of manganese into ambient air results from the emission of suspended manganese-containing particulates from industrial sources and the erosion of Mn-containing soils. About 80% of the manganese-containing particles possess a mean median equivalent diameter (MMED) of <5 μm with ~50% demonstrating an MMED of <2 μm.[9] Particle size varies by source. Large particles dominate near mining operations, whereas smaller particle sizes occur near ferroalloy production, iron and steel foundries, power plants, and dry-cell battery plants.[9] Gravitational settling and rain are the main mechanisms of manganese removal from the atmosphere. The half-life of these particulates in the atmosphere depends on the particulate size, density, wind speed, and wind directions with the half-life usually measured in days. Methylcyclopentadienyl manganese tricarbonyl (MMT) undergoes rapid photochemical degradation to manganese tetroxide (Mn_3O_4) and perhaps other forms of manganese with a half-life of ~15 seconds in sunlight.[39]

Water

Manganese exists in the aquatic environment as divalent and tetravalent forms with the dominant species determined by pH and redox conditions. Water solubility controls the transport of manganese in water. Divalent manganese, primarily in the form of $MnCO_3$, is the principal manganese source in water at pH 4–7; oxidation of manganese occurs at pH >8–9.[40] The limited solubility (i.e., 65 mg/L H_2O) of $MnCO_3$ restricts the amount of manganese present in water; the transport of manganese usually occurs by suspended sediment in rivers.[41] Anaerobic waters contain relatively high concentrations of dissolved Mn along with poorly soluble manganese sulfides. Reduction of Mn^{4+} to Mn^{2+} can occur in this environment with divalent form dominating at lower pH and redox potential. Significant bioconcentration of manganese exists in lower organisms (e.g., marine plants (10–20,000), invertebrates (10–40,000)). Manganese is an essential element for microorganisms, plants, and animals; this bioconcentration may reflect specific uptake mechanisms for manganese.[9] Significant bioconcentration of manganese occurs in aquatic biota

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at lower trophic levels, but fish do not accumulate manganese to a similar extent as plants and microorganisms. Typical bioconcentration factors (BCFs) for marine and freshwater plants are 2,000–20,000 for plants and 2,500–6,300 for marine macroalgae, whereas the average BCFs for fish are ~100–600.[9] The relatively smaller bioconcentration of manganese in higher organisms suggests that biomagnification of manganese in the food chain is probably **not** significant.[15]

Soil

Adsorption of soluble manganese compounds to soils and sediments varies substantially depending on cation exchange capacity and the organic composition of the soil.[42] At low manganese levels, clay soils bind manganese tightly with little release of manganese into solution.[43] At higher concentrations, some desorption of manganese occurs as a result of ion-exchange mechanisms.

DOSE EFFECT

Inhalation

Cases of chronic manganese poisoning (manganism) result from the prolonged exposure of workers to high levels of manganese dust or fumes in ferromanganese foundries or manganese mines.[17] Most cases of manganism occur following exposure to air Mn concentrations of >20–30 mg/m^3,[44,45] typically in the range of 100–900 mg/m^3.[46] The development of clinical manganism is rare below exposures to manganese concentrations of <5 mg/m^3.[47] Recent cohort studies suggest early sub-clinical changes in neuropsychological parameters (hand tremor, reduced memory, prolonged reaction time) may occur in workers chronically exposed to manganese concentrations in the range of 1–5 mg/m^3 for 20 years.[48] A more recent retrospective risk assessment study of bridge welders suggests the possibility that mild cognitive impairment (working memory index, verbal intelligence quotient, verbal comprehension index, design fluency, Stroop color word test) may develop in workers exposed to manganese concentrations below current standards; however, most of these measures did not demonstrate a dose-rate response.[49] Chronic exposure of animals to manganese does not reproduce the effects seen in manganese workers,[50] although some behavioral changes develop after prolonged exposure to high concentrations (60–70 mg Mn/m^3).[51]

Ingestion

The estimated safe and adequate dietary intake of manganese as defined by the US National Research Council is 2–5 mg for adults.[52] The daily reference dose (R_fD) is 10 mg Mn based on estimates of the dietary intake of manganese as calculated by the US EPA. A cohort study[27] and a case report[53] associated the ingestion of contaminated well water (0.08–2.3 mg Mn/L and 14 mg Mn/L, respectively) with the development of chronic neurological symptoms characteristic of Parkinson's disease. However, the lack of accurate exposure data and the absence of a clear dose-response effect limit definite conclusions about the role of manganese in the occurrence of the symptoms in these patients. The US EPA used a lowest-observed-adverse-effect level of 4.2 mg Mn/day for the Kondakis' study as a basis for determining water standards for manganese.[52] Furthermore, a more recent cross-sectional German study of 41 individuals exposed to well water containing high Mn concentrations did not confirm the results of the Greek study.[54] The German cohort of rural residents was exposed over 10–40 years to concentrations ranging from 0.3–2.16 mg Mn/L in well water. Compared with the control group (<0.3 mg Mn/L well water), the exposed group displayed no significant differences on clinical examination, structured questionnaires, or tests of fine motor coordination. The clinical examiner was blinded to the exposure status of the individuals.

Manganese balance studies and excretion data indicate that low gastrointestinal absorption and rapid elimination of manganese limit the toxicity of manganese by the oral route as a result of homeostatic mechanisms (reduced absorption rates, increased presystemic elimination) that regulate manganese blood concentrations. Manganese concentrations in drinking water vary by several orders of magnitude depending on the amount of leaching from manganese in minerals and rocks in aquifers. Some cross-sectional studies suggest that higher manganese concentrations in drinking water are associated with a reduction in IQ in children living in these households. In a cross-sectional study of 362 Canadian children (age 6–13 years) living in households with a median manganese concentration of 34 μg/L (range, 1–2,700 μg/L), a 10-fold increase in the drinking water manganese concentration was associated with a decrease of 2.4 full scale IQ point (95% CI: −3.9 to −0.9 IQ, $P = 0.01$) after adjustment for confounding factors.[55] The diminution in full-scale IQ was present only at higher quintiles of manganese concentrations in the drinking water. However, the findings of studies on the effect of environmental manganese exposures on

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intellectual functions are inconsistent, vary with exposure measures, and are subjected to confounding by factors with greater impact on the outcome measures. In a cross-sectional study of 299 Italian adolescents (aged 11–14 years) living in an industrialized area with ferroalloy plants, the whole blood manganese concentration (median = 10.9 μg/L; range, 4.00–24.1 μg/L) was not associated with cognitive (IQ) or behavioral (ADHD) outcomes.[56] The Canadian study did not detect an exposure-response relationship between Mn in drinking water and hyperactivity.[57]

TOXICOKINETICS

Absorption

Limited data are available on the retention and absorption of inhaled Mn particles; however, the solubility of MnO_2 and other inhaled manganese compounds is poor. Consequently, systemic absorption is restricted to a portion of those particles that reach the alveoli and are transferred to the stomach by mucociliary transport. Homeostatic mechanisms control Mn absorption of manganese compounds transferred to the stomach by mucociliary transport. Therefore, the amount of manganese absorbed depends on the amount ingested and the existing manganese concentrations. Manganese absorption occurs primarily in the small intestine as a result of the relative insolubility of manganese compounds in digestive fluids. Absorption of manganese from the gastrointestinal tract varies inversely with the amount of calcium in the diet and serum iron concentrations,[58] and directly with the water solubility of the manganese salt. Iron and manganese share the same transport system.[59] In a volunteer study, the concomitant administration of 7.5 mg or 15 mg manganese (as manganese chloride) with 3 mg iron (as ferrous sulfate) reduced manganese absorption by 20% and 34%, respectively, compared with the control (no manganese).[60] The amount of manganese absorbed from the diet averages about 3–5% based on ^{54}Mn isotope studies.[61] In a study of healthy miners, miners with chronic manganese poisoning, and anemic subjects, the amounts of absorption of $^{54}MnCl_2$ were 3%, 4%, and 7.5%, respectively.[62]

Distribution

Manganese occurs in all mammalian tissues with Mn concentrations varying from 0.3–2.9 μg/g wet tissue weight.[38] Manganese in the blood is highly bound (i.e., 80%) to β-globulin and albumin as Mn^{2+} with small amounts of Mn^{3+} complexed to transferrin.[63] The intracellular reaction with the superoxide anion converts the divalent form to the trivalent form present in enzymes. The β-globulin, transmanganin, transports part of the manganese in trivalent form to tissue stores. Additionally, some transport of the divalent forms of manganese bound to α-macroglobulin also occurs. A variety of transporters have potential roles in Mn transport including divalent metal transporter 1 (DMT1), the ZIP family metal transporters (ZIP-8, ZIP-14), the secretory pathway calcium ATPases (ATP13A2, SPCA1, SPCA2), ferroportin, transferrin/transferrin receptor complex (TfR), and the mutant SLC30A10 Mn transporter associated with familial hypermanganesemia, hepatic cirrhosis, and extrapyramidal motor disorder. However, the contribution of each of these transporters to Mn homeostasis remains unclear as none are specific transporters for Mn.[64] ATP13A2, ferroportin, SLC30A10, and SPCA1 transporters affect Mn homeostasis by transporting Mn out of cells. DMT1 is the main transporter for divalent Mn, whereas TfR is the primary transporter for trivalent Mn.[65] The transport of Mn across the blood–brain barrier involves both facilitated diffusion of the nonprotein-bound Mn^{2+} and active transport (e.g., divalent metal transporter 1-mediated transport, transferrin-dependent transporter).[66,67] The protein involved in the former transport mechanism is the intestinal protein responsible for iron regulation. Relatively higher diffusion of Mn across the blood–brain barrier occurs during iron deficiency.

The concentration of manganese in erythrocytes is at least five times higher than the Mn concentration in serum.[68] In a study of whole blood from 48 healthy adults, the plasma contained ~4% of manganese present in whole blood as measured by graphite furnace/atomic absorption spectrophotometry with Zeeman background correction.[69] The highest concentrations of manganese occur in the liver as a result of the efficient hepatic extraction of manganese, followed by the pancreas, the pituitary gland, bone, kidney, and portions of the brain (basal ganglia, cerebellum). Little accumulation of manganese occurs in the body with a majority of an average body burden of 8 mg distributed between the muscle and the liver.[70]

Elimination

Although manganese does not undergo biotransformation in the body, some changes in the manganese

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oxidation state occur. In the diet, manganese typically exists in the divalent or tetravalent oxidation state, whereas most enzymes require the trivalent form of manganese.[71] The elimination of manganese occurs primarily (i.e., 98%) by biliary excretion into the feces. Following the administration of manganese to rats, some manganese crosses directly from the blood to the bile; however, most manganese is secreted into the bile.[72] Animal studies suggest that renal excretion of manganese is small (<0.1% over 5 days).[73] In a study of healthy subjects in northern Italy, the mean manganese concentration in urine samples was 1.02 ± 0.05 μg/L.[74] The biological half-life of manganese in blood ranges from ~12 days in healthy miners to ~40 days in healthy volunteers.[75] Animal experiments indicate the elimination of manganese from the whole body is much faster than from the brain, particularly the cerebrum.[76,77]

Maternal–Fetal Kinetics

Manganese is an essential element that crosses the placental barrier bidirectionally in animal species and humans;[24] however, rodent models suggest the Mn concentration in fetal brains is relatively stable without clear evidence of clinically significant accumulation of manganese prior to birth.[78] Manganese concentrations are typically higher in umbilical cord blood than maternal blood. In a Chinese study of 125 mother–infant pairs, the mean manganese concentration in umbilical cord blood was 78.75 ± 30.53 μg/L compared with 54.98 ± 22.68 μg/L in maternal blood at admission.[79] A prospective birth cohort study of biological markers of fetal and early childhood exposure to metal mixtures and psychosocial stress demonstrated a mean manganese concentration of 42 ± 16 μg/L in 470 umbilical cord blood samples compared with 24 ± 9.5 μg/L in maternal blood at delivery.[80] Both studies suggested an inverted U-shaped dose-response curve for maternal blood and birth weight. In the US study, there was a slight but statistically significant reduction in birth weight at maternal manganese concentrations of >3.1 μg/L after adjustment for potential biological and socioeconomic confounders. The relationship between admission maternal blood manganese concentrations and birth weight was not statistically significant (unadjusted) in the Chinese study. Breast milk contains Mn. Some infant formulas contain manganese concentrations up to 200 times greater than breast milk,[38] but the absorption of manganese from the formula is ~10 times less than Mn absorption from breast milk.[81]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

Although there are no well-documented cases of manganese deficiency in humans, animal studies indicate that manganese is an essential cofactor for several important enzymes (e.g., phosphorylation, cholesterol, fatty acid synthesis), including arginase, glial cytoplasmic glutamine synthetase, phosphoenolpyruvate decarboxylase, hexokinase, mitochondrial superoxide dismutase, and xanthine oxidase.[82,83] Processes involving manganese-dependent enzymes include bone and cartilage formation, carbohydrate/lipid/amino acid metabolism, free radical detoxification, and, in the brain, ammonia clearance and neurotransmitter synthesis.[84] Specifically, manganese is a cofactor for arginase (hepatic urea production), superoxide dismutase (electron transfer process for limiting cellular oxidative stress), and pyruvate carboxylase (gluconeogenesis).

Manganese deficiency does not usually occur in humans because of the abundance of manganese in the diet. Most, but not all, men fed a manganese-deficient diet (0.1 mg Mn/day) for 35 days developed a fine, scaly, erythematous rash on the trunk along with biochemical changes (decreased plasma cholesterol, increased serum calcium, phosphorus, and alkaline phosphatase).[85] Deficiencies of manganese in animal studies produce abnormal glucose tolerance, impaired growth, skeletal defects, altered lipid and carbohydrate metabolism, ataxia, and reproductive abnormalities (i.e., reduced fertility and birth defects).[86,87]

The body strictly controls manganese concentrations through homeostatic mechanisms involving biliary excretion, various manganese importers (divalent metal transporter 1, citrate transporter, calcium channels, choline transporter, dopamine transporter, zinc transporters, transferrin receptor) and manganese exporters (ferroportin, secretory pathway Ca^{2+} ATPase 1, ATPase 13A2, solute carrier family 30 member 10).[65] These transports are permeable to other essential metals including iron and zinc. An autosomal recessive mutation in the *SLC30A10* gene is associated with a Mn transporter abnormality causing elevated blood manganese concentrations, hepatic cirrhosis, polycythemia, dystonia, and an extrapyramidal motor disorder.[88]

Mechanism of Toxicity

Pulmonary

Exposures to high Mn doses produce adverse effects, primarily in the lungs and brain. Inhalation of manganese

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dust leads to inflammation of the upper respiratory tract that is characteristic of nuisance dust. Animal studies indicate that the inhalation of manganese does not produce significant amounts of pulmonary fibrosis.[89]

Central Nervous System

Astrocytes are major sites of manganese accumulation in the brain as a result of the affinity of glutamine synthetase in these glial cells for manganese; this enzyme requires manganese as a cofactor. Ferromanganese workers and manganese miners develop a bradykinetic-hypertonic syndrome following long-term, high-dose manganese exposure (manganism) superficially similar to Parkinson's disease. Although Parkinsonism and chronic manganese exposure affect the basal ganglia, pathophysiological and clinical differences separate these two diseases. In contrast to the development of Parkinson's disease and reductions in dopamine synthesis, decreases in dopamine release occurs in manganism with preservation of dopamine synthesis. Pathological differences also separate chronic manganese poisoning from classic Parkinson's disease; manganese accumulates in the pallidum and striatum, whereas the hallmark of Parkinson's disease is the degeneration of the nigrostriatal dopaminergic neurons in the substantia nigra pars compacta that innervate the caudate and putamen.[90] Excessive manganese exposure produces neurological lesions (neuronal loss, gliosis) primarily in the output pathways distal to the dopaminergic projection (i.e., globus pallidus, striatum) rather than the midbrain dopamine neurons; consequently, the nigrostriatal dopaminergic pathway remains functional in manganism despite clinical evidence of Parkinsonian-like deficits.[91,92] Manganese also accumulates in the blood and basal ganglia of patients dying from liver failure.[93]

Manganism characteristically causes damage to the GABAergic cells of the caudate, putamen, and globus pallidus (i.e., primarily internal segment) with sparing of the substantia nigra pars compacta and the absence of Lewy bodies seen in Parkinson's disease. These changes correlate to early involvement of speech, gait and balance, minimal resting tremor, symmetrical changes in the globus pallidi, dystonia, and a poor response to levodopa.[94] In contrast to manganism, idiopathic Parkinson's disease is associated with the presence of intracellular inclusion bodies of α-synuclein protein (Lewy bodies), loss of striatal dopamine, and preservation of the pallidum. These changes correlate to resting tremor, asymmetry, and a good response to levodopa.

In experimental animals chronically exposed to manganese, this metal localizes in areas of the brain with high concentrations of non-heme iron (e.g., GABAergic cells in the globus pallidus and corpus striatum), impairing GABAergic signaling.[95,96] Primate studies indicate that neuropathological abnormalities are also present to a lesser extent in the caudate nucleus, putamen, and subthalamic nucleus-based MRI imaging of the brains of monkeys given $MnCl_2$ via inhalation.[77] Manganese toxicity probably results from the affinity of this element for neuromelanin along with the ability of manganese to disrupt the function of the dopaminergic systems. Hypotheses primarily involve alterations in dopaminergic transmission from some type of damage (e.g., increased production of free radicals through glutathione reduction, decreased glutathione peroxidase activity, the inhibition of mitochondrial respiration)[97,98] Some experimental evidence suggests the oxidation state of manganese affects the neurotoxicity of this element.[99]

Postmortem Examination

Autopsy findings in a 50-year-old man, who died from the daily ingestion of a liver-cleansing diet containing three tablespoons of manganese sulfate, demonstrated massive hemorrhagic necrosis in the liver and pancreas, diffuse hemorrhage of the gastrointestinal tract mucosa, and pulmonary edema. Microscopic abnormalities in the tissues involved characteristic changes of multiple organ failure (i.e., diffuse hepatocellular coagulative necrosis, acute tubular necrosis, alveolar hemorrhage).[100] Histopathological examination of a symptomatic Mn ore-crushing factory worker demonstrated gross atrophy and discoloration of the globus pallidus along with neuronal loss and moderately increased astrocytes in the corpus striatum; the substantial nigra was normal.[101] The nigrostriatal pathway remains intact following manganese toxicity in contrast to the damage to the substantia nigra seen in Parkinson's disease. Histopathological and immunochemical examination of a convenience sample of eight Mn miners without a history of neurological abnormalities also demonstrated a reduced ratio of astrocytes/microglial cells in the caudate compared with non-Mn mine workers.[102] A detailed exposure history was not available, but an industrial hygienist reviewing the available data suggested the miners were chronically exposed to relatively low Mn concentrations compared with published reports of symptomatic miners.

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CLINICAL RESPONSE

Acute Ingestion

Both dermal and oral toxicity of manganese is low because of the low solubility of metallic manganese and limited gastrointestinal absorption;[103] consequently, case reports of acute manganese toxicity are rare, primarily involving the more water-soluble inorganic manganese salts. A healthy 50-year-old man developed nausea, vomiting, diarrhea, abdominal pain, weakness, and lightheadedness after ingesting an Epsom salt preparation containing manganese instead of magnesium.[100] Despite intravenous hydration, he progressed to fulminant hepatorenal failure, acute respiratory distress syndrome, coagulopathy, lactic acidosis, and refractory hypotension. He died 3 days after ingestion. A 48-year-old woman developed nausea and severe vomiting 10 minutes after undergoing dialysis with a dialysate contaminated with 3.2% manganese sulfate.[104] She subsequently developed acute pancreatitis with fat necrosis extending into the greater omentum, hypocalcemia, perioral numbness, abdominal pain, drowsiness, and fever; she recovered after a prolonged hospital course.

Acute Inhalation

Studies from the 1940s suggest exposure to high ambient air Mn concentrations can cause mild to moderate inflammation of the lungs (i.e., chemical pneumonitis).[105] An excess incidence of pneumonia has been associated with exposure to high Mn concentrations (210 mg/m^3) in the work environment; however, no known permanent pulmonary sequelae (e.g., fibrosis) developed after these exposures.[106] Later studies have not detected an excess incidence of pneumonia in workers exposed to manganese concentrations near current workplace standards. Metal fume fever (dry cough, thirst, nausea, headache, diaphoresis, fatigue, arthralgias, dyspnea) occurs after exposure to high concentrations of manganese oxide.[107]

Environmental Exposure

Manganism is not usually associated with environmental Mn exposures. Although some studies suggest a possible association, data are conflicting. The lack of a good biomarker for long-term exposure (Mn is excreted primarily in the bile) limits the epidemiological studies on the effect of environmental Mn exposures; currently, sufficient data are not available to determine the best Mn biomarker (e.g., blood, urine, nails, hair, dentin) for observational studies.

Central Nervous System

Adult Observational Studies

A cross-sectional study of 186 residents living near a ferromanganese smelter or an open-air Mn storage and packaging facility reported mild cognitive deficits in working/visuospatial memory (Rey-O Immediate, Rey-O Delayed) and verbal skills (Similarities) based on age-stratified normative data.[108] Exposure data were based on air-Mn site surface emissions method modeling (range, 0.03–1.61 $\mu g/m^3$). In a Mexican study of 288 adults living in a mining district with ambient air manganese concentrations of >0.05 $\mu g/m^3$ (EPA guideline for environmental exposure), air Mn concentration was a risk factor for attention impairment (OR = 1.75, 95% CI: 1.01–3.06).[109] The mean blood Mn concentration was 9.5 ± 4.14 µg/L; however, the blood Mn concentration did not correlate to any neuropsychological test. A pilot study of 29 residents living near an Ohio ferromanganese refinery detected a mild, subclinical impairment of postural balance.[110] Postural balance was correlated to hair Mn concentrations, but not whole blood Mn concentrations. The mean whole blood Mn was 9.4 µg/L (range, 4.2–21.7 µg/L). Analysis of data from the prospective Nurses' Health Study did not detect an association between Parkinson's disease and manganese exposure.[111] The fully adjusted hazard ratio comparing the risk of Parkinson's disease in the highest and lowest quartiles of Mn exposure was 1.04 (95% CI: 0.77–1.40).

Neurodevelopment/Childhood Studies

A systematic review of epidemiology studies identified seven studies reporting adjusted associations between Mn biomarkers and childhood intelligence as an outcome.[112] The observational studies differed in Mn biomarkers (blood, dentin, hair), setting (highly exposed/general community), design (cross-sectional, prospective), and results (positive, inverse, null). Although cross-sectional studies suggested an inverse, mostly statistically nonsignificant association between blood or hair manganese and childhood intelligence tests, the prospective cohort study reported mostly null and some positive associations between Mn dentin concentrations and child intelligence.[113] Overall, the authors concluded the scientific evidence did not provide sufficient proof of an inverse causal association between child intelligence and Mn exposure biomarkers, given the cross-sectional designs, lack of consistency, and potential for confounding and selection bias.

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The Korean Mothers and Children's Environmental Study examined 232 infant–mother pairs for an association between peripartum maternal whole blood Mn concentrations (mean = 22.5 ± 6.5 μg/L) and Bayley Scales of Infant Development scores in 6-month-old infants.[114] After adjustment for potential confounders, the dose-response curve was U-shaped with lower scores on mental and psychomotor development indexes at low and high Mn blood concentrations. The inflection point between positive and negative outcomes in normal-weight infants occurred at whole blood Mn concentrations of 24–28 μg/L. In an agricultural area of California, where Mn-containing fungicide use was common, mental and performance development index scores on the Bayley Scales of Infant Development Test in 24-month-old Mexican-American infants were not associated with Mn dentin concentrations.[115] Small transient reduction of these scores occurred in girls 6 and 12 months old, particularly in infants with anemic mothers; however, the scores returned to the normal range by 24 months. A prospective birth cohort study examined the association between prenatal Mn concentration and mental/psychomotor development scores at age 2 years for infants living near the Tar Creek Superfund Site previously containing lead/zinc mines.[116] The maternal venous whole blood and infant cord blood Mn concentrations were 24.0 μg/L (IQR = 19.5–29.7 μg/L) and 43.1 μg/L (IQR = 33.5–52.1 μg/L), respectively. The maternal whole blood Mn interquartile range (19.5–29.7 μg/L) was associated with a reduction in the mental developmental index of −3.0 points (95% CI: −5.3 to −0.7 points) and −2.3 points (95% CI: −4.1 to −0.4 points) on the psychomotor developmental index. Cord Mn concentrations were not associated with neuro developmental scores. A study of children aged 7–9 years old recruited from residences near an Ohio ferromanganese refinery suggested a U-shaped association between the highest (>11.2 μg/L)/lowest (<8.2 μg/L) quartiles of whole blood Mn and the middle two quartiles for full IQ after adjustment for confounders.[117] Perceptual reasoning and processing speed were also negatively associated with the highest quartile when compared with the middle two quartiles. The lack of a good biomarker of the intensity of Mn exposure (e.g., whole blood reflects Mn exposure during the last few weeks) and selection bias limit conclusions about the effect of Mn exposure on cognitive function in this study.

A cross-sectional Korean study of 1,089 children aged 9–11 years compared neuropsychological scores of children with the highest (>21.4 μg/L) and lowest (<8.1 μg/L) blood Mn concentrations.[118] After adjustment for urine cotinine, blood lead, IQ, and other potential confounders, children with the highest blood Mn concentrations had lower scores in thinking, reading, and calculation. Other studies have not demonstrated a significant association between relatively low environmental Mn exposure and neuropsychological or developmental outcomes.[119] An Italian study used the Virtual Radial Arm Maze (VRAM) to assess visuospatial learning, reference memory, and working memory in 142 of 402 participants (35% participation rate) aged 10–14 years with naturally shed deciduous teeth available to examine prenatal and postnatal dentin Mn concentrations and neurodevelopment outcomes; the children resided near ferromanganese plants.[120] The results demonstrated a U-shaped dose-response curve between prenatal/early postnatal Mn exposure and VRAM outcome measures in girls, but not boys. The association between postnatal dentin MN concentrations and VRAM outcomes was null in girls and boys. In a Canadian study of 259 children aged 5.9–13.7 years consuming Mn-containing well water, drinking water, hair, toenail, and saliva Mn concentrations were not clearly associated with poor cognitive development in school-age children.[121] The percentage of children consuming Mn-containing water ranged from 4% (> 400 μg Mn/L) to 48% (<5 μg Mn/L) with 25% consuming drinking water containing >50 μg Mn/L. The association in girls was statistically significant only for toenail Mn and lower performance IQ ($\beta_{10\text{-fold}\uparrow Mn}$ = −5.65, 95% CI: −10.97 to −0.32), whereas the performance IQ results were positive and statistically significant for drinking water as well as positive and statistically nonsignificant for toenail Mn concentrations in boys. Verbal IQ was not associated with Mn biomarkers (water, hair, toenails, saliva) in girls or boys as measured by ICP-MS.

Case Report

A previously healthy 5-year-old girl developed behavioral changes (pica, incontinence, echolalia, emotional lability, apraxia), poor coordination, gait disturbances, subtle action tremor, polycythemia, and iron deficiency.[122] Her neurological abnormalities were attributed to manganese exposure based on an elevated serum manganese concentration (2.09 μg/L) and bilateral, symmetric hyperintense signals in the basal ganglia, brain stem, and cerebellum. Although the drinking water in the family vacation cabin had elevated manganese concentrations, no definite source for her manganese exposure could be identified, and her parents remained asymptomatic despite similar serum manganese concentrations.

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Pulmonary

The risk of lung disease from Mn exposure in the environment is small; however, there is limited evidence that an increased prevalence of respiratory symptoms occurs near point sources of manganese, such as ferromanganese factories.[123]

Occupational Exposure

The primary target organs following chronic exposure to manganese are the lungs and brain.

Lungs

The mild to moderate inflammatory properties of manganese lead to an increased incidence of cough and bronchitis in workers exposed to manganese concentrations exceeding current standards.[48,124] Dusts and fumes of manganese do not possess significant fibrogenic properties. High mortality from pneumonia occurred among English workers exposed to manganese oxides during the manufacturing of potassium permanganate.[106] A mortality study of ferroalloy workers employed at a ferromanganese/silicomanganese plant did not demonstrate a significant increase in mortality from pneumonia (SMR = 1.03, 95% CI 0.75–1.38) or pneumoconiosis (SMR 1.65, 95% CI 0.04–9.20).[125] The cohort consisted of 14,730 men employed for at least 6 months during 1933–1990. Rare case reports associate occupational asthma with manganese exposure during welding based on airway hyperreactivity, positive skin prick test for manganese nitrate, and a single-blind, placebo-controlled specific inhalation challenge with 0.1% manganese chloride solution.[126]

Central Nervous System

Manganism is a progressive, disabling neurological syndrome that produces dull affect, altered gait, fine tremor, and occasionally psychiatric disturbances; serious cases of manganism occur exclusively following inhalation of Mn-rich dust.[24] A large case series of heavily exposed manganese miners suggests manganism symptoms typically begin after several years of exposure to dust containing high manganese concentrations; however, some individuals develop symptoms within several months.[46] The onset of symptoms of manganism more than a decade after manganese exposure is unusual. The initial symptoms are often nonspecific (i.e., generalized weakness, muscle stiffness, myalgias, anorexia, nervousness, irritability, headache).[47,62] Associated adverse effects include apathy, lethargy, loss of libido, and impotence.[46] Early neurological manifestations of manganism involve slow, halting speech, followed by dull facial expressions and retarded movement of the extremities.[7,46]

Mining

In manganese workers, slow deterioration of neurological function characterizes manganism; these symptoms begin insidiously as nonspecific symptoms and subclinical neurological signs. Clinical features of manganism include anorexia, apathy, arthralgias, myalgias, asthenia, headaches, irritability, lethargy, and weakness in the lower extremities. Gradually, dysfunction of the basal ganglia develops that is characterized by alterations of gait, loss of balance, fine tremor, loss of facial expressions, and speech disturbances. Finally, a severe, disabling, Parkinson's-like clinical condition develops characterized by widespread muscle rigidity, dystonias, a staggering gait, dysphagia, and a course intention tremor.[46] Although this disease resembles Parkinsonism, there are significant differences between the two diseases. Neurological characteristics favoring manganism include the following: psychiatric disturbances early in the course of the disease, early onset of speech and gait disturbances with dystonia including the "cock walk" (i.e., walking on toes with elbows flexed and spine erect), propensity to fall backward when pushed, relatively less resting tremor and more dystonias, relative symmetry of neurological abnormalities, and failure to respond to drugs (e.g., levodopa) during the late stages.[127] Neurological symptoms may improve after withdrawal from exposure; however, many symptoms (e.g., gait disturbances) persist or worsen after cessation of manganese exposure.[128] In a long-term study of five patients with chronic manganese intoxication, neurological symptoms (gait disturbances, rigidity, dysdiadochokinesias, writing) progressed over a 10-year period despite the return to normal tissue Mn concentrations and normal T1-weighted images on MRI.[129] Longer-term follow-up of these patients suggests the neurological effects of manganism stabilize in the decade after Mn exposure ceases.[130] Although asymmetry of neurological signs (cock gait, dystonia) suggests idiopathic rather than Mn-induced Parkinson's disease, some patients with the latter disease have persistent asymmetrical neurological signs. Early presentation of cock-walk suggests manganese toxicity.

A progressive psychiatric disturbance known as "manganese madness" may precede or accompany the onset of neurological signs. Psychiatric features of this syndrome include apathy, somnolence, confusion, bizarre behavior, visual hallucinations, increased lability, poor memory, anxiety, impotence, and decreased

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libido.[131] Following exposure to high Mn concentrations, an acute psychiatric syndrome may develop characterized by aberrant behavior, emotional lability, and hallucinations.

Welding

Although case reports associate exposure of ferromanganese smelter workers to high ambient manganese concentrations with the development of manganism (atypical parkinsonism),[44] the association of the common form of Parkinson's disease with welding is more controversial. In contrast to manganese miners, the psychiatric and motor disturbances associated with clinical manganism are not well documented in welders exposed to manganese in welding fumes.[18,132] A meta-analysis of 13 epidemiological studies of welding and Parkinson's disease did not demonstrate an association between manganese exposure during welding and Parkinson's disease.[133] The pooled relative risk for all study designs (case-control, cohort, mortality) was 0.86 (95% CI: 0.80–0.92) for the association between welding and Parkinson's disease with similar effect measures (0.82–0.91) between study designs. The meta-analysis reported an absence of heterogeneity between studies ($I^2 = 0.0$). Although manganese exists in welding fumes, manganese exposures in welders are less than Mn exposures of miners and smelter workers with manganism.

A Swedish population-based study of welders and flame cutters in the 1960 and 1970 censuses ($n = 49{,}488$) did not detect an excess of basal ganglia or movement disorders (i.e., mostly in hospitalized patients) compared with the general population followed through 2003. The adjusted rate ratio for Parkinson's disease was 0.89 (95% CI: 0.79–0.99). Manganese exposure was based on a large survey of welding exposures conducted from 1974–1975 rather than direct measurements. Similarly, a retrospective cohort study of hospitalizations for neurodegenerative diseases in Denmark did not detect an excess of hospitalizations in welders or men in mild or stainless-steel welding departments.[134] The standardized hospitalization ratios for these 2 cohorts were 0.9 (95% CI:0.4–1.5) and 1.0 (95% CI:0.7–1.5), respectively. A follow-up study of bridge construction welders exposed to manganese in confined spaces for a mean of 16.5 months suggested some persistent depression, anxiety, and impairment of psychomotor speed, dominant postural hand tremor and body sway in these workers; however, the study design (e.g., confounding, low response rate) limited conclusions about the etiology of their abnormalities.[135]

Automotive Repair

A study of Canadian garage mechanics and blue-collar workers exposed to different Mn concentrations from methylcyclopentadienyl manganese tricarbonyl (MMT) combustion used personal air samplers, a dietary compilation, and residential water samples as measures of exposure. An epidemiological questionnaire and blood/hair samples did not detect a significant association between adverse health outcomes and chronic Mn exposure.[136]

Reproductive Abnormalities

Animal and human studies suggest that heavy consumption of manganese may produce developmental effects;[137] however, data are too limited to conclude that such effects exist in the human population as a result of Mn exposure.[17] No direct damage to testes in humans has been reported, but rodent studies suggest that manganese may produce degenerative changes in the testes at very high Mn concentrations.[138] Very high exposure to manganese has been associated with impotence,[139] but these reports involve seriously ill workers and there is little direct evidence of an effect on male reproduction. A cross-sectional study of alkaline battery workers exposed to manganese oxide (median atmospheric concentration of 0.71 mg Mn/m^3 as total manganese dust) for a mean of 6.2 years did not detect a reduced probability of live birth when compared with unexposed controls.[140] Although data are sparse, females appear less sensitive to the reproductive effects of manganese than males, based on rodent studies.[141]

Carcinogenesis

Neither the International Agency for Research on Cancer (IARC) nor the US National Toxicology Program recognizes manganese or its compounds as suspected human carcinogens. Although there are relatively few animal data on the carcinogenicity of manganese compounds, existing data indicate that manganese is not a significant carcinogen, despite some evidence of mutagenicity.[142] Exposure to dusts and fumes of manganese has not been identified as a risk factor for the development of lung cancer in workers exposed to manganese. Consequently, the potential for carcinogenic effects in humans appears small. A mortality study of 6,363 ferroalloy workers employed at a ferromanganese/silicomanganese plant did not demonstrate a significant increase in the overall incidence of cancer when compared with standardized rates for Norwegian men (SIR = 1.0, 95% CI: 0.93–1.17).[125] Although the

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incidence of several cancers was statistically significant (pancreas, larynx, pleura), the presence of confounding exposures (asbestos, crystalline silica) limits conclusions.

DIAGNOSTIC TESTING

SI Conversion Units

1 μg = 0.0182 μmol = 18.20 nmol
1 μmol = 54.94 μg
1 mg/m^3 (25°C) = 0.4450 ppm
1 ppm = 2.247 mg/m^3

Analytical Methods

Methods for the determination of manganese in biological samples include atomic absorption spectrometry (AAS),[143,144] inductively coupled plasma atomic emission spectrometry (ICP/AES), and inductively coupled plasma mass spectrometry (ICP/MS).[145] Spectrophotometric procedures require careful sample preparation; this method is not very specific or sensitive. Flame atomic absorption spectrophotometry is a common, relatively simple method for the determination of manganese in biological samples, but sensitivity is limited; graphite furnace/atomic absorption spectrometry is a more sensitive method at very low manganese concentrations. Significant spectral interferences are minimal with AAS and ICP/AES, but ICP/MS requires high mass resolution instruments or a collision/reaction cell to reduce interference. Prior to quantitation, analysis of whole blood typically requires digestion with nitric acid at elevated temperature and pressure. Methods used to determine manganese concentrations (e.g., mass spectrometry, neutron activation analysis, spectrophotometry, X-ray fluorometry) measure total manganese concentrations; therefore, these methods do not distinguish between various valences or compounds.[9] Most methods require wet digestion, derivation, and/or extraction prior to analysis. Detection limits range from <0.01–0.2 μg/g for biological fluids to 5–10 μg/m^3 in air and 0.01–50 μg/L in water. Nuclear magnetic resonance is a more sensitive method (<2 ng/L water) than spectrophotometric methods.[146]

Biomarkers

Diagnostic tests used to identify excessive manganese exposure primarily include estimation of Mn concentrations in urine, blood (whole, serum, plasma), dentin, toenails, and hair; less common testing involves a positive response to $CaNa_2EDTA$ chelation and reversal/improvement after *L*-dopa treatment. None of these tests are highly specific or sensitive for manganese toxicity; blood and urine Mn concentrations do not accurately reflect the total body burden as >95% of Mn elimination occurs via the bile/feces.[147] Manganese accumulates in toenails, fingernails, and hair; however, there are few data correlating manganese concentrations in these matrices to environmental exposures. A study of 46 apprentice welders assessed for manganese exposure by personal gravimetric samples suggested manganese concentrations in pooled toenail clippings correlated to the calculated cumulative manganese exposure index for the preceding 7–12 months.[148] The correlation of toenail manganese concentrations to whole blood manganese concentrations was poor. The median airborne manganese concentration of the personal samples during the work shift was 12.89 μg/m^3 (range, 2.02–137.41 μg/m^3). Other potential biomarkers of Mn exposure include erythrocyte Mn, the Mn/Fe ratio in plasma or erythrocytes, and the pallidal index comparing the pallidus and subcortical frontal white matter intensity in axial T1-weighted magnetic resonance images.[149]

Blood

Following absorption, sequestration of manganese occurs in tissues and intracellular compartments rather than the blood; additionally, the elimination half-lives of Mn in tissues including the brain, are substantially longer than blood Mn. Efficient homeostatic mechanisms regulate the absorption and excretion of manganese; these mechanisms limit the whole blood manganese concentration to a specific range. Consequently, blood Mn concentrations are a measure of recent exposure rather than the cumulative Mn burden. Blood manganese concentrations distinguish exposed from unexposed individuals on a group basis, but the blood Mn concentration is less sensitive for discriminating one individual from the rest of the study population. Issues of methodological differences and contamination complicate the interpretation of manganese concentrations in the older literature. Past manganese concentrations in whole blood measured by spectrometry are an order of magnitude higher compared with whole blood concentrations measured by atomic absorption or neutron activation.

General Population

Whole Blood The whole blood manganese concentration measured by inductively coupled plasma/mass spectrometry (ICP/MS) averaged ~9 μg/L (range,

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~4–18 μg/L) in 130 German adults without occupational Mn exposure.[150] The mean Mn concentration in whole blood samples from a control group of 90 Danish adult males (mean 59 years, range 40–79 years) was 8.7 μg/L with a range of 4.1–19.0 μg/L as measured by atomic absorption spectrometry with Zeeman background correction.[151] The 95% upper limit for whole blood Mn concentrations in an expanded adult Danish reference group (n = 189) was 15 μg/L (271 nmol/L).[152] Manganese concentrations in infants are usually slightly higher than in older children and adults.[38] Smoking, gender, and alcohol consumption did not significantly affect the blood Mn concentration. Regular use of underground subways increases blood manganese concentrations.[153] Liver failure elevates blood Mn concentrations because biliary excretion is an important route of Mn elimination. A study of 11 patients with moderately severe cirrhosis demonstrated a statistically significant difference (P = 0.0013) in the whole blood manganese concentration between the cirrhosis group (20.6 ± 10.2 μg/L) and healthy, age-matched controls (7.2 ± 2.7 μg/L) as measured by graphite furnace/atomic absorption spectroscopy.[154] The mean whole blood Mn concentration in 10 patients with liver cirrhosis was 34.4 μg/L compared with a mean whole blood Mn concentration of 10.3 μg/L in 10 controls (no liver disease).[93] This difference was statistically significant (P = 0.0058).

Serum/Plasma Mn concentrations are substantially higher in whole blood than plasma or serum. Hemoglobin in erythrocytes binds ~85% of the manganese in blood; therefore, average plasma and serum manganese concentrations are much lower than whole blood Mn concentrations. In a study of 48 healthy adults, plasma contained ~4% of the manganese in whole blood as measured by Zeeman graphite furnace atomic absorption spectrophotometry after digestion with nitric acid and hydrogen peroxide.[69] A study of 1,000 Swedish adults aged 70–79 years reported a mean whole blood/serum Mn ratio of 5.06 as measured by inductively coupled plasma/sector field mass spectrometry[155] compared with 14.7 in healthy Italians as measured by graphite furnace/atomic absorption spectrometry.[74]

The mean plasma Mn concentration in 68 healthy adult blood donors was 0.79 ± 0.3 μg/L (14.3 ± 5.7 nmol/L).[156] In a study of 250 healthy adult inhabitants of Barcelona, Spain, where methylcyclopentadienyl manganese tricarbonyl (MMT) is an approved gasoline additive, the geometric mean serum manganese concentration was 1.1 μg/L with a range 0.3–2.5 μg/L (95% upper CI: 1.8 μg/L) as measured by graphite furnace/atomic absorption spectrometry.[157]

Hemolysis of blood samples will falsely elevate the plasma and serum manganese concentrations in blood samples. In a study of 31 healthy volunteer blood donors, the mean serum Mn concentration was 0.6 ± 0.16 μg/L (10.8 ± 3.0 nmol/L) as measured by atomic absorption spectrometry.[158] Studies on the course of Mn in patients developing renal failure are in conflict with some studies demonstrating increasing plasma concentrations with progressive renal failure,[159] whereas other studies suggested the serum Mn decreases with decreasing glomerular filtration rate.[160] Alterations in serum protein concentrations (e.g., malnutrition, inflammation) may account for some of the differences in these studies.

Environmental Exposure

There is no scientifically confirmed biological indicator of cumulative manganese exposure. Average whole manganese concentrations reflect the total body burden on a group basis, but not on an individual basis. The rapid clearance of manganese from the body limits the correlation between chronic health effects and the blood manganese concentration, particularly after Mn exposure ceases.[161] Hence, whole blood concentrations document recent exposure (1–2 weeks), but little correlation exists between past Mn exposure and current whole blood Mn concentrations.[162] In a study of 273 non-occupationally exposed residents from a province that contained a former manganese alloy production plant, the whole blood Mn concentration ranged from 2.5–15.9 μg/L with a median concentration of 7.3 μg/L.[163] Higher Mn concentrations (>7.5 μg/L) were associated by MANOVA analysis with poorer upper limb coordination, recall, and learning as well as slower hand rotation. There were no identifiable sources of excessive manganese exposures in these residents other than proximity to the former manganese alloy plant; regression analysis indicated that location and the ingestion of leafy vegetables and cereal accounted for <7% of the variability in blood Mn concentrations.[164]

Toxicity

Toxic concentrations of manganese are not well defined. A 48-year-old woman developed gastrointestinal distress, hypocalcemia, and acute pancreatitis after undergoing dialysis with a manganese-contaminated dialysate.[104] Her serum manganese concentration on the day following the incident was 252.5 μg/L (4.55 μmol/L). Blood manganese concentrations associated with neurotoxicity have not been defined. Of the seven children on long-term parenteral nutrition including manganese supplements, four children had increased T1-weighted

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signal intensity in the globus pallidus and subthalamic nuclei.[165] Whole blood manganese concentrations ranged 13.8–28.6 μg/L (249–516 nmol).

Postmortem

A 50-year-old man died 3 days after inadvertently ingesting a preparation containing manganese sulfate.[100] His postmortem blood manganese concentration was 6,650 μg/L; his bile contained 376,000 μg Mn/L.

Urine

Manganese excretion in urine samples is low (i.e., <1% of the absorbed dose); urine Mn concentration reflects very recent exposure to manganese. Urinary manganese concentrations in spot samples from the general population without occupational exposure to manganese typically are <1–3 μg/L.[74] In a study of the US population (National Health and Nutrition Examination Survey, NHANES III), the 95th percentile Mn concentration was 3.33 μg/L as measured by inductively coupled argon plasma/mass spectrometry.[166]

Hair

Hair Mn concentrations are attractive, noninvasive measures of Mn exposure, but this biomarker is not a validated measure of Mn exposure. Several occupational studies suggest that proximal hair Mn concentrations increase with the duration of employment. In a study of dry-cell battery workers, the auxiliary hair Mn concentrations increased with the intensity of Mn exposure on a group basis; however, the wide variation in hair Mn concentrations in the controls limits the use of hair Mn concentrations on an individual basis. Interpreting the significance of dramatically elevated Mn hair concentrations in smelter workers was complicated by external contamination.[167] Scalp hair Mn concentrations did not correlate to neurological abnormalities in Mn-exposed Aborigines on an individual basis.[168]

Abnormalities

Neuropsychological Testing

Occupational Exposure

Overall, analysis of individual data on neuropsychological performance of manganese-exposed workers (male welders and non-welders) suggests some slowing of motor speed (simple reaction time), fine motor performance (pursuit aiming), dexterity (Santa Ana), and short-term/working memory (Digit Span) in these workers.[169] However, interpretation of the neurological effects of low-dose manganese exposure is conflicting, primarily as a result of the following factors: 1) difficulty matching the demographics of control (age, education, IQ) and Mn-exposure workers; 2) controlling for exposure to other neurotoxins along with a lack of validated biomarkers of exposure; 3) variability in sample size and neuropsychological tasks; 4) differences in Mn exposure; and 5) lack of dose-response relationships. Manual dexterity and visual recognition were not affected by these analyses.

A meta-analysis on 41 variables from 19 neuropsychological studies of Mn-exposed workers demonstrated the highest effect size for clerical substitution tasks, finger tapping endurance, digit span, and Swedish Performance Evaluation System "Additions" reaction times.[170] However, the effect size for these tasks did not exceed the effect size for education or aptitude; there was no dose-response relationship between exposure and effect size. A meta-analysis of 20 peer-reviewed published neuropsychological studies of occupational exposures to manganese suggested a small deleterious effect of manganese exposure on cognitive and sensory motor performance when comparing exposed and nonexposed workers.[171] Cohen's d statistic yielded a statistically significant weighted mean effect size of −0.17 ($P < 0.0001$) for manganese exposure, but this effect is too small (1/6 standard deviation) to detect on an individual basis. Although this study suggested slight impairment, the lack of a dose-response effect and abnormalities in the normally robust verbal comprehension domain indicated that current studies lack proper control of confounding variables and misclassification. In a cross-sectional study of 143 workers from an Australian ferroalloy smelter with estimated average cumulative manganese exposure of 3.51 mg-years/m^3 inhalable and 1.19 mg-years/m^3 respirable, correlation and hierarchical regression analyses demonstrated statistically significant relationships between increased exposure to inhalable/respirable manganese and tests of subcortical function (Digit Symbol Coding, Stroop color-work, Trail Making Part A).[172] However, the magnitude of the effects was smaller than the standard error of measurement, indicating that the demonstrated relationships were not clinically significant.

A meta-analysis of 13 studies examining 958 exposed (i.e., primarily metal alloy, Mn production) and 815 unexposed workers detected significant overall effects in some measures of motor speed (finger tapping) and information processing (simple reaction time, digit symbol).[173] The mean inhalable Mn concentration in these studies ranged from 0.05–1.59 mg/m^3, whereas the whole blood Mn concentration ranged from 8.1–48.4 μg/L. The size of the negative effects correlated to inhalable Mn

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concentrations rather than whole blood Mn concentrations. Refinement of the meta-analysis using individual participant data rather than aggregated data from 579 exposed men and 433 referents demonstrated lower performance of the exposed workers on speed of movements and processing speed, whereas manual dexterity and recognition of memorized visual material were not consistently affected.[169] The association between concurrent blood manganese concentrations (sample type not reported) and performance on cognitive and motor tasks was weak and inconsistent. Cross-sectional studies of active workers exposed long-term (mean 10–20 years) to concentrations near 5 mg Mn/m^3 demonstrate subtle, sub-clinical reductions on neuropsychological testing of rapid, alternating motor movements (finger tapping),[48] hand steadiness,[48,174] and postural tremor.[175] In cross-sectional studies of manganese workers, tests of motor function (e.g., performance of coordinated, rapid, and sequential movements) appear more affected by Mn exposure compared with intellectual functions.[176] Less consistent reductions occurred in some studies including tests of response speed (simple reaction time),[177] short-term memory (digit span),[178] and diadochokinesia[179] when the results from these tests were compared with controls. Other studies have not detected significant differences in the scores on tests of simple reaction time[176,178] or memory.[176] These studies have not demonstrated a clear dose-response effect between exposure parameters and specific neuropsychological abnormalities.[180] Although a follow-up study of Canadian ferroalloy plant workers detected elevated T-scores for depression and anxiety among the former Mn-workers compared with a normative population,[181] studies of Danish steel workers did not detect a causal relationship between cognitive/neuromotor function and chronic Mn exposure.[182,183] Therefore, these neuropsychological tests provide supportive data, but there is no diagnostic group of tests that provides definitive proof of chronic manganese poisoning. Longitudinal studies of ferroalloy workers suggest most abnormalities on neuropsychiatric testing resolve over time with the exception of hand movements and cognitive flexibility (Trail Making B, Symbol Digit Modalities Test, Stroop Color-Word Test) in older workers.[184] In a study of retired former welders (mean exposure time, 28 years, 18 years since last exposure), the former shipyard welders and referents (matched for age) performed similarly on neurobehavioral tests of tremor, motor speed, manual dexterity, diadochokinesis, eye-hand coordination, and postural stability with the exception of the grooved pegboard test.[185] The welders performed slightly better than referents on tests evaluating hand steadiness. There were no airborne measurement data available for manganese.

Environmental Exposure

Data on the effects of manganese on children are limited, primarily involving cross-sectional studies; available studies on the neurodevelopment effect of manganese exposure suggest a negative or U-shaped association with Full Score IQ, particularly in the verbal domain. A meta-analysis of four studies using hair Mn concentrations as a surrogate for Mn exposure demonstrated a significant decrease ($P < 0.001$) of −0.70 point (95% CI: −1.07 to −0.34) in Full Scale IQ of children aged 6–13 years for each 50% increase in hair Mn concentrations. In a case-control study of 18 children aged 5–15 years with attention deficit and hyperactivity disorder (ADHD) and 74 controls matched for age and gender, the risk of ADHD increased with increasing whole blood Mn concentrations.[186] The mean whole blood Mn concentration was not reported; the study examined 12 heavy metals, and whole blood Mn concentrations are measures of recent Mn exposure (i.e., few weeks). Logistic-regression analyses indicated the risk of ADHD significantly increased for increasing blood lead, manganese, and zinc concentrations (type of sample not reported), but the risks were not adjusted for multiple confounders. Stepwise multi-logistic regression suggested that zinc concentration was a better predictor of ADHD than lead or manganese. A cross-sectional study of elementary school children (8–11 years) in Bangladesh detected a negative correlation between mathematic achievement scores and Mn concentrations in water.[187] Mn water concentrations exceeding 400 μg/L (median = 1,302 μg/L) were associated with a 6.4% reduction in mathematic test scores after adjustment for socioeconomic factors and arsenic concentrations. There was no correlation between Mn water concentrations and language scores, arsenic water concentration, or urinary total arsenic concentration as measured by graphite furnace/atomic absorption spectrometry. Interpretation of these studies is complicated by methodological issues including the lack of a validated biomarker of the manganese body burden or Mn exposure in the distant past.

Manganese–Methcathinone Encephalopathy

The clinical features from the use of intravenous manganese-contaminated methcathinone vary in severity with pronounced motor disabilities and limited cognitive deficits. Determination of the domains affected by this drug of abuse is complicated by the rarity of this encephalopathy, comorbidities (e.g., HIV, hepatitis C), small sample sizes, and limited follow-up.

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A cross-sectional study of 14 methcathinone users (12 men, 2 women) and 14 age/education/sex-matched, healthy controls evaluated the 27 neuropsychological tests involving the Wechsler Adult Intelligence Scale with tests of attention, memory, motor skills, visuospatial skills, and executive abilities.[188] About half the users were actively using drugs with occasional use of other drugs (heroin, amphetamine). All users were positive for hepatitis C virus and six users were positive for HIV. The users displayed a Parkinson-like syndrome with dystonias, symmetric bradykinesia, and impairment of gait, posture, and speech; their Unified Parkinson's Disease Rating Scale (UPDRS) score as 43.0 ± 18.3 ranging from mild to severe disease. Although the cognitive performance of the users was slightly lower than that of the controls, the main differences involved motor skills. After adjustment for multiple comparisons, the users demonstrated modestly lower scores on executive abilities (verbal fluency), Grooved Pegboard tests (motor skills), and WAIS Object Assembly subtest (visuomotor skills).

Neuroimaging Studies

Welders

The pattern of MRI abnormalities in workers with manganese intoxication includes abnormal, bilateral, symmetrical signal hyperintensity in the corpus striatum (caudate and lentiform nuclei) and globus pallidus on T1-weighted images.[189,190] The thalamus and ventral pons are typically spared along with the nigrostriatal dopaminergic pathway.[191] In some studies of cross-sectional data on manganese workers, the relative T1-weighted magnetic resonance signal hyperintensity of the globus pallidus relative to frontal white matter (pallidal index) was correlated to Mn-exposure variables (blood, ambient air) and performance on neurobehavioral tests[192] as well as a positive dose-response association with cumulative Mn exposure.[193] There is no alteration of T2-weighted images;[194] T1 changes usually resolve within 6 months following cessation of manganese exposure.[195]

The MRI signal intensity increases following Mn accumulation from its strong paramagnetic properties that shorten T1 relaxation time; most earlier studies used T1-weighted images to estimate brain Mn accumulation because measuring T1 relaxation time required specific MRI sequences. The T1 relaxation time is more specific than the pallidal index because the former does not depend on Mn concentrations in the globus pallidus. Several cross-sectional studies of welders using T1 relaxation sequences suggest Mn accumulation in basal ganglia structures (globus pallidus, substantia nigra, caudate nucleus, anterior prefrontal lobe) is associated with early subtle cognitive changes (executive/verbal function), alteration of motor function, and modulation of movement.[196,197] The 3-month cumulative exposure index did not correlate to any neuropsychological test score. Manganese accumulation may occur in a nonlinear relationship requiring a critical exposure level to produce effects; however, these concentrations are not well-defined. Additionally, welding fumes contain several metals in addition to manganese (e.g., iron and copper) that may influence welding-associated neurotoxicity through competition with carrier-mediated transporters (e.g., transferrin, divalent metal transporter-1, ZIP8), particularly at low Mn exposures.[198,199]

A magnetic resonance imaging (MRI) study of a patient with manganese encephalopathy demonstrated that increased manganese concentrations in the basal ganglia and hypothalamus normalize within 5–7 months.[200,201] This pattern is similar to the MRI abnormalities seen in the scans of patients with chronic liver failure.[202] The intensity of images depends on the exact image parameters; therefore, the pallidal index varies between studies and is a semi-quantitative measure of Mn concentrations in the brain. Other causes of high-intensity signals on T1-weighted images include hepatic cirrhosis with portosystemic shunt, primary biliary cirrhosis, congenital biliary atresia, Rendu-Osler-Weber syndrome with diffuse intrahepatic portosystemic shunt, patent ductus venosus, total parenteral nutrition, Mn exposure during welding, lipid deposition, hemorrhage, iron and copper deposits, and neurofibromatosis.[203] Most welders with high signal intensity on T1-weighted images are asymptomatic.[204] Studies on *in vivo* dopaminergic presynaptic nerve terminal function within the nigrostriatal system are conflicting. In contrast to patients with idiopathic Parkinson's disease including those conditions induced by methylphenyltetrahydropyridine (MPTP), some studies on positron emission tomography (PET) scans with 6-fluorodopa have not demonstrated abnormalities of the nigrostriatal dopaminergic projections in manganese workers with mild Parkinsonism-like symptoms.[205,206] In a welder with clinical manganism, the ^{18}F-DOPA PET scan was normal, demonstrating the integrity of dopamine production and secretion up to the site of the damaged dopamine receptors in the putamen.[207] A case series of 27 Mn-exposed welders reported a modest reduction in ^{18}F-DOPA uptake in the caudate nucleus indicating presynaptic dopaminergic dysfunction in the nigrostriatal system; however, the study detected no clear dose-response association

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between Mn exposure or Parkinson (UPDRS3) scores and ^{18}F-DOPA uptake.[208]

Manganese–Methcathinone Encephalopathy

In Russia and Eastern Europe, the chronic, intravenous use of methcathinone (2-methylamino-1-phenylpropan-1-one, ephedrone, Jeff) prepared by adding pseudoephedrine to the oxidant, potassium permanganate, in the presence of acetic acid was associated with a neurological disease similar to manganism.[209,210] These individuals have MRI abnormalities in the globus pallidum and striatum along with speech impairment, typical cock-walk gait, symmetrical bradykinesia, dystonias, and difficulty with backward motion. MRI imaging of active intravenous ephedrone users indicates that the primary Mn deposits in the brain occur in the globus pallidus based on hyperintense T1-weighted images; increased signal intensities also may develop in the substantia nigra, periaqueductal gray matter, and cerebral pedunculi.[211] Typically, less signal intensity occurs in the dorsal striatum (caudate nucleus, putamen), internal capsule, and white matter; however, some abnormalities may develop in the white matter of active users.[212]

HEALTH SURVEILLANCE

Risk Assessment

The US EPA established the RfC for exposure to inhaled manganese of 0.05 μg/m^3 based on neurobehavioral and psychomotor impairment (finger tapping, hand steadiness) in workers exposed to manganese dioxide at a Belgian battery factory.[213] The estimated lowest-observed-adverse-effect level (LOAEL) was 150 μg Mn/m^3; this concentration was adjusted for nonoccupational lifetime exposure and an uncertainty factor (1,000) to yield an R_fC of 0.05 μg Mn/m^3. Based on benchmark dose methodology, safe occupational exposure guidelines for manganese are ~0.1–0.3 mg/m^3 as an 8-hour time–weighted average of the respirable particulate fraction only.[214] The US EPA reference dose (RfD) for oral manganese exposure is 0.14 mg/kg/day based on the upper range of dietary essentiality (10 mg/day)/70 kg.

Environmental Monitoring

Environmental monitoring of total and respirable dust remains the best method for monitoring workers exposed to manganese. The US OSHA PEL for manganese and manganese compounds is a ceiling limit of 5 mg/m^3 as the fume and a PEL–TWA of 1 mg/m^3 as dust. A cross-sectional study of manganese workers chronically exposed (mean exposure, ~20 years) to ambient air manganese averaging ~0.2 mg/m^3 did not detect any subclinical neurological effects as measured by the prevalence of neurological symptoms and neuropsychological testing.[215] NIOSH established an REL–TWA for manganese compounds and manganese fume of 1 mg elemental Mn/m^3 and a REL–STEL of 3 mg elemental Mn/m^3. The IDLH level was defined as 500 mg Mn/m^3. Table 19.3 outlines current occupational and environmental standards. In 2013, the ACGIH reduced the recommended TLV–TWA for

TABLE 19.3. Occupational and environmental exposure standards for manganese.

Exposure Limit	Value
OSHA	
PEL-TWA (8-hour)	
Mn (fumes)	0.2 mg/m^3
PEL–STEL (15-minute)	
Mn (fumes)	3 mg/m^3
Inorganic Mn	3 mg/m^3
PEL-Ceiling	
MMT	5 mg/m^3
NIOSH	
REL–TWA (10-hour)	
Inorganic Mn	1 mg/m^3
MMT	0.1 mg/m^3
REL–STEL (15-minute)	3 mg/m^3
IDLH	500 mg/m^3
ACGIH	
TLV–TWA	
Mn (respirable particulates, mostly <4 μm)	(8-hour, skin notation) 0.02 mg/m^3
Mn (inhalable particles, some >4 μm)	0.1 mg/m^3
MMT	0.1 mg/m^3
BEI	None
US EPA	
RfC (chronic inhalation exposure)	5×10^{-5} mg/m^3
RfD (chronic oral exposure)	0.14 mg/kg/day
Drinking Water Guidelines	
US EPA	0.05 mg/L
WHO	0.4 mg/L

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; BEI = biological exposure indices; IDLH = immediately dangerous to life and health; MMT = Methyl cyclopentadienylmanganese tricarbonyl; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency; WHO = World Health Organization.

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Mn to 0.02 mg Mn/m^3 (respirable particulate matter), 0.1 mg/m^3 (inhalable particulate matter), and 0.1 mg/m^3 for inorganic manganese compounds to reduce the potential for subclinical effects on neurological and neurobehavioral function. This recommendation is based on the reported development of subclinical effects (e.g., hand steadiness, finger tapping, hand-eye coordination, reaction time) in workers exposed to manganese fumes at concentrations below 1–5 mg/m^3.[213,216,217] The US OSHA established a PEL–TWA for manganese cyclopentadienyl tricarbonyl of 0.1 mg Mn/m^3 with a skin notation. The US EPA established a 50 μg/L limit for manganese in drinking water to prevent visual discoloration and undesirable taste associated with Mn concentrations above this guideline.

The World Health Organization increased the recommended manganese drinking water guideline to 0.4 mg/L based on a tolerable daily intake of 0.06 mg/kg body weight by dividing a NOAEL of 11 mg/day[218] by an uncertainty factor of 3 and an adult body weight of 60 kg.[30] Frequently, the presence of discoloration and/or a disagreeable odor limits consumer acceptability of drinking water containing Mn concentrations above 0.05 mg/L. The Mn guideline for children remains controversial because of concern about the effect of manganese on cognitive and motor function in the developing brain.[219,220]

Biological Monitoring

Blood

No practical biological marker (e.g., homovanillic acid)[221] accurately reflects the intensity of manganese exposure because the primary route of manganese excretion is the bile; additionally, efficient homeostatic mechanisms limit the fluctuation of manganese in the blood. Monitoring of blood manganese confirms recent Mn exposure (i.e., few weeks) based on the relatively short half-life of Mn in the blood, but correlation of these concentrations to cumulative exposure or chronic manganese poisoning depends on the type of exposure.[222] The high variability of whole blood manganese concentrations limits the usefulness of these biomarkers on an individual basis; however, blood Mn concentrations reflect current average daily air Mn concentrations when exposures are relatively consistent or cumulative exposure when exposures are highly variable in time and concentration.[223] Field studies of foundry furnacemen suggest the blood Mn concentrations return to baseline ~5 weeks after cessation of Mn exposure.[151] Because of large interindividual variation, the interpretation of biological monitoring data should be done on a group basis.

Dry-Cell Battery Production

In a cross-sectional study of 100 workers in a dry cell battery manufacturing plant, the mean whole blood concentration was significantly higher in samples from Mn-exposed workers than unexposed controls.[224] The mean whole blood Mn concentration in blood samples from controls was 7.5 ± 2.7 (range, 2.6–15.1 μg/L) compared with 13.8 ± 4.4 μg/L (range, 6.1–23.3 μg/L) for samples from workers exposed to a mean ambient air Mn concentration of 0.4 mg/m^3.

Ferroalloy Smelters

In a study of 94 ferroalloy production workers exposed to manganese oxides (mean airborne Mn concentration, 202.6 μg/m^3; range, 5–740 μg/m^3) and 87 maintenance workers matched by age and smoking habits, the whole blood Mn concentrations were 10.3 ± 3.8 μg/L and 5.9 ± 1.7 μg/L, respectively.[225] For the exposed group, the whole blood Mn correlated to airborne Mn concentrations, but there was very high variability in this correlation between workers. The study did not demonstrate a correlation between blood Mn and measures of cumulative Mn exposure. A study of blood Mn concentrations in ferroalloy smelter workers indicated that whole blood Mn concentrations of <10 μg/L were associated with exposure to airborne Mn concentrations of <200 μg/m^3.[226]

Welders

In a study of 96 welders exposed to air manganese concentrations ranging from 3–4620 μg/m^3 (geometric mean = 97 μg/m^3), the arithmetic mean of manganese in whole blood samples from the welders was 8.6 μg/L with a range of 3.7–24 μg/L.[227] This arithmetic mean was statistically different from the whole blood manganese concentration (mean controls = 6.9 μg/L; range, 2.5–14 μg/L) in turners and fitters from the same plant without exposure to welding fumes.

Urine

Urine Mn concentrations, plasma Mn concentrations, and serum prolactin concentrations are not reliable measures of exposure to Mn.[223] A cross-sectional study of ~100 workers exposed to manganese dioxide up to 794 μg/m^3 was not able to distinguish exposed workers and referents based on spot urine manganese concentrations.[224]

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Medical Monitoring

The medical examination should focus on abnormalities in the pulmonary and central nervous systems. Useful measures for screening tests include pulmonary function tests, simple reaction times, and hand tremor.[213] Neuropsychological testing must be used with caution because these tests are not specific, and the normal ranges are not well defined for specific populations.

TREATMENT

Treatment for chronic manganese toxicity is primarily supportive. There are no effective chelating agents available for clinical use during manganese intoxication.[228] Chelation therapy with $CaNa_2EDTA$ increases the urinary excretion of manganese; case reports suggest symptoms of an acute manganese-induced psychosis may improve following chelation.[229] However, the use of chelation therapy including $CaNa_2EDTA$, does not usually alter chronic neurological symptoms.[216,230] During a 21-day course of dimercaptosuccinic acid (DMSA), no significant improvement in symptoms or reduction of blood manganese concentrations occurred in two workers with chronic manganism.[231] A case report associated the use of para-aminosalicylic acid with improvement in two cases of chronic manganese poisoning,[232] but there is little experimental or clinical data to support the use of para-aminosalicylic acid at the present time. Occasionally, L-dopa and Sinemet (carbidopa/levodopa 25/250) may reverse some neurological symptoms (e.g., cogwheel rigidity, tremor), but these anti-Parkinson drugs are typically not effective,[233] particularly for dystonias.[147,234]

POTASSIUM PERMANGANATE

PHYSIOCHEMICAL PROPERTIES

Permanganates are strong oxidizing agents with +7 valence. Table 19.4 lists some physiochemical properties of potassium permanganate. The ingestion of potassium permanganate crystals/solution produces brown-black stains on the hands, lips, and oropharynx.

TABLE 19.4. Identifying information and physical properties of potassium permanganate.

Property	Value
Synonyms	Permanganic acid, potassium salt; Chameleon mineral
Chemical formula	$KMnO_4$
CAS RN	7722-64-7
Mass (g/mol)	158.04
Color	Purple
Physical state	Solid
Melting point (°C)	240–270
Boiling point	Decomposes
Solubility	Soluble in water (64 g/L at 20°C), acetone, and sulfuric acid

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.

EXPOSURE

The electrolytic oxidation of MnO_2 in KOH produces potassium permanganate. This compound is a corrosive, water-soluble cleansing and antiseptic agent for suppurative wounds; other uses include metal cleaning, bleaching, and as a preservative for flowers and fruits. Potassium permanganate is available as a 300-mg tablet or dark purple bronze crystals. Medicinally, a 1:10,000–1:20,000 dilution of potassium permanganate is applied to an oozing dermatitis for mild antiseptic and drying properties. Commercial applications of potassium permanganate involve the photographic, pharmaceutical, and chemical industries. Historical uses for potassium permanganate include the induction of abortion, urethral irrigation for gonococcal urethritis, stomach lavage for alkali poisoning, and treatment of snake envenomation.[235]

DOSE EFFECT

Solutions of potassium permanganate of >1:5,000 are corrosive. Most toxic exposures result from the mistaken ingestion of topical compounds with most deaths resulting from edema of the epiglottis or circulatory failure.[236] The estimated minimal lethal adult dose is ~10 g of solid $KMnO_4$ (1.5 teaspoons of the crystals) based on the corrosive effects of $KMnO_4$ on the upper airway rather than systemic effects.[237,238] A patient survived the ingestion of 25 g $KMnO_4$ powder with the development of esophageal strictures.[239] A fatal hemorrhagic pancreatitis was associated with the ingestion of an estimated dose of 20 g $KMnO_4$.[240]

The ingestion of two 325-mg potassium permanganate tablets followed by saline lavage produced a

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first-degree chemical burn of the esophagus and stomach without sequelae.[241] E. Gruyz-Harday described a 68-year-old man who consumed 15–20 g potassium permanganate, vomited, and died within 40 minutes.[242] The use of potassium permanganate as an abortifacient was fatal, probably as a result of hemorrhage and perforation of the gastrointestinal tract.[243] The subcutaneous injection of 7 g potassium permanganate resulted in hypermagnesemia (21.7 mg Mn/L 4 days after administration), local irritation, mild elevation of hepatic aminotransferase levels, and ultrastructural changes in the liver.[244]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Potassium permanganate is a powerful oxidizing agent that produces coagulation-type necrosis similar to that produced by an acid. A brown, purplish, or black stain forms on the skin or pharyngeal surfaces as a result of the formation of manganese dioxide. The brown stains are frequently difficult to differentiate from corrosive burns.[245] Perforation of the gastrointestinal tract is unusual. In rare circumstances, hepatorenal damage may result from systemic absorption. An autopsy of a patient dying 6 days after the ingestion of 5–10 g potassium permanganate crystals demonstrated severe fatty change of the liver, subcortical and papillary petechial hemorrhages of the kidneys, renal tubular necrosis, severe esophagitis, hemorrhagic gastritis, and cerebral petechial hemorrhages.[246] Rarely, the ingestion of potassium permanganate causes clinically significant methemoglobinemia that produces cyanosis and hypotension. Ingestion of herbal preparations containing potassium permanganate produced severe methemoglobinemia in two adults.[247]

CLINICAL RESPONSE

Ingestion of concentrated solutions or tablets of potassium permanganate causes local corrosion manifested by burning of the mouth, chest pains, abdominal pain, nausea, and vomiting. Deliberate ingestion of concentrated potassium permanganate may cause methemoglobinemia, hypotension, with cyanosis, metabolic acidosis, hemolysis, altered mental status (hallucinations, coma), and pancreatitis. In severe cases, disseminated intravascular coagulation, hepatorenal failure, acute respiratory distress syndrome, and cardiogenic shock may occur within 36 hours of ingestion.[248] Perforation of the gastrointestinal tract and septic shock may complicate the clinical course of potassium permanganate poisoning or the use of this compound as an abortifacient.[249,250] Dyspnea and stridor are serious clinical effects that indicate epiglottic and/or tracheal edema. Although the accidental ingestion of potassium permanganate is not usually associated with long-term sequelae,[251] strictures and perforations of the gastrointestinal tract occasionally occur following intentional ingestion of concentrated solutions. Pyloric stenosis developed after the ingestion of 8 g of potassium permanganate tablets by a suicidal patient, who initially presented with epigastric pain and vomiting.[252] A fatal hemorrhagic pancreatitis was associated with the ingestion of a large dose of $KMnO_4$.[240]

The mistaken ingestion of an 8% potassium permanganate solution over 4 weeks (cumulative dose, 10 g) produced initial gastrointestinal distress (the abdominal cramps remitted after several doses), hair loss, paresthesias, diaphoresis, decreased concentrating ability, somnolence, visual impairment, and muscle fasciculations.[253] Nine months post-ingestion, the patient developed parkinsonian syndrome. Gastrointestinal injury may occur without systemic toxicity.

DIAGNOSTIC TESTING

Although elevated manganese concentrations may appear in blood and urine after potassium permanganate toxicity, poisoning may exist without elevated Mn concentrations. Five days after the reported ingestion of 5–10 g potassium permanganate crystals, the whole blood Mn level was 90.5 μg/L (1.63 μmol/L), and 30 hours later, the Mn concentration decreased to 42.2 μg/L (0.76 μmol/L).[246] Shortly after the last Mn concentration was drawn, the patient died from fulminant hepatic failure.

After the unintentional cumulative ingestion of 10 g KMnO4 over 4 weeks and during $CaNa_2EDTA$ chelation, a 66-year-old man developed a resting tremor, paresthesias, hyperreflexia, poor concentration, and abdominal distress. His peak blood manganese concentration was 150 μg Mn/L (normal value 48 ± 20 μg Mn/L) as measured by flameless atomic absorption spectrometry.[253] The whole blood values should be interpreted cautiously because of methodological limitations and the timing of the specimen. In severe intoxication, methemoglobin levels, serum hepatic aminotransferase levels, serum creatinine, and complete blood count should be determined. Albuminuria may develop after the ingestion of concentrated (4–5%) $KMnO_4$ solutions.

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TREATMENT

Management is primarily supportive. The immediate life-threatening problems following intoxication with potassium permanganate are epiglottic edema, hemolysis, hemorrhage, metabolic acidosis, and hypotension. In unusually severe cases with evidence of methemoglobinemia, methylene blue therapy for methemoglobinemia may be necessary. Potassium permanganate ingestions should be treated similarly to acid ingestions. Do not induce emesis. Most accidental exposures require only dilution with water. Decontaminate the eyes and skin with copious saline irrigation. Areas of exposure display the characteristic dark purple staining that turns brown after the formation of MnO_2. Dilute oxalic acid removes the brown stain by converting the manganic ion to the colorless manganous ion. Currently, no effective measures are available to enhance manganese elimination. Neither dimercaprol (BAL) nor $CaNa_2EDTA$ increases manganese excretion.[244] Endoscopy within 12–48 hours of ingestion may be necessary as a method of evaluating the severity of the chemical burn when clinical evidence of upper gastrointestinal tract burns (drooling, dysphagia, abdominal pain) or large suicidal ingestions occurs. No studies are available to guide the clinical use of steroids in the management of potassium permanganate burns.

ORGANIC MANGANESE

HISTORY

There is little history on organic manganese because of limited exposure to organic manganese compounds. The risk of exposure to low concentrations of manganese is being reevaluated as a result of the potential exposure of the general population to manganese released from the combustion of unleaded gasoline containing the anti-knock agent methylcyclopentadienyl manganese tricarbonyl (MMT).

PHYSIOCHEMICAL PROPERTIES

The industrially important organometallic compounds are methylcyclopentadienyl manganese tricarbonyl

TABLE 19.5. Identifying information and physical properties of organic manganese compounds. (Data from International Programme on Chemical Safety).[11]

	MMT	Maneb	Mancozeb
Synonyms	Methylcyclopentadienyl manganese tricarbonyl, Methyl-cymantrene, Antiknock-33, Manganese tricarbonyl methylcyclopentadienyl	Manganese ethylene-bis-dithiocarbamate, Trimangol 80, Ethylene-bis (dithiocarbamic acid), manganous salt Dithane	Manganese ethylene-bis-(dithiocarbamate) (polymeric) complex with zinc salt, Dithane M-45, Manzate, Manzaeb, Zimaneb
Chemical formula	$C_9H_7MnO_3$	$C_4H_6MnN_2S_4$	$C_4H_6MnN_2S_4{\cdot}C_4H_6N_2S_4Zn$
CAS RN	12108-13-3	12427-38-2	8018-01-7
Mass (g/mol)	218.10	265.31	541.03
Color	Dark orange-red	Yellow-brown	Grayish-yellow
Physical state	Liquid	Powder	Powder
Melting point (°C)	1.5	Decomposes on heating	Decomposes without heating
Boiling point (°C)	232.8	Decomposes on heating	Decomposes
Solubility	Practically insoluble in water (0.029 g/L at 25°C); completely soluble in hydrocarbons	Slightly soluble in water; soluble in chloroform	Practically insoluble in water (0.006 g/L at 25°C) as well as most organic solvents
Log K_{ow}	3.7		1.33
HLC	0.019		

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; HLC = Henry's Law constant; K_{ow} = octanol–water partition coefficient.

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(MMT) and cyclopentadienyl manganese tricarbonyl (CMT). MMT is a yellow, water-soluble, volatile liquid with an herbal odor. Table 19.5 lists identifying information and physical properties of industrially important organic manganese compounds.

EXPOSURE

Uses for organomanganese compounds include an anti-knock additive in leaded gasoline, fuel oil additive, smoke inhibitor, and fungicide. The organomanganese additive for gasoline (MMT) is produced by the reaction of manganese chloride, cyclopentadiene, and carbon monoxide in the presence of manganese carbonyl. Although the use of MMT decreases the release of carbon monoxide, the US EPA originally banned the use of MMT because MMT increases hydrocarbon emissions from catalytic converters.[254] However, a US Federal Court decision allowed the use of MMT in the US beginning in December 1995. Recent risk analysis by the US EPA suggests that exposure to substantial portions of the urban population would exceed the RfC of 0.05 μg Mn/m^3 if all unleaded gasoline contained MMT at a concentration of 0.031 g Mn/gal.[39] MMT has been a fuel additive (maximum allowable, 0.018 μg Mn/L or 0.68 μg Mn/gal) in Canada since 1976.[136]

ENVIRONMENTAL FATE

The contribution of organometallic manganese compounds to ambient air Mn concentrations is relatively small (13 ng Mn/L) even in urban air because the use of these compounds is limited to anti-knock agents in leaded and unleaded gasoline.[255] Combustion products of MMT-containing gasoline in exhaust represent <15% of the Mn in gasoline.[256] Emissions from MMT in gasoline appear in submicron particles (mass median aerodynamic diameter <1 μm); the tailpipe exhaust products include manganese phosphate, manganese sulfate, and Mn_3O_4 that may disperse widely in inhalable forms.[257] Manganese oxides represent <20% of these combustion products. In countries (e.g., Canada) using MMT in gasoline, the air concentrations of manganese depend on the concentration of MMT in gasoline and the gasoline consumption patterns. From 1989–1992 (i.e., after the replacement of leaded gasoline with MMT), the Canadian air manganese concentrations as measured in particulate matter with an aerodynamic diameter ≤2.5 μm remained relatively constant. The ambient air concentrations during this period ranged from 0.11–0.013 μg/m^3 in small cities to 0.02–0.025 μg/m^3 in larger cities without industrial Mn sources (e.g., silicomanganese and ferromanganese facilities).[258] A year-long population-weighted study of personal exposures to particulate matter ($PM_{2.5}$) in Toronto, Canada, suggested the preponderance of personal Mn exposure was derived from non-MMT sources.[259] The mean and median exposure of participants to $PM_{2.5}$ Mn were 14 ng/m^3 and 8.5 ng/m^3, respectively; however, the omission of participants with non-MMT sources of Mn (e.g., tobacco smokers, metal workers, subway riders) reduced the mean and median $PM_{2.5}$ Mn exposure to 8.3 ng/m^3 and 7.0 ng/m^3, respectively. Although the use of MMT as an anti-knock agent increases the exposure of specific subsets of the general population to manganese in these countries, the exposure of these populations remains below international standards.[31]

DOSE EFFECT

Although current data indicate that exposure to manganese as a result of the combustion of MMT in gasoline is small compared with occupational exposure to manganese, there are few data that delineate the risks of the use of MMT in fuels.[260]

TOXICOKINETICS

There are few data on the toxicokinetics of organic manganese compounds in humans. Rodent studies suggest MMT is well absorbed from the gastrointestinal tract and excreted primarily as hydroxylated metabolites in the urine.[261] These studies indicate the gut absorbs most MMT excreted in the bile, and the kidney excretes most of the absorbed dose of MMT. Consequently, little MMT appears in the feces.

CLINICAL RESPONSE

MMT in car exhaust degrades to manganese salts (sulfate, phosphate, tetroxide). There are few human data on MMT toxicity; however, human exposures should be consistent with inhalational exposures to manganese salts.

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Chapter 20

MERCURY

Mercury exists in three forms: elemental mercury (Hg^0), inorganic mercury (Hg^+, Hg^{2+}), and organic mercury ($C_nH_nHg^+$). The sources, type of exposure, toxicokinetics, and biological effects vary between these different forms. The most common exposures to mercury result from metallic mercury vapor in occupational processes and use of dental amalgams, methylmercury in edible fish tissues, and ethyl mercury in preservatives (e.g., multidose vaccine vials). The latter has been removed from most vaccines in the United States.

ELEMENTAL MERCURY

HISTORY

Since early times, mercury has fascinated man; the mining of cinnabar (mercury sulfide) dates back at least to the late Neolithic/Chalcolithic period (3,400–2,100 BC) near Almadén, Spain.[1] Aristotle named metallic mercury quicksilver; this term has been associated with the misconception that mercury quickens a boxer's punches.[2] Later, Pliny recognized the severe illnesses associated with mining mercury ores. During the Arab domination of Spain, mercury was an important constituent in medicines and the extraction of gold (alchemy). The King of Spain established a penal colony at these mines in the 16th century to provide a labor force for mercury production. The penal colony was closed in 1801; however, mercury production continued there until 2000, when the Almadén mines became uneconomical as mercury prices fell.

Although inorganic mercury was the main chemotherapeutic agent, elemental mercury was also a treatment for syphilis during the 500 years before the introduction of less toxic heavy metals (bismuth, arsenic) in the late 1800s and the advent of penicillin therapy in the 1940s.[3] Paracelsus (Philippus von Hohenheim) and other physicians in the Middle Ages were early proponents of mercury chemotherapy for syphilis including the administration of elemental mercury vapor by fumigation as well as oral inorganic mercury salts (e.g., mercurous chloride).

Medicinal and dental uses of elemental and inorganic mercury became widespread in the 19th century.[4] The French dentist, Auguste Taveau, introduced the use of silver and mercury amalgams for filling dental cavities in 1826.[5] Silver, copper, and tin were the first metals used in various ratios for dental amalgam; however, many other metals were added later to amalgam including gold, platinum, zinc, bismuth, cadmium, nickel, manganese, indium, lead, and aluminum. With the discovery of *Treponema pallidum* in 1905 and the publication of the Oslo Study on untreated syphilis indicating many syphilitic cures attributed to mercury chemotherapy probably resulted from the natural fluctuation of cutaneous luetic infections, the use of mercury for this disease declined.[3] Bismuth replaced mercury after World War I as a more effective and less toxic alternative. Subsequently, the synthetic arsenicals (salvarsan, Neosalvarsan) became the mainstay of syphilis treatment; however, mercury chemotherapy remained in use until penicillin became the standard agent around 1940.

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PHYSIOCHEMICAL PROPERTIES

Mercury is a member of Group 12 (Group 2B) of the periodic table along with cadmium and zinc. Elemental mercury (Hg^0, CAS RN: 7439-97-6) is a silver-white, odorless liquid at room temperature with high surface tension. Synonyms for elemental mercury include colloidal mercury, hydrargyrum, liquid silver, metallic mercury, and quicksilver. Mercury is the only metal that is a liquid at room temperature. Above that temperature, elemental mercury quickly vaporizes. Thus, elemental mercury is the main volatile form of mercury in air. At 20°C, a saturated atmosphere of elemental mercury contains 15 mg Hg/m^3; this concentration is several hundred times higher than current occupational standards for elemental mercury as an 8-hour TLV–TWA.[6] Table 20.1 lists the identifying information and physical properties of elemental mercury. Mercury is a non-essential metal with no known physiological function in the human body.

Valuable commercial properties of elemental mercury include high specific gravity, uniform expansivity, electrical conductivity, fluidity at room temperature, and ability to alloy with metals.

EXPOSURE

Uses

Chloralkali plants use large quantities of mercury as cathodes in the electrolysis of sodium chloride solutions during the production of caustic soda and chlorine gas, resulting in the release of elemental mercury into ambient air. By-products (e.g., hydrogen, sodium hypochlorite, hydrochloric acid) of this process all contain mercury. Mercury is also a constituent of processes that produce dyes, urethane foam, and vinyl chloride monomers. Commercial applications of mercury-containing compounds include light sources (mercury vapor lamps), arc rectifiers, battery cells, control instruments (barometers, switches, thermostats), disinfectant and stool preservatives, and medical instrumentation. Liquid elemental mercury is a component of some gold extraction processes, particularly those processes used in small "cottage" industries.[7] Gold ores are ground mechanically to a fine powder with the addition of liquid mercury to bind the gold into a gold-mercury amalgam; heating the amalgam vaporizes the mercury and leaves a raw gold sponge. The latter step exposes the workers (amalgam burners) to high concentrations of elemental mercury. Nonspecific neuropsychiatric symptoms were associated with occupational exposure to mercury in a worker who repaired sphygmomanometers in a poorly ventilated shop.[8] A study of children from workers in a mercury thermometer manufacturing plant revealed elevated urine mercury concentrations; however, physical examination of these children revealed no obvious evidence of mercury toxicity.[9]

In the United States, dentists use >100 tons of mercury annually; individual dentists in private practice use ~2–3 pounds of mercury per year.[10] The use of mercury amalgams has decreased with the increasing use of composite materials. The exact mercury content of amalgam varies from 42% (conventional "dry" mouths) to 60% mercury ("wet"). Conventional silver amalgam typically contains 50% mercury, 35% silver, and 10% tin by weight, as well as traces of copper and zinc. Alternatives to dental amalgam include the following: 1) composites of plastic material, 2) porcelain, and 3) gold. The average life span of amalgam is ~10 years.

Many potential sources of mercury exposure exist in a dental office including the following: accidental spills, poor mercury hygiene, normal milling to express excess mercury for freshly mixed amalgam, mechanical amalgamators, ultrasonic analgesic condensers, heating of the amalgam carrier to dislodge set particles, failure to use high-vacuum suction while removing old amalgam restorations, and improper dry heat sterilization of amalgam-contaminated instruments. Depending on the procedure for handling amalgam and the type of ventilation, the mercury concentration in ambient air of some dental operation rooms may exceed current US occupational standards (50 µg Hg/m^3).[11] In a study of Swedish dental clinics with relatively low airborne mercury vapor concentrations (median, 3.6 µg/m^3 in private clinics), the urine mercury concentrations of the dental personnel were similar to the general population; there was no correlation

TABLE 20.1. Identifying information and physical properties of elemental mercury. (Based on International Programme on Chemical Safety).[6]

Physical Characteristic	Value
CAS RN	7439-97-6
Synonym	Quicksilver, mercury, elemental mercury, mercury vapor
Atomic weight (g/mol)	200.59
Melting point (°C)	−38.87
Boiling point (°C)	356.72
Density (25°C)	13.534 g/cm^3
Water solubility (25°C)	0.28 µmol/L
Vapor pressure (mmHg 25°C)	2×10^{-3}

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.

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between the prevalence of symptoms and urine mercury concentrations.[12]

Production Processes

Mining of elemental mercury involves the underground collection of mercury ore in the form of cinnabar (mercuric sulfide) followed by filtration, re-distillation, and electrolytic processing to purify the mercury in cinnabar. The Almadén mercury mine in Spain produced 90% of the total output of mercury for the European Community. Following the closure of mercury mines in the United States during the 1990s, recycling of mercury-containing products (e.g., mercury batteries, dental amalgams, switches/thermostats, manometers, chloralkali wastewater sludges, chemical solutions, fluorescent light tubes[13]) and by-products of gold mining became the primary sources of mercury.[14]

Sources

Mercury is ubiquitous in the environment. Comparing estimates of the amount of mercury contributed to the environment by anthropogenic sources (i.e., from human activity) and natural sources is complicated by the difficulty in estimating emissions from terrestrial and marine systems as well as the "recycled" anthropogenic sources. Some estimates suggest natural sources emit up to three times more mercury than anthropogenic sources.[6] Important human (i.e., anthropogenic) sources of mercury include combustion of fossil fuel[15] and household waste, smelting of metal sulfide ores, refining of gold, production of cement, and industrial metal applications.[16] The major natural sources of mercury include evaporation of elemental mercury from water, emissions from volcanoes, and off-gassing of mercury vapors from the soil. The major potential source of exposure to mercury and mercury compounds in the general population includes the inhalation of elemental mercury from the air, the ingestion of contaminated water and food, and dental and medical therapy (e.g., Ayurvedic medicines).[17] Rasa Shastra is the Ayurvedic practice of combining herbs with gems, metals, and minerals. Analysis of Ayurvedic medicines sold via the Internet indicated these Rasa Shastra medicines contained substantially higher total Hg concentrations than non-Rasa Shastra medicines.[17] For the general population, the three major sources of mercury include fish consumption (methyl mercury) and dental amalgams (elemental mercury); most vaccines in the United States no longer contain ethyl mercury.[18] Dental amalgam fillings release mercury vapor with a daily intake in the range of several micrograms of mercury; this relatively small amount is significantly below Hg exposures producing adverse effects.

Air

Elemental mercury vapor is the main chemical form of mercury released from anthropogenic sources into the atmosphere; the estimated daily mercury absorption from air is <1 μg in urban residents. Ambient air concentrations of elemental mercury are unlikely to exceed 0.05 $\mu g/m^3$, but the presence of point sources (e.g., smelters, mercury mines, application of mercury-containing fungicides) may increase the mercury concentration in ambient air near these sources to ~10–15 $\mu g/m^3$.[19]

The mercury concentration in the work environment may exceed general environmental concentrations. A survey of a mining operation revealed mercury concentrations ranging from 160–4,890 $\mu g/m^3$,[20] whereas some air samples from a milling operation exceeded 1,200 $\mu g/m^3$.[21] The average elemental mercury vapor concentration in 21 chloralkali plants during the early 1970s was 65 $\mu g/m^3$ with 85% of the values of <100 $\mu g/m^3$.[22] Heating mercury in a confined space (e.g., gold extraction processes in nonindustrial settings) may release high elemental mercury concentrations into the air, particularly in artisanal gold mining areas (e.g., rural Columbia, Brazil, Venezuela, Ecuador, Tanzania, Ghana) when the process involves adding Hg to the gold ore prior to milling (i.e., amalgamation of whole ore).[23,24] Inhalational mercury toxicity and pneumonitis also occur during the extraction of gold from recycled jewelry and electronic equipment by using heated Hg in homes in developed countries.[25]

Soil/Spills

Local spills of mercury in the home or work environment represent a potentially serious hazard.[26,27] The complete volatilization of 3 g (1/5 mL) Hg in a 10′ × 10′ × 8′ room can substantially exceed current mercury standards. Attempts to remove the mercury by vacuuming may result in the dispersal of the mercury over a larger surface area.[28] Even though visible traces of liquid mercury are not present, low ambient air concentrations of mercury may persist for several weeks.[29] Mercury in elemental form or an amalgam is necessary to generate ultraviolet radiation in fluorescent lamps via ultraviolet excitation of luminescent powder. Compact fluorescent lamps contain milligram quantities of mercury (i.e., up to 2.5–5 mg) that disperse into the surrounding air following breakage depending on room

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size, ventilation, room temperature, age of lamp (elemental mercury oxidizes to HgO with use), and location in the room, particularly during the first 4 hours after breakage.[30,31] In contrast to liquid mercury spills, modeling of releases from broken lamps suggests airborne mercury concentrations do not significantly exceed current recommendations, particularly following ventilation and clean-up.[32] More liquid mercury occurs in new than older fluorescent tubes.[33] Mercury vapor bulbs (self-extinguishing or "T"-type, non-self-extinguishing or "R"-type) are long-lasting, bright sources of light in gyms, sports arenas, banks, stores, and street lights.

Elemental mercury is volatile; the rate of evaporation depends on the temperature and surface area of the mercury spill.[34] Young children are particularly susceptible to the development of mercury toxicity including acrodynia following exposure to mercury vapor because of several factors including: 1) closer physical proximity to the source of mercury vapors in carpeting, 2) increased respiratory rate resulting in increased absorption of mercury vapor, and/or 3) decreased body size.[35,36] Volatilization of mercury from broken switches in incubators may increase the absorption of mercury by neonates, but symptoms of mercury toxicity do not usually develop.[37]

Water

Natural weathering of mercury-bearing minerals in igneous rocks directly releases mercury into the surface and underground water sources. Surface runoff transports mercury from the soil into surface waters, particularly from soils with high humic content.[38] The amount of elemental mercury in drinking water typically is toxicologically insignificant (i.e., ~0.05 μg/day).

Diet

For the general population, the most common source of mercury is methylmercury in fish; the amount of elemental mercury in the diet is very small. Uptake of mercury vapors from dental amalgam accounts for most of the exposure to mercury in persons without occupational or dietary exposures.

ENVIRONMENTAL FATE

The natural cycling of mercury involves evaporation of elemental Hg from soils and surface waters, followed by atmospheric transport, deposition of mercury on land and surface waters, and the absorption of mercury to soil or sediment particulates.[14] Figure 20.1 demonstrates

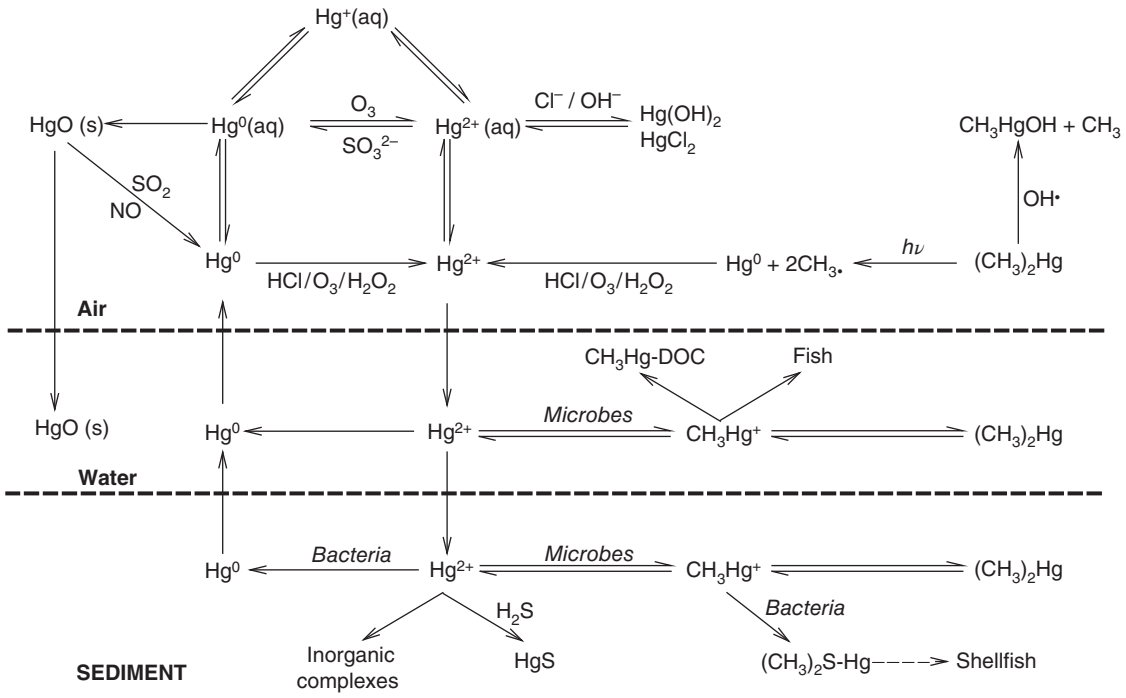


FIGURE 20.1. Mercury transformation in air, water, and sediment. Dashed lines are boundaries between environmental compartments of air, water, and sediment. *Abbreviations:* aq = associated with aqueous environment; DOC = dissolved organic carbon; hν = energy from light; s = solid. (Agency for Toxic Substances and Disease Control).[14]

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the global cycle of mercury. Elemental mercury vapor is the dominant form of mercury in the atmosphere with anthropogenic sources for ~25–50% of the total, primarily from the burning of fossil fuels.[39] This form is chemically stable; the residence time of mercury vapor in the atmosphere ranges from 0.4–3 years.[6] In the atmosphere, metallic mercury vapor (Hg^0) undergoes oxidation to divalent Hg by ozone before being removed from the atmosphere by precipitation.

Elemental mercury may travel long distances before wet or dry deposition deposits the mercury on soil or surface waters. Models of the transport of mercury indicate that sources up to 2,500 km away may account for mercury in precipitation.[40] Deposition of the mercury with precipitation accounts for the removal of about 2/3 of the mercury present in the atmosphere;[41] wet precipitation is probably the source of most mercury in lakes that do not receive industrial effluents.[42] In surface waters, biotransformation is the most important transformation process in the environmental fate of mercury. The source of most mercury in groundwater is the atmosphere as a result of the limited leaching of mercury adsorbed to the soil.[43]

Mercury is a highly mobile metal. Simulated studies of the transport of mercury from air to the soil indicate that the penetration of elemental mercury from the atmosphere is limited to the first 3–4 cm of topsoil.[44] In the soil, particulate-bound mercury enters several different pathways including formation and precipitation of insoluble mercury sulfide, off-gassing of volatile or soluble forms of mercury, or bioaccumulation in aquatic and terrestrial food chains.[14]

DOSE EFFECT

Acute Toxicity

Inhalation

Several case reports associate exposure to high elemental mercury concentrations with the development of fatal pulmonary damage similar to acute respiratory distress syndrome; however, the reports did not include airborne mercury concentrations.[45,46]

The accidental exposure of workers to estimated airborne mercury concentrations (>5–10 mg Hg/m^3) for a few hours produced an acute febrile illness with interstitial pneumonitis, gastrointestinal tract irritation, and inflammation of the oral cavity characterized by cough, chest pain, dyspnea, stomatitis, gingivitis, nausea, diarrhea, and salivation.[47,48] Animal studies in rabbits indicate that the inhalation of mercury concentrations of 28.8 mg Hg/m^3 over 4–30 hours produces mild to moderate pathological changes in the lungs, mild to marked cellular degeneration of the colon, marked cellular degeneration with some necrosis of cardiac muscle, moderate to severe liver necrosis, marked degeneration of the kidney, and necrosis of brain tissue.[49] Exposure of these rabbits to the same concentration of mercury vapor for 1–4 hours produced mild to moderate pathological changes in these organs.

Wounds/Injection

Case reports indicate that the absorption of elemental mercury over several days from subcutaneous wounds is relatively small.[50] A 1-mL (13.6 g) injection of elemental mercury caused no symptoms and an increase in the whole blood mercury concentration to 62 µg/L.[51] A 20-mL elemental mercury injection resulted in pleuritic chest pain, dyspnea, and malaise that resolved over several weeks with supportive care. Although the pulmonary embolization of mercury was extensive, no acute or chronic systemic symptoms developed.[52]

Ingestion

The oral bioavailability of elemental mercury is extremely low; therefore, toxicity from the ingestion of elemental mercury is unusual unless large elemental mercury doses are retained within the gastrointestinal tract or released into the peritoneum. A 17-year-old boy ingested 204 g of elemental mercury without systemic toxicity.[53]

Chronic Toxicity

Target Organs

The central nervous system is probably the most sensitive target organ for toxicity following exposure to elemental mercury vapors. Behavioral changes, gingivitis, and tremor occur without pulmonary symptoms following repeated exposure to airborne mercury concentrations near 1 mg/m^3. A study of chloralkali workers exposed to elemental vapor concentrations up to 0.1 mg/m^3 did not demonstrate any effects attributable to mercury exposure.[22] In a study of plant manufacturing thermometers, workers with mean Hg exposure to 0.076 mg/m^3 (range, 0.026–0.27 mg/m^3) demonstrated a greater incidence of static tremor and heel-to-toe gait disturbances compared with workers without occupational exposure to mercury.[54] In a cross-sectional study of 43 chloralkali workers and 22 age-matched, unexposed referents, there were no significant associations

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with current or cumulative mercury exposure and measures of eye-hand coordination or diadochokinesis.[55] The median mercury exposure time for the exposed workers was 13 years (range, 2–32 years) with a mean current urine mercury concentration of 7.7 μg/g creatinine (range, 1.3–25 μg/g creatinine) compared with 0.9 μg/g creatinine (range, 0.2–4.1 μg/g creatinine) for referents.

Few data support the liver or kidneys as target organs of mercury toxicity, particularly in humans. In rats exposed to elemental mercury vapor of 3 mg/m^3, 3 hours/day, 5 days/week for 15–42 weeks, behavioral changes included a decline in conditioned avoidance response and increased latency in the pole climb shock escape response. Pathological examination demonstrated slight degenerative changes (lysosomal inclusions, black intracellular deposits in tubular epithelium) developed in the kidneys without any detectable liver injury.[56]

Dental Amalgam

Dental amalgam is a solid emulsion composed of ~50% elemental mercury with the remainder consisting of a metallic powder (silver, tin, copper, indium, palladium, zinc).[57] For the general population, elemental mercury vapor released from dental amalgams is the second most common mercury source after methylmercury in fish; however, the amount of mercury vapor released during mastication remains substantially below concentrations associated with mercury toxicity. Three potential mechanisms for the release of mercury from fillings include: 1) a corrosive process that liberates mercury ions from the effect of saliva and oxygen on the amalgam; 2) mercury absorption from the dissolution of solid corrosion products and amalgam debris in the gastrointestinal tract; and 3) inhalation of vaporized mercury during mastication, dental filling procedures, or the removal of old amalgam restorations.[58] Abrasion of the dental amalgam is the primary process causing mercury release from the amalgam; this mechanism accounts for three times the mercury release from amalgam fillings than corrosion.[59] Chewing causes a several-fold increase in the release of mercury vapors from dental amalgam with the mercury concentrations returning to baseline after ~90 minutes.[60] Solid or dissolved forms of mercury enter the gastrointestinal tract where elemental mercury absorption is minute. Based on similar ratios of mercury in the erythrocytes and plasma of mothers and their fetuses, fetal exposure to elemental mercury vapor from dental amalgam probably does not exceed maternal exposure.[61]

Absorbed Dose

Even though the amount of mercury absorbed from dental amalgams is extremely small and clinically insignificant, the contribution of dental amalgams to the average mercury exposure of the general population may be a substantial portion of the average daily Hg uptake from all sources. Several studies correlated the number and surface area of dental fillings to mercury content in tissues.[62,63]

Accurate estimation of mercury uptake by the human body is complicated for technical reasons and substantial individual variation including the number of total and occlusal amalgam surfaces. Earlier estimates of daily mercury uptake from dental amalgams substantially overestimated the absorbed Hg dose (2.5–17.5 μg/day);[64] however, later estimates were lower (e.g., 1.4 μg Hg) from better instrumentation (intraoral flow rate, collection volume) and approximation of physiological Hg release rates without (i.e., nasal breathing) and with eating (i.e., saliva-covered surfaces), intraoral flow rate, and inspiratory volume per breath.[65,66] Estimates of daily mercury intake from dental amalgam based on volunteer studies range from 1–2 to 5–9 μg for subjects with an average number of dental amalgam.[67] A Norwegian study suggests individuals with over 26 restorative amalgam surfaces absorb 10–12 μg Hg/day,[68] whereas the estimated daily absorbed Hg dose from a randomized, controlled, three-armed trial comparing treatment and non-treatment strategies ranged from 2.3–2.7 μg for a medium amalgam load (median = 25 surfaces) to <7.4 μg for a high amalgam load (45 surfaces).[69] The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks concluded dental amalgam already in place is not a health risk for the general population; they recommended against removing amalgam restorations as a preventive measure.[70] In some situations (e.g., large cavities, cavity susceptibility), dental amalgam remains the preferable choice.

Mercury Kinetics

The release of mercury from amalgam restoration is relatively small with peak concentrations occurring shortly after amalgam placement in the dental cavity, then declining to a lower steady-state concentration within 10–15 days.[71] Although there was considerable interindividual variation, *serum* inorganic mercury concentration in 29 elderly women increased by ~0.02 μg/L/amalgam tooth surface corresponding to a daily Hg uptake of 0.2 μg/amalgam surface.[72] Following placements of up to eight new amalgam restorations, urine mercury concentrations were below recommended standards

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(<50 μg Hg/L whole blood; <30 μg Hg/L urine).[59] Complete removal of dental amalgams produces a transient rise in plasma mercury concentrations followed by a reduction in the plasma Hg concentration (i.e., elimination half-life ~30–60 days) to baseline values.[73,74] In an observational study of 12 healthy adults undergoing amalgam removal (mean amalgam surfaces = 18; range, 13–34), peak *plasma* mercury concentrations occurred within 48 hours.[75] Peak *plasma* mercury concentrations were an average of 32% higher than pre-removal plasma Hg concentrations. By 60 days after removal, the plasma mercury concentration had declined exponentially to ~60% of the pre-removal value. Methods to reduce Hg absorption during amalgam removal include high-speed cutting, water cooling, high-volume evacuator use by dental assistants, and rubber dam placement.[76,77] A 1-year observational study followed plasma and urine Hg concentrations in 18 subjects undergoing removal of all amalgam restorations during a single treatment session using a rubber dam and 10 subjects without a rubber dam.[76] The number of occlusal amalgam surfaces was similar in the two groups (12.9 ± 3.6 and 11.3 ± 3.6, respectively), whereas the mean number of total amalgam surfaces for the rubber dam group was 42.8 ± 13.3 compared with 19.9 ± 11.5 in the non-rubber dam group. The peak (1-day) plasma Hg concentration increased by 0.56 ± 1.65 μg/L in the rubber dam group compared with 2.67 ± 3.13 μg/L in the non-rubber dam group ($P = 0.012$). By 1 year, the reduction in plasma and urine Hg concentrations in the two groups was not statistically different (power not reported). Although some health complaints attributed to amalgam restorations may improve following amalgam removal,[78] no convincing scientific evidence supports the benefit of removing normally functioning dental amalgams to relieve non-dental-related symptoms other than the placebo effect.[79]

Dose Response

Despite lay concern about the release of some elemental mercury from occlusal surfaces containing mercury amalgam during mastication, no cases of acrodynia or other toxic effects are clearly caused by the presence or removal of mercury amalgam. Although chewing releases vaporized Hg^0 into the oral cavity, the release rate is probably too small to cause mercury toxicity. A review of 14 studies on these release rates indicated the mercury dose from fillings (i.e., <10 μg/day) is substantially below acceptable daily intakes even in symptomatic patients who believe their amalgam restorations cause toxicity.[80] Using direct measurements of intraoral mercury vapor, a Swedish case series compared 10 consecutively selected patients referred for evaluation of subjective symptoms they believed were caused by their amalgam restorations (mean occlusal surfaces = 13.0 ± 4.5, mean total amalgam surfaces = 44.4 ± 13.6) and 8 controls (mean occlusal surfaces = 12.9 ± 2.4, total amalgam surfaces = 40.9 ± 13.4).[81] The calculated daily uptake of inhaled mercury vapor and urine/blood Hg concentrations were similar in both groups. The 24-hour Hg uptake was 2.0 ± 1.4 μg in the symptomatic group and 2.4 ± 1.9 μg in the control group. The DMSA group reported a statistically significant decrease in fatigue-inertia; however, the symptom did not correlate to increased urinary Hg excretion or reduced blood Hg concentrations. The Hg uptake represented <5% of the 1991 WHO acceptable daily Hg uptake. Hg uptake in the range of 1–3 μg would require the presence of 450–530 amalgam surfaces in non-gum chewing patients to exceed the urine concentration (30 μg/g creatinine) associated with subtle, preclinical effects in the most sensitive individuals by the World Health Organization.[82] These numbers are consistent with the lack of a clear relationship between amalgam load and health effects in these studies. A retrospective case report suggested extensive grinding of old amalgam restorations during 12 visits over 2½ months was possibly associated with the development of stomatitis and other neurological symptoms; however, the urine Hg concentrations did not confirm a causal relationship.[83]

TOXICOKINETICS

Absorption

The systemic absorption of elemental mercury (Hg^0) is much higher from the lungs (~70–80%) compared with the gastrointestinal tract (i.e., ~0.01%).[67,84] In a study of nine healthy volunteers exposed to 400 μg/m^3 mercury vapor, the median pulmonary retention of Hg^0 was 69% (range, 65–72%).[67] The uptake of elemental mercury vapor by the skin is small (<1%) compared with pulmonary absorption based on studies in human volunteers. In a study of five male subjects, the calculated Hg^0 uptake was 0.01–0.04 ng/cm^2 skin surface/min for each ng Hg/cm^3 air based on the dermal application for <1 hour.[85] Large oral doses (200 g) of elemental mercury are required to produce toxicity, although occasionally the ingestion of mercury in broken thermometers may cause local tissue reactions from the incorporation of mercury into the intestinal wall.[86] In a study of 11 volunteers ingesting mercury-containing amalgam, the estimated absorbed fraction of the administered dose was ~0.04%.[87] Intravascular elemental

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mercury injections produce pulmonary mercury granulomas but little acute systemic toxicity as a result of the relatively poor absorption of elemental mercury.[88]

Distribution

The kidney is the major storage site of the elemental mercury (Hg^0) following absorption into the body with mercury causing relatively limited bioaccumulation.[84] Animal studies indicate that ~50–90% of the mercury body burden resides in the kidneys after administration of elemental Hg vapor.[6,89] Other tissues with an affinity for mercury include the brain, liver, ovaries, testes, pancreas, prostate, and thyroid. Studies of dental personnel document elevated mercury concentrations in the pituitary gland, but this low-grade chronic mercury exposure does not produce dysfunction of the pituitary gland; storage of mercury as the biologically inactive mercuric selenide may account for the lack of significant toxicity.[90] The high lipid solubility of elemental mercury allows the rapid transfer of this form of mercury across the blood–brain barrier where oxidation of elemental Hg to Hg^{2+} in the central nervous system limits back diffusion across the blood–brain barrier. Erythrocytes also oxidize Hg^0 to the divalent form. Mercury concentrations following Hg^0 vapor exposure are ~2 times higher in red blood cells than plasma. Total mercury concentrations from the consumption of mercury in the diet average several hundred ng/g tissue in the kidney and liver, whereas the mercury concentrations in the cerebrum, cerebellum, heart, and spleen average several tens of ng/g tissue.[91] For the general population, the average total mercury concentrations in the kidney, liver, and brain are ~0.3 μg/g, 0.05–0.1 μg/g, and 0.01–0.02 μg/g, respectively.[63,92,93] Renal mercury concentrations are much higher (i.e., up to 50–100 times) in Hg-exposed workers than in the general population.

Animal studies suggest the distribution of mercury to the brain is relatively higher (and correspondingly lower to the kidneys) following exposure to elemental mercury than mercury salts. In a study of squirrel monkeys, the mercury concentration of the brain was 25% higher and the kidneys 78% lower following the inhalation of mercury vapors than following the ingestion of an equivalent dose of mercuric salts.[94] Moderate alcohol concentrations considerably reduce the oxidation of elemental mercury vapor in the body.[95]

Elimination

Following absorption in the lungs, elemental mercury undergoes oxidation to divalent mercury by the hydrogen peroxide-catalase pathway. These reactions occur primarily in the red blood cells; however, some oxidation also occurs in the brain, liver, and lungs. Most absorbed elemental mercury leaves the blood within 2–4 days. Following the short-term exposure of nine workers to ambient air mercury concentrations exceeding 100 μg/m^3, the estimated whole blood half-lives were 3.1 days for the fast compartment comprising ~80% of the absorbed dose and 18 days for the slow compartment.[96] Elimination of mercury from whole blood appears somewhat longer after long-term mercury vapor exposures compared with short-term exposure for the fast and slow compartments. Measurement of whole blood mercury concentrations in 14 chloralkali workers exposed to mercury vapors for a median of 10 years (range, 1–24 years) demonstrated half-lives of 3.8 days for the fast phase and 45 days for the slow phase.[97] The fraction of mercury eliminated during the slow phase is ~50% following long-term exposure compared with 20% during the slow phase of elimination following short-term exposure. The mercury half-life in the plasma is relatively shorter during the fast phase compared with the mercury half-life in erythrocytes, whereas the opposite occurs during the slow phase.

Excretion of elemental mercury occurs primarily in the urine and feces with a half-life of 40–60 days following short-term exposure and ~90 days after long-term exposure. The intravenous administration of up to 60 g ascorbic acid did not significantly increase the urinary excretion of mercury in 89 adult volunteers with low blood Hg concentrations when compared with a placebo infusion of saline.[98] Expiration of elemental mercury is a relatively small (<7%) portion of the elimination pathway; little mercury excretion occurs 5–7 days after exposure to Hg vapors.[99]

Maternal–Fetal Kinetics

Elemental mercury (Hg^0) easily crosses the placenta and accumulates in the fetus. The limited data available indicate that maternal and cord blood are similar at delivery following *in utero* exposure to elemental mercury.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Mercury is a non-essential element. Elemental mercury is highly lipophilic, resulting in rapid penetration

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through the blood–brain barrier. Conversion of elemental mercury to the monovalent mercurous and divalent mercuric cations limits the ability of Hg in these forms to exit the nerve cell. Consequently, divalent inorganic mercury probably is the proximate toxic species producing the CNS effects associated with elemental mercury poisoning because elemental mercury does not react with tissue ligands.[100] Mercury in all forms will bind sulfhydryl (–SH) groups in thiols or proteins; several amino acids contain sulfur including cysteine, cystine, methionine, and taurine. Binding of mercury to amino acid residues in receptor or transport proteins alters the metabolic functions dependent on these proteins. The inhibition of a wide variety of enzymes and protein-transport mechanisms following the binding of divalent mercury to sulfhydryl groups probably accounts for mercury toxicity; however, the precise target for mercury is unclear.[100] Alteration of the tertiary and quaternary structures of various proteins by the binding of divalent Hg to SH-groups can affect cellular signaling, receptor binding, and cell membrane function. Mercury also forms strong bonds with other ligands (e.g., amine, phosphoryl, carboxyl groups) that may contribute to mercury toxicity.[101]

Pathological Changes

Central Nervous System

In addition to methylmercury, the central nervous system is a target organ of elemental mercury toxicity; however, the pathological changes in the brain following the inhalation of elemental mercury are generally mild compared with the changes following the chronic ingestion of organic mercury compounds. Exposure to elemental mercury vapor usually causes mild, reversible changes in the central nervous system. Although elevated mercury concentrations may persist for years in the brain, histological examinations of the brain of workers recovering from Hg^0-induced encephalopathy are frequently normal (i.e., no loss of granular cells in the cerebellum) despite the presence of mercury in central nervous system neurons.[102] In contrast to organic mercury toxicity, destruction of the endoplasmic reticulum and neurons does not usually occur. Additionally, pathological damage also develops in organs outside the central nervous system. Autopsies of four workers dying after exposure to elemental mercury vapors for 2 weeks demonstrated infarctions in the brain along with disseminated intravascular coagulopathy, renal cortical necrosis, and diffuse organized pneumonia.[103]

Kidney

The kidney is not a critical target organ even following acute, massive elemental mercury poisoning, except for the production of usually mild, transient proteinuria.[104] However, elemental Hg undergoes rapid oxidation to inorganic salts in the body that may cause acute tubular necrosis. Additionally, elemental mercury exposure has been associated with glomerular dysfunction ranging from proteinuria to nephrotic syndrome. Case series associate the development of a nephrotic syndrome with an immunological response that manifests as an immune complex (membranous) glomerulonephritis following chronic occupational exposure to mercury vapors.[105] The proteinuria primarily involves high-molecular-weight proteins that leak through damaged glomeruli.

Respiratory System

The inhalation of large amounts of elemental mercury produces capillary damage and pulmonary edema along with desquamation and hyperplasia of the bronchiolar lining, progressing to fibrosis and the obliteration of alveoli. The histology of the pulmonary tissue depends on the severity of the exposure and the time since the exposure ended. Acutely, erosive, necrotizing bronchitis and interstitial pneumonitis with hyaline membrane develop.[45,106] Obstruction from desquamation of bronchiolar epithelium results in severe ventilation/perfusion defects and hypoxemia similar to acute respiratory distress syndrome with postmortem examinations demonstrating various stages of fibrosis depending on the length of survival.[107] Histological changes include alveolar dilatation resulting from ruptured septa, exudation of inflammatory cells, hyperplastic pneumocytes, alveolar macrophages, and progressive interstitial fibrosis.[103] A follow-up 22 years after aspiration of elemental mercury demonstrated progressive fibrosis with pleural effusions, pulmonary granulomas, and bronchiectasis that was associated with local irritation from aspirated elemental mercury.[108]

Postmortem Examination

The smelting of mercury amalgam in poorly ventilated home environments is associated with the development of progressive, fatal acute pulmonary injury with histological changes related to the postexposure survival period. Extra-pulmonary changes do not usually occur in this setting. Postmortem examination of four fatal cases of elemental mercury vapor inhalation revealed severe diffuse alveolar damage, acute proximal renal tubular necrosis, vacuolar hepatotoxicity,

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and a variety of changes in the central nervous system including vasculitis, multifocal ischemic necrosis, and gliosis.[107] Postmortem analysis of tissue from a thermometer worker committing suicide 4 weeks after leaving a 14-year job involving mercury vapor exposure revealed the following mercury concentrations: kidney, 25 μg/g; liver, 1.2 μg/g; lung, 0.72 μg/g; and brain, 0.014–0.018 μg/g.[109]

CLINICAL RESPONSE

Acute Toxicity

Inhalation

Acute elemental mercury toxicity usually results from the heating of liquid mercury in a poorly ventilated space. The inhalation of toxic doses of elemental mercury produces the syndrome of mercurialism that primarily affects the central nervous system and lungs. Dyspnea is the initial symptom that typically develops within 1–4 hours. Additional clinical features include fever, chills, nausea, nonspecific chest pain, cough, and headache similar to acute metal fume fever[35,48] as well as diarrhea, abdominal cramps, and decreased vision.[110] Severe cases of elemental mercury poisoning may resemble toxic shock syndrome with progression to noncardiogenic pulmonary edema (dyspnea, cyanosis, extensive bilateral infiltrates, progressive respiratory failure) within several days.[111,112] Complications include subcutaneous emphysema, pneumomediastinum, pneumothorax, and death.[113]

The issue of whether or not large, acute exposures to elemental mercury cause permanent neurological sequelae remains unresolved. A 3-month follow-up report on a cohort of workers with acute, massive elemental mercury toxicity revealed that some workers demonstrated persistent, nonspecific neurological symptoms and reduced scores on some tests of visuomotor function (Trailmaking A and B, Stroop Color Word Test).[35] However, the lack of well-defined control groups, the use of normative data rather than pre-exposure test scores, and selection bias limit the interpretation of this study.

Elemental mercury vapor toxicity may simulate mucocutaneous lymph node syndrome (Kawasaki's disease). This disease is an acute febrile multiorgan vasculitis seen predominately (i.e., 75–80%) in children of <5 years of age with many symptoms and diagnostic criteria similar to acrodynia.[114] These two diseases share the susceptibility marker of glutathione *S*-transferase depletion. Although some case reports document elevated urine mercury concentrations in Kawasaki's disease patients,[115] most of these patients have normal urine mercury concentrations with some increased susceptibility in Asian children.[116] The etiology of Kawasaki's disease remains unknown.

Injection

Subcutaneous injections of elemental mercury cause local abscesses and granulomas; however, systemic symptoms are unusual,[117,118] despite the blood and urine mercury concentrations substantially exceeding normal concentrations.[119] Sequelae of intravenous elemental mercury injections include local and embolic complications (thrombophlebitis and granuloma formation); the development of elemental mercury poisoning is rare. A 35-year-old man injected Hg^0 subcutaneously into his right shoulder, creating a reservoir of elemental mercury under the skin. One year later, he presented with gait ataxia, nystagmus, diplopia, dysarthria, vertigo, headache, vomiting, left third nerve and bilateral sixth nerve palsies, and a large plaque in his right shoulder; the serum mercury concentration was elevated (84 ng/mL) at presentation.[120] Case reports associate pleuritic chest pain, exertional dyspnea, fatigue, low-grade fever, a low posterior pleural rub,[121] tremors, lower extremity weakness,[122] and persistent hemoptysis[123] with the intravenous administration of elemental mercury.[124] The oxidation of elemental mercury to the soluble mercuric ion is slow following the intravenous administration of Hg^0; this slow oxidation to the biologically active mercuric ion probably accounts for the relative rarity of mercurialism after intravenous injection of Hg^0. Elemental mercury causes local chronic inflammation with progressive fibrosis at the sites of elemental mercury globules without the development of pulmonary dysfunction from the mercury emboli. A follow-up examination of a patient 11 years after injecting elemental mercury revealed decreased diffusing capacity (55% of estimated normal) and reduced sperm motion, but the nerve conduction velocities, neuropsychological tests, and renal function were normal.[125]

Ingestion

The clinical course following elemental mercury (Hg^0) ingestion is typically benign unless pulmonary aspiration occurs after massive Hg^0 ingestion[126] or disruption of the gastrointestinal tract causes Hg^0 extrusion into the peritoneum with development of granulomas and/or abscesses;[127,128] consequently, systemic mercury toxicity is unusual.[129] Although rare care reports associate acute appendicitis with the filling of the appendix with Hg^0,[130] appendicitis does not usually result from Hg^0 retained

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in the appendix, depending on the risk of obstruction.[131] Intraperitoneal mercury contamination in a 64-year-old morbidly obese diabetic during a Roux-en-Y gastric bypass did not cause acute mercury toxicity.[132] His peak blood mercury and urine mercury concentrations were 146 μg/L (day 22) and 227 μg/L (day 43), respectively. The only observed sequela was an increase in his total urinary protein concentration from 480 mg/24 hours (preop) to 2,301 mg/24 hours (88 days postoperation). Although these patients had multiple complaints (abdominal pain, alopecia, dizziness, fatigue, gait disturbances, headaches, insomnia, irritability, loss of balance, proteinuria, pruritus), the presence of multiple comorbidities limits conclusions about the toxic effect of mercury absorption from the peritoneum.

Dermal

Broken non-self-extinguishing ("R"-type) mercury vapor light bulbs may emit sufficient UV radiation to cause keratoconjunctivitis and skin erythema.[133]

Environmental Exposure

For the general population, the elemental mercury vapor released from dental amalgams is the second most common source of mercury exposure after methylmercury in fish. There is no clear evidence that the Hg concentrations produced by dental amalgam cause adverse health effects, including renal damage or neurobehavioral abnormalities.[134] Furthermore, blood or urine concentrations of total and inorganic mercury do not separate asymptomatic adults with amalgams from adults with multiple, nonspecific complaints they attribute to amalgams.[135] In a study of 40 females claiming serious health damage from mercury in dental amalgam and 43 females without health complaints, there was no statistically significant difference in the median mercury concentration in blood or urine samples.[136] Clinical experience indicates the release of mercury from dental amalgam is less likely to cause allergic reactions than copper or silver.

Analysis of data from the Seychelles Child Development Nutrition Study did not detect an association between maternal amalgam surfaces and infant scores on mental or psychomotor development indices of the Bayley Scales of Infant Development administered 9 and 30 months after birth.[137] Several randomized clinical trials of children requiring dental restorations did not detect any statistically significant neurobehavioral or neuropsychological effects when comparing children with mercury amalgam and children with resin composites.[138,139] These trials involved annual follow-up for 7 years; the testing was designed to detect a difference of three to five IQ points. A randomized controlled trial of 534 6–10-year-old rural and urban children annually assessed the children with a battery of tests including attention, intelligence, language, achievement, learning, executive function, fine motor function, verbal fluency, and visual-spatial skills.[140] Although the group with dental amalgams had a higher average urine mercury concentration than the composite group (i.e., 0.9 μg/g creatinine vs. 0.6 μg/g creatinine), the neuropsychological test scores of the two groups during the 5-year follow-up period were statistically similar. A 5-year prospective study of children of 6–10 years of age demonstrated a higher prevalence of urinary albumin (>30 mg/g creatinine) in the amalgam group ($n = 267$) compared with the composite group ($n = 267$) at follow-up 3 years and 5 years after enrollment in the study.[141] The odds ratio (OR) was 1.8 (95% CI: 1.1–2.9). However, there was no dose-related increase in albuminuria between the number of amalgam fillings and albuminuria; therefore, chance could not be excluded as the cause of the results. There were no statistically significant differences in markers of renal tubular function (α-1-microglobulin, *N*-acetyl-β-D-glucosaminidase). Dental amalgams remain an option for the treatment of caries in children.

Occupational Exposure

Studies of occupational exposure to elemental mercury involve primarily neurological and renal effects. The classic triad of occupational exposure to elemental mercury in the range of 100–600 μg Hg/m^3 includes inflammation of the oral cavity (gingivitis, salivation, stomatitis), tremor, and behavioral/personality changes.[142] The latter involves excessive shyness, emotional instability, anxiety, irritability, loss of confidence, pathological fear of ridicule, vivid dreams, poor memory, insomnia, and anorexia. Erethism is a historical term applied in the early 19th century to describe all the clinical features of mercury vapor toxicity; however, the diagnostic utility of this term is limited by poorly defined behavioral changes and nonspecific features. The psychological effects of mercury vapor exposure differ from the clinical features of acute psychoses (hallucinations, delirium, suicidal ideations) because the patient retains some self-control and sense of reality.[100] Clinical features of chronic mercury toxicity of workers (e.g., amalgam burners in gold processing) exposed to high ambient air concentrations include ataxia, incoordination, tremor, excessive salivation, and metallic taste.[143]

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Primary hypersensitivity to elemental mercury is rare;[144] however, contact dermatitis has been associated with chronic exposure to elemental mercury.[145] The high incidence of false-positive patch tests complicates the interpretation of the significance of these case studies. The immune system is not a major target organ for elemental mercury toxicity. A cross-sectional study of 36 workers at a chloralkali plant occupationally exposed to mercury vapor did not demonstrate any abnormalities in immunological parameters (white blood cell count, cytokines, interleukin 1, tumor necrosis factor alpha, IgM, IgG, IgA) when compared with several groups of controls that included patients with mercury hypersensitivity.[146] The median blood mercury concentrations were >3-fold higher than controls.

Central Nervous System

Central nervous system symptoms are the most prominent adverse effects of chronic elemental mercury intoxication. The exposure of three workers to metallic mercury while gilding for <1–2 months was associated with the development of anxiety, restlessness, memory impairment, insomnia, depression, anorexia, weight loss, metallic taste, and dyspnea.[147] The patients had elevated urine mercury concentrations with normal nerve conduction velocities and electromyograms. All symptoms resolved within 6 months of cessation of mercury exposure. Chronic elemental mercury exposure may cause behavioral and personality changes as well as gingivitis and tremor.[148] The latter involves a rapid resting or an intention tremor abolished by sleep.[149,150] The most common tremors in workers exposed to elemental mercury are fine resting tremors with intention tremors more common in Minamata's disease (methylmercury toxicity).[151,152]

In the case series, psychological complaints of workers exposed to elemental mercury include depression, emotional lability and anxiety,[153] and decreased short-term memory.[154] A cross-sectional study of workers with moderate exposure to elemental mercury vapor for an average of 5 years revealed an increased prevalence of memory disturbances, depressive feelings, fatigue, and irritability, but the prevalence was not dose-related and neuropsychological tests did not reveal statistically significant differences between workers and unexposed controls.[155] Upon cessation of elemental mercury exposure, the motor impairments generally improve, but the cognitive disturbances (e.g., memory loss) often do not resolve.[156] Although the children of workers exposed to mercury may have increased urine mercury concentrations compared with unexposed controls, signs of chronic mercury poisoning typically do not occur in these children.[9]

Studies of workers exposed to mercury vapors suggest some subclinical differences in the color discrimination thresholds between exposed workers and controls in the blue-yellow and the red-green chromatic systems.[157,158] However, conclusions about a causal relationship between mercury vapor and these effects are limited by the lack of a clear dose-response relationship between exposure duration and mean urinary mercury concentration.

Peripheral Nervous System

Chronic over-exposure of workers to elemental mercury vapor may produce a mild sensorimotor neuropathy (weakness, paresthesias, muscle cramps) as defined by prolonged distal latencies on nerve conduction tests, even though urinary mercury concentrations may not be significantly elevated (average, <0.5 mg/L).[159,160] Cross-sectional studies of workers exposed to elemental mercury suggest that this neuropathy may be subclinical.[161] The common neurological abnormalities involve diminished vibratory sensation and hypoactive Achilles reflexes in the lower extremities that are consistent with the involvement of the large nerve fibers.[162] Examination of a cohort of 205 former workers with high cumulative elemental mercury exposure demonstrated persistent changes in motor nerve conduction velocity, motor nerve F-wave latency, and resting tremor, but cumulative mercury exposure did not correlate to cognitive neurobehavioral test outcomes when compared with the control group.[163]

Kidneys

The occurrence of renal changes (proteinuria, nephrotic syndrome, tubular dysfunction) following chronic elemental mercury exposure is uncommon.[164] The nephrotic syndrome is an idiosyncratic reaction to mercury involving edema and albuminuria. Studies of workers exposed to elemental mercury do not demonstrate consistent changes in renal function. Some, but not all, studies of mercury workers suggest that chronic elemental mercury exposure can cause reversible tubular dysfunction in active workers. A study of 53 miners (33 active and 20 retired) from the Idrija Mercury Mine demonstrated a statistically significant correlation between urinary α_1-microglobulin and the mean integrated exposure intensity in active workers.[165] The mean annual time–weighted mercury exposure was 0.29 mg/m^3, the mean integrated exposure intensity

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was 1413 mg/m^3/hours, and the average urine mercury concentration in miners was 68.24 μg/L. There was no similar correlation between measures of chronic mercury exposure and other measures of renal tubular function (*N*-acetyl-β-D-glucosaminidase) or glomerular function (urinary albumin, IgG). Measures of renal tubular and glomerular functions did not correlate with estimates of elemental mercury exposure in retired workers. Other studies have not demonstrated statistically significant differences in urinary measures of renal tubular and glomerular function of chloralkali workers chronically exposed to mercury vapor.[166,167] A cross-sectional study of 49 chloralkali workers with previous exposure to mercury vapor did not demonstrate any statistically significant differences in biomarkers of kidney function when compared with 49 age-matched referents.[168] These biomarkers included serum creatinine, urine albumin, urine alkaline phosphatase, urine *N*-acetyl-β-D-glucosaminidase, and serum anti-glomerular basement membrane. The mercury exposure of the chloralkali workers ceased a mean of 4.8 years (range, 4–25.4 years) prior to the study.

Reproductive Abnormalities

Currently, there is little evidence that elemental mercury produces reproductive or developmental effects at concentrations present in the current work environment or the general population. A pregnant woman in her third trimester developed elemental mercury toxicity following exposure to mercury vapors during the heating of mercury-gold amalgam.[169] She delivered a healthy infant without clinical signs of Hg toxicity 26 days after exposure. The blood mercury concentrations were similar in mother and infant (36 ng/mL and 34 ng/mL, respectively). A Swedish study of 8,157 infants born of dentists, dental assistants, or dental technicians suggests that there is no effect on spontaneous abortion rates, perinatal survival, or birth weight distribution that could be explained by occupational exposure in dentistry work.[170]

Carcinogenesis

Neither the International Agency for Research on Cancer (IARC) nor the US National Toxicology Program (NTP) lists elemental mercury as a potential human carcinogen.

DIAGNOSTIC TESTING

SI Conversion Units

1 μg/L = 4.985 nmol/L
1 μmol/L = 200.6 μg/L
1 μg/g creatinine = 0.5638 μmol/mol creatinine
1 μmol/mol creatinine = 1.773 μg/g creatinine
1 ppm = 8.204 mg/m^3
1 mg/m^3 = 0.1219 ppm

Analytical Method

Most techniques for the determination of mercury concentrations utilize atomic absorption spectrometry (AAS), atomic fluorescence spectrometry (AFS), or neutron activation analysis (NAA). During analysis with these methods, the mercury in the sample is reduced to elemental mercury, resulting in the measurement of total mercury. The most common method of analyzing blood and urine for mercury content involves cold vapor AAS after digestion of the samples with acids and the reduction of bivalent inorganic mercury to mercury vapor with stannous chloride. The possibility of contamination by natural mercury compounds exists at all phases of sample preparation; elemental mercury is relatively volatile, resulting in the potential loss of mercury during sample preparation and analysis. NAA is the most sensitive method of detecting Hg; this method is usually considered the reference standard. Atomic absorption spectrophotometry with the cold vapor technique is a relatively sensitive (0.5 ppb in 1-g sample), precise (<10% relative standard deviation) procedure for the detection of mercury in body fluids.[171,172] Simple, rapid techniques involving acid pressure decomposition followed by flameless atomic absorption spectrophotometry can detect mercury at 1 ng/mL.[173] Extensive mercury losses can occur from aqueous solutions of mercury compounds during storage.[174]

The preferred collection container is a Vacutainer-style evacuated blood collection tube for trace elements (royal blue-top) containing EDTA anticoagulant. Most analyses from routine EDTA tubes are usually adequate if the specimen is analyzed within 2–3 days of collection. If standard Vacutainer® are used, additional blank tubes should be sent to the laboratory to confirm the absence of mercury contamination. Blood specimens that contain visible clots do not provide an adequate sample for analysis of whole blood mercury.

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Substantial inter-individual and intra-individual variation in the urine mercury concentration occurs. Measures that help reduce this variability include correction of the sample for specific gravity or creatinine, collection of the sample at the same period during the workweek, and procurement of the samples during direct exposure following a time period sufficient to reach steady state.[175] Accurate measurement of urine mercury concentrations requires the collection of urine samples in glass or plastic containers that do not contain mercury (e.g., acid-washed). Urine samples should contain creatinine concentrations between 30 and 300 mg/dL.

Biomarkers

Inhalation of elemental mercury usually affects the lungs and central nervous system, whereas the kidney and central nervous system are critical organs for inorganic mercury in humans. In an analysis of kidney cortex biopsies, 24-hour urine collections, and blood samples from 109 living kidney donors, the total mercury concentrations in the kidney and creatinine-adjusted 24-hour urine collections were strongly correlated (Pearson correlation coefficient, $r_P = 0.80$, $P = < 0.001$) and approximately linear. The correlation with whole blood mercury was weaker ($r_P = 0.29$, $P = 0.002$).[176] The mean kidney/24-hour urine ratio was 0.22 compared with 0.19 for whole blood Hg. The mean 24-hour creatinine-adjusted mercury excretion was higher in women (1.9 μg/g creatinine) than men (1.4 μg/g creatinine).

Blood

Total mercury in whole blood is the sum of inorganic mercury (primarily elemental mercury vapor) and organic mercury (primarily methylmercury from fish). Elemental mercury does not persist in the blood as a result of the rapid oxidation of elemental mercury to inorganic mercury (Hg^{2+}) in red blood cells.[177] Although total mercury concentration in whole blood is the best biomarker of recent (i.e., within several days) Hg exposure,[178] total whole blood Hg concentrations reflect primarily methylmercury because whole blood contains primarily methylmercury (i.e., >80%). The vast majority of the methylmercury resides in erythrocytes; therefore, plasma and serum Hg concentrations primarily reflect exposure to inorganic Hg species including Hg^0. Although whole blood Hg concentrations increase in the first day after DMPS administration, the increase is not a reliable diagnostic biomarker to assess total mercury body burden or distinguish patients with and without symptoms attributable to dental amalgam.[179]

General Population

The main mercury sources for the general population are elemental mercury vapor (atmosphere, dental amalgam) and methylmercury in the diet, particularly fish. The mean total mercury concentration in whole blood of 51 asymptomatic Norwegian referents was 5.66 μg/L (range, 3–12.8 μg/L) with elemental/inorganic and organic mercury accounting for ~20% and ~80% of the total mean mercury concentration, respectively.[180] In a French study of 106 hospital staff volunteers, the mean total whole blood Hg concentration was 5.8 μg/L (median, 1.72 μg/L, 95% CI: 0.59–5.12 μg/L) as measured by inductive coupled plasma/mass spectrometry.[181] The corresponding mean plasma Hg concentration was 2.69 μg/L (median, 0.36 μg/L, 95% CI: 0.09–1.01 μg/L). In a study of 1,127 male US military personnel (mean = ~53 years), the mean whole blood concentration of *organic* mercury was 2.01 ± 2.69 μg/L compared with 0.54 ± 0.48 μg/L for *inorganic* mercury as measured by cold vapor AAS.[182] The average number of amalgam surfaces in the subjects was ~20 surfaces (range, 0–66 surfaces).

Toxicity

Subperitoneal deposition of elemental mercury resulting from the breakage of a rectal thermometer in a 10-month-old infant was confirmed by radiographic imaging; a surgical attempt to remove the mercury was unsuccessful.[183] The serum Hg concentration was 23.4 μg/L. Prior to dimercaprol chelation, the serum Hg concentration in a 40-year-old woman 6 days after smelting silver-mercury amalgam was 127 μg/L; she died of acute respiratory failure 21 days after exposure.[45]

Postmortem

Four adults attempted removal of silver from a silver-mercury amalgam by heating the mixture in a small smelter at the home of a family member.[45] All four died of acute respiratory failure despite intensive supportive care and dimercaprol chelation. The postmortem serum Hg concentration in the 88-year-old woman (survival, 15 days) was 212 μg/L, whereas the postmortem serum from the 69-year-old man (survival, 11 days) was 368 μg/L.

Urine

Analysis of urine mercury concentrations is a simple, rapid test for identifying patients with excessive exposure to elemental and inorganic mercury. Total mercury concentrations in urine probably reflect mercury accumulation in the kidneys, which accounts for ~80% of the body burden. Corrections of spot samples throughout

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a 24-hour period include adjustment for creatinine, osmolality, and specific gravity. Correction for creatinine is slightly more effective than other corrections to estimate 24-hour urine Hg excretion from spot urine samples; however, individual corrected Hg values may still vary 6-fold.[184]

The administration of chelating agents (e.g., DMSA, DMPS) produces a relative transient increase in urinary and blood mercury excretion above baseline levels that is not related to previous mercury exposure, specific symptoms, or clinical toxicity, probably as a result of the limited Hg bioaccumulation. The kidney excretes almost all absorbed Hg^0 in the urine.[84] Consequently, urine DMSA or DMPS chelation challenge tests are not useful biomarkers of past mercury exposure.[185,186] Collection of urine samples in close proximity to chelating agents (i.e., <24 hours) increases the excretion of various metals including essential metals (e.g., Cu, Zn) necessary for normal human function. Additionally, most of the metal excretion occurs soon after chelator administration (i.e., <6 hours), whereas creatinine excretion remains stable over 24 hours. The maximum DMSA-induced excretion of mercury occurs ~2 hours after DSMA administration.[35] Furthermore, standard reference ranges obtained from the general population are inappropriate to interpret the significance of post-provocation urine mercury concentrations; hence, there are no normal reference ranges for provoked urine metal concentrations in healthy asymptomatic individuals.[187] Consistent with recommendations by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control and Prevention (CDC),[188] the American College of Medical Toxicology recommends against the use of post-challenge urinary metal testing in clinical practice or the use of challenge tests as an indication for further chelation based on: 1) lack of scientific validation with the absence of well-documented reference ranges and unpredictable exposure-response relationship;[189] 2) no demonstrated benefit; and 3) potential harm (e.g., chelation of essential metals, hypersensitivity, misdiagnosis).[190,191]

General Population

The elimination half-life ranges from ~40–60 days after short-term exposure and about 90 days after long-term exposure.[99,192] Baseline total urine mercury concentrations in subjects with no unusual exposure to mercury range from 1–25 μg/L with the vast majority of the urine concentrations <5–10 μg/L. The mean total urinary Hg in 1,642 Tokyo children without specific sources of Hg exposure was 1.9 μg/L (1.9 μg/g creatinine) for boys and 2.1 μg/L (2.0 μg/g creatinine) for girls.[193] In a study of 130 Japanese men, the mean total mercury concentration in urine samples was 2.33 ± 1.5 μg/L (1.51 ± 0.68 μg/g creatinine) with a range of 0.27–10.26 μg/L (0.39–4.21 μg/g creatinine).[194] Inorganic mercury accounts for almost all of the Hg in urine samples.[195]

The amount of dental amalgam (i.e., amalgam surfaces) correlates weakly but positively to total urine mercury concentrations. In a study of a US military population, the urine mercury concentration increased by ~1 μg/L for every 10 surfaces of amalgam.[182] The number of dental amalgam fillings explained <1.5% of the total variance of urinary Hg in the Japanese study of 1,642 children.[193] The filling of cavities with dental amalgam produces a small, transient increase in the renal excretion of mercury. In a study of 43 children receiving dental amalgam, the urinary mercury concentrations before and 9–12 days after an amalgam filling were 3.38 ± 2.45 μg/L and 5.14 ± 3.14 μg/L, respectively.[196]

Toxicity

Urine mercury concentrations document mercury exposure; however, these values do not correlate well to specific symptoms of mercury toxicity. After intravenous injection of mercury, urine total mercury concentrations were elevated (600–1,050 μg/L).[123] A subperitoneal mercury deposit could not be surgically removed from a 10-month-old infant. The random urine mercury concentration 5 days after the incident was 21.8 μg/L. The urine mercury concentration did not change immediately after surgery; by 10 months post-incident, the random urine mercury concentration was 8.4 μg/L (reference <10 μg/L). The child remained asymptomatic despite the presence of residual mercury on CT imaging. Unprovoked urine mercury concentrations below 20 μg/L are usually not associated with adverse health effects.[14]

Hair

Potential external contamination and sorption limit the usefulness of hair analysis to determine past inorganic Hg exposures in occupational settings, particularly in the presence of ambient air containing elemental Hg vapor (e.g., chloralkali plants, small-scale artisanal mining operations). Other factors complicating the use of hair analysis include the effects of age, gender, hair color, and permanent hair treatments on the Hg concentration in hair. Elemental mercury concentrations in hair probably are not robust markers of dietary exposures to elemental Hg.[197] A 10-year follow-up study analyzed the mercury concentrations in the hair of residents living near a hazardous-waste-treatment plant.[198] The study detected a slight increase in the median mercury

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concentration in hair with mercury emissions from the plant occasionally exceeding 50 μg/m^3; however, the minimal increase in the mercury concentrations was not associated with a significant health risk. In a study of 20 dental students exposed to elemental mercury vapor during a 6-week operating dental course, Hg concentrations were analyzed in hair, erythrocytes, plasma, and urine at baseline, the end of the 6-week exposure, and 3 months after the exposure ceased. At baseline, hair mercury concentrations correlated moderately with erythrocyte Hg (Spearman's rank order correlation coefficient, r = 0.686) and slightly with monthly fish consumption (r = 0.448). Erythrocyte, plasma, and urine Hg concentrations did not correlate to hair Hg at the end of the 6-week course. After 3 months, only the erythrocyte Hg concentration had a slight correlation to the hair Hg concentration (r = 0.492).

Abnormalities

Following intravenous administration of elemental mercury, case reports associate a restrictive pattern and normal FEV_1/FVC with the presence of Hg emboli on X-ray.[200] A ventilation/perfusion scan in this patient demonstrated ventilation/perfusion deficits.

Imaging

Following the intravenous injection of elemental mercury, the chest radiograph may exhibit multiple, fine, radiodense, spherical particles in the lungs and a pooled elemental density in the right ventricle by echocardiography.[2] Despite the striking radiographic appearance, embolization of mercury in the lung does not typically produce significant vascular obstruction based on angiography. Pelvic and abdominal X-rays may indicate mercury in the paraspinal and pelvic areas in addition to the injection site. Radionuclide V/Q imagery differentiates the accidental intra-bronchial aspiration of the ruptured, mercury-filled intestinal tube from pulmonary arterial mercury emboli. Embolized mercury can coalesce and pool in the lumen of the apex of the right ventricle, whereas extravasated mercury at the venipuncture site in the extremities suggests embolization. The presence of small metallic beads in the colon suggests the ingestion of elemental mercury.

Neuropsychological Testing

Potential tests for chronic, symptomatic elemental mercury exposure include neuropsychological testing, peripheral nerve conduction, and measures of renal function (e.g., serum creatinine, glomerular filtration rate, lysosome enzymes). The results of these tests are not specific to mercury toxicity; the results must be interpreted in relation to the history and physical examination. Separation of the effects of elemental and inorganic mercury on neuropsychological test scores is complicated by: 1) the tendency to include exposures of elemental Hg and inorganic Hg together in epidemiology studies, 2) relatively small sample sizes, and 3) the intracellular conversion of elemental mercury to inorganic mercury.

A meta-analysis of 12 studies (1980–1999) involving 14 neuropsychological tests with 20 different tasks suggested the possibility of adverse effects on memory, attention, construction, and motor performance following inorganic Hg exposure producing urine mercury concentrations of <100 μg/g creatinine (mean = 32 ± 37 μg/g creatinine).[201] However, the lack of a clear dose-response relationship for specific tests and the lack of premorbid data limit conclusions regarding causation. A meta-analysis of 36 peer-reviewed studies of neuropsychological testing in workers exposed to mercury (elemental, inorganic) indicated that the prevalence of neuropsychological deficits following chronic occupational Hg exposure is small (weighted study-mean effect size = −0.23, $P < 0.0001$); consequently, these effects (i.e., mean shift of ¼ standard deviation) are difficult to detect on an individual basis.[202] The largest impairment occurred in psychomotor skills, whereas occupational mercury exposure had the smallest effect on verbal comprehension. These studies did not include occupational exposure to organic mercury.

A cross-sectional study of former chloralkali workers with past exposure to mercury vapor suggested that slight persistent neurological effects, mainly involving motor function and attention, may result from chronic exposure to mercury vapor when compared with unexposed, age-matched controls.[203] Neuropsychological testing demonstrated statistically significant differences between these two groups for scores on simple reaction time, grooved pegboard, and the Benton visual retention test. There were no significant differences in scores for measures of memory and learning, hand-eye coordination, hand steadiness, visuospatial ability, and perceptuomotor speed.

Neuropsychological testing during an epidemiological study of dentists indicated that early, subclinical changes may include motor speed (finger tapping), visual scanning (Trail making A), visuomotor coordination and concentration (digit symbol), and visual

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reproduction.[204] Two adolescent siblings developed behavioral problems, irritability, declining school performance, tremor, rash, headache, sleep disturbances, paresthesias, and anorexia, after an accidental 3-month exposure to excessive mercury vapors (50–400 μg/m^3) from an unsuspected mercury spill in their home.[205] Both adolescents received chelation with DMSA. Repeat neuropsychological testing 1 year after chelation demonstrated persistent deficits in visuoperceptual and constructional skills (Block Design), conceptual abstraction, and nonverbal memory (Rey-Osterrieth Complex Figure). Full-scale IQ during this testing was consistent with premorbid testing for both children. Specific comparisons between pre- and postexposure domains were not reported. The 15-year-old boy repeated the first and sixth grades; the 13-year-old half-sister repeated the first grade and required reading assistance.

HEALTH SURVEILLANCE

Risk Assessment

The ATSDR established a minimal risk level (MRL) of 0.2 μg/m^3 for chronic-duration inhalation exposure (i.e., ≥365 days) to elemental mercury vapor based on hand tremor measurements in a study of 26 mercury vapor-exposed workers from 3 industries (fluorescent tube factories, chloralkali plant, acetaldehyde production) and 25 unexposed controls (same factories without Hg exposure).[149] The mean duration of Hg exposure for the workers was 15.3 years (range, 1–41 years). The mean total urinary Hg concentrations in the exposure workers and controls were 19.2 ± 2.0 μg/g creatinine and 5.8 ± 1.2 μg/g creatinine, respectively. The US EPA has not derived an RfD value for elemental mercury. The EPA inhalation reference concentration (RfC) for elemental mercury is 3×10^{-4} mg/m^3 based on an LOAEL of 25 μg/g from adverse effects (hand tremors, ↓ memory testing, slight autonomic dysfunction) detected in epidemiology studies of exposure workers.

Environmental Monitoring

Table 20.2 lists the guidelines and regulations for exposure to mercury vapor (primarily elemental mercury). The US OSHA PEL–TWA for mercury vapor was 50 μg/m^3 with a skin notation; however, the 11th Circuit Court of Appeals vacated the regulation in 1992. These exposure levels were promulgated in 1989 to prevent systemic toxicity including subclinical neuropathies.[206] A study of chloralkali workers exposed to mercury vapors did not detect clinical evidence of chronic mercury toxicity at ambient air Hg concentrations of <100 μg/m^3.[22] The ACGIH recommends the same limit as the previous OSHA limit for mercury vapor exposure. NIOSH has established a Hg concentration immediately dangerous to life or health (IDLH) of 10,000 μg/m^3. Currently, there are few data to indicate the presence of elementary mercury concentrations in the current work environment sufficient to cause reproductive abnormalities, especially in males. For residential settings, the ATSDR guidelines recommend mercury concentration of <1 μg/m^3 in air samples following decontamination of mercury spills and the isolation of areas with airborne mercury concentrations exceeding 10 μg/m^3.

TABLE 20.2. Mercury vapor guidelines and regulations.

Exposure Limit	Value
OSHA	
PEL–TWA[a] (8-hour)	None
PEL-Ceiling	100 μg/m^3
NIOSH	
REL–TWA (10-hour)[b]	50 μg/m^3
IDLH	10,000 μg/m^3 (as total Hg)
ACGIH	
TLV–TWA (8-hour)[b]	25 μg/m^3 (as Hg)
US FDA	
Bottled water allowable limit	2 μg/L
US EPA	
RfC (chronic inhalation exposure)	0.3 μg/m^3
EPA carcinogenic unit risk (daily)	None
MCL	2 μg/L
ATSDR	
MRL (chronic inhalation exposure, ≥365 days)	0.2 μg/m^3

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; IDLH = immediately dangerous to life and health; MCL = maximum contaminate level; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time–weighted average; US EPA = US Environmental Protection Agency; US FDA = US Food and Drug Administration.
[a] Vacated by court order; [b]Skin notation.

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Biological Monitoring

Urine

Elemental mercury (Hg^0) rapidly crosses the alveolar membranes, resulting in the oxidation of elemental mercury to inorganic mercury (Hg^{2+}) in red blood cells; consequently, little elemental mercury (Hg^0) exists in the blood. In a study of workers from a thermometer manufacturing plant exposed to average ambient air mercury concentrations exceeding 100 μg/m^3, the urinary Hg^0 concentrations in urine samples from these workers ranged from 0.05–1.7 μg/L.[207] Elemental mercury accounted for <1% of the inorganic mercury present in the urine samples. Most occupational studies use total urine Hg concentrations as the biomarker of Hg exposure because peak urine mercury concentrations occur about 2–3 weeks after an acute exposure; urinary Hg elimination half-lives for short-term and long-term exposures are ~40–60 days and 90 days, respectively.[96]

In a study of chloralkali workers without kidney damage, the biological half-life of mercury in urine following mercury vapor exposure was ~3 months (mean = 90 days; range, 69–108 days).[208] In a study of 119 chloralkali workers retired at least 1 year before the examination, the 24-hour urine mercury concentration did not correlate to historical measures of mercury exposure.[185] The mean Hg excreted in the 24-hour urine samples was 4.3 μg. These studies suggest that after discontinuation of mercury vapor exposure, the urine mercury concentration reflects the amount of mercury stored in the kidney.

The ratio between mercury in air (μg/m^3) and mercury in urine (μg/L) ranges from 1:1–1:1.22. Recent data using personal samplers suggests that this ratio is closer to 1:1. Roels et al.[209] found a ratio of 1 μg/m^3 in air to 1.22 μg/g creatinine, whereas Lindstedt et al. reported a ratio of 1 μg/m^3 in air to 1.16 μg/L.[210] Although mercury concentrations in air and urine samples are correlated below 50 μg/m^3, urinary mercury is not an accurate measure of environmental exposures below 10 μg/m^3 because of the interference of other sources (fish, dental amalgam).[211]

Total Mercury

The process of mining and the heat extraction of gold from amalgam (gold-mercury alloy) during small-scale (artisanal) mining operations expose miners and smelters to elemental mercury vapor.[212] Typically, mercury exposure increases in the following order: residents, miners, millers, smelters, and refiners; however, individual mercury exposure varies between studies depending on extraction methods and work practices including the use of protective devices.[213] Analysis of convenience urine samples from two groups of Indonesian miners (i.e., panning) demonstrated median total mercury concentrations of 5.33 μg/L (n = 30; range, 0.60–788 μg/L) and 7.80 μg/L (n = 17; range, 0.79–57.6 μg/L) as measured by cold vapor/atomic absorption spectrometry.[214] For workers involved with smelting and vaporizing the mercury-containing amalgam, the median total mercury concentration in urine samples was 10.24 μg/L (n = 69; range, 0.43–5,249 μg/L) and 22.40 μg/L (n = 60; range, 0.72–564 μg/L).[215] After correction for creatinine, the median total mercury concentration in these samples ranged from 3.55–10.24 μg/g creatinine. The median total mercury concentration in urine samples from the local control group was 0.73 μg/L (n = 21; range, 0.10–3.16 μg/L). Approximately 24–43% of miners had signs of chronic mercury intoxication compared with 55–62% of the smelter workers.

The impact of occupational Hg exposure on dental personnel depends on several factors including local conditions, the number of amalgams restored, and the amount of Hg in the amalgam. On average, the urine mercury concentration following mercury exposure in dental personnel is similar to the mercury concentration of a person with 19 amalgam surfaces.[216] In general, the urine mercury concentrations of dentists correlate to the number of hours of practice/week and the number of amalgam restorations per week. In a cohort of dentists and dental nurses in Stockholm, the mean urine mercury concentration was ~3.5 μg/L compared with 0.5 μg/L in a control sample of an amalgam-free population with no occupational exposure to mercury.[217] In a study of dentists, the mean urinary mercury concentration was 14.2 μg/L urine with ~1.3% of these dentists having urine mercury concentrations exceeding 100 μg/L.[10] In a study of 234 university staff and students exposed to elemental mercury vapor during laboratory experiments (geometric mean = 1.61 μg Hg/g creatinine; range, 0.30–9.31 μg Hg/g Cr), multiple regression analyses did not detect a correlation between urinary Hg concentration and the number of amalgam fillings or surface area of these fillings in the workers and students.[218]

Effects

Central Nervous System The urinary mercury concentration following occupational exposure to mercury is ~2 orders of magnitude higher than the mercury concentration in urine from subjects with dental amalgams.[219] The presence of urine mercury concentrations of >500–850 μg Hg/L in workers was associated with the development of reversible polyneuropathies manifested by tremors, unsteadiness, and poor coordination.[153] Early neurological symptoms may appear at urine

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mercury concentrations of >150 μg/L. More recent data focus on subclinical effects on renal function and neuropsychological tests.

Kidney Clinical evidence of renal dysfunction is less common following exposure to elemental mercury vapor compared with inorganic mercury exposure. Increased urinary excretion of high-molecular-weight proteins and lysosomal enzymes may occur following exposure to elemental mercury that yields urine mercury concentrations of >50–60 μg Hg/L.[220] No glomerular or tubular dysfunction was detected in chloralkali workers exposed to elemental mercury vapor at concentrations producing urine mercury concentrations near 25 μg/L.[221]

Biological Exposure Indices

Occupational studies suggest a correlation between the intensity of recent Hg vapor exposure and total urine Hg concentrations following at least 1 year of exposure; a latent period is necessary while the body accumulates Hg, primarily in the kidney.[222] Clinical signs of acute Hg poisoning usually do not appear at urine Hg concentrations of <300 μg/L,[153] whereas some studies indicate increased prevalence of neuropsychological symptoms, tremor, and increased urinary *N*-acetyl-β-D-glucosaminidase, concentrations following urinary Hg concentrations of <100 μg/L.[155] Urine Hg concentrations are the preferred measure for long-term, integrated mercury vapor exposure. Recommendations for biological exposure indices following chronic mercury vapor exposure range from 20 μg/g creatinine in pre-shift urine based on adverse, subclinical renal and neuropsychological effects (ACGIH)[223] to 50 μg/g creatinine.[105,224] Urine Hg concentrations exceeding 100 μg/g creatinine indicate the need to remove the worker from Hg exposure; this value suggests the Hg vapor concentration in ambient air exceeds 80 μg/m^3.[222] Because of the large inter- and intraindividual variation in urine mercury concentrations, decisions regarding workers should be based on an average of several measurements rather than a single value. The creatinine adjustment method is the most sensitive method of reducing variation in the content of urine mercury samples used for biological monitoring. The steady-state urinary Hg concentration does not change significantly over the weekend in chronically exposed workers.

Blood

Concentrations

Occupational exposure to elemental mercury occurs primarily in the chloralkali industry, the manufacture of thermometers and fluorescent light tubes, and dental services. Elemental mercury (Hg^0) rapidly crosses the alveolar membranes; oxidation of elemental mercury to inorganic mercury (Hg^{2+}) occurs rapidly in red blood cells. Consequently, the Hg^0 concentration in plasma, serum, and whole blood is relatively small. In end-of-shift blood samples drawn from thermometer manufacturing workers exposed to elemental mercury vapors, the Hg^0 concentration in whole blood ranged from non-detectable to 0.22 μg/L compared with inorganic mercury concentrations of 22–230 μg/L.[177] A study of 42 chemical workers exposed to elemental mercury vapor revealed a rough correlation between the ambient air concentration of mercury (100 μg/m^3) and the whole blood mercury concentration up to 50 μg/L, but not with symptoms.[225] Whole blood mercury concentrations in chloralkali workers ranged from a mean of 11 μg/L (range, 3–60 μg/L) in Swedish workers[226] to a mean of 28.5 μg/L in Taiwanese workers.[227]

Effects

In a study comparing 89 chloralkali workers with 75 unexposed chemical workers matched for age, education, and verbal comprehension, the median whole blood mercury concentrations were 11 μg/L (3–60 μg/L) and 3 μg/L (range, 0.2–13 μg/L), respectively.[228] Although the exposed group had increased somatic complaints (tiredness, confusion), there were no statistically significant differences between groups for scores on hand-eye coordination, finger tapping, simple reaction time, symbol-digit, or digit span. Analysis of these studies indicates that smoking and alcohol consumption do not alter blood mercury concentrations. A study of 42 chemical workers exposed to elemental mercury vapor did not detect a correlation between total whole blood mercury concentrations up to 50 μg/L and neuropsychological symptoms.[225]

Biological Exposure Indices

The intensity of *recent* Hg vapor exposure correlates to the whole blood mercury concentration at the end of a work shift;[208] the urine Hg concentration is less responsive to recent Hg vapor exposure than whole blood concentrations. Several factors limit the usefulness of whole blood Hg concentrations as a BEI including the rapid initial elimination half-life of mercury in the blood (i.e., ~2–4 days)[99] and the influence of methylmercury in the diet on the total whole blood Hg concentration.

Medical Monitoring

Preemployment physical examinations should focus on the documentation of baseline renal and central

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nervous system function including a urinalysis. Subsequent examinations should emphasize the detection of signs and symptoms of central nervous system dysfunction (personality changes, tremors, gait disturbances, insomnia, weight loss, ataxia).

TREATMENT

Decontamination

Medical

Accidental elemental mercury ingestion is usually nontoxic; therefore, gastrointestinal decontamination measures are unnecessary. If technically feasible, local foci of elemental mercury remaining after the parenteral injection may require excision to avoid a reservoir for continued slow Hg absorption into the blood, depending on the location of the mercury.[2]

Environmental

Procedures for mercury cleanup depend on the amount of mercury spilled and the type of surface. Mercury-containing clinical thermometers are silver, whereas red thermometers contain dibutyl phthalate. The decontamination of mercury spilled from a broken thermometer can usually be accomplished in the home without professional help. Collection of the mercury on nonporous surfaces (e.g., kitchen counters, linoleum floors) requires the use of stiff paper (e.g., index cards) to gather the mercury into glass jars or zip-lock plastic bags. Neither vacuum cleaners nor brooms should be used to collect the mercury; gold jewelry should be removed prior to the cleanup.[229] Heat increases mercury volatility; therefore, heaters and house ventilation should be turned off prior to cleanup. The mercury should be discarded through the local hazardous waste program. Additional ventilation for several days in the area of the spill is desirable to reduce ambient mercury levels.

Larger spills of mercury or spills of mercury on porous surfaces (e.g., furniture, carpet, unfinished wood) may require special equipment/expertise to avoid the formation of toxic Hg concentrations including the creation of an insoluble compound (i.e., solidifying mercury with sulfide powder to form mercuric sulfide) or amalgamation (i.e., mixing with one or more metals to form a solid). The skin absorbs elemental mercury; therefore, dermal contact with elemental mercury should be minimized. The local health department or private consultants are resources for decontamination measures. The US EPA recommends that the ambient air Hg concentration should be reduced to $<1\ \mu g/m^3$.

Antidotes

Animal studies indicate current chelating agents do not efficiently remove elemental mercury from the brain but may reduce the renal accumulation of elemental mercury.[230] The chelating agent of choice for symptomatic chronic Hg^0 toxicity is probably DMPS; however, data on efficacy are very limited with existing data suggesting efficacy decreases with increasing time since exposure. BAL is an option in acute mercury vapor intoxication if administered soon after exposure. Clinical data on the efficacy of DMSA are weak. Rodent studies indicate most chelators do not cross the blood–brain barrier or remove metals directly from brain tissue.[231]

DMPS

2,3-Dimercaptopropane-1-sulfonate (DMPS) is an investigational oral analog of BAL that may be less toxic than DMSA; however, there is limited availability of this drug in the United States because this chelating agent is not approved by the US FDA for Hg or Pb poisoning. American pharmacies can compound DMPS (usual daily dose, 3–10 mg/kg body weight).[232] The typical oral adult dose is up to 300 mg three times daily for 7 weeks. DMPS may be administered intravenously in 0.9% saline with reported doses in severe poisoning of 250 mg q4h for the first 48 hours, 250 mg q6h for the next 48 hours, and then 250 mg q8h. Duration of treatment depends on clinical improvement, blood/urinary Hg concentrations, and the ability to switch to oral therapy. Adverse effects of DMPS include back pain, nausea, rash, and leukopenia. Essential minerals (Cu, Mg, Se, Zn) should be monitored; replacement of these essential metals may be necessary.[233]

There are inadequate clinical data to determine the effect of DMPS on the clinical outcome of elemental mercury poisoning; however, several case reports suggest improved outcomes following DMPS chelation after Hg^0 exposure. The urinary excretion half-life of mercury decreased from an average of 33.1 to 11.2 days in 2 workers with elevated mercury concentrations after an excessive elemental mercury vapor exposure.[234] The initial 24-hour Hg excretion of both workers exceeded 500 μg; the symptomatic worker was significantly improved after his course of chelation. A 36-year-old jewelry producer developed tremors, slurred speech, headaches, and poor coordination after chronic exposure to mercury vapors (blood Hg = 116 μg/L).[235] Three 5-day courses of 30 mg DMPS/kg/d in three divided doses over 9 weeks were associated with substantial improvement in speech and tremor; total urinary excretion of Hg during this period was about 49 mg. Although

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oral DMPS (1,200 mg on day 1, followed by 200 mg bid from day 2 on) initially increased urinary Hg excretion after the intentional injection of elemental Hg, the renal elimination of mercury was extremely small compared with the total Hg^0 dose.[236]

Dimercaprol (BAL)

Although BAL removes inorganic mercury from the kidney during severe acute inorganic mercury poisoning, the use of BAL for elemental mercury exposure is questionable. The administration of dimercaprol (BAL) is an option in severe, acute elemental mercury poisoning depending on clinical judgment of the potential risks and benefits;[237] however, there are no clinical data to confirm the effectiveness of chelation therapy in improving the toxic effects of elemental mercury. Some,[238,239] but not all,[240] rodent studies suggest BAL may redistribute mercury to the heart, lung, and brain when administered 24 hours after exposure. Case reports document the survival of patients after severe, acute elemental mercury poisoning without chelation.[23] The effectiveness of BAL decreases with time since acute exposure, particularly when initiated more than a few months after acute exposure.

DMSA (Succimer®)

DMSA (meso 2,3-dimercaptosuccinic acid) is a water-soluble analog of BAL. The advantages of DMSA compared with BAL include oral administration and mild adverse effect profile (e.g., nausea, vomiting, diarrhea, flatus, transient elevation of serum hepatic aminotransferases). Although DMSA is a potential chelating agent for mercury, this drug has not been officially approved for the treatment of mercury intoxication. Current data supporting the use of DMSA for the treatment of toxicity related to mercury vapor exposure are weak. A review of the medical literature recommended the use of DMPS rather than DMSA in elemental mercury toxicity based on experimental[241] and limited human data.[242] In studies of chloralkali workers given DMPS[243] and DMSA,[208] the increased urinary mercury excretion was not clinically significant when administered more than several months after the cessation of mercury exposure.

Case reports indicate that DMSA is a safe chelating agent that reduces the plasma mercury elimination half-life and increases the urinary excretion of mercury 2- to 3-fold following acute mercury toxicity.[244] Peak Hg urinary excretion occurs about 2–4 hours after the administration of DMSA;[245] however, at the present time, there is insufficient evidence that chelation therapy improves clinical outcomes, particularly when initiated more than a few months after cessation of mercury exposure. In studies of chloralkali workers given DMPS[243] and DMSA,[208] the increased urinary mercury excretion was not clinically significant when administered more than several months after the cessation of mercury exposure. A group of chloralkali workers developed a wide range of symptoms (e.g., fatigue, weakness, headache, irritability, anxiety, sleep changes, congestion, tremor, diarrhea) following exposure to mercury vapor lasting up to 16 hours.[246] Chelation of a sub-cohort of the workers with the highest mercury concentrations using DMSA (30 mg/kg every 8 hours) resulted in a ~3-fold increase in urine mercury excretion; however, the mercury excreted represented a small fraction of the total Hg dose. Chelation of these workers demonstrated no clear benefit. Similarly, the administration of a 5-day oral course of DMPS (200 mg q8h) followed by a 3-day rest period and then a 5-day oral course of DMSA (500 mg daily divided into three doses) eliminated negligible mercury from the injection of 1.5 mL Hg^0 by a 27-year-old man.[247] The total amounts of mercury excreted in the urine over the two 5-day courses were 8 mg and 3 mg, respectively. Animal studies indicate DMSA removes mercury from the kidney but does not efficiently reduce mercury content in the brain following inhalation exposure to elemental mercury vapor.[248] Rodent studies indicate the use of chelation with DMSA 1 week after exposure to elemental mercury vapors does not reduce mercury concentrations in the brain.[231]

Observation studies of patients with symptoms they attribute to dental amalgams do not provide strong scientific support for the administration of chelating agents (DMSA, DMPS) to alleviate self-related symptoms or assess Hg body burden.[249] Twenty subjects complaining of a variety of symptoms related to their dental amalgams received either a placebo or 20 mg DMSA/kg/day for 14 days.[250] Their symptoms and mood states were evaluated during the study and at a 3-month follow-up. Although DMSA treatment resulted in an average 65% increased urinary Hg excretion, and a 0.04 µg/L/day decreased blood Hg concentration, no dose-response related change occurred in subjective symptoms or mood state at the 3-month checkup. Urinary Hg excretion returned to baseline. A double-blind, randomized placebo-controlled trial involving 50 consecutive patients with self-diagnosed environmental illnesses related to dental amalgams demonstrated improvement in symptoms following enrollment in the trial.[251] Although symptoms decreased in the DMSA-treatment group, there was no statistical difference in the clinical response between the treatment and

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placebo groups. Analysis of the Symptom Check List revealed overall distress, somatization, depression, anxiety, and obsessive-compulsive symptoms were above the reference ranges in these patients at baseline.

D-Penicillamine and NAP

This oral compound is probably not a useful antidote for mercury vapor toxicity as a result of the adverse effect profile and lack of supportive clinical data. D-Penicillamine chelates copper, zinc, and iron in addition to mercury. The use of penicillamine is contraindicated in penicillin-sensitive patients. *N*-acetyl-D,L-penicillamine (NAP) is an investigational analog of D-penicillamine. Several case reports suggest some clinical improvement after administration of NAP following chronic elemental mercury toxicity;[252,253] however, chelation of 53 construction workers exposed to mercury vapor with NAP and DMSA resulted in the mobilization of a small fraction of the total estimated body mercury.[35]

Supportive Care

Supportive tests based on clinical symptomatology following acute elemental Hg intoxication include a complete blood count with platelets,[254] serum electrolytes, glucose and baseline creatinine, chest X-ray, arterial blood gases, hepatic enzymes, and prothrombin time depending on the amount of Hg^0 ingested. In serious mercury poisoning, electrocardiographic abnormalities (e.g., ST depression, QT prolongation, dysrhythmias) often occur.[255] Data on the benefit of prophylactic appendectomy for retained appendiceal Hg^0 is sparse based on rare case reports; recommendations are conflicting depending on the risk of obstruction and spillage of the Hg^0 into the peritoneal cavity during laparoscopy.[256] Whole bowel lavage and/or endoscopic aspiration often do not remove sufficient amounts of Hg^0. The risk of a subsequent inflammatory reaction producing acute appendicitis is unpredictable and sometimes delayed.[257]

INORGANIC MERCURY

HISTORY

In prehistoric times, cinnabar was a constituent of color drawings on cave walls; early Chinese workers used cinnabar to produce red ink. The transformation of cinnabar (mercuric sulfide, HgS) into a shining metallic fluid fascinated the Chinese Taoists, who believed that cinnabar represented the *One* (i.e., the nuclear energy of yang and yin). The belief in the immortal benefits of cinnabar resulted in the deaths of many Taoists, particularly the Tang emperors, during the early 9th century. Recognition of mercury toxicity predates the birth of Christ. The Romans used only slaves and criminals to mine cinnabar in the notorious Almadén mines in Spain. A number of Greek and Roman authors (e.g., Hippocrates, Pliny, Galen, Discoides, Aetius) considered mercury a toxic substance;[258] however, as early as 500 BC, mercury compounds were recommended drugs for chronic dermatological and infectious illnesses.[4] In Ayurvedic medicine, metal-containing medicines were common because the practitioners believed purified metal did not react adversely with tissues. Derived from cinnabar, *Rasasindura* was used in Ayurveda therapeutics as a metallic herb to treat deafness, insomnia, fever, pneumonia, and syphilis.[259]

Inorganic mercury was the main chemotherapeutic agent for the treatment of syphilis during the 500 years before the introduction of less toxic heavy metals (bismuth, arsenic) in the late 1800s and the advent of penicillin therapy in the 1940s.[3] Paracelsus (Phillipus von Hohenheim, 1493–1541) recommended both elemental mercury vapors and inorganic mercury salts for the treatment of syphilis. Calomel (85% mercurous chloride, Hg_2Cl_2) was the most frequently administered mercury salt. In addition to being used as an anti-syphilitic agent, calomel was a diuretic, teething powder, and cathartic. Mercuric chloride (corrosive sublimate, $HgCl_2$) was a less common form of medicinal mercury that produced local ulcerations on application to skin lesions, resulting in the name corrosive sublimate. Physicians in the 16th century used large doses of mercury to treat syphilis because they believed the diuretic action of mercury was necessary to excrete the "bad humors" from the body. Eventually, the dose of calomel was reduced after physicians realized the therapeutic action of the drug did not require the induction of drastic side effects (e.g., salivation, gingivitis, polyuria). Topical and systemic mercury probably reduced gummas and aided the healing of cutaneous lesions containing spirochetes; however, the use of mercury was not effective for the large numbers of spirochetes in secondary syphilis.

Medicinal and dental uses of inorganic mercury became widespread in the 19th century.[4] President Andrew Jackson's physicians used calomel for a variety of ailments; some authors suggested that President Jackson's tooth loss, renal dysfunction, irritability, mood shifts, and mistrust resulted from lead and mercury

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exposure.[260] Other authors believe his death was probably not due to heavy metal poisoning based on hair sampling;[261] however, the validity of hair sampling for inorganic Hg exposure is equivocal. Mercurous chloride (calomel) was a popular teething powder, anthelmintic, disinfectant, and cathartic during the 19th and early 20th centuries, particularly for children. Some of these children developed acrodynia (Feer syndrome, pink disease, erythredema polyneuropathy), an illness characterized by the insidious onset of anorexia, irritability, insomnia, sweating, and photophobia, followed by the appearance of swelling, paresthesia, and a painful pink, desquamating rash on the extremities. Although Swift first described the clinical features of acrodynia in 1914, the connection between the ingestion of mercurous chloride and acrodynia was not recognized until the late 1940s, in part because of the highly variable course and the occurrence of acrodynia in only a few of the children exposed to mercurous chloride or other mercury compounds (phenylmercury, elemental mercury vapor).[262] Between 1950 and 1953, the General Register Office recorded 174 deaths in children attributed to acrodynia.[263,264] In 1980, three sentinel cases of acrodynia alerted health authorities in Buenos Aires, Argentina, to the exposure of ~12,000 infants to phenylmercuric fungicide-contaminated diapers.[265,266] Various forms of mercury (e.g., mercury vapor, mercurous/mercuric salts, phenylmercuric compounds) cause acrodynia from the conversion of these compounds to inorganic mercury. This disease now occurs rarely, primarily as a result of exposure to elemental mercury vapor.[267]

Following the revocation of the Treaty of Nantes in 1685, many Huguenots immigrated to England, where they brought their process for treating felt hats with mercuric nitrate. Some writers believe the Mad Hatter in *Alice's Adventures in Wonderland* was based on English hatters, who frequently were exposed to heated inorganic mercury and potentially mercury vapors during the felting process when acidic solutions of mercuric nitrate and heat were applied to hairs from animal fur. In 1938, a study of hatters exposed to inorganic mercury in the fur-cutting industry reported an excess incidence of behavioral changes, tremors, and hyperreflexia.[268] Although shyness and timidity characterize mercury-induced behavioral abnormalities, Lewis Carroll (*nom de plume* for Charles Lutwidge Dodgson) knew an eccentric furniture dealer who more closely resembled his fictional character, the Mad Hatter.[269] He also regularly observed inmates at mental health facilities while traveling with his uncle and close friend, Skeffington Lutwidge.

In 1955, the English psychiatrist John Todd first published Alice in Wonderland syndrome to portray the bizarre illusions of size, shape, and motion (metamorphopsia) appearing to the fictional character Alice in her long, strange dream.[270] The etiology of these bizarre changes in perception includes infections, mind-altering drugs, complex partial seizures, and migraine headaches. Lewis Carroll long suffered from severe migraine headaches.[271]

PHYSIOCHEMICAL PROPERTIES

The common valences of inorganic mercury are Hg^{+} (mercurous) and Hg^{2+} (mercuric). Mercurous ions form a unique structure consisting of two mercury atoms possessing an overall divalent (+2) charge. This bond easily breaks to form elemental mercury and divalent inorganic mercury.[272] Mercurous chloride (Hg_2Cl_2, calomel) is an odorless, heavy, white powder. Mercuric compounds possess a high affinity for sulfhydryl groups common in important components of enzymatic processes in the body as well as selenium in the reduced form (selenide, Se^{2-}). Mercuric selenide is highly insoluble. Mercuric chloride ($HgCl_2$, corrosive sublimate, bichloride of mercury) is an odorless, white, crystalline powder that is the most corrosive mercury salt. Mercuric sulfide (HgS, cinnabar, quicksilver vermillion) is a black or grayish-black crystalline powder. In general, mercuric oxides and sulfides are water-insoluble, whereas water-soluble mercury salts include bromides, chlorates, chlorides (except mercurous chloride), cyanide, fluorides, and nitrates. Some mercuric compounds (e.g., mercuric chloride) are corrosive to mucous membranes.[142] Table 20.3 lists the identifying information and physical properties of several inorganic mercury salts.

EXPOSURE

Uses

Although mercury has many unique physical properties (e.g., ease of alloying with other metals, uniform expansion over wide temperature range, high surface tension, fluidity) for industrial applications, domestic consumption of mercury has decreased since the early 1970s including use in batteries and switching devices.[14] The production of galvanic cells in button batteries involves the use of mercuric oxide anodes in combination with zinc or cadmium cathodes. Mercury is an important part of alkaline batteries.

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TABLE 20.3. Identifying information and physical properties of inorganic mercury compounds. (Based on Satoh).[142]

Property	Mercuric Chloride	Mercuric Sulfide	Mercurous Chloride
CAS RN	7487-94-7	1344-48-5	10112-91-1
Molecular weight (g/mol)	271.52	232.68	472.09
Molecular structure	$HgCl_2$	HgS	Hg_2Cl_2
Valence	+2	+2	+1
Melting point (°C)	277	446 (sublimes)	400–500 (sublimes)
Boiling point (°C)	302	502 (Predicted)	384
Density	5.4 g/cm^3 (25°C)	7.55–7.70 g/mL (black)	7.15 g/mL
Water solubility	69 g/L (20°C)	Insoluble	0.002 g/L (25°C)
Vapor pressure (mmHg)	136.2°C	~0	NA

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.

Mercury bichloride solutions previously were administered in the United Kingdom as a lavage solution to kill abdominal metastatic cancer cells, resulting in toxicity.[273] Dark-skinned people use mercury-containing soap (mercuric iodine) and cream (1–10% ammoniated mercury) to lighten their skin color.[274,275] Copper is required for tyrosinase activity and melanocyte production; inorganic mercury produces lightening of the skin by replacing copper, resulting in the inhibition of tyrosinase activity. Many countries now ban the use of inorganic mercury-containing skin lightening creams as a result of case reports associating the use of these agents with inorganic mercury toxicity;[276] however, some African countries still produce soaps that typically contain 1–3% mercuric iodide.[6]

Sources

Environment

In contrast to ambient air where elemental mercury is the dominant species, inorganic mercury salts are the dominant Hg species in drinking water and soil; however, the inorganic mercury absorption from water is limited. The strong binding of inorganic mercury to organic matter substantially limits the availability of inorganic mercury to microorganisms for conversion to the more soluble methyl mercury. In soil and surface water, mercury exists in the form of mercuric (Hg^{2+}) and mercurous (Hg^{+}) salts. The predominant form of mercury in surface water is mercuric complexed or chelated with ligands. Overall, the concentrations of mercury species in water are low. Although considerable local variation occurs, average mercury concentrations in aquatic systems are as follows: rivers and lakes, 0.001–0.003 µg/L; coastal seawater, 0.002–0.015 µg/L; and open seas, 0.0005–0.003 µg/L.[277] Drinking water usually contains <0.025 µg Hg/L; however, in a survey of US groundwater, the mercury concentrations exceeded 0.5 µg/L in 15–30% of the wells tested.[278] The WHO guideline for Hg in drinking water is 1 µg/L, whereas the US EPA standard for drinking water is 2 µg/L. The mercury concentration in most terrestrial foodstuffs is low (<20 µg/kg), consisting primarily of inorganic mercury.

The mercury content in minerals is usually low (<50 µg/kg); the amount of mercury present in soil solution is also low (20–625 µg/kg) because mercury binds strongly to organic matter.[277] Higher mercury concentrations occur in surface soil compared with subsurface soil, urban soil compared with rural soil, and organic soil compared with minerals. Human uptake of mercury from cinnabar (HgS) in soil is limited because cinnabar ore is relatively insoluble;[279] the diet is a much stronger determinant of urine mercury concentrations than residence near sources of mercury-contaminated soil.[280] Higher mercury concentrations (255–360 mg/L) may occur in sediment from lakes near point sources (e.g., coal-fired power plants); however, the mercury concentration in sediment does not correlate with the mercury concentrations of fish swimming in the water above the sediment.[281] In a highly industrialized coastal marine ecosystem (Taranto Gulf, Ionian Sea, Italy), the mean total mercury concentration in samples from 2 inlets was 2,777 µg/kg dry weight (range, 36–7,730 µg/kg dry weight).[282]

Diet

The bioavailability of inorganic mercury in the diet is poor; therefore, this form of mercury probably contributes little to the overall mercury intake by the general population. Although animals in the food chain concentrate inorganic and organic mercury, humans absorb a much greater amount of methylmercury in

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their diet than inorganic mercury (90% vs. 10%, respectively). Consequently, methylmercury, rather than inorganic mercury, is the dominant Hg species absorbed by humans consuming fish.

ENVIRONMENTAL FATE

The migration of mercury in the soil depends on the Hg species. The dominant process in the distribution of mercury compounds in the environment is the sorption of inorganic mercury into soil, where mercury exists as complex ions of divalent mercuric and monovalent mercurous compounds with varying water solubilities. Particulate matter and sesquioxides strongly adsorb inorganic mercury at pH 4–9, forming mercuric sulfide in the presence of adequate sulfide stores; therefore, the transport of inorganic mercury in soil is very limited.[283]

Although leaching is a relatively insignificant transport process, surface runoff is an important means of moving mercury-containing particulate matter into water. A substantial portion of mercury deposited in coastal sea areas precipitates as a result of the very low solubility of inorganic mercury compounds; however, acidic conditions favor the formation of methylmercury as a result of decreasing sulfide ion activity. Most inorganic mercury binds to colloids, high-molecular-weight organic matter, and particles. Sediment is the principal sink for inorganic mercury. Bacterial activity converts some inorganic mercury to methyl mercury. Limited demethylation of organic mercury to inorganic Hg occurs in the cold layers of the sediment and lakes during winter. Inorganic mercury is rapidly eliminated from organisms; therefore, little inorganic mercury accumulates in animals.

DOSE EFFECT

The effects of mercury depend on the dose and form of mercury. Inorganic mercury affects the nervous system (central and peripheral) and the renal tubules.

Acute Toxicity

The low vapor pressure of inorganic mercury compounds limits exposure via inhalation to toxicologically insignificant concentrations. The lethal dose of mercuric chloride or mercuric acetate ranges from 10–42 mg Hg/kg. Consequently, the lethal dose of these two inorganic compounds is about 1–4 g based on the percentage of Hg in these salts (73% and 63% by weight, respectively). A 39-year-old woman vomited twice immediately after ingesting 0.675 g mercuric chloride. Within 2 hours, she received 5 mg BAL/kg; subsequently, she remained asymptomatic.[284] A 26-year-old woman survived after ingesting 0.9 g mercuric chloride after developing hematemesis, melena, and acute renal failure,[285] whereas a 27-year-old man ingested 6 g mercuric chloride and died after developing hypovolemic shock, acute renal failure, and necrosis of his stomach.[286] The ingestion of 7 g mercuric chloride by a 23-year-old female resulted in her death from progressive acute respiratory distress syndrome despite chelation, plasma exchange, and intensive supportive care.[287] The kidney is the critical target organ for the ingestion of inorganic mercury. A single ingestion of 15.8 mg Hg/kg as mercuric chloride produced nephrotoxicity including proteinuria in an 18-year-old; no permanent renal damage developed.[288]

Chronic Toxicity

At the present time, there is insufficient evidence to conclude that inorganic mercury concentrations typically present in the environment cause any adverse effects in the general human population; however, the general consensus of most regulatory organizations is the minimization of mercury exposure where practical.[289] The most sensitive target organs are the fetal and neonatal central nervous system, the kidneys, and the thyroid gland.

Neurotoxicity from the ingestion of inorganic mercury in humans usually results from the abuse of mercury-containing medications. A case report associated the development of dementia and irritability with the chronic ingestion (0.72 mg Hg/kg/d) of a mercurous chloride-containing laxative over many years.[290] A 14-day study in rats gavaged with mercuric chloride revealed a NOAEL of 0.93 mg Hg/kg/day, whereas a 6-month rodent study demonstrated a NOAEL of 0.23 mg Hg/kg/day based on the development of foci of tubular regeneration and thickened tubular basement membranes.[291]

TOXICOKINETICS

Absorption

The gastrointestinal tract is the primary route of inorganic Hg absorption with animal studies indicating the rate of absorption ranges from 2–40% depending on age and the solubility of the particular type of inorganic compound.[292] The bioavailability of mercuric chloride averages ~5–7%; this inorganic mercury compound

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accounts for most cases of inorganic mercury poisoning. The ingestion of mercury disk batteries may increase blood Hg concentrations following decomposition. An 18-month-old infant ingested a large mercury-containing disc battery. She remained asymptomatic during and after the 48-hour passage of split casing and a large amount of mercury following an enema.[293] Her physical exam and laboratory values were normal. *In vitro* human skin studies and case reports of elevated urine Hg concentrations in individuals using mercurous chloride-containing cosmetics indicate that transcutaneous absorption of this inorganic mercury compound may occur.[294]

Distribution

The distribution of inorganic mercuric (Hg^{2+}) is similar to that of elemental mercury with most inorganic mercury residing in the kidney and to a much lesser extent in the liver and intestines. Inorganic mercury concentrations increase with age in the cerebrum and heart. Unlike elemental mercury, the poor lipid solubility of mercuric mercury limits the amount of Hg^{2+} that crosses the blood–brain barrier; however, primate studies indicate the occurrence of some metabolism to inorganic mercury following absorption of elemental or organic mercury in the brain.[295,296] In the plasma, Hg^{2+} does not diffuse easily because of the binding of Hg^{2+} to albumin and globulins; consequently, inorganic Hg concentrations are similar in plasma and red blood cells.[297]

Elimination

Following the absorption of large doses of inorganic mercury, the urine is the principal route of elimination; the amount of inorganic mercury excreted in the feces is much smaller than the urine. Reductase and dismutase enzymes convert small amounts of inorganic mercury to elemental mercury with resultant elimination in expired air;[100] however, the expiration of elemental mercury after reduction of Hg^{2+} to Hg^0 accounts for only a very small portion of the elimination pathway. The elimination of inorganic mercury follows a complicated model with the biological half-lives depending on the tissue and time since exposure. The overall elimination rate of inorganic mercury follows the elimination rate of mercury from the kidney with a biological half-life of 40–60 days; the elimination rate from the blood and brain follows a biphasic pattern with an initial rapid phase of several days.[298] A fraction of the body burden of mercury probably has a long half-life including inorganic mercury in the brain,[299] but the toxicological significance of this prolonged half-life remains unclear because of the storage of at least some of this mercury in a biochemically inactive form (e.g., mercury selenide).[6]

Maternal–Fetal Kinetics

Only a small fraction of Hg^{2+} enters fetal blood as a result of limited lipid solubility; however, Hg^{2+} can accumulate in the placenta.[6] In a study of maternal guinea pigs injected with 1 mg $HgCl_2$/kg body weight, total Hg concentrations in their milk were lower than maternal plasma on days 3, 5, and 10 postpartum.[300]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

The mechanism of toxicity for inorganic mercury and organic mercury appears similar, resulting from the disruption of sulfhydryl-containing enzymes. Mercury impairs intracellular homeostasis of oxidation/reduction reactions with subsequent enhancement of oxidative stress, primarily in the kidney, brain, and liver.[301] Although the binding of mercury to thiol groups affects intracellular mercury transport and kinetics (distribution, excretion), this effect does not explain intracellular oxidative changes or alteration of calcium homeostasis. *In vitro* studies suggest selenoproteins in glutathione peroxidase and the thioredoxin system (thioredoxin reductase 1/2) are primary cellular targets of mercury toxicity.[302] The affinity of thiol groups is several orders of magnitude higher for selenium than mercury; consequently, the binding of mercury to selenoproteins (e.g., K, P, T) enhances oxidative stress by impairing the thioredoxin system and disrupting the cellular redox environment. Mercury induces a relative selenium deficiency depending on the form of mercury and selenium, dose, and organ; subsequent toxicity produces disturbances of calcium homeostasis, lipid peroxidation, mitochondrial injury, disruption of protein repair processes, and increased apoptosis.[301] Valence and chemical state influence mercury kinetics, target organs, and chemical processes (e.g., thioredoxin system) with inorganic mercury compounds being less potent inhibitors of the thioredoxin system than methylmercury.[303]

At relatively low doses, mercuric chloride produces nephropathy in the S_1 segment of the proximal tubule that spreads to the S_2 and S_3 segments as the dose increases. This action results at least partly from the selective distribution of enzymes and transport

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proteins (e.g., apical γ-glutamyl transpeptidase, the basolateral organic anion transport system) that affect Hg uptake into the proximal tubule.[304] Acrodynia (pink disease) may involve hypersensitivity; however, the immune system is not a major target organ for inorganic mercury toxicity. Although total urine mercury concentrations are always elevated in these children, neither the occurrence nor the severity of this disease is dose-related to mercury exposure.[6] Hypertension associated with acrodynia results from the inactivation of *S*-adenosylmethionine with subsequent inhibition of catecholamine-*O*-methyltransferase and increased epinephrine, norepinephrine, and dopamine concentrations.

Pathological Changes

The kidney is the main target organ following acute exposure to inorganic mercury, whereas exposure to elemental or organic mercury seldom causes renal dysfunction.[305] Acute inorganic mercury salt ingestion produces oliguric renal failure secondary to acute proximal tubular necrosis. Damage following inorganic mercury ingestion typically involves the distal renal tubule; renal biopsy 2 weeks after the ingestion of ~500 mg mercuric chloride demonstrated markedly dilated renal tubules with intratubular cell debris, interstitial edema, and mild inflammatory infiltrates in the interstitium consistent with acute tubular necrosis.[306] Histological changes in the renal vascular system, collecting ducts, and glomeruli are usually minimal.[307] Occasional case reports associate the use of inorganic mercury-containing compounds with nephrotic syndrome. These case reports describe an idiosyncratic, immunological response that manifests by an immune complex (membranous) glomerulonephritis. The exposures to inorganic mercury compounds include the use of teething powders by pediatric patients, application of skin-lightening creams by black African women, and occupational Hg exposure at an electrolysis unit in a chemical plant.[308] The proteinuria of membranous glomerulonephritis primarily includes high-molecular-weight proteins that leak through damaged glomeruli. Although glomeruli are normal by light microscopy, immunohistochemical studies demonstrated confluent finely granular epimembranous deposits of IgG and C3. Severe mucosal necrosis results from acute inorganic ingestion.

Postmortem Examination

A 36-year-old woman intentionally ingested mercuric chloride; she developed hemorrhagic nasopharyngeal mucosa, airway obstruction, respiratory failure, and hemodynamic instability with hepatorenal failure.[309] She died ~12 hours after ingestion. The postmortem examination demonstrated the following Hg concentrations: kidney, 284.3 μg/g; liver, 65.1 μg/g; spleen, 56.3 μg/g; lungs, 38.5 μg/g; myocardium, 16.9 μg/g; cerebral cortex, 1.4 μg/g; and cerebellum, 1.2 μg/g. The findings are consistent with the difficulty of inorganic mercury penetrating the blood–brain barrier.

CLINICAL RESPONSE

Inorganic mercury toxicity usually results from occupational exposure or the intentional/unintentional misuse/use of Hg-containing medicines. Classically, acute inorganic mercury toxicity (excluding elemental mercury vapor) involves divalent mercuric chloride (corrosive sublimate) and, previously, monovalent mercurous chloride (calomel, 85% Hg_2Cl_2). The former causes corrosive injury to the GI tract, renal damage, and secondary infections, whereas the latter produces acrodynia (pink disease) characterized by diaphoresis, weight loss, weakness, apathy, and a diffuse, painful rash. Mercuric chloride does not easily pass the blood–brain barrier, limiting CNS toxicity. The low solubility of mercurous chloride limits GI absorption and toxicity.

Acute Toxicity

Burning mouth, sore throat, nausea, and vomiting with severe gingivitis, stomatitis, and esophageal erosions develop after ingestion of large quantities of inorganic mercury. Abdominal pain, weakness, fatigue, pallor, hematemesis, hematochezia, shock, and vascular collapse may also occur. Severe ingestions cause acute tubular necrosis and acute renal failure. A 26-year-old woman was anuric for 14 days after ingesting mercuric chloride; she survived with hemodialysis, and normal renal function returned 4 months after ingestion.[310] A patient survived the injection of mercuric chloride in spite of the development of nausea, vomiting, darkened gums, abdominal pain, and anemia.[311]

Environmental Exposure

During the 1940s, case reports of young children (<5 years old) associated acrodynia (pink disease, Feer disease, erythredema polyneuropathy) with exposure to mercurous chloride (calomel, 85% H_2Cl_2) in teething powder and ointments.[262] Although acrodynia typically

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affects infants and young children exposed to mercurous chloride, adolescents and adults may develop acrodynia following exposure to elemental mercury vapor from broken thermometers or fluorescent light bulbs,[312] organic phenylmercuric compounds in latex paint, or other inorganic mercury compounds (mercuric chloride in diaper rinse;[313] ammoniated mercury (HgH_2NCl) ointment[27]). The highly variable clinical features of this disease include dermatological, cardiovascular, and neurobehavioral abnormalities. Acrodynia (pink disease) means painful extremities referring to the presence of an edematous, pink, painful, paresthetic, and desquamating rash on the extremities.

The onset of this illness is often insidious with anorexia, hypotonia, and irritability. Profuse sweating, photophobia, and hypertension often develop along with a prominent miliaria rash. Secondary infections may develop as a result of the traumatic denudation of the skin of the hands. In severe cases, dehydration and tooth loss occur along with ulceration of the gums. Clinical findings are less severe in older children. The extremities are not as pink in older children with acrodynia because the palms and soles are thicker. Antisocial behavior, poor school performance, tremor, fatigue, insomnia, and alopecia are more prominent in older children with acrodynia compared with infants. In adults, common presenting symptoms include insomnia, thirst, abdominal pain, aching extremities, and psychological disturbance. The differential diagnosis of acrodynia includes Kawasaki disease (mucocutaneous lymph node syndrome), measles, pheochromocytoma, and other viral exanthems. Lymphadenopathy, mucous membrane lesions, and conjunctival injection are much less common in acrodynia than Kawasaki disease.[267]

Occupational Exposure

Although some *in vitro* and animal data suggest mercuric chloride exposure may increase some serum cytokines and autoimmune responses,[314,315] insufficient evidence are available in epidemiology studies to link mercury exposure with autoimmune diseases.[316] Renal dysfunction (proteinuria) may develop; less commonly, the proteinuria progresses to the nephrotic syndrome with continued inorganic mercury exposure. Stomatitis and gastrointestinal distress also may occur. The appearance of a brown anterior band in the lens indicates the deposition of mercury on the anterior surface of the lens (mercurialentis).[317]

Developmental Abnormalities

Currently, there is little evidence that inorganic mercury exposure produces reproductive or developmental effects at mercury concentrations present in occupational or environmental settings. A case report associated a spontaneous abortion with the maternal ingestion of a large dose of mercuric chloride.[318]

Carcinogenesis

Neither the International Agency for Research on Cancer (IARC) nor the US National Toxicology Program (NTP) lists inorganic mercury compounds as potential human carcinogens. The former agency lists elemental and inorganic mercury in Group 3 (not classifiable as to their carcinogenicity in humans). A 2-year study by the NTP revealed a statistically significant incidence of squamous cell papillomas in the forestomach of male Fischer 344 rats gavaged with 1.9 and 3.7 mg Hg/kg/d as mercuric chloride, but there was equivocal evidence for squamous cell papillomas in female rats.[291] Additionally, there was a marginal increase in the incidence of thyroid follicular cancer in male rats, but not in female rats or mice. The US EPA classifies mercuric chloride as class C (possible human carcinogen) based on limited rodent data and no human data, whereas other inorganic mercury salts are class D (not classifiable) compounds.

DIAGNOSTIC TESTING

Analytical Method

Most techniques for the determination of mercury concentrations utilize atomic absorption spectrometry (AAS), atomic fluorescence spectrometry (AFS), or neutron activation analysis (NAA). In most methods, the mercury in the sample is reduced to elemental mercury. The most common method of analyzing blood and urine for mercury content involves cold vapor AAS after digestion of the samples with acids and the reduction of bivalent inorganic mercury to mercury vapor with stannous chloride. Gas chromatography/atomic fluorescence spectrometry can separate individual mercury species. *In vitro* studies indicate inorganic mercury is stable in whole blood at −70°C to –23°C for 1 year, whereas deterioration occurs at body temperature (37°C) after 2 weeks.[319]

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Biomarkers

Blood

Inorganic mercury distributes relatively evenly between serum and erythrocytes, whereas erythrocytes are the primary location of methylmercury.[320] Consequently, inorganic Hg concentrations in plasma, serum, and whole blood are similar. Although data are very limited, case reports suggest the body probably does not convert substantial amounts of inorganic Hg to organic Hg compounds following inorganic Hg poisoning. A 39-year-old man died 49 days after the intentional ingestion of ~50 g mercuric chloride; the postmortem blood contained total Hg and methylmercury concentrations of 11,700 μg/L and 150 μg/L, respectively.[321] The total Hg concentration in whole blood 1 day after admission was 6,750,000 μg/L. Potential biomarkers of a biologically effective dose include depletion of intracellular glutathione and induction of metallothionein; however, other metals and compounds affect the concentration of these substances complicating and confounding the results of analytical methods to detect glutathione and metallothionein.

General Population

The diet is the primary source of mercury with methylmercury in fish accounting for a major portion of the mercury in fish-eating populations. The typical total whole blood Hg concentration in non-fish-eating population is ~2 μg/L.[322] The total whole blood Hg/plasma Hg ratio depends on the Hg species involved with the mercury exposure. A study of unexposed referents and 40 Swedish chloralkali workers exposed primarily to elemental Hg demonstrated a mean whole blood Hg concentration of 7 μg Hg/L and a plasma Hg concentration of 6 μg/L.[323] The whole blood/plasma ratio for the general referent population (i.e., nonoccupational controls exposed primarily to methylmercury in fish) was 2.38 compared with 1.17 for chloralkali workers exposed primarily to mercury vapor. The higher whole blood/plasma Hg ratio in the controls reflects relatively lower plasma inorganic Hg than in the chloralkali workers.

Toxicity

A 31-year-old man complained of nausea, vomiting, and abdominal pain 4 hours after ingesting mercuric oxide.[324] The whole blood samples drawn during the first 24 hours after admission demonstrated total mercury concentrations of 0.13 mg/L (130 μg/L) and 0.185 mg/L (185 μg/L). He underwent chelation with BAL and DMSA; he developed only mild elevation of serum hepatic aminotransferases without specific complaints. Whole blood mercury concentrations returned to baseline within 1–2 months of acute poisoning. A 19-year-old woman presented with nausea, blood-stained vomitus, diarrhea, and abdominal discomfort after the suicidal ingestion of 2–4 g mercuric chloride powder.[325] The whole blood mercury concentration 3 and 24 hours after ingestion was 3.58 mg/L (3,580 μg/L) and 2.13 mg/L (2,130 μg/L), respectively. Dimercaprol was initiated within 2 hours of presentation along with supportive care. She developed mild hemodynamic instability, metabolic acidosis, hypokalemia, leukocytosis, and fever with symptoms improving within 48 hours of admission; the 48-hour post-ingestion whole blood mercury concentration was 1.77 mg/L (1,770 μg/L). She recovered without sequelae.

Postmortem

A 66-year-old woman ingested an undetermined amount of mercuric chloride and methyprylon; she developed rigidity and was taken to the emergency department, where she died shortly after admission.[326] The whole blood total mercury concentration was 22 mg/L (22,000 μg/L) as measured by flameless atomic absorption spectrophotometry; the postmortem methyprylon concentration was 0.6 mg/L. The postmortem blood from two patients dying after undergoing peritoneal lavage with mercuric chloride-contaminated fluid was 1,700 mg/L (1,700,000 μg/L) and 2,100 mg/L (2,100,000 μg/L) as measured by neutron activation analysis.[327]

Urine

General Population

Analysis of urine mercury concentrations is a simple, rapid test for identifying patients with excessive exposure to elemental and inorganic mercury. Elemental Hg rapidly oxidizes to inorganic mercury; consequently, total urine Hg concentrations reflect exposure to elemental and inorganic mercury; the kidney excretes little methylmercury from the diet. In the general population without occupational Hg exposure or excessive fish consumption, the total urine mercury concentrations average <5 μg/L.

Toxicity

Urine mercury concentrations document exposure to mercury and help monitor the effectiveness of chelation therapy, but urine total mercury concentrations do not correlate to specific symptoms of inorganic mercury toxicity. Spot urine collections are

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less reliable than 24-hour urine collections for mercury concentrations because glomerular filtration rates and creatinine clearance vary. Typically, signs of acute mercury poisoning do not usually occur until the urine mercury concentration exceeds 300 µg/L. Baseline urinary excretion of mercury can be normal in patients with overt acrodynia, depending on the timing of the urine sample.[328] A nonrandom survey of 150 women tested within 120 days after the use of a mercury chloride-containing beauty cream demonstrated a mean urine mercury concentration of ~147 µg/L (maximum, 1,170 µg/L).[274] Many of these women had health complaints consistent with mercury intoxication; however, there were inadequate data to correlate urine mercury concentrations to the dose of mercury or health complaints.

Hair

Accumulation of inorganic mercury in hair is limited. Typically, inorganic Hg including elemental forms represents <10% of the total Hg in hair. The simultaneous analysis of multiple (e.g., 15–39) metals in hair samples to provide vitamin supplements or chelation therapy is not a reliable method to determine the presence of toxic concentrations of heavy metals including mercury.[329,330] In contrast to methylmercury, there are limited data on the incorporation of inorganic mercury during hair growth. Correlating blood mercury concentrations with inorganic or elemental mercury concentrations in hair is more complex than methylmercury, particularly when volatile species of inorganic or elemental mercury in the environment contaminate the hair. Inorganic and elemental mercury concentrations in hair are probably not robust markers of dietary exposure to these mercury species; thus, hair and nail sampling are not recommended methods to evaluate inorganic mercury toxicity.[197]

Abnormalities

Urine

Mercury blocks catechol methyl transferase, the enzyme that converts catecholamines to metanephrine. Consequently, elevated levels of epinephrine and norepinephrine may appear in the urine along with increased concentrations of vanillylmandelic acid and homovanillic acid. Glucosuria may also result from the accompanying sympathetic hyperactivity following acute mercury intoxication.

Imaging

The MRI of a 38-year-old worker with the development of anxiety, tremulousness, chills, diffuse red rash, joint swelling, myalgias, and headache following a 5-day exposure to phenylmercury ammonium acetate demonstrated hypermetabolism of the posterior cingulate cortex; the changes correlated with attention/concentration deficits and marked anxiety on neuropsychiatric testing.[331] The CT scan of the brain was normal. The T2-weighted MRI images of a 10-year-old child with acrodynia, seizures, and visual impairment following chronic elemental mercury poisoning demonstrated multiple hyperintense lesions in the cerebral white matter (paracentral gyrus, posterior frontal region, parietal region, posterior cingulate gyrus), left globus pallidus, and putamen.[332] These findings resolved over 9 months with resolution of neurological symptoms and normalization of blood mercury concentrations. Sural nerve biopsy from a patient with chronic mercury toxicity secondary to exposure to ammoniated mercury salts demonstrated a mixed pattern of axonal degeneration and demyelination.[333]

Neuropsychological Testing

Neither blood nor urine mercury concentrations correlated to neuropsychological testing in 42 chemical workers from a plant producing inorganic mercury compounds; the major processes were production of mercuric oxides, mercury chlorides, and phenyl mercuric acetate along with drying and formulation operations.[225] A meta-analysis of 18 occupational studies (1,106 exposed, 1,105 controls) assessing the effect of inorganic mercury on neuropsychological tests suggests chronic exposure to inorganic mercury impairs motor performance (e.g., steadiness, grooved pegboard, Purdue pegboard, tapping, Santa Ana, eye-hand coordination) to a greater extent than memory or attention tests.[334] The mean total urine Hg concentration in these cross-sectional studies ranged from 3–192 µg/g creatinine. The lack of prospective studies, imprecise historical exposure information, and limited information on baseline test scores limit conclusions regarding exposure-response relationships.

HEALTH SURVEILLANCE

Risk Assessment

The ATSDR established an MRL of 7 µg Hg/kg/day for acute-duration oral inorganic mercury exposure

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(≤14 days) based on an NOAEL of 930 µg Hg/kg for renal effects (i.e., ↑ absolute and relative kidney weights) in rats gavaged with mercuric chloride for 14 days.[335] The MRL for intermediate-duration (15–364 days) oral exposure to inorganic mercury was 2 µg mercury/kg/day based on an NOAEL of 230 µg Hg/kg for renal effects (i.e., ↑absolute and relative kidney weights) in rats gavaged with mercuric chloride.[336] The US EPA established an oral RfD of 3×10^{-4} mg/kg/day (0.3 µg/kg/day) for mercuric chloride based on weight-of-evidence approach analyzing LOAELs of 226, 317, and 633 µg/kg/day of mercuric chloride derived from three studies demonstrating immunoglobulin deposits in glomeruli and intestinal glands of Brown Norway rats.[337,338,339]

Environmental Monitoring

Table 20.4 lists the guidelines and regulations for inorganic mercury exposure. These values are similar for elemental and inorganic Hg because the body converts almost all absorbed Hg^0 to inorganic mercury with subsequent urinary excretion of the inorganic mercury. The US OSHA regulation for inorganic mercury compounds is 100 µg/m^3 as a ceiling limit with a skin notation. This exposure value was promulgated to prevent systemic toxicity including subclinical neuropathies.[206] The ACGIH guideline for inorganic mercury compounds is a TLV–TWA of 25 µg/m^3 rather than a ceiling limit. The previous 100 µg/m^3 level was based on pharmacokinetic data that indicated inorganic mercury compounds deposit little mercury in the brain; subsequent concern about subclinical renal and neuropsychological effects resulted in the lowering of the ACGIH recommendation.[223] Currently, there are few data to indicate that inorganic mercury levels in the current work environment produce reproductive abnormalities, especially in males.

TABLE 20.4. Inorganic mercury guidelines and regulations.

Exposure Limit	Value
OSHA	
PEL–TWA (8-hour)	None
PEL-Ceiling	100 µg/m^3[a]
NIOSH	
REL–TWA (10-hour)	100 µg/m^3
IDLH	10,000 µg/m^3 (as total Hg)
ACGIH	
TLV–TWA (8-hour)[a]	25 µg/m^3 (elemental + inorganic)
BEI (urine)	20 µg/g creatinine, (as Hg)[b]
BEI (whole blood)	None[b]
US FDA	
Bottled water allowable limit	2 µg/L
US EPA	
RfD (chronic oral exposure)	0.3 µg/kg/day
MCL	2 µg/L
ATSDR	
MRL (acute oral exposure, ≤14 days)	7 µg/kg/day
MRL (intermediate duration oral exposure, 15–364 days)	2 µg/kg/day
WHO	
Drinking Water Guideline	1 µg/L

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; BEI = biological exposure indices; IDLH = immediately dangerous to life and health; MCL = maximum contaminate level; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = reference dose; TLV = threshold limit value; TWA = time–weighted average; US EPA = US Environmental Protection Agency; WHO = World Health Organization.

[a] Skin notation; [b] Total inorganic mercury in pre-shift urine sample; the total inorganic mercury at the end of shift at the end of workweek whole blood sample (15 µg/L) was withdrawn in 2013 because of the effect of dietary organic mercury on the whole blood Hg concentration.

Biological Monitoring

Urine

Total Mercury

The presence of urine mercury concentrations >500–850 µg Hg/L in exposed workers is a good predictor of the development of polyneuropathies manifested by tremors, unsteadiness, and poor coordination.[153] Early neurological symptoms may appear at urine mercury concentrations of >150 µg/L. More recent data focus on subclinical effects on renal function and neuropsychological tests. Chronic occupational exposure to inorganic mercury may produce alterations in the renal tubules and glomeruli. Most of these structural or functional changes occur when the urine mercury concentrations exceed 50 µg/g creatinine (28 µmol/mol creatinine).[340] Marked reductions in the urinary excretion of prostaglandin E_2 occur at concentrations near 35 µg Hg/g creatinine, but these changes appear reversible following a reduction in mercury exposure.[341]

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Increased tremor, reduced hand steadiness, increased reaction time, and poor hand-eye coordination have been associated with total urine mercury concentrations of >200 μg/L in workers chronically exposed to inorganic mercury.[342,343] Some, but not all, studies suggest that subclinical neurological effects (e.g., reduced short-term memory, verbal intelligence) may develop following chronic mercury exposures producing urine mercury concentrations exceeding 50–100 μg/L.[154] A small cross-sectional study compared workers chronically exposed to inorganic mercury with unexposed controls using the WHO test battery to detect preclinical signs of central nervous system impairment.[344] The results suggested that decrements in short-term memory (but not in other tests on the panel) may occur in workers with urine mercury concentrations near 25 μg Hg/L. However, there are inadequate data to determine a specific threshold of urine mercury for neurological abnormalities.

Some epidemiology studies have not detected abnormalities in neuropsychological testing in workers with urine mercury concentrations near 50 μg Hg/L.[155] In a study of chemical workers exposed to inorganic mercury, an increased prevalence of neuropsychological symptoms and elevated urine *N*-acetyl-β-D-glucosaminidase (a lysosomal enzyme present in renal tubular cells) were associated with urine mercury concentrations exceeding 100 μg/L when compared with unexposed controls.[225] There was also a reduction in the mean motor conduction velocities in the highly exposed group; however, abnormal nerve conduction did not correlate to neurological symptoms. Neuropsychological test scores also did not correlate to urine mercury concentrations.

Tubular Proteins

Tubular proteinuria consists of a variety of proteins and enzymes. Many of these potential biomarkers are low-molecular-weight proteins (e.g., β_2-microglobulin, retinol-binding protein) that are normally filtered through the glomerulus and reabsorbed in the proximal tubules. Other proteins (e.g., the enzyme, *N*-acetyl-β-D-glucosaminidase, NAG) are released directly into the urine from damaged proximal tubule cells. Several different urine proteins have been evaluated as biomarkers of renal injury; however, the specificity and predictive value of these biomarkers as early indicators of a more serious renal disease remain unclear. The pattern of urinary excretion of tubular proteins (structural proteins, prostaglandin metabolites, growth factors) is not unique to specific toxins including mercury. Tubular proteinuria increases in a variety of diseases (e.g., diabetes, hypertension, alcoholism, drug use, lupus erythematosus).[345] Other sources of variability in the urinary concentrations of tubular proteins include age, gender, urine flow rate, and circadian rhythms. Environmental exposure to mercury in contaminated condominiums did not produce tubular proteinuria, despite urine mercury concentrations averaging 26 ± 4.5 μg/g creatinine.[345] *Serum* concentrations of β_2-microglobulin (B_2G) do not correlate well with measures of chronic mercury exposure.[54]

Beta$_2$ Microglobulin This microglobulin (B_2G) is a low-molecular-weight protein with a molecular weight of ~10.8 kD. The glomerulus freely filters B_2G proteins. Individuals with normal proximal tubular renal function excrete ~0.3% (<370 μg/day) of the filtered load of B_2G. Increased excretion of B_2-microglobulin suggests but does not imply impairment of renal function.[288] Following the ingestion of 1.5 g mercuric chloride by an 18-year-old, B_2-microglobulins in the urine rose to 42,400 μg/day. The increased excretion of high-molecular-weight (albumin) and low-molecular-weight (B_2-microglobulin) proteins indicates the presence of both tubular and glomerular lesions.

N-Acetyl-β-D-Glucosaminidase (NAG) This high-molecular-weight (130–140 kD) protein is a lysosomal enzyme present in renal tubular cells; therefore, NAG is not normally filtered at the glomerulus. Elevated urinary NAG concentrations indicate tubular dysfunction following mercury exposure, producing urine mercury concentrations of 100–250 μg/L.

Biological Exposure Indices

The Biological Exposure Indices (BEI) recommended by the ACGIH for total urinary (i.e., primarily inorganic) mercury is 20 μg/g creatinine in a pre-shift urine sample as listed in Table 20.4. Although substantial interindividual variation in urine mercury concentrations occurs, urine mercury concentrations exceeding 50 μg/L indicate the need to investigate the individual's work environment; concentrations exceeding 100 μg Hg/L suggest the need to remove the worker from the work environment. Overt clinical evidence of mercury toxicity may not occur in mercury-exposed workers despite the presence of urine mercury concentrations of >100 μg/g creatinine.[346] Because of the large inter- and intraindividual variation in urine mercury concentrations,[210] decisions regarding workers should be based on an average of several measurements rather than a single value.[347] The creatinine adjustment method

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is the most sensitive method of reducing variation in the content of urine mercury samples used for biological monitoring.[348]

Blood

Most occupational studies use urine mercury rather than whole blood Hg concentrations as the biomarker of long-term inorganic Hg exposure because peak urine mercury concentrations occur ~2–3 weeks after acute exposure, and the urinary elimination half-lives for short-term and long-term exposures are ~40–60 days and ~90 days, respectively.[96] Additionally, methylmercury in the diet affects the whole blood Hg concentration, but not the urine Hg concentration.

Medical Surveillance

Preemployment physical examinations should focus on the documentation of baseline renal and central nervous system function including a urinalysis. Subsequent examinations should emphasize the detection of signs and symptoms of central nervous system dysfunction (personality changes, tremors, gait disturbances, insomnia, weight loss, ataxia).

TREATMENT

Decontamination

Studies reported in the 1940s suggest activated charcoal reduces the absorption of mercuric chloride in rats and *in vitro* solutions.[349] Although activated charcoal in the usual doses for ingestions of inorganic mercury is a therapeutic option, activated charcoal is not routinely recommended for inorganic mercury because there are no clinical data to confirm the efficacy of using activated charcoal in this setting, particularly when corrosion of the gastrointestinal tract occurs.

Enhancement of Elimination

Hemodialysis

Hemodialysis and hemofiltration remove relatively small amounts of mercury compared with the total body burden of mercury; therefore, the role of hemodialysis in the treatment of inorganic mercury toxicity is limited to the support of patients in renal failure.[350,351] In an adult developing anuria after the ingestion of mercuric chloride, 42 courses of hemodialysis did not increase the clearance of mercury.[286] The BAL-mercury complex is dialyzable, but the combination of chelation therapy and hemodialysis adds little to Hg clearance in patients with adequate renal function.

Experimental methods to improve the efficiency of hemodialysis include extracorporeal regional coupling hemodialysis (ERCH) and equilibrium dialysis. The insertion of dimercaptosuccinic acid into an arterial bloodline during the hemodialysis of a patient following the ingestion of mercuric chloride 6 days earlier resulted in a 10-fold increase in the amount of mercury in the dialysate compared with hemodialysis alone. However, an 80-minute treatment of DMSA-ERCH removed only ~1 mg of mercury from this anuric patient.[352] *In vitro* equilibrium hemodialysis with *N*-acetylcysteine and dimercaptosuccinic acid is an experimental method for the removal of mercury from the body during hemodialysis for acute mercury poisoning. *In vitro* studies with this method suggest that *N*-acetylcysteine enhances the transfer of mercury into the dialysate more than other chelates;[353] the efficacy of this procedure remains unclear.

Charcoal Hemoperfusion

Charcoal hemoperfusion and hemodialysis are ineffective methods to enhance the removal of mercury, even after the patient has been treated with dimercaprol (BAL).[354] Charcoal hemoperfusion does not offer a useful alternative to accelerate mercury elimination.[346,354,355]

Plasma Exchange/Exchange Transfusion

Although plasma exchange removes a relatively small amount of mercury, the removal of mercury by plasma exchange is larger than other methods used to enhance elimination. Following the ingestion of 6 g mercuric chloride, six plasma exchanges recovered 17 mg of mercury.[286] However, blood mercury concentrations rebounded after each plasma exchange similar to hemodialysis. Plasma exchange is most effective when instituted early, together with chelation therapy.[346]

Antidotes

Although chelating agents are often used to increase mercury excretion in severe acute inorganic mercury poisoning, the effectiveness of these drugs in organic and elemental mercury poisoning remains unclear. The initiation of chelation more than 1 month after an acute episode of mercury poisoning or the treatment of chronic mercury intoxication probably is not efficacious. Unlike lead, mercury undergoes relatively little bioaccumulation; the excretion half-life of mercury is ~1–2

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months.[97] Although chelating agents bind inorganic mercury and increase renal elimination of mercury, there are insufficient data from randomized clinical trials to confirm improved outcomes. Furthermore, current recommendations for chelation are based on clinical judgment and anecdotal data rather than consensus guidelines. Patient compliance is particularly important to prevent long-term sequelae of acute inorganic mercury toxicity (e.g., memory impairment, dementia, peripheral neuropathy).

Dimercaprol (BAL)

Previously, BAL (British Anti-Lewisite) was the primary chelating agent for the treatment of inorganic mercury poisoning; however, some,[238,239] but not all,[240] rodent studies suggest BAL may increase Hg distribution to the brain, heart, or lungs. As a result of these concerns and limited data on the efficacy of BAL therapy, the precise indications for BAL therapy or the use of other chelating agents are not well-defined. The decision to institute chelation therapy depends on clinical judgment regarding the severity of anticipated symptoms, the presence of toxic Hg concentrations in the urine or blood, and the adverse effects of BAL therapy. BAL is available only in intramuscular form solubilized in peanut oil.

The typical course of BAL is 4 mg BAL q4h for 5 days with 7–10 days of rest between courses. The duration of treatment depends on the chronicity of toxicity, the persistence of symptoms, the amount of mercury excreted in the urine, and the development of adverse effects. Because mercury is a non-essential metal in body function, urine mercury concentrations should be reduced to the lowest concentration possible (<10–20 µg/L) without inducing adverse effects as soon as possible after exposure. The frequent occurrence of multiple adverse effects (e.g., pain at the injection site, nausea/vomiting, abdominal pain, irritability, anxiety, paresthesias, headache, lacrimation, conjunctivitis, sore throat, myalgias, fever, hypertension) often requires the substitution of oral chelating agents (DMSA). Unfortunately, data are limited on the efficacy of oral chelating agents.

DMSA

DMSA (meso 2,3-dimercaptosuccinic acid, Succimer®) is a water-soluble analog of BAL. Although DMSA is a potential chelating agent for mercury, this drug has not been officially approved for the treatment of mercury intoxication;[356] however, animal studies support the use of DMSA for acute inorganic mercury toxicity when administered soon (minutes to hours) after poisoning as a method to reduce renal toxicity.[357] Although DMSA or DMPS increase renal excretion of mercury and reduce mercury concentrations in some tissues, the efficacy of chelation for chronic inorganic mercury is unproven.

Advantages of this drug are oral administration, mild adverse effect profile, and lack of redistribution of mercury to the brain. DMSA (Succimer®) is classified as a Category C agent for which the potential for adverse reproductive effects is not known. The most common adverse effects reported in clinical trials of children and adults have been primarily gastrointestinal including nausea, vomiting, diarrhea, and appetite loss. Rashes have been reported in about 4% of adults. Mild transient elevations in serum aminotransferase concentrations have been observed in 6–10% of treated patients.[358] The typical oral dose is 10 mg/kg twice a day for 14 days, followed by a rest period (of 2–3 weeks). Depending on the persistence of symptoms and the urinary response to chelation, a second round of DMSA may be needed.

DMPS

2,3-Dimercaptopropane-1-sulfonate (DMPS) is an investigational oral analog of BAL that may be less toxic than DMSA, but there is limited availability in the United States and few clinical data on the efficacy of DMPS during mercury toxicity. In oral doses of 100 mg three times daily, DMPS significantly increases the urinary excretion of some essential metals (e.g., copper, zinc, mercury).[359] Although the use of DMPS increases the urinary excretion of mercury,[360,361] there are few data on the effect of chelation therapy on clinical outcomes. A review of the medical literature recommended the use of DMPS for inorganic mercury toxicity based on experimental and limited human data, whereas DMSA was the preferred chelator for organic mercury poisoning.[241] Animal studies suggest that DMSA and DMPS appear superior to BAL and NAP (*N*-acetyl-D,L-penicillamine) in alleviating acute toxicity and preventing the undesirable distribution of orally administered mercuric chloride, especially to the kidney.[362] Complications of the maximum 15-day course were limited to a few patients with skin rashes. In a patient with serious ingestion of mercuric chloride, the administration of DMPS was associated with a reduction in the terminal half-life of mercury from 60 days to ~8 days.[363] However, the pharmacokinetic analysis indicated nonrenal mechanisms eliminated of >80% of the mercury; consequently, the clinical effectiveness of the DMPS treatment was not clear.

The usual course of treatment is 100 mg DMPS bid or tid for 21 days followed by a rest period.[364] Side effects

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observed during treatment with DMPS include erythema multiforme, maculopapular rashes, and mucous membrane reactions (mouth ulcers).

N-Acetylcysteine (NAC)

Animal studies suggest that the nephrotoxic effects of mercuric chloride (both functional and biochemical) are either enhanced by glutathione depletion or prevented by glutathione augmentation. A synergistic effect may exist between the direct effect of mercury and renal glutathione deficiency. *N*-acetylcysteine promotes a significant increase in renal nonprotein sulfhydryl content.[365] The use of NAC remains experimental because there are no clinical data regarding the effect of NAC on clinical outcomes.

D-Penicillamine and NAP

This oral compound may be useful in less severe symptomatic inorganic and elemental mercury inhalation exposures; however, the role of D-penicillamine in the treatment of mercury poisoning remains unclear without clinical studies. The use of D-penicillamine is based on case reports. D-Penicillamine reverses sulfhydryl binding in the blood and chelates copper, zinc, iron, and lead in addition to mercury. The use of penicillamine is contraindicated in penicillin-sensitive patients.

N-acetyl-D,L-penicillamine (NAP) is an investigational analog of D-penicillamine that was associated with improvement in patients with inorganic mercury-induced neuropathies (tremor, ataxia).[366] These case reports suggest that NAP may improve the outcome of patients with mercury intoxication. In both cases, urinary mercury, zinc, and copper excretion increased significantly. Both patients also had partial resolution of their neurological symptoms after chelation and removal from mercury exposure. The pediatric dosage is 30 mg/kg/day up to a maximum of 1 g, while the adult dosage is 250–500 mg/day.

ORGANIC MERCURY

HISTORY

In contrast to the long history of medicinal and industrial use of inorganic and elemental mercury, the use of organic mercury compounds dates back a little more than one century. The toxicity of organic mercury compounds was recognized in the 1860s when two laboratory technicians died of dimethylmercury poisoning in London.[367] Despite the recognition of severe central nervous system toxicity as an adverse effect of organic mercury compounds used for treating syphilis, organic mercurial diuretics were developed near the end of World War I. For the next 30 years, mercurial diuretics were the drugs of choice to enhance fluid excretion from the body until more effective and safer diuretics were discovered. During this period, the antibacterial and antifungal properties of many organic mercury compounds were discovered with applications including seed dressings for cereals. Contamination of food sources by methylmercury is associated with several public health disasters that resulted in irreversible central nervous system damage.

During the 1950s and 1960s around Minamata Bay of the Yatsushiro (Shiranui) Sea in Kumanoto Prefecture, Japan, methylmercury accumulated in fish from contaminated effluent discharge by a chemical plant producing methylmercury chloride as a byproduct of acetaldehyde production.[368] The chemical composition of the contaminants was never documented, but the effluent contained other toxins (e.g., arsenic) in addition to methylmercury. Initially, this contaminant was released into Minamata Bay; however, as the production of acetaldehyde increased to meet the demand for plastics, the drainage site changed from Minamata Bay to the mouth of the Minamata River. The change in the drainage site resulted in the contamination of fish in the Yatsushiro Sea; the release of the unusually high amounts of methylmercury into the seawater ceased in 1968. Methylmercury contamination of fish also occurred during the 1960s near the Agano River in the Niigata prefecture of Japan. The first reported cases of Minamata disease appeared in 1953; by 2000, the Japanese government recognized 2,264 patients as victims of methylmercury poisoning.[369] Ataxia, cerebral palsy, chorea, mental retardation, seizures, and tremors developed in the offspring of mothers eating large amounts of methylmercury-contaminated fish; these mothers developed only mild paresthesias.[370] Currently, consumption of fish contaminated by natural biomethylation processes has not been identified as a cause of methylmercury poisoning.[100]

Three epidemic outbreaks of organic mercury poisoning occurred in Iraq from 1955–1956, 1959–1960, and the largest from 1971–1972.[371] During the first two outbreaks from 1955–1960, rural residents unknowingly consumed bread prepared from contaminated grains that contained ethylmercury *p*-toluene sulfonanilide fungicides in seeds intended for planting. The identity

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of the exact organomercury compound causing these two epidemics was not well described. The last and largest Iraqi organic mercury epidemic was attributed to methylmercury, resulting in a slightly different clinical presentation.[372] Consumption of this contaminated bread by local women led to severe mental retardation and more subtle developmental effects (e.g., delayed developmental milestones) in offspring.[373] Approximately 6,500 cases of organic mercury intoxication occurred, resulting in ~450 deaths. Epidemiology studies did not detect an increased incidence of congenital defects; however, some children developed cognitive abnormalities, delayed speech, marked visual/hearing loss, and impaired sensorimotor function.

PHYSIOCHEMICAL PROPERTIES

Organic mercury compounds contain at least 1 carbon atom covalently bound to a mercuric ion. The common organic mercury compounds include short-chain alkyl (e.g., methylmercury, ethylmercury), long-chain alkyl, and aryl (e.g., phenylmercury) forms. Mercuric acetate, methylmercuric chloride, and phenylmercuric acetate are white or white-to-cream crystalline powders, whereas dimethylmercury is a colorless liquid with high vapor pressure. Alkyl mercury compounds possess a high affinity for sulfhydryl groups commonly present in important components of enzymatic processes in the body. Divalent mercury covalently binds to carbon atoms to form organic, relatively stable mercury compounds; however, some organisms metabolize these compounds in the environment. Table 20.5 lists the identifying information and physical properties of common organic mercury compounds.

Short-chained alkyl mercury compounds (methyl, ethyl, propyl) contain a mercury-carbon bond that is much stronger than other organic mercury compounds. The mercury-carbon bonds in aryl and alkoxyalkyl mercury compounds are less stable than similar bonds in alkyl mercury compounds (e.g., methylmercury); toxicity related to the former compounds primarily results from the release of divalent mercury. In contrast to most inorganic and organic mercury compounds, dialkyl mercury compounds (R–Hg–R) volatilize in sufficient quantity to occur in the atmosphere near sources.[374] Thimerosal (sodium ethylmercurithiosalicylate) is ~50% mercury by weight; this compound degrades in the tissues into ethyl mercury and thiosalicylate.

EXPOSURE

Uses

In the United States, organic mercury compounds are no longer commonly used as biocides in rice, marine and household paint, or laundry products. During the 1990s, some multi-dose, inactivated infant vaccines (e.g., hepatitis B, diphtheria-tetanus-acellular pertussis, *Haemophilus influenzae* type b) contained the ethyl mercury-containing preservative, thimerosal, to avoid bacterial overgrowth following repeated entry into multi-dose vials. Thimerosal is an ethyl mercury radical attached to the sulfur group of thiosalicylate that undergoes biotransformation to ethyl mercury.[375,376] Infants receiving several vaccinations may receive an ethyl mercury dose up to 175 mg; however, the rapid blood elimination (i.e., mean $t_{1/2}$ = 7 days) of ethyl mercury limits mercury exposure below estimated safe concentrations.[377] The use of thimerosal as a preservative is now limited by the adoption of single-dose packaging that does not contain thimerosal. Clinical studies have not supported the efficacy of chelation treatment for autism[378] or a causal role of thimerosal in a variety of neurodevelopmental disorders including autism.[379,380] There are limited uses for organic mercury compounds as antiseptic compounds

TABLE 20.5. Identifying information and physical properties of organic mercury compounds.

Property	Mercuric Acetate	Methylmercuric Chloride	Dimethyl Mercury	Phenylmercuric Acetate
CAS RN	1600-27-7	115-09-3	593-74-8	62-38-4
Molecular weight (g/mol)	318.70	251.1	230.66	336.75
Molecular formula	$C_4H_6HgO_4$	CH_3ClHg	C_2H_6Hg	$C_8H_8HgO_2$
Valence	+2	+2	+2	+2
Melting point (°C)	178–180	170	−42	~149
Boiling point (°C)	118 (predicted)	117 (Predicted)	92	291 (Predicted)
Density (g/mL)	3.28	4.06 (25°C)	3.19 (20°C)	NA
Water solubility (g/L)	250 (10°C)	<0.1 (21°C)	Insoluble	5.6
Vapor pressure (mmHg)	13.9−15.6 (25°C predicted)	0.0085 (25°C)	62.3 (25°C)	1.2×10^{-4} (25°C)

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.

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because of the development of safer, more efficacious anti-infective agents. Case reports associate the use of mercurochrome (0.2% aqueous methyl mercury) on the omphalocele of a neonate with mercury toxicity.[381] Less common uses include laboratory-based research and antifungal thimerosal agents on seed, bulb plants, and vegetation.[382] In some parts of the world, organic mercury compounds remain part of anti-fouling and mildew-proofing paints. The US EPA suspended the use of mercury compounds in interior paint in 1990.

Sources

For the general population, the major source of organic mercury is the consumption of large, predatory fish (e.g., pilot whales);[383] elephant seals, mink, and river otters also contain methylmercury.[384,385] Vaccines are no longer a significant source of exposure for the US population. In some countries, vaccines contain ethyl mercury in the form of the preservative thimerosal. With the exception of some flu vaccines, the switch from thimerosal-containing multi-dose vials to single-dose vials without thimerosal eliminated most childhood exposure to thimerosal in US vaccines.

Environment

Elemental mercury is the principal form of mercury in the air with negligible amounts of organic mercury. The only source of methylmercury in the environment is the methylation of inorganic mercury by microorganisms.[39] The amount of methylmercury depends on conditions within the lake or river, but usually, methylmercury constitutes a small portion (1–6%) of the total amount of mercury. Microorganisms in lake sediments possess the ability to methylate mercury; the amount of methylated mercury depends on overall microbial activity.[368] At a near-neutral pH, methylmercury is the dominant product of this methylation; the output of methylmercury doubles for each 10-fold increase in the amount of inorganic mercury.[277] The formation of new lakes may increase the production of methyl mercury, but this increase is usually temporary.[386]

Diet

The estimated daily intake of mercury in a US study averaged 2.3–3 μg/day (50 ng/kg/day),[387] whereas the daily intake in Belgium averaged 6.5 μg/day.[388] The provisional tolerable daily adult Hg intake of the World Health Organization (WHO) is 50 μg/day (i.e., ~5 μg Hg/kg body weight/ week). Cooking does not eliminate mercury from food; frying may increase the Hg concentration up to 2-fold as a result of water loss from the sample based on observational studies.[389] Methylmercury is the dominant species of mercury absorbed by humans following the consumption of fish; fish consumption accounts for almost all of the methylmercury present in the diet of the general population, particularly fish at the highest trophic levels (i.e., benthic and predatory pelagic species) that accumulate methylmercury in kidney, brain, muscle, and liver.[390,391] Methylmercury has a high affinity for protein sulfhydryl groups, resulting in the easy accumulation of this compound along the food chain. Consequently, large, long-lived predators (e.g., king mackerel, seals, swordfish, tilefish, blue-fin tuna, whales) have high Hg concentrations, as animals in the food chain concentrate both inorganic and organic mercury.[94] Dietary mercury content varies primarily with fish consumption and the mercury concentration in the fish. In general, seafood low in mercury includes catfish, cod, sardines, salmon, shrimp, tilapia, freshwater trout, and canned tuna.[392]

Freshwater and marine fish are the main sources of mercury in the diet. In a Japanese study, tuna and mackerel were the most common fish associated with elevated total hair mercury in 189 adults and children from the Karakuwacho Peninsula;[393] a study of Asians in Chicago also associated tuna consumption with elevated hair Hg concentrations.[394] Although mackerel typically contains low mercury concentrations, the authors attributed high intake as the etiology of the correlation between mackerel consumption and elevated total hair mercury. Typical total mercury concentrations in various fish species usually range from 0.01–4 mg/kg, depending on the surrounding environment (pH, redox potential), species, age, and size. In a study of UK seafood, the highest concentrations of total mercury occurred in swordfish, marlin, and shark with mercury concentration in five samples of sharks ranging from ~1–2.2 mg/kg.[395] Almost all samples of tuna contained total mercury concentrations below the European Commission limit of 1 mg/kg for predatory fish species. Canned tuna contained substantially lower (i.e., <0.5 mg/kg) total mercury concentrations.

Methylmercury accounts for most mercury (i.e., ~40–90%) in these fish with other organic mercury compounds (e.g., ethylmercury, phenylmercury) comprising the remaining portion. Humans absorb a much greater amount of methylmercury than inorganic mercury (90% vs. 10%, respectively). Additionally, the longer biological half-life of methylmercury than inorganic mercury favors the accumulation of methylmercury in

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fish.[277] Through natural processes and direct commercial discharge, most mercury species settle in the marine environment; consequently, some waters naturally contain high mercury concentrations. The Mediterranean basin contains large deposits of cinnabar; marine organisms from the Mediterranean have substantially higher total mercury concentrations compared with similar species in the Atlantic Ocean.[396]

Lifestyle

Phenylmercuric acetate (PMA) is a latex (water-based) paint additive that prolongs the shelf-life of these paints by inhibiting the action of bacteria and mildew. Elemental mercury vaporizes from these paints during the drying process with ambient air concentrations in some homes painted with interior latex containing >200 mg PMA/L exceeding the recommended ambient air Hg concentrations.[397] The actual Hg exposure depends on several factors: time since application, time spent in the painted room, minute ventilation, and the rate of air exchange in the painted room. A 4-year-old child developed acrodynia within 10 days of the painting of the inside of his home with latex paint containing ~950 mg PMA/L.[398] In a study of houses painted with organic mercury-containing paint ~30 days before testing, the average mercury concentration in ambient air was 2 μg/m^3 (range, <0.1–10 μg/m^3). The mean ambient mercury concentration substantially exceeded the recommended residential concentration of 0.5 μg/m^3.[399]

ENVIRONMENTAL FATE

Dimethylmercury is the only volatile form of mercury other than elemental Hg; however, the concentration of this compound in the atmosphere is small.

Soil

Methylmercury results from the biotransformation of elemental mercury deposited in water and soil. Methylation of inorganic mercury occurs mostly on sediments in fresh and ocean waters as a result of the non-enzymatic methylation of Hg^{2+} by methyl cobalamin compounds produced by bacterial synthesis. The solubility and mobility of methylmercury in soil allow methylmercury to enter the food chain rapidly. Very little mercury accumulates in terrestrial food chains with the exception of edible mushrooms (*Pleurotus ostreatus*) grown on compost containing mercury.[400] These mushrooms may present a health risk following heavy consumption as a result of estimated Hg bioaccumulation factors of 65–140. Most mercury reaching the ocean via wet deposition is recycled to the atmosphere with <10% reaching the sediment and ~2% methylated in biota.[401] The bottom sediment of the ocean is the ultimate sink for mercury, where the mercury exists as the highly insoluble mercuric sulfide.

Water

Most aquatic species contain methylmercury that undergoes biomagnification in long-lived predatory fish. The biomethylation of inorganic mercury to methylmercury occurs in lakes and wetlands, primarily as a result of microbial activity in the warm upper layer of sediment and the warm surface waters of lakes during the summer months.[402] Only a small percentage (i.e., ~2%) of the methylated mercury vaporizes into the atmosphere, primarily as dimethylmercury.[403] The most common organic form of mercury is methylmercury; this soluble, mobile form accumulates more rapidly in biological tissue than inorganic mercury.[404] Once released from microorganisms in surface waters, methylmercury quickly enters the food chain by rapid diffusion, binding to proteins in aquatic organisms.

Large predatory species at the top of the food chain (king mackerel, barracuda, bass, pike, trout, large tuna, marlin, scabbard, swordfish, walleye, shark), seals, and toothed whales contain the highest concentration of methylmercury as a result of biomagnification that produces mercury levels 10,000–100,000 times the concentrations of mercury found in ambient water.[19] In highly polluted environments, the Hg concentrations in liver and gonads increase relatively more than the mercury concentration in muscle tissue, particularly for predatory fish.[405] The relatively greater bioavailability of methylmercury compared with inorganic mercury also promotes the biomagnification of methylmercury in the food chain. Low pH, reduced oxygen concentrations, high levels of mercury in sediment, and conditions favoring the growth of microorganisms increase the amount of methylmercury present in water.[406] Other factors include temperature, calcium concentrations, total hardness, and conductivity.[407] The relocation or redirection of bodies of freshwater indirectly increases methylmercury concentrations by increasing the amount of humic material available for the growth of microorganisms.[408] Acid conditions favor the formation of methylmercury, probably by inhibiting the generation of insoluble mercuric sulfide that provides a sink for inorganic mercury in the sediment.

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DOSE EFFECT

The effects of mercury depend on the dose and form of mercury. Organic mercury exposure in adult populations and methylmercury exposure in children exposed *in utero* may cause neurological effects. The unborn fetus exposed to methylmercury is probably the most sensitive part of the general population; however, the thresholds for these effects are not well-defined.[409]

Acute Toxicity

Inhalation

There are little data on the inhalation of organic mercury compounds in humans as a result of the low volatility of most organic mercury compounds. In the 1940s and 1950s, no respiratory symptoms developed in workers exposed to undetermined levels of alkyl mercury compounds (e.g., methylmercury) over several months; however, these workers demonstrated evidence of neurological dysfunction characterized by ataxia, unsteady gait, tremor, dysarthria, paresthesia, irritability, short-term memory deficit, and constricted visual fields.[410,411,412]

Ingestion

Very limited data are available on the acute lethal dose of organic mercury compounds. Estimated fatal doses of methylmercury based on tissue Hg concentrations during epidemics of methylmercury poisoning range from 10–60 mg Hg/kg with mercury accounting for 80% of the dose of methylmercury by weight. The ingestion of 20 mL 2% mercurochrome by a 15-year-old female was associated with the development of nausea, vomiting, abdominal pain, and dizziness, along with slightly elevated urine mercury concentrations.[413] A 44-year-old man ingested 83 mg thimerosal/kg as the alkyl aryl organic mercurial bactericide, sodium ethylmercurithiosalicylate.[414] He developed renal tubular dysfunction (maximum serum creatinine, 2.4 mg/dL), delirium, gingivitis, coma, polyneuropathy, gastritis, and respiratory failure despite chelation therapy with DMSA. After 148 days, sequelae were limited to sensory deficits in the toes.

Injection

There is no convincing evidence that the use of thimerosal-containing vaccinations causes adverse neurological or psychological effects based on prospective cohort studies of vaccinated children,[415,416] particularly autism.[417]

Chronic Toxicity

Animal studies indicate methylmercury is a more potent neurotoxin than inorganic mercury compounds. Two deaths were associated with occupational exposure to an estimated 1 mg diethyl mercury/m^3.[418] A study of workers exposed to Hg concentrations of 10–100 μg/m^3 as alkyl mercury did not reveal any specific symptoms attributable to the exposure to alkyl mercury.[419] Based on studies on the consumption of methylmercury-contaminated bread in Iraq, the estimated lethal dose of methylmercury was ~200 mg.[371] In this study, paresthesia began when the total body burden exceeded 40 mg Hg.

Studies of fish-eating populations in the Republic of Seychelles off the east coast of Africa (779 infant-mother pairs) and the Faroe Islands north of Scotland (1,022 singleton births) did not confirm an association between low-dose, prenatal exposure to methylmercury (as measured by segmental hair analysis) and delayed developmental milestones; the latter study did report subclinical deficits in the language, attention, memory, and visuospatial domains on neuropsychological testing, primarily when maternal hair concentrations exceeded 10 ppm (μg/g).[420,421] These populations consumed substantially more fish than US populations with mercury concentrations in the range of 0.05–0.2 ppm (μg/g); the mean maternal hair total mercury concentration in the Faroe study group was 6.8 ppm.[422] The source of the fish in Seychelles was ocean fish, whereas the source in the Faroe Islands was pilot whale blubber that is potentially contaminated by PCBs. An Italian study of a birth cohort living near a mercury-contaminated coastal site did not detect a statistically significant difference in full scale, verbal, or performance IQ between 7-year-old children born to mothers with total mercury hair concentrations above or below 2 ppm;[423] however, the mean scores on these tests were four to five points lower in the former children than the latter. No neurological abnormalities were detected in 327 7-year-old Japanese children with hair mercury concentrations of <6.9 μg/g.[424] The estimated mercury concentration in methylmercury-contaminated fish associated with Minamata disease was 3–30 ppm compared with the US EPA maximum regulatory concentration of 1 ppm.[425,426] Based on regression coefficients and analysis of cord samples from Minamata, the estimated median daily maternal Hg intake was ~225 μg, and the estimated median maternal Hg hair concentration was 41 μg/g; the estimated median cord blood of the affected infants was 216 μg/L.[427]

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TOXICOKINETICS

Absorption

The gastrointestinal tract almost completely absorbs (i.e., up to 90%) an oral dose of methylmercury, whereas the absorption of phenyl mercury is less.[428] Little data exist on the systemic absorption of methylmercury from the lungs, but indirect evidence in animals suggests that the lungs easily absorb organic mercury compounds.[429,430] Dermal absorption of organic mercury compounds is small (<2%), but rarely mercury toxicity (tremor, fever, desquamation of the skin, renal dysfunction) may occur after the application of organic mercury compounds (e.g., Mercurochrome) to susceptible areas like the omphalocele of a premature infant.[431,432] Elevated mercury concentrations occur in infants exposed to diapers sprayed with phenyl mercury fungicide, but mercury toxicity is not clinically apparent.[266]

Distribution

Methylmercury diffuses across cell membranes as a small molecular-weight thiol complexed with L-cysteine and attached to neutral amino acid carriers. This transport is stereo-selective and competitively inhibited by large neural amino acids (e.g., methionine).[433] The highly lipophilic properties of methylmercury allow the diffusion of this compound across the blood–brain and placental barriers. As a result of the conversion of organic to inorganic mercury in the brain, most (i.e., >75%) of mercury in the brain appears in the form of inorganic mercury, even though the primary source of mercury is methylmercury. This conversion also results in the accumulation of Hg in the kidneys. Demethylation of methylmercury to inorganic mercury is species-, tissue-, dose-, and time-dependent.

From a toxicological perspective, there are two types of organic mercury compounds. The alkyl mercury group (e.g., methyl mercury) is readily lipid-soluble and distributes more uniformly throughout the body.[434] Methylmercury accumulates in red blood cells following the oxidation of methylmercury to less soluble mercurous and mercuric oxides via the catalase-hydrogen peroxidase pathway. After the ingestion of fish containing methylmercury, the erythrocyte/plasma ratio of methylmercury ranges 10–20.[435] The distribution of methylmercury compounds is usually complete within 4 days, but several more days may be necessary to reach equilibration in the brain.

In contrast to these compounds, phenylmercury and methoxyethylmercury behave pharmacokinetically, resembling inorganic mercury compounds in the body. Although phenyl mercury and methoxyethylmercury compounds are more easily absorbed than inorganic salts, once inside the body, these organic mercury forms undergo biotransformation by splitting the carbon–mercury bond to release inorganic mercury. Although the initial distribution of phenylmercury is similar to that of methylmercury, phenylmercury partitions to a greater extent into the erythrocyte compared with plasma. Additionally, phenylmercury deposits primarily in the liver rather than the kidney. The blood–brain barrier is less permeable to phenylmercury than to methylmercury. Consequently, phenylmercury and methoxyethylmercury toxicity more closely resemble poisoning with inorganic mercury salt than alkyl mercury poisoning.

Elimination

There is no definite evidence of the synthesis of organic mercury compounds in mammalian tissue.[436] The conversion of methylmercury to divalent mercury compounds is the key process for the excretion of methylmercury from the body. Because methylmercury easily penetrates the intestinal mucosa, a prominent enterohepatic circulation develops unless methylmercury is converted to the more poorly absorbed inorganic form. The major route of excretion of methylmercury is through the bile into the feces; this pathway accounts for most (i.e., ~90%) of the elimination of methylmercury in the form of inorganic mercury. Alkyl (methyl) mercury compounds accumulate in red blood cells where entrapment prolongs the excretion of these compounds, whereas aryl (phenyl) mercury compounds undergo conversion to inorganic mercury and more rapidly leave the body than alkyl Hg compounds.[428] The clearance of methylmercury from the blood and the body is longer than the clearance of inorganic mercury compounds. The elimination half-life of methylmercury in the blood averages ~50–65 days,[435] whereas the elimination half-life of the body averages ~70–80 days.[437] Enterohepatic recirculation accounts for the somewhat longer elimination half-life of organic mercury compared with inorganic and elemental mercury (30–60 days).

The clearance of ethylmercury from the body is >3-fold faster than that of methylmercury.[438] In a study of 15 patients receiving a thimerosal-containing vaccine monthly for several years, the estimated mean elimination half-life of ethylmercury from the blood was 5.6 days (95% CI: 4.8–6.3 days).[439] There was no evidence of accumulation of ethylmercury in the blood of these patients.

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Maternal–Fetal Kinetics

The alkyl mercury compounds easily pass the placental barrier and demonstrate a high affinity for fetal hemoglobin. Animal studies suggest that methylmercury concentrations are slightly higher in fetal blood than in maternal blood.[440] An epidemiological study of mothers and their offspring in Greenland revealed methylmercury concentrations in the blood of infants were 40% higher than maternal blood; however, biases in the study limit conclusions about the source of this difference.[441] Breast milk does not appear to be a major source of mercury exposure for infants. A study of women ingesting large quantities of fish indicated mercury does not accumulate in breast milk; Hg concentrations in breast milk and the plasma of breast-fed infants were similar to maternal plasma Hg concentrations.[442] Although most of the ingested mercury was methylmercury, only 20% of the total mercury in the breast milk was organic mercury.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Although differences in toxicokinetics produce dissimilar clinical effects from exposure to methyl and ethylmercury, the mechanisms of toxicity are similar. Methylmercury and ethylmercury bind sulfhydryl (–SH) groups in thiols, sulfur-containing amino acids (cysteine, methionine, cysteine-derivative taurine), and proteins. Methylmercury combines covalently with sulfhydryl (thiol) groups and selenoproteins to cause inhibition of sulfhydryl-containing enzymes).[443] The mechanism of toxicity for organic mercury and inorganic mercury appears similar; the differences in toxicity probably result from the differential accumulation of these Hg forms in sensitive tissue that results from variations in their toxicokinetics including the ability of methylmercury to disrupt the thioredoxin system and enhance oxidative stress.[301] Methylmercury forms a complex (MeHg-L-cysteine) with cysteine following absorption that mimics the molecular structure of methionine.[433] Subsequently, the L-type amino acid transport system enhances the uptake of methylmercury by the brain. Ethylmercury (e.g., thimerosal, merthiolate) does not share the same transport system as methylmercury; additionally, ethylmercury elimination is much more rapid than methylmercury.

The exact mechanism of organic mercury toxicity is complex and remains unclear. Potential mechanisms include the following: 1) impairment of calcium channels and intracellular calcium homeostasis from inhibition of sulfhydryl-containing enzymes; 2) over-activation of NMDA-type glutamate receptors and production of excessive calcium concentrations and cell death; 3) reduction of glutathione concentrations and increased generation of reactive species (e.g., hydrogen peroxide, nitric oxide) resulting in oxidative damage to nucleic acids, proteins, and lipids; generation of arachidonic acid; 4) overproduction of nitric oxide from increased nitric oxide synthase, particularly in the cerebrum and cerebellum; and 5) damage of the spindle apparatus during mitosis.[444,445] Methylmercury produces focal damage to specific areas of the adult brain and also destroys microtubules that are important for cell division and migration in the developing brain.[446] Methylmercury alters brain ornithine decarboxylase (an enzyme associated with cellular maturity) and neurotransmitter uptake at both presynaptic terminals and postsynaptic adrenergic receptor binding sites.[447]

Pathological Changes

The primary target organ of toxicity following exposure to methylmercury is the central nervous system, particularly cortical damage in the central and occipital cortex along with varying degrees of damage to the granular layer of the cerebellum.[448] High doses of methylmercury produce irreversible changes in the visual cortex and cerebellum, leading to permanent narrowing of the visual field and ataxia.

Postmortem Examination

Autopsies of adults with methylmercury poisoning indicate that central nervous system damage occurs in specific focal areas of the cerebral and cerebellar cortexes. Pathological changes include a granular cell-type cerebellar atrophy involving the granule cells of the neocerebellum with relative sparing of the Purkinje cells. Bilateral cortical atrophy also occurs, particularly in the calcarine fissures of the occipital lobe (visual cortex), pre- and postcentral cortex (motor and sensory centers), and temporal cortex (auditory center).[449] Disruption of the blood–brain barrier results in the extravasation of plasma protein. Postmortem examination of a chemical worker dying after exposure to dimethylmercury demonstrated similar changes in the cerebral cortex with loss of nerve cells and diffuse astrogliosis in the occipital and insular cortex; there was only slight pericellular edema and gliosis in the frontal and parietal cortex along with sparing of the subcortical

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white matter.[450] Although there was also degeneration in the cerebellar cortex, particularly the vermis, the loss of Purkinje cells occurred in the molecular layer with slight degenerative changes in the granular layer and sparing of the cerebellar white matter. A case report associated progressive cerebellar ataxia, dysarthria, generalized weakness, and stupor with exposure to ethylmercury at an insecticide manufacturing plant.[451] The worker died after developing infectious complications of lungs and kidneys; postmortem examination demonstrated pathological changes primarily in the corpus callosum, calcarine cortex, and the Purkinje cells in the cerebellum.

Autopsies of patients with Minamata disease demonstrated localized mercury deposits in microglial cells (macrophages) over wide areas of the brain in addition to mercury deposits in the calcarine fissures, pre- and postcentral cortex, temporal cortex, and the cerebellum.[452] The clinical features of Minamata disease (dysarthria, ataxia, deafness, constriction of visual fields, abnormal gait) correlate to the pathological damage detected on postmortem examinations.[453] Little or no deposition of mercury occurs in the Purkinje cells of the cerebellum or the epithelial cells of the choroid plexus. Histological changes in autopsies of patients dying within 2 months of the onset of Minamata disease demonstrated neuron loss with reactive proliferation of glial cells, microcavitation, vascular congestion, edema, and petechial hemorrhage in the calcarine, pre and postcentral, and transverse temporal cortices in the cerebrum along with loss of granule cells (but not Purkinje cells) in the cerebellar cortex.[103] Pathological lesions also appeared in the peripheral nervous system, manifested by the destruction of the anterior horn cells of the dorsal roots and the myelin sheaths. Degeneration is more prominent in sensory than motor neurons, perhaps as a result of the disruption of cellular metabolism. Postmortem analysis of these offspring indicated that the prenatal effects result from the incomplete and abnormal migration of the neuronal cells to the cerebral and cerebellar cortices.[454] Although seafood consumption correlated to elevated blood Hg concentrations in the brains (inferior/temporal/midfrontal cortex, cerebellum) of deceased participants in the Memory and Aging Project clinical neuropathological cohort study, the total mercury concentrations as measured by neutron activation analysis did not correlate to brain neuropathology or the presence of Alzheimer's disease.[455]

CLINICAL RESPONSE

Organic mercury poisoning usually develops from the consumption of methylmercury-contaminated food sources (e.g., Minamata Bay from consumption of fish contaminated by industrial discharges).[101] The clinical features of methylmercury and other organic mercury compounds typically involve the central nervous system. The classical signs of methylmercury compounds involve constriction of visual fields, cerebellar ataxia, and dysarthria (Hunter-Russell triad).[456] Some organic mercury compounds (e.g., phenylmercury) readily break down within the body into inorganic compounds, whereas alkyl mercury compounds (e.g., methylmercury) metabolize more slowly into inorganic mercury compounds. This difference in metabolism may account for the fact that acrodynia has been associated with phenylmercury poisoning but not with methylmercury poisoning Japan and Iraq. Ethylmercury organic compounds rapidly convert to inorganic mercury compounds, resulting in renal damage and CNS effects compared with methylmercury organic compounds that almost exclusively produce CNS effects.[100] Although elevated mercury concentrations may occur in the temporal lobes of patients with Alzheimer's disease,[457] no statistically significant difference in the blood mercury concentrations was demonstrated in a study of 18 patients with Alzheimer's disease when compared with controls.[458,459]

Acute Toxicity

The intentional ingestion of a large dose of thimerosal by a 44-year-old man caused gastritis, gingivitis, anuria, polyneuropathy, delirium, coma, and respiratory failure requiring intubation; there was no evidence of direct brain damage.[414] He recovered following supportive care with only minor paresthesias of the feet. A 48-year-old chemistry professor presented to the hospital with a 5-day history of rapidly progressive encephalopathy characterized by deterioration of balance, gait, visual fields, and speech.[460] Five months previously, she accidentally spilled dimethylmercury in her polyvinyl chloride-gloved hand while working under a ventilated hood. She was asymptomatic until 2 months before hospitalization, when she developed intermittent nausea, vomiting, abdominal pain, and weight loss. Her whole blood initial mercury concentration 154 days after exposure at the beginning of her neurological symptoms was 4,000 μg/L. Within the next 2 months, she became comatose with spontaneous episodes of agitation and crying. She failed to respond to supportive therapy and died 298 days after the dimethylmercury exposure. The medical investigation discovered no other mercury source. Another laboratory worker developed rapid, progressive neurological deterioration after using dimethylmercury for

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several months. The clinical features included severe nausea, anorexia, paresthesias, visual field constriction, dysarthria, and ataxia, followed by incontinence and coma; he developed pneumonia and died despite the early use of supportive care and chelation with D-penicillamine.[450]

Environmental Exposure

The clinical manifestations of organic mercury poisoning depend on the type of mercury compound involved. The classic presentation for methylmercury in Minamata disease includes paresthesias, tremor, ataxia, gait disturbances, bilateral concentric constriction of visual fields, speech/hearing impairment, and muscle weakness.[461] Aryl organic mercury compounds (e.g., phenylmercury, methoxyethylmercury) produce a pattern of toxicity similar to that associated with inorganic mercury salts. The alkyl mercury compounds (e.g., methylmercury, dimethylmercury) cause a toxic encephalopathy (psychiatric disorders, blurred vision, hearing impairment, olfactory and gustatory disturbances, ataxic gait, dysarthria, somatosensory changes) that includes a severe congenital form resulting from prenatal exposure based on epidemiological data from 1971–1972 Iraqi epidemic.[462,463] Both aryl and alkyl mercury compounds are potent skin sensitizers that produce a classic type IV cell-mediated delayed hypersensitivity reaction. Thimerosal (sodium ethylmercurithiosalicylate, CAS RN: 54-64-8) is a preservative in ophthalmological preparations that was the third most common sensitizer in a survey of the etiology of contact dermatitis in North America during the 1960s and 1970s.[464] Additionally, ammoniated mercury is a common sensitizer.[6]

Methylmercury

The classic triad of methylmercury toxicity is dysarthria, ataxia, and visual field constriction. Visual acuity, ocular movements, and pupillary reflexes are usually normal. Early symptoms manifest as sensory neuropathy with distal paresthesias, ataxia, and loss of position sense. Spasticity, hearing defects, intention tremor, slurred speech, insomnia, muscle weakness, decreased smell and taste, depression, emotional lability, loss of concentration, personality changes, intellectual disabilities, akinetic mutism, cerebellar ataxia (dysmetria, dysdiadochokinesia, gait disturbances), and somatosensory disturbances (distal paresthesias, hypesthesias, hypalgesia, poor two-point discrimination, decreased stereognosis) also occur. Tendon reflexes usually are preserved; sensory changes result from damage to the somatosensory cortex rather than damage to peripheral nerves.[369] Paresis usually does not occur, and hepatorenal function remains normal. The mean latent period in the last Iraqi epidemic from methylmercury poisoning was 3 weeks (range, 10–150 days).[372]

Studies of Samoan fishermen and tuna-packers with heavy fish consumption did not detect neurological abnormalities despite the daily fish consumption of up to ~10 oz.[465] The mean mercury concentration in hair samples from the fishermen and the tuna-packers was 17 ppm (maximum, 48 ppm) and 8 ppm (maximum, 24 ppm), respectively. Alkyl mercury poisoning may mimic amyotrophic lateral sclerosis.[466] Although fatty liver has been associated with exposure to methylmercury, an epidemiological study of 1,406 persons aged 50–69 living in a methylmercury-polluted area did not demonstrate an increased incidence of liver disease attributable to the methylmercury.[467] There is little evidence that exposure to moderate amounts of methylmercury from fish consumption increases the risk of cardiovascular disease (coronary heart disease, hypertension, stroke) based on exposure assessment by analyses of toenail mercury concentrations in 2 US cohorts totaling over 172,000 participants.[468,469] The studies did not differentiate organic from inorganic mercury.

Ethylmercury

Based on epidemics of methylmercury in Japan along with methylmercury and ethylmercury poisonings in Iraq, ethyl mercury (7.7% ethylmercury *p*-toluene sulfonanilide, Granoson M®, total mercury 3.2% w/w, Dupont) is a prominent renal toxin and a less potent neurotoxin compared with the prominent neurotoxicity and lack of renal toxicity associated with methylmercury exposures.[470,471] Clinical features involving the cardiovascular, gastrointestinal, hematopoietic, and urinary systems were more common in the earlier Iraqi epidemic of ethylmercury than in the later methylmercury epidemic.[372] During the Iraqi epidemic, the latent period between the end of exposure and onset of symptoms typically beginning with paresthesias was relatively long (weeks to a few months).

Reproductive Abnormalities

Congenital Minamata Disease

The fetal brain is substantially more susceptible to organic mercury poisoning than the adult brain. Children born to mothers with methylmercury toxicity

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develop severe derangement of the developing central nervous system that manifests as psychomotor retardation (delayed developmental milestones, seizures, spasticity) based on observations of children born to mothers exposed to methylmercury during the two major outbreaks of methylmercury poisoning in Iraq and Japan (congenital Minamata disease). The latter disease resembled cerebral palsy. The exact composition of the contaminated effluent discharged into Minamata Bay was not documented; however, the effluent probably contained other toxins (e.g., arsenic). The fetus is more sensitive to the effects of methylmercury than the mother; therefore, severe retardation may develop in the offspring of a mother without clinical features of serious methylmercury poisoning. A descriptive study of infant and birth outcomes in the Minamata area in 1950–1974 suggested the impact of prenatal exposure to contaminated discharge on infant mortality was equivocal.[472]

Maternal Fish Consumption

Neurocognitive Development

Studies on women with methylmercury exposure from high fish consumption have not demonstrated consistent findings in regards to the adverse effects on cognitive and behavioral development following large maternal fish consumption (i.e., 10-fold higher than typical US fish consumption).[473] Reviews of these studies suggest higher gestational methylmercury exposures are associated with lower neurological scores on some tests (e.g., finger tapping, naming tests, visual recognition memory scores), whereas other studies demonstrate either no dose-related effect or high scores on other neurodevelopmental tests.[474,475] Analyses of the three major epidemiology studies on methylmercury ingestion (Faroe Islands, Seychelles Islands, and North Island, New Zealand) suggested the size of the effect on child intelligence quotient points/μg methylmercury increase/g maternal hair ranged from −0.18 points (95% CI: −0.378 to −0.009)[476] to −0.7 points (plausible range, 0–1.5 points).[477] A cross-sectional analysis of 182 singleton term births in the Faroe Islands detected a statistically significant ($P = 0.03$) reduction in a measure of neonatal neurological function (neurological optimality score) with increasing cord whole blood Hg concentrations after adjustment for gestational age and PCB concentrations.[478] Although a study of 149 children from a Madeiran fishing community with high methylmercury consumption demonstrated some reduction in the brainstem visual and auditory evoked potentials, the changes were not related to measures of methylmercury exposure (e.g., hair-mercury concentrations in offspring).[479] Other epidemiological studies have not supported an association between high maternal fish consumption (i.e., methylmercury) and neurodevelopmental abnormalities in offspring. A study of 131 mother–infant pairs from a Peruvian coastal village found no association between prenatal exposure to methylmercury and infant development or neurological examination.[480] The mean maternal methylmercury concentration in hair samples was 7 ppm (μg/g) with a range of 0.9–28 ppm.

The longitudinal Seychelles Islands study did not detect an adverse association between prenatal exposure to methylmercury and six developmental outcomes (cognitive ability, receptive and expressive language, reading and math readiness, visual-spatial ability, social and adaptive behavior) when the children were tested at 66 months of age.[481] The mean methylmercury concentration in maternal hair was ~60% higher (median = 5.9 μg/g; range, 0.5–26.7 μg/g) in mothers from the Seychelles cohort than the Faroe Islands cohort. In addition, diets differed between the two populations with the Seychelles cohort ingesting primarily fish with no whale meat and less fats; factors that mitigate Hg toxicity may differ between these two populations including the presence of selenium and long-chain polyunsaturated fatty acids (e.g., docosahexaenoic acid, eicosapentaenoic acid). A follow-up longitudinal study of the Seychelles Islands cohort through age 11 years also did not detect any significant associations between prenatal methylmercury exposure and any of the study endpoints including a measure of developmental quotient or IQ (global cognition).[482] Analyses of postnatal mercury exposure in this cohort did not detect a consistent pattern suggestive of a causal relationship between methylmercury exposure from fish and adverse neurocognitive effects, as measured by the exposed children's intelligence quotient at 107 months.[483]

In a study of 780 US children enrolled in the Treatment of Lead-Exposed Children Trial, stratified, spline regression and generalized linear model data analyses did not detect an adverse effect of background methylmercury concentrations on the children's intelligence quotient or behavior.[484] The children were tested at ages 2, 5, and 7 years; the geometric mean organic mercury concentration of the group was ~0.5 μg/L (95% CI: 0.48–0.56 μg/L). In this study, blood lead concentrations (range 20–44 μg/dL) were associated with adverse effects on cognitive and behavioral development.

Available data indicate that the neurodevelopmental benefits of breastfeeding of infants outweigh the risk of methylmercury neurotoxicity from prenatal or postnatal maternal fish consumption, assuming exposure to

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methylmercury commonly found in fish.[485] In a study of Spanish children and their mothers during pregnancy, the geometric mean of the total mercury concentration in cord blood was 8.8 μg/L (95% CI: 8.4–9.2 μg/L). Testing of general cognition with the McCarthy Scales of Children's Abilities at age 4–5 years demonstrated improved scores with doubling of the cord blood mercury concentration (β = 1.29, 95% CI: 0.28–2.31).[486] The test scores of children from mothers consuming <3 fish serving/week during the first trimester tended to decrease with increasing cord blood Hg concentrations, suggesting maternal nutritional factors during the first trimester affect children's test scores.

Birth Outcomes

Studies on birth outcomes and maternal fish consumption are conflicting with some cohort studies suggesting a negative effect of mercury concentrations on birth weight,[487] whereas other studies demonstrate no negative Hg-related effects on birth weight.[488] In a community-based study of 1,024 in the Pregnancy Outcomes and Community Health (POUCH) study, the median total hair mercury concentration was 0.23 μg/g (range, 0.1–2.50 μg/g).[489] Compared with women delivering at term, women with very premature deliveries (i.e., <35 weeks gestation) had a higher risk of total hair mercury concentrations exceeding the 90th percentile (≥0.55 μg/g). The adjusted odds ratio was 3.0 (95% CI: 1.3–6.7) with covariates including total fish consumption, maternal age, ethnicity, Medicaid status, and community. Compared with women delivering full-term infants, the adjusted OR for high hair total mercury concentrations was not significantly elevated for all women delivering preterm infants (adjusted OR = 1.55, 95% CI: 0.7–2.9) or women delivering 35–36-week premature infants (adjusted OR = 0.4, 95% CI: 0.1–1.9). In a study of 367 Japanese mother–newborn pairs using total mercury in hair as a biomarker of MeHg exposure, the mean birth weight was 3,073 ± 37 g and the incidence of babies small for gestational age weight was 4.9%.[490] Multiple regression analysis with adjustment for confounding factors did not detect an overall association between mercury hair concentrations and birth weight/length or chest/head circumferences.

Carcinogenesis

The International Agency for Research on Cancer (IARC) lists methylmercury as Group 2B (possibly carcinogenic to humans) based on sufficient evidence of carcinogenicity in experimental animals and inadequate evidence in humans. The US National Toxicology Program (NTP) does not list organic mercury compounds as potential human carcinogens. A mortality study of a historic cohort of patients with Minamata disease did not demonstrate an increased risk of mortality from all cancers. Analysis of site-specific cancer using a Poisson regression model detected a statistically significant decrease in mortality from stomach cancer (RR = 0.49, 95% CI: 0.26–0.94) and an increase in the risk of death from leukemia (RR = 8.35, 95% CI: 1.61–43.3).[491] However, the increased risk of leukemia was not clearly related to methylmercury exposure alone as reflected in the wide confidence interval.

DIAGNOSTIC TESTING

Analytical Method

Typically, the determination of organic mercury concentrations in biological samples involves subtracting the results of the inorganic Hg concentration from the total Hg concentration. The latter analysis comprises complete conversion of all mercury to the volatile elemental form by harsh digestion (e.g., nitric acid/perchloric acid or bromate/bromide) and reduction of ionic mercury to the elemental form followed by cold vapor/atomic absorption spectrometry, whereas the determination of inorganic mercury involves milder digestions (HCl, sulfuric acid) and reduction. The use of gas chromatography/electron impact/mass spectrometry combined with inductively coupled plasma/mass spectrometry or gas chromatography/mass spectrometry with D_3-methylmercury as the internal standard allows the quantitation of methylmercury directly in whole blood samples with lower limits of quantitation of 0.3 μg/L and 0.5 μg/L, respectively.[492] At whole blood methylmercury concentrations of 10 μg/L, the precision of these methods is <6% and <3%, respectively. In contrast to the above methods, the results from isotope dilution/gas chromatography/mass spectrometry are not affected by incomplete recovery or matrix effects.[493] The use of high-pressure liquid chromatography to separate mercury species and triple spike isotopic dilution with solid-phase microextraction coupled to inductively coupled plasma/dynamic reaction cell/mass spectrometry allows the determination of organic and inorganic species in blood and urine samples.[494] Capillary electrophoresis (CE) is an alternative to chromatography for the separation of various mercury species; CE may be combined with electrothermal atomic absorption spectrometry, inductively coupled plasma/optical emission spectrometry, inductively coupled plasma/mass spectrometry, or atomic fluorescence spectrometry for mercury speciation.[495] Sample preservation is important because methylmercury is volatile.

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In vitro studies indicate methylmercury and ethylmercury are stable in whole blood −70°C to 23°C for 1 year, whereas deterioration occurs at body temperature (37°C) after 2 weeks.[319] Although freeze-drying may prevent methylmercury losses, repeat freezing-thawing cycles of biological samples may cause methylmercury losses depending on the matrix.[496] Acidification removes oxidizing agents that degrade methylmercury.

Biomarkers

Blood

In general, blood is superior to urine in the assessment of body burdens for metals with long biological half-lives (i.e., mercury) as a result of reduced variability in mercury concentrations.[494] Additionally, the feces eliminate almost all absorbed organic mercury (e.g., methylmercury and ethylmercury) with little organic Hg excretion in the urine.[320] Analysis of data from the National Health and Nutrition Examination Survey (NHANES 2007–2010) suggests BMI is inversely related to whole blood Hg concentrations after controlling for methylmercury exposure through fish/shellfish consumption and other confounders.[497] Compared with overweight/normal weight adults, the whole blood mercury concentration of obese adults averaged 22% (95% CI: 33% to −8.2%) lower than that of other adults; differences between obese and nonobese children were not statistically significant. In the general population without occupational mercury exposure, methylmercury accounts for ~80–95% of mercury present in blood; the remainder is inorganic mercury.[498] Consequently, total whole blood Hg concentrations reflect recent organic Hg (i.e., methylmercury) exposure. The short-chained alkyl mercury compounds (e.g., methylmercury) are relatively resistant to biotransformation; therefore, these compounds are toxicologically different than aryl or alkoxyalkyl mercury compounds. These latter compounds liberate inorganic mercury in the body.

General Population

Depending on the number of dental amalgams and the amount of fish in the diet, most whole blood total mercury concentrations in the general population are <10–20 μg/L with the mean whole blood mercury concentration <3–4 μg/L (15–20 nmol/L).[6,499] The consumption of large quantities (>4 meals/week) of predator fish may increase the total whole blood mercury concentrations 20 times above mean whole blood mercury concentrations depending on the Hg concentration in the fish.[500] A study of residents near the Elb River in Germany revealed a mean whole blood mercury concentration of ~12 μg/L with a range up to 79 μg/L in a fisherman.[501] In a study of 56 Japanese women without occupational Hg exposure, the mean total whole blood Hg concentration was 18.2 ± 9.9 μg/L (range 3.9–56.8 μg/L) as measured by reductive vaporization/gold amalgam capture/atomic absorption spectrophotometry.[194] Fish consumption was not reported, but presumably, fish was a prominent part of their diet.

In a study of US women, the geometric mean total Hg concentration in whole blood was 1.02 μg/L (95% CI: 0.85–1.20 μg/L).[502] About 8% of these women had whole mercury concentrations exceeding the US Environmental Protection Agency reference dose of 5.8 μg/L. This dose corresponds to the lower 95% confidence limit of the benchmark dose estimated to double the proportion of children with an abnormal score on a developmental assessment tool *and* an uncertainty factor of 10.[503] The geometric mean whole blood mercury concentration in samples from women of childbearing age during the US National Health and Nutrition Examination Survey (NHANES) 1999–2002 was 0.92 μg/L (upper 95% CI: 6.04 μg/L).[504] About 5.6% of the women aged 16–49 years had blood mercury concentrations exceeding the EPA reference level of 5.8 μg/L. In the 2009–2010 NHANES IV study of 5,765 subjects 20 years or older, the geometric mean total whole blood Hg concentration was 1.04 μg/L (95% CI, 0.956–1.14) with an upper 95% CI of 5.75 μg/L (5.14–6.50 μg/L).[505] Females had lower total Hg whole blood concentrations than men.

Toxicity

Four hours after the acute ingestion of 83 mg thimerosal/kg (5 g), the Hg concentration was 14 mg/L in whole blood and 1.7 mg/L in serum as determined by cold vapor/atomic absorption spectrometry.[414] The patient developed renal dysfunction, neuropathy, coma, and respiratory failure, but he recovered after 6 months with slight paresthesias in the toes.

Early symptoms (paresthesias, sensory disturbances) of acute methylmercury toxicity in adults initially appear at whole blood mercury levels near 200 μg Hg/L. In Iraq, paresthesias developed in persons with whole blood mercury concentrations >240 μg/L 65 days after exposure ceased.[506] Based on a biological half-life of 65 days for methylmercury in the blood, the minimal peak blood concentration associated with the development of paresthesias was 480 μg Hg/L. The fetus is very sensitive to methylmercury; therefore, the critical values for mercury in fetal blood are lower (e.g., 50 μg Hg/L) than adults.[507]

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Postmortem

The average concentration of total mercury in postmortem blood from two fatal cases of ethyl mercury toxicity from contaminated Iraqi grains was 15 mg/L (15,000 μg/L) as measured by flameless AAS.[508]

Urine

General Population

In contrast to inorganic mercury, the kidney excretes a very small portion (i.e., <10%) of the absorbed dose of methylmercury; therefore, whole blood or hair concentrations are better biomarkers of the organic Hg body burden than urine. Experimental studies do not support the use of chelation with DMSA as a method to evaluate organic or inorganic mercury toxicity. In a study of 24 healthy physicians assigned to 3 groups (non-fish eaters, 1–2 fish meals/week, ≥3 fish meals/week), there was no statistical difference in pre-chelation urinary mercury excretion (range, 0.12–2.2 μg/g creatinine, $P = 0.37$).[509] All groups demonstrated increased urinary mercury excretion with statistically significant differences ($P = 0.04$) between the three groups with higher Hg excretion in fish eaters. Using multiple linear regression, the only variable that predicted the post-chelation mercury concentration was the baseline whole blood mercury concentration ($P = 0.001$). The authors concluded that the increased Hg excretion over baseline after provoked DMSA chelation was not a reliable diagnostic indicator of mercury poisoning.

Toxicity

Urine total mercury concentrations document total Hg exposure, but urine mercury concentrations do not correlate to specific symptoms of mercury toxicity. Infants exposed to phenylmercuric acetate paints may develop acrodynia despite urine total mercury concentrations <50 μg Hg/g creatinine.[510]

Hair

The most prominent mercury species in hair and blood is methylmercury. In a Swedish study of 28 volunteers, the mean percentage of organic Hg species in hair was 91% (range, 79–95%) with the remainder being divalent inorganic mercury.[511] High inorganic mercury percentages suggest external mercury contamination and/or demethylation of methylmercury. The interindividual variation between total blood and hair mercury concentrations was very large, depending primarily on fish consumption. Typically, total Hg concentrations in terminal hair range from <1 μg/g (non-fish eaters) to ~30 μg/g in individuals frequently consuming Hg-contaminated fish.[512] In a study of 59 Japanese women with no occupational exposure to mercury, the mean total mercury concentration was 1.51 ± 0.91 μg/g (95% CI: 0.49–3.60 μg/g) in closely cut scalp hair compared with 0.86 ± 0.66 μg/g creatinine (95% CI: 0.28–2.06 μg/g creatinine) in morning urine samples.[513] Based on estimated daily mercury intakes from fish and other seafood using a food frequency questionnaire, fish accounted for ~30% of the total mercury in hair samples.[514] The arithmetic mean of total Hg concentrations in the hair of 118 Japanese children aged 3–6 years in 5 Japanese regions was 1.02 ± 0.63 μg/g (range, 0.17–3.20 μg/g). The study detected significant differences in the total hair Hg concentrations between the five regions consistent with traditional regional patterns of eating fatty fish (e.g., swordfish, tuna); however, the total Hg concentration did not vary significantly with age, sex, dental amalgams, or other types of seafood/shellfish. In a study of Louisiana anglers with relatively high fish consumption, the median total hair Hg concentration was 0.81 μg/g (n = 398; range, 0.02–10.7 μg/g) with 40% of participants exceeding the US Environmental Protection Agency's reference dose of 1 μg/g.[515] In contrast to the consumption of primarily commercial seafood by the general US population, ~74% of the angler's estimated Hg intake came from recreationally caught seafood based on interviews and Internet surveys; many of the fish species were unique to the region.

Hair analysis is an alternative to blood mercury concentrations for screening subjects with methylmercury exposure through seafood, particularly as a means to provide supplemental information to reconstruct prior methylmercury exposure. The usefulness of analyzing inorganic or elemental Hg concentrations in hair has not been established.

Sampling

The preferred sample is terminal hair from the occipital-neck junction, clamped to preserve strand alignment. Full-length hair strands (~100 g) from the occiput area should be collected with sharp scissors that cut the hair shaft close to the skin.[512] Terminal hair has a larger diameter and longer length than intermediate type (intermediate length and diameter found on arms and legs) and vellus type (small hairs on eyelids, forehead, bald scalp). The initial 0.5 cm adjacent to the scalp represents methylmercury exposure ~1–3 weeks before collection. Longitudinal analysis of hair for mercury suggests the approximate time of acute ingestion, based on average hair growth rates (~1 cm/month with a

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10-day lag period for the formation of the hair and a range of 0.6–3.4 cm/month).[285,516]

Hair/Blood Mercury Ratio

The hair (μg/g)/blood (mg/L) Hg ratio of 250:1 is a commonly used measure of past methylmercury exposure in nonoccupational environments;[517] however, estimating this ratio is a complex calculation that depends on a variety of factors including age, sex, diet, season, and analytical method. Frequently, these calculations differ from estimates based on the history of food consumption and methylmercury concentrations in ingested foods.[518] Consequently, total hair Hg concentrations do not always correlate to total whole blood Hg concentrations or Hg toxicity, particularly on an individual basis following chronic methylmercury exposure. In a study of paired hair and blood mercury samples from 1,000 children at birth, ages 7 and 14 the mean ratio at birth using cord blood was ~200.[519] The hair/blood mercury ratios of this cohort at 7 and 14 years of age were 360 and ~250, respectively. In a Canadian study of 1,333 individuals from aboriginal communities in Northern Quebec using ANOVA and Estimated Marginal Means, the error at the community level in blood Hg estimated from hair Hg using the 250:1 ratio was −25% to +25% with mean underestimation in females of −8.4% and mean overestimation in males of +5.8%.[520] The corresponding error at the individual level was −98.7% to +1,040%, resulting in observed hair/blood ratios of 3–2,845. Although properly handled hair samples are surrogate biomarkers for blood mercury concentrations in epidemiological studies of large groups exposed to methylmercury, the utility of hair testing for individuals in the clinical setting is limited because the correlation between hair and blood mercury concentrations varies substantially. In the clinical setting, hair mercury concentrations should be confirmed by measurement of mercury in blood samples as a result of the potential overestimation of the actual mercury concentration.[330] Even in the setting of epidemiology studies, there is substantial imprecision (i.e., coefficient of variation near 30%) in the maternal hair to cord blood mercury ratio; therefore, calibration of this ratio should be confirmed by analysis of cord blood in each study.[519] External contamination is a potential source of inaccurate analysis, particularly with methylmercury compounds that absorb more readily on the hair shaft than inorganic mercury compounds.[521]

General Population

Typically, total hair mercury concentrations (i.e., primarily methylmercury) are <1 μg/g in individuals with little fish consumption; however, this value may increase to >30 μg/g when the diet contains frequent amounts of fish with high Hg concentrations.[512] In a study of 559 human head hair samples from fish-eating populations around the world, the mean mercury concentration ranged from 0.5 ppm in Germany to 3.9 ppm in Japan.[522] The mean hair mercury concentration varied with fish consumption, ranging from 1.4 ppm for <1 fish meal/month to 11.6 ppm for ≥1 fish meal/day.

Toxicity

Methylmercury poisoning occurred around Minamata Bay, Japan (1940s–1950s) with the identification of the toxin in 1959; consequently, dose-response relationships between hair mercury concentrations and neurological disease were not well-characterized during the most prevalent time of the disease. Mercury concentrations in hair of >50 μg/g (ppm) suggest the possibility of the development of sensory disturbances based on analysis of patients with methylmercury poisoning in Niigata, Japan from eating contaminated fish from the Agano River during the 1960s;[507] however, retrospective analysis of methylmercury poisoning in Niigata suggested the occurrence of this disease in patients with hair Hg concentrations of <50 μg/g *at* the time of initial neurological examination.[523] In addition to the validity of hair analysis, the issue of the time of the poisoning in relation to the hair analysis complicates the interpretation of the latter study. Analysis of data obtained from 473 patients clinically diagnosed with methylmercury poisoning several months after eating contaminated Iraqi wheat and barley did not detect neurological symptoms when the total Hg hair concentration was <300 μg/g; however, neither whole blood total Hg nor total hair Hg correlated well to neurological symptoms.[524] The study did suggest that the fetus is particularly susceptible to the effects of methylmercury. The longitudinal Seychelles Child Development Study did not detect a relationship between prenatal Hg exposure and 21 endpoints for neurodevelopmental deficits; the study followed the 553 children to age 19 years.[525] Their mean prenatal Hg hair concentration was 6.9 μg/g, whereas the mean recent postnatal Hg Hair concentration was 10.3 μg/g. The Seychelles mothers averaged 12 fish meals/week.

The Faroe Islands Study enrolled 1,022 singleton births with neuropsychological testing at 7 and 14 years.[526] Pilot whale meat was the primary source of mercury in the mothers. The geometric mean of their prenatal hair Hg concentration was 4.2 μg/g with a range of <0.2–40 μg/g. Regression analysis indicated prenatal methylmercury exposure correlated to deficits in finger

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tapping speed, reaction time on a continued performance task, and cued naming; postnatal methylmercury exposure did not produce a discernible effect on the test results. Follow-up of 847 members of the cohort at 22 years of age indicated the cognitive deficits observed were smaller than at examinations at younger ages; deficits in Boston Naming Test (BNT) and other tests of verbal performance were significantly (negatively) associated with the cord-blood mercury concentration, whereas most other neuropsychological tests did not reach statistical significance.[527] A hierarchical model of general intelligence suggested a 2.2 IQ point reduction for a 10-fold increased prenatal methylmercury exposure. The issue of how to adjust for these exposures complicates the interpretation of the results of the Faroe Islands study.[528] The presence of co-contaminants (e.g., PCBs) or nutritional differences may account for some of the differences between the Seychelles and Faroe studies.

Abnormalities

Imaging

Abnormalities of fetal brains on CAT scanning following methylmercury poisoning are relatively mild compared with the clinical features of the disease. CAT scans of the brain do not effectively differentiate cerebral palsy from methylmercury poisoning.[529] For patients followed long-term with Minamata disease, the MRI demonstrates lesions of the calcarine area, cerebellum, and postcentral gyri that correlate to neurological abnormalities of visual field constriction, ataxia, and sensory deficits, respectively.[530] The slightly hypointense, T1-weighted images and the hyperintense, T2-weighted images of the visual cortex suggest status spongiosus. In alcoholism, the superior vermis of the cerebellum is more severely affected compared with the inferior vermis in the Minamata disease.

Neuropsychological Testing

There are few data on the effect of low mercury concentrations on cognitive function in adults. A cross-sectional study of 474 urban volunteers 50–70 years of age did not detect significant impairment of total whole blood Hg concentrations on neurobehavioral test scores in 7 domains (nonverbal reasoning and intelligence, language, verbal memory, visual memory, visuoconstruction and visuoperception, motor and manual dexterity, executive function).[531] The median total whole blood mercury concentration was 2.1 μg/L with a range of 0–16 μg/L. In the US Treatment of Lead-Exposed Children study of 780 children with elevated blood lead levels, whole blood methylmercury concentrations were measured simultaneously with high-performance liquid chromatography/inductively coupled plasma/mass spectrometry.[532] The geometric mean total methylmercury concentration was 0.56 μg/L (95% CI: 0.52–0.59 μg/L). Linear regression models did not suggest adverse neuropsychological effects from methylmercury. A 1 μg/L increase in methylmercury concentration was associated with an increase of 2.1 Full-Scale IQ points (95% CI: 0.4–3.8 points).

HEALTH SURVEILLANCE

Risk Assessment

The US Agency for Toxic Substances and Disease Registry (ATSDR) reduced the chronic-duration (≥365 days) minimal risk level (MRL) for methylmercury to 0.3 μg/kg/day based on neurodevelopmental outcomes in children exposed *in utero* to methylmercury from maternal fish ingestion.[14] The previous value was based on a no-observed-adverse-effect-level (NOAEL) of 0.23 mg/kg/d derived from a rodent study that detected developmental effects on operant behavioral performance in the offspring of rats given methyl mercuric chloride on gestation days 6–9. In addition, the previous calculation used data from developmental measurements in Iraqi children of mothers consuming bread contaminated with mercury-containing fungicide. The estimated maternal exposure sufficient to cause biological damage in offspring was 1 μg/kg body weight daily, based on maternal mercury concentrations of 10 ppm in hair samples.[373] More recent data from the Seychelles Child Development Study demonstrated no decrements in neurobehavioral tests of children born to mothers with 15.3 ppm mercury in maternal hair.[422] The overall uncertainty factor for the recent MRL was 4.5, consisting of 1.5 for variability in hair-to-blood ratios, 1.5 for interindividual variability, and 1.5 for extrapolation from a population outside the United States.

The US EPA also considers the developing human nervous system as the most sensitive end point for determining safe levels of exposure to mercury compounds. The previous chronic oral R_fD was 0.3 μg/kg/day based on paresthesias in Iraqi adults eating methylmercury-contaminated grain.[533] The current R_fD is 0.1 μg/kg/day based on a benchmark dose of 11 ppm methylmercury in maternal hair causing congenital neurological abnormalities in Iraqi children born to mothers consuming methylmercury-contaminated bread. The

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ratio of 250:1 (μg Hg/mg in hair to μg methylmercury/mL blood) was used to derive the R_fD critical dose and convert the maternal hair concentration to 44 μg/L fetal blood.[534]

The WHO tolerable limit for mercury in hair is 5 ppm based on the estimated threshold effect of 50 mg/kg and a safety factor of 10 for the greater estimated sensitivity of the developing brain.[535] Although some methylmercury may be converted to inorganic mercury in the environment, almost all mercury in water is inorganic; hence, exposure guidelines for water are based on total Hg consisting primarily of inorganic mercury. Examination of methylmercury concentrations in the cord blood of residents of Minamata indicated a dose-response relationship between methylmercury concentrations and the development of congenital Minamata disease.[536] The lowest no-observed-effect-level (NOAEL) in the Iraqi outbreak of methylmercury poisoning was ~400 μg/g hair as measured by the maximum hair mercury level of the mother during pregnancy.

Environmental Monitoring

Table 20.6 lists the guidelines and regulations for organic mercury. Organic mercury compounds contain at least one carbon atom covalently bonded to mercury. Because of the conversion of aryl (e.g., phenyl) and alkoxyalkyl (e.g., methoxyethyl) mercuric salts to inorganic mercury in the body, recommendations for exposure to these mercury compounds follow the guidelines for inorganic mercury. Short-chained alkyl Hg compounds (e.g., methylmercury, ethylmercury) are very stable compounds that resist biotransformation. US OSHA establishment of a PEL–TWA of 100 μg/m^3 and a STEL of 30 μg/m^3 for alkyl mercury compounds along with a skin notation was vacated by the 11th US Circuit Court of Appeals in 1992. The recommendations of ACGIH and most other countries are similar to the vacated OSHA values. NIOSH defines the level immediately dangerous to life (IDLH) as 2,000 μg/m^3 for alkyl mercury compounds.

TABLE 20.6. Short-chain alkyl organic mercury guidelines and regulations. For these compounds, mercury binds directly to simple straight-chain groups (e.g., methyl, ethyl) rather than to more complex carbon configurations.

Exposure Limit	Value
OSHA	
PEL–TWA[a] (8-hour)	10 μg/m^3[b]
PEL-Ceiling[a]	40 μg/m^3[b]
NIOSH	
REL–TWA (10-hour)[a]	10 μg/m^3 (as Hg)
STEL[a]	30 μg/m^3 (as Hg)
IDLH[a]	2,000 μg/m^3 (as Hg)
ACGIH	
TLV–TWA (8-hour)[a]	10 μg/m^3
STEL-Ceiling[a]	30 μg/m^3
US EPA	
RfD (chronic oral exposure, methylmercury)	0.1 μg/kg/day
ATSDR	
MRL (chronic oral exposure, ≥365 days)	0.3 μg/kg/day
US FDA	
Methylmercury (maximum edible seafood)	1 μg/g
WHO	
Tolerable weekly intake methylmercury[c]	1.6 μg/kg body weight
Tolerable limit hair methylmercury	5 μg/g (ppm)

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; IDLH = immediately dangerous to life and health; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time–weighted average; US EPA = US Environmental Protection Agency; US FDA = US Food and Drug Administration; WHO = World Health Organization.
[a] Skin notation; [b] Vacated 1992; [c] Proposed 2003.

Biological Monitoring

Urine

As a result of the primary excretion of alkyl mercury compounds (e.g., methylmercury) in the feces and very small amounts of these compounds in the urine, urine Hg concentrations do not correlate to the intensity of exposure to these compounds. Consequently, monitoring mercury concentrations in urine is not a practical method to evaluate alkyl mercury exposure. Aryl and alkoxyl mercury compounds behave pharmacologically similar to inorganic mercury compounds. The use of chelating agents to estimate the total body burden is not recommended because of the lack of baseline values, interindividual variability, and inadequate data on clinical efficacy.[188]

Blood

For workers chronically exposed to mercury, the intensity of exposure to mercury correlates to the whole blood Hg concentration at the end of a work shift.

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Organic mercury concentrates in the erythrocytes; therefore, serum and plasma mercury concentrations do not reflect the total body burden of mercury. The usefulness of whole blood mercury concentrations as biomarkers is limited to recent exposure because the initial elimination half-life of mercury in the blood is ~2–4 days. Although whole blood Hg concentrations correlate to the methylmercury body burden, the presence of alkyl mercury compounds in the diet complicates the interpretation of the results and limits the sensitivity of the whole blood mercury concentration following occupational exposure to low ambient air Hg concentrations. The ACGIH does not recommend a specific BEI for methylmercury or other organic Hg compounds.

Medical Monitoring

Preemployment physical examinations should focus on the documentation of baseline renal and central nervous system function including a urinalysis. Subsequent examinations should emphasize the detection of signs and symptoms of central nervous system dysfunction (personality changes, tremors, gait disturbances, insomnia, weight loss, ataxia).

TREATMENT

Decontamination

There are no specific clinical data to guide gut decontamination in the treatment of organic mercury poisoning.

Enhancement of Elimination

A 2-hour exchange transfusion removed ~6% of the estimated body burden of mercury from two children severely poisoned by methylmercury; however, no dramatic improvement occurred in the clinical condition of these two patients.[537]

Dimercaprol (BAL)

Although the use of BAL is indicated in severe acute inorganic mercury poisoning, the effectiveness of BAL in organic mercury poisoning remains questionable. Dimercaprol does not reverse the chronic neurological effects of alkyl mercury poisoning; however, BAL is an option for the treatment of acute ingestions of aryl organic mercury compounds (e.g., phenylmercuric acetate) that are converted to inorganic mercury in the body.

DMPS

2,3-Dimercaptopropane-1-sulfonate (DMPS) is an investigational oral analog of BAL that appears less toxic than DMSA. Based on a comparison of half-lives, DMPS was the most effective chelating agent in a series of 16 patients treated during the outbreak of methylmercury poisoning in Iraq based on reduction in blood elimination half-lives; the amount of methylmercury removed was not reported.[538] Treatment with DMPS (Dimaval®, Heyl and Co., Berlin) was associated with the resolution of hematuria and the reversal of electromyographic abnormalities in patients with methylmercury intoxication.[234]

DMSA

A review of the medical literature recommended the use of DMSA (meso 2,3-dimercaptosuccinic acid, Succimer®) in organic mercury toxicity based on greater Hg excretion in clinical studies than DMPS;[241] however, these studies did not document improved clinical outcomes. Although this water-soluble BAL analog is a potential chelating agent for mercury, this drug has not been officially approved for the treatment of mercury intoxication. Unlike elemental and inorganic mercury, organic mercury forms a thermodynamically stable bond with the deprotonated thiol group that limits DMSA effectiveness.[539] Animal and clinical studies suggest that pretreatment with DMSA chelation removes mercury primarily from the main peripheral site of deposition (i.e., the kidney) but not from the brain.[208,248]

There are few data on the use of DMSA in organic mercury poisoning. Despite the initial excretion of large amounts of mercury (39,800 µg/24 hours) following DMSA therapy, a 48-year-old chemist with suspected dimethylmercury poisoning died 4 months after the initiation of chelation.[460] Chelation began 14 days after neurological symptoms developed; 8 days later, she became comatose. The half-lives of mercury in the blood ranged from 29–37 days during chelation. During the treatment of severe thimerosal toxicity, the administration of both DMSA and DMPS did not significantly increase the renal excretion of mercury; the patient recovered with supportive care.[414]

Analysis of blood samples from 67 children receiving Succimer® (DMSA) in the Treatment of Lead-Exposed Children Trial demonstrated a modest decrease in the organic mercury concentration in blood samples compared with untreated children.[540] After three 26-day courses of DMSA, the organic mercury concentrations

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in the DMSA group ($n = 31$) were ~80% of the placebo group ($n = 33$); however, the difference was not statistically significant ($P = 0.19$) after adjustment for age, sex, race, center, and earlier organic mercury concentrations. DMSA treatment produced an initial reduction in the organic mercury concentration and slowed but did not reverse the accumulation of organic mercury. The average total mercury concentrations of the treated children were ~70% higher than children in the National Health and Nutrition Examination survey (0.56 ng/mL vs. 0.34 ng/mL, respectively). The clinical benefit of the use of succimer® for reducing organic mercury concentrations in this setting is equivocal.

N-Acetylcysteine (NAC)

In a study of mice fed methylmercury-contaminated water, the administration of NAC in the drinking water beginning 48 hours after the beginning of the experiment increased Hg excretion in the treatment group.[541] For the subsequent 48 hours, the treated group excreted 47–54% of the ^{203}Hg in the urine compared with 4–10% for the untreated (control) group. This compound increased the urinary organic mercury elimination rate in one case of acute methylmercury ingestion,[123] but the use of NAC remains experimental because there are no clinical data regarding the effect of NAC on clinical outcome.

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Chapter 21

MOLYBDENUM

HISTORY

The Greek name, *molybdos*, translates as lead-like; the Greeks and Romans did not distinguish molybdenum from lead, graphite, or other similar compounds. Analysis of 14th-century Japanese swords indicates molybdenum (Mo) was used in the production of weapons. The Swedish scientist, Carl Wilhelm Scheele, first discovered molybdenum as a substance different from graphite in 1778. Shortly thereafter, his colleague, Peter Jacob Hjelm, prepared an impure, black powder from an oxide of molybdenite that he called molybdenum. The pure form of molybdenum was not produced until Moissan separated the pure metal in 1893.[1] The physical properties of molybdenum allow the replacement of tungsten in some steel alloys; the use of molybdenum as an alloying metal in armaments containing plate steel began in the late 1800s. Commercial production of molybdenum started in 1885 with the opening of the Knaben Gruver mine in southern Norway. The shortage of tungsten during World War I accelerated the search for molybdenum sources, culminating in the opening of the massive Climax molybdenum deposit in Colorado in 1918.

PHYSIOCHEMICAL PROPERTIES

Molybdenum is a member of the Group 6 (Group VIb) series of the periodic table along with chromium and tungsten. Molybdenum does not exist naturally in its pure metallic state as a result of the association of molybdenum with other elements. Of the five oxidation states (2–6), the dominant oxidation states are Mo^{4+} and Mo^{6+} with the latter being the most stable. Molybdenum shares many physiochemical properties with tungsten.[2] Of the commonly available metals, only tungsten and tantalum have higher melting points. Molybdenum alloys with tungsten and several lighter alloys (aluminum, chromium, cobalt, iron, silicon) to increase strength and reduce weight of the alloys. The chemistry of molybdenum is complex with this metal forming a very complex series of compounds with the exception of some simple halides, oxides, and sulfides. The dominant form of molybdenum in dilute solutions (e.g., soil, natural waters) is the molybdate anion (MoO_4^{2-}).[2] In solutions containing moderate to high concentrations of molybdenum, this element readily polymerizes into a wide variety of complex structures involving polymolybdates.

Molybdenum exists as a silver-white to dark-gray/black powder, whereas molybdenum trioxide (CAS RN: 1313-27-5) is a white powder that converts to a yellow material when heated. The mineral molybdenite (molybdenum disulfide, MoS_2) is a gray, lustrous, and poorly water-soluble powder. Water-soluble molybdenum compounds include ammonium paramolybdate, ammonium molybdate (400 g/L, 20°C), calcium molybdate, sodium molybdate, and molybdenum trioxide. Water-insoluble molybdenum compounds include elemental Mo, molybdenum dioxide, lead molybdate, and molybdenum disulfide. Table 21.1 lists the identifying information and physical properties of common molybdenum compounds.

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TABLE 21.1. Identifying information and physical properties of molybdenum and molybdenum compounds.

Physical Characteristic	Molybdenum	Calcium Molybdate	Sodium Molybdate	Molybdic Oxide	Molybdenum Disulfide
CAS RN	7439-98-7	7789-82-4	7631-95-0	1313-27-5	1317-33-5
Molecular formula	Mo	$CaMoO_4$	Na_2MoO_4	MoO_3	MoS_2
Molecular weight (g/mol)	95.95	200.01	205.92	143.94	160.08
Valence	0	6	6	6	4
Color	Silver-white, dark-gray/ black	White	White	Colorless to white-yellow	Gray
Physical state	Powder	Powder, crystalline	Granular	Powder, dry	Powder
Density (g/mL)	10.28 (20°C)	4.35 (25°C)	3.28 (18°C)	4.70 (26°C)	4.8 (14°C)
Melting point (°C)	2629	965	687	795	1185
Boiling point (°C)	4612	ND	ND	1115[b]	1450[b]
Water solubility (g/L, 25°C)	Insoluble	Insoluble[a]	Insoluble	1.07 (18°C)	Insoluble

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number, ND = No data
[a] Decomposes in hot water; [b] Sublimes.

EXPOSURE

Production Processes

The United States is the world's largest producer of molybdenum as a result of large natural reserves in the western mountain regions. The major sources of metallic molybdenum include primarily mining operations and by-products of copper and tungsten mining operations. Molybdenum salts are by products of uranium mining. Molybdenite (MoS_2), ferrimolybdite ($Fe_2[MoO_4]_3$), and jordisite (amorphous molybdenum disulfide) are the most abundant and commercially important ores for the production of molybdenum with molybdenite the most important source. Less economically important molybdenum-containing ores in decreasing order of importance are as follows: powellite ($CaMoO_4$), wulfenite ($PbMoO_4 \cdot 8H_2O$), and ilsemanite (molybdenum oxysulfate).

Roasting of molybdenite ores produces technical-grade Mo oxides used in steel. Conversion of technical-grade Mo oxide to its purer form requires sublimation that requires precise temperature control to prevent material losses from sublimation and volatilization at temperatures of >700°C.

Uses

The vast majority of molybdenum is used in metallurgical applications (e.g., stainless steel, cast iron alloys, iron-based construction steel, high-temperature and tool steel alloys). Stainless steel typically contains 1–3% Mo. The addition of molybdenum to steel alloys improves the commercial characteristics of the alloy by increasing the strength, thermal resistance, and corrosion resistance of the alloy. Examples of the commercial applications of molybdenum-containing alloys include gas and steam turbines in power generation, missiles, and aircraft. Molybdenum exposure usually occurs during the production and fabrication of molybdenum-containing products in the form of elemental Mo oxides and Mo sulfides in dust or fumes.

Metallic molybdenum enhances the adherence of siliceous material to metals; therefore, molybdenum is useful in metal–ceramic composites. Molybdenum trioxide is a corrosion inhibitor, a reagent for chemical analysis, and a blue dye for ceramic glazes and enamels. Zinc molybdate provides stabilizing and anticorrosive properties for paint. Molybdenum acetylacetonate is a catalyst for the polymerization of ethylene and the production of polyurethane foam. Molybdenum disulfide possesses a sheet-like structure similar to graphite, commercially useful in dry lubricants and chemical catalysts. Fertilizers for leguminous plants contain molybdenum salts; standard commercial fertilizers have ~2–6 ppm Mo. Ammonium tetrathiomolybdate is an experimental chelating agent for conditions that increase copper concentrations (e.g., Wilson's disease).[3,4]

Sources

Molybdenum is a rare earth metal. Most Mo exposure results from the use of Mo in steel alloys and less commonly as biocides and constituents of photovoltaic technology. The major anthropogenic sources of molybdenum in the environment include combustion of coal, municipal sewage sludge, and industrial or mining

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operations. The daily intake of molybdenum from the air and drinking water is negligible compared with the absorption of molybdenum from the diet, except in molybdenum-mining areas.[5]

Air

The molybdenum concentrations in the ambient air are normally low compared with other trace elements (e.g., cadmium, copper, lead, zinc). Higher Mo concentrations occur in the ambient air of urban areas compared with rural areas (0.01–0.03 μg/m^3 vs. 0.001–0.0032 μg/m^3, respectively).[6] Although the release of molybdenum from natural sources far exceeds the release of molybdenum from anthropogenic sources, the mobilization of molybdenum from fossil fuel may produce substantial elevation of molybdenum in the immediate vicinity of the combustion site. Residues from the combustion of coal are important anthropogenic sources of molybdenum in the environment.[1] The Mo concentration in fly ash ranges from 7–160 mg/kg.[7]

Soil

Although the Mo concentration in soil averages ~1,000–2,000 μg/kg, the Mo concentration varies considerably depending on the particular type of geological materials present in the soil and soil pH.[1] Sedimentary-related material (e.g., shale) contains high Mo concentrations, whereas acidic soils are often deficient in molybdenum. Generally, molybdenum-deficient and molybdenum-excessive soils are defined by Mo concentrations of <200 μg/kg and > 700 μg/kg, respectively.[5] Uptake of molybdenum by plants depends on a variety of factors in the soil including mineral content (manganese, phosphorus, sulfur), moisture content, sesquioxide content, pH, and organic matter.[1] Mo uptake by plants occurs mostly from alkaline or neutral soil with Mo concentrations in plants grown in acidic soil (e.g., pH = 5.5) substantially lower than those grown in neutral or alkaline soil. Molybdenum commonly contaminates municipal sewage sludge with Mo concentrations averaging ~15,000 μg/kg and ranging from ~1,000–40,000 μg/kg.[8]

Water

Most natural waters contain low Mo concentrations in the range of <2–3 μg/L, unless local anthropogenic sources contaminate the water. Near industrial sources (e.g., molybdenum mining areas), the Mo concentration in surface water may reach 200–400 μg/L and 25,000 μg/L in groundwater.[9] Molybdenum concentrations in well water may vary significantly over short distances. In streams draining areas with high Mo content, the Mo concentration in water is usually <6,000 μg/L, similar to the Mo concentrations in streams that drain areas with low molybdenum concentration.[1] Increased water pH increases Mo solubility and leachability, whereas acidic conditions decrease the transfer of molybdenum from soil to water. The Mo concentrations in acidic groundwater in contact with soil containing 800 mg Mo/kg were <200 μg/L.[10]

Diet

The diet is the major source of molybdenum for most people. The average daily Mo intake ranges from 100–500 μg, although water contaminated by industrial Mo sources may increase the daily intake to 1,000 μg.[11] Daily adult intake of Mo typically ranges from ~50–240 μg. Analysis of the daily molybdenum intake of 56 German adults demonstrated a range of 47–89 μg as measured by the dithiol and Sandell–Kolthoff procedure.[12] In a study of adult residents in Denver, the daily dietary Mo intake ranged from 120–240 μg with a mean of 180 μg.[13] A study of older children and adults in the northeastern US demonstrated a daily Mo intake ranging from 74–126 μg.[14] The average daily Mo intake (i.e., ~225 μg) in Japanese residents is higher than in Western cultures as a result of the relatively higher intake of rice and soybean products.[15] The WHO estimates the minimum daily Mo requirement is 2 μg/kg body weight.

Molybdenum concentrations in plants range widely (<0.5 to over 100 mg/kg dry weight). Generally, foodstuffs from aboveground plant material (e.g., legumes, leafy vegetables, cauliflower) contain relatively high Mo concentrations compared with food from tubers or animals. The richest sources of molybdenum in the diet include beans, cereal grains, kidney, leafy vegetables (e.g., spinach), legumes, nuts, liver, and milk.[16] Fruits, sugars, oils, stem and root vegetables, and muscle from animals (cod, chicken, anchovies, sardines) usually contain relatively low Mo concentrations. The adult Recommended Daily Allowances (RDA) range is 150–500 μg/day. Tobacco contains small Mo concentrations (0.3–1.76 μg/g); therefore, smoking is probably not a significant Mo source.[17]

DOSE EFFECT

Humans

Molybdenum is an essential element for plants and animals, with molybdenum possessing relatively low

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toxicity. A balance study of 24 girls aged 7–9 years ingesting 75 μg Mo/day demonstrated elevated urinary Mo concentrations; the abstract of the study did not identify any adverse effects.[18] Rarely, deficiencies of dietary molybdenum are associated with adverse effects; however, the ubiquity of molybdenum in plants and animals significantly limits the ability to produce molybdenum-deficient diets. During prolonged parenteral nutrition, a patient developed amino acid intolerance, irritability, altered consciousness, and biochemical abnormalities (hypermethioninemia, elevated urinary xanthine and sulfite, reduced urinary uric acid and sulfate).[19] These abnormalities resolved after the administration of 160 μg Mo/day.

Animals

Molybdenum toxicity in animals depends on a variety of factors including age and species of the animal, previous dietary history, and the relative amounts of copper, sulfur, and molybdenum in the diet.[16] Ruminants (e.g., sheep, cows) develop adverse reactions to feed containing 2–30 μg/g Mo, whereas horses and pigs tolerate feed with Mo concentrations of >1,000 μg/g Mo. Low copper and sulfur concentrations in the diet enhance molybdenum toxicity; the clinical features of Mo toxicity are similar to those of copper deficiency. Chronic exposure of animals to molybdenum oxide fumes of 53 mg/m^3 for 1 hour daily produced pulmonary irritation and fatty changes in the liver and kidney; all animals survived.[20]

TOXICOKINETICS

Absorption

The gastrointestinal tract readily absorbs soluble, but not insoluble molybdenum compounds. The absorption rate of molybdenum from the diet of patients and healthy volunteers averaged ~50% in two patients with pancreatic insufficiency[21] and 88–93% in a study of patients receiving 22–1,490 μg Mo/day for 24 days.[22] Animal studies indicate that the poorly soluble compound, molybdenum disulfide, is not well absorbed in the lungs or the gastrointestinal tract compared with the more soluble hexavalent molybdenum compounds. The ingestion of Mo in food decreases the bioavailability of Mo compared with purified Mo. In a study of four men receiving labeled and unlabeled molybdenum, the mean bioavailability of food-bound Mo was 83%.[23]

Distribution

In the blood, molybdenum binds to α_2-macroglobulins in the form of molybdate. The binding of molybdenum to the protein, spectrin, also occurs on the erythrocyte membrane. Based on analysis of postmortem tissues, the highest concentrations of molybdenum appear in the kidney and liver with smaller concentrations found in the adrenal glands and long bones.[24] Little molybdenum exists in the brain and gastrointestinal tract (except the jejunum). Retention of molybdenum probably is small.

Elimination

Animal and volunteer studies indicate elimination of absorbed molybdenum compounds occurs rapidly, primarily via renal excretion with urinary Mo excretion increasing as the Mo dose increases. In a study of four adults, the mean renal excretion of Mo over 12 days increased from 26.7% after ingesting 23.8 μg Mo/day to 84.5% when fed 1,378 μg/day.[22] Very little excretion of molybdenum into the bile occurred in a volunteer study following the administration of daily Mo doses up to 1,500 μg. In a radiotracer study of five volunteers, Mo elimination was biexponential with plasma half-times ranging from 4–70 minutes for the fast component and 3–30 hours for the slow component.[25] The presence of high concentrations of copper and sulfates in the diet enhances the elimination of molybdenum by blocking protein carriers and inhibiting tubular Mo reabsorption.[26] Elimination is usually complete within several weeks.

Maternal–Fetal Kinetics

The correlation of umbilical cord blood Mo concentration in newborns with maternal concentrations of molybdenum suggests molybdenum compounds easily cross the placental barrier with similar values between the umbilical cord and maternal serum. The mean plasma Mo concentration in 33 mothers was 1.44 μg/L with a range up to ~3 μg/L, similar to their infants (mean = 1.44 ± 0.89 μg/L, r = 0.48) as measured by flameless atomic absorption spectrophotometry.[27] The mean Mo concentration in 29 maternal serum samples was 0.7 ± 0.3 μg/L (range, 0.3–1.4 μg/L) compared with 0.8 ± 0.3 μg/L (range, 0.4–1.6 μg/L) in umbilical cord blood from their infants, as measured by inductively coupled plasma/mass spectrometry.[28] The mean Mo concentration in colostrum obtained from 27 of these mothers between postpartum days 1–3 was 7.0 ± 3.8 μg/L (range, 3.4–18.8 μg/L). The mean Mo concentration in

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breast milk in a study of six French mothers breastfeeding during the first month of their babies lives was ~10 μg/L at birth with the Mo concentration in breast milk decreasing to ~1 μg/L 2 months postdelivery.[29] The mean Mo concentration in breast milk from 13 postpartum women decreased from 15.0 ± 6.1 μg/L on postpartum day 1 to a stable concentration of ~2 μg/L at 1 month.[30] In this study, the estimated daily Mo intake of seven breastfeed infants at 35 ± 3 days after birth was 2.1 ± 1.5 μg. A 28-year-old breastfeeding mother underwent a metal-on-metal hip implant 13 weeks after delivery.[31] During the first 3 months after surgery, breast milk Mo concentrations peaked at 5 days postop (1.32 μg/L) and 77 days postop (1.67 μg/L), whereas the serum Mo concentration peaked at 5 days (5.46 μg/L). The serum and breast milk Mo concentrations did not correlate.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

Molybdenum is an essential metal for humans and most forms of life except blue-green algae because several important enzymes contain molybdenum including xanthine oxidase/dehydrogenase, aldehyde oxidase, and sulfite oxidase. The former two enzymes are involved with the terminal metabolism of purines and the oxidation of aldehydes, whereas the latter enzyme is involved with the oxidation of sulfite to sulfate. Enzymes containing molybdenum (molybdoflavoproteins) catalyze basic metabolic reactions in the carbon, sulfur, and nitrogen cycles. In plants, molybdenum acts as an enzyme activator for nitrogen metabolism via reactions with nitrogenase, a nitrate reductase that reduces nitrogen to ammonia. Consequently, molybdenum deficiency in legumes produces effects similar to those of nitrogen deficiency.[1] All these molybdenum-containing enzymes catalyze oxidation-reduction reactions. The two major types of reactions involving molybdenum-containing enzymes are as follows: 1) the transfer of oxygen atoms to/from the electron pair of a substrate (DMSO reductase, sulfite oxidase), and 2) oxidative hydroxylation of aldehydes and aromatic compounds (xanthine oxidase, aldehyde oxidoreductase).[32] The cofactor, molybdopterin, anchors the molybdenum atom to the active site of a protein in reactions involving the sulfur and carbon cycles.[16] Deficiency of this cofactor has been associated with seizures, mental retardation, severe cerebral atrophy, and early death.[33,34] Substantial variation in aldehyde oxidase activity occurs between species with humans demonstrating the highest activity, rats and mice low activity, and dogs with no detectable activity, whereas xanthine oxidoreductase activity is common among animal species.[35]

Mechanism of Toxicity

Molybdenosis (teart) is a disease affecting primarily ruminants (cattle, sheep) that occurs during grazing on pastures with high molybdenum and sulfate content with low copper availability.[36] In animals, the clinical appearance of molybdenum toxicity is similar to the disease of copper deficiency. The formation of trithiomolybdate by the replacement of oxygen by sulfide in the stomachs of ruminants probably alters the affinity of copper for competing ligands; this reaction produces disturbances in copper distribution and elimination.[37] Signs of molybdenum toxicity in animals include anemia, anorexia, profound diarrhea, joint abnormalities, osteoporosis, hair discoloration, reduced sexual activity, and death. Diets low in sulfates and copper enhance the toxicity of molybdenum,[38] whereas copper supplementation reduces the prevalence of molybdenosis in cattle grazing on soil heavily contaminated with Mo.[39]

CLINICAL RESPONSE

Little data on human molybdenum toxicity are available. The acute toxicity of Mo and Mo compounds is very low.

Environmental Exposure

Exposure to molybdenum from environmental sources is negligible because this metal rarely occurs naturally. In 1961, Kovalskii et al. associated a gout-like syndrome with excessive environmental Mo exposure (10–15 mg molybdenum/day).[40] The disease occurred in Armenians living in areas rich in molybdenum. The predominant clinical features associated with increased Mo intake included hyperuricemia, arthralgias, erythema, edema, and deformity of the knees, hands, and feet. The exact cause of this disease remains unclear as a result of serious study limitations. In this study, the mean serum copper concentration of 1.13 mg/L in the 52 subjects was significantly below the normal mean serum copper concentration of 1.83 mg/L in the 5 controls.[41]

Occupational Exposure

A self-employed, overweight, 36-year-old industrial electrician developed acute arthritis with hyperuricemia

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and elevated serum C-reactive protein; the family history was positive for rheumatoid arthritis, but not gouty arthritis.[42] A limited reconstruction of the patient's workshop demonstrated total Mo dust concentrations of 2–10 mg/m^3 with background concentrations of 1 mg/m^3 from the cutting, grinding, and heating of molybdenum-containing metals. No other cause for his arthritis was established; however, his serum uric acid level remained elevated 1 year after the cessation of his Mo exposure. There is a lack of case reports and epidemiological studies on the occurrence of gouty arthritis in individuals with heavy occupational Mo exposure.

High Mo concentrations may irritate the upper respiratory tract. A 1963 Soviet study associated the development of pneumoconiosis in 3 of 19 workers exposed over 4–7 years to 1–19 mg Mo/m^3 as metallic molybdenum and molybdenum trioxide.[11] Nonspecific symptoms (anorexia, arthralgias, fatigue, headache, weakness) occurred in workers receiving an estimated Mo exposure of 10 mg/day as dust in a molybdenite roasting plant, but the lack of control groups and adequate follow-up complicates the interpretation of the clinical significance of this study.[43] These workers did not report arthritis-related symptoms despite elevated plasma/urine Mo concentrations, low urine copper concentrations, and moderately elevated serum uric acid concentrations compared with controls. This study did not detect any permanent sequelae.

Carcinogenesis

Neither the IARC nor the US Toxicology Program lists elemental molybdenum suspected carcinogens; however, the IARC added molybdenum trioxide to the list of possible carcinogens (Group 2B) based on sufficient evidence of carcinogenicity in animals (i.e., ↑ bronchioloalveolar carcinomas in mice) and inadequate evidence in humans.[44] A hypothesis-generating, hospital-based, retrospective case-control study demonstrated a statistical association (adjusted OR = 2.1, 95% CI: 1.2–3.7) between jobs with ever-exposure to molybdenum and lung cancer after adjustment for smoking, age, marital status, and socioeconomic status.[45] Evaluation of exposure involved both self-reporting (21 cases/12 controls) and job-task exposure matrices (52 cases/34 controls). The only duration of exposure of >21 years was associated with a statistically significant increased odds ratio (OR = 3.3, 95% CI: 1.3–8.3; 19 cases/12 controls) for lung cancer; however, self-reported Mo exposure did not correlate to an increased lung cancer risk. The poor exposure data, the uniqueness of these findings, and the multiple comparisons in this study prevent any conclusions regarding cancer causation. In this study, the association between chromium exposure and lung cancer was not statistically significant.

DIAGNOSTIC TESTING

SI Conversion Units

1 mg = 10.42 μmol
1 μmol = 95.95 μg

Analytical Methods

Older techniques for determining the molybdenum concentration in environmental samples include colorimetry (e.g., thiocyanate) and dithiol methods;[46] whereas atomic absorption spectrometry was the common method for analyzing Mo in biological samples.[47] Currently, neutron activation analysis and inductively coupled plasma/mass spectrometry or atomic emission spectrometry are the current methods of choice for confirmation of Mo concentrations in biological samples. The use of double-focusing magnetic sector/inductively coupled plasma/mass spectrometry operated in medium-resolution mode allows the detection of Mo in the range of 0.06 μg/L.[48] Using ion-exchange chromatography/inductively coupled plasma/mass spectrometry, the limit of detection for Mo in plasma samples was 1 ng/L with a coefficient of variation of <2%.[49] Potential contamination from glassware, reagents, syringes, and the environment complicates the interpretation of Mo concentrations in biological samples.

Biomarkers

Blood

There are few data comparing plasma and whole blood Mo concentrations; some Mo binding to the erythrocyte membrane and plasma proteins occurs.[50] In a study of 998 Swedish adults in their 70s, the mean whole blood/serum Mo ratio was 0.73 as measured by inductively coupled plasma/sector field mass spectrometry.[51] The mean whole blood/plasma Mo ratio in blood from 106 healthy French subjects was 0.90 (3.57 vs. 3.98 μg/L) as measured by inductively coupled plasma/mass spectrometry/collision cell technology.[52]

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Balance studies in metabolic units suggest plasma Mo concentrations reflect Mo exposure over the preceding 14 days at daily Mo intake up to 1,500 μg with plasma Mo concentrations correlating well to dietary Mo intake.[53] Prior to 1973, some studies reported mean whole blood Mo concentrations up to ~150 μg/L in subjects from areas rich in molybdenum including molybdenum mining areas. In a study of 26 residents of Missoula, Montana, the mean Mo concentration in 26 whole blood samples was 157 μg/L with a range of 5–410 μg/L as measured by fluorometry;[54] however, the reliability of these early methods is equivocal.

General Population

Most people in the general population have low whole blood Mo concentrations (i.e., <5 ng/mL); however, substantial individual variation in the blood Mo concentration occurs in the general population depending on the local Mo concentrations and diet.[55] The geometric mean whole blood Mo concentration in samples from 418 Venezuelan blood donors was 2.66 ± 0.66 μg/L (range, 1.20–4.80 μg/L).[56] In general, the average daily Mo intake is higher in Japanese residents than in residents of Western cultures. The geometrical mean and median serum Mo concentrations in blood samples from 70 healthy Japanese adults were 1.21 ± 1.34 μg/L and 0.90 μg/L, respectively, with a range of <0.1–9.11 μg/L as measured by inductively coupled plasma/mass spectrometry.[57] A majority (55.7%) had serum Mo concentrations of <1 μg/L and only 8.6% ($n = 6$) above 2 μg/L.

The serum Mo increases in patients with renal or liver dysfunction. In a study of 60 patients with renal failure requiring hemodialysis, the mean predialysis and postdialysis serum Mo concentrations were 21 ± 19 μg/L and 14 ± 7 μg/L, respectively, as measured by flameless atomic absorption spectrometry.[58] The reported reference range for serum Mo in this study was 0.2–1.3 μg/L. The serum Mo concentration in 14 Belgian patients with acute viral hepatitis was 6-fold higher (3.1 ± 1.46 μg/L) than 50 healthy adults (0.55 ± 0.21 μg/L) as determined by neutron activation analysis.[59]

Toxicity

Molybdenum is a minor constituent of hip implants; serum Mo concentrations are not usually elevated in a patient with either metal-on-metal Birmingham hip resurfacing or metal-on-metal total hip arthroplasties.[60] In a study of 132 MoM hip replacements followed for an average of 7 years, the mean whole blood Mo concentration remained stable between 1.70 (1–3 years) and 1.46 μg/L (6–7 years) as measured by inductively coupled plasma/mass spectrometry.[61] The mean preoperative plasma Mo concentration in 59 patients receiving standard MoM hip implants (4.5–7.0% Mo) was 1.21 ± 0.74 μg/L compared with 0.97 ± 1.09 μg/L 1 year after the implant as measured by graphite furnace atomic absorption spectrometry.[62] Patch testing demonstrated no hypersensitivity to 0.5% molybdenum chloride at the 1-year follow-up. The whole blood concentration of molybdenum in exposed workers frequently exceeds the Mo concentrations present in the general population; however, signs of clinical illness do not usually appear in these workers.[63] A study of 219 subjects from a fertility clinic suggested an inverse association between whole blood Mo concentrations and measures of male fertility (serum testosterone, sperm concentration, sperm morphology) based on linear regression analysis comparing low, medium, and high categories of Mo concentrations.[64,65] The clinical significance of this study is unclear because 70% (low Mo group) of the subjects had Mo concentrations below the limit of detection (1.0 μg/L). The upper 95% of the whole group was 2.0 μg/L; these values are well within normal reference ranges for whole blood Mo concentrations in the general population without excessive exposure to molybdenum.

Urine

A study of the urine from US residents [National Health and Nutrition Examination Survey (NHANES III)) demonstrated a 95th percentile Mo concentration of 168 μg/L.[66] The maximum Mo concentration was 688 μg/L as measured by inductively coupled argon plasma mass spectrometry. The urine Mo concentrations were similar in the NHANES IV study. In a sample of 2,019 adults 20 years and older, the geometric mean urine Mo concentration was 39.6 μg/L with a 95% upper CI of 144 μg/L. The median Mo concentration was 42.0 μg/L. In a study of the Danish population using inductively coupled plasma mass spectrometric analysis with ^{95}Mo as an isotope, the mean urine molybdenum concentration in urine was 42.5 μg/L (3.89 μg/mmol creatinine) with a 95% parametric reference interval of 10–124 μg/L (0.89–11.50 μg/mmol creatinine).[67] Age did not influence the urine Mo concentration.

Abnormalities

Several cohorts exposed to high Mo concentrations had hyperuricemia and low copper concentrations;[40,68] however, the design of these studies prevents the establishment of a definite causal relationship between Mo exposure and hyperuricemia or hypocupremia.

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HEALTH SURVEILLANCE

Risk Assessment

An estimated adequate and safe adult daily Mo intake based on balance studies was 150–500 µg.[69] A tolerable daily intake of 9 µg/kg was calculated from a NOAEL and LOAEL of 0.9 and 1.6 mg Mo/kg/day, respectively, based on adverse reproductive and fetal developmental effects in rats and mice, an uncertainty factor of 10 for intraspecies differences, and an uncertainty factor of 10 for interspecies differences.[70]

The NOAEL for students receiving supplemental molybdenum in their drinking water was 8 µg/kg/day.[68] A balance study of 24 girls aged 7–9 years ingesting 75 µg Mo/day demonstrated elevated urinary Mo concentrations, but the study did not identify any adverse effects.[18] Kovalskii et al. described a syndrome of hyperuricemia and arthralgias in Armenians consuming an estimated 10–15 mg Mo/day while living in an Armenian province.[40] This area contained high Mo concentrations in the soil. This cross-sectional epidemiology study compared the incidence of gout and uric acid concentrations of residents from Ankawa (average estimated daily Mo intake, 10–15 mg) with individuals in a new, adjoining settlement (average estimated daily Mo intake 1–2 mg). Of the 184 Ankawa villagers examined, 31% had clinical evidence of gout, whereas 17.9% of the 78 control villagers had similar findings. The average serum uric acid concentration of 52 Ankawa adults was 6.2 mg/dL compared with a mean of 3.8 mg/dL in five controls. Limitations of this study included inadequate statistical analysis, inconsistent methods of ascertainment, and lack of control of confounding variables (e.g., copper deficiency); therefore, the validity of the results of this study is debatable.[41] The US EPA (IRIS database) used this study to set 140 µg Mo/kg/day as the lowest observable adverse effect level (LOAEL).

Environmental Monitoring

The US OSHA PEL–TWA for soluble molybdenum compounds of 5 mg Mo/m^3, as total dust, and 10 mg/m^3 for insoluble Mo compounds as total Mo was vacated by court order. The existing US OSHA PEL–TWA for Mo and other insoluble Mo compounds is 15 mg Mo/m^3. The ACGIH TLV–TWA recommendations for poorly water-soluble Mo compounds (molybdenum disulfide, molybdenum dioxide) and metallic Mo are 10 mg/m^3 as inhalable particulate mass and 3 mg Mo/m^3 as respirable particulate mass. These recommendations are formulated to prevent local irritation and chronic respiratory effects.[71] The TLV–TWA recommendation for soluble Mo compounds (ammonium paramolybdate, ammonium molybdate, calcium molybdate, sodium molybdate, molybdenum trioxide) is 0.5 mg Mo/m^3 as a respirable particulate mass based on inflammation (chronic alveolar inflammation, squamous metaplasia of larynx, hyaline degeneration of respiratory epithelium) in rodent studies.

TREATMENT

Treatment of molybdenum toxicity is supportive. The low acute oral toxicity of Mo compounds (e.g., <100 mg Mo based on animal studies) limits the usefulness of gut decontamination (lavage, activated charcoal), particularly after the first 1–2 hours post-ingestion. The association of increased molybdenum toxicity with deficiencies of copper and sulfate suggests that diets rich in these substances may enhance recovery from the chronic ingestion of molybdenum, but no data are available to evaluate the efficacy of these supplements.

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Chapter 22

NICKEL

INORGANIC NICKEL

HISTORY

Nickel (Ni) is a ubiquitous metal used since antiquity as a common alloy for weapons.[1] Several hundred years after the birth of Christ, Chinese craftsmen incorporated a nickel alloy (white copper) into household objects and art.[2] Agricola recognized the toxic effects of nickel on the lung in the 16th century. By the 17th century, an inexpensive nickel–zinc–copper alloy from China had appeared in Europe. The Swedish chemist A.F. Cronstedt recognized nickel as the 28th element of the periodic table in 1754 by separating an impure form of nickel from niccolite (NiAs). In 1820, Berthier isolated nickel as a pure metal. Full-scale commercial production of nickel began in 1865 when J.F. Wharton produced malleable nickel for a US 3-cent piece. In the early 20th century,[3] nickel sulfate was a medicinal agent for the treatment of chorea, epilepsy, migraine, and neuralgia; however, the medicinal use of nickel was abandoned in the 1930s despite studies indicating nickel was an essential element for metabolism in animals.[4] Although animal studies associated nickel deprivation with depressed growth, reduced reproductive rates, and alterations of lipids and glucose, a deficiency state in humans was never clearly defined.[5]

By the early 1930s, nickel was a recognized cause of contact dermatitis.[6] Elevated incidences of lung cancer appeared in Germany during the 1930s. In 1958, Doll reported an increased incidence of lung and nasal cancer in UK workers primarily exposed to nickel in the first part of the 20th century.[7]

PHYSIOCHEMICAL PROPERTIES

Nickel is a silver-white metal that forms the first transition series Group 10 (Group VIII) of the periodic table along with palladium and platinum. Nickel is the 24th most abundant metal constituting ~0.16% of the earth's crust.[8] There are five natural isotopes with ^{58}Ni (68.27%) and ^{60}Ni (26.10%) being the most abundant. ^{63}Ni is a β-emitter with useful properties as a tracer element (half-life of 100.1 years). The oxidation states of nickel range from 1− to 4+ with the divalent (2+) oxidation state being the most stable species in aqueous solutions and biological systems. Nickel is a common constituent of metal alloys (e.g., stainless steel, copper–nickel) that increases the corrosion resistance, hardness, and strength of the alloy. The siderophilic properties of nickel facilitate the formation of nickel–iron alloys. Nickel possesses fair thermal/electrical conductivity and ferromagnetic properties; the conductive and magnetic properties are lower than those of silver and iron, respectively. As a member of the transition metal series, nickel is resistant to corrosion by air, water, and alkali, but nickel dissolves readily in dilute oxidizing acids. Nickel salts of strong acids and organic acids are soluble in water, whereas nickel salts of weak inorganic acids are water-insoluble. In contrast to the soluble nickel salts (acetate, chloride, nitrate, sulfate), metallic nickel, nickel sulfides, and nickel oxides are poorly water-soluble. Nickel carbonates and nickel hydroxides

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TABLE 22.1. Physiochemical properties of selected nickel compounds.

	Nickel	Nickel Acetate	Nickel Carbonate	Nickel Chloride
Formula	Ni	$Ni(CH_3CO_2)_2$	$NiCO_3$	$NiCl_2$
Synonym	Metallic nickel	Nickel diacetate	Nickel monocarbonate	Nickel dichloride
CAS RN	7440-02-0	373-02-4	3333-67-3	7718-54-9
Valence	0	+2	+2	+2
Molecular weight (g/mol)	58.69	176.80	118.70	129.61
Color	Silvery-white	Dull green	Light green	Golden yellow
Physical state	Solid	Solid	Solid	Solid
Melting point (°C)	1,455	Decomposes	Decomposes	1,001
Density (g/mL)	8.91	1.798	4.39	3.55
Odor	Odorless	Acetic odor	Odorless	Odorless
Water solubility (mg/L)	1.13 at 37°C	Very soluble	93 at 25°C	642,000 at 20°C
Vapor pressure (mmHg)	1 at 1,810°C	NA	NA	1 at 671°C

	Nickel Nitrate	Nickel Oxide	Nickel Subsulfide	Nickel Sulfate
Formula	$Ni(NO_3)_2$	NO	Ni_3S_2	$NiSO_4$
Synonym	Nickel dinitrate, nickel bis(nitrate)	Nickel monoxide, mononickel oxide	Trinickel disulfide, nickel sesquisulfide	Nickel monosulfate, nickelous sulfate
CAS RN	13138-45-9	1313-99-1	12035-72-2	7786-81-4
Valence	+2	+2	+2	+2
Molecular weight (g/mol)	182.72	74.69	240.26	154.77
Color	Green	Green or black	Pale yellow	Green–yellow
Physical state	Solid	Solid	Solid	Solid
Melting point (°C)	56.7	1,955	787	840
Density (g/mL)	2.05	6.72	5.87	4.01
Odor	Odorless	Odorless	NA	Odorless
Water solubility (mg/L)	Very soluble	1.1 at 20°C	517 at 37°C	Soluble
Vapor pressure (mmHg)	NA	NA	NA	NA

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.

are moderately water-soluble. Green nickel oxide is chemically inert, whereas black nickel oxide is relatively reactive. Table 22.1 lists the identifying information and physical properties of metallic nickel and inorganic nickel compounds. When heated, nickel acetate releases irritating fumes. Other potentially toxic thermal decomposition products of nickel compounds include sulfur oxides from the heating of nickel subsulfide.

Rather than speciation, airborne nickel exposure is typically divided by sequential extraction techniques into the following four nickel fractions: 1) soluble ($NiSO_4 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$); 2) sulfidic (NiS, NiS_2, Ni_2S_3); 3) metallic (elemental nickel, nickel alloys); and 4) oxidic [NiO, Ni_2O_3, $Ni(OH)_2$, $NiCO_3$, $Ni_3CO_3(OH)_4$, complex nickel oxides].[9] The composition of these fractions varies somewhat with the type of nickel process. Examination of fly ash from a power plant demonstrated $NiSO_4$ and lesser amounts of NiS and NiS_2; Ni_2S_3 was not detected as measured by carbon paste electrode voltammetry.[10] Analysis of coal by XANES spectroscopy demonstrated nickel oxides and sulfides, whereas the ash contained nickel sulfate and complex nickel oxides.[11] The bottom and fly ash from this Canadian power plant contained nickel sulfate, but there were no detectable amounts of potentially carcinogenic nickel sulfides.

EXPOSURE

Production Processes

In the United States, there are no commercial nickel mines. Nickel production results from the processing of by-products of copper mining or the recycling of nickel products. The major producers of nickel include Canada, the former USSR, New Caledonia, and Australia. Nickel occurs in several ores in combination with sulfur, arsenic, antimony, and hydrated silicon dioxide (silicic acid).[8] The two main types of nickel ores are oxide ores (laterites) and sulfide ores (hydrous nickel silicate, garnierite). Lateritic ores are usually mined by

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strip mining methods, whereas most sulfide ores are found in underground mines. The main sulfide ores are chalcopyrite ($CuFeS_2$), pentlandite ($[FeNi]_9S_8$), and pyrrhotite (Fe_7S_8). Nickel arsenide ores are relatively rare. Extraction of nickel from oxide ores (laterites, nickeliferous) accounts for ~45% of the Ni production, whereas the extraction of sulfide ores accounts for the rest of the commercial nickel. These ores typically contain up to 3% nickel.

Insoluble Ni is the predominant type of nickel in Ni-producing industries. Sampling of underground miners indicates that mining operations involving nickel ores expose the miners to respirable particles (<10 μm) in the range of 5 μg Ni/m^3, whereas the time-weighted average of total nickel in the ambient air averages ~25 μg Ni/m^3.[12] Blasting, crushing, drilling, and hauling operations typically generate ambient concentrations of insoluble nickel in the range of 0.1–1 mg/m^3. Newer processes (e.g., chloride leaching, fluid-bed roasting) substantially reduce the exposure to insoluble nickel compared with the older, dusty roasting processes.[13] During the converting operation for sulfide ores, substantial amounts of sulfur dioxide are generated during the removal of sulfur from the matte (CuNiFeS).

Pyro- and hydro-metallurgical refining processes extract the nickel from the oxide ores (laterites). These processes expose workers to insoluble nickel. Refining is the final step in the production of nickel. This step usually involves exposure to soluble nickel compounds during the electrolytic treatment process or nickel carbonyl during the Mond process. Electroplating and production of chemicals also produce exposure to soluble nickel compounds (e.g., nickel chloride, nickel nitrate). Welding stainless-steel and high-nickel alloys releases nickel fumes into the work environment.

Metal-inert-gas (MIG) welding of stainless steel produces fumes with particle sizes <0.1 μm and concentrations of 3–6.5% Ni, whereas manual metal arc (MMA) welding releases fumes with lower nickel concentrations (0.4–1% Ni) and larger particle sizes (>0.1 μm).[13] However, MMA techniques generate three to four times the volume of fumes from welding stainless steel compared with MIG techniques. The inhalation of nickel also occurs in flame spraying and mold-making in glass and ceramics factories, where hollow molds are formed by the flame spraying of metallic particles containing 70–98% Ni.

Uses

Soluble nickel is the predominant type of Ni exposure in the Ni-using industries. Historically, metallic Ni exposures were higher in Ni-producing industries with mean inhalable Ni concentrations sometimes exceeding 5 mg/m^3 compared with an order of magnitude less for airborne Ni concentrations in Ni-using industries.[14] The majority of nickel production is used for the creation of stainless steel, nickel alloys, and nickel cast iron that comprise objects (e.g., coins, electrical equipment, tools, machinery, armaments, appliances, household utensils). Nickel alloys include iron–nickel alloys (0.3–5% Ni), stainless steels (8–10% up to 25–30% Ni), nickel–copper alloys (25% Ni, 75% Cu in US coins), nickel–chromium alloys, corrosion-resistant nickel–iron–chromium/nickel–molybdenum alloys, and cast irons. Figure 22.1 demonstrates the common uses of nickel. Other uses for nickel compounds include electroplating soluble forms of black oxide, carbonate, chloride, sulfate, electroforming (nickel sulfamate), nickel–cadmium alkaline batteries (hydroxide), dye mordant (ammonium chloride, acetate), catalysts

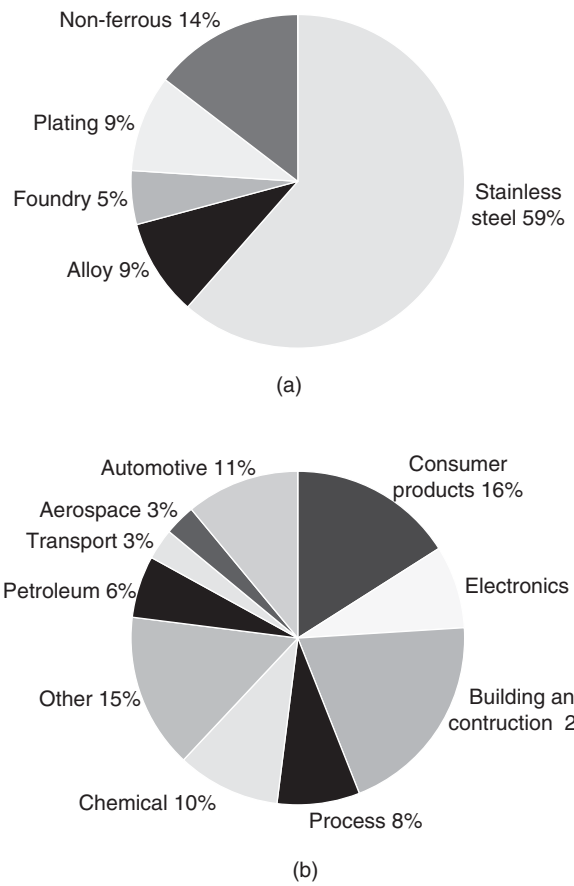


FIGURE 22.1. Common uses of nickel. (a) Nickel use by product, (b) Nickel use by industry. (Data from Morgan and Usher).[15]

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(acetate, arsenate, carbonate, chloride, cyanide, formate, hydroxide, nitrate hexahydrate, sulfides), and electronic equipment (carbonates, ferrites). There is no specific commercial use for nickel subsulfide; therefore, exposure to this compound occurs during the processing of nickel ores in surface smelting–refining facilities. Nickel subsulfide does not occur naturally in ores. The widespread use of nickel alloys in jewelry and associated products causes adverse effects from contact dermatitis in a substantial segment of the population sensitive to nickel. Potential Ni sources for sensitized patients include nickel plating, stainless steel, white gold, German silver (argentan), monel (70% copper, 30% nickel), solders, nickel-plated silver, gold plating, silver-, rhodium-, or gold-plated silver, hard-gold plating, and sterling silver.[16] Uses of nickel-containing alloys include nickel plating of non-precious metals, surgical steel (0.5–30% Ni), white gold (10–15% Ni), German silver (10–15% Ni), solders, hard-gold plating, and sterling silver. Nickel coating of silver items reduces oxidation; gold plating may be combined with nickel undercoating. Additional occupational exposure to nickel results from dermal contact with cutting oils contaminated with nickel or nickel alloys.

Sources

Nickel and nickel compounds occur naturally in the earth's crust, resulting from natural (dust, volcanic eruptions, forest fires) and anthropogenic (fossil fuel combustion, waste incineration, mining, smelting, refining, production of nickel-containing alloys) sources. Nickel exposure for the general population is usually low (ambient air, food, water, tobacco smoke).

Air

Nickel exists in ambient air primarily as suspended particulate matter and rarely as an aerosol; fine particulate matter (i.e., 0.6–10 μm) contains most of the airborne nickel. Ambient air is usually a minor route of exposure for the general population, typically <0.05 μg/day.[17] The nickel concentration in ambient air is low (~<6–20 ng/m^3); however, Ni concentrations up to 150 ng/m^3 may occur in air contaminated by aerosols from anthropogenic sources including high-temperature metallurgical operations (gray-iron foundries), chemical or catalytic processes, combustion sources, or incineration of waste and sewage sludge.[18] The US EPA estimated an average ambient air nickel concentration in the United States during the middle 1990s of ~2 ng/m^3.[19] Nickel concentrations in indoor air are typically <10 ng/m^3.[20]

Combustion of fossil fuels (coal- and oil-fired boilers, coke ovens, diesel-fuel burning) produces the majority of nickel released into ambient air with nickel sulfate being the predominant form of nickel; consequently, urban ambient air contains higher Ni concentrations (5–35 ng/m^3) than rural ambient air (1–3 ng/m^3).[21] The ambient air near these sources also contains lesser amounts of nickel oxides, complex metal (iron) oxides, metallic nickel, and nickel subsulfide.[22] Other anthropogenic sources include nickel metal refining and other nickel alloy production, municipal incineration, steel production, and coal combustion.[17]

Water

Divalent nickel is the predominant form of nickel in aquatic sources, but other forms may exist depending on pH, soil use, depth of sampling, and the occurrence of organic and inorganic ligands. Most nickel compounds are water-soluble at pH <6.5.[23] Uncontaminated freshwater and seawater usually contain ~0.3 μg Ni/L. The degradation of soils and the deposition of nickel in the atmosphere release nickel into the surface-and groundwater. Local industrial discharges also contribute to the presence of nickel in these waters. The amount of total nickel in water varies widely depending on anthropogenic sources and the nickel content of pipes/containers. A survey of US surface water indicated that nickel concentrations range from 5 μg/L (Southern Nevada) to 600 μg/L (Ohio River Basin).[22] Average total nickel concentrations in drinking water ranges from 3–7 μg/L with concentrations seldom >35 μg/L.[24] Nickel concentrations increase in vessels containing corroded nickel plating. The first drawn water from hot water taps plated with nickel may contain Ni concentrations of 1–1.3 mg/L.

Soil

Nickel is the 24th most abundant element in the earth's crust, comprising about 3% of the composition of the earth, averaging ~50 ppm Ni. The molten core of the earth contains ~7% nickel, whereas the nickel content of meteorites ranges from 5–50%. The nickel concentration in soil depends on the presence of natural and anthropogenic sources with typical ranges of ~5–500 ppm up to 24,000 ppm in the soil near metal refineries and 53,000 ppm in dried sludge.[22] Farm soils contain ~3–1,000 mg Ni/kg soil.[25] In a study of soil samples from urban parks in six large European cities, mean nickel concentrations in surface samples (0–10 cm) ranged between 11–207 ppm and 10–210 ppm in subsurface samples (10–20 cm).[26]

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Diet

Food is the dominant source of exposure to nickel for the general population.[27] Nickel occurs in the food chain through uptake by plants and leaching of nickel from processing equipment/utensils. The estimated daily nickel intake in the Danish diet averaged 150 μg with a range up to 900 μg,[28] whereas the average daily intake of dietary nickel in US studies ranged from ~70–160 μg.[29,30] In a study of Montreal residents, the estimated daily nickel intake from the diet was 286 μg,[31] whereas the estimated daily intake of nickel from a UK diet was 140–150 μg.[32] The leaching of nickel from kitchen utensils and water pipes may add up to 1,000 μg to the daily intake of nickel, but the use of newer stainless-steel pans adds much smaller amounts of nickel to the diet.[33] Most foods contain <0.5 mg Ni/kg wet weight. Foodstuffs with nickel concentrations exceeding 1 ppm include oatmeal, dry legumes, hazelnuts, dark chocolate, soy beans, and soys products. Cocoa usually contains the highest nickel concentrations ranging from 8.2–12 mg/kg of fresh wet weight based on a Danish study using flame atomic absorption spectrophotometry.[28] The Ni concentration in edible marine species is usually low. Typically, the Ni concentrations in freshwater fish, marine fish, and mollusks growing in uncontaminated areas range from <0.2–2.0 ppm, nondetectable–4.0 ppm, and 0.4–2.0 ppm, respectively, by wet weight.[17] Nickel is a compound generally recognized as safe (GRAS) when used as a direct ingredient in human food.

Lifestyle

Ni is a constituent of cigarette smoke with yields in mainstream smoke ranging from 0–0.51 μg/cigarette depending on growing conditions.[34] Nickel is divided approximately equally between the particulate and vapor phases. An average cigarette contains 1–3 μg Ni; smoking 1-ppd cigarettes increases the daily nickel amount inhaled by ~4 μg.[35] Most nickel in tobacco remains in the ash after smoking. About 1% of the nickel in tobacco is transferred to mainstream smoke based on studies using smoking machines; however, nickel concentrations in blood and urine from smokers and nonsmokers in nickel refineries are not significantly different.[36]

In vitro studies suggest that stainless steel prostheses (14–36% nickel) with a surface area of 200 cm^2 release 22 μg Ni/year; however, the clinical significance of this amount of nickel remains unclear.[37] A study of 13 patients with stainless-steel hip prostheses revealed that only 1 patient had an elevated serum Ni concentration (1.1 μg/L) above the reference range; he had mild renal dysfunction.[38] The amount of nickel absorbed during dialysis depends on the composition of the equipment in contact with the dialysate. The estimated Ni uptake during a typical dialysis procedure in the 1980s was 100 μg/treatment;[39] however, a meta-analysis of 128 studies on trace elements in hemodialysis patients did not identify nickel as a toxic trace metal in excess in these patients.[40]

ENVIRONMENTAL FATE

Chemical and physical forces (e.g., erosion, runoff, leaching, precipitation, and weathering) constantly distribute nickel between land, water, and air. Wet deposition accounts for about half of the removal of nickel from the air.[41]

Soil

The mobility of nickel in the soil is highly dependent on the soil type and pH.[42] Most nickel exists in soil as insoluble hydroxides at pH >6.7. The presence of sulfur and anaerobic conditions limit nickel mobility as a result of the formation of poorly soluble nickel sulfides. At pH <6.5 and aerobic conditions, most nickel compounds are relatively soluble, and divalent $Ni(H_2O)_6$ is the dominant nickel species. Consequently, acid rain increases nickel mobilization in soil by reducing the soil pH.[25] The mobility of nickel is limited in sandy aquifers unless the pH is very low (<5).[43] The addition of organic material to the soil reduces Ni mobility when compared with Ni mobility in sandy soil.[44] The large specific surface area of iron oxides (e.g., ferrihydrite, goethite, hematite) in soils provides very efficient sinks for trace metals including Ni.[45]

Water

Adsorption of nickel onto suspended particles in water is one of the primary mechanisms for nickel removal from water. Nickel is strongly adsorbed at mineral surfaces (e.g., aluminum, iron, manganese oxides) and complexing agents (humic acid, biopolymers); these reactions influence the nickel concentration in water.[17] The ultimate sink for nickel is the ocean, where deep-sea nodules contain manganese and nickel.

The bioaccumulation of nickel in aquatic and plant species is limited.[46] The range of nickel concentrations in plants averages 0.05–5 mg/kg dry weight with concentrations of >50 mg/kg dry weight being toxic for most plants.[47] Certain genera (e.g., *Alyssum*) accumulate

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nickel above 1 g/kg dry weight when grown on infertile serpentine soils rich in nickel.[48] Based on laboratory studies, nickel probably does not accumulate in fish. In a study of mussels and oysters grown in seawater containing 5 µg Ni/L for 12 weeks, analysis of tissue demonstrated average Ni concentrations of 9.62 µg/g (dry weight) and 12.96 µg/g (dry weight), respectively.[49] There is little evidence for the biomagnification of nickel in the food chain.[25]

DOSE EFFECT

Acute Toxicity

Oral

Oral nickel sulfate doses of 65–195 mg were a recommended treatment for diarrhea and epilepsy during the 1800s; however, the estimated ingestion of 325 mg nickel sulfate (73 mg Ni) produced nausea, giddiness, and decreased pulse.[50] The estimated ingestion of 0.5–2.5 g Ni from nickel sulfate and nickel chloride-contaminated drinking water was associated with nausea, vomiting, abdominal discomfort, diarrhea, giddiness, lassitude, headache, cough, and dyspnea in 32 workers; symptoms resolved within 1–2 days without sequelae.[51] A 2½-year-old girl developed stupor, nuchal rigidity, and pulmonary congestion after ingesting 10–15 g $NiSO_4$ (2.2–3.3 g Ni). She developed a cardiac arrest 8 hours after the ingestion; resuscitation was unsuccessful.[52] The ingestion of nickel may exacerbate skin lesions and produce contact dermatitis on patients sensitized to nickel.[53] Re-exposure of these lesions to nickel 1 month after the development of contact dermatitis suggests that these areas remain more reactive to nickel than non-involved areas of skin.[54] This reaction is dose-dependent with doses of 0.5–5.6 mg usually necessary to cause a cutaneous reaction.[55,56,57]

In single oral acute toxicity studies on female Sprague-Dawley rats, the LD_{50} of nickel chloride, sulfate, fluoride, and acetate salts ranged from 300–550 mg/kg compared with >11,000 mg/kg for nickel oxide, nickel subsulfide, and nickel ash.[58] The no-observed-effect-level (NOEL) for nickel acetate, chloride, fluoride, and sulfate ranged from ~150–175 mg/kg, whereas the NOEL for nickel matte (73% Ni) and nickel oxide exceeded 5,000 mg/kg.

Inhalation

A 38-year-old worker developed acute respiratory distress syndrome after spraying nickel with a metal arc process without personal protective equipment; he died 13 days after exposure.[59] The estimated nickel exposure during a simulation of the incident was 382 mg Ni/m^3 for 90 minutes (~1 g Ni), primarily metallic nickel nanoparticles (<1.4 µm). Examination of the lungs demonstrated organizing diffuse alveolar injury with alveolar hemorrhage and marked hemorrhagic consolidation. Numerous macrophages contained Ni nanoparticles (<25 µm).[60] The presence of other potential toxins in the ambient air and urine was not measured.

Chronic Toxicity

In a study of 745 nickel sinter plant workers exposed to total airborne nickel concentrations up to 100 mg/m^3 as nickel subsulfide and nickel oxides, there was no increase in small irregular opacities suggesting pulmonary inflammation or fibrosis.[61]

TOXICOKINETICS

Absorption

The absorption of nickel compounds depends on the solubility of the compounds. Generally, the absorption of nickel compounds follows this order: nickel carbonyl > soluble nickel compounds (acetate, chloride, nitrate, sulfate) > insoluble nickel compounds (metallic Ni, oxides, sulfides).

Gastrointestinal Tract

Following ingestion, the absorption of metallic nickel and sparingly soluble nickel compounds from the gastrointestinal tract is small. The absorption of soluble Ni compounds is relatively high compared with other metals, depending on dose, degree of water solubility, and the presence of food in the stomach. In a study of four volunteers ingesting the stable isotope tracer ^{62}Ni (571–879 µg), the mean Ni absorption over 5 days was 33.1 ± 4.9% with a range of 29–40%.[62] The gastrointestinal absorption of soluble nickel compounds (chloride, nitrate, sulfate) is relatively rapid with peak serum nickel concentrations occurring within ~2–3 hours after ingestion.[62,63] The presence of food in the stomach significantly reduces the bioavailability of nickel salts. In a study of volunteers ingesting 18–50 µg Ni/kg as $NiSO_4$, the mean absorption of Ni from the gastrointestinal tract over 4 days was 27 ± 17% when administered in drinking water compared with ~1% when administered in food.[64]

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Inhalation

Biological monitoring of workers (e.g., stainless-steel welders) exposed to insoluble Ni suggests that some Ni absorption occurs. Although some experts suggest an average absorption rate of 20% of inhaled Ni,[65] well-designed studies have not quantified the exact value. Based on the kinetics of oral Ni compounds, water-soluble Ni salts are probably better absorbed than insoluble Ni compounds.

Skin

Dermal absorption of nickel and nickel compounds is minimal compared with absorption from inhalation and ingestion. An *in vitro* study indicated that <1% of a solution of soluble nickel salts (acetate, chloride, nitrate, sulfate, divalent nickel) penetrated cadaver skin over 96 hours.[66] Ionizable nickel compounds permeate intact skin slowly and poorly, depending on the vehicle and type of salt (e.g., nickel chloride > nickel sulfate). An *in vitro* study demonstrated a lag time of ~2 days when nickel chloride was applied to cadaver skin as an occlusive patch.[67] Percutaneous absorption is important toxicologically primarily from the development of contact dermatitis rather than diffusion through the skin (e.g., sweat releases allergenic soluble nickel salts from the corrosion of metallic nickel or nickel-bearing alloys).[68] Corrosion of nickel-containing alloys in orthopedic prostheses may release sufficient amounts of nickel to produce local or systemic allergic reactions, but the amount of nickel absorbed from the prostheses would not produce nickel toxicity.

Distribution

The estimated Ni body burden of a healthy adult with ordinary nickel exposure is ~0.5 mg (7.3 μg/kg body weight).[69] In the blood, the main nickel transport protein is albumin. Other transport proteins binding nickel include nickel-containing α_2-macroglobulin (nickeloplasmin), transferrin, and divalent metal transporter-1.[65] Nickel competes with iron for the latter two transporters; however, the amount of nickel bound to these transporters is substantially less than albumin.

The distribution of nickel in the tissues following absorption depends on the route of exposure. Animal studies indicate the highest nickel concentrations occur in the kidney after the parenteral administration of soluble nickel salts with significant nickel concentrations in the lungs, liver, and endocrine glands.[70] Relatively large amounts of nickel occur in the cartilage and connective tissue following nickel absorption.[71]

Elimination

Following absorption, the kidney is the primary route of elimination; nickel is not a cumulative toxin. The urinary excretion of nickel is rapid without evidence of dose-dependent Ni excretion. In a radiotracer study (^{62}Ni) of four adults, urinary Ni excretion accounted for 51–82% of the absorbed dose.[62] Excretion of nickel also occurs in saliva and sweat that may contribute significantly to the elimination of nickel in hot environments. Biliary excretion of nickel occurs in experimental animals, but significant biliary excretion of nickel in humans remains unclear.

Plasma half-lives of nickel typically range from ~24–36 hours, depending on the water solubility of the Ni species. The estimated plasma half-lives of nickel in four electroplaters exposed to nickel sulfate and nickel chloride ranged from 20–34 hours based on a one-compartment model.[72] In a follow-up study of a German worker accidentally overexposed to nickel while flame spraying with a wire containing 80% Ni, the elimination of Ni from blood was biphasic with half-lives of 30 and 240 days.[73]

In a study of eight volunteers ingesting 12 μg of the stable isotope ^{61}Ni/kg in drinking water, the median urinary elimination half-life ranged from ~20–27 hours.[74] Measurement of the urinary elimination of nickel in 2 welders exposed to nickel fumes revealed an elimination half-life of ~50 hours[75] compared with 17–39 hours in four welders exposed to soluble Ni ($NiCl_2$, $NiSO_4$).[72] These relatively short half-lives do not exclude the possibility of the storage of insoluble nickel deposits in the body with much longer biological half-lives. Poorly water-soluble nickel compounds may persist in the upper respiratory tract following exposure. Following inhalation, the clearance of insoluble nickel compounds from the lungs is slow, resulting in low blood Ni concentrations. The biological half-life of nickel oxide in the lung depends on particle size ranging from 11–21 months in animal studies.[76] In a study of retired nickel refinery workers exposed to nickel subsulfide and nickel oxide, the estimated half-life of nickel in the nasal mucosa following cessation of occupational exposure was 3.5 years.[77] Acute nickel toxicity developed in 23 dialysis patients when Ni leached from a nickel-plated stainless steel water heater tank and contaminated their dialysate; the urinary elimination half-life of nickel on dialysis ranged from ~20–60 hours.[78]

Maternal–Fetal Kinetics

Nickel probably crosses the placenta with nickel concentrations appearing in the cord blood of full-term

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infants.[79] Nickel concentrations in the fetus are similar to maternal nickel concentrations. The mean nickel concentration in the milk of lactating mothers exceeds the serum Ni concentrations in these mothers. In specimens of milk obtained within 1 week postpartum, the mean Ni concentration was 17 ± 2 μg/L.[80] A study of 13 women providing breast milk samples during the first month postpartum detected a mean nickel concentration of 1.2 ± 0.4 μg/L (range, 0.5–2.0 μg/L) as measured by graphite furnace atomic absorption spectrophotometry.[81] Consequently, the average breastfed infant consumes ~5–15 μg Ni/day in the milk.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

Nickel is an essential element for several animal species;[5,82] Ni-dependent processes in these animals include the synthesis of phospholipids and lipid metabolism, particularly the regulation of lipid content in tissues.[83] In studies of rats fed nickel-deficient diets (2–15 μg/kg), increased perinatal mortality occurred along with alterations in grooming behavior and liver development.[84] Although a deficiency disease for nickel in humans has not been identified and there is inadequate evidence to verify that Ni is an essential trace element for humans, some evidence suggests that Ni has some nutritional benefit.[85,86] Based on animal studies, nickel probably is involved in the action of biotin, folate,[87] and vitamin B_{12}.[88] Studies in chicks indicate that nickel deficiency impairs the absorption of iron from the intestine; thus, nickel deficiency reduces iron concentrations in these animals.[89] Nickel deficiency (13 μg Ni/kg) in rats produced disturbances in lipid metabolism and the accumulation of triacylglycerol in the liver.[90] The alterations in serum and hepatic lipids are similar to the changes developing after moderate iron deficiency. A hypothesis for the biochemical action of Ni is the CO_2-fixation of propionyl-CoA to form D-methylmalonyl-CoA.[91] Nickel-containing enzymes include carbon monoxide dehydrogenase, methyl coenzyme M reductase, hydrogenase, and urease.[5] The minimal daily dietary intake of nickel necessary for human health probably is ~100–300 μg.

Mechanism of Toxicity

Acute Toxicity

In vitro and *in vivo* experiments indicate nickel compounds bind a variety of enzymes including hepatic microsomal enzymes, enzymes catalyzing carbohydrate metabolism, and enzymes transporting ions across membranes.[22] Ni^{2+} crosses cell membranes via calcium channels and competes with Ca^{2+} for specific intracellular receptors.[92] In animal studies, exposure to metallic nickel and soluble nickel compounds (e.g., $NiCl_2$) causes direct pulmonary toxicity as demonstrated by an increase in both the number and size of type II alveolar cells, increased production of surfactant, and alteration of the morphology and function of alveolar macrophages.[93] Studies of animals given large doses of soluble nickel salts (acetate, chloride, nitrate, sulfate) suggest that lipid peroxidation may cause disruption of the cellular membrane, Ca^{2+} influx, and cell death.[94,95]

Carcinogenesis

Depending on the form of nickel, exposure may produce oxidative DNA damage and disrupt DNA repair activity via inhibition of zinc finger-containing DNA repair proteins;[96] however, nickel compounds are only weakly mutagenic in most assay systems and the mechanism of toxicity is primarily epigenetic.[97,98] Divalent nickel compounds bind sulfhydryl, azo- and amino-groups on a variety of macromolecules including nucleic acids and proteins. Although divalent Ni inhibits JmjC domain-containing histone demethylase activity,[99] Ni^{2+} is not highly reactive with DNA. Ni^{2+} promotes cell proliferation and cell survival by increasing the accumulation of hypoxia-inducible factors (HIFs) and their subsequent gene expression via DND methylation and histone modifications.[100,101] Major intracellular targets of nickel include iron- and 2-oxoglutarate-dependent dioxygenases (HIF-α, HIF-prolyl hydroxylases, H3K9 demethylases).[102]

Ni modulates gene expression by the activation of transcription factors or the silencing of genes through DNA methylation.[97] High Ni concentrations increase intracellular calcium concentrations and oxidative stress; however, Ni is a weak oxidative stress inducer that depletes glutathione. Additionally, divalent Ni activates nuclear factor kappa B (NF-κB) and other oxidation-sensitive transcription factor pathways (p53, c-MYC), resulting in the promotion of cell-cycle arrest and apoptosis.[103] This tumor suppression allows tumor cells to remain dormant until suitable microenvironments for the proliferation of micrometastases exist. Besides weak oxidative stress induction, divalent Ni modulates transcription factors and histone modifiers through alteration in iron homeostasis, resulting in the early transformation of cells.

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Nickel exists in several forms including metallic nickel, water-insoluble nickel compounds (e.g., subsulfide, oxide), and water-soluble nickel compounds (e.g., sulfate). Animal studies indicate that substantial variation in the carcinogenic potential of nickel compounds occurs. This variation probably results from varying effects on different mechanisms of carcinogenesis including, the following: 1) genetic and epigenetic mechanisms (nickel subsulfide); 2) threshold effect for induction of tumors (high-temperature nickel oxides); and 3) promotion of carcinogenesis (nickel sulfate).[104,105] Generally, nickel compounds with higher valences (+3, +4) are more carcinogenic in animal models than soluble divalent nickel compounds (chloride, sulfate, ammonium sulfate). Of these nickel compounds, long-term studies in rodents demonstrate that nickel subsulfide is the most carcinogenic nickel compound. Immune mechanisms appear vulnerable to the effects of nickel subsulfide with experimental studies revealing that the local instillation of Ni_3S_2 inhibits pulmonary alveolar macrophage function and increases the NK cell-mediated killing of target cells.[106] Differences in the carcinogenic potential of various nickel compounds may also result from variations in the ability of nickel ions to enter the cell and bind to critical target areas. In animal studies, the coadministration of manganese[107] and magnesium[108] antagonizes the carcinogenic effect of nickel subsulfide.

Postmortem Examination

The postmortem examination of a 2-year-old child, who died after ingesting nickel sulfate crystals, revealed acute hemorrhagic gastritis.[52] Examination of lung tissue from a long-time welder with an extensive history of welding fume exposure demonstrated grainy material (protein, fat) in the alveoli and inflammatory cell influx.[109] Alveolar macrophages contained numerous welding particle agglomerates consisting primarily of iron, chromium, and nickel with some silicates; the presence of these metals was consistent with his history of welding chrome-molybdenum steel (Cr, Fe, Mn, Mo, Ni) for most of his career. The presence of multiple metals and his 52-pack-year history of smoking complicate the interpretation of the effect of Ni on the development of his COPD, asthma, and progressive respiratory failure.

Nickel does not accumulate in tissue with the exception of the lungs. Mean postmortem concentration (μg Ni/kg dry weight) of nickel in various tissues from 10 consecutive adult autopsies was the following: lung, 173 (range, 71–371); thyroid, 141; adrenal, 132; kidney, 62; heart, 54; liver, 50; brain, 44; spleen, 37; and pancreas, 34.[110] In a study of eight adults and two infants with occupational or para-occupational exposure to Ni, the mean Ni concentration in lung tissue was 740 ± 440 μg/kg (range, 110–2,200 μg/kg) dry weight.[111] The following nickel concentrations, as expressed in μg Ni/g wet weight, were found on postmortem examination of a 2-year-old girl who died after ingesting nickel sulfate: bile, 60; urine, 47; gastric contents, 38; liver, 27; dura mater, 10.5; salivary gland, 10; blood, 7.5; bone marrow, 5.2; fat, 2.6; and muscle, 2.5.[52]

The amount of nickel in pulmonary tissue depends on age, sex, location, and occupational exposure to nickel. A German study of 110 autopsies from an area with relatively high ambient levels of nickel revealed that the nickel concentration was twice as high in lung tissue from men as women.[112] The concentration of nickel in the lungs increased at the rate of 3% per year. Although some overlap in the concentration of nickel in the lungs occurs between the general population and workers exposed to nickel compounds, the mean concentration of nickel in workers with occupational exposure to nickel is several orders of magnitude greater than pulmonary concentrations in the general population.[113] Based on limited evidence from postmortem examination of workers with exposure to a variety of Ni compounds, nickel concentrations in lung tissue do not correlate closely with the risk of developing lung cancer.[111] Autopsies of 39 nickel workers did not demonstrate statistically significant differences between the nickel concentration in workers with lung cancer and those without lung cancer;[114] however, there was no correlation between the nickel concentration at a specific pulmonary site and the development of lung cancer at that site.

CLINICAL RESPONSE

Acute Toxicity

There are few cases of acute inorganic nickel toxicity in the medical literature. The ingestion of > 10 g nickel sulfate in a 2-year-old girl produced erythema, mydriasis, tachycardia, nuchal rigidity, pulmonary congestion, coma, and cardiac arrest.[52] The leaching of nickel from nickel-plated surfaces of a water-heating tank produced elevated concentrations of nickel in patients receiving dialysis. During dialysis, these patients developed nausea, vomiting, weakness, headache, and palpitations that resolved within several hours following the cessation of dialysis.[78] Once recovery occurs, long-term sequelae following the ingestion of nickel compounds do not usually occur.

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Environmental Exposure

The typical clinical lesion associated with nickel dermatitis is a pruritic, papular, or papulovesicular dermatitis with some lichenification. This presentation is characteristic of atopic dermatitis rather than eczematous dermatitis. Nickel alloy or nickel plating is a common constituent of a variety of products including identification bands, zippers, coins, metal shoelace tips, metal underwear snaps, safety pins, metal toys, magnets, doorknobs, keys, scissors, bracelets, earrings, curlers, necklaces, bra straps, thimbles, handles, and most costume jewelry. Nickel is the most common sensitizing metal with a high prevalence rate (25–29%) in studies of patients attending an allergy clinic.[115,116] Women are more frequently affected by nickel hypersensitivity than men as a result of more frequent exposure to nickel-containing consumer items such as wristwatches, metal buttons, jewelry, cell phones, and body piercings.[117] Of 368 nickel-allergic patients presenting to a contact dermatitis clinic over a 5-year period, 91% were women.[118] Occupational Ni exposure accounted for ~1/4 of the cases of nickel sensitivity. Other common Ni-associated consumer products include dental work, dimethylglyoxime-positive surgical suite materials (e.g., chairs, tables, racks, trolleys, valves),[119] clothing fasteners, laptop computers, video game controllers, and wind-up toys.[120,121] Ear piercing is an important risk factor for the development of nickel sensitization.[122] Patients with atopic dermatitis do not have an increased risk of developing nickel sensitivity;[123] however, patients with psoriasis probably have a lower incidence of nickel sensitivity than healthy adults.[124] Once sensitization occurs, hypersensitivity to nickel usually persists; however, long periods between exposures tend to diminish the hypersensitivity reaction. Pressure, sweat, moisture, and friction increase the severity of nickel hypersensitivity. 24-karat gold does not contain nickel; however, the majority of jewelry contains nickel as an alloy.

Occupational Exposure

Cardiorespiratory

Direct effects of chronic nickel inhalation include asthma, chronic hypertrophic rhinitis and sinusitis, nasal polyposis, and perforations of the nasal septum.[125] Asthma resulting from chronic exposure to nickel is rare, but occupational asthma in metal plating workers occurs with a positive inhalation challenge to nickel sulfate[126] and the presence of nickel-specific antibodies.[127] Lymphocyte transformation tests (LTTs) with nickel suggest that nickel sensitivity may contribute to the development of hard metal asthma.[128] Although benign pneumoconiosis has been reported in workers exposed to nickel dust,[129] co-exposure to other substances causing pneumoconioses limits conclusions about the causal role of nickel dust in the development of pulmonary fibrosis. The concentrations of nickel-containing dust in these workers were an order of magnitude above current workplace standards with values representing total airborne dust rather than respirable dust. Nickel is a potent coronary vasoconstrictor in animal models, and whole blood Ni concentrations may be higher in patients with multiple myocardial infarctions than healthy controls;[130] however, there is no direct evidence that exposure to nickel in the work environment increases the prevalence of cardiovascular disease.[131,132]

Kidneys

Nephrotoxicity is not a prominent feature of chronic nickel toxicity. There are few data to indicate occupational Ni exposure causes clinically significant renal impairment. In a study of stainless-steel welders with exposures resulting in urine concentrations ranging from 2–78 μg Cr/g creatinine and 1.3–19 μg Ni/g creatinine, no dose-related alterations of renal tubular function were detected.[133] However, a study of workers exposed to high ambient air Ni concentrations (mean = 0.75 mg/m^3; range, 0.04–2.86 mg/m^3) substantially exceeding recommended TLV–TWA guidelines demonstrated subclinical changes in renal tubular function.[134] Nickel was present primarily as nickel sulfate and nickel chloride. Regression analysis demonstrated dose-related increases in the urinary excretion of β_2-microglobulin in both sexes and *N*-acetyl-β-D-glucosaminidase in men. No significant abnormalities were detected in markers (albumin, transferrin) of glomerular dysfunction. The geometric mean nickel concentrations in end-of-shift urine samples collected on the fourth workday were 5.0 μg/g creatinine (range, 0.3–123 μg/g creatinine) for 13 men and 10.3 μg/g creatinine (range, 1.5–222.6 μg/g creatinine) for 11 women.

Skin

The role of occupational exposure as a source of sensitization is difficult to evaluate; occupational allergens were suspected in ~23% of 368 patients evaluated at an allergy clinic for nickel sensitivity.[118] The most common occupations were hairdresser, retail clerk, domestic cleaner, caterer, and metalworker; however, determining the source of these allergens is complicated by the frequent presence of nickel sensitivity in the general population. A review of published

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articles on contact allergens indicated nickel was the most prevalent contact allergen with a median prevalence of 8.6% (range, 0.7–27.8%) in the general population.[135] Nickel-associated contact dermatitis typically occurs symmetrically in a pattern related to the nickel-containing object (e.g., seating, jewelry); however, the presentation may differ as a result of variations in contact with the object (e.g., school chair sign).[136]

Reproductive Abnormalities

Although nickel crosses the placental barrier, it is not a recognized cause of fetal abnormalities following maternal nickel exposure in the environment or occupational setting. In the current medical literature, the association between Ni exposure and adverse child outcomes (birth defects, autism spectrum disorder, prematurity, small for gestational age) is weak.[137] A Russian study of 22,836 births (>27 weeks of gestation) and small-for-gestational-age infants (<10% birth weight) in the Kola Birth Registry did not detect elevated risks of reproductive abnormalities in infants born to mothers occupationally exposed to water-soluble Ni at the *beginning* of their pregnancy.[138] The abnormalities tested included self-reported spontaneous abortions, congenital musculoskeletal defects, and small-for-gestational age using logistical regression of the assigned exposure categories (background, low, high exposures). The adjusted odds ratio for Ni-exposed mothers giving birth to small-for-gestational-age infants was 0.84 (95% CI: 0.75–0.93). Analysis of this cohort demonstrated no statistically significant association between Ni exposure at the beginning of pregnancy and congenital musculoskeletal birth defects (adjusted OR = 0.96, 95% CI: 0.76–1.21)[139] or self-reported spontaneous abortions (adjusted OR = 1.14, 95% CI: 0.95–1.37).[140]

Reproductive effects following Ni exposure occur in animals exposed to high concentrations of nickel salts. Although intraperitoneal administration of high doses of nickel salts ($NiCl_2$, $NiCO_3$, $NiSO_4$) to pregnant rodents during organogenesis produces fetal malformations,[141] obvious nickel toxicity occurs at these Ni concentrations. Studies in male rats reveal degenerative changes in the testis and the epididymis including abnormalities of the spermatozoa. Studies in female animals suggest that a reduction in embryo viability and successful implantations develop following exposure to high concentrations (1.2–20 mg Ni/kg).[22,142] Reduction in litter size and decreased viability of the fetus also occur in the presence of nickel deficiency.

Carcinogenicity

Humans

In 1990, the International Agency for Research on Cancer (IARC) listed nickel compounds as Group 1 carcinogens based on sufficient evidence of cancer in animals and studies of Canadian, Norwegian, and Finnish nickel workers.[143] These studies involved exposure to metallic nickel, nickel oxides, nickel subsulfide, soluble nickel compounds, and nickel carbonyl; the identity of the nickel compound or compounds causing the increased risk of cancer was not well defined. The strongest evidence of carcinogenicity of a particular nickel species was exposure to sulfidic nickel in the nickel refinery industry. In contrast to the increased risk of lung cancer in nickel refinery workers, most studies of workers in other nickel-producing industries (i.e., nickel mining and smelting facilities, hydrometallurgical refinery, nickel alloy and stainless-steel production facilities, stainless-steel welders, nickel–chromium electroplating) did not demonstrate significant increases in the risk of lung cancer from nickel exposure.[144,145]

The IARC listed metallic nickel and nickel alloys as possibly carcinogenic (Group 2B) in 1990. A subsequent IARC review of nickel carcinogenicity concluded there is sufficient evidence (Group 1) for human carcinogenicity of nickel mixtures that include nickel compounds and metallic nickel, whereas there is only sufficient evidence in experimental animals for the carcinogenicity of metallic nickel.[146] The US National Toxicology Program lists metallic nickel as reasonably anticipated to be human carcinogens and nickel compounds as known to be human carcinogens, whereas nickel alloys are not listed as suspected human carcinogens.

Carcinogenic Nickel Fractions

The available evidence from experimental and epidemiological studies indicates that crystalline nickel compounds in the sulfidic fraction of refinery dust (e.g., NiS, NiS_2, Ni_2S_3, Ni_3S_2) and to a lesser extent nickel oxide are more potent carcinogens compared with water-soluble nickel compounds (chloride, sulfate) present in nickel smelters and refineries.[147] There is evidence that exposure to soluble nickel salts (estimated range, 0.5–2.0 mg/m^3) in the complex ambient air of the electrolysis department and other refinery workers increases the risk of lung and nasal cancer, sometimes exceeding the estimated cancer risks from exposure to less soluble nickel compounds (estimated range, 0.1–0.5 mg/m^3).[148] In a cohort of Norwegian workers at the Falconbridge nickel refinery, there was

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a dose-response relationship between the risk of lung cancer and cumulative exposure to water-soluble nickel with elevated SIRs for all exposure categories based on estimations of total airborne Ni concentrations.[149] The SIR for lung cancer in the highest cumulative exposure category (≥2 mg/m^3 for years) was 4.5 (95% CI: 3.6–5.5) compared with 1.3 (95% CI: 0.6–2.3) for workers without soluble nickel exposure. Examination of data from this Falconbridge nickel refinery in Norway suggested that smoking caused a multiplicative effect on the development of lung cancer with a relative risk for smokers exposed to nickel compounds and for nonexposed smokers of 5.1 and 2.9, respectively.[150] Analysis of cumulative total Ni exposure data and relative risk of lung cancer from this cohort using Poisson regression analysis adjusted for age and smoking demonstrated a positive test for linear trend for soluble nickel ($P < 0.001$) and nickel oxide ($P = 0.05$). The relative risks for the highest exposure group (≥15 mg/m^3/year) were 3.1 (95% CI: 2.1–4.8) and 1.5 (1.0–2.2), respectively. The relative risks for the cumulative exposure categories 1–14 mg/m^3/year were not statistically significant compared with the referent group (<1 mg/m^3/year).

No excess risk of lung cancer occurred in studies of electrolysis workers in the Port Colborne refinery,[151] a Canadian hydrometallurgical nickel refinery and fertilizer complex,[152] or a Finnish smelter and nickel refinery,[153] where mean exposure to soluble nickel compounds was smaller (<0.5 mg/m^3 and <0.3 mg/m^3, respectively). An update of the Finnish refinery cohort with exposure only to nickel sulfate demonstrated a statistically significant increase (SIR = 3.38, 95% CI: 1.24–7.36) for lung cancer in workers with at least 20 years of employment.[154] This SIR did not clearly increase with the duration of employment. There was a definite increase in nasal cancer (SIR = 41.1, 95% CI: 4.97–148) among this cohort; however, the wide confidence interval suggests instability in the estimate. Concomitant exposure of these workers to insoluble nickel salts (subsulfide, oxides) and possible exposure misclassification complicate definitive conclusions regarding the contribution of soluble nickel exposure to the development of lung cancer in nickel refinery workers.[155,156] The carcinogenic potency of soluble and insoluble nickel compounds probably differs.[157,158] There is little epidemiological evidence that exposure to metallic nickel or nickel alloys alone produces an increased risk of lung cancer.[104,159,160] In a mortality study of 1,999 workers employed at a nickel alloy manufacturing plant from 1958–2000, the SMR for lung cancer was 87 (95% CI: 67–111); there were no cases of nasal cancers.[145] The SMRs for all cancers were below 100, suggesting the possibility of a healthy worker effect.

Nickel Refining

Ambient air in nickel smelters and refineries contains a variety of carcinogens (asbestos, arsenic) along with several nickel fractions including metallic Ni and aerosols of soluble/insoluble nickel. The presence of these multiple factions complicates the determination of which nickel compounds are human carcinogens. Epidemiological studies indicate that exposure to more than one nickel species produces excess cancers of the upper respiratory tract in the affected workers; however, the carcinogenic potency of these nickel species varies widely along with the water solubility (i.e., absorption) of these Ni species. Early epidemiological studies document an increased prevalence of nasal and pulmonary cancers in nickel refinery workers, particularly following exposure to nickel compounds during roasting, calcining, and sintering operations prior to 1950.[161,162,163] These early studies associated occurrence of these cancers with older, dusty processes involving exposure to the impure dusts of nickel oxides and nickel sulfides.[7,164] Nickel arsenide was a contaminant in these dusts. The risk of cancer occurred primarily in workers exposed to high concentrations (>10 mg total Ni/m^3) of nickel refinery dust, nickel subsulfide, and high-temperature nickel oxide in several different geographic regions.[165] In these studies, exposure data and smoking histories were sparse; there are few data on the Ni species or the particle size of the dust involved. A study of Norwegian nickel refinery works detected an additive effect of smoking and nickel exposure in the development of respiratory cancers.[166] In a study of 812 nickel refinery workers employed from 1953–1992 for at least 5 years, the elevation of the SMR for lung cancer to 139 (95% CI: 92–201) was not statistically significant.[167] There was one death from nasal cancer compared with an expected rate based on national mortality tables of 0.1.

In epidemiological studies of refinery workers, the relative risk of nasal cancer was substantially higher than the relative risk of lung cancer.[168] The minimal latency period for lung and nasal cancer usually exceeds 10 years.[169] The mean latency period for workers granted compensation for lung and nasal cancer at the Port Colborne sinter plant was 33.4 years (range, 17–55) and 33.5 years (range, 19–46 years), respectively.[163] This plant produced nickel and nickel oxide from sulfide matte between 1918–1958. For workers receiving compensation after working from 1948–1963 in the Copper Cliff sinter plant, the mean latency for lung and nasal cancer was 22.5 years (9–30 years) and 23.7 years (range,

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12–28 years), respectively. The anterior curvature of the middle turbinate is the primary site of nasal cancer in workers exposed to nickel dust.[170] The major histological types of lung cancer are squamous cell carcinomas and undifferentiated carcinomas with a much smaller portion (<10%) of adenocarcinomas.[171] Although some studies associate nickel exposure with cancer risks (e.g., stomach) other than lung tumors,[154] current epidemiological data do not consistently demonstrate elevated cancer risks at sites other than the lungs and nasal sinuses. The association between exposure to nickel compounds and laryngeal or gastrointestinal cancers remains controversial.[146]

Nickel Use

An excess risk of cancer is smaller in industries that *use* rather than *produce* nickel. Although there are data associating exposure to soluble nickel compounds with an increased incidence of lung cancer, this increase usually occurs in complex nickel environments with soluble and insoluble nickel compounds.[15] Similar risks of lung and nasal cancer occurred in workers exposed to soluble nickel (copper sulfate extraction, electrolysis, hydrometallurgy), often in association with exposure to nickel oxide but not with exposure to nickel subsulfide.

The risks of lung and nasal cancers were not significantly elevated in a group of 1,155 workers exposed primarily to soluble nickel compounds at moderate to low concentrations (<0.3 mg/m^3).[153] Generally, the excess risks of lung and nasal cancers were associated with exposure to soluble nickel concentrations above 1 mg Ni/m^3 and to less soluble forms of nickel (oxide, subsulfide) exceeding 10 mg Ni/m^3. Several studies of nickel and chromium platers exposed from 1953–1992 to <1 mg Ni/m^3 as metallic nickel and nickel oxide detected no increase in the SMRs for nasal or lung cancer when compared with national mortality rates.[144,145,172] The principal source of exposure was a mist of nickel sulfate and nickel chloride. The relatively short exposure period, the lack of exposure data, and the modest size of the studies complicate conclusions regarding the carcinogenicity of soluble nickel compounds based on these data.

Based on previous epidemiology studies, the risk of developing lung cancer following exposure to airborne metallic Ni concentrations currently present in the workplace appears small without concurrent exposure to other soluble or insoluble Ni compounds.[173] In general, the risk of developing lung cancer from nickel-containing welding fumes is small compared with lung cancer risk from chromium present in these fumes; the exception is MIG welding operations that use pure nickel filler wire.[174]

Animals

Insoluble nickel compounds are generally stronger animal carcinogens than soluble nickel compounds.[97] Susceptibility to upper respiratory tract cancers following exposure to nickel compounds differs substantially between animal species. Hamsters and mice are much less susceptible to the carcinogenic effects of certain nickel compounds than rats. Lifetime exposure (6 hours/day, 5 days/week for 2 years) of male and female F344/N rats to nickel subsulfide (0.15 and 1 mg/m^3) and nickel oxide (1.25 and 2.5 mg/m^3) produced an exposure-related increase in the incidence of adrenal medulla and pulmonary neoplasms.[175] A similar exposure to nickel oxide and nickel subsulfide produced little evidence of an exposure-related increase in pulmonary neoplasms in mice. Furthermore, there was no increased incidence of neoplasms in rats or mice exposed to the soluble nickel compound, nickel sulfate (0.125–1.0 mg/m^3). A study of Wistar rats exposed by whole-body inhalation to 0 mg Ni/m^3 (control), 0.1 mg Ni/m^3, 0.4 mg Ni/m^3, and 1.0 mg Ni/m^3 as Ni metal powder (MMAD = 1.8 μm with GSD of 2.4 μm) for 6 hours/day, 5 days/week for up to 24 months detected no increased incidence of lung tumors.[176] Pathological examination of the exposed animals demonstrated alveolar proteinosis and histiocytosis, chronic inflammation, and bronchiolar-alveolar hyperplasia.

DIAGNOSTIC TESTING

SI Conversion Units

1 μg/L = 0.0170 μmol/L
1 mg = 17.04 μmol
1 μmol = 58.71 μg Ni
1 nmol/L = 0.0587 μg/L
1 nmol/mmol creatinine ≈ 0.5189 μg Ni/g creatinine as an approximation

Analytical Methods

Techniques

Common and sensitive methods for the determination of nickel concentrations in biological specimens include electrothermal (graphite furnace) atomic absorption spectrophotometry (EAAS), inductively coupled

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plasma/atomic emission spectrometry (ICP/AES), and differential pulse absorption voltammetry (DPAV). Estimated nickel detection limits in biological materials using EAAS are the following: urine, 0.45 μg/L; whole blood, 0.1 μg/L; serum, 50 ng/L; and dry tissue, 10 μg/kg.[177] Using EAAS to analyze total nickel in wet digested samples of human body tissues, the limit of detection (LOD) was 0.23 μg/L and the lower limit of quantitation was 0.76 μg/L with precision (as relative standard deviation) up to 10% and accuracy of 97.1%.[178] Analysis by ICP/AES is less sensitive (LOD, 3 μg/L) than EAAS,[179] whereas DPAV is more sensitive (1 ng/L blood); however, the latter technique is more complicated and time-consuming. Reference values for nickel have decreased significantly since 1970, when improved techniques and reduced contamination improved the precision and reliability of analytical determinations of nickel.[13] Consequently, measurements of nickel published before 1980 should be interpreted cautiously.[180]

Methods for nickel determination in environmental samples include flame or graphite furnace AAS, ICP/AES, or inductively coupled plasma/mass spectrometry (ICP/MS). Sample preparation depends on the nickel concentration, presence of interfering substances, and solubility of the sample. For food or tissues, wet ashing with sulfuric acid or dry ashing by dissolution of the ash with a dilute acidic solution (sulfuric, hydrochloric) is usually sufficient. Liquid chromatography with UV/VIS spectrophotometric detection is a highly sensitive method (LOD, 8.7 ng/mL) for the detection of nickel in environmental samples.[181]

Fractionation

Instead of speciation, the analysis of nickel in environmental samples is typically reported as total nickel and classified based on analytical methods that separate total nickel into metallic, sulfidic, oxidic, and soluble nickel fractions. The usual four-step sequential extraction of nickel from filters of airborne samples involves the following phases: 1) leaching of soluble nickel compounds by ammonium citrate solution; 2) extraction of sulfidic nickel salts by ammonium citrate/hydroxyl peroxide mixture; 3) dissolution of metallic nickel by bromine in anhydrous methanol; and 4) dissolution of the remaining nickel oxides by concentrated nitric acid/perchloric acid.[182] Alternate procedures substitute EDTA, ammonium citrate/H_2O_2, $KCuCl_3$, and nitric acid, respectively, for these four phases of nickel extraction.[183]

Biomarkers

Electrothermal atomic absorption spectrophotometry with Zeeman background correction detected an average Ni concentration of 2.3 ± 0.8 μg/L in 5 postmortem bile samples from people without occupational exposure to nickel.[110]

Blood

There are few data on nickel distribution between erythrocytes and serum. In a study of 1,016 Swedish adults in their 70s, the mean whole blood/serum nickel ratio was 3.2 as measured by inductively coupled plasma/sector field mass spectrometry. The nickel concentrations were correlated to kidney function (glomerular filtration rate).[184] In a series of healthy Italians, the mean whole blood/serum Ni ratio was ~2.[185] Serum nickel concentrations reflect recent exposure (i.e., several days) to soluble nickel compounds rather than exposure to insoluble nickel salts or unabsorbed deposits of metallic nickel in the lung. The use of stainless-steel needles during venipuncture may contaminate the blood sample when nickel leaches from the needle.

General Population

A study of 30 healthy adults with no significant exposure to nickel demonstrated a mean whole blood Ni concentration of 0.34 ± 0.28 μg/L with a range of <0.05–1.05 μg/L.[37] In this group, the serum nickel concentrations were similar to the whole blood concentration with a mean of 0.28 ± 0.24 μg/L (range, <0.05–1.08 μg/L). The average nickel concentration in serum collected from 38 healthy adult volunteers was 0.14 ± 0.09 μg/L as measured by atomic absorption spectrometric method with Zeeman-effect background correction.[186] Plasma nickel concentrations in the general population are usually <2 μg/L. In an analysis of nickel reference values in the medical literature (TRACY Protocol), the mean Ni concentrations for the general adult population ranged from 0.14–0.63 μg/L for eight serum and plasma studies compared with <0.05–3.8 μg/L for four whole blood studies.[187] The estimated mean serum nickel concentration in 75 Danish volunteers without occupational exposure to nickel was 0.80 ± 0.04 μg/L; the calculated upper 95% was 1.53 μg/L based on a noncentral t-distribution.[188] A variety of conditions affect the Ni concentration in blood. Serum nickel concentrations increase following acute strokes, extensive burns, myocardial ischemia, and renal failure requiring hemodialysis, whereas the serum Ni concentration decreases in hepatic cirrhosis, probably as

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a result of hypoalbuminemia.[79] The mean serum nickel concentration in 27 dialysis patients was ~46 times higher (6.38 ± 3.36 μg/L) than the mean of a control group (mean = 0.14 μg/L; n = 40).[186] The serum nickel concentration in blood samples from nickel-sensitive individuals may be lower than reference concentrations because of lower environmental or occupational nickel exposure. The mean serum concentration of nickel in 35 nickel-sensitized patients was 0.24 μg/L compared with 0.425 μg/L in the control group.[189]

Toxicity

There are few data on toxicity associated with specific Ni concentrations in blood. In a group of patients with renal disease, symptoms of nickel intoxication (nausea, vomiting, headache, weakness) appeared at plasma Ni concentrations exceeding 3,000 μg/L.[78]

Urine

Following absorption, the kidneys excrete most of the absorbed Ni dose in the urine. Both the blood and a 24-hour urine sample are good measures of exposure to soluble nickel compounds over the previous 1–2 days. Urine specimens are usually preferred to blood samples for determination of recent exposure to nickel because of convenience, analytical accuracy, and sensitivity.[13] Normalization for dilute urine is important, but adjustments based on creatinine overestimate nickel excretion because renal nickel increases with urine flow, whereas the rate of creatinine excretion remains relatively stable. Hence normalization of urine dilution to a standard specific gravity rather than urine creatinine is probably more accurate.[13] At the present time, the speciation of nickel in urine is not a practical biomarker of exposure.

General Population

Urine nickel concentrations in individuals without occupational Ni exposure are typically <5 μg/L. In a EURO-TERVIHT study of 189 healthy, non-occupationally exposed Danish adults aged 40–70 years, the upper 95% Ni concentration was ~3.1 μg/L[190] compared with 10 μg/L (GM = 4.8 μg/L) in 299 healthy Finnish adults without occupational Ni exposure as measured by graphite furnace/atomic absorption spectrometry.[191] In an analysis of nickel reference values in the medical literature (TRACY Protocol), the mean urine Ni concentrations for the general adult population in four studies ranged from 0.9–3.2 μg/L.[187]

The mean urine Ni concentration in a cross-sectional study of 371 adult residents living near a Russian nickel refinery near Nikel was 4.9 μg/L (range, 0.3–61.9 μg/L) compared with 2.6 μg/L (range, 0.3–17.0 μg/L; n = 220) in the Russian city of Apatity and 4.0 μg/L (range, 1.0–17.0 μg/L; n = 20) in the Russian city of Umba.[192] The difference between the city of Nikel and the control cities was statistically significant; however, comparisons of urine nickel concentrations between 418 Russian residents (mean = 2.8 μg/L; range, 0.3–24.2 μg/L) near the nickel refinery town of Zapolyarny were not statistically different than the Russian control cities. The authors concluded that industrial nickel pollution alone did not account for the observed differences between the nickel refinery cities or between Russian and neighboring Norwegian cities. In a study of 55 Polish residents living in an industrial town with large ironworks, the mean nickel concentration in random samples was 7.8 ± 3.3 μg/L (range, 4.0–15.9 μg/L) as measured by atomic absorption spectrometry.[193] This value did not differ significantly from the mean nickel concentration (7.7 ± 4.1 μg/L) in urine samples from 76 residents of a Polish health resort. The influence of gender and smoking status on urine nickel concentrations in the general population is small.[190]

Toxicity

A 38-year-old worker died 13 days after developing acute respiratory distress syndrome following spraying nickel during a thermal arc process for coating metal surfaces; his urinary nickel concentration was 700 μg/L several days after exposure.[59]

Abnormalities

NIOSH-certified B-readers identified 47 cases of pulmonary fibrosis among 1,046 Norwegian nickel refinery workers.[194] In logistic-regression models controlling for age and smoking, there was a statistically significant (P = 0.04) increased risk of moderate pulmonary fibrosis with cumulative exposure to soluble nickel or sulfidic nickel. The dose-response trend was less clear for exposure to sulfidic nickel than soluble nickel. Comparing the highest and lowest soluble nickel exposure groups, the crude odds ratio for pulmonary fibrosis was 4.34 (95% CI: 1.75–10.77); however, the odds ratio decreased to 2.24 (95% CI: 0.82–6.16) after adjustment for age, tobacco consumption, asbestos exposure, and cumulative sulfidic nickel exposure. The odds ratio comparing the highest and lowest nickel sulfidic exposure groups also decreased after similar adjustment including soluble nickel exposure from a crude value of 5.06 (95% CI: 1.70–15.09) to an adjusted value of 2.04 (95% CI:

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0.54–7.70). Workers from this plant had an elevated risk of lung cancer.

Clinical history and patch tests are the primary methods to determine Ni hypersensitivity; however, technical and interpretative limitations of patch testing resulted in the development of the *in vitro* lymphocyte transformation test (LTT).[195] However, some false-positive reactions occur in nonallergic subjects using the LTT.[196] Other *in vitro* research-oriented tests include the enzyme-linked immunospot assay (ELISpot) with interleukin-2 (IL-2) secreting cells;[197] this test depends on cytokine production at the single-cell level.[196,198]

HEALTH SURVEILLANCE

Risk Assessment

The ATSDR derived an intermediate-duration inhalation minimal risk level (MRL) of 0.2 μg Ni/m^3 for nickel based on a NOAEL of 60 μg Ni/m^3 and a LOAEL of 110 μg Ni/m^3 for the development of chronic active lung inflammation in F344/N rats exposed to nickel sulfate 6 hours/day, 5 days/week for 13 weeks.[199] The MRL included an uncertainty factor of 30 extrapolating animal data to human and human variability.

The MRL chronic-duration inhalation for Ni is 0.09 μg Ni/m^3 based on a NOAEL of 30 μg Ni/m^3 and a LOAEL of 60 μg Ni/m^3 for chronic active lung inflammation and bronchiolization of alveoli (i.e., metaplastic lesions characterized by cells resembling bronchiolar epithelium lining normal or thickened alveolar walls) in F344/N rats exposed to nickel sulfate 6 hours/day, 5 days/week for 2 years along with the same uncertainty factor.

The WHO provisional guideline value for nickel in drinking water is 20 μg/L based on an NOAEL of 5,000 μg Ni as nickel sulfate/kg/day for 2 years in a study of rats.[27] The lowest LOAEL was 7,000 μg/kg/day in a 6-month study of Wister rats exposed to nickel sulfate in drinking water based on increased kidney weights in female and male rats along with increased albumin excretion in the exposed female (but not male) rats.[200] A development study of rats suggested that the LOAEL for the second generation of a litter of rats exposed to nickel chloride was lower (1,300 μg/kg/day).[201]

Environmental Monitoring

Table 22.2 lists regulations and guidelines for exposure to metallic nickel and nickel compounds. The US OSHA PEL–TWA is 0.1 mg Ni/m^3 for soluble nickel compounds and 1 mg Ni/m^3 for metallic nickel and insoluble Ni compounds. Although some epidemiological evidence and experimental data indicate certain nickel compounds (nickel subsulfide, nickel oxide) are more potent carcinogens than soluble nickel compounds, an accurate dose-response relationship has not been established for soluble and insoluble nickel compounds. Consequently, the ACGIH lowered the TLV–TWA for exposure to nickel compounds, as inhalable nickel particulate mass, to the following: elemental nickel, 1.5 mg/m^3; soluble compounds and nickel subsulfide, 0.1 mg/m^3; and insoluble nickel compounds, 0.2 mg/m^3. These recommended limits now are based on inhalable particulates rather than particulate sampling using a 27-mm open-faced cassette. Nickel subsulfide and insoluble nickel compounds are classified as carcinogenic compounds. Extrapolation of animal and epidemiological data to these low-dose occupational nickel exposures indicates these recommended exposure limits provide adequate safety factors to manage respiratory cancer risks at acceptable occupation levels (e.g., 10^{-4}).[202] The United Kingdom and the Federal Republic of Germany allow metallic and insoluble nickel at concentrations of <0.5 mg Ni/m^3, whereas the Swedish limit for nickel subsulfide is 0.01 mg Ni/m^3.

Biological Monitoring

Biological monitoring is not a substitute for the measurement of nickel in air and other appropriate media. Because of the lack of standardized human data and well-defined toxic endpoints, biological monitoring supplements rather than replaces environmental nickel monitoring. Consequently, there are few health-based biological limit values for nickel compounds in the blood or urine. For soluble nickel compounds, suggested action levels for nickel exposure are 5–8 μg Ni/L serum and 30–50 μg Ni/L urine.[203] The latter urine Ni concentration corresponds to ~0.5 mg Ni/m^3 in ambient air.[204] A study of nickel platers indicated that exposure to 0.1 mg Ni/m^3 as a TWA corresponded to 70 μg Ni/L urine corrected to a specific gravity of 1.018.[205] Accurate biological monitoring requires that the urine sample should not be contaminated by nickel-containing dust from the air or the clothes or hands of workers.

Urine

Sparingly Soluble Nickel Compounds

Depending on the Ni fraction present in the workplace, the airborne Ni concentration does not necessarily correlate closely to urine nickel concentrations. Significant

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TABLE 22.2. Regulations and guidelines for exposure to metallic nickel and nickel compounds.

Exposure Limit	Value
	OSHA
PEL–TWA (8-hour)	
Metallic nickel and insoluble nickel	1.0 mg/m^3 (as total Ni)
	NIOSH
REL–TWA (10-hour)	0.015 mg/m^3
IDLH	10 mg/m^3 (as total Ni)
	ACGIH
TLV–TWA (8-hour)	
Metallic nickel	1.5 mg/m^3 (as Ni)
Insoluble nickel salts	0.2 mg/m^3
Soluble nickel salts	0.1 mg/m^3
Nickel subsulfide	0.1 mg/m^3
	WHO
Drinking water guideline	70 µg/L
Air quality guideline nickel unit risk	3.8×10^{-5}/(µg/m^3)
	US EPA
RfD (soluble salts, chronic oral exposure)	20 µg/kg/day
Carcinogenic unit risk (daily, inhalation)	
Nickel refinery dust	2.4×10^{-4}/(µg/m^3)
Nickel subsulfide	4.8×10^{-4}/(µg/m^3)
Drinking water health advisory	
1-day (10 kg-child)	1,000 µg/L
Lifetime exposure	100 µg/L
	US FDA
Bottled water allowable limit	100 µg/L
Food	Generally recognized as safe as direct human food ingredient with no limitation other than current good manufacturing practices
	ATSDR
MRL	
Intermediate inhalation	0.2 µg/m^3
Chronic inhalation	0.09 µg/m^3

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; IDLH = immediately dangerous to life and health; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = reference dose; TLV = threshold limit value; TWA = time–weighted average; US EPA = US Environmental Protection Agency; US FDA = US Food and Drug Administration; WHO = World Health Organization.

amounts of sparingly soluble Ni compounds (e.g., welding fumes from stainless steel, nickel oxides) may be deposited in the lungs without rapid changes in urine Ni concentrations. Consequently, urine Ni concentrations reflect the release of poorly soluble Ni compounds from the Ni lung burden rather than recent Ni exposure.[206] These concentrations may remain elevated 3–4 years after exposure ceases.[207] As with the serum/plasma nickel, urine nickel concentrations of workers exposed to sparingly soluble compounds may increase as a result of increased nickel lung burdens; however, the absence of an increased urine Ni concentration does not exclude a risk of developing adverse health effects in workers exposed only to sparingly soluble compounds.

In a German cross-sectional study of welders (gas metal arc, flux-cored arc, tungsten inert gas, shielded metal arc), the median airborne respirable and inhalable nickel fraction in welding fumes was <3 µg/m^3 and 6 µg/m^3, respectively, compared with 4 µg/m^3 and 9 µg/m^3 for chromium.[208] These welders were not wearing personal protective equipment. An airborne nickel concentration of 10 µg/m^3 correlated to urinary

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nickel concentration of ~3 μg/L; however, there was substantial variation as a result of a significant number of welders with urine nickel concentrations below the LOQ (1 μg/L).

When workers are exposed to soluble and sparingly soluble nickel compounds, the urine nickel concentrations primarily reflect the exposure to soluble compounds because exposure to the less soluble nickel compounds produces relatively small increases in the urine nickel concentration compared with soluble nickel compounds. Biological monitoring studies suggest that nickel hydroxide yields lower urine nickel concentration than soluble nickel salts following airborne exposure; therefore, nickel hydroxide is more similar to insoluble nickel salts than soluble nickel salts.[209] The mean urine nickel concentration in 92 workers with >2 years exposure in a nickel and cadmium battery factory was 13.4 μg/L (range, 1.6–47.4 μg/L) 0.9-8.3 μg/L compared with 3.1 ± 2.3 μg/L (range, 0.9–8.3 μg/L) for 20 unexposed, nonsmoking hospital staff.[210]

Soluble Nickel Compounds

Urine Ni concentrations reflect primarily recent exposure to soluble Ni compounds (e.g., electroplating industry, nickel chloride, nickel sulfate) in the absence of significant Ni release from sparingly soluble Ni deposits in the lungs. Depending on workplace conditions and practices, the urine nickel concentration may or may not correlate well to nickel concentrations in the air because of the contribution of ingested soluble nickel compounds.[211] The mean ratio of nickel in the air (μg/m^3) to urine nickel (μg/L) for electroplaters, arc welders, and bench mechanics was 0.076, 0.95, and 4.33, respectively.[212] At relatively high ambient air Ni concentrations, the correlation is relatively good (e.g., 100 μg/m^3 ≈ 40–70 μg/L) among electroplaters,[213] whereas correlations at low ambient air Ni concentrations are worse (e.g., $r = 0.68$ at 10 μg Ni/m^3).[214] The mean urine Ni concentration in seven electroplating workers on three regular workdays ranged during the workday 34 ± 32 μg/L (pre-shift) to 64 ± 63 μg/L (mid-shift) and 46 ± 32 μg/L (end-shift). The 19 controls (hospital workers) had a mean urine Ni concentration of 2.7 ± 1.6 μg/L (pre-shift).[215] The correlation coefficient for personal air samples and urine Ni concentrations in six of these workers was 0.70 ($P \ll 0.05$). Urine nickel concentrations decreased rapidly following cessation of exposure to soluble Ni compounds. On the first day returning from a 2-week vacation, the mean urine Ni concentrations in six electroplating workers ranged from 5 ± 3 μg/L (pre-shift) to 9 ± 6 μg/L (mid-shift) and 12 ± 6 μg/L (end-shift).

The mean nickel concentrations in post-shift urine samples from 10 exposed workers at a galvanizing plant using nickel sulfate and 10 unexposed controls working in a zinc electroplating plant were 20.6 ± 18.1 μg/L (range, 2.3–54.9 μg/L) and 4.9 ± 2.2 μg/L, respectively.[216] The corresponding mean post-shift value (μg Ni/g creatinine) for the exposed workers was 14.7 ± 13.5 μg/g creatinine (range, 2.1–58.7 μg/g creatinine) compared with 3.7 ± 2.5 μg/g creatinine for controls. The post-shift urine nickel concentration of exposed workers correlated well ($r = 0.96$, $P \leq 0.001$) to ambient air Ni concentrations in the range of 2.8–116.7 μg/m^3. An ambient air Ni concentration of 100 μg/m^3 correlated to a urine Ni concentration of 50 μg/g creatinine. Increased concentrations of biomarkers of subclinical renal tubular damage (e.g., β_2-microglobulin, retinol-binding protein, *N*-acetyl-β-D-glucosaminidase) may occur in workers with nickel exposures producing urine nickel concentrations exceeding 100 μg/L.

Blood

Blood concentrations of nickel are indicators of recent exposure to soluble Ni compounds rather than measures of the risk of adverse health effects. Plasma Ni concentrations fluctuate less than urine Ni concentrations following occupational exposure to soluble nickel compounds.[217] Generally, the blood Ni concentrations are an order of magnitude higher in workers exposed to soluble nickel compounds compared with unexposed adults. Serum/plasma Ni concentrations of >8–10 μg/L indicate excessive nickel exposure, the need to review work processes, and the importance of evaluating the need for respiratory protection.[218] In nickel workers exposed only to sparingly soluble nickel compounds (e.g., Ni_3S_2, NiO), serum/plasma nickel reflects the lung burden of nickel.

Medical Monitoring

A health surveillance program includes initial and periodic medical examinations supplemented when appropriate by testing (e.g., biological monitoring, environmental sampling, chest x-rays, sputum cytology, pulmonary function tests, and patch testing).[219] Such examinations are appropriate for workers exposed to ambient nickel concentrations exceeding 50% of permissible exposure limits. Recommended screening for preplacement medical examinations includes comprehensive medical and work history with special emphasis on respiratory illness, skin conditions, allergies, asthma, and smoking because these workers may be hypersensitive to nickel exposure. The physical examination

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should concentrate on evidence of irritation and ulceration of the mucous membranes and upper respiratory tract as well as evidence of chronic dermatitis. Preemployment testing includes a chest x-ray and screening pulmonary function tests. Determination of urine or serum/plasma nickel concentrations is a measure of exposure rather than a determination of the risk for adverse effects. Periodic medical examinations should be available for workers who develop skin or respiratory complaints. Patch testing (0.5% nickel sulfate), respiratory questionnaires, and pulmonary function testing with bronchodilators should be administered to workers with signs of dermatitis or asthma. Routine use of sputum cytology, chest x-rays, or nasal biopsy for the early detection of cancer has not been established.

TREATMENT

Little data are available to guide the treatment of ingestions of divalent nickel compounds. Generally, decontamination measures (e.g., lavage) are useful only in the first 1–2 hours post-ingestion and are often limited by the severe gastrointestinal effects of these nickel salts. Serum or urine nickel measured within 1–2 after exposure correlates to the severity of the nickel exposure. Supportive care is the mainstay of treatment. Hemodialysis is an option in cases of renal failure or life-threatening complications; however, the effectiveness of this procedure in reducing the body burden of nickel remains inadequately documented. Chelation with DDC is not recommended for divalent nickel poisoning because animal studies indicate that DDC increases nickel uptake into the brain.[220] Studies in rodents indicate that D-penicillamine is superior to DDC as a chelating agent for divalent nickel;[221] however, clinical data on the use of D-penicillamine and DMPS during divalent nickel poisoning are lacking.

NICKEL CARBONYL

HISTORY

In the 1890s, LF Mond discovered nickel carbonyl [$Ni(CO_4)$]; subsequently, he developed the Mond carbonyl process to separate nickel from nickel ores processed in nickel refineries.[222] Soon after commercial use of the Mond carbonyl process began, reports of the severe toxicity of acute exposure to nickel carbonyl appeared in the medical literature. Two fatalities following exposure to nickel carbonyl were reported in 1903.[223]

PHYSIOCHEMICAL PROPERTIES

Table 22.3 lists the identifying information and physical properties of nickel carbonyl. This highly volatile, flammable (flash point < −20°C) pale-yellow liquid vaporizes rapidly to amorphous hydrous nickel carbonate oxide with a half-life of <2 minutes. The "sooty" or "musty" odor is difficult to detect at concentrations producing mild-to-moderate toxicity depending on the familiarity of the individual with the smell; the relative vapor density of nickel carbonyl is ~6 compared with room air. Carbon monoxide is a potentially toxic thermal decomposition product from heating nickel carbonyl above 50°C.

EXPOSURE

In rotary kilns using the Mond Process for refining nickel, the nickel oxide in fine particulate form combines with carbon monoxide to form nickel carbonyl. At 200°C, the carbon monoxide dissociates from the nickel carbonyl with the deposition of relatively pure nickel. Accidental exposure to nickel carbonyl may occur at these kiln plants. Other processes that use nickel carbonyl include nickel-catalyzed coal gasification, the Reppe process for catalytic synthesis of alkyl methacrylate compounds, and the nickel vapor-plating process. Commercial uses for nickel carbonyl include the extraction of nickel (Mond process), catalyst and

TABLE 22.3. Identifying information and physical properties of nickel carbonyl.

Physical Characteristic	Nickel Carbonyl
CAS RN	13463-39-3
Synonyms	Nickel tetracarbonyl
Molecular formula	$Ni(CO)_4$
Molecular weight (g/mol)	170.73
Color	Colorless
Physical state	Volatile liquid
Odor	Musty
Melting point (°C)	−25
Boiling point (°C)	43
Water solubility (9.8°C)	0.18 g/L (poorly soluble)
Vapor pressure (mmHg)	339 (21°C)
Odor threshold air	1–3 ppm

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.

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reactant in chemical synthesis (carbonylation reactions), vapor-plating nickel, gas plating, and fabrication of nickel and nickel alloys.

ENVIRONMENTAL FATE

Nickel carbonyl is unstable in air decomposing to nickel carbonate oxide. Depending on the carbon monoxide concentration, further degradation occurs to Ni and carbon monoxide. As a result of the high reactivity of nickel carbonyl, the half-life of this compound in the air is only a few minutes. Consequently, nickel carbonyl is not usually found in ambient air samples. Similarly, this compound is not usually found in drinking water because of its poor water solubility.

DOSE EFFECT

Most case reports on nickel carbonyl do not provide estimations of nickel carbonyl concentrations in ambient air at the time of exposure. Nickel carbonyl is a highly volatile liquid that produces potentially fatal concentrations following exposure to 30 ppm nickel carbonyl for 30 minutes.[224]

TOXICOKINETICS

In severe poisoning with nickel carbonyl, dermal absorption of this nickel compound may contribute to toxicity;[225] however, the amount of dermal absorption of nickel carbonyl is difficult to separate from inhalation of this highly volatile substance. Once absorbed, nickel carbonyl probably undergoes decomposition to metallic Ni, followed by oxidation to divalent Ni.[226] Following exposure to nickel carbonyl, the highest concentrations of nickel appear in the lung, brain, kidney, liver, and adrenals. Animal studies suggest ~40% of an intravenous dose of $^{63}Ni(CO)_4$ is exhaled, whereas ~30% of the dose is excreted in the urine as divalent Ni over 4 days.[227] In a Chinese study of 179 cases of acute nickel carbonyl toxicity, maximum urinary nickel excretion occurred 1–2 days after exposure with return to baseline within 1 week.[228]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Nickel carbonyl is a volatile carcinogen in rodent studies that readily diffuses across cell membranes; intracellular oxidation of this compound releases Ni^{2+} that binds to nucleic acids.[229] A 47-year-old chemical operator was exposed to nickel carbonyl during a malfunction of a chemical processing unit.[230] Analysis of the urine 24 hours after exposure was consistent with a severe nickel carbonyl exposure (535 µg Ni/L). He died of respiratory failure 4 days after exposure. The autopsy demonstrated pulmonary and cerebral edema. The kidneys and liver appeared relatively normal. In a case series of three workers dying ~2 weeks after exposure, the autopsies demonstrated diffusely consolidated lungs with congestion, edema, hemorrhage, sterile pleural inflammation, and early organizing pulmonary fibrosis along with an edematous, mildly dilated heart, cerebral edema, and mild renal parenchymal pallor and edema.[231] Microscopic changes in the lungs include interstitial edema, cellular proliferation, capillary congestion, fibrinous intra-alveolar exudates, and hypertrophy of the alveolar cells.[232]

CLINICAL RESPONSE

Almost all cases of acute nickel toxicity involve exposure to nickel carbonyl.[233] Typically, acute nickel carbonyl poisoning appears in two stages: immediate and delayed. The initial symptoms primarily involve irritation of the respiratory tract and nonspecific, flu-like symptoms.[234] The most common immediate symptoms include dizziness, frontal headache, weakness, nausea, and vomiting, followed by tightness in the chest, pleuritic chest pain, dyspnea, and a nonproductive cough. In patients with mild nickel carbonyl poisoning, these symptoms are minimal with gradual resolution within 1 day. Patients with more severe poisoning develop the onset of more intense pulmonary (pulmonary edema, acute pneumonitis, acute respiratory distress syndrome) and gastrointestinal symptoms within 12–120 hours postexposure.[228,235] Other features of severe poisoning include fever, myalgias, fatigue, profound weakness, pneumothorax, respiratory failure, delirium, and convulsions.

Fever is usually not a prominent part of the clinical picture of mild nickel carbonyl poisoning; however, body temperatures of >39°C may occur in severe poisoning.[231] Additional complications of severe nickel carbonyl poisoning involve hepatorenal dysfunction, adrenal insufficiency, and hyperglycemia. Diffuse interstitial pneumonitis and cerebral edema and/or hemorrhage are the primary causes of death in patients with severe toxicity secondary to acute nickel carbonyl exposure.[13] Patients surviving severe exposure to nickel carbonyl may develop pulmonary fibrosis;[22] however, most survivors do not develop pulmonary abnormalities as measured by pulmonary function tests.[236]

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The onset of bronchial asthma has been associated with acute nickel carbonyl poisoning.[234] Exposure of pregnant animals to high doses of nickel carbonyl during organogenesis produces fetal malformations;[141] however, obvious nickel toxicity occurs at these concentrations.

DIAGNOSTIC TESTING

SI Conversion Units

1 ppm nickel carbonyl = 6.983 mg nickel carbonyl/m^3
1 mg nickel carbonyl/m^3 = 0.1432 ppm nickel carbonyl

Analytical Methods

Although gas chromatography is the best method for detecting nickel carbonyl in expired air, the rapid dissolution of nickel carbonyl in the body into carbon monoxide and divalent nickel means that atomic absorption spectrometry is the best method for measuring nickel carbonyl in biological media.

Biomarkers

Because of the rarity of nickel carbonyl toxicity, data are limited to case reports. During the first 3 days postexposure, the concentration of nickel in the urine correlates well with the severity of acute nickel carbonyl poisoning; however, later urine Ni concentrations lack correlation with clinical outcome. Eight days after exposure, the urine Ni concentration in a worker surviving exposure to nickel carbonyl was higher (78.5 μg/L) than the urine Ni concentration (23 μg/L, 43 μg/L, 71 μg/L) in three workers eventually dying from acute respiratory distress syndrome.[231] In the absence of chelation, the urine nickel concentration peaks at 24–48 hours postexposure, returning to baseline concentrations within 1–2 weeks.[236] Sunderman et al. classified the severity of acute nickel carbonyl poisoning with the following urine concentrations obtained during the initial 18 hours postexposure: mild, 60–100 μg Ni/L; moderately severe, 100–500 μg Ni/L; and severe, >500 μg Ni/L.[237] A 50-year-old industrial technician developed flu-like symptoms followed by acute pneumonitis, hypoxemia, and pulmonary infiltrates 2 days after exposure.[235] Disulfiram and prednisone were initiated within 12–24 hours after exposure. The reported urine nickel concentration 2 days after exposure was ~200 μg/L. His urine nickel concentration peaked 3 days after exposure at ~1,600 μg/L initially returning to baseline within 10 days with some later mild rebound. He recovered without sequelae.

The postmortem blood (site not reported) of three workers developing fatal nickel carbonyl toxicity contained nickel concentrations of 8.9 μg/L, 3.3 μg/L, and 8.6 μg/L; the latter patient died 14 days after exposure, whereas the former two patients died 17 days after exposure.[231] These patients received no chelation. The serum nickel concentration in the nonsmoking industrial technician 2 days after exposure was 28 μg/L.[235] The blood carboxyhemoglobin was 4%, typical of the mild elevations of blood carboxyhemoglobin associated with nickel carbonyl poisoning.

HEALTH SURVEILLANCE

The US OSHA PEL–TWA for nickel carbonyl is 0.001 ppm (0.007 mg/m^3) Ni. The TLV–TWA recommended by the ACGIH is 0.05 ppm (0.12 mg Ni/m^3) based on a level sufficient to minimize the potential for acute and chronic nickel intoxication including cancer.[224] The NIOSH REL–TLV (10-hour) is 0.001 ppm (0.007 mg/m^3), whereas the IDLH is 2 ppm (13.9 mg/m^3).

TREATMENT

First Aid

Nickel carbonyl is the only nickel compound that causes acute poisoning following inhalation; the primary target organ of acute $Ni(CO)_4$ poisoning is the respiratory tract. Patients with excessive $Ni(CO)_4$ exposure should be removed immediately from the source of exposure. Because of potential dermal absorption of $Ni(CO)_4$, contaminated clothes should be removed. Initial attention should be directed toward maintaining oxygenation by supplemental oxygen and assisted ventilation as needed. Symptomatic patients and those with heavy exposure to $Ni(CO)_4$ should be transported to an emergency department for evaluation.

Antidotes

Sodium diethyldithiocarbamate (DDC) is an investigational antidote in the United States with no manufacturer assigned to sponsor this orphan drug. Dr. F. William Sunderman, Sr, holds the Investigational

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New Drug Application at the Institute for Clinical Science, Pennsylvania Hospital in Philadelphia (215-829-7068). Tetraethylthiuram disulfide (disulfiram, Antabuse®) is split during metabolism into two molecules of diethyldithiocarbamate (DDC). There are insufficient clinical data to judge the clinical effectiveness of disulfiram as a chelator of nickel following nickel carbonyl poisoning. In rodent models, *N*-benzyl-D-glucamine dithiocarbamate and, to a lesser extent, meso-2,3-dimercaptosuccinic acid (DMSA) are more effective nickel chelating agents than DDC.[238,239] However, there are no clinical data regarding the efficacy of these chelating agents. Patients have developed severe acute respiratory distress syndrome after nickel carbonyl and survived with intensive supportive care alone.[231]

Dithiocarb

Experimental Studies

DDC forms lipophilic chelates with divalent nickel and reduces the accumulation of nickel in the lungs of mice by redistribution;[240,241] however, the nickel-diethyldithiocarbamate complex also has an affinity for lipid-rich brain tissue. In studies of mice given low doses (0.05 μmol Ni/kg) via gavage, the simultaneous oral administration of 13 μmol DDC/kg was associated with elevated nickel concentrations in the brain compared with controls.[242] The effectiveness of DDC as a chelator of nickel in the lungs was greater when administered parenterally than orally; however, the redistribution of nickel to the brain was similar. In a rodent study, large doses (0.92 g DDC/kg) intramuscularly significantly reduced mortality from nickel carbonyl toxicity when administered within 10 minutes, but not 6 hours or 24 hours after exposure.[243] D-Penicillamine (2.52 g/kg) reduced mortality when administered intramuscularly at 10 minutes and 6 hours, but not at 24 hours after nickel carbonyl exposure.

Clinical Cases

Anecdotal experience with nickel carbonyl poisoning suggests that the affinity of nickel bisdiethyldithiocarbamate chelates for lipid tissue does not produce a clinically significant Ni uptake by the brain of patients with nickel carbonyl poisoning.[244] There were no reported deaths in a group of ~400 patients treated with DDC within 4 days of nickel carbonyl exposure;[244] however, the lack of control data and clinical details on the patients in this series limits conclusions regarding the efficacy of DDC. Vuopala et al. published a case series of 25 patients with nickel carbonyl intoxication including 15 patients with pneumonitis.[236] All patients recovered without the use of DDC; follow-up pulmonary function tests eventually normalized. The administration of DDC within 48 hours does not always prevent serious sequelae. A 47-year-old chemical operator with severe nickel carbonyl poisoning died 4 days after exposure despite receiving 4 g DDC beginning 40 hours postexposure.[230]

Indications

The decision to use DDC is a clinical judgment involving the availability of DDC, the severity of the poisoning, the amount ingested, and patient stability. Patients with moderate or severe poisoning as defined by initial 8-hour postexposure urine concentrations of >100 μg Ni/L are potential candidates for the administration of sodium DDC to reduce the nickel burden in the lungs;[245] however, there are no published clinical trials using DDC and no peer-reviewed data to confirm DDC efficacy in nickel carbonyl poisoning. Consequently, there are no definite indications for DDC use.

Administration

The protocol developed by Dr. Sunderman for an adult oral dose is 35–45 mg DDC/kg in divided doses during the first 24 hours followed by 400 mg every 8 hours until the patient is symptom-free and the urine nickel concentrations are near normal values.[246] The parenteral administration of DDC at a dose of 12.5 mg DDC/kg may be necessary for critically ill patients unable to tolerate oral medication. An Antabuse-like reaction may result from the co-ingestion of DDC and alcohol.

Disulfiram

Animal studies suggest that disulfiram (Antabuse), which the body metabolizes to two molecules of DDC, may be useful as a temporary chelating agent because of the time needed to obtain DDC. In a study of rodents, the effectiveness of disulfiram in reducing the acute toxicity of nickel carbonyl was ~70% of DDC.[247] However, animal studies suggest that disulfiram increases Ni uptake by the brain, potentially accounting for the limited efficacy of disulfiram in the treatment of acute nickel poisoning in rats.[248] Although adverse drug reactions have not been reported following the use of disulfiram in nickel intoxication, cases of hepatitis have been associated with the use of disulfiram to chelate nickel in patients with nickel allergies.[249]

A patient with severe nickel carbonyl poisoning (initial concentration, 172 μg Ni/L urine) received 750 mg

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disulfiram orally every 8 hours for 24 hours and then 250 mg disulfiram orally every 8 hours for 1 day until the DDC arrived.[225] The patient required continuous positive airway pressure (CPAP) to maintain adequate oxygenation requiring 18 days of hospitalization. There were no abnormalities on pulmonary function testing 3 months after exposure. A 50-year-old nonsmoking industrial technician with moderately severe acute pneumonitis following acute nickel carbonyl survived without sequelae. During hospitalization, he received disulfiram 1 g 12–24 hours after exposure, 500 mg 6 hours later, and then 250 mg twice daily for 5 days along with 60 mg prednisone daily for 5 days.[235] He survived with supplemental oxygen. His only complication was a mild elevation of his serum hepatic aminotransferases that resolved without sequelae.

Supportive Care

Patients with evidence of more than minor irritation of the upper respiratory tract should be evaluated for acute chemical pneumonitis (arterial blood gases, chest x-ray, pulse oximetry) and associated carbon monoxide exposure (carboxyhemoglobin). In severe cases of $Ni(CO)_4$ poisoning, the patient should be monitored for the development of respiratory failure and cerebral edema; these patients typically develop oxygen desaturation with minimal activity. Case reports suggest pulmonary function tests usually demonstrate a restrictive defect that improves significantly within 1 week after exposure.[225] Respiratory support includes continuous positive airway pressure (CPAP) and intravenous corticosteroid therapy.

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Chapter 23

PHOSPHORUS AND PHOSPHORUS COMPOUNDS

ELEMENTAL PHOSPHORUS AND BISPHOSPHONATES

HISTORY

While searching for the "Philosopher's stone" to create gold from base metals in 1669, the Hamburg physician and alchemist, Hennig Brandt, first isolated white phosphorus by precipitating the vapors from a boiling mixture of sand and human urine in water. Commercial phosphorous production began from the reduction of animal bones.[1] In 1832, the incorporation of white phosphorus into a binder of antimony sulfide and potassium chlorate produced the first "strike anywhere" (Lucifer) match.[2] The convenience of lighting a fire anywhere, despite adverse conditions, resulted in enormous demand for these matches. Friedrich Wilhelm Lorinser of Vienna first described phosphorus-induced maxillary and mandibular necrosis in 1845; in the same year, Heyfelder of Erlangen published a case series on mandibular necrosis in nine workers from a match plant in Nuremberg. During the mid- to late-1800s, an epidemic of exposed osteonecrosis of the jaw (phossy jaw) developed in match-making factory workers exposed to heated fumes from white (also known as yellow) phosphorus (P_4O_{10}). These abnormalities (i.e., painful, suppurative mandibular enlargement, debility, increased mortality) did not occur in office-based workers at these factories. Safer matches were produced in the middle 1800s after the discovery of red phosphorus by the[1] Viennese Professor Schrötter and later the use of phosphorus sesquisulfide (tetraphosphorus trisulfide, P_4S_3) replaced the more toxic white phosphorus. The recognition of the toxic effects of white phosphorus during the production of matches led to the Berne Convention of 1906 and the Match Act of 1912 that introduced a prohibitive US tax on the use of white phosphorus.[3] Although most cases of the phossy jaw (Lucifer's jaw) occurred in the match industry, sporadic cases also occurred in phosphor-bronze workers producing phosphorus-containing rat poison, and fireworks production workers during the early 20th century.[4] Increased demand for phosphorus during both World Wars resulted in increased occupational exposure to phosphorus and sporadic cases of osteonecrosis of the jaw.[5]

In the early 1900s, white phosphorus was administered as a treatment for osteomalacia, nonunion of bone fractures, and rickets.[6] Although the medicinal use of white phosphorus was associated with chronic phosphorus poisoning, osteonecrosis of the jaw was not associated with this medical use.[7] Currently, acute phosphorus toxicity results primarily from suicidal ingestion of firecrackers (totes)[8] or the accidental ingestion of white phosphorus rodenticides.

In the early 2000s, rare case reports documented the development of osteonecrosis in the jaw (bis-phossy jaw) with bisphosphonate therapy.[9] Bisphosphonate-induced osteonecrosis of the jaw was first recognized in 2003. The bone lesions and clinical course of the phossy jaw are similar to this rare complication of bisphosphonate therapy including treatment with alendronate

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(Fosamax®, Merck, Whitehouse Station, NJ), ibandronate (Boniva®, Roche Laboratories, Nutley, NJ), pamidronate (Aredia®, Novartis Pharmaceuticals, East Hanover, NJ), risedronate (Actonel®, Procter and Gamble Pharmaceuticals, Cincinnati, OH), and zoledronate (Zometa®, Novartis Pharmaceuticals). The clinical presentation of these patients was similar to the 19th-century disease (phossy jaw) associated with white phosphorus exposure;[10] however, other mitigating factors (e.g., oral health, chemotherapy, immune status, bacterial infections) probably contributed to the development of bisphosphonate-associated osteonecrosis of the jaw.[11] Almost all of these patients had signs of infection with a majority of them requiring dental extractions.

PHYSIOCHEMICAL PROPERTIES

Elemental phosphorus is a metalloid in the nitrogen group that does not exist naturally in the environment. The allotropic forms of elemental phosphorus include white (or yellow) phosphorus, red phosphorus, and black phosphorus. The most important allotropic form of elemental phosphorus is white phosphorus; this relatively pure (99.9%) form has a slight yellow color resulting from the presence of traces of red phosphorus. Consequently, white phosphorus is also known as yellow phosphorus, particularly commercial grades of white phosphorus that contain more impurities than technical grades. This soft, translucent solid darkens following exposure to light. White phosphorus is a water-insoluble compound that dissolves in oils (e.g., ether, olive oil); this compound is highly fat-soluble and emits a garlic-like odor. The saturation vapor pressure is 170 mg/m^3 at 20°C; spontaneous ignition occurs on drying at 34–46°C (30°C in moist air) producing phosphorus oxides (e.g., phosphorus pentoxide, P_4O_{10}; phosphorus trioxide, P_4O_6).[12] These compounds are strong desiccants and dehydrating (corrosive) agents. The reaction of these oxides with moist air forms phosphorus-containing acids including phosphoric acid (H_3PO_4, CAS RN: 7664-38-2), pyrophosphoric acid ($H_4P_2O_7$, CAS RN: 2466-09-3), phosphorus acid (H_3PO_3, CAS RN: 13598-36-2), phosphinic acid (H_3PO_2, CAS RN: 6303-21-5), and polyphosphoric acids (CAS RN: 8017-16-1). Consequently, storage under water is necessary to prevent phosphorus ignition. Phosphine gas is a decomposition product of white phosphorus ignition in aqueous alkaline solutions at 100°C. Table 23.1 lists the identifying information and physical properties of white phosphorus. Red phosphorus is a violet–red amorphous powder that is poorly soluble in most solvents and much less reactive than white phosphorus. Black phosphorus is a solid similar to graphite.

TABLE 23.1. Identifying information and physical properties of white phosphorus.

Physical Characteristic	White Phosphorus
CAS RN	12185-10-3
Molecular formula	P_4
Molecular weight (g/mol)	123.89
Melting Point (°C)	44.15
Boiling Point (°C)	280.5
Density (g/mL)	1.82 (20°C)
Water solubility (mg/L)	3 (slight, 15°C)
Vapor pressure (mmHg)	0.025 (20°C)
Saturated vapor concentration (mg/m^3)	170 (20°C)
Partition coefficients	
Log K_{ow}	3.08
Log K_{oc}	3.05
Henry's Law constant (atm m^3/mol)	2.11×10^{-3} (20°C)

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.

Bisphosphonate compounds are analogs of pyrophosphate (P_2O_7) with the P–O–P bond replaced by P–C–P as displayed in Figure 23.1. Simple bisphosphates typically contain hydroxyl, methyl, or chloride groups in the R^1 and R^2 positions, whereas aminobisphosphonate compounds contain nitrogen and more complex carbon groups. The P–C–P and R^1 portion of the bisphosphonate molecule bind strongly to hydroxyapatite in bone minerals, whereas the R^2 portion imparts potency to inhibit osteoclast activity and induces apoptotic death of osteoclasts.

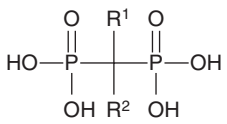
EXPOSURE

Production Processes

The production of elemental phosphorus involves refining phosphorus rock including calcium phosphate [$Ca_3(PO_4)_2$], chlorapatite [$3Ca_3(PO_4)_2CaCl_2$], hydroxyapatite [$3Ca_3(PO_4)_2Ca(OH)_2$], and fluorapatite [$3Ca_3(PO_4)_2CaF_2$]. Central Florida is the source of about 1/3 of the world's supply of elemental phosphorus. Coke or anthracite, silica chippings, and phosphate rock are heated to ~1,500°C with carbon electrodes passing an electric current through the mix in a carbon-lined furnace. The molten slag containing ferrophosphorus and calcium silicate migrates to the bottom, whereas phosphorus vapor and carbon monoxide off-gas from the furnace with the conversion of white phosphorus to phosphoric acid by aerobic hydration. The reaction of phosphate rock with sulfuric acid in the wet acid method is an alternate method of producing phosphoric acid.

The refining of phosphorus rock exposes workers to several respiratory irritants including phosphoric acid,

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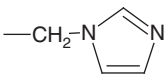
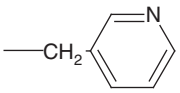
Drug	Relative Potency	R^1	R^2
Etidronate	1	—OH	—CH_3
Clodronate	10	—Cl	—Cl
Pamidronate	100	—OH	—CH_2-CH_2NH_2
Ibandronate	500 – 1,000	—OH	—CH_2-$CH_2N(CH_3)(C_5H_{11})$
Alendronate	1,000 – 2,000	—OH	—CH_2-CH_2-CH_2NH_2
Risedronate	2,000	—OH	—CH_2– 
Zoledronic acid	10,000	—OH	—CH_2– 

FIGURE 23.1. Chemical structures and relative potencies of bisphosphonate derivatives. (Modified from Vance).[13]

phosphorus pentoxide (volatile form of phosphoric acid), fluorides, and coal tar pitch volatiles.[14] The phosphate deposits contain significant quantities of natural radioactive material, principally ^{238}U and members of its decay series;[15] the risk of lung cancer is elevated in residents of this region compared with standardized US rates.[16] Impurities in white phosphorus at concentrations exceeding 10 ppm include aluminum, arsenic, boron, calcium, iron, and silicon. Red phosphorus is obtained by the catalytic heating of white phosphorus. The heating of white phosphorus under pressure produces black phosphorus.

Uses

Uses of white phosphorus include military applications, industrial processes, and agricultural products. Occupational exposure to phosphorus compounds includes acetyl cellulose makers, bronze alloy makers, munitions workers, smoke bomb (screens) and incendiary makers, pesticide rat poison workers, fertilizer makers, electroluminescent-coating makers, and semiconductor workers. Most white phosphorus is consumed during the production of phosphoric acid, phosphates, and, to a lesser extent, red phosphorus and phosphorus salts (trichloride, pentoxide, pentasulfide).[17] White phosphorus is a constituent of hand grenades, mortar shells, and smoke screens; combustion of white phosphorus produces a yellow flame and thick white smoke obscuring vision and weapon-tacking devices. Indications for biphosphate pharmaceuticals include osteomalacia and metastatic bone disease.

Sources

Phosphate rocks provide an abundant source of phosphorus. One of the most common methods to produce illicit methamphetamine involves the use of red phosphorus, hydrogen iodide (hydriodic acid, HI, CAS RN: 10034-85-2), and ephedrine or pseudoephedrine. The heating of red phosphorus in the presence of acids may produce phosphine gas. Consequently, law enforcement personnel potentially are exposed to phosphine gas during the investigation of clandestine methamphetamine laboratories.[18]

ENVIRONMENTAL FATE

The persistence of elemental phosphorus in the air is very short because this substance quickly oxidizes

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to phosphorus oxides and ultimately to phosphorus acids; however, the atmospheric half-time of phosphorus particles may be extended as a result of the formation of a protective layer of oxides.[17] Phosphine formed during the combustion of white phosphorus persists in the atmosphere longer than reaction products because of its slower reactivity, lower water solubility, and physical state. Phosphorus enters water primarily as phosphates with smaller amounts as elemental phosphorus; phosphate partitions primarily into the sediment. The half-life of elemental phosphorus in water is ~2–20 hours compared with ~3–7 days in soil. The disappearance half-life of elemental phosphorus from water depends on dissolved oxygen concentration, temperature, physical state (dissolved, colloidal, particle), and pH. The rate of disappearance increases with temperature, oxygen concentration, and pH.[17] The presence of anoxic conditions substantially prolongs the half-life of elemental phosphorus up to years. Volatilization of elemental phosphorus from water is the significant route of release as determined by Henry's law constant, depending on the depth of the particles and the turbulence of the water. Exposure of soil to phosphorus aerosols reduces the soil pH depending on the amount applied and the buffering capacity of the soil. In soils, rapid oxidation is the predominant route of white phosphorus degradation in <3–7 days, where the diffusion of oxygen is sufficient. The bioconcentration factor of white phosphorus in aquatic organisms is relatively low.[17]

DOSE EFFECT

White (Yellow) Phosphorus

White phosphorus is highly toxic. The acute fatal dose of white phosphorus in adults is 15–100 mg (i.e., ~1 mg/kg),[19] although survival occurred after ingestions up to 1.5 g.[20,21] In a study of 56 patients ingesting white phosphorus-containing rat poison, the fatality rate of patients ingesting >1.57 mg/kg exceeded 90%.[22] The intentional ingestion of nine firecrackers containing white phosphorus (constituents not reported) was associated with acute hepatic failure and mild encephalopathy that resolved over 2 weeks without liver transplantation, whereas the suicidal ingestion of 12 white phosphorus-containing firecrackers produced fatal hepatorenal failure.[23]

Red Phosphorus

This compound is nonvolatile, insoluble, and practically nonabsorbable. These characteristics almost always result in nontoxic ingestions. Modern matches contain no yellow phosphorus. The regular, rough surface contains red phosphorus, phosphorus sesquisulfide, potassium chlorate, and glue. The tips of safety matches contain potassium chlorate and antimony sulfide, whereas red phosphorus or sesquisulfide, sand, and glue constitute the surface. Twenty wooden matches contain 330 mg of potassium chlorate, a mucosal irritant and methemoglobin producer.

TOXICOKINETICS

The involvement of phosphorus in many cellular processes (e.g., energy transfer, carbohydrate metabolism, phospholipids, nucleotides, buffering systems) complicates the understanding of the toxicokinetics of white phosphorus and other phosphorus compounds. Consequently, there are limited data on the toxicokinetics of white phosphorus in humans.

Absorption

Although white phosphorus is poorly water-soluble, this compound is highly reactive in the presence of oxygen; the rapid conversion to oxidation products (phosphates, orthophosphates, phosphorus peroxide) potentially allows an important route of absorption. The gastrointestinal tract and respiratory tract absorb white (yellow) phosphorus based on case reports of oral toxicity and radiolabeled animal data. In rodent studies, ~80–90% of the administered dose of ^{32}P was absorbed from the gastrointestinal tract within 2–3 hours.[24] Dermal absorption of white phosphorus is not well documented. Red phosphorus is practically nonabsorbable.

Distribution

Following the oral administration of white phosphorus to rats, the highest phosphorus concentrations occur in the liver, kidney, gastrointestinal tract, and skeletal muscles.[24] After inhalation of ^{32}P, the highest ^{32}P concentration appears in the lungs, followed by bone, liver, and kidney. The concentration of ^{32}P decreases rapidly in soft tissue; however, the release of ^{32}P from bone is slow.

Elimination

Animal experiments indicate the kidney excretes white phosphorus, primarily in the form of inorganic and much smaller amounts of organic phosphates.[25] At least 96% of phosphorus excreted in the urine and feces occurs as inorganic phosphate; the remainder is organic phosphorus (e.g., phosphoproteins, nucleoproteins, nucleotides,

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and phospholipids).[17] Potential inorganic oxidation products of white phosphorus include phosphates, orthophosphates, pyrophosphates, and polyphosphates; however, there are inadequate data to determine the ratio of these oxidation products following white phosphorus absorption in humans.

HISTOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Phosphorus

White phosphorus is a general protoplasmic poison that uncouples oxidative phosphorylation. The primary targets of white phosphorus include the gastrointestinal tract, liver, kidney, and bone. Death usually results from cardiovascular collapse, probably secondary to metabolic changes or a direct effect of phosphorus on the myocardium.[26] White phosphorus burns result from thermal and chemical injuries. These mechanisms of toxicity potentially include thermal damage from the heat generated by the formation of phosphorus pentoxide, the hydroscopic effect of the phosphorus pentoxide, and the corrosive effect of phosphoric acids produced during combustion.[27]

Bisphosphonates

The exact mechanism of bisphosphonate toxicity is unclear with several possibilities including direct toxicity to bone/soft tissue, avascular necrosis, altered immunity (monocyte/macrophage/γ-δ B cell function), and suppression of bone remodeling.[28] Bisphosphonate compounds concentrate in areas of active bone resorption including osteoclasts. These drugs decrease bone resorption by inhibiting osteoclast activity and increasing osteoclast apoptosis through interference with ATP-dependent enzymes (simple bisphosphonates)[29] or disrupting prenylation of regulatory proteins including guanosine triphosphatases.[30] At high concentrations, bisphosphonates alter bone mineralization by interfering with the formation of the crystalline salt of calcium (hydroxyapatite).

Pathological Changes

White Phosphorus

Pathological changes following acute exposure to white phosphorus include severe ulcerative gastritis, rarely with luminescent stools, acute yellow liver atrophy with peripheral zone necrosis and fatty degeneration, and proximal convoluted tubular and renal cortical necrosis. Liver biopsies of explanted livers from cases of acute white (yellow) phosphorus intoxication demonstrate hepatocyte necrosis with balloon degeneration.[23] Direct damage to the walls of blood vessels may develop, resulting in the exudation of fluid. Fatty degeneration of the myocardium with necrosis can occur after white phosphorus exposure. The intentional ingestion of white phosphorus by a 17-year-old girl was associated with a moderate decrease in granulocytes.[31] Bone marrow aspiration 24 hours after ingestion demonstrated interstitial edema, mild necrotic foci, and hemorrhage. She recovered within 48 hours without sequelae.

Phossy Jaw and Bisphosphonate-Induced Osteonecrosis

Chronic degenerative bone changes (phossy jaw) and osteoporosis occur after chronic phosphorus exposure exceeding 5 years, particularly in the mandible. Characteristically, pathological changes include thickening of the mandibular periosteum with distortion of architecture and a subsequent predisposition to fractures and infections. The histological abnormalities of phossy jaw and bisphosphonate-induced osteonecrosis are similar. Histological examination of patients receiving bisphosphonate therapy reveals acellular bone devoid of osteocytes, osteoclasts, or osteoblasts with signs of acute/chronic inflammation and bacterial colonization.[11]

Postmortem Examination

The most common pathological changes noted during autopsy of patients dying of acute white phosphorus poisoning are fatty degeneration of the liver and kidneys. Explanted livers from six children undergoing liver transplantation for acute white phosphorus-induced hepatic toxicity were very hard and pale; histological examination demonstrated extensive necrosis, balloon degeneration, and steatosis.[32]

CLINICAL RESPONSE

Adverse Drug Effects

Osteonecrosis of the jaw is a rare complication occurring during the treatment of osteoporosis, Paget's disease, or metastatic bone disease with bisphosphonate drugs,

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primarily aminobisphosphonate therapy. The administration of receptor activator of nuclear factor κ-B ligand inhibitors is also associated with osteonecrosis of the jaw. This complication occurs typically in the mandible and to a lesser extent in the maxilla. The occurrence of this adverse effect depends on drug potency (aminobisphosphonate ≫ simple bisphosphonates), duration of treatment, and route of exposure (intravenous ≫ oral).[33] Some patients may not respond to treatment for bisphosphonate-induced osteonecrosis.[34] In a case series of 112 patients (70% women) with osteonecrosis of the jaw, 74% had underlying malignancies; all patients had underlying jaw infections, commonly with *Actinomyces*.[11] Other risk factors include maxillary or mandibular bone surgery, poor oral hygiene, ill-fitting dentures, chronic inflammation, diabetes mellitus, and the use of glucocorticoid or antiangiogenic agents.[35]

Oral Exposure

In 1949, Rubitsky and Myerson described three stages of severe white (yellow) phosphorus toxicity after summarizing the clinical features in 16 patients almost exclusively ingesting white phosphorus in rat bait.[36] The initial stage (first day) involved gastrointestinal irritation (nausea, vomiting, hematemesis, abdominal pain) with occasional fever and garlic odor, followed by a variable quiescent period (1–3 days) characterized by transient improvement of gastrointestinal symptoms despite increasing serum aminotransferases and bilirubin. Subsequently, the final phase of multiorgan failure develops manifested by hepatorenal dysfunction, encephalopathy, coagulopathy, and shock depending on the severity of exposure. In severe cases, coma and cardiovascular collapse follow soon after the gastrointestinal phase with acute liver failure often requiring a liver transplant.[32] The most common clinical features in 85 patients admitted to 7 Ecuadorian hospitals after ingesting white phosphorus and potassium chlorate in pyrotechnics (*diablillos*) were abdominal pain, diarrhea, nausea, vomiting, jaundice, elevated serum hepatic aminotransferases, prolonged prothrombin time, and hypoglycemia.[37] Diarrhea and garlic breath are less common than vomiting and abdominal pain during the gastrointestinal stage; luminescent stools/vomitus and mucosal burns appear infrequently.[38] Case reports also associate upper abdominal pain, vomiting, lethargy, respiratory distress, hypotension, severe hepatic failure, and death with the ingestion of white phosphorus fireworks by children.[39] In a case series of 15 adult patients ingesting phosphorus-containing fireworks (14 with suicidal intention), the mortality rate was 27%.[40] Two patients had no clinical or biochemical evidence of hepatic damage, whereas four patients had a subclinical hepatic injury, five patients developed varying severity of hepatocellular necrosis, and four patients died of fulminant hepatic failure. The presence of altered consciousness and generalized myalgia indicates serious poisoning, whereas jaundice, serum aminotransferase concentrations, and abdominal pain have less prognostic significance.[21]

McCarron et al. believe acute white phosphorus toxicity has three specific forms rather than sequential stages.[41] In their retrospective review of 91 personal patients and cases culled from the medical literature, 53% of cases demonstrated the gastrointestinal form manifested by initial vomiting and abdominal pain followed by diarrhea, hepatorenal dysfunction, shock, bleeding, and central nervous system toxicity. The mortality rate was 23%. Twenty-eight percent of their reviewed cases initially displayed central nervous system toxicity. Lethargy, stupor, coma, restlessness, hypotension, and shock developed after ingestion followed by hepatorenal dysfunction, bleeding, vomiting, and diarrhea. The mortality rate was 73%. Nineteen percent of the reviewed cases demonstrated combined effects with the central nervous system and gastrointestinal toxicity occurring simultaneously followed by hepatorenal toxicity, bleeding, diarrhea, and hypotension. The mortality rate was 47%. Indicators of poor prognosis include generalized muscle tenderness and clouded sensorium. Most patients surviving for at least 6 days will recover. The degree of liver enlargement, severity of abdominal pain, intensity of jaundice, and serum hepatic aminotransferase concentrations have little prognostic value.

Dermal Exposure

White phosphorus is a yellowish to transparent combustible solid that spontaneously ignites to produce a yellow flame and dense smoke. Dermal contact with white (yellow) phosphorous produces yellowish, waxy, necrotic, full-thickness burns that penetrate deeply into underlying tissues, causing second and third burns.[42,43] After the removal of prehospital dressings, smoke may emanate from retained particles in wounds created by incendiary devices containing white phosphorus. These wounds fluoresce under ultraviolet light (e.g., Wood's lamp). Hypertrophic, tender scars may develop despite debridement of white phosphorus particles and skin grafting. Although case reports associate topical contact with white phosphorus with sudden death,[44] there are few experimental data to determine the amount of

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dermal absorption following topical exposure to white (yellow) phosphorus.

Ocular Exposure

White phosphorus is a highly reactive substance that spontaneously ignites in moist environments at room temperature; the associated explosion and white smoke cause severe eye irritation, photophobia, lacrimation, and blepharospasm. Sclerokeratitis subsequently may develop with multiple recurrences of inflammation. In contrast to the fulminant cases of recurrent inflammation of the eye following the explosive seeding of the cornea and conjunctiva with white phosphorus, multiple foreign bodies of red phosphorus produced a more benign course without late complications. A 15-year-old boy sustained bilateral conjunctival and corneal burns with multiple corneal foreign bodies after an explosion involving red phosphorus powder and potassium chlorate.[45] On examination, he had chemosis, corneal epithelial erosions with multiple red particles extending into the stroma, 1+ flare in the anterior chamber, a clear lens, normal intraocular pressures, and first-degree burns of the upper and lower eyelids. He left the hospital 10 days after admission with corrected vision of 20/60 OD and 20/100 OS. His vision improved 1½ years later to 20/30 OD, 20/40 OS, and 20/25 corrected.

Occupational Exposure

Classic phossy jaw develops after years of white phosphorus exposure, beginning with toothaches, recurrent pain, ulceration of the gum and surrounding tissue, and tooth extractions with persistent ulceration of the gums.[1] The surrounding soft tissue becomes tender, swollen, and purulent. Typically, the disease progresses slowly causing more extractions, larger ulcerations, denuded skin, and spongy alveolar bone. The destruction of soft tissue and bone may continue despite cessation of white phosphorus exposure, eventually involving large portions of the jaw that cause severe deformities. Radiographic changes may lag behind the clinical presentation. Although refining phosphorus rock exposes workers to several respiratory irritants (e.g., volatile coal tar compounds, fluorides, phosphorus oxides, phosphoric acid), a cross-sectional and 7-year follow-up study of 31 phosphorus rock refinery workers did not detect a significant reduction in pulmonary function testing attributable to their occupational exposure.[14]

Carcinogenicity

Little data exist on the carcinogenicity of phosphorus or phosphorus compounds. Neither the IARC nor the NTP lists these compounds as suspected carcinogens.

DIAGNOSTIC TESTING

SI Conversion Units

1 ppm (25°C) = 5.07 mg/m^3
1 mg/m^3 = 0.197 ppm (25°C)

Analytical Methods

Extensive pretreatment and pre-fractionation procedures required for phosphorus analysis introduce variations in the results and complicate the interpretation of the values. Sensitive methods for quantitation of phosphorus compounds in biological media include inductively coupled plasma/mass spectrometry, nuclear magnetic resonance spectroscopy, and ultra-performance liquid chromatography/mass spectrometry.[46] The use of X-ray absorption near-edge structure (XANES) spectroscopy with sequential chemical fractionation allows the characterization of dominant solid-phase species of phosphorus in soils.[47]

Biomarkers

The serum phosphate concentration in the general population is ~3.0–4.5 mg/dL. During white phosphorus poisoning, the serum phosphate concentrations do not correlate well to toxicity or prognosis.

Abnormalities

Liver failure (elevated serum aminotransferases, hypoprothrombinemia, hypoglycemia, hyperbilirubinemia), acute pancreatitis,[48,49] kidney failure (elevated BUN/creatinine, urinary casts, albumin, red blood cells, amino acids, bile pigments), and abnormal blood chemistries (hypoglycemia, leukopenia or leukocytosis, lymphocytosis, anemia or polycythemia, hypocalcemia, hypo- or hyperphosphatemia) may result from acute white phosphorus intoxication. In a series of 15 adults ingesting white phosphorus, metabolic acidosis, hypoglycemia, and severe elevation of the prothrombin time indicated a poor prognosis, whereas jaundice was not necessarily a poor prognostic sign.[40]

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Large dermal burns from white phosphorus may cause systemic complications including hypocalcemia, hyperphosphatemia, and cardiac dysrhythmias. Electrocardiographic changes include T wave inversions, QT prolongation, ST-segment depression, low-voltage QRS complex, atrial fibrillation, and reduced ventricular contractility.[37,50]

HEALTH SURVEILLANCE

The Minimal Risk Level for white phosphorus derived by the ATSDR is 0.2 µg/kg/day based on a NOAEL of 0.015 mg/kg/day and a hepatic endpoint.[17] The acute inhalation MRL for acute-duration inhalation exposure to white phosphorus smoke is 20 µg/kg/day based on a minimal LOAEL of 187 mg/m^3 (throat irritation after 5-minute exposure). Table 23.2 lists the guidelines and regulations for exposure to white phosphorus.

The lack of data on white phosphorus metabolites complicates the use of biomonitoring to measure the exposure of white phosphorus workers. The high serum/urine phosphate concentrations in the general population and large interindividual variability in these concentrations limit the usefulness of these measures in biomonitoring programs. In a convenience sample of five workers from a phosphorus manufacturing plant and five controls, there was no statistically significant difference in the plasma inorganic phosphorus, calcium, or magnesium concentrations between the two groups (method, *P* value, and normal ranges not reported).[1] The mean plasma inorganic phosphorus concentration in the exposed workers was 2.85 mg/dL compared with 2.9 mg/dL in controls. This paper also reported a normal serum inorganic phosphate concentration (3.5 mg/dL) in a worker with osteonecrosis of his jaw after a 4-year exposure to white phosphorus at a phosphate manufacturing plant.

TABLE 23.2. Guidelines and regulations for white phosphorus.

Exposure Limit	Value
OSHA	
PEL–TWA (8-hour)	0.1 mg/m^3 (0.02 ppm)
NIOSH	
REL–TWA (10-hour)	0.1 mg/m^3
IDLH	5 mg/m^3
ACGIH	
TLV–TWA (8-hour)	0.1 mg/m^3 (0.02 ppm)
REL–STEL (15-minute)	None
US FDA	
Bottled water allowable limit	None
US EPA	
RfC (chronic inhalation exposure)	None
RfD (chronic oral exposure)	None
MCL (EPA carcinogenic unit risk, daily)	None
US Federal Drinking Water Guidelines	None
ATSDR	
MRL (intermediate oral)	0.2 µg/kg/day
MRL (acute inhalation)	20 µg/kg/day (white phosphorus smoke)

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; IDLH = immediately dangerous to life and health; MCL = maximum contaminate level; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure level/limit; RfC = reference concentration; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average; US EPA = United States Environmental Protection Agency; US FDA = United States Food and Drug Administration.

TREATMENT

Decontamination

Emesis is a therapeutic option in the prehospital setting for an ingestion that presents within 1 hour unless contraindicated by alteration of consciousness or the presence of protracted vomiting; however, there is no clear evidence that this procedure improves clinical outcome. The role of activated charcoal has not been defined in this setting. Anecdotal gut decontamination measures for phosphorus poisoning include lavage with 1:5,000 potassium permanganate solution (500 mL in a child, 1–2 L in an adult), sodium bicarbonate, or oils (coconut, vegetable, liquid paraffin)[51] and the use of a mineral oil cathartic.[41] There are inadequate clinical data to recommend any of these decontamination measures. Contaminated skin should be washed copiously with water; skin with embedded phosphorus particles should be kept moist to prevent further oxidation and tissue damage before removal.[52] Health workers should wear gloves and carefully wash off all phosphorous-containing vomitus and stools. These fluids should be handled as hazardous materials and double-bagged.

Elimination Enhancement

The efficacy of exchange transfusion for white phosphorus poisoning is questionable based on current data. In a study of 15 patients with Grade IV hepatic encephalopathy from acute white phosphorus toxicity,

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2 of 5 patients died compared with 7 of 10 in the group without exchange transfusion.[8] Blood availability determined the patients receiving exchange transfusions; therefore, the groups were not randomized and conclusions regarding efficacy are limited. Hemodialysis is recommended only for the treatment of renal failure.

Antidotes

There are no antidotes for white phosphorus toxicity.

Supportive Care

1. Admit all symptomatic patients to an intensive care setting for a minimum of 72 hours of observation with careful monitoring of electrolyte balance. Patients remaining asymptomatic 6 hours after ingestion may be discharged from the ED with a close follow-up established.[53]
2. Monitor for hypoglycemia, hypomagnesemia, dysrhythmias, hypoxia, metabolic acidosis, hyperkalemia, rhabdomyolysis, and renal failure.
3. Replace fluids/electrolytes. Watch for the development of hypocalcemia, hypokalemia, hyperphosphatemia, and hypomagnesemia.
4. Follow blood chemistries (calcium, phosphorus, glucose, prothrombin time, CBC) and hepatorenal function at least daily.
5. Phosphate toxicity depends on dose and retention time. Predisposing factors in adults include co-morbidities (renal dysfunction, cardiovascular disease, extreme age) Hirschsprung's disease, and small infants in children.

Wounds

The presence of white vapor emanating from a wound with or without a garlic odor indicates the continuing formation of phosphoric acid and destruction of tissue; the presence of these vapors does not necessarily indicate spontaneous ignition.[54] Initially, white phosphorus burns should be copiously irrigated with cool saline, followed by prompt debridement of easily identifiable particles of phosphorous;[55] a Waterpik® may be necessary for mechanical debridement. The use of warm water facilitates the conversion of solid particles to liquid with a concomitant increased risk of autoignition.[56] Once removed, phosphorus particles should be kept wet with water or sterile saline to prevent reignition. Experimental evidence from rodent studies suggests copious irrigation with saline and manual debridement with forceps and scalpel may be the most effective means of decontamination.[57] The use of a Wood's lamp helps to identify retained large phosphorus particles by fluorescence of the phosphorus.[58] The burn site should be covered with saline-soaked pads after irrigation and debridement.

Irrigation with 0.5–1% copper sulfate solution and 5% sodium bicarbonate *theoretically* helps reduce phosphorus absorption while improving identification of remaining phosphorus particles in the wound by turning the particles black.[59] The development of copper toxicity depends, in part, on the extent of the burn; however, the use of copper and other solutions (e.g., 1–3% silver nitrate)[60] remains controversial as a lavage solution for phosphorus wounds because of the risk of developing copper toxicity (hemolysis, renal failure).[27,61] The wound should be kept moist until debridement eliminates all phosphorus particles to prevent spontaneous ignition of the phosphorus particles. The wound should be inspected several times daily during the first several days to identify phosphorus particles deeply embedded in the tissue.[62]

PHOSPHORIC ACID AND PHOSPHORUS SALTS

PHYSIOCHEMICAL PROPERTIES

Phosphorus trichloride (empiric formula PCl_3, molecular formula P_2O_6) is a colorless, noncombustible liquid with a high vapor pressure (100 Torr at 21°C). This compound reacts exothermically with water to form hydrochloric and phosphonic acids. Phosphorus pentachloride (empiric formula PCl_5, molecular formula P_2O_{10}) is a white to slightly yellow, noncombustible solid that sublimates without melting. This solid fumes in contact with moist air release irritating fumes containing hydrochloric acid and phosphoric acid (H_3PO_4). Phosphorus oxychloride ($POCl_3$) is a clear, colorless liquid that also spontaneously decomposes, producing a pungent odor secondary to the formation of hydrochloric and phosphoric acids. The vapor pressure is 40 Torr at 27.3°C. Phosphorus trichloride (CAS RN: 7719-12-2, PCl_3) is a colorless, noncombustible, fuming liquid with a molecular weight of 137.35; this liquid decomposes to hydrochloric acid and phosphonic acid in water or moist air.

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Phosphorus pentasulfide (P_4S_{10}) is a yellow to slightly green solid with a rotten egg odor secondary to the spontaneous formation of hydrogen sulfide in moist air. The odor threshold is near 0.005 ppm. In the presence of moist air, P_4S_{10} decomposes into hydrogen sulfide and phosphoric acid.

Although phosphorus sesquisulfide (P_4S_3) is a mucous membrane, respiratory, and skin irritant, the low vapor pressure of this compound limits significant occupational exposure. Phosphorus pentachloride decomposes to hydrogen chloride and phosphoric acid following hydrolysis with water.

Phosphoric acid (H_3PO_4, orthophosphoric acid, white phosphoric acid) is a noncombustible, odorless, colorless solid or viscous liquid that is very soluble in water. Phosphoric acid mist is a mild mucous membrane and respiratory irritant. The decomposition products at temperatures above 213°C of this compound include pyrophosphoric acid ($H_4P_2O_7$). The saturation vapor concentration of phosphoric acid exceeds the recommended TLV–TWA.[63] Table 23.3 lists the identifying information and physical properties of common phosphorus compounds.

EXPOSURE

Phosphates are widely used in fertilizers, animal diets, food and beverages, industrial cleaning agents, water and waste treatments, and metal treatments. Phosphorus trichloride is an industrial catalyst and chlorinating agent also used as an intermediate in the manufacturing of surfactants, gasoline additives, plasticizers, pesticides, and dye stuff. Phosphorus oxychloride is a chlorinating agent, catalyst, and component of the manufacturing of gasoline additives, hydraulic fluids, plasticizers, and fire retardants. Phosphorus pentachloride is also a chlorinating agent and catalyst, whereas phosphorus pentasulfide is an intermediate in the synthesis of sulfur-containing organic compounds and several manufacturing processes (e.g., safety matches, lubricant additives, insecticides, igniting chemicals).

TOXICOKINETICS

Phosphate absorption occurs in the duodenum, jejunum, and, to a lesser extent, in the colon by passive diffusion and a sodium-dependent, carrier-mediated pathway with the latter demonstrating a linear relationship between phosphate absorption and intestinal phosphate concentrations. Consequently, large sodium loads (e.g., sodium phosphate enemas) enhance phosphate absorption. The kidneys excrete up to 20% of the filtered phosphate load depending on renal function and fluid status; renal impairment and volume depletion enhance phosphate retention.

TABLE 23.3. Identifying information and physical properties of common phosphorus compounds. (Based on Perez and Solderholm).[63]

Physical Characteristic	Phosphorus Trioxide	Phosphorus Pentoxide	Phosphorus Oxychloride	Phosphorus Pentachloride	Phosphorus Pentasulfide	Phosphorus Acid	Phosphoric Acid
CAS RN	114-24-5	1314-56-3	10025-87-3	10026-13-8	1314-80-3	13598-36-2	7664-38-2
Physical state	Solid	Solid	Liquid	Solid	Crystalline mass	Solid	Solid or liquid
Color	White	White	Colorless	White-pale yellow	Light yellow – greenish-yellow	Yellow	Colorless
Molecular formula	P_4O_6	P_4O_{10}	$POCl_3$	PCl_5	P_2S_5	H_3PO_3	H_3PO_4
Molecular weight (g/mol)	219.89	283.89	153.35	208.24	222.29	82.00	98.00
Melting point (°C)	23.8	340[a]	1.25	Sublimes[b]	290	73.6[c]	42.35[d]
Boiling point (°C)	173.8[e]		105.8		515		
Density (g/mL)	2.135 (21°C)	2.39	1.645 (25°C)	1.6	2.09	1.651 (21.2°C)	1.834 (15°C)
Water solubility (g/L) (20°C)	Decomposes to H_3PO_3	Decomposes to H_3PO_4	Reacts exothermally with water	Fumes in moist air	Decomposes to H_2S and phosphoric acid in most air	6,940 (very soluble)	5,480 (very soluble)

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.
[a] Sublimes at 360°C; [b] Sublimes at 159°C; [c] Decomposes at 200°C; [d] Decomposes at 213°C; [e] In N_2.

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CLINICAL RESPONSE

Phosphate toxicity occurs in children and adults following the oral or rectal administration of large doses of sodium phosphate enemas. Complications include electrolyte abnormalities (hyperphosphatemia, hypocalcemia, hypokalemia), metabolic acidosis, and dehydration. Clinical manifestations of hyperphosphatemia are vomiting, diarrhea, lethargy, fever, tetany, seizures, coma, shock, and cardiac arrest.[64] Risk factors include young age (e.g., <2 years), predisposing intestinal conditions (e.g., Hirschsprung's disease, anorectal malformations), renal dysfunction, and fluid loss. In severe cases, cardiac arrest and death may occur in children[65] and adults.[66]

Most of the commercial phosphorus compounds (PH_3, PCl_3, P_2S_5, $POCl_3$) are severe respiratory and mucous membrane irritants in rodents[67] and humans;[68,69,70] whereas phosphoric acid mist is a mild irritant of the eyes and mucous membranes. Phosphorus trichloride reacts exothermally with water to produce phosphoric acid, hydrochloric acid, phosphorus oxides, and phosphine. In a convenience sample of 17 of 450 workers and residents exposed to the decomposition products of phosphorus trichloride after a tanker accident, complaints included nausea, vomiting, lacrimation, eye irritation, and dyspnea.[71] Pulmonary function tests demonstrated some small and large airway dysfunction that cleared within 1 month in most of these patients. The sample size was too small to adjust for preexisting conditions and smoking. Other incidents associated with mixed exposure to chlorinated phosphorus compounds were associated with acute airway obstruction, mild interstitial and alveolar edema, diffusion defects, and ventilation and perfusion mismatching; the contribution of PCl_3 to these abnormalities is unclear as a result of the mixed exposure (i.e., HCl, oxalyl chloride, PCl_5, oxalic acid) and limited analysis of the exposure scenario. These abnormalities resolved rapidly.

DIAGNOSTIC TESTING

SI Conversion Units

The conversion factor for phosphorus oxychloride at 25°C is 1 ppm = 6.26 mg/m^3, whereas 1 ppm phosphorus pentachloride = 8.51 mg/m^3 and 1 ppm phosphorus trichloride = 5.60 mg/m^3.

Analytical Methods

The use of inductively coupled plasma/mass spectrometry with molecular mass spectrometric techniques and various separation techniques (liquid chromatography, gas chromatography, gel electrophoresis, capillary electrophoresis) allows the speciation of inorganic phosphorus.[72] Inductively coupled plasma/atomic emission spectrometry analyzes total and inorganic phosphorus in soils. Sediments and waters may contain substantial amounts of organic phosphorus compounds (e.g., organic condensed phosphorus species, aminophosphoric acids, sugar phosphates, phosphoamides, phosphoproteins, inositol phosphates, phospholipids, nucleic acids) as well as inorganic phosphorus compounds (orthophosphate, polyphosphate, pyrophosphate, phosphate monoesters/diesters).[73] The classical analytical method to detect dissolved organic phosphorus in soils and aquatic systems is phosphomolybdenum blue spectrophotometry; newer methods include enzymatic hydrolysis procedures, ^{31}P nuclear magnetic resonance spectroscopy, and soft X-ray fluorescence. The use of enzymatic hydrolysis techniques in natural waters and sediments is limited by the difficulty of detecting orthophosphate in the low dissolved organic phosphorus concentrations in natural waters.

Abnormalities

Electrolyte abnormalities associated with phosphate toxicity include hyperphosphatemia, hypocalcemia, hypokalemia, and metabolic acidosis.

HEALTH SURVEILLANCE

Phosphoric acid mist has an ACGIH TLV–TWA and US OSHA PEL–TWA of 1 mg/m^3. The ACGIH TLV–STEL is 3 mg/m^3, whereas the NIOSH IDLH is 1,000 mg/m^3. Table 23.4 lists the guidelines and regulations for exposure to certain phosphorus compounds.

PHOSPHIDES AND PHOSPHINE GAS

HISTORY

Aluminum and zinc phosphide are inexpensive, effective grain fumigants and rodenticides that release phosphine

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TABLE 23.4. Guidelines and regulations for exposure to some phosphorus compounds.

Exposure Limit	Phosphoric Acid	Phosphorus Oxychloride	Phosphorus Trichloride	Phosphorus Pentachloride	Phosphorus Pentasulfide
			OSHA		
PEL–TWA (8-hour)	1 mg/m^3	NE	3 mg/m^3 (0.5 ppm)	1 mg/m^3 (0.118 ppm)	1 mg/m^3
			NIOSH		
REL–TWA (10-hour)	1 mg/m^3	0.63 mg/m^3	1.5 mg/m^3	1 mg/m^3	1 mg/m^3
REL–STEL (15-minute)	3 mg/m^3	3.15 mg/m^3	3 mg/m^3		3 mg/m^3
IDLH	1,000 mg/m^3	None	25 ppm	70 mg/m^3	250 mg/m^3
			ACGIH		
TLV–TWA (8-hour)	1 mg/m^3	0.63 mg/m^3	1.1 mg/m^3	0.85 mg/m^3	1 mg/m^3
TLV–STEL (15-minute)	3 mg/m^3	None	2.75 mg/m^3	None	3 mg/m^3

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; IDLH = immediately dangerous to life and health; NE = not established; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure level/limit; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average.

gas on contact with water and stomach acid. Lack of toxic residues, preservation of seed viability, and low cost encourage the use of these agents in developing countries (e.g., India, Iran, Sri Lanka, Morocco). These compounds are common suicidal agents in southeast Asia.[74,75] In a prospective study of 559 cases of acute poisoning in India, 91.4% of the cases involved suicidal intent.[76] Aluminum phosphide was an agent of choice in ~2/3 of these cases.

PHYSIOCHEMICAL PROPERTIES

The common metallic phosphides are aluminum (AlP, phostoxin, quickfor, alutal, celphide, detia gas), magnesium (trimagnesium phosphide, Mg_3P_2), and zinc (trizinc diphosphide, Zn_3P_2, detiaphos, magtoxin). These metallic phosphides are gray to gray/yellow solids that react with moisture to form phosphine gas and metallic hydroxides (i.e., nontoxic residues). Magnesium phosphide reacts with excess white phosphorus and water to form phosphine gas, whereas water directly hydrolyzes aluminum phosphide to phosphine gas and aluminum hydroxide. The formation of a protective layer of aluminum hydroxide over aluminum phosphide may reduce the production of phosphine gas from aluminum phosphide. Zinc and aluminum phosphide tablets react with acids to produce phosphine gas and chloride salts.[77] These tablets are stable under dry conditions, but they deteriorate rapidly under damp conditions. Phosphine gas blackens silver nitrate paper as a result of the formation of silver phosphate, even in trace amounts; hydrogen sulfide also turns silver nitrate paper black, but the addition of ammonium molybdate to the blackened paper will turn blue only in the presence of phosphine.[78]

Phosphine (PH_3) is a colorless, flammable gas at ambient temperature with poor odor warning properties as a pure gas. Although pure phosphine gas is not easily detectable at highly toxic concentrations (200 ppm), technical phosphine contains odoriferous impurities (methanethiol, diphosphine, substituted phosphine) that impart a fish or garlic odor detectable at a threshold of 1–5 ppm technical phosphine.[79] Phosphine readily ignites at room temperature when the ambient air phosphine concentration exceeds 1.9% (v/v), particularly in the presence of other phosphine compounds.[80] Phosphine gas causes severe corrosion of copper-containing alloys; electrical equipment that contains copper may be damaged during fumigation with phosphine gas. Phosphine gas is water-soluble; in solution, phosphine forms a neutral solution.[12] Table 23.5 lists identifying information and physical properties of phosphine gas.

EXPOSURE

Production Processes

The two major production processes for phosphine gas are the hydrolysis of magnesium-aluminum phosphide or aluminum phosphide and the electrolysis of phosphorus with nascent hydrogen. Phosphine gas is a by-product of the production of acetylene. Production of metal phosphides involves the reduction of the metal phosphate with hydrogen at 600°C, the direct reaction between amorphous phosphorus and powdered metal under heat and pressure, or the passing of phosphorus

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TABLE 23.5. Physiochemical characteristics of phosphine gas. (Based on American Conference of Governmental and Industrial Hygienists (Based on ACGIH)).[12]

Physical Characteristic	Phosphine Gas
CAS RN	7803-51-2
Physical state	Gas
Color	Colorless
Odor Garlic	
Melting Point (°C)	−133.89
Boiling Point (°C)	−87.7[a]
Molecular formula	PH_3
Molecular weight (g/mol)	34.00
Melting point/boiling point (°C)	−133.5/−87.7[a]
Density (g/L)	1.39 (25°C)
Water solubility (g/L)	0.398 (17°C)[b] 0.381 (25°C)[b]
Vapor pressure (mmHg)[c]	760 (−87.4°C)

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.
[a] Autoignition at 37.7°C; [b]poor; [c] relative air vapor pressure 1.18.

vapor over the metal at 400°C. Uses for phosphorus compounds include chlorinating agents and catalysts (PCl_3, PCl_5), chemical intermediate for surfactants and pesticides (PCl_3, P_2S_5), and the manufacturing of plasticizers and gasoline additives ($POCl_3$, PCl_3). Phosphoric acid has a wide variety of commercial applications including rust-proofing metals, water treatment, fertilizers, detergents, foods, and beverages.

Uses

Phosphine gas is a chemical intermediate in the synthesis of organic phosphonium derivatives (flame retardants) and organophosphines (oil additive and pharmaceutical preparations). Industrial exposures occur most commonly after the use of PH_3 in the production of acetylene gas or following the use of phosphine gas as a doping agent for the manufacture of silicon crystals. The production of phosphine gas for fumigation usually involves the hydrolysis of aluminum or magnesium phosphide at the site of fumigation; this product is the only economically viable fumigant for widespread use after phasing out ozone-depleting substances in accordance with the United Nations Montreal Protocol. Satisfactory fumigation with phosphine gas requires a moisture content of ≥10%.[81] The principal use of zinc phosphide is as a rodenticide in the form of a 2.5–5% paste added to food as bait. Formulations of phosphorus-containing rodenticides include Patterson's Zinc Phosphide Rodent Bait (2%), Pearson's Rat Poison (2%), Stearn's Electric Brand Paste (3%), Rat Doom Zinc Phosphide (5%), Rough-on-Rats, 5-0 paste, and Paste Electrica. Ammonium carbamate is a common additive to commercial phosphide tablets to prevent the combustion of phosphine gas; aluminum oxide and diphosphine gas are by-products present in commercial aluminum phosphide tablets.

Sources

Phosphine gas appears rarely in nature. Transiently, the anaerobic degradation of phosphorus-containing material yields phosphine gas. Otherwise, phosphine gas in ambient air results from the use of phosphides as fumigants and rodenticides; however, the amount of phosphorus released into the air from this source is small compared with the amount of phosphate added to the environment by agricultural runoff and urban effluent.[79] The residue of phosphine in food following fumigation is usually low after aeration, except following the incomplete reaction of metal phosphides in the fumigated material.

ENVIRONMENTAL FATE

The ultimate fate of phosphine and phosphide in the environment is the formation of phosphates.[79] Phosphine and the common metal phosphides are degradable; therefore, these substances do not persist in the environment. Phosphine decomposes to several intermediates (e.g., P_2H_4) and ultimately to phosphoric acid (H_2PO_4), salts, and water.[17] Few phosphates are formed from the degradation of phosphine. Hydroxy radicals remove phosphine from the air with a half-life of <24 hours.

Phosphine is unstable in aqueous solutions, even under anaerobic conditions. Depending on the redox potential of water, the oxidation products are diphosphine (P_2H_4), phosphorus, hypophosphorous acid, phosphorus acid, and phosphoric acid.

Under moist conditions, aluminum and magnesium phosphides rapidly hydrolyze, whereas little hydrolysis of zinc phosphide occurs unless the pH is <4. Oxidation of zinc phosphide transpires in soil containing 50% water within 5 weeks.[81]

DOSE EFFECT

Aluminum phosphide grain fumigants and zinc phosphide rodenticides release phosphine gas upon contact with moisture, leading to fatalities.[82] Aluminum phosphide tablets weigh 3 g and release about 1 g phosphine gas after complete dissolution. The potentially lethal dose in an adult is 500 mg phosphine gas; hence, one

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tablet of aluminum phosphide is a potentially fatal dose. Most patients ingesting >10 g (>3 tablets of aluminum phosphide) develop cardiovascular collapse. In a series of 20 cases of poisoning from zinc phosphide, the lowest fatal dose was 4 g zinc phosphide (~80 mg/kg), whereas survival occurred after ingestion of 50 g zinc phosphide.[83] A 36-year-old schizophrenic patient presented 1–2 hours after ingestion of an estimated 400 mg zinc phosphide. He received decontamination measures (syrup of ipecac, activated charcoal); he was released asymptomatic after 4 hours of observation.[53]

Nausea, vomiting, diarrhea, dizziness, headache, cough, and tightness of the chest developed in workers exposed to an average concentration of <10 ppm phosphine gas (range up to 35 ppm phosphine).[84] Serious effects develop from exposure to phosphine gas at levels above 100 ppm (140 mg phosphine/m^3) for 0.5–1 hour; the IDLH (immediately dangerous to life or health) level is 50 ppm phosphine.[85]

TOXICOKINETICS

Absorption

The rapid onset of toxicity following exposure to phosphine gas indicates the lungs absorb phosphine gas easily. In addition to the absorption of phosphine gas following the ingestion of metal phosphides, the presence of hydrolyzable phosphide in the liver and the blood following the ingestion of aluminum phosphide indicates the stomach directly absorbs metal phosphides.[86] Dermal absorption of phosphine gas and metal phosphides is insignificant from a toxicological perspective.

Distribution

Muscles of animals poisoned by zinc phosphide do not usually contain detectable concentrations of phosphine or phosphide; however, acid-hydrolyzable phosphide was present in the kidney and liver of a patient who died from zinc phosphide poisoning.[87]

Elimination

In the body, metal phosphides are hydrolyzed to phosphine and the corresponding metal cation. Elimination of unchanged phosphine occurs primarily through the lungs with lesser amounts oxidized and excreted by the kidneys as hypophosphite and phosphite.

HISTOPATHOPHYSIOLOGY

Mechanism of Toxicity

The ingestion of aluminum and zinc phosphides results in the release of phosphine gas in the stomach, inhibition of cellular respiration, gastrointestinal irritation, and circulatory collapse. Although phosphine inhibits cytochrome C oxidase *in vitro*, phosphine gas is not a potent inhibitor of this enzyme *in vivo* compared with cyanide or hydrogen sulfide.[88] Profound shock results from inhibition of cellular respirations, fluid loss, direct myocardial toxicity, and adrenal dysfunction.[89] Although histopathological findings following phosphine poisoning suggest cellular hypoxia,[90] the exact mechanism of phosphine-induced cardiopulmonary injury is not well defined.

Additionally, phosphine is a corrosive that causes lipid peroxidation and reduction in glutathione concentrations. Indicators of oxidation stress (e.g., reduced glutathione, malonyldialdehyde) peak ~48 hours after exposure and normalize within ~5 days.[91] Severe cases of phosphine poisoning produce refractory hypotension secondary to myocardial damage, fluid loss, and peripheral vasodilation.

Postmortem Examination

In a retrospective descriptive study of fatal phosphine poisoning, the most common histological findings in the liver were fine cytoplasmic vacuolization of hepatocytes and sinusoidal congestion.[92] The vast majority (86%) of these cases were suicides. In a histological study of explanted livers from patients intentionally ingesting zinc phosphide, the major findings included microvesicular steatosis, periportal necrosis, intracellular vesiculation, reticulin collapse, and vessel wall damage.[93] Besides visceral congestion and patchy centrizonal necrosis of the liver, there are no histological changes that characterize phosphine poisoning.[94] In fatal cases of phosphine poisoning, gross examination at autopsy revealed marked pulmonary edema,[95] congestion and hemorrhage of the mucosa of the gastrointestinal tract, and petechial hemorrhages of the surface of the liver and brain.[96] Histopathological changes include centrilobular necrosis of the liver with vacuolar degeneration of the hepatocytes and dilation of central veins, desquamation of the epithelium of the bronchioles, pulmonary edema, and focal necrosis of the myocardium including contraction band necrosis, pyknosis of cardiac myocytes, and coagulation necrosis.[97,98] During postmortem examination of patients

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dying from phosphide poisoning, an intense garlic-like odor may emanate from the body, particularly following opening of the stomach.[90]

CLINICAL RESPONSE

The signs and symptoms of phosphine poisoning are nonspecific; onset of toxicity depends on the route of exposure and the dose. Following inhalation, symptoms include immediate onset of dyspnea and airway irritation along with dizziness, weakness, headache, and ataxia. The ingestion of metal phosphides (e.g., aluminum phosphide tablets) results in the release of phosphine gas in the stomach and a slightly more delayed onset than inhalation. Exposures to phosphine gas cause severe gastrointestinal tract symptoms as well as respiratory, cardiovascular, and secondary central nervous system effects. Early symptoms of phosphine poisoning include epigastric pain, nausea, vomiting, fatigue, sweating, palpitations, cough, and headaches. These patients initially are oriented, anxious, and agitated, occasionally with the smell of garlic on their breath.[99] These symptoms may develop as soon as 5–10 minutes after the ingestion of metal phosphides. Most fatalities result from cardiovascular collapse soon after ingestion and, less often, inhalation;[100] case reports associate the intentional ingestion of aluminum phosphide with ischemia, myocardial infarction, ventricular dysrhythmias, and congestive heart failure.[101] Clinical manifestations of more serious exposure to phosphine include dyspnea, paresthesias, jaundice, ataxia, diplopia, intention tremor, dysrhythmias, and myocardial dysfunction.[102,103] In severe cases, coma, convulsions, hypotension, metabolic acidosis, tetany, hepatorenal failure, and pulmonary edema develop.[104,105] The ingestion of aluminum phosphide tablets may cause serious long-term esophageal injuries including esophageal strictures and tracheoesophageal fistulas.[106] In patients with phosphide-induced esophageal strictures, dysphagia develops within 2–8 weeks after exposure; patients unresponsive to endoscopic dilation require surgical intervention to relieve the strictures.[107] Unlike arsine gas, phosphine gas rarely produces hemolytic anemia.[99]

DIAGNOSTIC TESTING

SI Conversion Units

1 ppm (25°C) = 1.39 mg/m^3
1 mg/m^3 = 0.719 ppm

Analytical Methods

Techniques to detect and quantitate phosphine gas include headspace/gas chromatography with nitrogen phosphorous detection[86] and headspace gas chromatography/mass spectrometry.[108] The limit of quantitation for the former method is 2 μg/kg.[109] Methods to quantitate reduced phosphorus compounds (phosphite, hypophosphite, phosphine) include ion chromatography, spectrophotometric analysis in flow injection systems, and ^{31}P NMR with the former being the most selective.[110]

Biomarkers

There are no well-validated blood or urine biomarkers of phosphine poisoning. The presence of detectable amounts of phosphine following poisoning by aluminum phosphine is variable. A case series of aluminum phosphide poisoning was detected significantly higher ($P < 0.001$) blood phosphine concentrations in 30 patients with severe toxicity (i.e., shock) than the group with mild toxicity (i.e., occasional vomiting without vital sign abnormalities) as measured by colorimetry.[111] Typically, phosphine concentrations in blood and urine are not detectable, but phosphine is usually detectable in the stomach and small intestine.[108] In these cases, elevated concentrations of phosphorus and aluminum usually occur in the blood and liver, when compared with normative values.[109]

Abnormalities

Liver failure (elevated serum aminotransferases, hypoprothrombinemia, hypoglycemia, hyperbilirubinemia), acute pancreatitis,[48,49] kidney failure (elevated BUN/creatinine, urinary casts, albumin, red blood cells, amino acids, bile pigments), and abnormal blood chemistries (hypoglycemia, leukopenia or leukocytosis, lymphocytosis, anemia or polycythemia, hypocalcemia, hypo- or hyperphosphatemia) may result from phosphine intoxication. Exposure to phosphine gas does not typically cause methemoglobinemia or hemolysis.

Electrocardiographic changes associated with the intentional ingestion of aluminum phosphide are highly variable; abnormalities include ischemia (T wave inversions, ST-segment elevation/depression), conduction disturbances, and dysrhythmias.[112] In a study of 30 intensive care patients with severe aluminum phosphide poisoning, ventricular fibrillation occurred in 23.3%, symptomatic ventricular tachycardia in 40% of cases,

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and atrial flutter/fibrillation cases in 20%.[113] Approximately 47% of these patients also had supraventricular tachycardias. The electrocardiogram may show changes suggestive of acute myocardial infarction, nonspecific ST–T wave changes, QT prolongation, heart block, sinus bradycardia or tachycardia, atrial fibrillation, or ventricular dysrhythmias (ventricular tachycardia, ventricular fibrillation).[114] Rare case reports associate aluminum phosphide poisoning with methemoglobinemia, particularly in severely intoxicated patients.[115] Zinc is a potentially radiopaque material; the presence of radiopaque material after the ingestion of zinc phosphide suggests serious ingestion.[116]

HEALTH SURVEILLANCE

The recommended WHO/FAO level for phosphine in food is 0.1 mg PH_3/kg for raw cereal and 0.01 mg PH_3/kg for other food products. Table 23.6 lists some guidelines and regulations for exposure to phosphine gas.

TREATMENT

Stabilization

Phosphine gas is a multisystem poison that may cause cardiopulmonary collapse soon after exposure.[117] The adequacy of oxygenation, ventilation, and circulation should be evaluated quickly. Patients should be removed from further phosphine exposure; contaminated skin should be washed thoroughly with soap and water after the removal of contaminated clothes. Health care providers may require personal protection measures (rubber gloves, full face masks) during decontamination and intubation. Symptomatic patients should have intravenous lines and fluid resuscitation along with monitoring for respiratory depression, cardiac dysrhythmias, and hypoglycemia. Patients with altered consciousness may require respiratory support (supplemental oxygen, assisted ventilation). There are no antidotes for phosphine exposure.

TABLE 23.6. Guidelines and regulations for exposure to phosphine gas.

Exposure Limit	Value
OSHA	
PEL–TWA (8-hour)	0.3 ppm
NIOSH	
REL–TWA (10-hour)	0.3 ppm
REL–STEL (15-minute)	1 ppm
IDLH	50 ppm
ACGIH	
TLV–TWA (8-hour)	0.05 ppm
TLV–Ceiling (15-minute)	0.15 ppm

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; IDLH = immediately dangerous to life and health; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure level/limit; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average.

Decontamination

Emesis is not a typically recommended option because of the risk of rapid loss of consciousness, gastrointestinal irritation, and aspiration. The role of activated charcoal has not been defined in this setting. There are inadequate clinical data to recommend any decontamination measures.

Contaminated skin should be washed thoroughly; health workers should wear gloves and carefully wash off all phosphorous-containing vomitus or stools. Nausea, vomiting, and lightheadedness may occur in health workers exposed to phosphine gas released from residuals stored in the bodies of patients dying of phosphine poisoning.[118] Consequently, these fluids should be handled as hazardous materials and double-bagged.

Elimination Enhancement

Hemodialysis is recommended only if renal failure develops.

Antidotes

There are no antidotes for phosphine gas toxicity. Experimental therapy for phosphine poisoning includes the use of *N*-acetylcysteine, pralidoxime, hyperinsulinemia with hyperventilation, and trimetazidine for dysrhythmias; however, there are few clinical data to recommend any of these potential therapies.[89] A prospective, open-label pilot study of 60 patients over the age of 13 years in a north Indian tertiary care hospital suggested the addition of glucose–insulin–potassium infusions to standard supportive care for aluminum phosphide poisoning improved outcomes (↓ in-hospital case fatality, ↓ requirement for mechanical ventilation).[119] The authors opined that multicenter, double-blinded clinical trials are necessary to confirm the benefit of glucose–insulin–potassium infusions for aluminum phosphide poisoning. The presence of

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cyanosis unresponsive to oxygen therapy suggests methemoglobinemia; the need for methylene blue will be determined by cooximetry and the methemoglobin concentration.

Supportive Care

1. Admit all symptomatic patients to an intensive care setting for a minimum of 72-hours of observation. Patients who remain asymptomatic 6 hours after ingestion may be discharged from the ED with a close follow-up established.[53]
2. Monitor for hypoglycemia, hypomagnesemia, dysrhythmias, hypoxia, metabolic acidosis, hyperkalemia, rhabdomyolysis, and renal failure. Poor prognostic signs include metabolic acidosis (pH <7.0), low serum bicarbonate, and ventricular dysrhythmias.[120]
3. Replace fluids/electrolytes. Watch for the development of hypocalcemia and hypomagnesemia. Although earlier studies suggested intravenous magnesium sulfate (i.e., 2 g over 30 minutes followed by 5 g over 12 hours) reduced mortality from phosphine poisoning,[121] a controlled study did not demonstrate the ability of intravenous magnesium sulfate to reduce mortality.[122] Furthermore, there was no correlation between serum magnesium concentrations and the severity of the poisoning.
4. Follow blood chemistries (calcium, phosphorus, glucose, prothrombin time, CBC, creatinine) and hepatorenal function at least daily until stabilized.
5. Before discharge, patients with dysphagia should undergo barium swallow and esophagogastroduodenoscopy to detect esophageal complications secondary to the corrosive effects of phosphine gas.
6. Extracorporeal membrane oxygenation is a potential bridge therapy for patients with intractable cardiorespiratory failure from phosphide poisoning, when this therapy is available and the patient is not responding to conventual treatment.[123] Complications include thrombocytopenia, bleeding from the cannulation site, and dysrhythmias.
7. Zinc phosphide poisoning may cause acute liver failure. In a study of 41 patients with acute liver failure primarily (93%) from ingesting zinc phosphide, the best prognostic indicators for the need for a liver transplant included a MELD (Model for End-Stage Liver Disease) score of 36 (sensitivity, 86%; specificity, 90%) and the presence of encephalopathy with INR ≥6 (sensitivity, 100%; specificity, 83%).[93]

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Chapter 24

PLATINUM AND RELATED METALS

PLATINUM

PHYSIOCHEMICAL PROPERTIES

Platinum is a member of Group 10 (Group VIII) metals that include palladium and nickel. The platinum group metals include platinum, palladium, as are iridium, osmium, rhodium, and ruthenium. These metals have useful catalytic properties and high resistance to heat. Platinum occurs most commonly in the divalent (Pt^{+2}) and tetravalent (Pt^{+4}) valences combined with various halogens, sulfurs, and hydroxides. Metallic platinum (Pt^0) is the thermodynamically favored oxidation state for platinum. Mild reducing agents can convert tetravalent and divalent platinum to the metallic form; however, the conversion of Pt^0 to platinum salts requires extremely potent oxidants and acids (e.g., a mixture of nitric and hydrochloric acid, aqua regia).[1] Pentavalent and hexavalent platinum compounds (e.g., platinum hexafluoride) are rare because they are highly oxidizing agents that are unstable in air and water. The reduction of platinum in an aqueous solution produces a black powder (platinum black).

Platinum is a silvery-white, malleable, radiopaque, substance that belongs to the noble metal group characterized by high resistance to corrosion. Platinum occurs naturally in three approximately equally occurring isotopes (^{194}Pt, ^{195}Pt, ^{196}Pt). Although metallic platinum and platinum oxides are water-insoluble and *cis*-diamminedichloroplatinum (cisplatin) is only slightly water-soluble, many of the halogen and nitrogen complexes of platinum are water-soluble including most of the complex chloroplatinate salts. Table 24.1 lists some identifying information and physical properties of platinum and platinum compounds.

EXPOSURE

Uses

Valuable industrial properties of platinum include resistance to chemical corrosion over a wide range of temperatures, high tensile strength (particularly in alloys), good ductility (i.e., ability to form long, thin wires), excellent catalytic properties (i.e., along with palladium and rhodium), and high melting point. Platinum and its alloys appear in jewelry, the chemical and electrical industries, dentistry, and fiberglass production.[3] Platinum and platinum-rhodium alloys are useful for thermoelectrical applications (train gauges, thermocouples), electric contacts for relays, printed circuits, and switch gears. Complex platinum salts are catalysts in the preparation of sulfuric acid in the petroleum and pharmaceutical industries. Potassium tetrachloroplatinate is a soluble platinum salt used in developing photography paper as a toner. One of the major uses of platinum in the petroleum industry is catalytic upgrading (naphtha-reforming) to increase the octane rating of gasoline. Cisplatin (*cis*-diamminedichloroplatinum, *cis*-dichlorodiammine platinum, DDP), carboplatin, and oxaliplatin are platinum-based chemotherapeutic agents administered for the treatment of a variety of solid tumors. These indications include testicular, ovarian,

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TABLE 24.1. Identifying information and physical properties of platinum and platinum compounds. (Adapted from International Programme on Chemical Safety).[2]

Name	CAS RN	Mass (g/mol)	Melting Point (°C)	Density (g/mL)	Form	Valence
Platinum	7440-06-4	195.09	1772	21.45	Silver-metallic crystals	0
Platinum chloride	10025-65-7	266.00	581[a]	6.05	Olive-green crystals	+2
Platinum oxide	12035-82-4	211.09	550[a]	14.9	Violet-black crystals	+2
Ammonium tetrachloroplatinate	13820-41-2	373.00	140	2.936 (25°C)	Dark red crystals	+2
Potassium tetrachloroplatinate	10025-99-7	415.26	265	3.38	Ruby-red crystals	+2
cis-Diamminedichloroplatinum[b]	15663-27-1	300.07	270[a]	3.74	Orange crystal	+2
Platinum chloride	13454-96-1	336.90	370[a]	4.303	Brown-red crystals	+4
Platinic oxide	1314-15-4	227.03	450	10.2	Black powder	+4
Sodium hexachloroplatinate	16923-58-3	453.77	110	2.5	Yellow crystals	+4
Potassium hexachloroplatinate	16921-30-5	486.03	250	3.50	Orange-yellow[c]	+4
Ammonium hexachloroplatinate	16919-58-7	443.91	380	3.06	Orange-red crystals[d]	+4

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.
[a] Decomposition; [b] Cisplatin; [c] Crystal or powder; [d] Also forms a yellow powder.

bladder, head and neck, small cell lung, prostate, and thyroid tumors that are sensitive to these drugs and do not respond to standard chemotherapy.[4] Serious adverse effects (renal failure, emesis, myelosuppression) limit the use of this chemotherapeutic agent.

Catalytic Converters

Because of the extensive use of platinum in vehicle exhaust catalysts since the mid-1970s, the automobile industry now consumes more platinum than the chemical and petroleum industries. The history of catalytic exhaust converters involves the following four main generations: 1) 1976–1979, 2-way platinum/palladium converters; 2) 1970–1986, 3-way catalysts containing platinum, palladium, and rhodium; 3) 1986–1992, 3-way converters using primarily platinum and rhodium; and 4) 1992–mid-1990s, 3-way palladium-rich converters. These catalysts convert carbon monoxide, nitrogen oxides, and hydrocarbons into carbon dioxide, nitrogen, and water, respectively. Typically, catalytic converters now contain thin layers (100–200 μm) of platinum and palladium in a ratio of ~5:2 overlying a supporting structure composed of porous, honeycombed ceramic material (aluminum, manganese oxide, silicon). This honeycomb structure contains about 400 channels/square inch covered by a washcoat consisting of Al_2O_3 and base metal oxides. The noble metals (platinum, palladium, rhodium) are impregnated on the washcoat; variations in the concentrations and combinations of these noble metals with base metals in the catalysts allow a wide range of performance characteristics necessary for specific vehicle models to meet applicable standards. Hence, the ratio of individual noble metals in catalytic converters varies between different countries. Other applications of the technology used in platinum oxidation catalysts include the reduction of trichloroethylene to ethane in water and the reduction of the emission of CO and hydrocarbons from large gas turbines.[5]

Silicone Implants

Silicone breast implants consist of silicone gel surrounded by a thin silicone elastomeric shell reinforced by hydrophobically modified amorphous silica. The shell comprises ~2–15% of the total weight of the implant.[6] Platinum (i.e., platinum-cured gel or liquid silicone rubber) is part of one of three broad categories of manufacturing processes used to produce silicone implants; the other two categories include room-temperature vulcanized rubber and heat/gum-based peroxide-cured (i.e., heat-cured). Design changes occurred over several generations of silicone breast implants to reduce the migration of the gel into breast tissue. Karstedt's catalyst is the organosoluble Pt^0 complex formed by the reduction of the tetravalent compound, chloroplatinic acid (H_2PtCl_6); this catalyst replaced Speier's catalyst [Pt^{4+}] as the most common catalyst used to cure silicone elastomers including silicone breast implants.[1] Cross-linking of the silicone elastomers results from platinum-catalyzed hydrosilylation (i.e., the addition of Si–H residues across π-bonds). The cross-linking changes the physical properties of the silicone polymers and increases their viscosity, cohesiveness, and ability to withstand degradation by solvents. After curing, almost all of the platinum catalyst is transformed into metal [Pt^0] nanoparticles. The risk of adverse effects from

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the relatively low metallic platinum concentrations diffusing from silicone implants is very small.[6]

Production Processes

Platinum occurs naturally as Pt^0 in alluvial deposits in Alaska, Columbia, and Russia or in copper, iron, or nickel sulfide ores in Canada, Russia, and the Bushveld Complex in South Africa. These ores typically contain iridium, osmium, and/or palladium. The content of common platinum-containing minerals (e.g., braggite (Pt, Pd, Ni)S, cooperite (Pt, Pd)S, sperrylite ($PtAs_2$)) ranges from 1–500 mg Pt/kg.[2] Sources of platinum for refining include dredging of native placer platinum, platinum recycling, and mining of copper and nickel sulfide ores (i.e., as a byproduct). The isolation of platinum from ores occurs during the extraction of a concentrate containing the ore or the refining of the concentrate to separate platinum from other members of the platinum group. The latter process involves complex chemical techniques (e.g., precipitating crystallization, liquid–liquid extraction).[2] This purification process includes the dissolution of platinum with aqua regia (hydrochloric and nitric acids) or Cl_2/HCl and the addition of ammonium chloride to precipitate platinum as ammonium hexachloroplatinate $(NH_4)_2(PtCl_6)$. The Bushveld Complex in South Africa contains a variety of metals (gold, copper, nickel, chromium, selenium, cobalt, arsenic, zinc, vanadium pentoxide) in addition to platinum group metals and crystalline silica. Histological examination of 3,863 South African platinum miners revealed the presence of silicosis in 2.2% of the miners (n = 85), suggesting co-exposure to silica during platinum-mining processes may be sufficient to produce silicosis.[7] Recycling of platinum involves similar wet-chemical processes. The complex halogenated platinum salts are part of the manufacturing process for the valuable industrial catalyst, platinum sponge. Besides platinum refineries, occupational platinum exposures occur in recycling plants, automotive catalyst production plants, and metal-coating facilities; however, relatively high platinum exposures typically occur in only a few workers from these facilities.

Sources

Air

The primary form of platinum in air is elemental or oxidic compounds. Automobile catalytic converters are mobile emission sources that release noble metal catalysts (platinum, palladium, rhodium) into the air, mostly in the form of particulates. Data on the amount released into air are limited with current studies suggesting a wide variation (i.e., one to two orders of magnitude) in the amount of noble metals released from current catalytic converters.[8] A study of the older pellet-type catalyst revealed an emission rate of 800–1,200 ng Pt/km during simulated low-speed driving and 1,900 ng Pt/km during high-speed driving.[9] Newer cars in the United States and all cars in Europe use the newer monolithic catalysts. Limited studies on the exhaust from these catalysts indicate Pt emission from catalytic converters is several orders of magnitude below (i.e., ~10–20 ng Pt/m^3) the platinum levels released by pellet-type catalysts with the highest emissions occurring during initial use.[2] In a European study using a light-duty driving cycle, gasoline catalysts released 6–8 ng Pt/km after 30,000 km compared with 100 ng Pt/km during initial use.[10] The vast majority of platinum is released in the metallic form (0 valence); however, the amount of platinum present as soluble salts varies with the type of catalytic converter and mileage. Based on laboratory testing of emissions from catalytic converters analyzed new and after a light-duty vehicle aging cycle simulating urban driving, the soluble fraction of platinum in exhaust fumes is <10% of the total amount of platinum released.[8]

The platinum concentration in ambient air and platinum deposition on soil near roads increased with the introduction of catalytic converters depending on the most common type of noble metal catalytic converters in use, car speed, and traffic density;[11] however, the platinum concentration in air usually remains very low (few pg/m^3), even near freeways.[12] As with other platinum group elements, the distribution of platinum in fractionated airborne dust is heterogeneous with ~75% of platinum present in coarse dust (>2 μm).[13] Consequently, the total platinum concentration in air samples also depends on the sampling technique. In a German study of air samples (PM <22 μm) near a major highway, the average total airborne platinum concentration was 23 pg/m^3 (range, 2.4–55.4 pg/m^3) compared with a mean of 5.1 pg/m^3 (range, 0.4–26.6 pg/m^3) in a nonurban area.[14] In a German study during the early 1990s, the platinum concentration in small particles (0.5–8 μm) ranged from 0.02–5.1 pg/m^3 in urban air compared with 30 pg/m^3 near a highway.[15] The portion of soluble platinum in the airborne particulate matter ranged from 30–43%. The mean platinum concentrations in PM10 particles collected in Rome on a tram in moderate-high car traffic density were 14.1 ± 10.8 pg/m^3 (range, 4.07–40.1 pg/m^3).[16] The distribution of platinum in airborne particulate matter is probably not homogeneous based on the presence of higher platinum

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concentrations in smaller particles in European studies of particulates ranging from <0.39–65.3 μm.[17]

Soil

The average platinum concentration in the earth's crust and upper mantle (lithosphere) is ~1–5 μg/kg (ppb).[18] The platinum concentration in soil is highly dependent on traffic density, wind direction, distance from the road, and the most common type of catalytic converter (e.g., pellet type releases more platinum than monolithic catalysts) with platinum concentrations typically ranging from background to several hundred ppb.[18] A study of dust near a heavily traveled freeway demonstrated platinum concentrations in dust samples of 680 μg Pt/kg dry weight (680 ppb) near the edge of the freeway, with the concentrations decreasing to ~100 ppb 34 m from the freeway edge.[19]

Water

In contrast to the relatively recent increase in the lead content in sediment, a study of platinum concentrations in the sediment of Lake Michigan indicated platinum concentrations (0.3–0.43 μg Pt/kg dry weight) have remained relatively constant over the last 50 years.[20] The platinum concentration in seawater ranges from ~100–250 pg/L.[21]

Diet

The estimated daily adult intake of platinum from the UK diet is <2.3 μg[22] based on the 2006 UK Total Diet Study compared with 1.44 μg for 21 residents of Sydney, Australia, as measured by adsorptive voltammetry.[23] Liver contains a relatively high platinum concentration compared with dairy products.[24] In the Australian study, the platinum concentration (fresh weight) was highest in liver (8.11 ppb), breakfast biscuit (4.98 ppb), beefsteak (3.67 ppb), and eggs (3.54 ppb), whereas the lowest Pt concentration occurred in whole milk (0.13 ppb), grapes (0.16 ppb), and carrots (0.27 ppb). Additionally, food-grade wrapping materials may contain platinum.

Devices

Platinum and/or platinum alloys are constituents of medical devices (e.g., pacemaker leads, vagus nerve stimulators, radiopaque markers in catheters), silicone breast implants, and dental alloys. Silicon elastomer shells contain 6–8 μg platinum/g silicone, whereas the platinum content in silicone gels is somewhat less (5 μg/g gel) as a result of lower crosslink densities.[6,25] However, the total amount of platinum in breast implants depends on the specific manufacturing process and the total size of the implant with platinum contents as low as 0.1 μg/g gel. Consequently, the total weight of platinum in a silicone implant may range from ~0.1–10 mg.[1] Studies on a few women demonstrated small amounts of platinum (ppb range) in a breast implant may diffuse through the shell into the surrounding tissues in some, but not all, women;[26,27] however, serious methodological limitations (lack of adequate control tissue, chemical matrix effects, very small sample size) and inconsistent data restrict conclusions regarding the leakage rate of platinum into the surrounding tissues. In a study of breast tissue from three women at the time of explantation (7, 8, 16 years after implant) and three women without silicone breast implants, the platinum concentration was 90 ppb (ng/g) in fatty tissue surrounding one implant with evidence of disruption of the shell, but not in muscle tissue; the platinum concentration in the fibrin layer of another implant was 25 ppb as measured by inductively coupled plasma/high-resolution isotope dilution/mass spectrometry. Platinum was not detectable (limit of detection, 2–6 ppb) in fatty or muscle tissue of a woman explanted after 8 years, whereas two of the controls without silicone breast implants had detectable platinum concentrations (i.e., 0.3 ppb, 1 ppb). Current evidence indicates that platinum in silicone breast implants is present as metallic platinum (Pt^0). Although some authors claim platinum occurs in higher oxidation states,[28] inadequate experimental detail and methodological limitations (lack of standards, separation artifacts) cause substantial uncertainty about the validity of these studies. The transformation of clinically significant amounts of metallic platinum in silicone breast implants to soluble platinum salts is unlikely.[6]

ENVIRONMENTAL FATE

Platinum is a rare metal; most commercial operations avoid significant losses of this precious metal. Furthermore, the release of platinum into the environment is limited by the fact that metallic platinum and platinum oxides are practically insoluble, resistant to most chemical reactions, and volatilize poorly. However, analysis of recent snow and ancient ice in central Greenland suggests that noble metals in catalytic converter exhausts may spread substantial distances from urban sources via the troposphere of the Northern Hemisphere.[29] Prior to the use of catalytic converters in the mid-1970s, the platinum concentration in the central Greenland snow was 6-fold (~0.06 pg/g) higher than the platinum

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concentrations in ancient ice from 7 millennia ago. By the mid-1990s, the platinum concentration in recent snow had increased to 40-fold greater than in ancient ice. The platinum/rhodium mass ratio in recent snow was similar to the mass ratio of these two metals in newer catalytic converters.

Increasing platinum concentrations in water ecosystems including sediments also suggest that platinum is mobile in the environment to some degree as a result of the release of platinum as finely dispersed particles in the nanometer range.[30] Although initially released from catalytic converters as insoluble metallic platinum or platinum oxides, at least a part of the emitted particles are probably soluble as a result of contact with various compounds in the environment.[18] The mobility of platinum in water and soil depends on pH, redox potential, chloride concentration, and type of primary rock.[2] In general, platinum is mobile primarily in highly acidic environments containing high chloride concentrations.[31] Plants may absorb platinum from the environment, but the bioavailability of platinum depends on the solubility of the platinum compound.[32]

DOSE EFFECT

The intentional ingestion of 600 mg potassium tetrachloroplatinate (K_2PtCl_6) by a 31-year-old man was associated with acute oliguric renal failure, metabolic acidosis, fever, muscle cramps, rhabdomyolysis, gastroenteritis, and mild hepatitis.[33] Signs and symptoms of toxicity resolved within 6 days. The ingestion of 6 grains (389 mg) of K_2PtCl_6 by an infant in an 1896 case report attributed gastroenteritis, dehydration, cardiovascular collapse, and death to the ingestion.[34]

The usual dosage of cisplatin is 50–100 mg cisplatin (0.65 mg Pt)/m^2 body surface area daily. Immediate hydration ameliorates the toxicity of cisplatin. The infusion of 200 mg cisplatin/m^2 over 8 hours with hydration was associated with emesis, acute renal failure, and myelosuppression that resolved.[35] Severe emesis, renal failure, deafness, myelosuppression, seizures, hallucinations, and loss of vision developed in a 68-year-old patient after receiving a single dose of 280 mg cisplatin/m^2 without hydration.[36] After a kidney transplant, the patient survived with some residual hearing loss. The infusion of 480 mg cisplatin/m^2 over 4 days without hydration produced irreversible renal failure along with hearing loss, dysarthria, and peripheral neuropathy.[37] The creatinine clearance 18 months after the incident was 26 mL/minute.

TOXICOKINETICS

Little human data are available on the kinetics of platinum. The estimated gastrointestinal absorption of platinum from the diet during an Australian study of 21 healthy adults was 42–60% based on the ratio of dietary intake/urine Pt excretion; the actual absorption was not directly measured. These values are substantially higher than the calculated Pt absorption in rodents. Animal studies indicate little absorption of metallic platinum (^{191}Pt) or simple platinum salts ($^{191}Pt(SO_4)_2$, $^{191}PtO_2$, $^{191}PtCl_4$) in the lungs or gastrointestinal tract. The gastrointestinal tract absorbs only minute amounts of platinum oxide despite the administration of large amounts (4.3 g Pt/4-week period) to rats.[38] The principal sites of distribution are the kidney, liver, spleen, and adrenals. The highest level of ^{191}Pt appears in the kidney, where excretion of the absorbed platinum occurs. For both simple platinum salts and cisplatin complexes, an initial rapid clearance phase ($t_{1/2}$ = 24 hours) precedes a slower secondary elimination phase ($t_{1/2}$ = 8–12 days).[39,40] The uptake of platinum by erythrocytes is rapid following cisplatin infusion; these studies indicate that cisplatin may reduce the life of erythrocytes, resulting in prolonged excretion of platinum. Two male volunteers with urine platinum concentrations near control values for the general population handled platinum salts (dry $(NH_4)PtCl_6$) powder for 4 hours.[41] The mean air platinum concentrations in personal air samples were 0.15 and 1.7 μg/m^3. Based on urine samples obtained daily for 4 days and weekly samples for 6 months, the initial platinum elimination half-life was ~50 hours (95% CI: 36–66 hours) as measured by UV photolysis followed by absorptive voltammetry. The urinary excretion pattern suggested a longer terminal half-life (e.g., 24 days). The diffusion of platinum across the placenta in rats is limited.[42]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Hypersensitivity

Adverse reactions in platinum refinery workers result primarily from the potent sensitizing properties of chlorinated platinum salts including ammonium tetrachloroplatinate [$(NH_4)_2PtCl_4$], ammonium hexachloroplatinate [$(NH_4)_2PtCl_6$], and hexachloroplatinic acid ($H_2(PtCl_6)$.[43] These low-molecular-weight platinum compounds induce type I immediate hypersensitivity reactions, particularly following exposure to complex

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platinum salts with high chloride content.[44] Platinum salts with relatively low molecular mass are haptens that bind to serum proteins forming complete antigens, whereas complex platinum salts are complete antigens without any binding. The allergic response usually increases with increasing numbers of chlorine atoms.[2]

Cohort studies indicate smoking and intensity of exposure to platinum salts are risk factors for conversion to positive platinum skin prick tests. In a 5-year prospective cohort study of 159 catalyst production workers, the relative risk of skin prick conversion was 3.9 (95% CI: 1.6–9.7).[45] Atopy and bronchial hyperresponsiveness were not risk factors in this study. The incidence rate of skin prick test conversion was 5.9/100 person-years in new employees compared with 2.1/100 person-years in workers employed at the time of the initial survey. In general, this incidence rate is lower in catalyst production plants than in precious-metal refineries, probably as a result of lower platinum exposure in catalyst production plants.[46] Metallic platinum and platinum oxides are relatively nonreactive with very low sensitization potential. The term platinosis is an old term applied to the spectrum of allergic reactions (asthma, rhinorrhea, dermatitis) associated with dermal or pulmonary exposure to soluble, halogenated platinum salts;[47,48] however, the term is inappropriate because the condition is neither fibrotic nor chronic like other pneumoconioses.

Cisplatin Toxicity

Cisplatin probably produces cytotoxicity by the formation of intracellular, intra-strand cross-links (DNA adducts) that cause cell-cycle arrest and apoptosis.[49] Cisplatin toxicity produces gastrointestinal upset, nephrotoxicity, myelosuppression, ototoxicity, peripheral neuropathy, allergic reactions, hypomagnesemia, and rarely cardiotoxicity. Cisplatin can mobilize body lead stores and increase renal lead accumulation that theoretically enhances cisplatin nephrotoxicity.[50]

CLINICAL RESPONSE

Acute Toxicity

The acute toxicity of platinum salts depends on solubility. Insoluble compounds (e.g., metallic platinum, $PtCl_2$, PtO_2) possess extremely low toxicity. Toxicity secondary to exposure to soluble platinum salts is also rare, but may be serious. The intentional ingestion of a photographic toning solution containing potassium tetrachloroplatinate (CAS RN: 10025-99-7, potassium chloroplatinite) by a 31-year-old man caused gastroenteritis, dehydration, acute oliguric renal failure, fever, and myalgias that resolved over 6 days.[33]

Environmental Exposure

Metallic platinum is biologically inert and nonallergenic.[2] Because platinum emitted from catalytic converters is released mostly in the form of metallic platinum rather than halogenated compounds, the risk of sensitization in the general population is probably very low; there is no clear evidence at the present time that environmental exposure to platinum or other members of the platinum group metals causes asthma or other hypersensitivity reactions in the general population.[51] Smoking and intense platinum exposures are potential predisposing factors for the development of platinum hypersensitivity,[52] whereas nonspecific airway hyperreactivity and atopy are not clearly related to an increased risk of platinum hypersensitivity.[53]

Occupational Exposure

Exposure to potential platinum sensitizers depends on the industry type, solubility of the metal salts in workplace air, and tasks/location of the exposure.[54] The most important medical effect of platinum exposure in the workplace is an IgE-mediated, type I allergic reaction to respiratory sensitization with hexachloroplatinate and tetrachloroplatinate salts being the most potent sensitizers, particularly in smoking workers with atopy and recent platinum exposure.[55] Following sensitization, wheezing, tearing, eczematous and urticarial skin lesions, inflammation of the mucous membranes, tightness of the chest, dyspnea, and cough may develop following occupational exposure to complex platinum salts.[56] Symptoms usually abate soon after terminating exposure unless sensitized workers remain exposed to platinum salts. Platinum skin sensitivity and airway hyperresponsiveness may persist for years after the termination of exposure to platinum salts.[57] In a nested case-control study of 14 workers at a catalyst production plant converting positive skin prick tests to platinum salts during the 5-year study, symptoms of occasional dyspnea or wheezing persisted in four subjects following cessation of platinum exposure.[58] Symptoms were not accompanied by changes in FEV_1 or bronchial responsiveness to histamine. Nasal and conjunctival irritation, sore throat, and rhinitis may also occur. Signs of platinum dermatitis include erythema, urticaria, vesiculation, and fissures. In a laboratory refining platinum

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during the 1940s, the latency period for the development of asthma ranged from a few months to 6 years.[59,60] Particle concentrations in the ambient air in these work environments ranged up to 1,700 μg/m^3. The risk of developing hypersensitivity to platinum salts correlates with the severity of exposure because the highest rates of sensitization occur in workers with the greatest exposure to platinum salts. Cross-sectional studies of workers exposed to platinum indicate that platinum salts' sensitization is associated with cigarette smoking but not with atopic tendencies as defined by sensitivity to common aeroallergens.[61]

In a case series of six catalyst production operators exposed to high concentrations of platinum salts, three workers developed hypersensitivity to platinum salts over a period of 5 years.[62]

Cisplatin Toxicity

Adverse reactions to the use of cisplatin include nausea and vomiting in almost all patients, but diarrhea, metallic taste, and mucositis are less common. Protracted vomiting may begin within the first 24 hours and persist for 2 weeks. Nephrotoxicity develops in 2/3 of patients, manifested by acute tubular necrosis of the distal convoluted tubules;[63] the onset of acute oliguric or nonoliguric renal dysfunction occurs within 2–6 days after a cisplatin overdose.[64] Large single doses with vigorous prehydration and the use of osmotic diuretics help reduce, but do not eliminate, renal toxicity. Ototoxicity often is nonreversible, characterized by tinnitus and hearing loss in the high ranges. Peripheral neuropathies, memory loss, and intention tremor may occur. Other complications reported following cisplatin overdose include seizures, hallucinations, visual loss, severe emesis, and mild hepatic dysfunction. Rare case reports associate allergic reactions, dermatitis and anaphylaxis, with the therapeutic use of cisplatin.[65] Cardiomyopathy is a rare complication of cisplatin toxicity.

CARCINOGENICITY

Little data exist on the carcinogenicity of metallic platinum or platinum salt. Neither the IARC nor the US NTP lists these compounds as suspected carcinogens. The IARC does list cisplatin as a probable human carcinogen (Group 2A) with sufficient evidence in animals and inadequate data in humans.[66] Although cisplatin is a potent carcinogen in experimental animal studies, the issue of whether patients treated with cisplatin develop secondary cancers remains unresolved. A review of the literature indicated that most of the secondary cancers in these patients are acute nonlymphocytic leukemias or myelodysplasia; however, most of these cases do not directly implicate cisplatin alone or suggest that the combination of chemotherapeutic drugs is leukemogenic in humans.[67]

DIAGNOSTIC TESTING

SI Conversion Units

1 ppm = 7.979 mg/m^3
1 ng/mL = 5.126 nmol/L

Analytical Methods

The use of electrothermal atomic absorption spectrometry (ETAAS, single-element mode), absorptive voltammetry, and neutron activation analysis allows the detection of platinum and palladium with sufficient sensitivity in biological samples,[68] whereas X-ray fluorescence spectrometry and flameless atomic absorption spectrometry lack sufficient sensitivity in the sub-ppm range.[69] For quantitation in the ppb range necessary for environmental samples, the preferred multielement instrumental techniques include inductively coupled plasma/optical emission spectrometry (ICP/OES; LOD, 10 μg/L) and inductively coupled plasma/mass spectrometry (ICP/MS; LOD, <1 μg/L). The lower limit of quantitation for platinum in plasma using high-pressure decomposition and absorptive voltammetry was 6 pg/g compared with ~35 μg/g for flameless atomic absorption spectrophotometry.[70]

Quantitation of platinum group metals in air and blood is complicated by the low sensitivity (ng/L) required and the presence of interfering matrix constituents. Although inductively coupled plasma/mass spectrometry has sufficient sensitivity, sufficiently high spectral resolution, matrix separation, or mathematical correction is necessary to avoid spectral interference from other metals (e.g., copper, strontium, yttrium, zinc, zirconium).[71] Other sensitive methods for analyzing platinum in air samples include absorptive striping voltammetry following acid digestion in a high-pressure asher (HPA, Kuner, Rosenheim, Germany).[14] The redistribution of platinum from serum into the clotted cell mass may cause erroneously low platinum concentrations in plasma samples that are not immediately separated.[72]

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Biomarkers

Blood

The median platinum concentration in whole blood samples from 18 Australian volunteers without known exposure to platinum was 0.6 µg/L (range, 0.1–2.8 µg/L) as measured by adsorptive voltammetry after dry-ashing of the blood samples in a muffle furnace.[73] In a study of 21 urban residents from Sydney, Australia, the median platinum concentration in whole blood was 0.56 µg/L (range, 0.09–1.72) with similar concentrations in 3 rural residents of Lord Howe Island, as measured by adsorptive voltammetry.[23]

The initial serum platinum concentration 12 hours after an overdose of 600 mg potassium tetrachloroplatinate was 2,450 µg/L; the patient developed oliguric renal failure, metabolic acidosis, rhabdomyolysis, myalgias, gastroenteritis, and fever that resolved over 6 days.[33] In plasma samples from six patients, an intravenous dose of 100 mg cisplatin produced an approximate mean platinum concentration of 2,500 µg/L 1 hour after administration, decreasing to 1,600 µg/L at 6 hours post-administration.[74]

Urine

In samples from 178 German workers without known exposure to platinum, the median urine platinum concentration was 4.3 ng/g creatinine with a maximum value of 45 ng/g creatinine, as measured by adsorptive voltammetry (limit of detection, 1 ng/L).[75] The platinum concentration was <20 ng/g creatinine in 96% of the urine samples; all participants with urine platinum concentrations exceeding this value had gold/platinum dental alloys. Studies of urine platinum concentrations in samples from populations outside Europe demonstrated higher median platinum concentrations. The median urine platinum concentration from 21 residents of Sydney, Australia, without known occupational exposure to platinum was 230 ng/g creatinine (180 ng/L) with a range of 30–820 ng/g creatinine as determined by adsorptive voltammetry.[23] In comparison, the median urine platinum concentration in a convenience sample of 496 participants in the third US National Health and Nutrition Examination Survey (NHANES III, 1988–1994) was 900 ng/g creatinine (1,190 ng/L) with a 95% upper limit of 3,590 ng/g creatinine (4,220 ng/L), as measured by inductively coupled argon plasma/mass spectrometry (LOD, 400 ng/L).[76] Although the ages of the participants ranged from 6–88 years, the samples were not selected to represent the US population.

For the general population without occupational exposure to platinum or platinum-containing drugs, the main source of platinum exposure is dental gold/platinum alloys. In a study of urine samples from 50 subjects with gold dental restorations, the mean urinary platinum concentration was 11.9 ± 8.5 ng/g creatinine (range, 1.9–45.8 ng/g creatinine).[77] For 42 subjects in this study without gold dental restorations, the mean urinary platinum concentration was 6.2 ± 3.2 ng/g creatinine (range, 1.9–14.4 ng/g creatinine). In a pilot study of urine samples (mostly morning collections) from 27 dental technicians, 17 road construction workers, and 17 construction students (control group), the median platinum concentration of the dental technicians was 11.4 ng/L (95% upper limit, 104.8 ng/L) compared with 0.5 ng/L (95% upper limit, 4.3 ng/L) for the road construction workers and 1.2 ng/L (95% upper limit, 2.2 ng/L) for the control group as measured by sector field/inductively coupled plasma/mass spectrometry.[78] Five of the 27 dental technicians had a total of 11 noble metal fillings based on questionnaires.

Abnormalities

Mild metabolic acidosis, eosinophilia, hypophosphatemia, and leukocytosis developed following an overdose of potassium tetrachloroplatinate.[33] Skin prick tests are sensitive and specific biological markers of platinum salt sensitization, but not all cases of platinum-induced asthma will demonstrate a positive skin prick test.[44]

Abnormalities in the blood following the administration of cisplatin as an antitumor agent include metabolic acidosis, hypomagnesemia, hypocalcemia, hypophosphatemia, hypokalemia, and hyponatremia, particularly in the presence of renal tubular dysfunction. Leukopenia and thrombocytopenia (onset 6–26 days after administration) also may occur. Normocytic anemia appears in 9–40% of patients. Myelosuppression and renal failure are serious complications of a cisplatin overdose; mild liver dysfunction may also develop. Platinum is radiopaque.

HEALTH SURVEILLANCE

Environmental Monitoring

The American Conference of Governmental and Industrial Hygienists (ACGIH) TLV–TWA for platinum dust is 1 mg Pt/m^3, whereas the TLV–TWA for soluble salts of platinum is 0.002 mg Pt/m^3 measured as total platinum. The lower values for exposure to soluble platinum salts are recommended to minimize the risk of developing respiratory irritation, asthma, and skin

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sensitization.[79] There is no recommended TLV–STEL. The OSHA PEL–TWA for platinum metal dust of 1 mg Pt/m^3 was vacated by the 11th Circuit Court of Appeals 1992 decision in AFL-CIO vs. OSHA; however, the OSHA TLV–TWA and the NIOSH REL–TWA for platinum salts are the same as ACGIH.

Biological Monitoring

Although the few studies of platinum-exposed workers suggest plasma and urine concentrations are elevated when compared with unexposed workers, air platinum concentrations do not correlate closely to plasma or urine Pt concentrations. Consequently, there are no validated biomonitoring methods to assess platinum-exposed workers.

Blood

Serum platinum concentrations are neither specific nor sensitive for predicting platinum salt sensitization. Potential confounders to the interpretation of serum platinum concentrations include gold/platinum dental alloys, platinum-containing medications, exposure to insoluble platinum salts/metallic platinum (non-sensitizing), the timing of the sampling in relation to exposure, and smoking.[80] In a study of blood from pharmacists preparing cisplatin and graduate/staff nurses attending patients receiving cisplatin, the mean total platinum concentrations in whole blood samples from the three groups were 0.47 ± 0.31 ng/mL, 2.2 ± 1.7 ng/mL, and 3.8 ± 4.0 ng/mL, respectively.[81] The mean values for the nurses were higher than the unexposed control group (1.2 ± 0.69 ng/mL); however, the coefficient of variation (CV) exceeded 50% for all groups. Air monitoring data demonstrated increased platinum concentrations in ambient air. In blood samples from 11 workers with platinum exposure and positive skin tests for platinum hypersensitivity, the serum platinum concentration was above the limit of detection (100 µg/L) in 8 workers with a mean of 240 ± 100 µg/L (range, 150–440 µg/L).[46]

Urine

In a study of 161 police employees, the mean urine platinum concentrations of patrol officers and office workers were 4.45 ± 2.42 ng/L (95% upper CI: 10.1 ng/L) and 4.56 ± 2.84 ng/L (95% upper CI: 8.91 ng/L), respectively, as measured by inductively coupled plasma/mass spectrometry coupled to a pneumatic nebulizer.[82] These results between office workers and traffic officers potentially exposed to airborne platinum from automobile exhaust were not statistically different. In a study of workers at a plant producing and recycling catalytic converters, the highest platinum concentration (2.39 µg/m^3, 4.83 µg/m^3) in ambient air samples occurred in the department that coated supports with acid metal solutions.[83] The most reliable biomarker of the current platinum exposure was urine collected in the morning of the last day of the work week. The mean urine platinum concentration in workers from the coating department was 1,860 ± 1,120 ng/L compared with 5 ± 0.1 ng/L for unexposed controls. The urine platinum concentration in platinum refinery and catalyst production workers may substantially exceed (e.g., 6,000 ng/g creatinine) that of unexposed workers.[41]

Medical Surveillance

Preemployment screening includes questionnaires (respiratory disease, smoking, allergies, employment exposures) and a complete physical examination with pulmonary function tests. The use of skin prick tests and tests of bronchial reactivity is an option for workers with suspected sensitivity to platinum. The development of allergic hypersensitivity to platinum salts usually precludes continuing occupational exposure to platinum salts.

TREATMENT

Platinum Salts

The treatment of acute toxicity secondary to soluble platinum salts is supportive.

Cisplatin Toxicity

The treatment of cisplatin toxicity is primarily supportive (e.g., hydration, ondansetron, dexamethasone, lorazepam) with no specific antidotes available. Hydration within several hours following an overdose of cisplatin probably reduces the severity of the renal toxicity. Amifostine is approved by the US FDA as a protective agent in the prevention of cisplatin-induced nephrotoxicity; however, the efficacy of amifostine in reversing neurotoxicity is unproven.[84] Animal studies suggest that the administration of thio-reducing agents (*N*-acetylcysteine,[85,86] diethyldithiocarbamate,[87,88] sodium thiosulfate) may reduce the toxicity of cisplatin when administered within 1–2 hours after the overdose; clinical data to confirm experimental data are limited with some evidence for the efficacy of sodium thiosulfate.[89] The initial protective effects may not persist.[90]

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Consequently, the use of these agents remains investigational including the administration of amifostine, fosfomycin, and colestipol.[89]

Hemodialysis is probably not effective for overdoses of cisplatin because cisplatin rapidly distributes to tissue receptors and binds to proteins.[35] A case report associated a reduction in the cisplatin concentration and clinical improvement following plasmapheresis, but three treatments with plasmapheresis removed only ~6 mg cisplatin compared with the initial infusion of 480 mg cisplatin.[36] This patient also received granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate platelet production and reduce myelosuppression. A case report associated complete recovery from a cisplatin overdose of 400 mg/m^2 over 4 days with the use of 9 cycles of plasma exchanges beginning on the first day after the discovery of the overdose.[91] Complete blood count with differential, serum electrolytes, and serum creatinine/BUN should be monitored daily during acute intoxication. Baseline laboratory tests include serum hepatic aminotransferases, magnesium, calcium, phosphate, and uric acid; these tests should be repeated when abnormal.

PALLADIUM

PHYSIOCHEMICAL PROPERTIES

Palladium is a rare, steel-white, ductile metal that commonly exists in nature with other members of the Group 10 (Group VIII) platinum metal group (iridium, osmium, platinum, rhodium, ruthenium). Palladium exists in the following three oxidation states: Pd^0 (metallic), Pd^{2+}, and Pd^{4+}. This corrosion-resistant metal occurs most commonly in the divalent state (e.g., *cis*-diamminedichloropalladium, tetraamminepalladium, palladium chloride, palladium oxide, palladium acetate, palladium nitrate, hydrogen tetrachloropalladate). Tetravalent palladium is less common and more unstable than divalent palladium.[92] The water-insoluble metal forms a number of coordination and organic complexes. Palladium is soluble in aqua regia and nitric acid. Table 24.2 lists the identifying information and physical properties of elemental palladium. High surface energy and high surface area/volume ratio of palladium nanoparticles favor the use of these nanoparticles in catalyst materials.[93]

TABLE 24.2. Identifying information and physical properties of metallic palladium. (Based on Narayanan and El-Sayed).[93]

Physical Characteristic	Data
CAS RN	7440-05-3
Atomic symbol	Pd
Atomic Mass (g/mol)	106.42
Melting point (°C)	1554
Boiling point (°C)	2940
Density (g/mL)	12.02 (20°C)
Water solubility	Insoluble (25°C)
Odor threshold	Odorless

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.

EXPOSURE

Uses

The main uses of palladium are automobile catalytic converters, dental materials, and electrical equipment (e.g., diodes, integrated circuits, memory, transistors). Palladium is one of several constituents of 3-way catalytic converters for reduction of carbon monoxide, hydrocarbons, and nitrogen oxides in vehicle exhausts; the typical composition of noble metals in these converters includes 0.04% palladium, 0.08% platinum, and 0.005–0.07% rhodium.[18] In this application, palladium is less costly and more resistant to contamination by lead, phosphorus, zinc, and sulfur. Palladium is also a constituent of electrical equipment (Ag–Pd alloys for relays, switching systems, contacts), jewelry (ruthenium/platinum alloys), and dental restorations (Ag–Cu–Au alloys). Many divalent palladium compounds (e.g., chloride, nitrate, oxide salts) are catalysts in metallic palladium refining, chemical synthesis (vinyl acetate, methanol, acetaldehyde), high-antiknock-gasoline refining, photography, and electroplating. Commercial applications for palladium nanoparticles include electrocatalysis, hydrogen storage, electrochemical reactions in fuel cells, chemical sensors, production of electrical equipment, and glucose biosensors.[94]

Production Processes

Commercial palladium is mostly a by-product of nickel, platinum, or other base-metal refining. Melting of the sulfide pulp formed by the froth floatation of the crude ore produces a matte containing copper, nickel, and iron sulfides along with palladium. Acid leaching separates the nickel and copper. Selective dissolution

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and precipitation or a solvent extraction process forms ammonium-chloro-complexes (e.g., chloropalladosamine, CAS RN: 14323-43-4) that decompose under heat to produce impure palladium sponge.

Sources

Air

Similar to platinum, catalytic converters are the primary source of palladium in the environment as a result of physical stress (sintering, thermal degeneration) on the washcoat part of the equipment.[95] The rate of emission depends on driving speed, type of catalyst, age of catalyst, and engine type. The palladium concentration in ambient air is usually in the low pg/m^3 range even near freeways, depending on the sampling techniques.[12] As with other platinum group elements, the distribution of palladium in fractionated airborne dust is heterogeneous; however, the fraction of palladium in fine dust (<2 μm) is relatively greater than that of platinum or rhodium. In a German study of air samples (PM <22 μm) near a major highway, the average total airborne palladium concentration was 14.7 pg/m^3 (range, <0.6–44.3 pg/m^3) compared with a mean of 2.8 pg/m^3 (range, <0.5–11.2 pg/m^3) in a nonurban area.[13] In samples of suburban air in Berlin, the palladium concentration ranged from 0.2–14.6 pg/m^3 as measured by graphite furnace atomic absorption spectrometry (GFAAS) and laser absorption fluorescence spectrometry (LAFS).[96] The mean concentration of palladium in PM_{10} particles collected on a tram in moderately high car traffic density in Rome was 58.0 ± 46.8 pg/m^3 (range, 16.8–168 pg/m^3).[16] In a study of heavy traffic sites in Goteborg, Sweden, the mean concentration of palladium in PM_{10} particles ($n = 7$) was 4.9 ± 3.1 pg/m^3 (range, 1.3–9.7 pg/m^3) compared with 14.1 pg/m^3 (range, 7.6–19.2 pg/m^3) for platinum.[97] The palladium concentration in air samples from low-traffic density urban areas was ~4–5-fold lower than samples from the high-traffic density urban areas. Based on laboratory testing of emissions from catalytic converters analyzed new and after a light-duty vehicle aging cycle simulating urban driving, the soluble palladium fraction in exhaust fumes is substantially higher than the soluble platinum fraction.[8]

Soil

The average palladium concentration in the earth's crust and upper mantle (lithosphere) is <1 μg/kg (ppb).[92] The maximum concentration of palladium in roadside dust from two major British highways during a 12-month study was <70 ppb compared with maximum values >500 ppb for platinum.[98] As the use of palladium-rich catalytic converters increases, the palladium concentration in soils near highways increases. In a study of a German highway, the mean palladium concentration (83 ppb; range, 20–191 ppb) in 23 samples of adjacent topsoil from the downwind side of the highway increased 15-fold between 1994–2004 compared with a 2-fold increase in platinum concentrations.[11] During this time interval, the rhodium concentration in topsoil samples increased by 1.6-fold.

Water

The intake of palladium from food and drinking water is small with an estimated daily dietary intake of <2 μg.[99] Surface waters typically contain palladium concentrations in the low ppb (ng/L) range. In a study of Canadian lakes and groundwater near sites with known palladium production, the palladium concentration averaged <5 ppt (ng/L) as measured by inductively coupled plasma/mass spectrometry (LOD, ~1 ppt).[100] Spring water samples in Nevada contained ~3 ppb Pd.[101]

Diet

There are few data on the intake of palladium in the diet. The estimated daily adult intake of palladium in the United Kingdom is 0.7 μg based on the 2006 UK Total Diet Study.[22] In this study, beverages, bread, miscellaneous cereals, and potatoes accounted for the largest portion of palladium in the diet, whereas the palladium content in eggs, fresh fruit, and offal was nondetectable (LOD, 0.03–0.2 μg/kg).

ENVIRONMENTAL FATE

The physiochemical properties including the thermodynamics of palladium and aqueous species suggest that palladium is mobile in air and water as hydroxide, chloride, and bisulfide complexes depending on pH, oxygen fugacity, ligand concentration, and temperature.[92] Palladium is more mobile in the environment than platinum and rhodium.[99] Analysis of recent snow and ancient ice in central Greenland suggests that palladium in catalytic converter exhausts may spread substantial distances from urban sources via the troposphere of the Northern Hemisphere.[29] Prior to the use of catalytic converters in the mid-1970s, the palladium concentration in the central Greenland snow was 15-fold (0.15 pg/g) higher than concentrations in ancient ice from 7 millennia ago. By the mid-1990s, the palladium concentration in recent snow had increased to 80-fold higher than in ancient ice.

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DOSE EFFECT

There are limited data on dose-related palladium toxicity. The adverse effects of palladium are usually attributed to the presence or release of palladium ions rather than metallic palladium. In general, the acute toxicity of palladium and related compounds is very low to moderate after ingestion, depending on solubility.[2] Several palladium salts may cause severe primary skin and eye irritation along with skin sensitization.

TOXICOKINETICS

There are few data on the absorption of palladium in humans. In general, insoluble compounds (e.g., metallic palladium) are poorly absorbed from the gastrointestinal tract. In most animal experiments using divalent palladium chloride or sodium tetrachloropalladate, feces and urine are the main routes of excretion. In a subchronic study of rats receiving tetravalent potassium hexachloropalladate for up to 90 days in drinking water, palladium excretion was rapid, primarily via feces.[102]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Allergic reactions are the most common cause of adverse reactions to platinum group salts including palladium; however, palladium salts are relatively poor skin sensitizers that rarely cause a type IV hypersensitivity reaction.[103] Allergic reactions to these salts are typically associated with contact dermatitis rather than asthma or urticaria.[104] Although *in vitro* studies suggest that Pd nanoparticles may produce cytotoxic and proinflammatory effects, inadequate data are available to determine if these effects significantly affect ecosystems or human health.[94]

CLINICAL RESPONSE

Sensitization may occur to low palladium doses, particularly in patients with nickel allergies,[99,105] Pd-containing dental restorations,[106] or multiple body piercings;[107] however, the sensitivity of the general population to palladium is low.[92] In a study of 910 patients presenting to a dermatology clinic, 12.1% ($n = 110$) had a positive result for a 2% palladium patch test.[108] The diagnoses given to these positive patients were as follows: hand and body dermatitis, 29.2%; stomatitis, 27.4%; lichen planus-like eruptions, 15.1%; and burning mouth, 13.2%. In contrast to platinum, allergic reactions to pallidum are primarily limited to contact dermatitis based on case reports of patients exposed to palladium-rich dental restorative alloys.[109] Metallic palladium is a relatively less sensitizing agent than palladium chloride.[2] Case reports also associate palladium-containing dental restorations with bronchial asthma and chronic urticaria;[110,111] however, the contribution of palladium in the development of these effects is unclear because of the many metals used in these restorations including platinum.[112] Rarely, case reports associate dental alloys with stomatitis and asthma in patients with patch test sensitivity to palladium but not to nickel or platinum.[113] Immediate hypersensitivity reactions in refinery workers exposed to palladium usually occur in workers with sensitization to platinum salts; however, the prevalence of cross-reactivity between both metals in these workers is relatively low.[114] Rhinoconjunctivitis and asthma developed in a previously healthy worker exposed to fumes from an electroplating bath containing palladium chloride but no platinum.[115] The skin prick test and bronchial provocation test for divalent tetramminepalladium chloride were positive, whereas the skin prick test for the platinum salt was negative. There are few data on the carcinogenicity or reproductive abnormalities associated with palladium. Neither the International Agency for Research on Cancer (IARC) nor the US National Toxicology Program (NTP) lists palladium as a suspected carcinogen or reproductive toxin.

DIAGNOSTIC TESTING

SI Conversion Units

1 ppm = 4.353 mg/m^3
1 ng/mL = 9.340 nmol/L

Analytical Methods

Techniques for analyzing palladium in biological and environmental samples typically report total palladium concentrations without speciation. The methods for the quantitation of palladium include total reflection X-ray fluorescence after mercury coprecipitation,[14] neutron activation analysis, graphite furnace/atomic absorption spectrometry, inductively coupled plasma/mass spectrometry, and isotope dilution/inductively coupled plasma/quadrupole mass spectrometry (limit of detection in air samples, 0.01 pg Pd/m^3).[71] The limits of detection for palladium in blood and urine after acidification with nitric acid were 3 ng/L and 10 ng/L, respectively, as measured by flameless atomic absorption spectrophotometry.[116] Analytical methods for quantitation of palladium in blood usually require

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destructive methods (e.g., ashing) to remove organic material, followed by the addition of strong acids (e.g., nitric acid) that restricts quantitation to total palladium without speciation. Similarly, urine samples require pretreatment with UV photolysis, freeze-drying, or a wet-ashing procedure with subsequent reduction of urine volume before analysis by inductively coupled plasma/mass spectrometry. Palladium is a chemical modifier used in analytical laboratories to reduce interferences associated with the determination of various trace elements in biological samples; consequently, contamination may complicate the analysis of palladium in laboratories using this chemical modifier.

Biomarkers

There are few data on the concentration of palladium in the general population without occupational exposure to palladium. Typically, the palladium concentration in blood samples is <0.1 μg/L.[92] The mean palladium concentration in whole blood from seven volunteers was 0.05 μg/L (range, 0.03–0.08 μg/L) as measured by sector field inductively coupled plasma/mass spectrometry (LOD, 0.00017 μg/L).[78] The palladium concentration in urine samples from the general population is usually <1–2 μg/L.[117] In a pilot study of urine samples (mostly morning collections) from 27 dental technicians, 17 road construction workers, and 17 construction students (control group), the median palladium concentration of the dental technicians was 97.1 ng/L (95% upper limit, 323.5 ng/L) compared with 44.7 ng/L (95% upper limit, 127.9 ng/L) for the road construction workers and 26.7 ng/L (95% upper limit, 48.3 ng/L) for the control group as measured by sector field inductively coupled plasma/mass spectrometry.[78] Five of the 27 dental technicians had a total of 11 noble metal fillings based on questionnaires.

HEALTH SURVEILLANCE

Currently, no validated methods for the biological monitoring of workers exposed to palladium exist. In a study of 84 palladium-exposed workers from the Production of Catalysts and Refining Departments, 17 occasionally exposed employees, 21 controls (administrative offices), and 25 unexposed volunteers (external controls), airborne Pd concentrations as measured by personal devices correlated with urine palladium concentrations ($r^2 = 0.684$; $P \leq 0.01$).[118] The highest mean airborne palladium concentration in personal samplers occurred in the Production of Catalysts Department (mean = 1.44 μg/m^3) and the Refining Service (mean = 5.75 μg/m^3); the corresponding mean urine Pd concentration in those departments was 1.71 μg/L (range, 0.84–3.02 μg/L) and 1.20 μg/L (range, 0.65–2.25 μg/L), respectively.

Preemployment screening should include a questionnaire for skin disease specifically for allergy to metals (nickel, cobalt, and palladium); however, routine patch tests with nickel and palladium compounds are not recommended unless applied to determine the cause of occupational dermatitis. Workers with a known nickel allergy should be cautioned about developing palladium sensitization while working with palladium salts. In general, workers with palladium allergies should avoid contact with palladium or palladium salts. During employment, regular screening for skin and respiratory health through questionnaires and examinations should be done as needed.

TREATMENT

The primary treatment for palladium sensitization is prevention of exposure to palladium compounds. Otherwise, the treatment of adverse effects from palladium exposure is supportive.

RHODIUM

PHYSIOCHEMICAL PROPERTIES

Rhodium is a rare, soft, silvery-white member of Group 9 (Group VIII) that forms alloys with other platinum group metals; this metal also occurs in gold ores. The typical oxidation state in the environment is trivalent;[103] Rh is the only stable isotope. The tendency to form soluble complexes suggests that the mobility of rhodium in the environment and bioavailability are greater than those of platinum.[119] Rhodium is insoluble in acids and aqua regia.

EXPOSURE

The most common uses of rhodium include a platinum/rhodium alloy for high-temperature thermocouples, catalytic converters, and electroplating of metals. There are few data on the intake of rhodium in the diet. The estimated daily adult intake of rhodium in the United Kingdom is <2.3 μg based on the 2006 UK Total Diet Study.[22] In this study, beverages, bread, and

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miscellaneous cereals accounted for the largest portion of rhodium in the diet, whereas the rhodium content in nuts and offal was nondetectable (LOD, 0.5–3 μg/kg).

As with other platinum group elements, the distribution of rhodium in fractionated airborne dust is heterogeneous with ~95% of rhodium present as coarse dust (>2 μm).[13] Consequently, the total rhodium concentration in air samples depends on the sampling technique. In a German study of air samples (PM <22 μm) near a major highway, the average total airborne rhodium concentration was 3.9 pg/m^3 (range, <0.5–11.6 pg/m^3) compared with a mean of 0.5 pg/m^3 (range, <0.1–2.8 pg/m^3) in a nonurban area.[14] The platinum/rhodium and palladium/rhodium ratios in this study demonstrated wide variations (i.e., 2.4–10.1 and 1.7–23.3, respectively, in urban air samples). Based on laboratory testing of emissions from catalytic converters analyzed new and after a light-duty vehicle aging cycle simulating urban driving, the soluble fraction of rhodium in exhaust fumes is substantially higher than the soluble platinum fraction.[8]

Analysis of recent snow and ancient ice in central Greenland suggests that rhodium in catalytic converter exhausts may spread substantial distances from urban sources via the troposphere in the Northern Hemisphere.[29] Prior to the use of catalytic converters in the mid-1970s, the rhodium concentration in the central Greenland snow was 45-fold (0.031 pg/g) higher than the rhodium concentration in ancient ice from 7 millennia ago. By the mid-1990s, the rhodium concentration in recent snow had increased to 120-fold higher than in ancient ice. The platinum/rhodium mass ratio in recent snow was similar to the mass ratio of these two metals in newer catalytic converters.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

The sensitizing potential of rhodium salts is relatively low, and most cases associating rhodium salts with allergic reactions involve sensitivity to multiple agents including other platinum group salts\ (e.g., platinum, palladium).[120] In a study of 720 eczematous patients, 2 patients had positive patch tests for rhodium chloride.[121] These two patients also had positive patch tests for cobalt and nickel. Sensitivity to metallic rhodium does not usually occur.

CLINICAL RESPONSE

Contact dermatitis associated with rhodium salts typically involves multiple platinum group allergens, primarily in jewelry workers using acidic electroplating solutions containing rhodium sulfate.[122] A 47-year-old goldsmith developed dermatitis of his hands while working with an electrogalvanic bath containing hexa-chlororhodiate solution.[123] His patch test for this solution was 3+ compared with 1+ for cobalt chloride. A 45-year-old self-employed jeweler developed a pruritic, scaly rash on her fingertips, eyelids, wrists, and legs while working in a poorly ventilated area with rhodium solutions, cyanide, and ammonia.[124] She had a prior history of allergic rhinoconjunctivitis along with the recent onset of asthma. She had a positive skin patch test for rhodium chloride and cobalt chloride; skin prick and bronchoprovocation tests for precious metal salts were not performed. A 27-year-old atopic electroplating plant operator developed work-related dyspnea and rhinitis 3 years after beginning work around electrolysis baths containing rhodium salts. He had positive skin prick tests and bronchial challenges to chloride salts of both rhodium and platinum, but the response to rhodium was 256-fold and 16-fold higher than platinum, respectively. Rarely, case reports associate the development of contact dermatitis with the use of rhodium sulfate-containing electroplating solutions by workers with positive patch tests to only 2% rhodium sulfate.[125]

TABLE 24.3. Guidelines and regulations for exposure to rhodium and rhodium compounds.

Exposure Limit	Value
	OSHA
PEL–TWA (8-hour)	0.1 mg/m^3 (metal/insoluble)[a]
	0.001 mg/m^3 (soluble compounds)[a]
	NIOSH
REL–TWA (10-hour)	0.1 mg/m^3 (metal/insoluble compounds)[a]
	0.001mg/m^3 (soluble compounds)[a]
IDLH	100 mg/m^3 (metal/insoluble compounds)[a]
	2 mg/m^3 (soluble compounds)[a]
	ACGIH
TLV–TWA (8-hour)	1.0 mg/m^3 (metal)[a]
	1.0 mg/m^3 (insoluble compounds)[a]
	0.01 mg/m^3 (soluble compounds)[a]

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; IDLH = immediately dangerous to life and health; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; TLV = threshold limit value; TWA = time-weighted average.
[a] As total Rh.

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DIAGNOSTIC TESTING

Methods for analyzing rhodium in air samples include absorptive striping voltammetry following acid digestion in a high-pressure asher (HPA, Kuner, Rosenheim, Germany),[14] graphite furnace atomic absorption spectrometry, inductively coupled plasma/atomic emission spectrometry,[126] and quadrupole inductively coupled plasma/mass spectrometry.[127] Using the latter method and online sample cleanup/pre-concentration steps in a sequential injection analysis system incorporating a column filled with chelating resin, the limit of detection for rhodium in biological samples is 0.4 ng/L.

Rhodium salts produce positive skin prick, which results in platinum salt allergic workers in catalyst production and precious metals refineries. Three of the 153 workers in a catalyst manufacturing and recycling plant had positive skin prick tests for platinum, rhodium, and iridium salts, whereas 22 (14.4%) had positive skin prick reactions to platinum salts.[128] In a study of 306 South African platinum refinery workers, 6 of 38 workers with positive RAST tests for platinum salts also had antibody responses to rhodium salts.[104]

HEALTH SURVEILLANCE

There are few data on human toxicity from rhodium exposures. The standards set for rhodium exposures are usually based on the similarity of rhodium to platinum and the minimization of the risk of sensitization. Table 24.3 displays exposure levels for rhodium.

TREATMENT

Treatment is supportive.

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Chapter 25

POTASSIUM

HISTORY

The English chemist, Humphry Davy, first isolated elemental potassium in 1807 via electrolysis by decomposing molten potassium hydroxide (caustic lye) with a voltaic battery. Potassium was named after potash; the latter word is a combination of "pot" and "ash" reflecting the discovery of potassium in the water-soluble fraction of wood ash. Since antiquity, potash has been part of manufacturing processes for ceramics, glass, and soap. Leaching of the water-soluble fraction in wood ashes from the burning of broad-leaved trees in Europe, Russia, and North America was the dominant production process for potash compounds until the 1860s.[1] Extraction of lye (potassium hydroxide) from hardwood ash provided material for soap and the production of potash after boiling. During the latter 1800s, inorganic compounds and mineral potassium sources became more common sources than the old method of ash lixiviation.

Germany became the world leader in transforming the ash market for glass and soap production into a global mining operation with agriculture being the primary market.[2] The economic disruptions of World War I required the development of alternate potassium sources (Nebraska brines, California kelp) to German potassium sources. The mining of newly discovered potassium deposits in the Northern Hemisphere ultimately became a stable source of potassium. Glucose–insulin–potassium solution was suggested as a repolarizing solution to prevent dysrhythmias in patients with acute myocardial infarction; however, the benefit of this solution was never proven.[3] In the 1980s, potassium intoxication occurred after the use of potassium as a salt substitute, a nonprescription agent to alkalinize the urine, and a nutritional protein calorie supplement.[4]

Potassium chloride has a long history of use for suicides, homicides, and lethal procedures for state-sanctioned punishment.[5] Dr. Jack Kevorkian euthanized 69 people in Oakland County, Michigan, in 1990–1998 before he was incarcerated for forging the will of his last victim.[6] He used licit drugs (e.g., barbiturates) with KCl as the main fast-acting agent. He committed suicide in 2004 while in custody.

PHYSIOCHEMICAL PROPERTIES

Potassium (CAS RN: 7440-09-7) is one of the Group 1 (Group Ia) metals with lithium, sodium, rubidium, cesium, and francium; these alkaline metals are strong bases and easily form hydroxides with moisture. Potassium is a soft, waxy, and highly reactive metal that does not exist in the natural environment as elemental potassium. Potassium hydroxide (KOH, caustic potash) is a white material that dissolves easily in water. KOH (CAS RN: 1310-58-3; atomic weight (g/mol): 56.11; specific gravity: 2.044; melting point: 360°C) is a strong alkali; a 1% aqueous solution of KOH possesses the same alkaline pH as a 0.77% aqueous solution of NaOH. The relatively innocuous taste of strong alkali allows ingestion of greater volume than the sour taste of acidic substances.[7]

Metallic potassium and sodium react vigorously with water to produce heat, hydrogen gas, and hydroxide ions. The heat generated by this reaction is sufficient to ignite the evolved hydrogen gas and cause thermal burns.

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Consequently, storage of elemental potassium requires submersion in mineral oil to reduce the risk of explosion.

EXPOSURE

Production Processes

Mining and manufacturing processes produce potash. Mining involves the removal of potash from an ore consisting of crystalline sodium and potassium chloride in a ratio of 3:2 along with ~5–10% clay impurities. The leading producers of potash include Canada (Saskatchewan), Russia, Belarus, Germany, Jordan, and Israel. The latter two countries use solar evaporation pans in the Dead Sea to produce carnallite (potassium chloride). The former four countries mine potash from potassium-rich salt layers formed by ancient evaporated sea beds. Sedimentary rocks are the potash source for potassium-containing fertilizers; these materials are mixtures of soluble potassium salts and elemental potassium in fertilizers, as displayed in Table 25.1. The main supply of potash occurs in the Northern Hemisphere with Canada, Russia, and Belarus producing >90% of the world's annual production.[2]

Uses

Medical

Potassium chloride is the most common potassium supplement. Other potassium salts include acetate, bicarbonate, citrate, and gluconate. The primary indication for the administration of potassium supplements is the treatment of potassium depletion in patients with inadequate potassium intake. Previous uses of potassium supplements include: 1) a salt substitute for persons on a table salt (sodium chloride)-restricted diet; 2) an aid in restoring muscular strength in some patients with myasthenia gravis in conjunction with anticholinesterase agents; and 3) an ancillary measure in the treatment of thallium poisoning. Potassium iodide is an oral medication for inflammatory dermatoses (e.g., erythema multiforme, erythema nodosum, nodular vasculitis, subacute nodular migratory panniculitis, Sweet's syndrome).[8] The use of potassium nitrate (KNO_3) as a saltpeter for the treatment of priapism resulted in hyperkalemia.[9]

TABLE 25.1. Common and chemical names of potassium-containing potash salts. Although potash technically refers to potassium carbonate, generically potash refers to several potassium salts including potassium oxide and hydroxide. (Based on Ciceri et al.).[2]

Common Name	Alternate Name	Formula	Potassium Salt
Potash fertilizer		K_2O	Oxide
Caustic potash	Potash lye	KOH	Hydroxide
Carbonate of potash	Pearlash, salts of tartar	K_2CO_3	Carbonate
Chlorate of potash		$KClO_3$	Chlorate
Muriate of potash		KCl	Chloride
Nitrate of potash	Saltpeter	KNO_3	Nitrate
Sulfate of potash		K_2SO_4	Sulfate

Industrial

Potassium fertilizers account for the vast majority of potash production (i.e., ~95%). Potassium hydroxide is a substitute for the less expensive sodium hydroxide when the greater solubility of KOH is important for industrial processes. Examples include photoengraving, lithography, electroplating, battery manufacturing, fuel cells, and the manufacture of liquid soaps and detergents. Products containing KOH include drain cleaners and paint/varnish removers. Metallic potassium is a catalyst and heat-transfer medium in the production of sodium–potassium alloys. Potassium nitrate is a constituent of match heads, fireworks, and fertilizers.

Sources

The daily intake of potassium in the US diet is ~50–150 mEq/day with 90% of the daily potassium load excreted by the kidneys.[10] Herbal medications associated with excessive potassium consumption include alfalfa, dandelion, hawthorne (berries), noni juice, and horsetail.

DOSE EFFECT

Salt Substitutes

Salt substitutes contain primarily potassium salts with the potassium content ranging from ~100–500 mg/g supplement. The calculated potassium content (mEq/teaspoon) for salt substitutes includes Morton's Lite Salt, 38; Morton's Salt Substitute, 72; No-Salt, 64; Nu-Salt, 67; and Adolph's Salt Substitute (unseasoned), 65.[11] Consumption of a large amount (26 mEq K^+/kg body weight) of Morton's salt substitute (90% KCl) resulted in a near fatal case of hyperkalemia in an 8-month-old infant.[12] This infant became unresponsive and developed difficulty in breathing. The ECG demonstrated an idioventricular rhythm with bigeminy, absent P waves, and a wide QRS interval.

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Blood chemistries indicated potassium of 10.2 mEq/L, sodium of 149 mEq/L, CO_2 of 22 mEq/L, and creatinine of 0.6 mg/dL. With treatment, the serum potassium decreased to 5.4 mEq/L; the patient survived.

Potassium Supplements

Potassium chloride is available orally in capsules, powders, solutions, tablets, and parenterally for intravenous injection (0.8–3.2 mEq of K^+ and Cl^-/mL). The usual potassium maintenance requirements are 2 mEq K^+/kg/day for infants and 40–80 mEq K^+/day for adults; 40 mEq K^+ is equivalent to ~3.0 g KCl.

The ingestion of 47 slow-release KCl tablets caused the death of a 32-year-old woman (18-hour postmortem ocular fluid potassium concentration, 10.8 mEq/L).[13] A 50-year-old woman developed life-threatening arrhythmias with a peak potassium concentration of 9.7 mEq/L 13 hours after the intentional ingestion of 100 (7.5 g KCl) sustained-release K-Dur® tablets.[14] The inadvertent intravenous administration of undiluted potassium chloride instead of sodium chloride led to several deaths.[15] An intravenous bolus of 60 mg KCl can produce asystole and cardiac arrest.[16] A 2-month-old with colic was given 3 g KCl mixed with breast milk in the evening, followed by 1.5 g KCl in the morning. In a few hours, the child was listless, cyanotic, and apneic. The admission potassium concentration was 10.1 mEq/L; he died 28 hours later.

Intravenous Administration

The intravenous administration of 40 mEq of potassium chloride to a 71-year-old man with multiple medical problems (diabetes, congestive heart failure, anasarca, recent subendocardial myocardial infarction) caused a cardiac arrest within several minutes.[17] Flushing a central line with 26.4 mEq potassium phosphate produced the immediate onset of ventricular fibrillation in an 81-year-old man with atherosclerotic coronary artery disease and chronic renal failure.[17]

TOXICOKINETICS

Potassium chloride is well absorbed orally. The intracellular fluid compartment contains 98% of the body burden of potassium (150–160 mEq/L water). Total body potassium in adults averages 53–55 mEq/kg body weight; this value decreases with age and decreasing muscle mass. The kidney accounts for ~90% of the elimination of an absorbed K^+ dose, primarily by distal renal tubule secretion; however, the distal renal tubule excretes little K^+ in the presence of an *acute* potassium load. Although hyperkalemia is common in acute renal failure, elevated potassium concentrations are unusual in chronic renal failure until the serum creatinine rises above 10 mg creatinine/dL.[16] In addition, an insulin-dependent mechanism may contribute to the elimination of large potassium doses.[18] Renal potassium excretion depends on chloride ion concentration, acid-base status, and adrenal hormone secretion. Healthy patients excrete ~40–50 mEq of potassium daily in the absence of potassium supplements.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Burns

Elemental Potassium

Metallic potassium reacts exothermically with water to form hydrogen gas and potassium hydroxide. This reaction produces thermal and chemical burns including heat from the reaction and flames ignited by the release of hydrogen gas as well as the potential for explosions.

Potassium Hydroxide

KOH is a severe corrosive similar to sodium hydroxide; concentrated aqueous solutions of both substances are highly alkaline exceeding pH 13. Alkalis are proton acceptors that remove hydrogen ions from protonated amines and carboxylic groups. Strong alkali substances solubilize fat (saponification) and proteins. Once solubilized, the alkaline proteinates produce hydroxyl ions and chemical reactions (liquefaction necrosis), resulting in rapid tissue destruction and deep penetrating lesions as the KOH destroys the natural barrier of the lipid layer to water. Saponification is an exothermic reaction that produces heat and enhances tissue destruction. The amount of tissue damage depends on pH, amount ingested, physical state, and duration of exposure.

Fatal ingestions of potassium hydroxide involve burns of the upper respiratory tract, esophagus, and stomach along with hemorrhage and perforation. A 30-year-old woman died soon after ingesting a potassium hydroxide-containing drain cleaner.[19] Postmortem examination demonstrated circumoral/oropharyngeal burns, necrotic hemorrhage and edema of the tracheal and main bronchial mucosa, extensive mucosal burns of the esophagus with perforation of the cardioesophageal junction, and 100 mL clotted hemorrhage in the right pleural cavity. The greater curvature of the stomach was almost completely dissolved resulting in 600 mL of hemorrhagic material in the peritoneal cavity.

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Electrolyte Imbalance

Hyperkalemia

Normal transmembrane voltage gradients and physiological function require large, stable intracellular potassium (K^+) concentrations compared with extracellular K^+ concentrations. The subsequent voltage gradients establish action potentials that allow the conduction of impulses in cardiac, skeletal/smooth muscle, and nerve cells. Like magnesium toxicity, hyperkalemia often results from reduced renal excretion in association with increased potassium loads. Aldosterone antagonist drugs may contribute to toxicity, particularly in chronic renal failure patients with low glomerular filtration rates (<15–20 mL/minute) and metabolic acidosis. Patients with normal renal function rarely develop hyperkalemia unless the poisoning is associated with severe rhabdomyolysis. Digitalis toxicity produces hyperkalemia as a result of the inhibition of Na^+/K^+ ATPase activity that normally allows potassium efflux from cells. Other mechanisms of hyperkalemia include activation of K^+ channels (e.g., fluoride toxicity) and disruption of intermediary metabolism (e.g., cyanide poisoning).

The toxic effects of hyperkalemia result from interference with normal excitation of skeletal and cardiac muscle. The Purkinje fibers are the most sensitive cardiac cells to the effects of hyperkalemia; the sinoatrial and atrioventricular nodes are more resistant. Consequently, delayed intraventricular conduction occurs before a loss of atrial conduction. Fatal potassium injections are not associated with any specific macroscopic or histological changes. A study of two fetuses terminated with KCl injections for serious medical reasons demonstrated whitish deposits on tissues and lanceolate crystals on histological examination of internal organs.[20] Two other fetuses terminated with other drugs did not demonstrate similar changes.

Hypokalemia

At least two hormonal signals maintain the normal, relatively high intracellular potassium concentration by promoting intracellular diffusion of this cation. Insulin, β-adrenergic catecholamines, and thyroid hormone reduce extracellular potassium by enhancing cell-membrane Na^+/K^+ ATPase and potassium uptake. For insulin and thyroid hormone, a negative feedback loop maintains potassium homeostasis, whereas β-agonists decrease serum potassium concentrations independent of potassium body stores. Aldosterone is the other major regulator of potassium stores by enhancing the renal elimination of potassium. Consequently, hyperinsulinemia, hyperaldosteronemia, and β-agonist ingestion are associated with hypokalemia. Other mechanisms of action include competitive blockage of the K^+ channels (chloroquine, barium), alkalosis, gastrointestinal potassium loss, increased urinary potassium excretion, and inadequate dietary potassium uptake. In contrast to hyperkalemia, hypokalemia can persist despite normal regulatory systems and renal function.[21] Hypokalemia usually results from potassium depletion secondary to abnormal potassium losses, particularly during the induction of metabolic alkalosis and excessive chloride losses from vomiting or nasogastric drainage.

The most common cause of hypokalemia is drug-induced potassium depletion, particularly diuretics. A wide range of drugs and disorders reduce serum potassium concentrations including β_2 sympathomimetic agents, xanthines, calcium-channel blockers, diuretics, mineralocorticoid/glucocorticoid agents, some antibiotics, emetics/laxatives, barium salt ingestion, hyperthyroidism, hyperinsulinemia, hypomagnesemia, and a variety of diseases (familial hypokalemic periodic paralysis, infectious diarrhea, malabsorption, Zollinger–Ellison syndrome, primary hyperaldosteronism, leukemia, type I distal renal tubular acidosis). Table 25.2 lists drugs associated with hypokalemia separated by mechanism of action. Although hydrocortisone and prednisone do not directly affect potassium secretion, the chronic administration of these drugs slightly reduces serum potassium indirectly by increasing glomerular filtration and distal sodium delivery rates.

CLINICAL RESPONSE

Burns

Dermal contact with elemental potassium exposes the skin to thermal and chemical burns. A 16-year-old boy sustained burns to his hands, groin, and thigh when he clandestinely placed elemental potassium in his pants pocket and the potassium subsequently exploded.[22] His pants caught fire; he underwent three showers clothed. One hour later in the emergency department, he had first and second-degree burns and an initial pH of 8–9 in the lavage fluid by litmus paper. He subsequently developed deep second- and three-degree burns that required split-thickness grafting (13 by 20 cm). Potassium hydroxide ingestion produces alkali burns of the esophagus and stomach similar to sodium hydroxide. Symptoms and signs of alkali ingestion are not reliable indicators of the severity of the ingestion. Grade 3 injuries typically result in esophageal scarring and gastric cicatrizations (pyloric/antral stenosis, gastric deformities, shortening/irregularity of the lesser curvature).[23]

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TABLE 25.2. Drug-induced hypokalemia and associated mechanisms of action.

Class	Drug Type	Drug
	Intracellular K^+ Shift via Cell-Membrane Na^+/K^+ ATPase	
β_2-Adrenergic agonists	Epinephrine	
	Decongestant	Phenylpropanolamine, pseudoephedrine
	Bronchodilators	Albuterol, ephedrine, fenoterol, isoetharine, isoproterenol, metaproterenol, pirbuterol, terbutaline
	Tocolytic agent	Ritodrine, terbutaline
	Xanthines	Caffeine, theophylline
	Overdose	Barium salts,[a] chloroquine, insulin, verapamil
	Increased Renal K^+ Loss	
Diuretics		Acetazolamide, bumetanide, chlorthalidone, ethacrynic acid, furosemide, indapamide, metolazone, thiazides, torsemide
High-dose penicillins	Ampicillin, carbenicillin, nafcillin, penicillin	
High-dose glucocorticoids		
Magnesium depletion	Aminoglycosides, amphotericin B, cisplatin, foscarnet	
	Increased Fecal K^+ Loss	
Laxatives	Phenolphthalein	
Resin exchange	Sodium polystyrene sulfonate	

[a] Barium blocks passive potassium efflux rather than increasing efflux through the sodium–potassium pump.

Electrolyte Imbalance

Hyperkalemia

Hyperkalemia is an uncommon complication of poisoning, except in the presence of renal failure or severe rhabdomyolysis.[24] The clinical picture following a potassium overdose depends on a number of variables including the degree of serum potassium elevation, the chronicity of elevated concentrations, and the presence of underlying cardiovascular and/or renal disease. Hyperkalemia affects many organ systems (cardiac, neuromuscular) and acid–base status producing a wide spectrum of clinical features as outlined in Table 25.3. The most serious manifestation of potassium toxicity is the development of acute cardiovascular changes (bradycardia, slowed conduction, hypotension, ventricular fibrillation, asystole, death).[25] Neuromuscular symptoms include weakness, paresthesias, hyporeflexia, and ascending paralysis. Sensory and cognitive functions usually remain intact until the cardiovascular effects of hyperkalemia reduce brain perfusion. Serious cardiac abnormalities may develop without prominent early symptoms of systemic toxicity. The ingestion of slow-release preparations may delay the onset of serious cardiac effects up to 6–12 hours after ingestion.[26,27] Small-bowel ulcerations may result from the use of enteric-coated potassium chloride tablets.[28] Local pain and inflammation may occur after the intravenous administration of potassium chloride.

TABLE 25.3. Clinical features of hyperkalemia. The clinical presentation depends on the serum potassium concentration, the rate of rise of the potassium concentration, and the presence of underlying disease (cardiovascular, renal). (Based on Saxena).[16]

Organ System	Effect
Cardiovascular	Syncope, cardiac dysrhythmias, hypotension, cardiac arrest/asystole
Endocrine/ Metabolic	Weakness, metabolic acidosis, hypoaldosteronemia
Gastrointestinal	Nausea, vomiting, abdominal pain, ileus, ulceration, bowel perforation
Neuromuscular	Dysarthria, dysphagia, dysphonia, weakness, ascending paralysis, flaccidity
Renal	Oliguria, uremia

Hypokalemia

Mild hypokalemia is usually asymptomatic. Nonspecific symptoms, ileus, and generalized muscle weakness develop from hypokalemia of <2.5–3.0 mEq/L.[29] Cardiac changes include ventricular dysrhythmias (tachycardia, fibrillation), atrial tachycardia, AV disassociation, and electrocardiographic alterations (flat T waves, ST segment depression, prominent U waves).

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Occupational Exposure

Although potash is an irritant that causes nasal perforation at airborne concentrations of >2,000 mg/m^3,[30] mortality studies of potash miners have not revealed increased mortality from chronic pulmonary disease.[31] Symptoms of chronic bronchitis (cough, sputum production, breathlessness) are more prevalent in potash workers that are exposed to ambient air concentrations exceeding current standards; however, statistically significant differences in pulmonary function have not been detected in these workers when compared with controls or workers exposed to lower potash concentrations in ambient air.[32]

DIAGNOSTIC TESTING

SI Conversion Units

1 mEq = 1 mmol

Biomarkers

General Population

The normal range of serum potassium is ~3.5–5.3 mEq/L when analyzed by clinical laboratories with spectrophotometry; total body potassium stores are ~50 mEq/kg. Daily fluctuations of potassium concentrations in healthy adults range up to 1.3 mEq K^+/L.[33] Vigorous exercise may increase the potassium concentrations up to 6.5 mEq K^+/L in healthy adults; however, the potassium concentration soon normalizes after exercise ceases.

Hyperkalemia

In general, mild acute hyperkalemia ranges from 5.5–6.5 mEq K^+/L with ECG changes usually absent. Moderate hyperkalemia varies from 6.5–7.5 mEq K^+/L with minor ECG changes. Severe hyperkalemia occurs at potassium concentrations of >7.5–8.0 mEq K^+/L, typically in association with significant ECG changes. Between 9 and 10 mEq K^+/L, the QRS widens significantly to join the T wave and forms a sine wave that deteriorates into ventricular fibrillation and asystole. The K^+ concentration alone does not determine the severity of the body's response to hyperkalemia, particularly following a slow rate of rise. Some accommodation to hyperkalemia occurs in end-stage renal hemodialysis patients chronically exposed to high potassium concentrations, resulting in significant attenuation of the electrocardiographic changes compared with acute hyperkalemia at similar K^+ concentrations.[34]

The primary causes of hyperkalemia include: 1) factitious elevation; 2) transmembrane shifts that increase K^+ release; and 3) reduced K^+ excretion. Factitious elevation of serum potassium may result from laboratory error, hemolysis during collection or storage, leukocytosis, or thrombocytosis. Hence, laboratory tests indicating hyperkalemia should be repeated to confirm elevated potassium concentrations. The transmembrane shift of potassium from intracellular to extracellular sites results from alterations in acid-base status or dysfunction of the Na-K-ATPase pump. Examples include acidosis or acute intoxications (digitalis, α-adrenergic, β-blocker, fluoride). In these situations, the total body potassium stores remain stable while the serum potassium increases. Reduced potassium excretion results from renal failure, Addison's disease (↓ aldosterone), medications (angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, spironolactone, succinylcholine), renal tubular disease, and impairment of distal renal tubule responsiveness to aldosterone.[35] Neuromuscular effects depend on the ratio of intracellular and extracellular potassium. Consequently, neuromuscular effects do not always closely parallel the serum potassium concentration.

The appearance of hyponatremia, hypermagnesemia, hypocalcemia, and metabolic acidosis enhances the risk of potassium toxicity at a given potassium concentration. For every 0.1 decrease in the blood pH, the plasma potassium concentration increases by ~0.6 mEq K^+/L.[36] Factitious hyperkalemia may result from the release of intracellular potassium stores (e.g., hemolyzed blood samples, prolonged tourniquet time, thrombocytosis). The serum potassium concentration is directly proportional to the platelet count; therefore, pseudo-hyperkalemia occurs commonly when the platelet count exceeds 10^{12} platelets/L. In this situation, the plasma potassium is a more accurate reflection of potassium homeostasis than the serum potassium concentration.[37]

Hypokalemia

Patients typically have no symptoms when the reduction in potassium is mild (3.0–3.5 mEq/L); however, the appearance of symptoms correlates to how quickly the serum potassium declines. Nonspecific symptoms may occur at potassium concentrations below 3.0 mEq/L including weakness, lethargy, and constipation. More serious complications occur at concentrations of <2.5 mEq/L (muscle necrosis) and <2.0 mEq/L (ascending paralysis, respiratory insufficiency). Although

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dysrhythmias are uncommon in patients without cardiovascular disease, even when the serum potassium declines below 3.0 mEq/L, the likelihood of dysrhythmias increases in patients with cardiac disease (left ventricular hypertrophy, failure, ischemia) and mild/moderate hyperkalemia.

Postmortem

Blood

The potassium concentrations increase erratically in postmortem blood; therefore, elevated potassium concentrations in postmortem samples of blood or clear plasma do not necessarily indicate potassium poisoning. Furthermore, venous injection of potassium may not produce elevated potassium concentrations in postmortem blood samples.[38] The potassium concentrations in a 30-year-old suicide victim found with a potassium-containing syringe in her arm were 54 mEq/L in clear plasma from her blood and 9.2 mEq/L in vitreous humor.[39] In a 41-year-old ICU nurse found dead following an intravenous KCl injection, the cardiac and femoral postmortem blood potassium concentrations were 160.0 mEq/L and 87.3 mEq/L, respectively.[40] The median potassium concentration in postmortem femoral blood samples in 55 cases from the same institution was 35.3 mEq/L (range, 27.2–50.1 mEq/L). None of these cases involved drug overdoses.

Vitreous

Postmortem changes in the potassium concentration are more consistent in samples from the vitreous humor than blood. A variety of charts[41] and equations are published to estimate the postmortem interval (PMI) based on the vitreous humor K^+ concentration including PMI (hours) = $(4.32 \times K^+$ [μmol/L] − 18.35)[42] or = $(2.749 \times [K^+] - 11.978)$.[43] However, these equations are rough estimations of the postmortem interval with wide confidence intervals (i.e., 95% CI: 4–20 hours) depending on a variety of factors.[44] The relationship between these variables is not always linear,[45] depending on sampling methods, analytical techniques, ambient temperatures, electrolyte and fluid balance prior to death, age, length of the postmortem interval, and nitrogen retention.[46,47,48] In studies of postmortem vitreous humor samples up to 4 days after death, the potassium concentration increased rapidly, whereas the urea nitrogen concentration remained relatively stable.[49] Because of the substantial, sometimes unpredictable changes in these variables for most postmortem cases, the vitreous humor potassium concentration must be interpreted cautiously along with other factors (rigor, livor, body temperature).[50] Calculations of the postmortem interval using the vitreous potassium concentration are most accurate in adults when ambient temperature after death was <50°F, the postmortem interval was relatively short (i.e., <24–48 hours), and electrolyte concentrations were relatively normal prior to death (e.g., traumatic death in a healthy individual).[46] Other studies suggest the postmortem interval calculation is more reliable when the interval exceeds 24 hours.[51] Good sampling technique (i.e., careful withdrawal of all vitreous humor fluid without surrounding tissue) also improves the accuracy of these calculations.

Abnormalities

The sequential electrocardiographic manifestations of hyperkalemia include tall, peaked T waves, depressed S-T segments, low - amplitude R waves, P-R interval prolongation, decreased P waves, widened QRS complexes, Q-T prolongation, a sine wave appearance, and asystole. Depression of intraatrial conductions occurs when the serum potassium concentration exceeds 7 mEq/L (Figure 25.1); peaked T waves reflect resting membrane potential changes and early excitatory reaction, primarily in the precordial leads.[52] The P waves disappear as the serum potassium concentration exceeds 8.5 mEq/L (Figure 25.2). The QRS complex gradually widens with the T wave and QRS complex blending together in the range of 9–11 mEq/L to form a sinusoidal wave pattern (Figure 25.3).[52] Several factors modify the electrocardiographic response to hyperkalemia including blood pH, osmolality, and a variety of serum substances (calcium, catecholamines, insulin, sodium). Alkalemia, hypercalcemia, and hypernatremia attenuate the electrographic response to hyperkalemia. Consequently, the ECG alone is not a sensitive marker of hyperkalemia.[53] Additionally, ECG changes more commonly occur with a rapid rise in the K^+ concentration.[54] Sustained-release potassium tablets are radiopaque, but the presence of potassium capsules on x-ray examination does not necessarily indicate the presence of intact potassium capsules.

HEALTH SURVEILLANCE

The US OSHA PEL–TWA for KOH was 2 mg/m^3; the 1992 11th Circuit Court of Appeals decision in AFL-CIO vs. OSHA vacated more protective PELs set by OSHA in 1989 for 212 substances including potassium hydroxide. The NIOSH REL–TWA is 2 mg/m^3. The ACGIH recommends a TLV-Ceiling of 2 mg/m^3 to minimize the risk of eye, skin, and respiratory tract irritation.[55]

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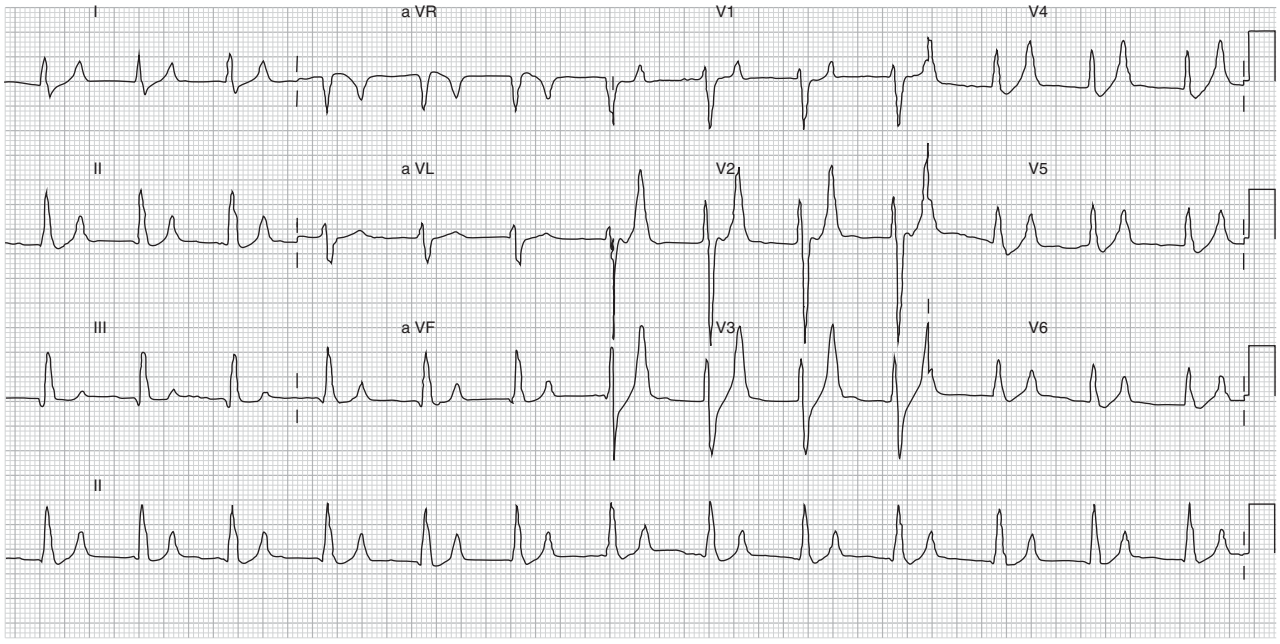


FIGURE 25.1. Early electrocardiographic changes demonstrating peaked T waves and flattening of P waves as serum potassium concentration reaches 7.0 mEq/L. (Modified from Cadogan).[52]

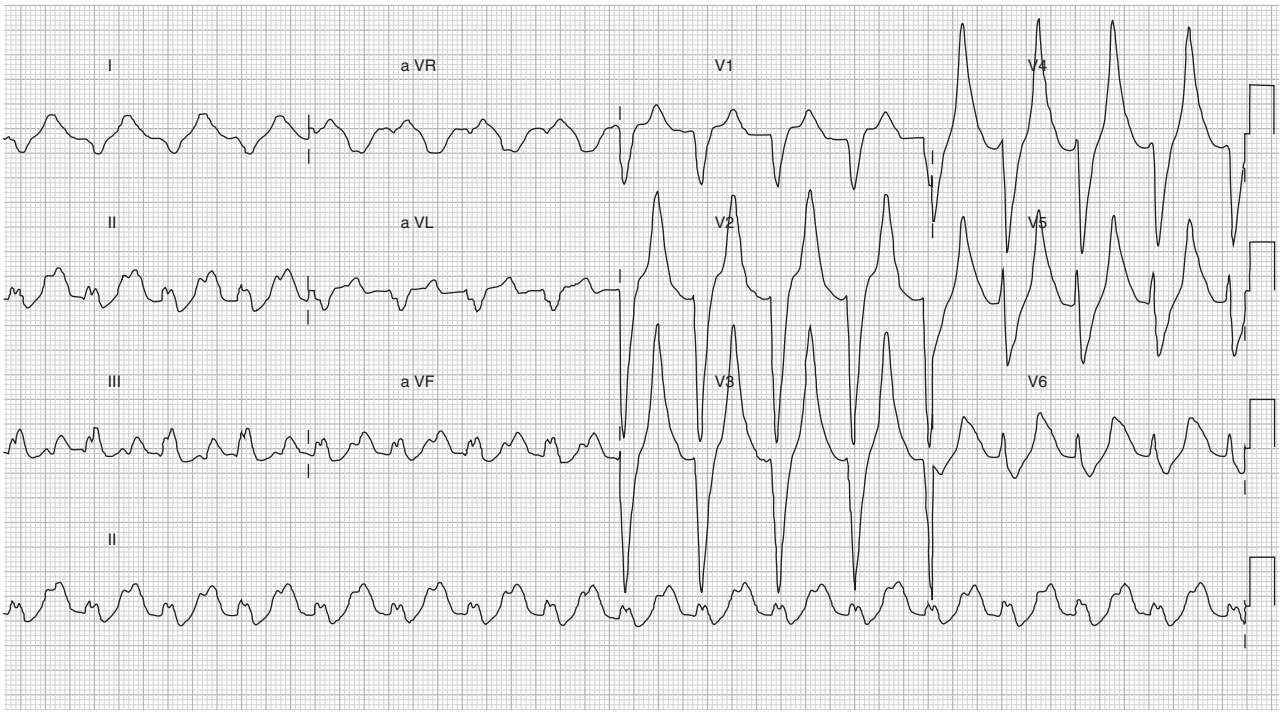


FIGURE 25.2. QRS widening and P wave loss as serum potassium concentration approaches 8.5 mEq/L. (Modified from Cadogan).[52]

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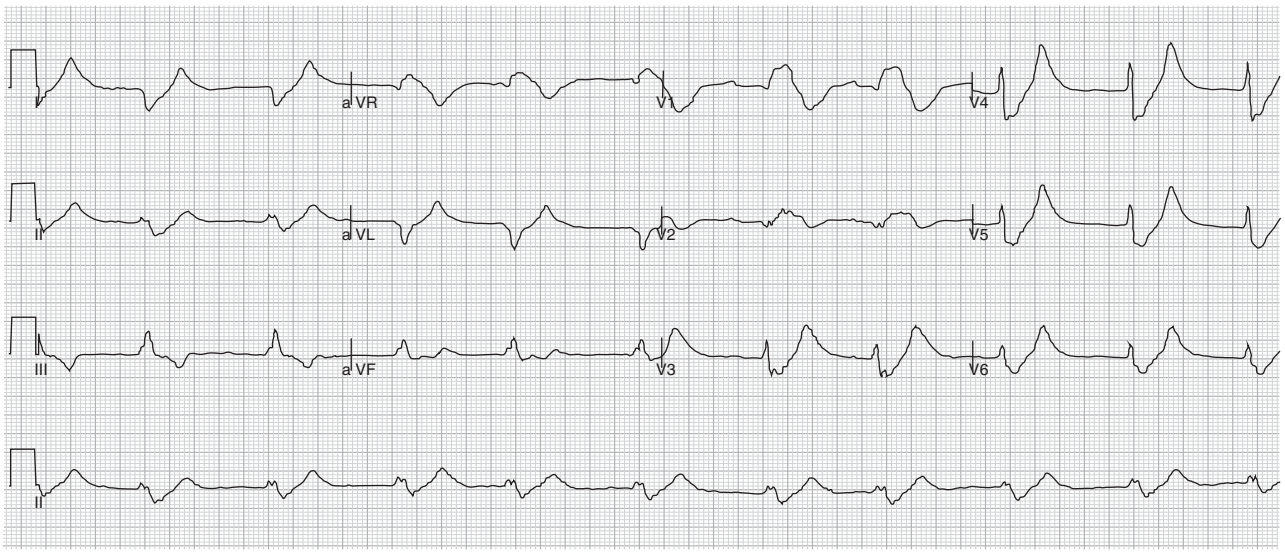


FIGURE 25.3. Continued QRS widening as rhythm becomes more sinusoidal when the serum potassium concentration exceeds 9.0 mEq/L. (Modified from Cadogan).[52]

TREATMENT

Initial Stabilization

Elemental Potassium

Water is contraindicated in the initial treatment of injuries secondary to *metallic* potassium. The wounds should be covered with oil until the removal of all unreacted metal.[22] At the scene of the injury, clothing should be removed rapidly, and obvious metal particles should be extracted from the wound. In the Emergency Department, the remaining metal fragments should be debrided, and then the wound may be irrigated with water similar to other alkali burns. The extracted metallic potassium particles should be placed in tertbutyl alcohol.

Potassium Hydroxide

Contaminated clothes should be immediately removed; all particulate debris must be removed from the skin including brushing off any remaining dry chemical. The burn area should be promptly irrigated copiously with tap water or saline for 20–30 minutes.[56] The extent of an alkaline burn is frequently deeper than initial inspection suggests. Similarly, exposure of the eye to KOH also benefits from prompt irrigation of the eye with copious amounts of water or physiological saline, if available.[57]

There is no consensus on the duration of irrigation in the emergency department with some authorities recommending 1–2 hours of continuous irrigation depending on the pH of the substance and decline in the pH of the irrigation solution.[58] Alkali burns to the eye require ophthalmological consultation. Skin burns also require consultation in the emergency department depending on the extent of the burn and potential need for skin grafting.

Gut Decontamination

Gastric aspiration/lavage is an option when the stomach contains potassium capsules or the patient presents within 1 hour of ingesting potassium capsules depending on physician judgment. There are no data to indicate whether or not activated charcoal adsorbs potassium salts; however, most metals are not well absorbed by activated charcoal. The efficiency of decontamination measures should be confirmed with abdominal x-ray. A whole bowel lavage is an option for patients ingesting sustained-release potassium preparations, particularly if numerous capsules remain on the abdominal x-ray or pass into the duodenum.[59]

Hyperkalemia

Mild hyperkalemia (i.e., <6.5 mEq/L) usually responds to dietary restriction, cessation of potassium supplements, and increased intake of dietary sodium. Potassium concentrations exceeding 6.7 mEq/L indicate the need for emergent therapy. The presence of heart block, wide QRS, or ventricular dysrhythmias or serum potassium concentrations exceeding 7.5 mEq/L indicate a medical emergency requiring an intravenous line,

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drug therapy, and constant cardiac monitoring.[16] Drug therapy for hyperkalemia includes: 1) membrane stabilization to reverse cardiovascular and neuromuscular effects (calcium gluconate); 2) redistribution of serum potassium from extracellular to intracellular spaces (β-agonists, intravenous insulin, glucose as necessary) as a temporizing measure until hemodialysis; and 3) enhancement of potassium elimination (hemodialysis, loop diuretics unless the patient is hypovolemic or unable to produce urine).[60] Serious dysrhythmias may occur suddenly, despite moderate serum potassium elevations. Patients with suspected hyperkalemia should receive an electrocardiogram, serum creatinine/BUN, and serum electrolytes including calcium and magnesium concentrations.

Cardiac Membrane Stabilization

Calcium improves the transmembrane voltage gradient transiently rather than reducing the K^+ concentration; therefore, concomitant administration of other drugs is necessary to prevent clinical deterioration. The intravenous injection of 10 mL of 10% calcium gluconate in adults over 2–5 minutes antagonizes the cardiac and neuromuscular effects of hyperkalemia. This antagonistic effect occurs soon after administration. The onset of action for intravenous calcium is <5 minutes, whereas the duration of action is ~20–60 minutes.[61] Calcium salts do not increase potassium excretion from the body. The dose may be repeated in 10 minutes if needed because of an inadequate response. Calcium gluconate may be administered in a peripheral vein, whereas the use of calcium chloride usually requires a central catheter because of its irritant properties unless the patient develops a cardiac arrest. The amount of calcium is ~3 times higher in calcium chloride (13.6 mEq/10 mL) compared with calcium gluconate (4.6 mEq/10 mL). Although routinely used, the efficacy of intravenous calcium in severe hyperkalemia has not been validated in randomized clinical trials.[62]

Calcium is not traditionally recommended in patients with hyperkalemia secondary to digoxin intoxication because of concern about the induction of serious ventricular dysrhythmias; however, calcium use in this situation is controversial. A retrospective chart review of calcium use in 23 digoxin-toxic patients (mean peak potassium = 5.99 ± 0.988 mEq/L) reported no life-threatening dysrhythmias within 1 hour of intravenous calcium administration.[63] Mortality in these digoxin-toxic patients was similar for those treated with intravenous calcium (5/23, 22%) and the group not receiving intravenous calcium (27/136, 20%). The mean peak potassium concentration in the latter group was 5.30 ± 0.959 mEq/L. Hypertonic saline (3%) is usually limited to symptomatic hyperkalemic patients with hyponatremia.

Potassium Redistribution

Glucose/Insulin

Insulin alone can lower serum K^+ concentrations in a dose-dependent manner through activation of the Na^+-K^+-ATPase pump and GLUT4 receptors, resulting in increased intracellular K^+ uptake and extracellular sodium excretion. Traditionally, 25 g of glucose (1 ampule of 50 mL of $D_{50}W$) is administered with 10–20 units of regular insulin over 5 minutes in adults with serum glucose 100–200 mg/dL. Insulin with glucose increases the intracellular transport of potassium rather than increasing potassium excretion. A reduction of the serum potassium by ~0.6–1.2 mEq K^+/L occurs within 30–60 minutes and lasts ~2 hours.[64] The onset of action is <15 minutes with peak effects at 25–30 minutes.[60] Hypoglycemia is a potential adverse effect of this therapy during the first 1–3 hours after regular insulin administration. If the initial serum glucose is <100 mg/dL, the patient should receive 50 g D_{50} (100 mL) initially and the serum glucose should be monitored every 30 minutes during the first hour, then hourly for 3 hours. Serum glucose of <70 mg/dL indicates the need for supplemental dextrose as displayed in Table 25.4. The use of intravenous glucose is not necessary for patients with existing hyperglycemia (serum glucose >200 mg/dL).[65] The kidney metabolizes insulin; consequently, hypoglycemia may occur in patients with renal dysfunction or trauma from the prolonged duration of action for insulin.[66] Short-acting synthetic insulin (e.g., aspart, lispro) with shorter half-lives and more rapid absorption than regular insulin are potential alternatives in hyperkalemic patients with renal insufficiency;[67] however, clinical experience in these patients is limited.

β-agonists

Catecholamines (e.g., albuterol, salbutamol) increase potassium redistribution by enhanced Na^+-K^+-ATPase pump and Na-K-2Cl cotransporter activity. Albuterol (Ventolin®, Proventil®) is an adrenergic agonist that increases plasma insulin concentrations and enhances the intracellular shift of potassium in adult doses of 10–20 mg via nebulization (4 mL normal saline over 10 minutes) or metered-dose inhaler. The albuterol dose is higher for the treatment of hyperkalemia than for chronic obstructive airway disease. The onset of action is ~30 minutes, peak action occurs at 2 hours after administration, and the duration of action lasts ~2–6 hours.[68]

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TABLE 25.4. Dextrose administration based on initial serum glucose concentrations during treatment of hyperkalemia with regular insulin. (Adapted from Long et al.).[60]

Glucose Concentration (mg/dL)	Initial Dextrose	Supplemental Dextrose	Glucose Monitoring
>200	None	25 g $D_{50}W$ if serum glucose <70 mg/dL	Hourly × 3 hours
100–200	25 g $D_{50}W$ (50 mL)	25 g $D_{50}W$ if serum glucose <70 mg/dL	Hourly × 3 hours
<100	50 g $D_{50}W$ (100 mL) or 25 g $D_{50}W$ (50 mL) in $D_{10}W$ infused at 250 mL/hr for 1 hour	25 g $D_{50}W$ if serum glucose <70 mg/dL	Every 30 minutes first hour, then hourly for 3 hours

Declines in serum potassium range from 0.4–1.2 mEq/L at 1 hour based on small studies in chronic hemodialysis patients.[69,70] The R-enantiomer (levalbuterol, 2.5 mg) and racemic albuterol (albuterol, 10 mg) administered via nebulization over 30 minutes are equipotent in reducing potassium concentrations.[71] The initial onset of action was more rapid for levalbuterol than albuterol with slightly fewer adverse effects (i.e., tachycardia, tremor, nervousness); however, the K^+ reductions in potassium concentrations were similar at 30 and 60 minutes after the nebulization treatment ended. The combination of insulin/glucose and β-agonists produces synergistic reduction in potassium concentrations.[68,72]

Sodium Bicarbonate

Bicarbonate boluses alone do not reliably reduce serum potassium concentrations within 1 hour of administration in patients with end-stage renal disease on dialysis.[72] Although sodium bicarbonate currently is not recommended for acute management of hyperkalemic patients with normal pH, hyperkalemic patients with metabolic acidosis and intact kidney function may benefit from bicarbonate use acutely.[73] In these adults, the intravenous injection of 50 mEq of bicarbonate may increase intracellular potassium movement via the sodium–hydrogen exchange system and Na^+-K^+-ATPase pump activity; however, the effect on potassium concentrations is substantially less than that of insulin or β-agonists. Cardiac and renal dysfunction limits bicarbonate use because of high sodium and fluid loads.

Enhancement of Potassium Elimination

The kidneys are the primary route of potassium excretion with euvolemia, and adequate urine output is important to maintaining satisfactory urinary potassium elimination. Hemodialysis is the most effective method to remove serum potassium. A diuresis is an initial option while awaiting hemodialysis, particularly in patient able to produce urine. Chronic anuric renal failure patients are unlikely to benefit from diuretics. Hypovolemic patients require intravenous fluids to increase potassium excretion. Loop diuretics (e.g., furosemide) are the diuretics of choice with an onset of action of ~1 hour. Other diuretics (e.g., thiazides) provide synergistic effects; however, fluid and electrolyte balance must be followed closely. Cardiac arrest secondary to hyperkalemia necessitates emergency hemodialysis with advanced cardiac life support and intravenous medications (10 mL calcium chloride 10%, epinephrine 1 mg every 3–5 minutes, short-acting insulin 10 units with 25 g dextrose) to emergently reduce serum potassium concentrations. Blood gases should be drawn early in the clinical course to determine the need for sodium bicarbonate. Medications can be administered via the hemodialysis access site if no other vascular access is available.[74]

Hemodialysis

Hemodialysis effectively removes potassium with serum K^+ concentrations declining to 1 mEq/L in the first hour and 2 mEq/L within 2–3 hours depending on blood flow rates and K^+ dialysate concentration. The release of K^+ from intracellular stores may produce a significant rebound in serum K^+ concentrations. Patients with severe renal dysfunction and moderate-to-severe hyperkalemia usually require immediate hemodialysis. Arrangements for dialysis should be initiated as soon as possible. The early use of hemodialysis is particularly useful when rapid reduction of the total body burden of potassium is necessary, particularly in patients with renal failure, poor response to other therapy, massive tissue destruction (e.g., severe rhabdomyolysis), and acute oliguric renal dysfunction (daily urine output of <400 mL).[75] Hemodialysis may be necessary for patients with persistent hyperkalemia and cardiac instability, even in the presence of normal renal function.[76]

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Cation-Exchange Resin

An oral cation-exchange resin (sodium polystyrene sulfonate, Kayexalate®, Sanofi-Aventis US, Bridgewater, NJ) exchanges cations (K^+, Mg^{2+}, Ca^{2+}, ammonium) for sodium with elimination through the feces in the distal colon and lower gastrointestinal tract. The Kayexalate® resin swells with water contact; therefore, sorbitol is usually administered with the resin to prevent constipation and/or obstruction. Although uncontrolled studies with little statistical analysis from the early 1960s suggest this resin reduces potassium concentrations over 1–2 days,[77,78] no controlled human or animal experiments confirm the efficacy of this treatment for acute hyperkalemia. Potential adverse effects include constipation, gastrointestinal obstruction, colonic necrosis, and fluid overload in patients with cardiac and renal dysfunction. Because of the lack of proven efficacy within the first several hours of administration and serious potential adverse effects, Kayexalate® is not recommended for the treatment of moderate to severe acute hyperkalemia.[79]

The typical oral dose is 20–50 g Kayexalate® dissolved in 100–200 mL of 20% Sorbitol. The dose is repeated every 4 hours up to 4–5 daily doses until the potassium concentrations normalize. Rectal administration involves the suspension of 8 g of Kayexalate® and 50 g of Sorbitol in 200 mL of water; the solution is administered as a retention enema. Serum electrolytes should be monitored every 2–4 hours during therapy.

Experimental Drugs

Patiromer and sodium cyclosilicate (ZS-9) are novel cation exchangers that are potentially useful cation exchangers with less adverse effects and better efficacy than sodium polystyrene sulfonate; however, these drugs require further clinical testing to determine their exact role in treating hyperkalemia. The former is a synthetic polymer using nonabsorbable spherical beads to enhance fecal potassium excretion by exchanging distal colonic calcium for K^+. The polymer does not swell or require the use of sorbitol. The onset of action is 7–48 hours and the duration of action is 12–24 hours with a resulting ~1 mEq/L reduction in serum potassium concentration.[60] Potential adverse effects include hypomagnesemia, hypercalcemia, and increased oral drug interactions during the first 6 hours.[80,81] An open-label, randomized pilot study of 30 adult patients with end-stage renal disease and serum potassium concentrations exceeding 6.0 mEq/L were divided into 15 patients with standard care only (insulin, albuterol) and 15 patients with standard care plus a single dose of 25.2 g oral patiromer.[82] The serum potassium concentrations were lower in the patiromer group at 2 hours (mean = 5.90 mEq/L, 95% CI: 5.63–6.7 mEq/L, $P = 0.009$) than the standard of care only group (mean = 6.51 mEq/L, 95% CI: 6.25–6.78 mEq/L). The difference between the two groups was not statistically significant at 1 hour ($P = 0.075$), 4 hours ($P = 0.329$), or 6 hours ($P = 0.115$) after the initiation of treatment. No power analysis was performed *a priori* because of the small sample size.

ZS-9 is a nonabsorbable, non-polymer, selective cation exchanger that excretes K^+ throughout the gastrointestinal tract by exchanging sodium and hydrogen for potassium. The onset of action is 1–6 hours with a duration of action lasting 4–12 hours. Subgroup analysis of the HARMONIZE randomized clinical trial suggests ZS-9 may significantly reduce serum potassium

TABLE 25.5. High-potassium foods. (Adapted from Gennari).[29]

Potassium Content (K^+/g Food)	Food Class	Food
Highest (>10 mg/g)		Dried figs, molasses, seaweed
Very high (>5 mg/g)	Avocados	
	Bran cereals	
	Dried fruits	Dates, prunes
	Lima beans	
	Nuts	
	Wheat germ	
High (>2.5 mg/g)	Fruits	Bananas, cantaloupe, kiwis, mangos, oranges
	Meats	Ground beef, lamb, pork, steak, veal
	Vegetables	Beets, broccoli, carrots, cauliflower, potatoes, spinach, tomatoes, winter squash

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acutely.[83] A group of 45 patients with a mean baseline serum potassium of 6.3 mEq/L (95% CI: 6.2–6.4 mEq/L; range, 6.1–7.2 mEq/L) received 10 g ZS-9 orally.[84] The mean serum K^+ concentration decreased by 0.4 mEq/L (95% CI: 0.2–0.5 mEq/L) at 1 hour after administration, 0.6 mEq/L (95% CI: 0.4–0.8 mEq/L) at 2 hours after administration, and 0.7 mEq/L (95% CI: 0.6–0.9 mEq/L) at 4 hours after administration.

Supportive Care

The safest approach to minimizing adverse effects from dietary potassium is matching potassium intake to individual patient needs. Table 25.5 lists foods with high potassium content.

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Chapter 26

RARE EARTH ELEMENTS

PHYSIOCHEMICAL PROPERTIES

The rare earth elements (REEs) refer to the following Group 3 transitional metals: scandium (Sc, atomic number 21), yttrium (Y, atomic number 39), lanthanum (La, atomic number 57), and the 14 lanthanide elements (atomic numbers 58–71). Light lanthanides beside lanthanum include cerium (Ce), praseodymium (Pr), neodymium (Nd), promethium (Pm), samarium (Sm), and europium (Eu), whereas heavy lanthanides include gadolinium (Gd), terbium (Tb), dysprosium (Dy), holmium (Ho), erbium (Er), thulium (Tm), ytterbium (Yb), and lutetium (Lu). The molecular structure of the lanthanide series is similar with two electrons in the outer shell and eight to nine electrons in the next outer shell. Consequently, the physical and chemical properties of these rare elements are similar. Table 26.1 lists the identifying information and physical properties of rare earth elements.

Most of these very reactive rare earth elements are soft and malleable with a bright silver luster and high melting points; however, some of these elements (e.g., cerium, europium, lanthanum, neodymium, praseodymium) oxidize easily. Tetravalent cerium is a strong oxidant, whereas trivalent cerium is very resistant to oxidation and has an affinity for calcium in many biomolecules. These elements are not naturally part of biological processes in humans or other animals. The 4f-electrons in rare earth nanoparticles have unique magnetic and luminescent properties useful in imaging and detecting abnormal tissues.[2] In an oxygen-lean environment, CeO_2 nanoparticles act as oxygen donors to increase the combustion of hydrocarbons and soot. Lanthanides form alloys with most metals. Yttrium is a dark gray lustrous metal that is insoluble in water; however, some yttrium compounds (e.g., nitrates) are water-soluble. In general, water solubility and ionic stability increase for the heavier rare earth elements. Usually, trivalent nitrate, chloride, and sulfate salts of rare earth elements are water-soluble, whereas carbonates, phosphates, and hydroxides are water-insoluble. Most lanthanides (e.g., La) occur in the stable trivalent state, although some lanthanides exist in the divalent (e.g., Eu, Sm, Yb) and quadrivalent (e.g., Ce, Pr, Tb) states. In physiological solutions, most lanthanides are stable only in the trivalent form with the exception of Ce^{4+} and Eu^{2+}.[3] Trivalent La cations have a high affinity for oxygen door atoms (e.g., phosphate). Lanthanide ions are fluorescent or phosphorescent with emissions covering the visible and near-infrared ranges.

EXPOSURE

Production Processes

Although the concentration of most rare earth elements in the earth's crust is small, some rare earth elements are abundant; cerium, neodymium, and yttrium are more common in the earth's crust than lead or cadmium.[4] Promethium is a fission product rather than a natural element in the earth's crust. Thulium is the rarest lanthanide existing in its natural state. Most rare earth metal-containing ores (e.g., apatite, bastnaesite, euxenite, fergusonite, gadolinite, monazite, samarskite, xenotime) are mixtures of rare earth oxides rather than

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TABLE 26.1. Identifying information and physical properties of rare earth elements. (Adapted from Barbara and Eula).[1]

Element	Atomic Number	CAS RN	Atomic Mass (g/mol)	Melting Point (°C)	Density (g/mL)	Corrosion Resistance (Oxidation)
Cerium	58	7440-45-1	140.12	798	6.16	Corrodes[a]
Dysprosium	66	7429-91-6	162.50	1,410	8.56	Resistant
Erbium	68	7440-52-0	176.26	1,522	9.01	Resistant
Europium	63	7440-53-1	151.96	817	5.24	Corrodes[a]
Gadolinium	64	7440-54-2	157.25	1,313	7.87	Resistant
Holmium	67	7440-60-0	164.93	1740	8.80	Resistant
Lanthanum	57	7439-91-0	138.91	921	6.15	Corrodes[a]
Lutetium	71	7439-94-3	174.97	1,663	9.85	Resistant
Neodymium	60	7440-00-8	144.24	1,016	7.01	Corrodes[a]
Praseodymium	59	7440-10-0	140.91	931	6.77	Corrodes[a]
Promethium	61	7440-12-2	146.92	1,168	7.26	—
Samarium	62	7440-19-9	150.40	1,072	7.54	Moderately resistant
Scandium	21	7440-20-2	44.96	1,541	2.99	—
Terbium	65	7440-27-9	158.93	1,357	8.25	Resistant
Thulium	69	7440-30-4	168.93	1,525	9.32	Resistant
Ytterbium	70	7440-64-4	173.04	824	6.96	Resistant
Yttrium	39	7440-65-5	88.91	1,522	4.47	Resistant

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number.
[a] Flammable.

pure substances. The ores containing relatively high rare earth metal content include bastnaesite (90% rare earth metal oxides) and monazite (>60% rare earth metal oxides).[5] Monazite ore may contain up to 5% thorium oxide that potentially may contribute to the pulmonary effects following the inhalation of rare earth metal dust.

Most production of rare earth elements occurs as a by-product of other mining operations (e.g., iron, lead, zinc); expensive, specialized techniques are necessary to separate individual rare earth elements because of the similar reactivity between lanthanides.

Uses

Lanthanum, cerium, and neodymium are major constituents of carbon arc lamps; heavy exposure to these compounds usually involves printers or photoengravers using these high-intensity light sources.[5] Groups of workers with exposure to rare earth elements include the following industries: arc lamps, chemical, electronic, glass, metallurgical, nuclear, and optical. Table 26.2 outlines the industrial uses of rare earth elements.

Cerium is a component of glass coloring agents, abrasives for glass polishing (mirrors, plate glass, precision optics, electronic wafers, ophthalmic lenses, television tubes), lighter flints, tracer bullets and pyrotechnics, stabilizers (fluorides) in carbon arc lamps and gas-mantle industry, control rods in nuclear reactors, color television tubes, mercury vapor and fluorescent lamps, and mischmetal (alloy of rare earth metals) as a deoxidizer for metallurgic applications (e.g., magnesium and ferrous alloys) and the production of flints for lighters. Nanoscale cerium oxide (CeO_2) is primarily a combustion catalyst used to increase fuel efficiency and reduce diesel soot emissions, potentially resulting in the release of some ultrafine (<100 nm) poorly water-soluble particles following combustion.[6,7] Other applications of these nanoparticles involve a wide variety of uses (biomedical, coatings, electronics, energy additives). Cerium sulfadiazine (2.2% cerium nitrate in 1% flamazine cream) is an antibacterial cream used to treat severe burns.[8] Historical uses of cerium include anticoagulants, antiemetic in pregnancy, and antineoplastic agents.[3] Uses of gadolinium include a neutron absorbent in the nuclear reactor control rods in marine nuclear propulsion systems, a component of the production process for manufacturing gadolinium-yttrium garnets in microwave applications, and a popular contrast agent for magnetic resonance imaging. The latter involves the sequestration of gadolinium to large organic molecules (e.g., aminopolycarboxylic acids) to form stable and biochemically inert complexes (chelates); however, de-chelation releases free Gd^{3+} ions with potential toxicity from interaction with similar-sized Ca^{2+} ions

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TABLE 26.2. Uses for rare earth elements. (Adapted from Hirano and Suzuki).[4]

Element	Symbol	Uses
Cerium	Ce	Lighter flints, catalysts, glass additives (blue fluorescence, clarity, yellow coloration, resistance to UV light), ceramics, magnets, abrasives, tracer bullets, automobile catalysts
Dysprosium	Dy	Magnets, magneto-optical materials
Erbium	Er	Lasers, color glass, metallurgy, nuclear research, porcelain, fiber optic communication cables
Europium	Eu	Fluorescent materials (televisions, fluorescent lamps), imaging plates, nuclear reactor control rods
Gadolinium	Gd	Magnets, glass additives, ferrous and chromium alloys, contrast for magnetic resonance imaging
Holmium	Ho	Electric materials
Lanthanum	La	Superconductors, lighters, automobile catalysts, glass additives, ceramics, batteries, phosphate binder
Lutetium	Lu	Superconductors
Neodymium	Nd	Magnets, lighters, lasers, purple glass additives, magneto-optical material, production of promethium
Praseodymium	Pr	Magnets, lighters, alloys, intense light sources (searchlights, movie projection machines), color glass
Promethium	Pm	Luminescent dials
Samarium	Sm	Lighters, magnets, condensers, nuclear reactor control rods, dopant for lasers, color television phosphors, infrared-absorbing glass
Scandium	Sc	Cathode-ray tubes, lasers, fluorescent material
Terbium	Tb	Fluorescent lamps/televisions, magneto-optical materials, laser and solid-state dopant
Thulium	Tm	Fluorescent materials, lasers, portable radiation units
Ytterbium	Yb	Condensers, x-ray sources for portable irradiation devices, lasers, alloys
Yttrium	Y	Superconductors, fluorescent material, catalysts, ceramics, nuclear technology, ferrous, magnesium and aluminum alloys, coatings of high-temperature metals, metal deoxidizers, television screen phosphors (oxides), yttrium-aluminum-garnet (YAG) lasers

in calcium-dependent enzymes, particularly nonionic linear agents (e.g., gadodiamide).[9] The interaction of gadolinium with nearby water molecules alters the signal intensity of MR imaging, allowing the detection of pathological processes (e.g., inflammation, infection, malignancy). The stability and disassociation rates vary with the four main categories of Gd chelates (ionic, nonionic, linear, macrocyclic). Yttrium is an additive in fine ceramics and superconductors (Y–Ba–Cu oxides) and a component of yttrium-aluminum-garnet (YAG) lasers.

Sources

Air

Rare earth elements in ambient air differ between countries depending on local anthropogenic sources and natural sources of REEs. In a study of REE concentrations, the main sources of atmospheric REEs in Beijing, China, were local soils and coal fly ash compared with industry and traffic in the Netherlands.[10] The most common rare earth elements in a study of urban air in Japan were Ce, La, Nd, and Pr.[11] In coal, rare earth elements are more abundant than more toxic metals (e.g., Be, Cd, Hg, Sb, Tl). Thulium is the rarest metal in the lanthanum series. Analysis of ambient air in Ankara, Turkey, revealed the following approximate concentrations of rare earth elements: lanthanum, 2–5 ng/m^3; cerium, 2–9 ng/m^3; samarium, 0.1–0.5 ng/m^3; europium, 0.05–0.1 ng/m^3; and yttrium, 2–3 ng/m^3 as measured by neutron activation analysis.[12] In a sampling of ambient air above a university building in Tokyo, Japan, the mean concentration of Eu was 7.77 ± 0.01 pg/mL compared with 4.31 ± 0.08 for Tb; the sources were attributed to television sets (Eu, Tb) and magneto-optical disks (Tb).[13] The light REEs (La–Nd) in the airborne samples <1.1 μm were similar to automobile catalyst with mean concentrations as follows (pg/mL): La, 300 ± 23; Ce, 370 ± 10; Pr, 70.1 ± 0.1; and Nd, 269 ± 2.

Water

Runoff from the application of REE-containing fertilizers in China and industrial processes using lanthanides are anthropogenic sources of REEs in water and sediment.[14] In two areas of China with rare earth element mining facilities, the total rare earth element concentrations in drinking water averaged 1.9 and 47.0 μg/L, whereas the third region without mining activity had an average total rare earth element concentration in drinking water of 0.92 μg/L.[15] The mean total rare earth element concentration in well water near a Chinese rare earth metal mining facility was 2.87 μg/L (range, 0.59–10.26 μg/L) compared with a mean of 0.054 μg/L in drinking water from Fuzhou City, China.[16] Seawater contains extremely low REE concentrations. In a study

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of coastal seawater at Nikkawa Beach, Japan, the mean lanthanide concentration ranged from 0.25 ± 0.02 pg Eu/mL to 4.7 ± 0.3 pg La/mL as measured by ICP/MS.[17]

Soil

The approximate concentrations of rare earth elements in the earth's crust range from ≪0.1 µg Pm and 0.5 µg Tm/g to 40 µg Nd/g and 66 µg Ce/g; these elements typically exist in a variety of minerals (e.g., carbonates, fluorides, phosphates, silicates) in granites, pegmatites, and related metamorphic igneous rocks.[18] The mean total rare earth elements in soil samples collected near a rare earth metal mining facility was 242.92 ± 68.98 µg/g dw (range, 135.85–327.56 µg/g dw); the mean bioavailable portion of the total rare earth elements was ~48%.[16] Typical concentrations of Ce, La, and Nd in coal average ~10 ppm.

Lifestyle

In a study of the area surrounding a Russian phosphorus fertilizer plant, increased uptake was detected in apples, beets, carrots, and potatoes.[19] Table 26.3 compares the maximum rare earth metal concentrations in the snow near the fertilizer plant with measures of contamination (ratio of rare earth metal concentrations to snow samples 10 km from the plant) and rare earth metal concentrations in the air near the plant. Sampling of eight vegetables grown near a rare earth metal mining facility demonstrated the highest total REEs in the vegetable group occurred in water spinach (mean = 6.12 ± 6.45 µg/g dry weight, dw) and lettuce (mean = 0.73 ± 0.34 µg/g dw).[16] In general, soil acidity and higher rare earth element soil concentrations enhance REE uptake.[18] Limited data suggest REEs in environmental tobacco smoke are higher than in nonsmoking ambient air samples. In a study of 11 ambient air samples from 3 smoking households, the median concentrations were 9.6 ng Ce/m^3 and 5.9 ng La/m^3 compared with 0.4 ng Ce/m^3 and 0.2 ng La/m^3 in 28 samples from nonsmoking households.[20]

ENVIRONMENTAL FATE

The transport and biotransformation of rare earth elements (REEs) in the environment is generally low with limited mobility; consequently, increased rare earth metal concentrations occur near anthropogenic sources of these transitional elements. Soil processes in humid environments typically reduce average REEs concentrations in soil.[18] Transfer of rare earth elements from soil to plants is typically low.

DOSE EFFECT

There are few human data on the dose-response relationship of these transitional elements. Five cancer patients received single intravenous injections of ^{90}yttrium ranging from 7.4 ng/kg–1.38 mg/kg; two cancer patients received ^{177}lutecium injections of 0.04 mg/kg and 3.28 mg/kg. These patients survived ½–17 days without evidence of acute hepatic necrosis or peritoneal inflammation. Peritonitis did not develop in a cancer patient surviving for 45 days after receiving

TABLE 26.3. Maximum rare earth concentrations (C_{max}) in the snow next to a Russian phosphorus fertilizer plant using rare earth metals and a comparison of the intensity of plant pollution using the ratio (R_c) of rare earth metals near the plant with background snow concentrations 10 km from the plant source. All rare earth metals were determined by neutron activation analysis in mg/L (ppm) for snow and ng/m^3 for air 200 m from the plant. (Adapted from Volokh et al.).[19]

Rare Earth Metal	Maximum Concentration (C_{max}, ppm)	Concentration Ratio (R_c, ppm)	Mean Air Concentration 200 m from Plant (ng/m^3)
Cerium	660	7.7	10.2
Dysprosium	15.1	9.4	NR
Europium	23	8.5	0.4
Lanthanum	454	9.5	8.0
Lutetium	1.0	3.8	NR
Neodymium	126	8.4	NR
Samarium	44	6.5	0.9
Scandium	31.4	2.3	0.5
Terbium	5.6	7.0	NR
Ytterbium	5.0	5.0	NR

Abbreviation: NR = not reported.

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3.16 mg ^{177}lutecium/kg intraperitoneally, whereas 3 out of 10 cancer patients given intraperitoneal ^{90}yttrium (1.53–2.94 mg/kg) developed peritoneal inflammation. Evidence of peritoneal inflammation was not detected in seven patients receiving 1.03–3.10 mg ^{177}lutecium/kg. One patient developed acute hepatic necrosis following the administration of 1.5 mg ^{177}lutecium/kg; this intraperitoneal dose was 40 times smaller than a similar dose causing liver damage in a rodent study.[21]

In a plant using europium-activated yttrium orthovanadate during the manufacturing of color television sets, ambient air monitoring demonstrated yttrium concentrations ranging from 0.29 mg/m^3 (top of cone cleaning exhaust enclosure) to 5.64 mg/m^3 (breathing zone of puffer operator).[22] Conjunctivitis, tracheobronchitis, and contact dermatitis were attributed to vanadium pentoxide rather than yttrium. Symptoms resolved within 1 week of exposure; no systemic complaints or pneumonitis were observed.

The toxicity of rare earth elements to animals is relatively low.[4] Focal hepatic necrosis occurred in 11 of 117 rats receiving intraperitoneal doses of cerium, lanthanum, praseodymium, neodymium, or yttrium chloride in doses ranging from 25–200 mg/kg.[21] Most of the animals developed massive fibrinopurulent peritonitis with most dying within 1 month.

TOXICOKINETICS

Human data on the kinetics of rare earth elements are extremely limited. Animal experimentation provides most of the current data. In general, the gastrointestinal tract and the lungs absorb rare earth elements poorly.[23] Complexing these elements with water-soluble salts (e.g., citrates) increases absorption, but nitrate salts of rare earth elements are not well absorbed.[24] The skin does not absorb rare earth elements; the subcutaneous injection of these compounds results in granulomas underneath the skin.[25] Lanthanides with lower atomic numbers tend to deposit in the liver, whereas lanthanides with higher atomic numbers usually transfer to bone based on animal studies.[26] Some, but not all, occupational cerium exposures may result in the long-term pulmonary retention (4–30 years) of cerium.[27] Excretion of rare earth elements occurs primarily in the feces with relatively small amounts (10%) eliminated by the kidney. Lanthanum carbonate is a phosphate binder with very low oral bioavailability (~0.001%), very high protein binding, hepatobiliary excretion with little renal elimination (<2%), and low steady-state concentrations (<3 ng/L).[28] Lanthanum does not cross the blood–brain barrier or accumulate in bones.[29] An exception is gadolinium-based contrast agents. These complexes have small volumes of distribution (~0.3 L/kg body weight) similar to extracellular water, limited protein binding, no biotransformation, and almost exclusive renal elimination via glomerular filtration.[30] However, some deposition of Gd occurs in the tissues including the brain.[31] The distribution half-life is ~4 minutes with blood–brain barrier restricting diffusion of the chelated Gd (but not ionic Gd) into the brain and other tissues.[32] Fecal excretion accounts for <3% of the elimination. The terminal half-life depends on creatinine clearance. In healthy patients with normal renal function, the terminal half-life of Gd is ~1½ hours with >95% excreted within 1 day. As creatinine clearance decreases, the terminal half-life increases to ~4–8 hours (glomerular filtration rate, 30–60 mL/minute) and 18–34 hours (glomerular filtration rate, <30 mL/minute).[33]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Most experimental studies in animals indicate rare earth element oxides (e.g., gadolinium) are mild respiratory irritants that require heavy exposure over prolonged periods to produce pulmonary inflammation.[34,35] Case reports suggest at least some rare earth elements (e.g., cerium) may persist in the lungs for years when converted to insoluble compounds (e.g., cerium phosphate).[36] Multiple confounding variables (smoking, asbestos, silica, quartz) complicate the establishment of causation between rare earth exposure and fibrotic lung disease. Subacute studies of animals exposed via inhalation to a blend of rare earth oxides and fluorides demonstrated little fibrogenic activity.[37] Although the extent of pulmonary damage depends on particle characteristics, dose, and type of rare-earth complex, all these elements demonstrate minimal fibrogenic potential. The pathological potential of lanthanides to produce fibrosis is mild compared with silica and quartz.[38] Direct instillation of rare earth oxides into the lungs produced a fatal delayed chemical pneumonitis in some animals, but no chronic cellular reactions or fibrosis occurred in surviving animals.[39] Compared with rare earth metal oxides, exposure of animals to fluoride salts of rare earth elements caused a more prominent acute chemical pneumonitis that progressed with continued exposure to chronic bronchitis and bronchiolitis.[40]

Radioactive contamination of dust from rare earth elements probably does not contribute significantly to

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the pulmonary effects of these transition elements.[26,41] The ionic size of lanthanides and calcium is similar; consequently, these transitional elements bind to calcium sites on biological molecules including lanthanum.

Pathological Changes

Humans

Experimental and epidemiological data suggest prolonged inhalation of high concentrations of stable lanthanides can produce pneumoconiosis and progressive pulmonary fibrosis; however, the occurrence of pulmonary damage following rare earth metal exposure is rare with frequent confounding exposures. No pathognomonic lesion is characteristic of REE exposure; concurrent radiation exposure (e.g., thorium) does not account for the fibrotic changes.[26] Nephrogenic systemic fibrosis associated with Gd chelates used in MRI scanning occurs with dermal abnormalities (nephrogenic dermal fibrosis).[42] Pathological changes include thickened, indurated skin resulting from diffuse dermal fibroplasia with spindle cells extending into subcutaneous tissues, interstitial mucin deposition, and minimal/mild inflammation. Histological features depend on the stage of the disease. Early changes include scant proliferation of spindled fibroblasts and minimal collagen production, whereas later lesions involve more numerous fibroblasts and collagen deposition in the reticular dermis and subcutis. Calcium deposits may occur in collagen as well as in other organs (kidneys, heart, lungs, muscles, testes).[43,44]

Animals

No pathological lesions distinguish the effects of rare earth elements. Following the intravenous administration of 1 mg YCl_3 to rats, the spleen and liver are the primary target organs with some elevation of plasma Ca concentrations occurring probably as a result of bone resorption.[45] The ingestion of chloride salts of rare earth elements in doses up to 1% of the diet for 12 weeks produced some minor alterations in liver histology, but no changes in growth or blood abnormalities.[46,47] Although rare earth elements do not usually damage intact skin, the application of rare earth elements to abraded skin may cause scarring and epilation. Animal studies indicate terbium is the most irritating rare earth metal for skin; however, terbium did not produce scarring in these studies when applied to intact skin.[48] Little irritation occurs following the application of lutetium chloride to intact skin, but extensive necrosis develops following the intradermal injection or the application of lutetium chloride to abraded skin.[49] Similarly, europium chloride produces transient ocular irritation without permanent scarring; the application of europium chloride to abraded skin causes scar formation in animal studies.[50]

Postmortem Examination

A 68-year-old man presented with progressive dyspnea 13 years after retiring from a 35-year career as an optical lens grinder.[51] Open lung biopsy demonstrated nonspecific interstitial fibrosis, while scanning electron microscopy with energy-dispersive x-ray analysis revealed numerous pulmonary deposits primarily consisting of cerium alone or in combination with other elements. Pathological findings included early honeycomb changes, vascular thickening, reactive alveolar pneumocytes, numerous intra-alveolar macrophages, and chronic interstitial inflammation consistent with interstitial pneumonitis. A 66-year-old projectionist with 25 years of exposure to carbon arc lamp fumes died of congestive heart failure.[52] Histological examination of lung and liver tissue demonstrated large deposits of rare earth elements in macrophages of the tracheobronchial lymph nodes and hepatic Kupffer's cells; however, he had no histological or clinical evidence of interstitial lung disease.

CLINICAL RESPONSE

Acute Toxicity

The acute toxicity of rare earth elements depends on the route of exposure; however, the rare earth element toxicity is low and increases with increasing atomic weight.[24] Case series associate nonspecific symptoms with exposure to high concentrations of rare earth element dust including nausea, headaches, and weight loss.[53,54] Acute kidney injury (i.e., >0.5 mg/dL increase in serum creatinine) may occur in chronic renal disease patients (Stage 4 or higher) receiving gadolinium-based contrast agents; the incidence of renal damage is substantially less than iodinated contrast agents. In a retrospective study of 163 patients with chronic renal disease, 5.3% of the patients receiving gadolinium developed acute kidney injury compared with 20.6% in the iodinated contrast group ($P < 0.01$).[55] Risk factors for the occurrence of acute kidney injury include poor renal function, intraarterial injections, and high Gd contrast volumes. Case series associate the use of large cumulative doses of linear

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gadolinium-based contrast agents with the development of nephrogenic systemic fibrosis predominately in patients with Stage 5 renal disease.[56] This disease affects multiple organs including the kidneys and skin characterized by skin abnormalities (thickening/woody, edema, cobblestone texture, dimpling, hyperpigmentation) over limbs and occasionally the trunk similar to scleroderma.[57] Fibrotic changes also may occur in the heart and lungs (pleura, interstitial pulmonary fibrosis).

The onset of nephrogenic systemic fibrosis typically begins within 1–8 weeks after gadolinium-based contrast exposure with a range of up to ~3 years.[58] Nephrogenic systemic fibrosis occurs exclusively in patients with renal impairment exposed to gadolinium-based contrast agents (GBCAs), primarily with glomerular filtration rates <30 mL/minute/1.73 m^2 and receiving GBCAs with high dissociation rates.[59] The implementation of restrictions on GBCAs use in patients with known risk factors has eliminated most cases of nephrogenic systemic fibrosis.[60]

Recent data suggest gadolinium deposition from the release of free Gd^{3+} ions from less stable GBCAs with high dissolution rates (e.g., macrocyclic, linear) may occur in the presence of normal renal function.[61] Clinical studies to date indicate gadolinium deposition within brain tissues (i.e., dentate nucleus, globus pallidus) occurs in patients with neoplastic or systemic inflammatory diseases that potentially cause disruption of the blood–brain barrier.[62] The clinical consequences of potential brain tissue gadolinium deposition remain unclear in the absence of well-designed studies with established reference gadolinium levels.[61]

Occupational Exposure

Several case reports of workers in the photographic, photoengraving, and printing industries associate prolonged exposure to dust containing rare earth elements from carbon arc lamps with lung irritation and mild[63] to moderately severe[64] pulmonary fibrosis. In a 34-year-old man with an ~10-year history of handling a dry concentrate of rare earth elements, routine chest x-ray demonstrated profuse, discrete nodules throughout the lung fields, primarily in the mid-lung area.[65] He was asymptomatic with normal exercise tolerance and pulmonary function tests. A 58-year-old light smoker with a 46-year history of exposure to rare earth elements at photoengraving laboratories presented with dyspnea on exertion and a slightly productive cough for 2 years.[66] He had evidence of pulmonary hypertension on cardiac catheterization and reticulonodular changes on chest x-ray with both obstructive and restrictive abnormalities on pulmonary function testing. Lung and lymph node biopsies demonstrated elevated cerium, neodymium, lanthanum, and samarium concentrations compared with controls without occupational exposure to rare earth elements.[41]

There are no clinical data to compare rare earth metal workers with and without evidence of pulmonary fibrosis. A 66-year-old adult-onset diabetic with a history of heavy smoking, chronic alcohol abuse, and angina pectoris presented with terminal congestive heart failure.[52] His occupational history included a 25-year exposure to rare earth elements from carbon arc lamp fumes; however, he had no radiological, histological, or clinical evidence of interstitial lung disease. The contribution of confounding variables (graphite, thorium) to the development of pneumoconiosis in workers exposed to rare earth elements remains undefined.

Carcinogenesis

Rare earth elements are not recognized as animal or human carcinogens, but the neoplastic potential of isotopes of rare earth elements remains to be determined. $^{144}CeO_2$ emits beta radiation that causes an increased incidence of lung tumors in rats exposed to aerosols of $^{144}CeO_2$ based on the cumulative dose of beta radiation.[67] In these animal studies, the predominant pulmonary tumor is a squamous cell carcinoma that exhibits more malignant behavior compared with squamous cell carcinomas of the lung that result from prolonged inhalation of heavy particle loads.[68]

DIAGNOSTIC TESTING

Analytical Methods

The separation of rare earth metals is difficult because the chemical activity of the metals in this group is almost identical. Techniques for the determination of lanthanides in biological specimens include neutron activation analysis, graphite furnace atomic absorption spectrometry, inductively coupled plasma/atomic emission spectrometry, and inductively coupled plasma/mass spectrometry.[69] The latter has detection limits well above serum concentrations of rare earth elements, typically in the pg/mL (ppt) range;[70] some pretreatment of the sample is necessary to overcome matrix and spectral interferences secondary to polyatomic ions in the plasma including pre-concentration with chelating resin after acid digestion and heating.[71,72] Atomic absorption spectrometry (AAS) is the most frequent method used to quantify the concentrations of rare

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earth elements in biological specimens. The use of a spectroscopic detection system avoids the precipitation of rare earth elements as hydroxides at neutral pH in the column.[73] Neutron activation analysis is a more sensitive method compared with AAS, but the cost is much higher. Examination of bronchoalveolar lavage fluid allows the detection and determination of rare earth elements in patients exposed to these elements by neutron activation analysis and energy-dispersive x-ray fluorescence.[74] The use of electrothermal vaporization/inductively coupled plasma/mass spectrometry allows the determination of REEs in environmental and biological samples with limits of detection in the range of 0.02–0.09 pg/mL in the former and 1–10 pg/mL in the latter.[75,76]

Biomarkers

There are few data on the concentrations of rare earth elements in samples of blood or urine; existing data indicate that the concentration of rare earth elements in biological tissues is very low. The mean lanthanide concentrations in serum from five healthy volunteers ranged from 0.66 pg Eu/mL to 235 pg Ce/mL as measured by ICP/MS.[71] Table 26.4 displays the mean lanthanide concentrations in the five healthy volunteers. In a convenience sample of blood collected from Chinese residents near a rare earth metal mining facility, the mean *total* rare earth element concentration was 689.74 ± 254.25 μg/L (range, 424.76–1,274.80 μg/L).[16] Total rare earth metals included 15 rare earth elements excluding scandium and promethium as measured by inductively coupled plasma/mass spectrometry.

TABLE 26.4. Mean rare earth element concentrations of 14 lanthanides in serum samples from 5 healthy volunteers as measured by ICP/MS. (Based on Inagari and Haraguchi).[71]

Element	Atomic Number (symbol)	Mean (μg/L, ppb)
Cerium	58 (Ce)	214 ± 22
Dysprosium	66 (Dy)	9.6 ± 1.1
Erbium	68 (Er)	9.5 ± 1.9
Europium	63 (Eu)	0.82 ± 0.19
Gadolinium	64 (Gd)	7.2 ± 1.4
Holmium	67 (Ho)	2.55 ± 0.54
Lanthanum	57 (La)	62.7 ± 7.1
Lutetium	71 (Lu)	2.46 ± 0.58
Neodymium	60 (Nd)	33.7 ± 4.2
Praseodymium	59 (Pr)	11.1 ± 1.5
Samarium	62 (Sm)	5.8 ± 1.1
Terbium	65 (Tb)	1.30 ± 0.22
Thulium	69 (Tm)	1.69 ± 0.42
Ytterbium	70 (Yb)	13.2 ± 3.2

In a study of 28 healthy French men, morning samples of plasma and urine contained concentrations of rare earth elements (Ce, Gd, La, Tb, Yb) were <0.3 μg/L, as determined by inductively coupled plasma/mass spectrometry; the single exception was a urine sample containing 1.5 μg Ce/L.[77] In a study of a convenience sample of 58 healthy Italian volunteers, the mean lanthanide concentration in urine samples ranged from ~2.5–20 pg/mL as measured by electrothermal vaporization/inductively coupled plasma/mass spectrometry.[76] Table 26.5 lists the results from this study.

TABLE 26.5. Analytical results from the study of urine samples from 58 healthy Italians without known exposure to lanthanides as measured by EVT/ICP/MS. (Based on Bettinelli et al.).[76]

Element (Atomic Symbol)	Atomic Number	Mean (pg/mL)	Median (pg/mL)	Range (pg/mL)	Samples Below Limit of Detection
Cerium (Ce)	58	15.7	14.2	>7.0–58.8	5
Dysprosium (Dy)	66	10.3	7.8	3.3–55.4	0
Erbium (Er)	68	7.5	5.6	>3.0–35.0	3
Europium (Eu)	63	4.3	3.6	>1.5–17.8	5
Gadolinium (Gd)	64	14.5	15.1	>9.0–31.1	6
Holmium (Ho)	67	3.7	2.4	>1.5–19.8	5
Lanthanum (La)	57	16.0	12.2	>6.0–49.7	2
Lutetium (Lu)	71	2.8	2.3	>1.5–11.8	9
Neodymium (Nd)	60	19.6	18.2	5.0–37.7	0
Praseodymium (Pr)	59	7.5	6.2	3.0–25.6	0
Samarium (Sm)	62	18.4	15.7	4.6–69.2	0
Terbium (Tb)	65	4.7	3.9	>2.0–18.1	5
Thulium (Tm)	69	2.5	1.7	>1.0–13.2	9
Ytterbium (Yb)	70	7.2	5.2	2.4–33.4	0

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Abnormalities

Because of their high atomic numbers, chest x-rays of workers exposed to rare earth elements demonstrate dense infiltrates in a diffuse, nodular pattern; these patients are often asymptomatic. Characteristic radiological findings following prolonged exposure to the smoke of carbon arc lamps are small, diffuse, highly radiopaque nodules that occur primarily in the mid-lung zones.[65] Pulmonary function tests frequently are normal. Case reports associate mild-to-moderate restrictive defects in patients with the diagnosis of rare earth metal pneumoconiosis, but the presence of confounding factors (smoking, fibrogenic dust exposure) complicates the interpretation of these tests.[78] Obstructive defects are not usually present without the occurrence of confounding exposures.

HEALTH SURVEILLANCE

Currently, permissible exposure limits exist only for yttrium among the rare earth compounds. The US OSHA PEL–TWA for yttrium and yttrium compounds is 1 mg Y/m^3 as a measure to reduce the potential for pulmonary damage. NIOSH has a similar REL–TWA. The IDLH is 500 mg Y/m^3. The ACGIH TLV–TWA for yttrium and yttrium compounds is also 1 mg Y/m^3 to minimize the risk for respiratory fibrosis following large exposures. There are no biological markers established for rare earth elements.

TREATMENT

Treatment primarily is supportive. Contact with eyes or with abraded skin may require decontamination. Rare earth elements, particularly terbium and yttrium, may cause ulcerations when introduced into the dermis through abrasions or lacerations. Consequently, wounds contaminated by rare earth elements should be thoroughly cleaned and debrided. Incidental ingestion of rare earth metals is usually harmless with no decontamination measures typically necessary.

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Chapter 27

SELENIUM

ELEMENTAL AND INORGANIC SELENIUM

HISTORY

Marco Polo probably recorded the first observations of selenium (Se) toxicity when he described a disease called "hoof rot" in horses in the Nan Shan and Tien Shan mountains of Turkestan, where selenium-rich soils exist.[1] In 1817, the Swedish chemist, Jöns Jacob Berzelius, isolated and identified selenium by analyzing a red deposit on the wall of a lead chamber used to produce sulfuric acid.[2] In the late 19th and early 20th centuries, livestock grazing on plants growing on highly seleniferous soils in areas of the Great Plains of the United States developed alkali disease (also known as selenosis). This disorder is caused by the chronic ingestion of grain and forage contaminated with 5–50 ppm of selenium. Signs of alkali disease in livestock include dystrophic changes in hooves, stiffness, lameness, and bilateral symmetrical alopecia (e.g., loss of the tail switch). During the first half of the 20th century, several papers associated the development of skin lesions and neuropathy in horses, sheep, and cattle grazing on plants (genera *Astragalus, Xylorhiza*, *Oonopsis*, and *Stanleya*) with high selenium concentrations in the soils of the northern Great Plains of the United States.[3,4,5,6] This subacute disease (blind staggers) occurred in livestock feeding on plants that contained up to 10,000 ppm selenium. Clinical features included anorexia, weight loss, blindness, ataxia, respiratory distress, and disorientation, resulting in the animal straying from the herd or continuously circling. The association between chronic selenosis and neurological disease in grazing animals remains controversial because the disease was not replicated in animals fed excessive selenium; alternate explanations (e.g., sulfate-related polio encephalomalacia, malignant catarrhal fever, swainsonine-induced locoism, viral infections, starvation) were not excluded.[7] Additionally, separating the effects of inorganic and organic selenium is very complex because plants contain variable amounts of both Se types depending on plant species, environmental conditions, the bioavailability of selenium species, and the type of selenium present in the environment. Pigs fed extracts from *Astragalus bisulcatus* developed more severe and disseminated neurological lesions compared with pigs fed sodium selenate or D,L-selenomethionine; however, there was no direct correlation between blood selenium concentrations and the severity of pathological changes.[8] The administration of selenocysteine did not produce any neurological lesions. Furthermore, the foraging of obligate selenium accumulators is highly unpalatable, even for grazing animals.[9]

In the early 20th century, high doses of selenium dioxide (3 mg/day) and potassium selenate (300 µg/day) briefly were advocated as a treatment for hematological malignancies.[10] This practice stopped in 1943 after an animal study reported the occurrence of low-grade

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tumors (adenomas, carcinomas) in female rats that developed cirrhosis following the ingestion of high doses of ammonia potassium selenide and ammonium potassium sulfide.[11] These hepatic neoplasms occurred only after 18 months of dosing and only in rats with cirrhosis.

The first indication of the nutritional importance of selenium appeared in the 1950s, when the replacement of vitamin E in the diets of experimental animals by selenium did not produce adverse effects.[12] In the early 1970s, experiments revealed that selenium was an essential component of glutathione peroxidase, which is an important enzyme for the process that protects polyunsaturated membrane lipids from oxidative degradation.[13] The status of selenium as an essential trace element was confirmed by the discovery of a clinical condition in China called Keshan disease that resulted, at least in part, from inadequate selenium concentrations in the diet. The incidence of multifocal myocarditis and periacinar pancreatic fibrosis declined dramatically after supplementation of selenium in the Chinese diet. Selenium deficiency occurs in the geographic areas where Balkan nephropathy appears, but there is no direct evidence that selenium deficiency contributes to the development of this chronic, progressive kidney disease.[14] Selenium often is added to the feed of animals in doses up to 0.3 ppm in order to prevent selenium deficiency diseases.

Within the last several decades, research interest in selenium has increased dramatically as a result of several lines of scientific inquiry that demonstrated an *increased* risk of cancer with *low*-selenium diets.[15,16] However, there is no convincing evidence that routine use of selenium supplements reduces the risk of cancer (prostate, skin, other unspecified cancer), except possibly in areas where profoundly low selenium concentrations occur in the soil.[17,18,19]

PHYSIOCHEMICAL PROPERTIES

Selenium (Se) is a metalloid (i.e., having intermediate properties between metals and nonmetals) belonging to Group 16 (formerly Group VIA with oxygen, sulfur, polonium, tellurium) of the periodic table. The chemical properties of selenium resemble those of sulfur and, to a lesser extent, tellurium including similar atomic size, bond energies, ionization potentials, and primary oxidation states.[20] Selenium is a stable element that does not oxidize at room temperature and has a strong tendency to complex with heavy metals directly or in aqueous solutions. Selenium dioxide forms following combustion of selenium in air. The four natural oxidation states of inorganic selenium include the following: (0), elemental selenium, selenium sulfides (Se_nS_n); (2−), sodium selenide (Na_2Se), hydrogen selenide (H_2Se), mercury (II) selenide (HgSe); (4+), sodium selenite (Na_2SeO_3), selenium dioxide (SeO_2), selenious acid (H_2SeO_3); and (6+), sodium selenate (Na_2SeO_4), selenic acid (H_2SeO_4). The reduced form of selenium (i.e., selenide) is the ionized form of hydrogen selenide (H_2Se); selenide is unstable in aqueous solutions except at low oxidation–reduction potential and alkaline conditions. Elemental selenium is stable and exists in the following three allotropic forms: deep red crystals (melting point 144°C), red amorphous powder, and the black vitreous form.[21] Colloidal selenium forms a red-orange allotrope in aqueous solution that precipitates. Selenium has six stable natural isotopes divided as follows: ^{74}Se (0.89%), ^{76}Se (9.37%), ^{77}Se (7.63%), ^{78}Se (23.77%), ^{80}Se (49.61%), and ^{82}Se (8.73%). The most common artificial radioisotope is ^{75}Se, which is a gamma emitter with a half-life of ~120 days used as a diagnostic agent in medicine. The reduced heavy metal selenides (2−) and elemental selenium (0) are insoluble in water; however, the inorganic alkali selenites (4+) and the selenates (6+) are water-soluble. Therefore, these latter oxidation states possess greater bioavailability compared with selenides or elemental selenium. The salts of selenious acid (selenites) and selenic acid (selenates) are usually water-soluble, but most selenites are less soluble than the corresponding selenates. Selenium forms stable compounds with oxygen, particularly selenium dioxide. Hydrogen selenide is a colorless gas with a disagreeable odor and an odor threshold of ~0.3 ppm,[22] whereas selenium hexafluoride is a colorless gas that decomposes in water. Table 27.1 lists the identifying information and physical properties of elemental selenium and inorganic selenium compounds.

Upon contact with water, selenium dioxide (4+) forms the weak acid, selenious acid (H_2SeO_3), which has a $pK_{a1} = 2.8$ and $pK_{a2} = 8.5$. In water, selenium trioxide (6+) produces selenic acid (H_2SeO_4), which is a stronger acid than selenious acid with a $pKa_1 = -3$ and $pKa_2 = 1.7$. Selenate is the most stable oxidized form of selenium in alkaline and oxidizing solutions.

Hydrogen selenide is a highly reactive compound formed by the reaction of water or acids with metallic selenides. Alternately, H_2Se forms from the reaction of hydrogen with soluble selenium compounds. Selenious acid is a weak dibasic acid that sometimes acts as an oxidizing agent rather than a reducing agent. Hydrogen selenide (2−) is a strong reducing agent, and H_2Se is a relatively strong acid.

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TABLE 27.1. Identifying information and physical properties of selenium and selenium compounds.

Physical Characteristic	Selenium	Hydrogen Selenide	Selenium Disulfide (Selenium (IV) Sulfide)	Sodium Selenide	Selenium Dioxide
CAS RN	7782-49-2	7783-07-5	7488-56-4	1313-85-5	7446-08-04
Molecular formula	Se	H_2Se	SeS_2	Na_2Se	SeO_2
Color	Red, grey, black	Colorless	Bright orange	Crystalline; red on air exposure[b]	Yellow-green vapor, needles
Physical state	Solid	Gas	Powder	Solid	Solid
Odor	Rotten horseradish on combustion	Disagreeable	Insufficient data	NA	Pungent sour smell
Molecular weight (g/mol)	78.96	80.98	143.09	124.94	110.96
Oxidation state	0	2−	4+	2−	4+
Melting point (°C)	221 (red/grey) 180 (black)	−64	<100	>875	340
Density (g/mL, 20 °C)	4.39 (red) 4.81 (grey) 4.28 (black)	2.12 (−42°C)	2.44	2.625 (10°C)	3.95 (15°C)
Water solubility (20 °C)	Insoluble	7.3 mL/L	Insoluble	Decomposes	384 g/L (14°C)
Vapor pressure (mmHg)	1 (356°C)	1,330 (30°C)	NA	NA	12.5 (70°C);39.0 (181°C)

Physical Characteristic	Selenious Acid	Selenium Oxychloride	Sodium Selenite	Sodium Selenate	Selenium Trioxide	Selenic Acid
CAS RN	7783-00-8	7791-23-3	10102-18-8	13410-01-0	13768-86-0	7783-08-6
Molecular formula	H_2SeO_3	$SeOCl_2$	Na_2SeO_3	Na_2SeO_4	SeO_3	H_2SeO_4
Color	White prisms	Clear/pale yellow	White tetragonal crystals	White crystals	White crystals	White hexagonal prisms
Physical state	Solid	Liquid	Solid	Solid	Solid	Solid
Odor	NA		ID	ID	NA	ID
Molecular weight (g/mol)	128.97	165.87	172.94	188.95	112.96	144.97
Oxidation state	4+	4+	4+	6+	6+	6+
Melting point (°C)	70[a]	8.5	710[a]	NA[a]	118	58
Density (g/mL, 20 °C)	3.00 (15°C)	2.42 (22 °C)	>1	1.61	3.44	2.95 (15 °C)
Water solubility (20 °C)	Soluble	Hydrolyzes	Soluble	Very soluble	Soluble	Very soluble in hot water
Vapor pressure (mmHg)	4.5 (33°C)	NA	<0.001 (20°C)	Negligible	NA	ID

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not applicable; ID = insufficient data.
[a] Decomposes; [b] Deliquesces.

EXPOSURE

Uses

Elemental and inorganic selenium has many commercial uses (e.g., electronics, glass, ceramics, steel, pigment manufacturing, livestock food additives). Selenium is an essential trace element added to animal feed at concentrations of 0.1–0.3 ppm in the total diet. The principal applications of elemental and inorganic selenium include manufacture of ceramics, glass (ammonium selenite, sodium selenite, sodium selenate), photoelectric cells, pigments (cupric selenate), rectifiers, semiconductors, and steel. Other uses involve photography and pharmaceutical production (dehydrogenation-catalyst) for niacin and cortisone. Selenium dioxide is the most common industrial selenium compound. Applications include the production of photographic cells, low-voltage rectifiers, and photographic chemicals; a decolorizer for green glass; a vulcanizing agent for rubber; and an alloy with copper and steel (photocopy machines).

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Selenium hexafluoride is a gaseous insulator in electric transformers. Selenite salts are red pigments for glass and enamels; selenium oxychloride is a solvent. In addition to dietary supplements, the medicinal uses of selenium include use of selenium sulfide for the treatment of seborrheic dermatitis and tinea versicolor. Gun bluing solutions contain lethal amounts of selenious acid in addition to lesser amounts of copper nitrate and nitric acid. The artificial radioactive isotope, ^{75}Se, is a gamma emitter for biochemical studies with a half-life of 120 days. The six stable isotopes of selenium do not have well-defined uses. Selenite cysteine broth is an enrichment medium for the isolation of *Salmonella* species that typically contains 4 g sodium selenite/L.

Production Processes

Although selenium is a common constituent of most rocks and soils, selenium seldom occurs naturally in its elemental form.[21] Commercial selenium is a by-product of sulfide ores (copper, gold, lead, nickel, silver) that forms during the refining of copper when selenium accumulates in electrorefining tanks. The manufacture of sulfuric acid produces small amounts of selenium. Commercial production of selenium involves either soda ash roasting or sulfuric acid roasting of copper slime. Soda ashing refining involves the roasting of a paste formed by soda ash binder and copper slime followed by the grinding and leaching to reduce hexavalent selenium to sodium selenate. Controlled heating reduces sodium selenate to sodium selenide followed by oxidation to elemental selenium by percolation of air through the leachate. Other reducing agents for hexavalent selenium in this process include hydrochloric acid and ferrous salts catalyzed by chloride ions. The sulfuric acid process involves the volatilization of selenium dioxide formed from the roasting of sulfuric acid and copper slime at 500–600°C followed by reduction to elemental selenium during scrubbing with water and sulfur dioxide.

Coal usually contains up to ~4 ppm selenium.[23] In a sample of coal from the United States, the selenium concentration ranged from 1–5 ppm Se with an average of 3.2 ppm Se.[24] Selenium also occurs in some crude oil depending on locations with selenium deposits (e.g., shale). Samples of US crude oil demonstrated Se concentrations ranging from 0.06–0.35 ppm with a mean value of 0.17 ppm. Higher Se concentrations (i.e., 0.5–0.8 ppm) occur in crude oil from seleniferous areas (e.g., San Joaquin Valley, California).

Sources

Air

Atmospheric selenium results from natural and anthropogenic sources; ambient background Se concentrations in the air are typically very low (i.e., <10 ng/m^3).[21] Combustion of fossil fuels and coal is the primary anthropogenic source of selenium in ambient air. The incineration of rubber, municipal waste, and paper adds lesser amounts of selenium to the air. Volcanic gas is the major *natural* source of selenium in ambient air; biomethylation of selenium releases small amounts of selenium into the air.[21] Although the burning of fuel produces selenium dioxide, the presence of sulfur dioxide rapidly reduces the selenium dioxide to elemental selenium.[25] Consequently, most selenium in ambient air is present in the form of elemental selenium bound to fly ash and particles. The majority of the selenium discharge from coal-fired steam plant partitions occurs via fly ash removal to nearby slag ponds rather than to air. Background Se concentrations in ambient air generally average 0.1–10 ng/m^3 with ranges up to 500 ng/m^3 near point sources.[26] In a study of seven UK sites, the selenium concentrations in the ambient atmosphere ranged from 0.1–42.3 ng/m^3 with the lowest mean (0.9 ng/m^3) in the rural area of Windermere and the highest mean (16.7 ng/m^3) in the industrial area of Walsall.[27]

Soil

The primary source of selenium in the soil is the weathering and leaching of parent bedrock materials that contain selenium in the form of selenites and selenides in association with sulfide minerals (arsenopyrite, chalcopyrite, galena, marcasite, pyrrhotite, pyrite). Selenium occurs in soil as elemental selenium, calcium selenate, basic ferric selenite, and organic selenium compounds as a result of the decay of plant and animal material; elemental selenium is rare in nature. Coal-mining operations release selenium because of the oxidation of selenium-bearing pyrite.[28] Most soils contain Se concentrations of 0.1–2 mg/kg;[29] however, the selenium content in soil varies widely between specific localities with areas of high selenium content containing up to 1,200 mg/kg. Parts of the Western and Midwestern United States contain highly seleniferous soil including parts of South and North Dakota, Wyoming, Nebraska, Kansas, Utah, Colorado, Arizona, and New Mexico. In 45 soil samples from the high-selenium areas of Enshi Prefecture of Hubei Province, China, the distribution of the total Se concentration was log normal and ranged from 2.89–87.3 μg/g (GM = 9.36 ± 18.6 μg/g).[30] Most of the selenium was bound to organic matter.

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The amount of selenium in the soil is not a good indicator for the bioavailability of selenium to plants because the accumulation of selenium from soil varies between plant species. Plant genera that easily accumulate selenium as soluble selenates and selenites are *Astragalus* (several thousand ppm), *Machaeranthera* (~800 ppm), *Oonopsis* (~800 ppm), *Stanleya* (~700 ppm), and *Xylorhiza* including alfalfa (0.23 mg/kg dw), yeasts, white grains, and cruciferous species (e.g., cabbage, broccoli, cauliflower, mustard). Secondary accumulators include *Aster* (~72 ppm), *Atriplex* (~50 ppm), *Comandra*, *Grindelia*, *Gutierrezia* (~60 ppm), and *Haplopappus* (120 ppm).[12] These plants grow in soil containing 1–50 ppm selenium and accumulate Se concentrations of 100–100,000 mg/kg of plant tissue for primary accumulators and 25–100 mg/kg of plant tissue for secondary accumulators.[31] Plants that do not accumulate selenium usually contain <25 mg/kg of plant tissue.

Water

Selenium appears in water as a result of wet and dry deposition from the atmosphere and by surface and subsurface drainage. Concentrations in seawater are generally low (0.04–0.12 µg Se/L),[32,33] whereas the concentration in ground and surface water varies widely (0.06–400 µg Se/L).[34] Concentrations in public water supplies seldom exceed 10 µg Se/L.[31,35] High concentrations of selenium in surface and ground water usually occur in farm areas where irrigation water drains from soils with high selenium content. Selenium in water exists as the salts of selenic (strong) and selenious (weak) acids. The soluble selenate salts of selenic acid occur in alkaline waters with sodium selenate being one of the most mobile selenium compounds in the environment. The poor adsorption of sodium selenate to soil particles enhances the mobility of this salt in soil. Because selenious acid is a weak acid, the diselenite ion predominates in waters with pH 3.5–9. The presence of iron decreases the selenium concentration as a result of the precipitation of insoluble ferric selenite. To date, there are no published reports of selenium toxicity in humans consuming fish or fowl from selenium-contaminated areas.

Kesterson Reservoir, California

The Kesterson Reservoir near Gustine in western Merced County, California, was a series of 12 shallow, drain water-evaporation ponds fed by an 85-mile subsurface agricultural drain (San Luis Drain). This reservoir was the storage and evaporation facility for water traveling through the drain in 1978–1986. The connection between the Kesterson Reservoir and the Pacific Ocean via Suisun Bay was never built. Consequently, drain water entering the Kesterson Reservoir either percolated into groundwater or evaporated into the air. Elevated Se concentrations appeared in the Kesterson Reservoir as a result of the impounding of selenium-laden, agricultural drainage water into evaporation ponds without a natural drain.

A similar mechanism produced elevated selenium concentrations in the Tulare Basin, ~160 km south of the Kesterson Reservoir. Soluble selenium leached from the arid, saline soils, primarily in the form of selenates; the irrigation water carried the selenium into ponds or groundwater. Although selenate was the major fraction of dissolved selenium in the Kesterson Reservoir, a study of the drainage water indicated that up to ~25% of the Se species were methylated forms.[36]

Deaths and deformities (anophthalmia, microphthalmia, abnormal beaks, amelia, micromelia, ectrodactyly, hydrocephaly) in fish and resident waterfowl living in the nearby Kesterson Wildlife Refuge were associated with contamination of intake waters by high selenium concentrations that averaged ~300 µg/L[37,38] and often exceeded 1.35 mg/L.[21] Selenium concentrations in decomposing detritus in the reservoir were as high as 440 µg/g dry weight.[39] The selenium concentrations typically increased in the following order: water > sediment > plants > animals. The Se concentrations exceeded normal environmental Se concentrations at nearby reference sites by >100-fold. The average Se concentrations in Kesterson groundwater and surface water surrounding the reservoir were 31 µg/L and 22 µg/L, respectively.[36] Only 3 of the 27 evaporation basins tested in other portions of the San Joaquin Valley had total Se concentrations exceeding 0.1 mg/L.[21]

A community health survey of residents in the area surrounding the Kesterson National Wildlife Refuge did not reveal any adverse health effects in the local population, despite the presence of high selenium contamination. Examples of the extent of selenium contamination included the following: local fish (≥96 ppm Se, wet weight), aquatic birds (≥130 ppm in liver, dry weight), and waterfowl (≥5.3 ppm flesh, wet weight).[36] Selenium toxicity was not detected in any domestic animals near the Kesterson Reservoir. Biological monitoring of workers stationed at the Kesterson Reservoir and the San Luis Drain vicinity did not reveal any elevated blood or urine selenium concentrations.

Belews Lake, North Carolina

Belews Lake is a man-made reservoir that provided condenser-cooling water for a large coal-fired electric

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power plant. At Belews Lake, contaminated effluent (100–200 µg dissolved Se/L) from a coal ash disposal basin near a newly constructed coal-fired plant produced Se concentrations (>10 µg/L) sufficient to eliminate most fish species from the reservoir.[40] The long hydrological retention time (i.e., 1,500 days) and relatively low sedimentation rate (<0.5 cm/year) in this lake contributed to Se accumulation. Discharge of selenium-containing waste into the lake stopped in 1986; the peak selenium concentration in lake water was 20 µg/L at the time discharge ceased compared with <1 µg/L in 1996.[41] Selenium concentrations in birds from Belews Lake were not high enough to produce reproductive abnormalities. Elevated selenium concentrations also occurred at other power plant cooling basins in the Hyco Reservoir, North Carolina, and the Martin Reservoir, Texas. Experimental studies in England indicate Se concentrations of >25 µg/L in freshwater ponds are sufficient to eliminate about half the resident population of perch.[42]

San Francisco Bay

Besides agricultural runoff from seleniferous soil, commercial sources of selenium in water include discharge from coal fly ash settling ponds, municipal sewage discharge (e.g., ranging up to 0.28 mg Se/L),[43] and oil refineries. The concentration of Se in crude oil depends on the source. Reported Se concentrations in crude and heavy petroleum were 0.5–0.95 g/kg and 0.5–1.65 g/kg, respectively.[44] In a study of direct discharge from oil refineries in the San Francisco Bay, the effluent contained an average of 0.067 mg/L with a range of 0.006–0.156 mg/L. The portion of selenium in the form of selenite (50–76%) was relatively high compared with natural sources.[45] This study indicated that the cycling of selenium in the San Francisco Bay was complex as a result of large temporal and spatial variation in the chemical speciation of selenium. Substantial variation in the contribution of anthropogenic sources (oil refineries, municipal sewage plants) to the total selenium depended, in part, on the variation in the discharge of water from rivers into the Bay. Despite the input of selenium from these anthropogenic sources, the highest Se concentrations present in the South Bay (i.e., near the sewage plants) and the North Reach (i.e., near the refineries) were 0.36 µg/L and 0.29 µg/L, respectively. These values were within the range measured in other estuaries.

Diet

For the general population, the primary pathway of selenium exposure is food followed by water and air.[21,46] Estimates of the daily intake of selenium in various countries include the following: United States, 60–216 µg (mean = 71–152 µg, 1–2 µg/kg/day);[21,47,48] Canada, 113–220 µg;[49] Spain, 60–106 µg;[50] and Greece, ~95–110 µg.[51] The estimated mean daily intake of selenium in eight adults living in Southern California was 127 g (range, 90–168 µg).[52] In comparison, the estimated daily selenium intake by residents of high-selenium areas in China was 2,144 µg.[30] Factors affecting the Se concentration in foods include food type, soil type, time of selenium application, time of harvest, and soil conditions. Sodium selenite is a common source of selenium in multivitamins in doses ranging from 50–100 µg/tablet.

Selenates enter the food chain through plants; the contribution of drinking water to selenium in the human diet is small. Meats, fish, poultry, grains, and cereal products are the major food sources of selenium in the diet of the general population.[49,53] In a survey of the typical US diet, selenium in beef, white bread, pork, chicken, and eggs accounted for ~50% of the total selenium consumed in the diet; dairy products account for <10%.[54] Fish and feed animal organs (liver, kidney) are the foods containing the highest Se concentrations followed by meat and eggs; however, the best Se sources in the diet are selenium-enriched yeast, wheat, and other plant material because of the greater Se bioavailability these sources have compared with animal sources.[55]

Selenium Species

Selenate and selenite are the main inorganic selenium species in the diet. Higher plants absorb selenium preferentially as selenate via the sulfur-binding enzyme, permease; however, organic selenium compounds account for the major portion of selenium in vegetables and cereals.[56] Wheat is a non-selenium accumulating plant. In a study of spring wheat grown in selenium-rich soil in India, the total selenium concentrations in two samples were ~83 µg/g and ~183 µg/g, respectively, dry weight.[57] Selenate accounted for ~2–6% of the total selenium species. Selenium in animal tissue occurs in a variety of forms including organic (e.g., selenomethionine, selenocysteine) and inorganic (e.g., selenotrisulfide, selenopersulfides, metallic selenides) selenium species.[58] Over half of the selenium in straw eluted as selenate; selenite was not detected. Inorganic selenate and selenite predominate in water.

Bioavailability

Selenium bioavailability depends on a variety of factors affecting Se content in food including Se soil content, animal feed use, Se-containing fertilizers, plant uptake/metabolism, and Se species with inorganic Se typically being less than organic Se.[59] Furthermore, the

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bioavailability of inorganic selenium in plant-derived foods (e.g., wheat) is relatively high, whereas the bioavailability of selenium in animal-derived foods (e.g., fish)[60] is low to moderate.[61,62] No statistically significant differences in serum selenium were detected in 11 volunteers consuming Se-rich fish (mean = 115 ± 31 μg Se/day) compared with a control group eating a normal diet (77 ± 25 μg Se/day).[63] In the group of volunteers fed similar amounts of selenium as selenium-enriched wheat, the mean selenium concentration in the serum and the platelets increased by 17% and 30%, respectively, compared with controls. The difference was statistically significant ($P < 0.01$). Most,[64,65,66] but not all, animal studies[67] indicate that Se in seafood has relatively low (i.e., 35–60%) bioavailability compared with selenium as selenite (100%). These studies also indicate that the Se bioavailability as selenite in animal species is less than the bioavailability of selenate or selenomethionine.

The predominant Se species in drinking water is selenate depending on the pH, oxidation–reduction potential (E_h), and the presence of metals. Based on comparisons of average daily selenium intake and whole blood selenium concentrations in humans, the bioavailability of selenium is lower in water than in food.[68] The differences in bioavailability depend on a variety of factors including the criteria for an end point (e.g., platelet glutathione peroxidase activity),[69] physiochemical properties (e.g., pH, E_h), and dietary factors (selenium deficiency, lipids, metals). The formation of metal complexes with selenium reduces Se bioavailability in fish and water. Although the specific selenium compound in fish has not been identified, animal studies indicate that selenium absorption and uptake by erythrocytes in birds fed marine selenium (fish, mussel, and/or shrimp meal) differ depending on the type of selenium (e.g., selenite, selenate, selenocystine, selenomethionine).[70]

Concentration

Most agricultural crops contain <1 mg Se/kg dry weight. Fruits and vegetables typically contain <0.01 mg Se/kg, although root vegetables usually have higher Se concentrations.[71] In a Chinese study of plants from areas of high Se content and the occurrence of selenosis, corn samples contained an average Se concentration of 8.66 mg/kg (range, 0.55–44 mg/kg) and rice contained an average Se concentration of 4.0 mg/kg (range, 0.3–20.2 mg/kg).[72] Fruits and vegetables usually contain low Se concentrations (<0.01 mg/kg), whereas cereals contain intermediate Se concentrations (0.01–0.31 mg/kg fresh matter). A study of fruits and vegetables grown in saline drainage water containing 30–350 μg Se/L near the Kesterson Reservoir demonstrated statistically significant increases in Se concentrations in tomatoes (mean = 0.068 mg/kg) and cantaloupes (mean = 0.034 mg/kg), but not in honeydew melons (mean = 0.24 mg/kg) when compared with controls.[73] Based on the average consumption of these foods, the ingestion of these foods was not considered a public health concern.

The South American nut, coco de mono (*Lecythis ollaria* Loefl., monkey's coconut), contains high Se concentrations. When grown on selenium-rich soil in South America, coco de mono nuts contain substantial amounts of selenocystathionine (7–12 g/kg dry weight).[74] Brazil nuts (*Bertholletia excelsa* Bonpl.) also contain high Se concentrations (2.54 mg/kg) because they are cultivated in the seleniferous soils of the Andes Mountains.

The Se concentration in grain and dairy products varies considerably; however, these foods typically contain lower Se concentrations than meats (i.e., ~0.3 mg Se/kg) and fish. A study of 315 *whole* fish samples from 109 stations across the United States demonstrated a geometric mean of 0.42 mg Se/kg with a maximum of 2.3 mg Se/kg (85th percentile, 0.73 mg Se/kg).[75] Fish spending their life in the open ocean away from the shoreline also contain detectable Se concentrations. The ranges of Se concentrations as wet weight in the muscle of black marlin and blue marlin were 0.4–4.3 mg/kg and 2.5–4.2 mg/kg, respectively.[76] Selenium concentrations in beef and poultry organs (e.g., liver, kidney)[77] are usually higher (~0.5 mg/kg) than muscle.[54,78] A study of Swedish fishermen consuming a mean of 800–900 g marine fish/week demonstrated a 10–15% higher plasma selenium concentration than age-matched controls consuming ~½ the amount of fish as the fisherman.[79] Although the difference was statistically significant, the overall clinical impact was limited because the mean plasma Se concentration in the high-fish consumption group was low (~0.1 mg/L). Considerable loss of volatile Se compounds from food may occur during the cooking process.

ENVIRONMENTAL FATE

The primary factor determining the fate and bioavailability of stable selenium compounds in the environment is the oxidation state; selenides (2−) and elemental selenium (0) are water-insoluble, whereas inorganic alkali selenites (4+) and selenates (6+) are water-soluble. Elemental selenium is stable in soil. The alteration of selenium bioavailability and subsequent partitioning of selenium in the environment primarily depend on several factors including pH, E_h (oxidation–reduction potential), biological activity, and the presence of

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metal oxides.[21] Selenium concentrations in water are usually low because of the precipitation of elemental selenium in sediment. Both selenite and selenate demonstrate substantial bioavailability; however, plants preferentially absorb selenates and convert them to organic compounds (selenocysteine, selenomethionine, dimethylselenide, dimethyldiselenide). Aquatic organisms (e.g., bivalves) can accumulate and magnify selenium in the food chain. The methylation of selenium, the subsequent volatilization of methylated Se species into the atmosphere and the deposition of selenite in rainwater are probably the major natural processes that recycle selenium in the environment.[21]

Air

The selenium concentration in ambient air typically is low (1–10 ng/m^3).[80] Biogeochemical cycling of selenium results from the volatilization of methylated selenides to the atmosphere from higher plants and freshwater algae; however, a net flux occurs from the atmosphere to the ocean.[81] Volatile selenium compounds include dimethylselenide, dimethyldiselenide, hydrogen selenide, and selenium dioxide. Hydrogen selenide rapidly oxidizes to water and elemental selenium.

Elemental selenium in fuel oxidizes to form selenium dioxide. Sulfur dioxide rapidly reduces airborne selenium dioxide released in emissions from combustion of fossil fuel to elemental selenium. Dry and wet deposition transports selenium from air to surface waters and soil.

Soil

Mobility

The major factors determining the transport of selenium in soils are pH and E_h. Figure 27.1 demonstrates the effect of these two parameters on selenium speciation. Elemental selenium is insoluble; thus, this form of selenium is not mobile under anaerobic conditions. Humic acids are the main Se reservoir in the soil.[82]

Selenium appears primarily as salts of selenic acids and selenious acids in the water present in soil. Insoluble heavy metal selenides and selenium sulfides predominate in acidic soils with large amounts of organic material. These forms of selenium also lack mobility.[83] Sodium and potassium selenites dominate in neutral, well-drained soil; however, aluminum and ferric oxides bind selenite in acidic or neutral soil. This interaction significantly limits the mobility of selenites under these conditions. Soluble selenate salts (6+) form in aerobic, alkaline (pH >7.5) soil. Sodium selenate is especially mobile in these environments as a result of its high water solubility and low adsorptive capacity for soil particles.[31] Most selenites (4+) are less soluble in water than the corresponding selenates as a result of their binding to iron and aluminum oxides; therefore, selenites are less mobile than the corresponding selenates.[84]

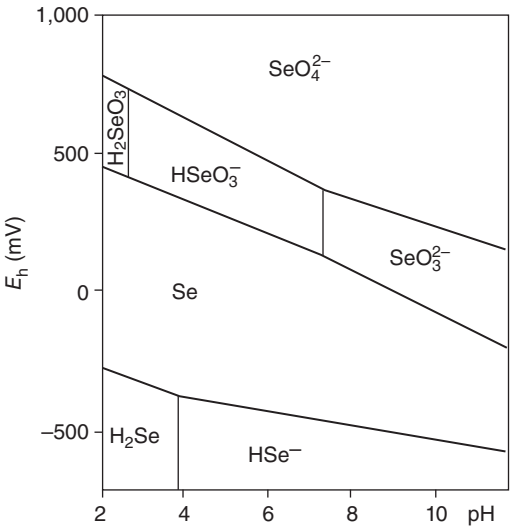


FIGURE 27.1. Effect of pH and redox potential (E_h) on selenium speciation in an aqueous system. (Adapted from Lauchli).[81]

Uptake

Metal selenides and elemental selenium (Se^0) are essentially insoluble; therefore, biological uptake is very limited. Plants preferentially accumulate selenates (i.e., principally sodium selenate) because this form is less bound to soil particles compared with selenites;[85] higher plants absorb selenium preferentially as selenate via high-affinity sulfate permease. Plants do not actively absorb selenites. Sulfate salinity inhibits the uptake of selenate by many plant species. Other factors that affect the uptake of selenium by plants include oxidation–reduction potentials (E_h), pH, soil type, the amount of organic material, and total selenium concentration.

Loss

Microorganisms methylate substantial amounts of elemental selenium and inorganic selenium compounds (e.g., sodium selenite) in soil to dimethylselenide and dimethyldiselenide. The return of selenium to the soil as selenite by rainwater completes the major natural process by which selenium recycles in the environment.

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Water

Speciation

The primary forms of selenium in aqueous environments are salts of selenious and selenic acids. Selenates and selenites predominate in fresh water under aerobic and alkaline conditions rather than organic selenium, whereas selenate is the thermodynamically stable form in seawater. In groundwater and ocean, selenate is the dominant Se form.[82] In acidic conditions, mild reducing agents (SO_2, ascorbic acid) easily reduce selenite to elemental selenium; the metalloid is stable over a wide range of pH. Elemental selenium is insoluble and poorly mobile in sediment. A study of estuarine wetlands in the San Francisco Bay demonstrated that ~50% of the selenium in sediment was present as elemental selenium and ~25–30% as organic selenium.[86] In the subtropical, selenium-rich areas of the Enshi Prefecture of the Hubei Province, China, the predominant form of selenium in 48 samples of surface water was hexavalent Se; the selenium leached from rock weathering and mine tailings.[30] Rainwater in the area contained ~29% hexavalent Se. Hydrogen selenide is unstable in water, resulting in rapid Se volatilization into the atmosphere.[29]

Concentrations

Accumulation of Se in the environment depends, in part, on the Se species present in the environment. *In vitro* studies indicate that organic selenium (i.e., selenomethionine) is more readily accumulated by organisms compared with selenite and selenate.[87] Concentrations above 2–5 μg dissolved Se/L water may cause bioaccumulation in the food chain with the *potential* to cause adverse effects, whereas concentrations of >1 μg dissolved Se/L water are safe for habitation by fish.[88] The relationship between the Se concentration in water and the development of toxicity in the environment is complex and depends on site-specific processes.[89]

In a study of the Kesterson Reservoir during the period of peak contamination, mosquito fish contained up to ~170 mg Se/kg compared with average concentrations in US fish of ~0.5 mg Se/kg.[90] The relative concentrations of selenium remained stable over several years as follows: fish > benthic insects > annelids > mollusks and crustaceans > periphyton. Over 50% of the selenium present in the sediments of these ponds appeared in the organic form. The fish present in these ponds concentrated selenium in visceral tissue (25–35 mg Se/kg wet weight) to a greater degree than in skeletal tissue (6–11 mg Se/kg wet weight).[91] During the period of heavy contamination at the Kesterson Reservoir, the intake waters averaged ~0.3 mg Se/L with peak Se concentrations exceeding 1.35 mg/L.[21,38] The maximum conductance in the water at the Kesterson Reservoir was greater than that in seawater with sodium and sulfate being the predominant ions.[81] Additionally, boron and molybdenum were present in this water at relatively high concentrations.

Selenium concentrations in contaminated environments decline following reduction in the selenium input to the environment. During the subsequent 10 years after Se discharges from the coal-fired plant to Lake Belews ceased, the Se concentration in lake water decreased from a peak of 20 to <1 μg/L without remediation measures. The Se concentration in sediments decreased by 65–75%, but the Se concentrations in sediment (1–4 mg/kg) were sufficient to contaminate bottom-dwelling fish as reflected by reproductive impairment.[41] In this ecosystem, sediment-detritus pathways replaced water as the primary route of Se exposure when the Se concentration in water significantly decreased.

Bioaccumulation

Chemicals accumulate in organisms by the direct uptake from the surrounding media and ingestion of particle-bound selenium (bioconcentration or bioaccumulation) as well as the uptake of the chemical by higher trophic levels of the food chain (biomagnification). Bioconcentration is the passive uptake of the chemical directly from water or sediment across biological membranes to the aquatic organism. The bioconcentration factor (BCF) is an estimate of the extent to which an organism accumulates a chemical from the aquatic environment; this value is defined as the steady-state concentration of a chemical in the aquatic organism divided by the concentration of that chemical in water. The octanol–water partition coefficients (K_{ow}) are theoretical measures of BCFs; the BCF may be estimated by the K_{ow} or derived from experimental studies. These estimated BCFs may differ from the actual bioaccumulation of the chemical based on experimentally derived bioaccumulation factors (BAFs). These differences result from the following: degradation of the chemical in the water (e.g., hydrolysis), rapid elimination of the chemical from the organism, inadequate equilibrium time, and the presence of substances (e.g., humic acid) that alter bioavailability and solubility.[92] The general categories of the potential for bioaccumulation of a chemical based on BCFs are as follows: <30, low; 30–100, moderate; 100–1,000, high; and >1,000, very high. However, calculated BCFs do not always correlate to the actual bioaccumulation of a chemical in aquatic

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organisms because of factors listed above, particularly the rate of elimination.[93]

The bioconcentration of selenium in aquatic organisms primarily involves that the dominant waterborne Se species, selenite, and, to a much lesser extent, selenate. Experimental studies suggest the uptake of selenium by organisms varies in different trophic levels; these differences reflect alternate mechanisms for the uptake of selenate, selenite, and selenomethionine. For example, marine bacteria (*Pseudomonas marina*)[94] and marine phytoplankton[95] actively concentrate selenite, whereas little adsorption of selenate occurs. In aquatic systems, the selenate uptake is usually less than that of selenite, which more easily adsorbs and incorporates into the organic Se pool of the organism.[96]

The ratio of selenium in the organism at equilibrium to the Se concentration in water defines the bioconcentration (i.e., calculated BCFs) and bioaccumulation (i.e., experimentally derived BAFs) factors. The greatest increase in Se uptake in freshwater lakes and reservoirs occurs at the lower end of the food chain (i.e., between water and algae),[96] where the bioconcentration factor is at least several hundreds to several thousands. Certain benthic organisms (e.g., clams) accumulate Se from the intake of phytoplankton and, to a lesser extent, marine water in the sediment zone. Therefore, the estimated bioconcentration factors based on regression equations using physical properties (octanol/water partition coefficients, water solubility) may not correlate with experimentally derived bioaccumulation factors observed in the field. The bioaccumulation factors for selenium are not well defined for specific animal species because of variations in several factors including Se kinetics, Se species in the diet, Se concentration/species in aqueous environment, sample size, analytical methods (wet vs. dry weight), location (freshwater vs. saltwater), and the type of sample (skeletal muscle vs. internal organ).

Most published bioconcentration factors for selenite and selenate in freshwater fish are relatively low, ranging from 8–52.[97] Fish accumulate much more Se from the food chain than from the aquatic environment. The bioconcentration factors for an experimental study on trout were as follows: viscera (62.1), muscle (3.2), and whole trout (10.5).[21] *In vivo* studies suggest that Se bioaccumulation is slower with selenite or selenate than selenomethionine.

When the bioaccumulation of selenium results from the consumption of selenium-contaminated diets, hazards to fish and birds are more closely correlated with their tissue levels of selenium rather than the concentration of selenium in their aqueous media. The difference in the toxicity of various selenium species and the rate of biochemical transformation (i.e., formation of organic selenium in the aquatic environment) complicates the assessment of the risk from specific Se concentrations in water and animal tissue. Elevated selenium concentrations in marine waters do not result from high mercury concentrations[98] as suggested by a previous study that suggested selenium counteracted mercury toxicity.[99]

Biomagnification

Higher organisms may accumulate chemicals via biomagnification that involves the uptake of substances via the food chain. Biomagnification is highly dependent on the bioavailability and toxicokinetics of the specific chemical species.[93] In the food chain, selenium occurs both as organic selenium (e.g., selenomethionine) and as inorganic selenium (selenite, selenate). Selenium speciation in food is not well defined; however, substantial portions of the selenium in the food chain probably exist as selenomethionine rather than inorganic Se.[88] Biomagnification causes progressively higher concentrations of an element or substance in organisms at successively higher trophic levels. Selenium does accumulate in most aquatic organisms; these organisms can usually convert Se to inert and soluble forms. However, the Se concentration does not increase significantly between trophic levels once selenium enters the food chain via lower aquatic organisms. Additionally, the relatively rapid Se elimination from organisms and the wide variation of selenium in organisms limit selenium biomagnification in the higher portion of the food chain.

Although fish predators accumulate selenium from Se-contaminated food, the bioaccumulation of selenium among fish species is not necessarily related to trophic status. In a study of the San Joaquin River system, the Se concentration increased in the food chain from filamentous algae to invertebrates but not usually from invertebrates to fish.[100] This study implies that Se-enriched detritus is an important vector for Se transfer through the food chain. Fish predators from higher trophic levels accumulate less selenium than their prey that consumes higher Se concentrations in their diet. A study of Chinook salmon-fed fishmeal from high-selenium mosquito fish indicated that fish do not accumulate selenium to concentrations greater than those present in food based on whole-body samples. Additionally, there are substantial differences in Se distribution within the body. In adult fish, Se accumulates in ovaries more than muscle. Consequently, the hazard of selenium contamination to fish and wildlife may be limited to a relatively few species in a restricted area

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depending on the exposure pathway (e.g., food sources) and the selenium concentration in the water.

DOSE EFFECT

Acute Toxicity

Toxicity depends on the chemical form of selenium; however, the toxicity of most forms of selenium (elemental selenium, organoselenium) is low. Human toxicity from environmental exposure to elemental selenium and selenium salts is rare; most acute toxicity results from inorganic selenium. Exposure to selenious acid or selenium dioxide can cause serious toxicity. In animal studies, selenite is slightly more toxic than selenate.

Selenite and Selenate Compounds

Consumption of 1–5 mg sodium selenite/kg by five adults caused nausea, vomiting, abdominal pain, and tremor that resolved in 24 hours. In a study of 201 patients ingesting a liquid selenium supplement containing over 200 times the labeled amount of sodium selenite, the median amount consumed was 989 mg (range, 41–5,875 mg) over 29 days (range, 1–109 days).[101] These patients complained of nausea, vomiting, diarrhea, fatigue, hair loss, joint pain, nail changes, headaches, and tingling. The symptoms gradually resolved over a few months, but some symptoms remained at 90-day follow-up. A case report associated the ingestion of an estimated 10 g sodium selenite (96% purity) with the development of vomiting, diarrhea, metabolic acidosis, and refractory hypotension.[102] The 75-year-old man died soon after admission to the intensive care unit, despite cardiopulmonary resuscitation and supportive care.

Vitamin C reduces selenite to the less toxic elemental form of selenium. Over 77 days, a 57-year-old female ingested 31 mg total Se/day along with 1,000 mg vitamin C and many other vitamins and trace metals.[103] Speciation of the selenium indicated that the tablets contained ~80% sodium selenite and ~20% elemental/organic selenium. Four days after stopping these supplements, her serum Se concentration was 0.528 μg/mL. During the time she ingested these supplements, she developed white horizontal streaks on her fingernails and a diffuse paronychia. Additionally, she had marked alopecia, nausea, vomiting, sour-milk breath, and fatigue. She recovered without sequelae. Following the daily ingestion of ~24 mg Se for 7 weeks, a 55-year-old woman developed diffuse, symmetrical hair loss, myalgias, arthralgias, fatigue, and poor concentration.[104] She recovered without sequelae following cessation of Se use. Frequent loose stools, increased serum hepatic enzymes, and transient T-wave inversions in the anterior and lateral leads developed in a young girl following the intentional ingestion of sheep drench containing 1.16 g sodium selenate (22 mg sodium selenate/kg).[105] She recovered without sequelae. The initial serum Se concentration was 3.1 μg/mL (normal range, 0.066–0.111 μg/mL).

Selenium Dioxide

Selenium dioxide is a white crystalline solid that decomposes in the aqueous environment of the gastrointestinal tract to selenic acid. A 17-year-old adolescent died after developing coma, asystole, and apnea 2 hours after ingesting an unknown amount of selenium dioxide,[106] whereas the estimated ingestion of 2 g selenium dioxide produced hematemesis and erosion of the gastrointestinal tract that resolved with supportive care.[107]

Selenious Acid

Selenious acid is the most toxic form of selenium; ingestion of this compound often causes fatalities as a result of refractory hypotension from direct myocardial depression and peripheral vasodilation. A 15 mL ingestion of gun blue (2% selenious acid) by a 2-year-old[108] and a 30–60 mL ingestion by an adult[109] resulted in death.

Chronic Toxicity

No clinical or biochemical signs of toxicity were observed in an American study of 142 volunteer farmers, who were exposed to selenium (mean daily intake of 239 μg Se/day with a range of 68–724 μg Se/day) in highly seleniferous areas of South Dakota and Wyoming.[110] Selenium doses of >900 μg Se/day are usually necessary to cause selenium toxicity with an average estimated selenium dose in Chinese residents with selenosis of ~200 μg/kg/day based on total selenium estimated from *retrospective* studies in the Wudang Mountains in Western China.[111,112] The inhabitants ingested food primarily from plants grown in this highly seleniferous area with mean Se concentrations in water of 0.54 mg/L and soil of 0.01 mg/L. The diagnostic sign of chronic selenosis was morphological changes in their fingernails. The selenium content was not speciated; hence, higher selenium concentrations may be tolerated when the selenium in the diet is less bioavailable (e.g., marine diet).

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The estimated dietary Se intake was much higher (15,000–38,000 μg/day) during an epidemic of chronic selenosis (1961–1964), when a severe drought altered normal dietary habits, health, and cultural practices in that part of China.[113] Food was cooked over indoor, open pits that allowed the volatilization of large amounts of selenium from highly seleniferous coal (mean = 300–400 mg Se/kg). There was also increased consumption of high Se-containing vegetables. Consequently, the data should be extrapolated cautiously to different dietary sources (e.g., plant vs. animal) or different geographic areas, where the Se toxicity and exposure pathways are more limited. American diets contain more protein, methionine, and zinc that reduce Se toxicity from animals.[114] Additionally, vitamin E deficiency and low dietary sulfates enhance the chronic toxicity of selenium.[115]

Analysis of the Chinese studies indicates that daily Se doses up to ~1,500 μg Se can be ingested without the development of selenosis. Analysis of corn and rice grown in the Enshi area of China indicates that selenomethionine was the main Se species present in the diet of those Chinese developing chronic selenosis.[116] The ingestion of an average of 5,000 μg Se/day over a 10-year period during a severe drought in China was associated with nail deformities, alopecia, skin lesions, tooth decay, and neurological changes (paresthesias, hyperreflexia).[117] This study also reported the daily ingestion of 1,000 μg over 2 years by a 62-year-old Chinese male. He was asymptomatic, but nail changes (fragile, thickened) and a garlic odor were present. In chronic studies of rats, no apparent toxicity was observed following the administration of 4 ppm Se as sodium selenite in drinking water when compared with controls.[118]

TOXICOKINETICS

Absorption

Inhalation

Human data on the retention rate of inhaled selenium are limited. A study of workers exposed to selenium dioxide in a plant that manufactured rectifiers suggested that Se absorption occurs through inhalation based on the two to four times reduction in the urine selenium concentrations of workers after their selenium dioxide exposure was substantially decreased following the completion of engineering controls.[119] Animal studies indicate that the lungs absorb selenium compounds well, but the rate of absorption depends on the chemical form of selenium. In animals exposed to aerosols for 4 hours, the absorption of elemental selenium from the lungs was less (57%) than selenious acid (97%).[120]

Oral

The gastrointestinal tract absorbs most selenium compounds well, primarily in the duodenum and cecum by active transport via the sodium pump.[121] In volunteers receiving 1 mg Se in solution as sodium selenite or selenate, the apparent absorption (i.e., total Se dose minus fecal Se excretion) of selenate-Se was greater (94% ± 4%) than selenite-Se (62% ± 14%).[122] Data on the bioavailability of different Se species are limited. Animal studies indicate that the mechanism of absorption differs with various selenium species and Se sources.[123] Some elements decrease Se absorption including arsenic, calcium, iron, lead, and sulfur.

Whereas Se absorption as selenite occurs via passive diffusion, the absorption of selenate results from the action of sodium-mediated carrier transport shared with sulfate. The absorption of selenate-Se from the gastrointestinal tract is usually greater than selenite-Se. The absorption of selenate, but not selenite, occurs in the intestine without prior metabolism.[21] Animal studies suggest that the gastrointestinal tract also absorbs selenious acid well (i.e., ~85%), but the absorption of elemental selenium is substantially less (~50%).[120] For unknown reasons, Se bioavailability from tuna and other seafood is significantly lower than other foods.[124]

Dermal

Limited data on the dermal absorption of selenium compounds do not suggest that selenium is significantly absorbed through the skin. In a study of 15 volunteers applying 2.5% selenium disulfide to their torso and leaving the suspension on their skin overnight, the serum Se concentrations were not statistically significantly increased, when measured the following day and compared with pre-application concentrations.[125] A study using rat skin demonstrated that ~10% of a 0.1 mol solution of sodium selenite applied to the skin was absorbed within 1 hour.[126]

Distribution

In the blood, selenium binds primarily to plasma proteins (selenoprotein P, glutathione peroxidase, albumin).[127] Following an intravenous injection, selenium selenite distributes primarily to the liver and kidney.[128] The total amount of selenium in the body averages ~14 mg Se in the US general population with

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a range of 3–20 mg Se depending on the intake of Se.[36] The plasma contains ~2/3 of selenium in selenoprotein P and ~1/4 in glutathione peroxidases with the remainder attached to albumin.[129] The main storage form of selenium in the tissues is selenomethionine.

Biotransformation

Methylation is the detoxification pathway for elemental selenium prior to the dose-dependent excretion of these metabolites in urine or expired air.[130] In biological systems, selenium is methylated after the reduction of selenite and selenate to hydrogen selenide, similar to the reduction of sulfites and sulfates to hydrogen sulfide; glutathione is an essential component of the reduction of selenium compounds.[131] The major reactions in selenium metabolism include: 1) reduction of selenite by cellular glutathione to selenide similar to the reduction of sulfites and sulfates to hydrogen sulfide; 2) incorporation of selenide into selenoproteins (selenoprotein P, glutathione peroxidase, type I 5′-iodothyronine deiodinase) via selenocysteine after transformation to selenocysteinyl tRNA or selenophosphate; and 3) methylation of selenide to metabolites (monomethylselenol, trimethylselenonium, dimethyldiselenide, dimethylselenide) followed by renal excretion of the methylated metabolites.[132] Formation of hydrogen selenide by stepwise reduction is the key intermediate step in the biotransformation of inorganic selenium as demonstrated in Figure 27.2. The methylated forms are generally less toxic than the non-methylated selenium compounds.[133] The conversion of selenates to dimethylselenide is more complicated than the conversion of selenide to dimethylselenide. There are a variety of potential selenium metabolites for selenium biotransformation in humans including trimethylselenonium ion, selenite, selenate, selenosugar 1, and selenosugar 2.[134]

Elimination

Humans

In humans at low selenium doses, the kidneys and intestines each excrete ~1/2 of the absorbed Se dose;[135] trimethylselenonium is a minor component (1%) of urinary excretion of selenium in diets supplemented with either selenomethionine or selenate.[136] A tri-exponential elimination phase appears after the ingestion of therapeutic selenite doses. The initial elimination phase is rapid (i.e., 1 day), whereas the second phase (8–20 days) and third phase (65–116 days) are much longer.[137] The initial elimination Se half-lives during acute intoxication by ingestion with selenious acid[138] and selenic acid[139] were 12 hours and 17.5 hours, respectively. Differences in the excretion pattern occur between selenium species. In a study of volunteers given 200 µg Se supplements as selenomethionine or selenate over 32 weeks, the mean daily selenium excretion for selenate was 57% of the daily Se dose compared with 27% for selenomethionine.[136]

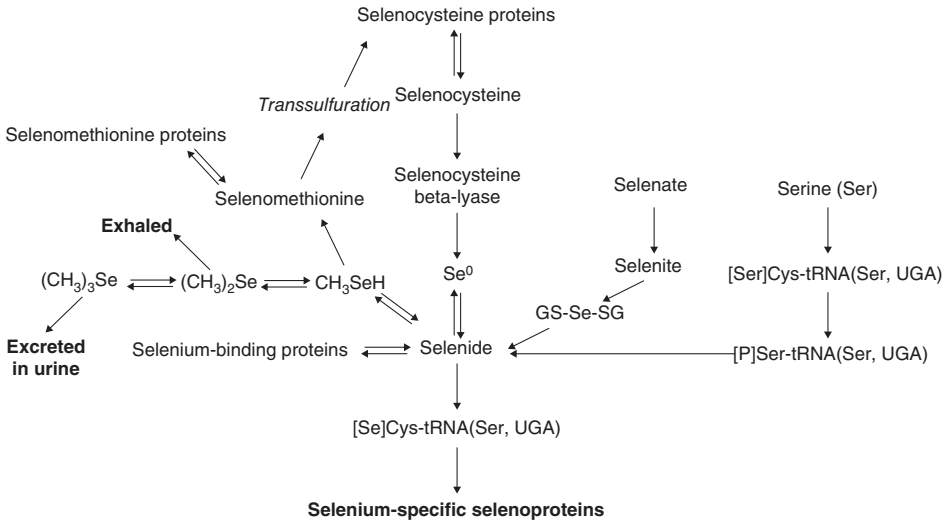


FIGURE 27.2. Inorganic and organic selenium metabolism. *Abbreviations:* dimethylselenide = $(CH_3)_2Se$; GSSeH = selenopersulfide (unstable); GSSeSG = glutathione selenotrisulfide; methylselenide = CH_3Se; S_0 = selenium; trimethylselenide = $(CH_3)_3Se$. (Adapted from ATSDR)

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Animals

Studies in animals suggest that the formation of the inactive metabolite, trimethylselenonium ion, becomes an important mechanism of detoxification following the absorption of high Se doses. At doses of 1.5 mg ^{75}Se/kg body weight, trimethylselenonium ion was the major urinary metabolite, accounting for 57–69% of the urinary metabolites.[140] The excretion of this metabolite represented 16–25% of the original ^{75}Se dose. At near-lethal Se doses, the excretion of dimethylselenide into expired air becomes an important route of Se elimination. After the injection of 0.5 μg sodium selenite/kg body weight in marine fish, the biological half-lives of selenium in the liver, gills, and skin were ~2.1 days, 2.1 days, and 5.3 days, respectively.[141] Following the inhalation of an aerosol of selenious acid, the dogs excrete ~50% of the absorbed selenium (mostly in the urine) with a biological half-life of 1.2 days.[142] The terminal half-life representing ~20% of the absorbed dose was 30–70 days.

Maternal-Fetal Kinetics

Animal[21] and human[143] studies indicate that selenium has limited potential to cross the placenta with longitudinal dietary Se supplementation studies on lactating mothers indicating Se concentrations in breast milk vary with maternal Se intake.[144] Limited data on maternal and cord blood concentrations are inconsistent. In an Indian study of 82 mothers and full-term infants, the mean plasma selenium concentration was 54.17 ± 1.34 μg/L in the neonates compared with 70.63 ± 1.62 μg/L in their mothers.[145] Maternal age, parity, and socioeconomic status did not affect the plasma selenium concentrations. However, a study of 216 mothers from three geographic regions in Northern Europe (Finland, Estonia, Russia) found higher whole blood Se concentration in full-term infants than mothers at term as measured by electrothermal atomization/atomic absorption spectrometry; these findings suggest an active transport system for fetal selenium.[146]

A study of rats suggests some transfer of selenium from the mother to the offspring occurs via breast milk.[147] A Greek study of babies breastfed up to 6 months of age demonstrated that these babies received ~5–11 μg Se/day.[51] The selenium concentration in breast milk is variable depending on maternal diet, the phase of nursing (e.g., selenium concentration declines during the first month of lactation), and the type of milk (e.g., colostrum > mature milk). In a cross-sectional study of 100 Italian breastfeeding women with 82 exclusively breastfeeding, the mean Se concentration in mature milk samples was 12 ± 3 μg/L (ng/g) with a range of 6.5–20 μg/L (ng/g) as measured by hydride generation/atomic fluorescence spectrometry.[148] The selenium concentration in milk decreases with the time since delivery. The Se concentration in 78 milk samples from 38 Austrian mothers declined during the first 10 months of lactation from 23.9 ± 12.0 μg/L in postpartum colostrum to 11.4 ± 3.0 μg/L in mature milk.[149]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

Selenium is an essential trace metalloid incorporated as selenocysteine in several enzymes including thioredoxin reductase (antioxidant/intracellular control of redox potential), glutathione peroxidases (antioxidants),[150] and type I and II iodothyronine 5′-deiodinase (biotransformation of thyroxine (T_4) to triiodothyronine (T_3)).[59] There are ~25 selenoproteins involved in deactivation of thyroid hormone, antioxidant activity, T cell immunity, and modulation of inflammatory responses. The catalytic activity of all three members of the deiodinase enzyme family requires selenocysteine at the active site.[151] The selenium-containing enzyme, glutathione peroxidase, facilitates antioxidant defenses by the destruction of hydrogen peroxide and the reduction of tissue peroxide concentrations.[20] Consumption of selenium-poor diets results in deficiencies of this enzyme in animals and humans.[152] Selenium supplementation in healthy subjects with low Se concentrations increases glutathione peroxidase activities, but Se supplementation does not alter changes in the lipid peroxidation defense mechanisms. A double-blind, randomized study of 24 patients in New Zealand with asthma detected a statistically significant clinical improvement in the selenium-supplemented group despite the absence of alterations in lung function.[153] The exact role of low selenium concentrations in the pathogenesis of asthma in New Zealand remains unclear.

Animal studies suggest that Se cytotoxicity results from the prooxidant catalytic activity of the selenide (RSe^-) anions that produce superoxide anions, hydrogen peroxide, and other reactive metabolites (e.g., hydroxyl radicals).[154,155] Methylating reactions in plants and animals along with antioxidant defenses counteract the toxicity of selenium species.[154] In animals fed selenium-deficient diets, glutathione peroxidase activity and glutathione synthesis increase. These animals are more resistant to acetaminophen and aflatoxin B_1 toxicity and more sensitive to diquat toxicity than

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controls. Nevertheless, the effectiveness of dietary selenium repletion on human diseases linked to selenium deficiency (e.g., the familial cerebral degenerative cases known as Batten's disease) remains unproven.[156]

Deficiency

Selenium is a key component of the antioxidant glutathione peroxidase enzymes, thioredoxin reductase, iodothyronine deiodinases, and sperm capsule selenoproteins present in the mid-piece region of the sperm tail. Fatal cardiomyopathy developed in patients on long-term parenteral nutrition with **low** selenium concentrations (i.e., 5–12% of normal plasma and other tissue values).[157] Myalgias along with elevated serum muscle enzymes may occur in selenium-deficient patients without cardiomyopathy.[158] Selenium deficiency may impair the activity of Se-containing type I deiodinase, particularly in older patients, therefore, inhibiting the conversion of T_4 to T_3. T_4 is the most sensitive measure of selenium deficiency and subsequent iodine repletion. In iodine-deficient patients, the Se supplementation (e.g., 2,500 μg Se over 7 days) may produce hypothyroidism.[159]

Keshan Disease

Keshan disease (KD) is a cardiovascular disease affecting primarily children and young women,[160,161] particularly in northeastern China, where the disease was first reported in 1935.[162] Selenium-containing glutathione peroxidase 1 (GPx-1 gene product) is the most prevalent glutathione peroxidase occurring in the cytosol of all cells; this selenoprotein catalyzes lipids to lipid alcohols and hydrogen peroxides to water, resulting in a reduction of oxidative stress.[163] Keshan disease results from an environment–gene interaction with the main risk factors including low GPx-1 activity (variance at codon 198 in *GPx-1* gene), family history of KD, and living in an endemic (Se-deficient) area.[164] The principal pathological findings are that multifocal pallor, necrosis, myocytolysis, and fibrosis of the myocardium manifest clinically as cardiac enlargement, congestive heart failure, cardiogenic shock, and death, respectively. Keshan disease is endemic in Se-deficiency areas of China. The incidence of acute and subacute KD in these areas diminished dramatically with selenium supplementation; however, chronic KD appeared in endemic areas of China after adequate Se supplementation. This occurrence indicates that Se deficiency is a predisposing condition rather than the primary cause of this disease.[165] The estimated number of cases of KD and chronic KD in Chinese patients is 1,675,500 (95% CI: 1,608,500–1,747,300) and 379,800 (95% CI: 346,700–412,800), respectively.

Kashin–Beck Disease

Kashin–Beck ("Big Bone") disease is an endemic, chronic osteoarthropathy of young children in China, Russia, and Korea that primarily involves the cartilage (atrophy, degeneration, necrosis). The main features of the disease are shortened stature resulting from multiple focal necroses in the growth plate of tubular bones, degenerative joint disease, and joint deformities. The Russian surveyor, I.M. Yurensky, first described bone deformities in eastern Siberian residents along the Urov River. Several years later, the Russian military physician, Nikolai Kashin, documented bony abnormalities that he associated with Urov disease.[166,167] In 1906, the Cossack Army physician, Evgeny Beck, published a monograph, *Osteoarthritis Deformans Endemica*, describing his medical observations of this degenerative disease; subsequently, the disease became known as Kashin–Beck disease.[168]

Currently, the disease occurs primarily in China where an estimated 1–3 million people are afflicted with the disease in a pattern consistent with areas of Se deficiency in the soil.[169] The etiology of this disease is probably multifactorial[170,171] with potential contributing factors including Se deficiency (and the resultant decrease in antioxidant activity), contamination of grain by fungi (*Fusarium sporotrichiella*), high organic matter concentrations (e.g., fulvic acid) in the soil, and complex genetic susceptibility involving multiple pathways affecting articular chondrocytes.[172,173] Selenium supplementation alone does not completely prevent the occurrence of Kashin–Beck disease.

Mechanism of Toxicity

Substantial variation in the toxicity of various selenium species results from differences in physiochemical properties and the natural distribution of these species. Selenium readily substitutes for sulfur in biomolecules and many biochemical reactions, potentially disrupting cellular processes and weakening support structures (e.g., keratin); however, the mechanism of toxicity is unclear. Various substances (e.g., arsenic, cysteine, heavy metals, sulfate, vitamins C and E) can alter Se toxicity. Complex interactions of selenium with metals, vitamins, and other nutrients usually reduce the toxicity of selenium.[56] Furthermore, selenium modifies the toxic effects of a variety of metals (e.g., arsenic, cadmium, copper, lead, mercury, silver, zinc).[36]

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Postmortem Examination

Humans

Typical autopsy findings following fatal selenious acid ingestions include a strong garlic-like odor emanating from the body cavity along with diffuse mucosal hyperemia and focal hemorrhage of the gastric cardia and fundus.[174] The postmortem examination of a patient dying from the inhalation of *selenious acid* demonstrated myocardial and pulmonary infarctions, ascites, obstructive mucous plugs in the bronchi, interstitial pulmonary emphysema, bronchopulmonary dysplasia, barotrauma, and *Hemophilus and Legionella dumoffii* infection.[108] Other histological abnormalities associated with the absorption of toxic amounts of selenious acid include hemolysis, liver necrosis, edema of the kidneys, and red pigmentation of all viscera.

Postmortem examination of patients dying after suspected surreptitious Se administration (Se species unknown) includes pulmonary edema with pleural effusion, lymphoid infiltrates surrounding smaller bronchi and bronchioles, vascular congestion, congestion of the kidney, and necrosis of the proximal renal tubules.[175,176] The highest Se concentrations occurred in the stomach, lungs, and kidneys with the selenium concentrations declining over time. Postmortem analysis of cases with no abnormal Se sources demonstrated tissue Se concentrations in the following descending order: kidney, liver, spleen, pancreas, heart, brain, lung, bone, and skeletal muscle.[177]

Animals

Acute Se intoxication produces myocardial necrosis in sheep, pigs, and cattle.[178] Porcine poliomyelomalacia is the only form of selenium intoxication that produces obvious damage to the central nervous system. An autopsy of pigs dying after the ingestion of feed containing high (i.e., 3%) Se concentrations revealed abnormalities in the following areas: skeletal muscle (disintegration of myofibrils, hyperplasia of sarcolemma in nuclei, hyalinization, loss of striations, diffuse swelling), myocardium (vacuolation, pyknosis, eosinophilia), and spinal cord (demyelination of the ventral horns, loss of neurons, proliferation of glial cells).[179] Because keratin contains substantial Se following ingestion, keratinocyte abnormalities frequently occur during selenium intoxication. Early changes include abnormal maturation of the keratinocytes in the stratum spinosum; more advanced lesions involve ballooning degeneration and necrosis of the keratinocytes.[9] Alopecia results from atrophy of the primary hair follicles.

CLINICAL RESPONSE

Acute Toxicity

The acute ingestion of large doses of selenate and selenite produces gastrointestinal irritation manifested by nausea, vomiting, abdominal pain, loose stools, tremor, and mild hepatic inflammation. Although the toxicity of most selenium compounds is relatively low, exposure to selenious acid or selenium dioxide can cause serious human toxicity.

Selenious Acid

Acute ingestion of selenious acid is almost invariably fatal. Stupor, respiratory depression, hypotension, and death can occur several hours after ingestion.[180] Severe hypotension develops as a result of decreased myocardial contractility and reduced peripheral vascular resistance.[181] Terminal respiratory failure occurred after a selenious acid ingestion (15 mL gun bluing solution), despite the use of an extracorporeal membrane oxygenator. Red pigmentation of the nails, hair, or teeth along with a garlic odor on the breath is characteristic of selenium poisoning.[182]

Selenium Dioxide

Selenium dioxide forms the weak acid and strong oxidant, selenic acid, following contact with water. The ingestion of a product containing about 2 g selenium dioxide produced nausea, vomiting, abdominal pain, hematemesis, and gastric ulcerations that resolved with supportive care.[107] Ingestion of larger amounts of selenium dioxide caused apnea, asystole, and death.[106]

Environmental Exposure

The interpretation of reports associating excessive environmental selenium exposures with adverse effects is complicated by case series design, lack of confirmatory laboratory tests, inadequate exclusion of alternate explanations, and conflicting results. The effects of chronic selenium poisoning (selenosis) in residents of geographical areas with high selenium content characteristically involve a pruritic rash, brittle hair, and yellow, brittle, dystrophic nails with paronychia. Yellowish-white or red longitudinal streaks or transverse lines may appear on the nail surface beginning on the thumb. Loss of the fingernail occurs frequently. Skin lesions develop primarily on the limbs and scalp manifest by erythema, vesiculation, secondary infection,

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and reddish discoloration. Temporary alopecia occurred after the large consumption of the South American nut, coco de mono (*L. ollaria* Loefl., monkey's coconut), containing high Se concentrations.[183,184] Garlic odor on breath develops as a result of excessive selenium exposure because of the expiration of dimethylselenide in exhaled air.[56] In a study of 201 patients ingesting a liquid selenium supplement containing over 200 times the labeled amount of sodium selenite, the most frequent complaints were as follows: diarrhea (78%), fatigue (72%), hair loss (70), joint pain (67%), nail discoloration/brittleness (61%), nausea (57%), headache (45%), foul breath (37%), and rash (26%).[101] Less frequently reported symptoms included memory loss, mood changes, and tingling. Complete loss of scalp hair occurred in ~18% of the patients with alopecia. A follow-up questionnaire suggested that some of the symptoms persist over 90 days including nail changes, fatigue, hair loss, arthralgia, myalgias, and memory loss. In a case series of nine patients ingesting the same product, symptoms began within 1 week of starting the supplement; these patients complained of similar symptoms with the exception of three patients with tinnitus.[185]

Additional clinical effects reported in Chinese residents with chronic selenosis include dental caries, fatigue, irritability, muscle tenderness, tremor, hyperreflexia, emotional lability, depression, nervousness, nausea, vomiting, and metallic taste. However, the exact role of selenium in the causation of these symptoms remains unclear because of the concurrent effect of severe climatic conditions on the health of the Chinese populations exposed to excessive selenium.

The data linking excessive Se exposure with neurological diseases are weak. In a study of this population, abnormalities of the central nervous system occurred in only *one of five* villages with a high prevalence of selenosis. No autopsies or objective neurological testing were done to confirm the role of selenium in producing neurological abnormalities.[186] A cohort study of 5,182 Italian residents in an area with high selenium concentrations in drinking water (7–9 μg/L) demonstrated a standardized incidence ratio of 4.22 (95% CI, 1.15–10.8) for amyotrophic lateral sclerosis when compared to surrounding residents using drinking water with low selenium content (<1 μg/L).[187] A number of study limitations prevent conclusions regarding the causal role of selenium including the lack of control of confounding variables, small case numbers, and no selenium exposure data to document selenium concentrations in cases or controls. Furthermore, there was no indication that the affected patients were exposed to Se concentrations exceeding the acceptable daily intake (ADI). A retrospective case-control study of 66 patients with amyotrophic lateral sclerosis and 66 age- and sex-matched controls found no association between the disease and Se exposure based on a self-administered questionnaire.[188] This study did not confirm earlier case reports associating areas of high selenium content in South Dakota with an increased incidence of this disease.[189] Cross-sectional studies have not demonstrated a significant increase in the Se concentrations in patients with amyotrophic lateral sclerosis compared with controls.[190]

Chronic selenium poisoning in humans is not well documented in the United States. Limited data from one study suggested that chronic elemental selenium exposure can cause dental caries, but adverse effects following exposure to selenium are unusual.[191] A study of 111 rural families living in areas with high selenium content in the soil did not reveal any symptoms directly attributable to selenium poisoning.[192,193] Members of a family that consumed local well water with a concentration of 9 ppm selenium developed changes (discoloration, brittleness, loss) of their fingernails, hair loss, and lassitude. Reports from their school indicated that the child became more alert after the excessive Se exposure ceased.[194] This case study did not report any blood or urine selenium concentrations; therefore, there was no documentation of excessive Se exposure.

Occupational Exposure

Hydrogen Selenide

Hydrogen selenide is a water-soluble gas that produces irritation to the skin and mucous membranes as well as painful orange skin lesions depending on the duration of exposure and decontamination measures. The acute inhalation of high concentrations of hydrogen selenide initially causes upper respiratory tract irritation and metallic taste in the mouth followed by bronchopneumonia and pulmonary edema. The accidental inhalation of hydrogen selenide gas produced severe mucous membrane irritation, rhinitis, and wheezing followed in 18 hours by progressive dyspnea, pneumomediastinum, and markedly reduced expiratory flow rates.[195] Improvement occurred over 5 days; however, some restrictive and obstructive changes remained on pulmonary function testing 3 years later. A 21-year-old research lab student associated the development of bitter metallic taste in her mouth, garlicky breath, transverse ridges on the nails, chronic diarrhea, and abdominal pain with a weekly exposure to hydrogen selenide gas in the laboratory; however, no selenium concentrations were available to document exposure.[196]

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Selenium and Selenium Dioxide

Selenium dusts produce respiratory tract irritation manifested by nasal discharge, loss of smell, epistaxis, and cough. Exposure of workers to fumes containing high Se concentrations caused acute, intense irritation of the mucous membranes and throat along with headaches; however, the workers did not develop systemic complaints.[197] Following exposure to selenium dioxide for 20 minutes during a fire, 40 workers exhibited symptoms and signs of metal fume fever characterized by headaches, chills, bronchitis, and pulmonary infiltrates.[198] There were no exposure data on airborne selenium or other metal concentrations in the ambient air. Coughing persisted for 4 days; all symptoms resolved within 1 week. Chronic exposure of workers to selenium concentrations exceeding 0.2–0.4 mg Se/m^3 was associated with garlic odor on the breath, gastrointestinal discomfort, skin lesions, metallic taste in mouth, and various psychological complaints.[119] Dermal exposure to selenium dioxide or selenium oxychloride may produce dermatitis and skin burns.[199]

Reproductive Abnormalities

Although selenium is a demonstrated teratogen (limb reductions, craniofacial, and axial skeletal malformations) in birds and crosses the human placenta, the evidence for teratogenesis in mammals is inconclusive with a lack of evidence that selenium or selenium compounds are fetotoxic to humans.[21] The teratogenic potential of selenium was suggested by case reports associating several miscarriages and minor birth defects (bilateral clubfoot) with exposure of pregnant laboratory workers to sodium selenite.[200] However, the urine selenium concentrations of these workers were comparable to controls. The presence of confounding factors indicates an alternative explanation for the reproductive abnormalities other than a direct causal connection to selenite. A study of Italian women exposed to concentrations of inorganic selenium (selenate) in drinking water ranging up to 10 µg/L did not demonstrate a statistically significant increase in adverse reproductive outcomes compared with reproductive outcomes of women from the same province without excessive selenate exposure.[201] A 41-year-old pregnant woman accidentally ingested 200 mg/day of galenic formulation of selenium from gestational week 7–12 (15th gestational week plasma selenium concentration = 29 µg/L); she developed nausea, vomiting, and hand/foot paresthesias followed by fatigue, loss of fingernails, and alopecia.[202] The child was born full term without complications (cord blood selenium = 58.1 µg/L, method not reported) or evidence of toxicity at 3 months of age (normal clinical evaluation, imaging studies, serum electrolytes/liver enzymes).

The difference in Se sensitivity between animal species may result from the accumulation of high Se concentrations (e.g., 64 ppm) in eggs compared with the mammalian fetus, which excretes excess fetal selenium and maintains lower selenium concentrations than the maternal circulation.[203] In laboratory animals, the administration of inorganic selenium compounds at concentrations that do **not** produce maternal toxicity has not caused teratogenic effects.[204] Embryonic death and congenital malformation occur in animal studies only at Se doses producing marked maternal intoxication. The primate fetus has much better protection against selenium toxicity compared with avian species.[205,206]

Carcinogenicity

Current human epidemiological and demographic studies do not suggest selenium is carcinogenic.[21] Selenium induces some genotoxic effects in animals, but other studies suggest that selenium is antimutagenic and anticarcinogenic.[207] In general, low serum selenium concentrations are not associated with an increased incidence of cancer. Neither the International Agency for Research on Cancer (IARC) nor the US National Toxicology Program (US NTP) lists selenium as a suspected carcinogen. Selenium and selenium compounds are classified as group 3 (not classifiable as to its carcinogenicity to humans) by the IARC.

Selenium sulfide is a separate compound rather than a salt of selenium. When administered by oral gavage to rodents, sodium sulfide produces hepatocellular carcinomas in rats (male and female) and female mice as well as alveolar or bronchiolar carcinomas and adenomas in female mice. Consequently, the US NTP lists selenium sulfide as a substance that may reasonably be anticipated to be a carcinogen based on the animal data.[208] Because selenium sulfide is not absorbed through the skin, the use of this compound as a shampoo is considered safe. In a long-term animal study, the application of 2.5% selenium sulfide (Selsun®) did not induce an increased incidence of tumors in mice or in rabbits.[209]

Despite early reports that associated Se exposure with elevated tumor rates in animals, most,[210,211,212] but not all,[213] recent studies in humans and animals have either demonstrated no relationship or an inverse relationship between cancer rates and elemental selenium exposure. In animals, high Se concentrations (5–60 times the nutritional requirement of Se) inhibit the growth of transplantable tumors[214] and the induction of

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cancer by chemicals/viruses.[215,216] These experimental studies suggest that selenium inhibits the initiation and promotion phases of carcinogenesis; however, reduction of the risk of cancer requires Se supplementation over the entire period of exposure to carcinogens because selenium does not appear to provide long-term protection against cancer. A randomized controlled trial of 1,312 patients followed up to 8 years (mean = 6.4 years) did not detect a difference in the incidence of basal cell or squamous cell skin cancer between patients receiving 200 μg Se/day (mean = 4.5 years) and placebo.[217] The blinded phase of the trial stopped early because of an apparent reduction (RR = 0.5, 95% CI 0.31–0.8) in total mortality from cancer. Further studies are necessary to confirm the hypothesis that selenium decreases the incidence of cancer because overall mortality was a secondary endpoint of the study.[218]

DIAGNOSTIC TESTING

SI Conversion Units

1 μg = 0.01267 μmol
1 μmol Se = 78.96 μg

Analytical Methods

Biological Samples

The low Se concentration in biological samples requires sensitive and accurate analytical techniques. Analytical methods for determining total Se concentrations in the ppb range include spectrofluorometry, neutron activation analysis (NAA), graphite furnace and hydride generation atomic absorption spectrometry (GF/AAS, HG/AAS), inductively coupled plasma/atomic emission spectrometry (ICP/AES), inductively coupled plasma/mass spectrometry (ICP/MS), gas chromatography (GC), and x-ray fluorescence analysis. Except for the latter method[219] and instrumental neutron activation analysis,[220] most analytical techniques determine total selenium in biological material rather than individual Se species or metabolites (e.g., trimethylselenonium). Neutron activation analysis is the most sensitive technique (LOD, 1–10 ng/g material), but the instrumentation is very expensive. The advantages of ICP/AES with hydride vapor generation (NIOSH method 7,300) are small sample size and high sensitivity (LOD, 0.4 μg/L).[221] This method determines total selenium concentration after the sample undergoes wet-ashing with nitric, perchloric, and sulfuric acids at high temperatures (e.g., 310 °C), resulting in Se reduction in the sample by sodium borohydride to hydrogen selenide.

Classic flame atomic absorption spectrometry is not sensitive to the low Se concentrations usually present in biological fluids. GF/AAS offers good sensitivity (LOD, 0.005 ng/g sample), but interference from the matrix may complicate analysis and requires correction (e.g., Zeeman effect) for background absorption.[222] HG/AAS produces less chemical interference, low detection limit (0.1 μg/L), and good precision (RSD = 1.0–1.5%);[223] however, this method requires a larger sample size compared with GF/AAS (e.g., 20 μL of serum). HG/AAS is specific for selenite (4+); this method allows Se speciation based on the preparation of samples with oxidative digestion and/or reduction processes prior to analysis. Oxidative digestion of organic selenide (2−) and elemental selenium (0) converts these species to selenite, whereas reduction processes convert selenate (6+) to selenite. The amount of selenium in the sample after these processes represents total selenium. HG/AAS allows the determination of the amount of selenate (6+) in the sample by measuring the difference between the sample after reduction of selenate to selenite and the amount of selenite in the original sample. Comparison of various methods for Se determination indicates that the accuracy of acid decomposition fluorometry, HGAAS, and electrochemical atomic absorption spectroscopy is similar.[224]

Environmental Samples

Determination of Se species in food sources and biological media is difficult as no method reliably extracts all selenium from food without altering the composition of selenium species.[55] Hyphenated techniques based on coupling chromatography separation with inductively coupled plasma/mass spectrometry followed by molecular mass spectrometry (ESI/MS, ESI/MS/MS, and MALDI/TOF) and isotopic dilution allow quantification of selenium species.[225] Separation of Se species by ion-pair liquid chromatography/inductively coupled plasma/mass spectrometry (LC/ICP/MS) after hot-water extraction followed by online reversed-phase liquid chromatography/electrospray ionization/tandem mass spectrometry (LC/ESI/MS/MS) allows the determination of selenium species in food samples.[226] The limit of detection for selenium species in biological fluids using capillary electrophoresis coupled with ICP/MS was 10–20 μg/L for inorganic Se species and 35–50 μg/L for organic Se species.[227] GF/AAS with selective extraction procedures and hydride-generation atomic absorption spectrometry (HGAAS) can distinguish

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Se^{6+} and Se^{4+} in environmental samples because Se^{6+} does not readily form the hydride without reduction.[228]

Storage

In contrast to most trace elements, Se contamination of containers is unusual.[229] Consequently, Vacutainer® -type storage tubes are sufficient for collecting serum to analyze Se concentrations when basic principles of cleanliness are observed. Selenium compounds are usually stable under refrigerated storage conditions (4°C/39°F); however, repeated thawing and freezing may alter concentrations if protein denaturation occurs. The presence of hemolysis will increase the plasma selenium because of the relatively higher selenium content in erythrocytes than plasma or serum. Analyses of biological samples may underestimate the total Se concentration in urine as a result of the loss of volatile selenium compounds; storage of samples in polyethylene containers in the acid medium reduces these losses. The immediate freezing of biological samples following collection limits the enzymatic formation of volatile selenium compounds.

Biomarkers

Blood

The mean selenium concentration is ~30% higher in erythrocytes than whole blood,[230] whereas the plasma selenium concentration is ~65–85% of the whole blood concentration.[231,232] In a study of trace metals in a representative sample of over 400 urban, suburban, and rural northern Italian residents, the mean whole blood selenium concentration was 108 ± 6 µg/L with a range of 40–180 µg/L compared with 81 ± 1 µg/L (range, 33–121 µg/L) in plasma as measured by neutron activation analysis.[233] The plasma/erythrocyte Se ratio decreases as the whole blood concentration increases.[111] In a study on trace metal concentrations in Swedish adolescents, the median serum Se concentration was ~10% lower than whole blood.[234] Consequently, the difference between the serum and the whole blood selenium concentrations probably narrows substantially following large selenium ingestions; however, there are few clinical data to determine the precise difference during selenium intoxication. The 5-hour post-ingestion, whole blood Se concentrations were ~25% higher than plasma in a fatal case of acute selenium poisoning secondary to the ingestion of selenious acid in a gun-bluing compound.[138] In a study of New Zealand women receiving 200 µg selenium supplementation as either selenomethionine or selenate, selenium was preferentially distributed to hemoglobin with the former supplement, whereas selenium evenly distributed to hemoglobin and glutathione peroxidases following administration of selenate.[235]

At plasma Se concentrations of >0.16 mg/L, the plasma-carrying capacity becomes saturated; erythrocytes then carry an increasing amount of selenium.[236] Plasma and serum selenium concentrations reflect changes in Se intake more rapidly than Se concentrations in erythrocytes where proteins firmly bind selenium. Consequently, whole blood and, in particular, selenium content in the erythrocytes are theoretically better measures of long-term exposure to selenium than plasma or serum. However, a year-long study of 77 Wyoming and South Dakota residents of high seleniferous areas indicated that whole blood and serum were equally good sampling sites for the measurement of long-term selenium intake.[237] An exception is selenite, which produces elevated plasma selenium concentrations.[69]

General Population

Whole Blood The average whole blood selenium concentration in the general population is <100–200 µg/L;[238,239,240] however, the whole blood selenium concentrations vary widely between different localities depending on Se intake.[241] The mean whole blood selenium in 210 blood samples from residents of 19 US cities was ~210 µg/L with a range of 100–340 µg/L as measured by fluorometry.[242] In a study of random blood samples from healthy residents in three different locations, the mean whole blood selenium concentrations were as follows: 1) Oregon (n = 23), 202 ± 25 µg/L (range, 155–278 µg/L); 2) South Dakota (n = 21), 397 ± 128 µg/L (range, 221–640 µg/L); and New Zealand (n = 34), 59 ± 11 µg/L (range, 41–101 µg/L).[243] In newborns, the whole blood selenium may be as low as 30 µg/L, but the concentration increases to 100 µg/L by 1 year of age.[244] Factors affecting the blood selenium concentration other than the amount ingested include the Se species ingested (selenomethionine, selenate, selenite), vitamin E intake, the presence of serious illness,[245] ingestion of selenium-containing seafood, and exposure to inorganic mercury and cadmium.[36]

Serum/Plasma In a study of 122 Czechoslovakian volunteers, the median serum selenium concentration was ~67 µg/L with a range of 40–105 µg/L.[246] The administration of 90 µg Se as selenite over 17 weeks increased the mean plasma Se concentration in seven subjects by ~36 µg/L compared with a mean increase of ~102 µg/L following the administration of 100 µg Se as selenomethionine to four subjects.[247] There were

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no statistical comparisons between these two groups. The addition of 150–200 g fish (~40–50 μg Se) to the diet of healthy Swedish subjects for 11 weeks was associated with a mean plasma concentration of ~96 μg Se/L.[248] This concentration represented an average 13% increase over baseline concentrations. The fish included mackerel, salmon, and herring. The estimated optimum concentration of serum selenium based on cytosolic glutathione peroxidase (i.e., indicator of selenium repletion) is 100 μg/L.[249]

Supratherapeutic

In a study of 16 subjects receiving 3,200 μg selenized yeast daily for an average of 1 year, the mean plasma selenium concentration was ~0.64 ± 0.49 mg/L.[250] A small minority of these patients complained of garlic breath, brittle nails/hair, and nausea. There was no biochemical evidence of liver, kidney, or hematological abnormalities. In a case series of nine patients ingesting a nutritional supplement containing 200 times the labeled selenium selenite dose over ~1–2 months, the median whole blood selenium concentration collected between 7 and 118 days (mean = 27.3 days; median = 14 days) after the last dose was 318 μg/L with a range of 150–732 μg/L.[185] A 36-year-old man presented with generalized alopecia, nail changes, paresthesias, fatigue, and diarrhea after ingesting excessive amounts of selenium supplements over 2 weeks. Two weeks after cessation of selenium intake, the serum contained ~0.66 mg Se/L; the Se concentration was normal when repeated 2 months later.[251]

Environmental

Whole blood concentrations exceeding 0.6 mg Se/L suggest overexposure to selenium. A study of 77 residents of South Dakota where the average daily intake was high (~0.6 mg Se) demonstrated a mean whole blood Se concentration of 0.025 mg/L with a range up to 0.521 mg/L.[252] In a study of 33 New Mexico residents exposed for at least 1 year to excessive selenium in well water (0.026–1.8 mg/L) contaminated by a uranium mill tailing pond, the mean Se whole blood concentration was 0.171 ± 0.025 mg/L with a range of 0.133–0.248 mg/L.[253] The blood selenium concentrations did not correlate to glutathione peroxidase activity; the study did not investigate any symptoms related to the whole blood selenium concentrations. In a study of a Chinese population exposed to high concentrations of environmental selenium, individuals with signs of chronic selenosis (brittle nails, hair loss, nail deformities, skin lesions) had a mean Se concentration of 3.2 mg/L blood with a range of 1.3–7.5 mg/L.[117]

Overdose

There are limited data correlating blood selenium concentrations with outcome following intentional overdose. Plasma selenium concentrations of <1 mg/L within 3–6 hours after ingestion suggest mild toxicity, whereas plasma selenium concentrations of >2 mg/L during this period suggest serious toxicity. A 75-year-old man presented to the emergency department 3.5 hours after ingesting 10 g sodium selenite; he had vomiting, diarrhea, hypotension (75/45 mm Hg), QT prolongation, and mild hypokalemia.[102] His serum selenium concentration was 5.4 mg/L. He was admitted to the ICU where he received magnesium and potassium; he remained hypotensive with worsening metabolic acidosis. Subsequently, he developed cardiac arrest and was unresponsive to resuscitation. During the cardiac resuscitation, an ABG demonstrated a serum potassium concentration of 8.8 mEq/L.

A 48-year-old schizophrenic had a serum Se concentration of 2.4 mg/L ~2 hours after the ingestion of 2 g selenium dioxide.[107] She recovered after developing gastric ulcerations and mild hepatic inflammation. A 2-year-old child accidentally ingested selenious acid; the plasma Se concentration reached 285 mg/L on the second hospital day. He developed multiple complications (esophageal burns, cardiomyopathy, hepatorenal dysfunction, acute respiratory failure).[108] Although the plasma Se concentration returned to normal limits 4 days after exposure, he died 13 days later despite aggressive treatment (e.g., extracorporeal membrane oxygenation).

Postmortem

Because of the limited number of autopsy cases with selenium concentrations, selenium concentrations should be interpreted cautiously. The postmortem whole blood selenium concentration in a peripheral blood sample from a 24-year-old, who died 4 hours after ingesting gun-bluing solution containing selenious acid, was 13 mg/L compared with 30 mg/L in serum drawn 1 hour after ingestion.[174] The postmortem bile sample also contained high Se concentrations (15 mg/L), whereas the vitreous humor contained low Se concentrations (0.031 mg/L). The postmortem blood from a 40-year-old dying 8 hours after the suicidal ingestion of 4% selenious acid contained 2.6 μg Se/g wet weight.[175]

Urine

Selenium excretion is rapid with the maximum urinary excretion occurring in the first 4 hours after absorption with renal excretion accounting for ~50% of the

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absorbed dose. Urine selenium is an indication of recent (1–2 day) exposure to selenium.[254] In populations with normal Se intake without occupational Se exposure, the urine selenium level is usually <30 μg/L with most urine samples <100 μg/L.[255] In a study of trace metals in a representative sample of >400 urban, suburban, and rural northern Italian residents, the mean urine selenium concentration was 22 ± 2 μg/L with a range of 2–68 μg/L.[233] A study of 230 healthy Croatian adults found no difference in the urine selenium concentrations of groups based on age, sex, and smoking habits.[256] Using a fluorometric method, the average urine selenium concentration was 16.96 nmol Se/mmol creatinine with a SD = 5.44.

Typically, no symptoms are associated with urine selenium concentration of <100–200 μg/L,[257] whereas urine selenium concentrations of >400–700 μg/L suggest excessive recent selenium exposure.[126] Residents in areas of high seleniferous soil may ingest up to 750 μg of selenium daily without signs of selenosis.[258] In a study of 28 New Mexico residents exposed for at least 1 year to excessive selenium in drinking water (mean = 0.337 ± 549 μg/L; range, 26–1,800 μg/L) contaminated by a uranium mill tailing pond, the daily urinary excretion of selenium ranged from 14.4–337.5 μg (mean = 79.21 ± 48.12 μg).[253] No clinical symptoms were observed in ranchers in the highly seleniferous areas of South Dakota and Wyoming where livestock developed selenosis.[110] Urine samples from these ranchers contained Se concentrations up to 2,200 μg/L.

Hair/Nails

There are inadequate data to confirm the usefulness of nail or hair selenium concentrations as biomarkers of selenium exposure including supplementation.[259] The mean selenium concentration ranged from 0.54 ± 0.91 to 1.56 ± 0.58 μg/g in a review of studies on the selenium concentrations in nails, whereas the mean concentrations in hair ranged from 0.36 ± 0.17 to 3.70 ± 2.3 μg/g (ppm).[21] The mean selenium concentration in hair samples obtained from 56 adult residents of a highly seleniferous region of Glasgow, Scotland, was 18.92 ± 52.77 ppm (range, 1.27–248 ppm) as measured by neutron activation analysis.[260] In this study comparing three different regions, the mean Se concentration in 22 adults from Iran was 5.72 ± 18.7 ppm (range, 0.80–89.1 ppm) and 1.81 ± 1.32 ppm (range, 0.0037–0.2 ppm) in hair samples from 62 Icelandic adults.

Abnormalities

Electrocardiograms, liver and kidney function tests, and serum electrolytes are usually normal following chronic exposure to elemental selenium and selenium compounds. Yang et al. reported prolonged clotting times and low serum glutathione levels in Chinese patients with excessive Se exposure;[111] however, insufficient documentation of the normal values in the general Chinese population limits extrapolation of these findings. Furthermore, this abnormality did not occur in other patients with similar exposures. The administration of selenium may alter thyroid function and produce hypothyroidism in iodine-deficient patients.[159] Selenium deficiency is common in elderly patients; this deficiency may impair the activity of Se-containing type I deiodinase, resulting in a subsequent reduction in the conversion of T_4 to T_3.

Following exposure to selenious acid, laboratory abnormalities include thrombocytopenia, moderate hepatorenal dysfunction, and elevated serum creatine kinase concentrations. The electrocardiogram may demonstrate ST elevations and T wave changes characteristic of myocardial infarction. Mildly elevated serum hepatic aminotransferases and transient T-wave inversions developed after the ingestion of large amounts of selenium selenate; these changes resolved without sequelae.[105]

HEALTH SURVEILLANCE

Risk Assessment

Factors that influence the chronic Se toxicity include chemical species, bioavailability of the form of selenium in the diet, and animal species. The recommended daily allowance for selenium is 55 μg Se/day in women and men.[21] The ingestion of up to 200 μg Se/day in humans does not produce adverse effects.[261] The chronic oral reference dose (R_fD), as defined by the US EPA, is 5 μg Se/kg/day based on a no-observed-adverse-effect level (NOAEL) of 15 μg Se/kg/day and an uncertainty factor of 3 for sensitive individuals. The minimal risk level for chronic oral ingestion of selenium is also 5 μg/kg/day as determined by the Agency for Toxic Substances and Disease Registry.[21] Studies on chronic selenosis in China by Yang et al. were the basis for this calculation. Based on Chinese studies of subjects in areas containing high Se concentrations in soil (average, 10 ppm) and water (average, 54 ppb), the authors calculated the following: lowest-observed-adverse-effect level (LOAEL), 1,570 ± 653 μg Se/day; mean NOAEL

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was 819 ± 126 μg Se/day.[72] The maximum safe dietary Se intake was 400 μg with a minimum value of 40 μg. The Joint Food and Agriculture Organization (World Health Organization) Expert Committee on Human Vitamin and Mineral Requirements recommended the intake of 6 μg/day in infants aged 0–6 months.[262]

The California Department of Health (CDH) issued a health advisory for the consumption of two species of diving ducks in Suisun Bay, near San Francisco, during 1987. These diving ducks (i.e., surf scoter, lesser and greater scaup) feed on bottom-dwelling animals (clams, mussels) that concentrate selenium from sediment and phytoplankton. In a study by the California Department of Fish and Game, the mean selenium concentrations wet weight in the muscle of ducks were 3.6 ppm in scoters and 2.2 ppm in scaups. These concentrations were up to five times higher than mean Se levels in similar species in control areas (i.e., Humboldt Bay near the border of Oregon and California). The CDH recommended limiting the consumption of scoters to 4 oz/2 weeks and scaups to 4 oz/week. Because of the known Se effects on the reproduction of birds, the CDH recommended that women of childbearing age and children less than 15 years of age not consume these ducks. The basis of this advisory is Equation 27.1.

$$\text{PI (diving ducks)} = (\text{ADI} - \text{DI}) \div \text{C} \quad \text{(Equation 27.1)}$$

where

PI = Permissible intake of duck flesh
ADI = Acceptable daily Se intake
DI = Daily Se intake of US population
C = Se concentration in duck flesh

The ADI was 210 μg Se/day based on applying a 15-fold safety factor to the lowest mean Se intake (3,200 μg Se/day) that produced toxicity.[117] Additional safety factors include the following: 1) the assumption of 100% bioavailability (e.g., the bioavailability of Se from animal sources is lower than plant sources used to set the ADI); 2) the release of volatile selenium compounds during the cooking process; 3) the beneficial interaction of dietary factors (vitamins, methionine, protein, sulfates, zinc, iron) with selenium; and 4) the use of the upper range of daily selenium ingestion (170 μg Se) for the local population.[52] Equation 27.2 outlines the CDH calculation for the permissible Se intake from the consumption of scaup flesh.

$$\begin{aligned}\text{PI (scaup)} &= (210\ \mu\text{g Se} - 170\ \mu\text{g Se}) \quad \text{(Equation 27.2)}\\ &\div 2.2\ \mu\text{g se/g flesh wet weight}\\ &= 18.18\ \text{g flesh/days}\\ &= (18.18\ \text{g} \times 7\ \text{days/week})/28.35\ \text{g/oz}\\ &= 4.5\ \text{oz/week}\end{aligned}$$

Environmental Monitoring

Table 27.2 lists the guidelines and regulations for elemental selenium and selenium compounds. The ACGIH recommends a TLV-TWA for Se and Se compounds except hydrogen selenide and selenium hexafluoride of 0.2 mg/m^3 to minimize the risk of eye/upper respiratory tract irritation and systemic complaints (rash, headache, metallic taste, garlic odor).[263] Preemployment and periodic physical examinations of selenium workers should focus on the liver, the respiratory tract, the eyes, and the skin. In particular, the nails should be examined for the red pigmentation characteristic of excessive Se exposure. The EPA Office of Drinking Water's Maximum Contaminant Level (MCL) for selenium was 50 μg/L. Recently, the EPA national water quality criterion for chronic Se exposure in freshwater was reduced to 5 μg/L. The WHO standard for drinking water is 10 μg Se/L.

Biological Monitoring

Biomarkers for selenium exposure are not well defined. Selenium concentrations in plasma/serum and urine reflect short-term exposure, whereas erythrocyte and whole blood Se concentrations reflect Se exposure over the 3-month life span of red blood cells. A study of the Greenland Intuit population suggests that plasma Se concentrations stabilize near 140 μg/L, whereas whole blood Se concentrations continue to increase with increasing Se dose.[264] The mean Se concentration in Uummannaq men was 488 μg/L in whole blood compared with 113 μg/L in plasma. The large variation in blood and urine Se concentrations complicates the interpretation of individual Se concentrations that depend on multiple factors including age, gender, smoking/drinking habits, race, environmental exposure, and supplement use.[265] Little data correlate airborne Se concentrations with blood or urine; therefore, blood and urine Se concentrations should be compared with local control concentrations and clinical manifestations of Se exposure. The suggested biological equivalent of a safe Se dose based on the EPA RfD and ATSDR MRL is 400 μg/L in whole blood, 180 μg/L in plasma, and 90 μg/L in urine.[266]

Blood

Among French miners aged 34–50 years exposed to selenium in coal dust in an area of low environmental

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TABLE 27.2. Guidelines and regulations for selenium compounds. (Adapted from ATSDR).[21]

Exposure Limit	Value
Water	
WHO	
Drinking water	0.04 mg/L
US FDA	
Permissible level in bottled water	0.01 mg/L
US EPA	
MCL (drinking water)	0.05 mg/L
Air	
OSHA	
PEL-TWA (8-hour)	
Selenium and compounds except selenium hexafluoride (as Se) compounds (as Se)[b]	0.2 mg/m^3
Selenium hexafluoride[a]	0.16 mg/m^3
Hydrogen selenide	0.16 mg/m^3
NIOSH	
IDLH	
Selenium compounds	1 mg/m^3
Selenium hexafluoride	2 ppm
REL-TWA (10-hour)	
Selenium and compounds[b]	0.2 mg/m^3
ACGIH	
TLV–TWA (8-hour)	
Selenium and compounds (as Se)	0.2 mg/m^3
Selenium hexafluoride and hydrogen selenide (as Se)	0.05 ppm (0.16 mg/m^3)
Ingestion	
NAS	
Adequate and safe intake of selenium for adults	50–200 µg/day
Tolerable upper intake level	400 µg/day
NRC	
RDA	
Men	55 µg/day
Women	55 µg/day
General	0.87 µg/kg/day
WHO	
Recommended adult daily intake	0.9 µg/kg body weight
US EPA	
ADI	213 µg
RfD (oral)	
Selenious acid	3 µg/kg/day
Selenourea	5 µg/kg/day
Thallium selenite	0.5 µg/mg/kg/day
AIC	
Selenium (oral)	3 µg/kg/day
Selenium (inhalation)	3.5 µg/m^3
MCL (in water)	0.05 mg/L
Water quality standards	
Freshwater	
Maximum	20 µg/L
Continuous	5.0 µg/L
Saltwater	
Maximum	290 µg/L
Continuous	71 µg/L

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ADI = acceptable daily intake; AIC = acceptable intake chronic; IDLH = immediately dangerous to life and health; MCL = maximum contaminate level; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; NRC = National Research Council; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RDA = recommended dietary allowances; REL = recommended exposure limit; RfD = reference dose; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency; US FDA = US Food and Drug Administration; WHO = World Health Organization.
[a] Except construction industry = 0.05 ppm (0.16 mg/m^3); [b] Except selenium hexafluoride and hydrogen selenide.

selenium, plasma selenium concentrations significantly decreased (P = 0.01) with age and current tobacco consumption; however, no correlation was found with alcohol consumption.[267] The plasma selenium concentration ranged from ~35–100 µg/L with a mean of 60.2 µg/L for workers with long-term and current exposure. The plasma Se concentration correlated with the glutathione peroxidase activity; the authors opined that decreased Se concentration reflected increased antioxidant activity in smokers and workers exposed to coal mine dust.[268] In a study of 20 workers at a Mexican rubber tire repair shop, the mean serum Se concentration was 148 ± 56 µg/L (range, 70–296 µg/L).[269] The mean selenium concentration in serum samples from 18 healthy Mexican volunteers without occupational Se exposure was 100 ± 18 µg/L (range, 70–127 µg/L). The plasma Se concentration of 20 copper refinery workers working in the selenium department ranged from 114–174 µg/L (mean = 137 ± 17 µg/L) compared with 120–187 µg/L (mean = 155 ± 19 µg/L) in the non-occupationally exposed control group as measured by fluorometry.[270] The study did not report any measures of selenium exposure in the occupational group; exposure apparently was based on job title.

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URINE

In a study of Norwegian workers with no occupational selenium exposure, the mean urine level was 39 nmol Se/mmol creatinine.[271] At ambient air levels of <0.1 mg inorganic Se compounds/m^3, the urine selenium is usually <0.1 mg/L, whereas average urine Se concentration in workers exposed to air concentrations as high as 3.6 mg Se/m^3 was 0.25–0.45 mg/L.[119,272] The workers at the selenium rectifier plant were probably exposed to elemental selenium and selenium oxide (Se species was not reported). The urine selenium concentration in post urine samples from 20 copper refinery workers ranged from 34–190 µg/L (mean = 93 ± 43 µg/L) compared with 27–118 µg/L (mean = 74 ± 25 µg/L) in the non-occupationally exposed control group as measured by fluorometry.[270]

TREATMENT

First Aid

The most important first aid measure following dermal exposure to selenium compounds (selenium dioxide, selenium oxychloride, selenious acid) is copious water irrigation. These compounds are potentially absorbed through the skin. Contaminated clothes should be immediately removed. Following the inhalation of selenium compounds (hydrogen selenide, selenium oxide) with respiratory irritant effects, the patient should be removed from the contaminated area with symptomatic patients receiving oxygen as needed.

Decontamination

Although data are limited, the ingestion of elemental selenium or selenium salts usually does not require decontamination; however, selenious acid commonly present in gun-bluing solution is a potent toxin. Small amounts of this chemical are potentially lethal. All patients ingesting selenious acid require evaluation by a physician and hospitalization for observation. Gun-bluing compound containing selenious acid is corrosive and will produce esophageal burns following ingestion; however, because this acid is a serious systemic poison, the decision to use gastric aspiration and lavage judiciously is based on clinical judgment. Factors to consider in the decision to use these measures include the time since exposure (<1–2 hours), the amount of spontaneous emesis, the clinical condition of the patient, and the amount ingested.

Antidotes

There are no antidotes to selenium poisoning. In experimental animals, dimercaprol (BAL) inhibits the recovery from selenium poisoning.[273] Similarly, experiments in rats indicate that calcium disodium ethylenediaminetetraacetate ($CaNa_2EDTA$) does not improve survival rates when administered >15 minutes after an intramuscular dose of 7.5–12.5 mg sodium selenite/kg.[274] Additionally, animal studies suggest that the newer derivatives of BAL (2,3-dimercaptopropane-1-sulfonic acid or DMPS, meso–2,3-dimercaptosuccinic acid or DMSA) do not enhance Se excretion when administered 15 minutes after a subcutaneous dose of 2.24 mg sodium selenate/kg.[275]

Supplemental Care

No entirely satisfactory treatments for selenium poisoning are available. Management of acute and chronic intoxication with selenium is supportive including elimination of the selenium source. Treatment is expectant (cardiopulmonary monitoring in an intensive care setting for selenious acid ingestion) and supportive (intravenous infusion, supplemental oxygen, and ventilation as needed). Calcium gluconate jellies may be necessary for workers sustaining dermal injury from selenium hexafluoride similar to hydrogen fluoride exposure. A reductant-containing bathing solution (e.g., 10% sodium thiosulfate) may decrease pain and necrosis following dermal exposure to selenium oxides or hydrogen selenide;[36] however, the evidence is anecdotal with no clinical studies confirming efficacy.

ORGANIC SELENIUM

PHYSIOCHEMICAL PROPERTIES

Selenomethionine and selenocysteine are the main organic forms of selenium. Figure 27.3 displays the chemical structure of selenocysteine, selenomethionine, and other organic selenium compounds. The latter structure is the form of selenium present in all currently known selenium-containing enzymes (e.g., selenoprotein P, glutathione peroxidase).[277] Selenocystine is an oxidation product of selenocysteine resulting from the conversion of two –SH groups to one S–S group. The four natural oxidation states of organic selenium include (0) selenodiglutathione (dipeptide); (2−),

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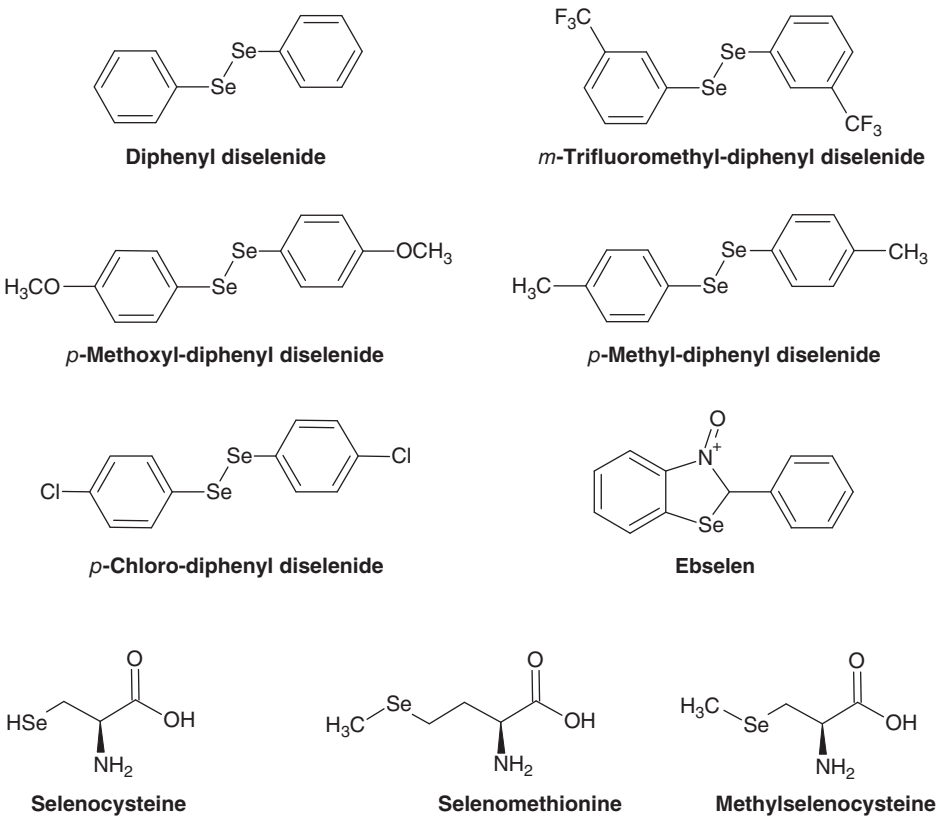


FIGURE 27.3. Chemical structure of selenocysteine, selenomethionine, and other organic selenium compounds. (Adapted from Flury et al.).[276]

dimethylselenide (C_2H_6Se); (4+); and (6+). The body metabolizes selenocystine to selenocysteine. Selenium easily replaces sulfur to form a large number of organic selenium compounds (dimethylselenide, trimethylselenium). In general, organoselenium compounds are more reactive than similar sulfur-containing compounds with selenols (i.e., R-SeH) being more acidic and more readily oxidized than thiols.

Selenomethionine in nature exists almost exclusively as the L-enantiomer.[278] Dimethylselenide is a volatile, methylated metabolite of selenium that has a strong garlic-like odor. At physiological pH, selenium occurs primarily as selenides on the side chains of selenocysteine. Table 27.3 lists identifying information and physical properties of selenocystine and selenomethionine.

TABLE 27.3. Identifying information and physical properties of selenocystine and selenomethionine.

Physical Characteristic	Selenocystine	Selenocysteine	Selenomethionine
CAS RN	1464-43-3	10236-58-5	1464-42-2
Molecular formula	$C_6H_{12}N_2O_4Se_2$	$C_3H_6NO_2Se$	$C_5H_{11}NO_2Se$
Color	ID	White-light yellow	Transparent
Physical state	Solid	crystals or powder	Hexagonal sheets or plates
Molecular weight (g/mol)	334.12	167.06	196.11
Melting point (°C)	ID[a,b]	143–146	265[a]
Water solubility (25 °C)	Moderate	≈400 g/L	1×10^{-6} mg/L
Vapor pressure (mmHg)	ID	ID	7.5×10^{-8}

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; ID = Insufficient data.
[a] Decomposes; [b]Selenocystine is a selenoamino acid functionally related to selenocysteine.

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Alkyl selenium compounds are flammable liquids that do not react with air, oxygen, or water at room temperature. The alkyl compounds are the least toxic selenium compounds; these compounds (e.g., dimethylselenide, trimethylselenonium) are the primary products of selenium detoxification in the body. Under conditions of excessive Se intake, the rate of trimethylselenonium formation exceeds the rate of methylation resulting in dimethylselenide. This compound produces a strong garlic odor in the breath during exhalation.[279]

EXPOSURE

Uses

Selenium diethyldithiocarbamate is a fungicide and rubber vulcanizing agent. Selenoproteins are common in marine organisms (fish, algae); however, there is little evidence that selenoproteins are physiologically important in higher plants and fungi.[280] Selenomethionine is a common source of selenium in multivitamins in doses ranging from 50–100 μg/tablet.

Sources

Environment

In addition to selenium dioxide, methylselenide and dimethylselenide are the most prevalent forms of selenium found in the atmosphere. Terrestrial plants can synthesize organic selenium compounds (e.g., selenomethionine and, to a lesser extent, selenocysteine).[281,282] Organic selenium species may constitute substantial portions of the selenium species in water including selenoamino acids and volatile organoselenium species (e.g., dimethylselenide, dimethyldiselenide, dimethylselenenyl sulfide). In a study of the dissolved selenium in drainage water from the Kesterson Reservoir, up to ~25% of the Se species were methylated forms (dimethylselenide, unidentified organic dimethylselenium derivatives).[36] In estuaries, biomethylation of selenium by marine microbes probably occurs rapidly; most selenium in the sea exists as organic selenium compounds.[115] Microorganisms in lake sediment can convert selenite, selenate, and organic selenium compounds to volatile methylated selenium compounds (dimethylselenide, dimethyldiselenide).[283] Determining the amount of organoselenium compounds in soil and sediment is complicated by the strong affinity of selenium for natural organic matter; current techniques probably overestimate the concentration of organoselenium compounds in solid environmental material.[284]

In vivo studies suggest that Se bioaccumulation is faster from selenomethionine than selenite or selenate. The bioconcentration factors for selenomethionine in an experimental setting are substantially higher than those for inorganic selenium.[285]

Diet

Organic selenium occurs naturally in the diet in highly variable quantities, particularly in cereals, grains, and forage crops. The predominant Se species in non-selenium accumulating plant foods are selenate and selenomethionine with less selenocysteine. The bioavailability of selenomethionine and selenocysteine in plant-derived foods is good, whereas the Se bioavailability from animal-derived foods (e.g., especially fish)[60] is low to moderate.[61,62] In a study of spring wheat grown in selenium-rich soil in India, the total selenium concentrations in 2 samples were ~83 μg/g and ~183 μg/g, respectively, dry weight.[57] Selenomethionine accounted for 72–85% of the total Se species. Se-methyl-selenocysteine was a minor constituent (0.2–0.5%). Selenium-accumulating plants (e.g., rapeseed, broccoli, cabbage, garlic, onions, leeks, wild leeks) contain primarily Se-methyl-selenocysteine and γ-glutamyl Se-methyl-selenocysteine.[286] An exception to the latter plants is Brazil nuts, which contain primarily selenomethionine and smaller amounts of selenocystine.[287] Cereal crops (e.g., barley, oats, rye, wheat) are non-accumulators. The major portion of selenium in vegetables and cereals is organic selenium compounds (e.g., selenomethionine, selenocysteine) as a result of the incorporation of these selenium species into plant proteins.[56] Organic selenium compounds (e.g., selenomethionine) constituted ~50% of the selenium in cereal.[288] Chromatographic analysis of seeds and gluten of wheat indicated that ~40% of the selenium occurred as protein-bound selenomethionine, whereas the rest of the selenium species were not identified.[289] The authors felt that the chromatographic findings of this unidentified area in the chromatograph were most consistent with selenocysteic acid and oxides of selenomethionine.

In general, foods from plant sources contain a greater portion of selenomethionine than animal sources.[55] Selenium in animal tissue exists in a variety of forms including selenomethionine and selenocysteine along with inorganic selenium.[58] The bioavailability of selenomethionine and selenocysteine in plant-derived foods is good, whereas Se bioavailability from animal-derived foods (e.g., especially fish) is low to moderate; hence, marine diets rich in selenium may be tolerated better than vegetable diets containing similar amounts

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of selenium.[60,62] Cooking may reduce the selenium content up to 50%, particularly in acidic, salty conditions.[281] Selenized yeast contains primarily selenomethionine bound in proteins as well as selenium-containing glutathione and unknown selenium species.[290]

ENVIRONMENTAL FATE

Air

Dimethylselenide and methylselenide are volatile organic compounds that partition into the atmosphere and persist in the atmosphere. The atmospheric lifetime of these volatile organoselenium species is short (5 minutes to 6 hours) as a result of rapid oxidation.[291] Other organic Se compounds released to the atmosphere as dust are removed by dry or wet deposition.

Soil

Decomposition of Se-accumulating plants is the primary source of organic selenium in the soil with Se concentrations ranging from ~0.1–0.7 mg/kg. The selenium content in tropical soils is relatively high concentrations, whereas volcanic and granite soils have low Se concentrations.[292] Iron hydroxides, clay minerals, and organic matter bind selenium in soil; therefore, the availability of organic selenium in the soil is highly variable. Figure 27.4 outlines Se depletion from soil. Microorganisms (*Aeromonas*, *Flavobacterium*, *Pseudomonas*) methylate substantial amounts of elemental selenium and inorganic selenium compounds (sodium selenite) present in soil to dimethylselenide and dimethyldiselenide. Over 100 months, ~68–88% of the selenium present in the topsoil (i.e., upper 15 cm) near the Kesterson National Wildlife Refuge dissipated with tillage and irrigation increasing selenium dissipation more than soil amendments (casein, albumin, glutin). These organic selenium compounds then volatilize in the air.[293]

After uptake of inorganic selenium, terrestrial plants metabolize selenium to selenomethionine and, to a lesser extent, to selenocysteine. Selenocysteine is readily incorporated into proteins. In contrast to non-accumulators of selenium, plants that accumulate selenium sequester selenium primarily in nonprotein selenoamino acids (methylselenocysteine, selenocystathionine).[81] The use of plant ash and lime for fertilizer in China enhanced selenium uptake; these conditions probably contributed to the development of chronic selenosis.

Water

Selenium usually exists in freshwater as selenite or selenate; however, the presence of microorganisms of algae favors the production of methylated or volatile organic Se species. As a result of the synthesis and bioaccumulation of organic selenium prior to decay, >50% of the selenium contained in sediments in the ponds and reservoir in the Kesterson National Wildlife Refuge exists as organic selenium.[21] A field study at the Kesterson Reservoir demonstrated that leaching dominated selenium depletion in the winter; volatilization dominated the environmental fate of selenium during the summer.[276]

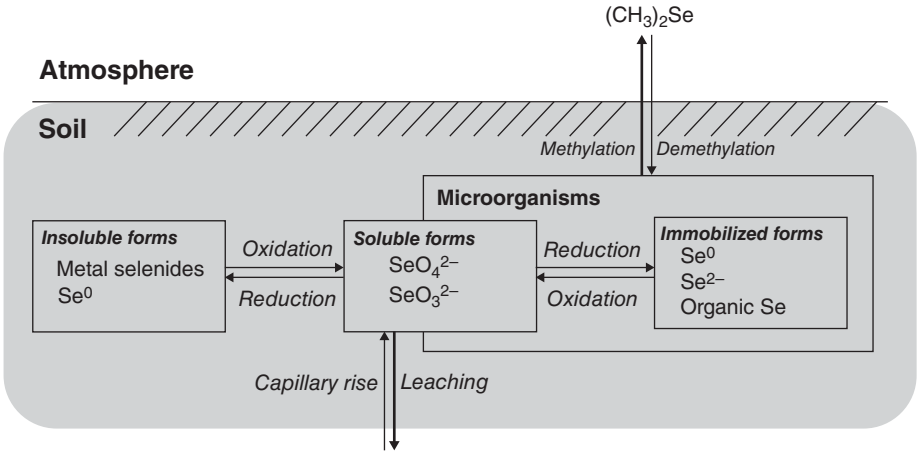


FIGURE 27.4. Schematic representation of selenium dissipation in soil. The preferred directions (bolded arrows) of these processes are methylation to dimethylselenide and leaching of soluble forms. (Modified from Nogueira and Rocha).[280]

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In a study of estuarine wetlands in the San Francisco Bay, organic selenium accounted for ~25–30% of the selenium in sediment in contrast to ~50% for elemental selenium.[86] The formation of selenoamino acids by microorganisms (phytoplankton, bacteria, fungi) does *not* produce significant levels of these compounds in the environment because of the rapid catabolism of selenoamino acids by bacteria. Additionally, studies in closed-system microcosms indicate that volatilization is an important pathway for loss of selenomethionine compared with other selenium species (e.g., selenite or selenate, ~1%).[87] Following formation, methylated forms of selenium rapidly volatilize into the atmosphere. The accumulation of selenomethionine in aquatic organisms is greater than either selenate or selenite. Selenium bioaccumulates in the aquatic food chains with Se concentrations orders of magnitude higher in aquatic organisms than surrounding water; however, biomagnification factors are small (i.e., 1–2) based on examination of Se data from the San Francisco Bay.[294]

Higher plants including algae volatilize significant portions of selenium present in their structure as methylated selenides. Non-accumulators emit primarily dimethyldiselenide, whereas accumulators emit mainly dimethylselenide. At least in sewage, dimethylselenide predominates at low selenite concentrations (1–10 mg Se/kg); dimethyldiselenide and dimethylselenenyl sulfide (previously reported as dimethylselenone)[295] predominate at high concentrations (>100 mg Se/kg). These reactions are temperature dependent with a reduction in temperature from 20 to 4°C causing a 90% decrease in the formation of dimethylselenide.[283]

DOSE EFFECT

Acute Toxicity

Toxicity depends on the chemical form of selenium. The toxicity of organic selenium is low. Although selenocysteine possesses similar toxicity in animals compared with selenite, selenomethionine is somewhat less toxic.[296] Other organic selenium compounds (dimethylselenide, trimethylselenonium ion, selenoethers, selenobetaine) are much less toxic in animal studies compared with selenite.[154,297]

Chronic Toxicity

Human

Organic-bound selenium (e.g., selenomethionine) is relatively less toxic than inorganic salts, but there are limited data on the toxicity of individual compounds.[298,299] In a randomized, controlled clinical trial, 653 patients received 200 μg Se as high-selenium brewer's yeast tablet daily.[217] A total of 35 patients (21 in treatment group, 14 in control group) withdrew from the study because of adverse effects (i.e., primarily gastrointestinal complaints); there was no difference in the plasma selenium concentration between patients reporting adverse effects and the rest of the test group. The mean plasma selenium concentrations of the control and treatment groups after 9 months of selenium supplementation were 114 μg/L and 190 μg/L, respectively. In a study of 10 volunteers receiving 600 μg Se as high-selenium yeast (selenomethionine), no clinical or laboratory abnormalities were detected during the 18-month course of the study.[300] The mean whole blood Se concentration of this group was 620 μg/L. In nutritional studies, volunteers tolerate daily selenium intake from selenium supplementation (e.g., selenomethionine, high-selenium yeast, selenite) up to ~800 μg without adverse effects.[301]

Animal

Selenocysteine is the most toxic *organic* selenium compound in animal studies. In these studies, selenocystine and selenite toxicities were similar.[302] In general, methylated metabolites are less toxic than the parent compound. Methylselenocysteine (from Se-accumulator plants) produces less toxicity than selenocysteine.[154] Selenomethionine is less toxic than selenite; the L-isomer (natural) is slightly more toxic than the D-isomer (synthetic). Other organic selenium compounds (selenobetaine, trimethyselenonium ion, dimethylselenide, selenoethers) are not very toxic in comparison to selenite.[297] Substantial variation in Se toxicity in various animal species occurs with hamsters being more resistant to Se effects than rats.[303]

TOXICOKINETICS

Absorption

The absorption of selenium is greater from amino acids (i.e., selenomethionine, selenocysteine) than inorganic species (i.e., selenite, selenate);[301] however, there is substantial inter-subject variation in Se absorption in humans.[304,305] Following the ingestion of 200 μg Se by 6 volunteers, gastrointestinal absorption accounted for ~97% of the selenium dose when administered as L-selenomethionine compared with ~84% when administered as selenite.[306] In an isotope tracer study of

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fasting volunteers receiving 26.5 μg ^{74}Se, the gastrointestinal tract absorbed ~85% of the selenium when administered as L-selenomethionine.[304] In comparison, the gastrointestinal tract absorbed ~25–43% of 41.6 μg ^{76}Se as sodium selenite. The estimated mean absorption of 100 μg Se as D,L-selenomethionine over 10 weeks in this study was ~75%. The absorption of selenomethionine from the gastrointestinal tract occurs via an active transport mechanism shared with methionine. Selenocysteine may share a common active transport mechanism with basic amino acids. The absorption of selenomethionine, but not selenocysteine, occurs in the intestine without prior metabolism.[21]

Distribution

In primates receiving 600 μg selenomethionine/kg body weight orally, the highest Se concentrations in tissues occurred in the following descending order: liver, kidneys, spleen, pancreas, cardiac muscle, brain, and skeletal muscle.[307] Slightly less than ½ of the body burden of selenium resides in skeletal muscle and bone with muscular tissue accounting for the largest portion, primarily as selenomethionine.[177,306]

Metabolism

A variety of selenium compounds appear in the urine after the ingestion of selenium species including selenosugars; analytical issues complicate the determination of the chemical composition of urinary selenium metabolites in humans following ingestion of organoselenium compounds. Although earlier studies suggested that trimethylselenonium ion was a major metabolite, subsequent studies indicate that trimethylselenonium is a minor metabolite.[134] Selenosugar 2 (methyl 2-acetamido-2-deoxy-1-seleno-β-D-galactopyranoside) is probably a major metabolite with selenosugar 1 (isomer of selenosugar 2); selenosugar 3, selenite, and perhaps trimethylselenonium ion are minor metabolites.[130] Although selenosugar 2 is the primary metabolite in urine samples from most humans, substantial amounts of trimethylselenonium ions may occur in some individuals, particularly following the metabolism of selenocysteine.[308]

The metabolism of selenomethionine ultimately yields primarily monomethylated forms of selenium. The metabolism of selenomethionine to selenide and the incorporation of selenium into selenium-specific proteins occur by the following two pathways: 1) metabolism to methane selenol and selenide and 2) via selenocysteine and the transsulfuration pathway (methionine to cysteine) as demonstrated in Figure 27.2.[309] Selenocysteine β-lyase catalyzes the metabolism of selenocysteine to alanine and hydrogen selenide.[310] Pyridoxal-5-phosphate is a cofactor for this reaction. Humans metabolize the L-enantiomer of selenomethionine, whereas the kidney excretes the D-enantiomer unchanged without any significant biotransformation.[311] Biotransformation of selenobetaine and selenomethylselenocysteine involves conversion to methylselenol via β-lyase and demethylation, respectively.

Elimination

In humans ingesting low doses of selenium, the kidneys and the intestines each excrete ~1/2 of the absorbed Se dose; exhalation of selenium is a minor pathway.[135] Similar to other nonmetals, methylation of elemental selenium occurs prior to renal excretion or exhalation in air with the amount of methylation being dose-dependent.[130] Selenomethionine elimination is triphasic similar to sodium selenite; however, the terminal half-life of selenomethionine is longer than that of sodium selenite. In an isotope tracer study of four women, the average half-lives of selenomethionine for the three phases were ~0.4–2 days, 5–19 days, and 207–290 days, respectively.[312] Differences in the excretion pattern occur between selenium species. In a study of volunteers given 200 μg Se supplements as selenomethionine or selenate over 32 weeks, the mean daily Se excretion for selenomethionine was 27% of the daily dose compared with 57% for selenate.[136]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

In humans, there are at least 25 selenoproteins; these proteins all contain the amino acid, selenocysteine. The latter amino acid is structurally similar to cysteine except for the substitution of selenium for sulfur.[313] Selenocysteine is formed in the body rather than consumed in the diet as a result of the reaction of phosphoserine with monoselenophosphate. There are two classes of selenoproteins: 1) the *N*-terminal position of the function domain contains selenocysteine (e.g., glutathione peroxidases, selenoprotein P, selenoprotein W), and 2) the *C*-terminal sequence contains selenocysteine (e.g., thioredoxin reductase). Selenoamino acids (i.e., selenocysteine, selenomethionine) mediate antioxidant defense mechanisms in mammalian cells.

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Glutathione peroxidase and glutathione disulfide catalyze the redox reactions that reduce various simple and lipid hydroperoxides to phospholipids. Selenomethionine has glutathione-like activity, whereas the active site of glutathione contains selenocysteine residues. Additionally, glutathione peroxidases and thioredoxin reductases are the main selenoproteins expressed by endothelial cells; these selenium-containing enzymes modulate vascular tone by several processes including maintaining the superoxide anion/nitric oxide balance and regulating inflammatory processes.[314] Thioredoxin reductase also stimulates the proliferation of normal and tumor cells as part of the repair mechanisms essential for DNA synthesis.[315]

At least 13 selenoproteins contain selenium as selenocysteine.[316] A unique stop codon UGA in mRNA encodes the endogenous synthesis of selenide and serine to selenocysteine. This reaction involves a unique tRNA, which implies that this process is under genetic control. Animals cannot synthesize selenomethionine. Other proteins that incorporate or require selenium include the following: a selenoprotein in muscle, selenoprotein P (catalytic function unknown), and the selenodeiodinases, which catalyze the deiodination reactions that convert the prohormone, thyroxine, to the active thyroid hormone, 3,5,3′-triiodothyronine.[317] The amino acid sequence of the active site of the latter enzyme requires selenocysteine for full activity. Organoselenide compounds can form selenooxides that oxidize endogenous cellular molecular targets containing thiol groups.[280]

CLINICAL RESPONSE

The toxicity of most selenium compounds is low, particularly organic selenium compounds. No statistically significant developmental abnormalities were detected in primates given toxic Se doses ranging up to 300 μg/kg as selenomethionine during organogenesis.[318] In this study, maternal toxicity included anorexia, vomiting, and decreased body weight.

DIAGNOSTIC TESTING

The identification and quantification of selenium species is challenging as a result of low selenium concentrations, oxidative degradation during sample preparation (e.g., selenomethionine), and the complexity of the matrix including the presence of polyatomic interferents (e.g., arsenic isotopes) in biological samples. Typically, hyphenated techniques that couple chromatography separation with inductively coupled plasma/mass spectrometry (ICP/MS) in combination with molecular mass spectrometry (ESI/MS, ESI/MS/MS, MALDI/TOF) and isotopic dilution allow structural characterization of selenium species.[225] High-pressure liquid chromatography/inductively coupled plasma/mass spectrometry separates and detects various selenium species including selenium isotopes. The latter distinguishes between different sources of organoselenium.[319] For the presence of organoselenium compounds in water, selective sequential hydride generation with atomic absorption spectroscopy is a common method of analysis based on selenite forming volatile hydrogen selenide after reacting with borohydride under acidic conditions.[284] Speciation of selenium in soils and sediments typically involves direct spectroscopic analysis (e.g., x-ray absorption spectroscopy) and sequential extraction procedures.

Gas chromatography is a valid separation technique for volatile selenium species (e.g., methaneselenol, dimethylselenide, dimethyldimethyldiselenide). The use of capillary electrophoresis/inductively coupled plasma/mass spectrometry allows the chiral separation of L- and D-selenomethionine previously derivatized with 1-fluoro-2,4-dinitrophenyl-5-L-alanine amide in digested yeast samples pretreated with enzymatic hydrolysis.[225]

HEALTH SURVEILLANCE

Plasma selenium consists of selenocysteine in two selenoproteins and selenomethionine at methionine positions in all proteins along with small molecular forms (<3% of the total selenium).[320] Both animals and humans retain more selenium as selenomethionine compared with selenium as selenite or selenate, probably as a result of the uptake of selenomethionine by nonspecific cellular proteins.[321] Supplementation with selenomethionine produces higher blood Se concentrations than the same amount of inorganic Se species (selenite, selenate). During a 32-week study of 33 women receiving 200 μg Se as selenomethionine or as selenate, the whole blood Se concentration reached a plateau of ~100 μg/L following selenate supplementation.[249] The mean whole blood level of Se following selenomethionine supplementation was about 280 μg/L.

TREATMENT

The toxicity of organic selenium compounds is relatively low; treatment is supportive.

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Chapter 28

SILVER

HISTORY

Silver is a nonessential trace element that demonstrates relatively low toxicity in mammals. Humans probably separated silver from lead several millennia BC with silver used for currency mentioned in the first book of the Old Testament. Lunar caustic (silver nitrate) was administered to patients with nervous disorders in the Middle Ages.[1] Silver has a long history of use as an antimicrobial agent. Crede introduced the use of silver nitrate drops into medical practice in 1884 by recommending the application of these drops to the eyes of newborns in order to prevent the development of gonococcal ophthalmia.[2] Camillo Golgi developed a histological silver stain for the study of the nervous system in 1873; later, he received the Nobel Prize in medicine for his work.[3] Several colloidal silver formulations were developed for the treatment of infectious diseases in the late 19th century including Collargol (Crede's colloidal silver antimicrobial for wounds) and Protargol (silver colloidal compound for gonorrhea).[4] By the early 1900s, a mild silver protein-stabilized solution (Argyrol) was used as an anti-infective cleansing agent for mucous membranes of the eyes and upper respiratory tract. This latter substance remains available online today (http://www.argyrol.com/agprotein.phtml).

In 1907, Dr. Paul Ehrlich recommended the parenteral administration of silver arsphenamine for the treatment of syphilis and yaws (i.e., chronic dermal, bone, and cartilage disease caused by *Treponema pallidum* subspecies *pertenue*).

Following the prolonged use of silver compounds (silver nitrate, colloidal silver preparations), a permanent bluish-gray discoloration of skin, eyes, and nails occurred during the 20th century.[5] In the late 1920s, an autopsy of the famous "blue man" of the Barnum and Bailey's Circus demonstrated large deposits of silver in his body estimated at 90–100 g.[6] This condition was called argyria; fortunately, these patients remained relatively asymptomatic. The use of silver as an antimicrobial agent declined in the 1940s with the widespread introduction of antibiotics. Medical interest in silver resurged in the 1990s with the use of silver nanoparticles in a variety of medical products. Other uses include silver nitrate for burns, prevention of gonococcal ophthalmia neonatorum, and the use of silver alloy (dental amalgam) in dentistry.

PHYSIOCHEMICAL PROPERTIES

Silver is a hard, lustrous, and malleable transitional metal that possesses the highest thermal and electrical conductivity of all metals. Copper and other metals form important alloys with silver. There are four oxidation states (0, 1+, 2+, 3+) with the metallic and monovalent forms being the most common Metallic silver, silver halides, and silver oxide are relatively insoluble in water, whereas silver nitrate and colloidal silver are water-soluble. The latter contains substantially less silver (~6%) than silver nitrate (50%).

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TABLE 28.1. Identifying information and physical properties of silver and silver compounds.

Physical Characteristic	Silver	Silver Chloride	Silver Oxide	Silver Suboxide	Silver Nitrate	Silver Sulfide
CAS RN	7440-22-4	7783-90-6	20667-12-3	1301-96-8	7761-88-8	21548-73-2
Form	Lustrous white solid	White, solid	Dark brown-black	Gray-black crystals	Colorless-white crystals	Gray-black
Molecular formula	Ag	AgCl	Ag_2O	AgO	$AgNO_3$	Ag_2S
Molecular weight (g/mol)	107.87	143.32	231.8	123.87	169.87	248.81
Melting point (°C)	961.93	455			212	
Boiling point (°C)	2,212	1,550	200–300[a]	100[a]	440[a]	810[a]
Density (g/mL, 20°C)	10.5	5.56	7.14	7.48	4.35 (19)	7.36
Water solubility (mg/L, 25°C)	Insoluble	1.93	0.022	Decomposes	≥100 (16)	0.00014
Vapor pressure	100 mmHg (1,865°C)	NA	NA	NA	NA	NA
Odor threshold	Odorless	NA	Odorless	NA	Odorless	NA

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.
[a] Decomposes.

Silver has two stable isotopes (^{107}Ag, ^{109}Ag); the radioisotopes of silver do not occur naturally in the environment. Table 28.1 lists the identifying information and physical properties of silver and silver compounds. Silver oxide (Ag_2O) is a strong oxidizing agent. Light is a catalyst that reduces silver compounds in the skin to metallic silver similar to the photoreduction of a photographic plate.

Historically the term colloidal refers to silver-impregnated macromolecules, often prepared from casein (milk) or serum proteins. The final product contained silver complexed to polypeptides, very small silver particles in polypeptide coating, or a mixture of the 2 Ag forms. Silver nanoparticles (<100 nm) are substantially more reactive than elemental silver with their properties dependent on size, shape, charge, stability, and impurities.

EXPOSURE

Production Processes

The production of silver primarily involves the recovery of silver during the retrieval of copper, gold, lead, and zinc ores. The main silver-containing ores are argentite (Ag_2S) and cerargyrite (Horn Silver, AgCl) with the recovery of silver by cyanide extraction, electrolytic processes, or zinc reduction. At the present time, the acquisition of silver by recycling exceeds silver production from ores. Workers in silver refineries have mixed exposures to other metallic substances including antimony, arsenic, cadmium, selenium, and tellurium.

Uses

Photographic materials and batteries (silver–lead) account for the majority of silver consumption, particularly radiographic material, along with brazing alloys and solder (silver–copper–zinc). Photographic emulsions use silver halides to produce light sensitivity. The use of silver for esthetic purposes (jewelry, sterling ware, electroplated ware) accounts for a much smaller portion of the silver produced for commercial uses. Less common uses include dental amalgam, burn treatment, cloud seeding (silver iodide), catalyst in the production of ethylene oxide and formaldehyde, and purification of water.[7] Silver nanoparticles have antimicrobial properties against bacteria and fungi; the small size and large surface area increase antibacterial potencies while reducing particle concentrations and avoiding adverse mechanical properties.[8] Medical applications include enhanced antimicrobial activity by incorporation of nanosilver in endotracheal tubes, surgical instruments, wound sutures, bone prostheses, dental/bone prostheses, and implants.[9] Other potential uses of nanosilver include site-specific delivery of cancer therapy (radiotherapy, phototherapy),[10] a biomarker, an imaging agent for signal enhancement, optical sensing, and various consumer products (toothpaste, mouthwash, pet products, pillowcases, shower filters, food containers, vacuum cleaners, washing machines, clothes, laundry detergent, shampoos, carpets).[11,12] The use of nebulized colloidal silver for the treatment of upper respiratory tract infections is a homeopathic method that may cause pulmonary infiltrates. Silver nitrate is a caustic and astringent used to cauterize bleeding surfaces.

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Sources

The major source of silver in the general population is drinking water and food. Silver is a normal trace element in many organisms. In the environment, silver occurs primarily as silver sulfide (Ag_2S) or as silver sulfide associated with other metallic sulfides (e.g., copper, iron, gold, lead). Only a small portion of the total silver present in environmental samples is available as a biologically important metallic species.[13] Consequently, potential silver toxicity correlates to the concentrations of free silver ions rather than the concentration of total silver (i.e., ionic silver and silver compounds).

Air

The major forms of silver in the air are metallic silver and silver salts (carbonate, halides, sulfide, sulfate). The release of silver from natural sources includes the erosion of soil and the weathering of rocks. Important industrial sources for the release of silver into the atmosphere include cement manufacturing, cloud seeding, fossil fuel combustion, municipal waste incineration, processing of ores, and steel refining.[7] Background Ag concentrations in ambient air are typically <1 ng/m^3 with anthropogenic sources raising the ambient concentrations to 1–5 ng/m^3 based on measurements recorded with older techniques that lack the ultra-clean sampling methods currently available.[14,15] These methods also indicate that cloud seeding with silver iodide increases the silver concentration in precipitation from 0–20 ng/L to 10–4,500 ng/L;[16] associated Ag concentrations in nearby air may increase to ~0.1 ng/m^3.

Soil

Silver is the 67th most abundant element in the earth's crust with an average concentration of ~0.07 mg/kg, predominately in basalt and igneous rocks.[13] In the soil, silver exists primarily as sulfides associated with gold, iron (pyrite), lead (galena), and tellurides. The major source of elevated silver concentrations in cultivated soil is the application of silver-containing sludge as soil amendment. Biotransformation of silver in the soil probably does not occur because microorganisms are susceptible to silver toxicity. Coal-fly ash may contain Ag concentrations of 1–15 ppm (mg/kg); therefore, soil near coal-fired power plants may contain higher Ag concentrations than surrounding areas.[17,18] The US EPA Contract Laboratory Program analyzed soil samples from 2,783 Superfund hazardous sites; the 1,807 positive samples contained a geometric mean silver concentration of 4.5 ppm.[7]

Water

The major anthropogenic source of silver is effluent from photographic processes.[7] The major forms of silver in the water are monovalent ions of sulfate, bicarbonate, and sulfate salts. Complexation with chloride and sulfate ions along with adsorption of silver to particulate matter accounts for smaller amounts of silver.[19] Reducing conditions favor the formation of silver sulfide, whereas oxidizing conditions favor the formation of silver halides. Background ambient Ag concentrations in freshwater and seawater average ~0.2 μg/L and 0.25 μg/L, respectively. Surface waters leaching silver from mining operations may contain up to 100 times greater Ag concentrations than background concentrations, particularly in waters with low pH.[20] US drinking water usually contains low Ag concentrations except for waters with Ag-containing disinfecting agents. Most drinking water supplies demonstrate silver concentrations of 0.1–10 μg/L with few supplies containing Ag concentrations exceeding the current US EPA standard.[21] Typical background Ag concentrations in rivers are 0.001–0.002 μg/L.[22] Although bioconcentration of silver in fish and invertebrates occurs to a moderate degree, biomagnification in the food chain is unlikely.[7]

Lifestyle

The major sources of silver in the diet are crops grown in areas with high silver content in the soil and seafood from areas near industrial Ag sources.[7] Estimates of daily Ag intake in the diet range from ~4 μg (US men 25–30 years old)[23] to 88 ± 10 μg (single subject analyzed by older spectrometry method)[24] and 27 ± 17 μg (UK diet estimated by mass spectrometry).[25] The highest Ag concentrations in foods from the latter study occurred in milk (25–50 μg/L) and mushrooms (~100–200 μg/L). The silver concentrations in tobacco are relatively low with the high melting point limiting inhalation of silver during smoking. The release of silver from dental amalgams is extremely low; fecal excretion resulting from dental amalgams is lower for silver than mercury.[26] Food and drink are not sources of silver exposure associated with argyria or argyrosis.

ENVIRONMENTAL FATE

Coarse particles (>20 μm) of silver released from mining operations settle near the point source, whereas fine particles (<20 μm) may be transported >100 km until deposited by precipitation.[27] Factors reducing Ag mobility in soil include: 1) well-drained soil; 2)

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oxidation–reduction and pH conditions favoring the formation of iron and manganese complexes with silver; and 3) the silver adsorption to organic matter. Soil is the main deposition site for silver nanoparticles; effluent from waste treatment plants may carry nanosilver into the aquatic environment, primarily to sediment.[28] Although sediment-dwelling animals (clams, oysters, scallops) do concentrate silver, there are few data to support biomagnification of silver (i.e., the systematic increase of silver concentrations moving up the food chain).[7] Most silver entering the ecosystem is immobilized in the form of alloys, metals, or minerals.[13] Divalent (Ag^{2+}) and trivalent (Ag^{3+}) species are more effective oxidizing agents than metallic silver (Ag^0), but Ag^{2+} and Ag^{3+} are unstable in aqueous environments. In freshwater and soils under oxidizing conditions, the common silver compounds are bromides, chlorides, and iodides, whereas metallic silver and silver sulfide dominate under reducing conditions.[7] The availability of free silver in marine environments strongly depends on salinity with adsorption decreasing with increasing salt concentrations.[29]

DOSE EFFECT

The toxicity of metallic silver and silver salts is relatively low. The older medical literature indicates that the administration of ~2.3 g Ag intravenously produces argyria[30] with a range of ~1–8 g Ag. The metallic form of silver is poorly absorbed from the gastrointestinal tract; therefore, cases of argyria are unlikely except for the use of the colloidal silver preparation (Argyrol). Relatively higher doses of soluble silver salts (1–30 g) are necessary to produce argyria following ingestion compared with the intravenous route.[17] The ingestion of 60 mL 24% silver nitrate (i.e., ~62 g) by a 15-year-old boy produced spontaneous vomiting but no complaints of sore throat or dysphagia.[31] An esophagram 4 weeks later was normal. A second child developed a painless, desquamating rash where the vomitus stained the skin, but the lesion healed without sequelae.

TOXICOKINETICS

Absorption

Although studies of workers suggest the lungs absorb silver compounds,[32,33] data are inadequate to determine the extent/rate of Ag absorption. A study in dogs demonstrated absorption of ~3% of metallic silver *deposited* in the lungs.[34] Data are also limited on gastrointestinal and dermal Ag absorption. Clinical experience with a patient ingesting silver-containing anti-smoking lozenges suggests that the body absorbs ~20% of a silver acetate dose within 1 week after ingestion.[35] Absorption of silver nitrate across the oral mucosa is sufficient to produce systemic argyria following the repeat application of silver nitrate to the gums.[36] The absorption of silver compounds across the skin appears minimal, even following the application of silver nitrate on burned skin.[37] Some precipitation of silver sulfide in the stratum corneum may occur following the application of silver ions to intact skin in the presence of moisture.[38] The transdermal absorption of silver is relatively slow. The dermal flux in healthy subjects ($n = 15$) and patients with atopic dermatitis ($n = 15$) wearing a sleeve containing 3.6% (w/w) silver on their lower arms for 8 hours/day for 5 consecutive days was ~20 ng/cm^2/hour.[39] Urine Ag concentrations remained similar in the two groups during the study. Animal studies indicate that following a 5-hour application of silver compounds to the skin, <1% of the dose crosses the skin;[40] however, case reports associate prolonged, excessive application of silver sulfadiazine with elevated blood silver concentrations and Ag deposition in the tissues.[41] Experimental data suggest that the dermal absorption of Ag nanoparticles through intact and damaged skin is detectable, but very low.[42] In a study of consumer products with Ag nanoparticles, leaching of silver occurred primarily via dissolution of ions rather than particulates, particularly in liquids with high salt concentrations. The resulting silver concentrations were well below current regulatory standards.[43] Wiping these products produced silver concentrations in the wipes ranging from 0.3–23 μg/m^2.

Distribution

The liver is the primary site of deposition of silver absorbed into the body, particularly the area of the portal vein.[34] Following silver exposure, animal studies indicate Ag distributes to many tissue sites, particularly the glomerular basement membrane, the walls of the blood vessels near renal tubules, the choroid plexus in the brain, the thyroid, and the choroid layer of the eye.[44,45] Most of the silver appears in the cytosol fraction bound to high-molecular-weight proteins and the metallothionein fractions.[46] Diffusion of silver across the blood–brain barrier appears minimal.

Elimination

Following the oral administration of silver acetate, biliary excretion accounts for the vast majority of silver

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elimination with only minor amounts excreted in the urine.[35] Rapid silver excretion occurs in the first week. The estimated Ag biological half-life in the lungs was 1 day compared with 52 days in the liver.[32] In studies on dogs, the biological half-life of silver followed a tri-exponential pattern (0.1 day, 7.6 days, 33.8 days) with an average amount of silver excreted during each period of 90%, 7%, and 3%, respectively.[47] The terminal elimination half-life of silver in a 78-year-old patient undergoing an operation using silver-containing prosthetic cement was ~6 months.

Interactions

High selenium concentrations in the diet increase deposition of insoluble silver salts in the body tissues of animals by increasing the formation of silver selenide.[48] Although there are few data available, these higher deposition rates of insoluble silver salts potentially may increase the risk of developing argyria.

Maternal–Fetal Kinetics

Silver was present in 16% of the samples of amniotic fluid with mean Ag concentrations of 25 μg/L and a maximum value of 540 μg/L.[49]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Silver has no known physiological or biochemical functions in the human body.[50] The production of silver toxicity depends on the degree of water solubility/absorption, binding to biological sites, sequestration of silver complexes, and ease of excretion. The formation of insoluble silver salts (silver chloride, silver phosphate) deposits silver in the tissue. The fate of these insoluble salts includes complexation with amino or carboxyl groups in nuclear material, reduction to metallic silver by ascorbic acid or catecholamine, or transformation of soluble silver sulfide albuminates.[51] Exposure of the skin to ultraviolet light reduces the silver chloride in the skin to metallic silver. The oxidation of metallic silver to black silver sulfide produces the characteristic blue-gray color of the skin associated with argyria.[52] There is no direct evidence to link the deposition of these silver compounds with toxic effects.[7] Silver binds to phosphate, amino, carboxyl, and imidazole groups as well as apoceruloplasmin forming silver-bound ceruloplasmin that limits copper absorption and may produce hypocupremia. Silver compounds can inactivate enzymes by forming silver sulfides that bind to sulfhydryl groups as well as reducing the activity of glutathione peroxidase and lactate dehydrogenase.[53] There is no conclusive evidence that silver crosses the blood–brain barrier or causes neurotoxicity.[54] Silver nanoparticles bind avidly to proteins and thiol groups, potentially disrupting cellular functions depending on several factors including dose, duration of exposure, temperature, and physical property (shape, size, surface coating, surface charge). Coating the surface of these particles with hydrocarbons or polysaccharides reduces cytotoxicity; however, the effectiveness of these barriers may decrease over time in physiological systems.[55] Animal models suggest silver nanoparticles have the potential to produce reactive oxygen species and oxidative stress, resulting in an inflammatory reaction as demonstrated by increased proinflammatory cytokines (e.g., IL-4, IL-6, TNF-α) and stimulation of amyloidosis.[11,56]

Pathological Changes

Typically, skin biopsies of patients with argyria demonstrate inert black-silver granules surrounding elastic fibers, eccrine glands, and walls of blood vessels primarily composed of silver sulfide and lesser amounts of silver selenide; melanocytes typically remain normal.[57,58] Histological changes in bluish macules that resulted from prolonged exposure to silver needles included the deposition of brown granules in the basement membrane of adjacent eccrine sweat glands, walls of local blood vessels, and elastic fibers.[59] Postmortem examination of a 68-year-old man with severe generalized argyria (i.e., "blue man" from the Barnum and Bailey Circus) demonstrated silver deposits primarily in connective tissues and phagocytic cells (e.g., spleen, lymph nodes, bone).[6] Compared with other organs, the silver concentrations in the brain and spinal cord were very low. X-ray microanalysis, dark-field microscopy, and electron microscopy help to confirm the diagnostic changes of argyria. Examination of biopsies from the kidney of a patient with argyria revealed electron-dense particles (30–100 nm) located in the basement membranes of the kidney.[60] The predominant component of these deposits was silver selenide.

Argyrosis produces blue-gray discoloration of the cornea, tarsal conjunctiva, and bulbar conjunctiva. Deposition of silver typically occurs in Descemet's membrane rather than the Bowman membrane.[61] Slit-lamp examination of silver workers with corneal argyrosis demonstrates diffuse, gray opacities in the deep

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layers of the corneal stroma.[62] These highly reflective deposits are anterior to the corneal endothelium; however, these opacities do not frequently contain silver.

CLINICAL RESPONSE

Adverse Medicinal Effects

Argyria is an irreversible clinical condition characterized by blue-gray discoloration of the skin following prolonged exposure to Ag or silver compounds, particularly in sun-exposed areas (e.g., face, hands).[63] Hyperpigmentation develops when light reduces silver-containing compounds complexed with proteins in the skin to elemental silver. Silver also stimulates melanocyte tyrosinase activity and melanin production, resulting in hyperpigmentation of the nail bed, sclerae, and mucous membranes. Localized cutaneous argyria (blue-gray macules) develops from the leaching of silver from prolonged exposure to needles and jewelry that contain silver.[64] Skin abnormalities do not typically progress following cessation of Ag exposure. Little change occurred in the skin of a 72-year-old man despite the development of argyria during his early 20s when he was treated with silver nitrate for abdominal pain.[65] The differential diagnosis of blue-gray pigmentation of the skin includes drugs (chlorpromazine, antimalarials), hemochromatosis, methemoglobinemia, cyanosis, and disseminated melanoma.[66] The discoloration of the skin is permanent. Discoloration of open wounds/burns treated with silver nitrate or silver sulfadiazine may occur as a result of Ag-induced protein precipitation; however, the discoloration of the superficial layers of the epidermis sloughs as the wound heals.[67] Most cases of argyria and argyrosis result from exposure to water-soluble Ag compounds.[68] A case report associated the use of silver-containing prosthetic cement in a failed hip prosthesis with elevated serum Ag concentration of 6.3 μg/L and focal ipsilateral quadriceps femoris weakness; the latter resolved slowly.[69]

Argyrosis involves Ag deposition in the eye including pigmentation of the conjunctiva with localization to the inner canthus as an early sign; argyrosis may spread to the tarsal conjunctiva, bulbar conjunctiva, and cornea.[70] Corneal and conjunctival argyrosis can occur following chronic application of silver-containing professional eyelash tint.[71] Widespread deposition of silver in tissues may occur with continued exposure including other tissues in the body. Although several case reports associate neurological effects (seizures, myoclonus, corticobasal degeneration, coma) with the chronic ingestion of large doses of colloidal silver and elevated serum silver concentrations,[72,73] the presence of serious underlying medical diseases (diabetes, ischemic heart disease) in these cases limits conclusions regarding the causal role of silver. Argyria is not typically associated with neurological symptoms.

Occupational Exposure

Case reports associate localized and generalized silver deposition in the eye (argyrosis) with silver nitrate/oxide manufacturing,[74] silver refining,[75] and silver soldering.[62] In a study of workers exposed to silver compounds, silver deposits in the Descemet membrane of the cornea and the skin correlated with complaints of decreased night vision.[33] Electrophysiological examination of seven of the silver nitrate and oxide manufacturing workers with argyrosis and complaints of decreased night vision did not detect any visual deficits.[74] A case report associated development of argyrosis with work in a silver refinery over 7 years. After reduction of airborne silver concentrations, he remained asymptomatic and his argyrosis did not progress over 18 months of medical surveillance.[75] Although the total body burden of silver may be increased in workers exposed to insoluble silver salts as reflected in the ocular deposition of silver, toxic effects are uncommon.[76] Occupational exposure to silver dust (silver oxide, silver nitrate) may produce upper respiratory tract irritation (rhinitis, sore throat, watery eyes) as well as cough and chest tightness;[33] the corrosive effects of nitrate probably contribute substantially to the irritant effects of silver nitrate. Exposure to silver dust is not associated with the development of occupational asthma. A study of workers' exposure to silver nitrate, silver oxide, silver chloride, and silver cadmium oxide detected some marginal changes in the presence of the urinary enzyme *N*-acetyl-β-D-glucosaminidase (NAG), but co-exposure to cadmium limits the conclusions regarding the renal effects of silver dust.[77] Percutaneous exposure to powdered silver, dental amalgams, and silver compounds occasionally causes allergic contact dermatitis.[78,79]

Reproductive Abnormalities

There are few data on the reproductive effects of silver. Although data are insufficient to provide a definite conclusion regarding the reproductive effects of silver, current evidence does not suggest silver is a reproductive toxin.[7]

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Carcinogenesis

Neither the IARC nor the US National Toxicology Program lists silver or silver compounds as suspected carcinogens. The weight of the evidence suggests that silver is not mutagenic, but silver may be genotoxic; however, existing animal and epidemiological studies have not provided evidence to suggest that silver or silver compounds are carcinogens.[7]

DIAGNOSTIC TESTING

SI Conversion Units

Troy ounce = 31.10 g
1 μg/L = 9.271 nmol/L
1 nmol/L = 0.1079 μg/L

Analytical Methods

Most analytical techniques measure total silver concentrations rather than silver species. Silver concentration in the range of 10^{-6}–10^{-9} g/g sample is detectable by several analytical methods including neutron activation analysis (NAA), graphite furnace (flameless) atomic absorption spectrometry (GFAAS; LOD, 0.4 μg/L),[80,81] flame atomic absorption spectroscopy (FAAS), voltammetric techniques with anodic stripping (LOD, 0.1 μg/L), high-frequency plasma torch-atomic emission spectroscopy (HFP-AES), and micro-cup atomic absorption spectroscopy (MCAAS).[7] The detection limit of atomic absorption spectroscopy is ~2 μg/L, whereas the more expensive NAA allows the detection of 2 ng Ag. Electrothermal atomic absorption spectroscopy has a detection limit of 0.1 μg/L (CV = 4.6% at 10 μg/L).[82] Accurate analysis of low silver concentrations in environmental and biological samples requires the use of ultra-clean sampling techniques with NAA, inductively coupled plasma/atomic emission spectrometry, or inductively coupled plasma/mass spectrometry that were uncommon before the late 1980s.[13]

Biomarkers

Blood

General Population

In a study of 394 healthy Italians, the mean serum Ag concentration was 0.18 μg/L (range, 0.06–0.3 μg/L), whereas the whole blood Ag concentration in 437 Italian subjects was 0.37 μg/L (range, 0.13–0.61 μg/L).[83] In a study of 15 agricultural workers without occupational Ag exposure, the mean whole blood Ag concentration was below the detection limit (0.1 μg/L) with only four samples containing detectable Ag concentrations (0.2 μg/L).[82] The plasma silver concentrations in a convenience sample of 26 Melbourne residents without known silver exposure were <2.3 μg/L, as measured by flameless atomic absorption spectrometry.[80]

Medical Therapy

After 12 weeks of using silver acetate-containing chewing gum as an antismoking aid, the mean serum silver concentration in 21 individuals was 41.7 μg/L with a maximum concentration of 117 μg/L as measured by atomic absorption spectrometry.[84] The higher silver concentrations reflect the relatively high water solubility of this Ag salt compared with water-insoluble Ag salts. No individual developed argyria; serum silver concentrations declined to a mean value of 3.2 μg/L within 14 weeks. The use of silver nitrate for cauterization of anterior epistaxis transiently may increase blood silver concentrations. In a study of nine healthy volunteers, the cauterization of the nasal mucosa with one silver nitrate applicator produced peak whole blood silver concentrations of 2.89 ± 3.12 μg/L with the peak ranging from 3 hours to 14 days.[85]

Argyrosis/Argyria

The serum silver concentration may be within the normal range in patients with localized argyria. In an asymptomatic 58-year-old man with facial changes and black-silver granules on dermal biopsy characteristic of argyria on his face, the serum Ag concentration was 11 μg/L (reference range, 0–14 μg/L).[86] A 60-year-old man with schizoaffective disorder and long history of ingesting colloidal silver presented with a generalized silvery sheen on his face and neck along with blue-gray sclera. His serum silver concentration was 11 μg/L (reference range, <5 μg/L).[63] A 27-year-old worker exposed to aerosolized silver presented with 4 months of progressive blue-gray discoloration of his facial skin; he was asymptomatic with a serum silver concentration of 154.4 μg/L (upper reference limit, 25 μg/L).[87] In an asymptomatic 51-year-old silver refiner with argyrosis and a 7-year history of Ag exposure during the electrolytic purification of silver ingots, the initial Ag concentration was 740 μg/L.[75] He remained asymptomatic during an 18-month follow-up without evidence of argyria or progression of his argyrosis. His Ag concentration at the end of this medical surveillance was 60 μg/L as measured by atomic absorption spectrometry.

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URINE

The kidneys excrete small amounts of the absorbed Ag dose. In a convenience sample of 26 Melbourne residents without known silver exposure, the spot urine silver concentrations were <2 μg/L as measured by flameless atomic absorption spectrometry.[80] The mean urine Ag concentration in 472 healthy Italian volunteers was 0.46 μg/L (range, 0.04–0.88 μg/L).[83]

HEALTH SURVEILLANCE

Risk Assessment

For the general population, the US EPA reference dose (Rfd) for silver exposure is 5 μg/kg/day with an estimated critical dose of 14 μg/kg/day. The proposed Maximum Contaminant Level Goal for silver in drinking water is <0.1 mg/L.

Environmental Monitoring

Table 28.2 lists the current regulations and guidelines regarding exposure to silver and silver compounds. The ACGIH TLV–TWA for soluble silver compounds is lower than the regulations for insoluble metallic silver and insoluble silver compounds because of the greater toxicity and absorption of soluble silver compounds; however, OSHA and NIOSH do not separate the toxicity of soluble and insoluble Ag compounds. The regulations and recommendations for silver exposure are designed to minimize the risk of argyria. The risk of argyria following exposure to insoluble Ag compounds (e.g., AgCl, Ag_2S) is substantially less than that of soluble Ag compounds (e.g., silver nitrate, silver sulfadiazine, colloidal silver).

TABLE 28.2. Identifying information and physical properties of silver and silver compounds.

Exposure Limit	Value
OSHA	
PEL–TWA (8-hour)	0.01 mg/m^3 (as Ag)
NIOSH	
REL–TWA (10-hour)	0.01 mg/m^3 (as Ag)
IDLH	10 mg/m^3 (as Ag)
ACGIH	
TLV–TWA (8-hour)	
Metal dust and fume	0.1 mg/m^3
Soluble Ag compounds	0.01 mg/m^3 (as Ag)
US EPA	
RfD (chronic oral exposure)	0.005 mg/kg/day
US federal drinking water guidelines	0.1 mg/L

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; BEI = biological exposure indices; IDLH = immediately dangerous to life and health; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency.

Biological Monitoring

BLOOD

Silver is rapidly eliminated from the body, primarily in the feces; current data are inadequate to recommend blood as a reliable biomarker of Ag exposure.[88] Analysis of whole blood from 70 silver refinery workers demonstrated a mean Ag concentration of 2.5 μg/L with a range of <0.1–16 μg/L.[82] The highest whole blood Ag concentrations in this study occurred in 19 silver reclamation workers (mean = 6.8 μg/L; range, 1.3–20 μg/L). In a study of 27 silver reclamation workers and 27 employees without occupational Ag exposure, the mean Ag concentration in whole blood from 21 workers with detectable Ag concentrations (>5 μg/L) was 10 μg/L.[76] Although 29% of the reclamation workers had ocular Ag deposits, no pulmonary, visual, or dermal dysfunctions were detected. In a workplace with exposure primarily to insoluble metallic silver dust (TWA = 0.001–0.1 mg Ag/m^3 for 80% of workers), the mean Ag whole blood concentration in 37 workers engaged in the smelting and refining of silver was 11 μg/L.[88] Two silver reclamation workers had blood Ag concentrations of 49 and 74 μg/L (sample type not reported).[89] Both workers were asymptomatic with the only physical signs being silver deposits in the skin and eyes of the latter worker. The former worker was exposed to insoluble silver compounds (halides, oxide) for 2 years, whereas the latter worker was exposed to soluble silver nitrate for 7 years.

URINE

Urine has limited utility for biological monitoring of silver because of inadequate data and minimal Ag excretion (i.e., <10%) by the kidneys. Following occupational exposure primarily to insoluble metallic silver dust (TWA = 0.001–0.1 mg Ag/m^3 for 80% of workers), the mean urine Ag concentration in spot samples from

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37 workers engaged in silver smelting and refining was below the limit of detection (0.005 μg/L) as measured by atomic absorption spectroscopy.[88]

Medical Surveillance

Medical monitoring for silver compounds should focus on the detection of argyria as well as kidney and liver dysfunction.

TREATMENT

Soluble Silver Compounds

Clinical experience with soluble silver compounds is limited. Silver oxide and silver nitrate are potential mucosal irritants. Dilution is probably an appropriate first aid measure. Symptomatic patients may require endoscopy to determine the extent of mucosal damage.

Argyria

The primary treatment for argyria is the discontinuation of Ag exposure and supportive care.[1] The dermatological changes are permanent; no specific treatment (e.g., potassium ferrocyanate, thiosulfate sodium, hydroquinone, dermabrasion, depigmenting creams) reverses the abnormal skin coloration.[65] Experimental treatment of the hyperpigmentation of argyria includes the use of the Q-switched double-frequency Nd:YAG laser.[90] Chelation with 2,3-dimercaptopropanol (BAL), D-penicillamine, or 2,3-dimercaptopropane-1-sulphonate (DMPS) removes only a small fraction of the total body burden of silver. Two 5-day courses of DMPS (0.5–2.5 g/day) removed <1% of the total amount of silver in the body of a patient with argyria.[91] Sunscreens and opaque cosmetics may conceal the skin's discoloration and prevent further darkening of the skin.

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Chapter 29

TELLURIUM

PHYSIOCHEMICAL PROPERTIES

Tellurium (CAS RN: 13494-80-9; atomic mass: 127.6 g/mol) is a chalcogen metalloid that exists as a lustrous, silvery-white, crystalline solid (specific gravity, 6.25 at 20 °C) or dark gray-brown amorphous powder. As a metalloid, tellurium is an effective, one-way semiconductor that displays improved conductive properties following exposure to light. Both tellurium hexafluoride and hydrogen telluride (H_2Te) are colorless gases with offensive, garlic-like odors. Dimethyltellurium is the most common, volatile product of Te biomethylation in the environment.[1] Of the 21 known isotopes of tellurium ranging in mass numbers from 115–135, 8 occur naturally with the only unstable natural isotope being ^{127}Te.[2] Elemental tellurium is insoluble in water, whereas tellurium dioxide is sparingly soluble. Combustion of elemental tellurium (melting point 450 °C) produces a blue flame; elemental tellurium does not easily form oxides, even in the presence of heat. Most tellurite and tellurate compounds are water-soluble. Tellurium belongs to Group 16 (Group VIa, oxygen, polonium, selenium, sulfur) of the periodic table, sharing similar chemical properties with selenium and sulfur.

Tellurium exists in multiple redox states. Of the members of Group 16, tellurium is the most electropositive with valence states including −2, 0, +2, +4, and +6.[3] The tetravalent (Te^{4+}) and tellurite compounds (TeO_3^{2-}) are the most chemically stable Te compounds. The oxidation state of organotellurium compounds is usually 2+; however, the presence of a Te–Te bond results in a monovalent state. Divalent organotellurium compounds readily oxidize to the tetravalent state.[4] Dimethyltelluride is associated with the characteristic garlic-like odor following ingestion or inhalation of tellurium compounds.[5]

EXPOSURE

Production Processes

Tellurium occurs in its elemental state in nature, usually combined with other metals in the form of tellurides. Occupational exposure to Te occurs most commonly as a by-product of copper refining and, less commonly, as a by-product of silver, gold, and lead refining. Electrolytic copper refining is the major commercial source of elemental tellurium. The most common tellurium-containing ore is sylvanite [$(AgAu)Te_2$]. The anodic slime contains ~4% tellurium; recovery of Te results from the dissolution of the mud in caustic soda and the electrolysis of the solution with stainless-steel electrodes.[2] Tellurium hexafluoride is a by-product of refining the ore.

Uses

Metallurgy accounts for a majority of the production of tellurium; tellurium improves the characteristics of

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a variety of alloys (bronze, copper, iron, lead, steel). During electrolytic lead refining, tellurium is emitted as an impurity, primarily as tellurium oxide.[6] Currently, the most rapidly expanding application of tellurium compounds involves the semiconductor industry; nanomaterials (e.g., quantum dots) contain Te alloys of cadmium, zinc, and other metals.[7] The latter includes experimental probes for biomedical applications (cell tracking, drug delivery, gene delivery, cancer detection, tumor therapy, *in vivo* tissue imaging).[8] Additional commercial applications that may contain Te include dopants, catalysts, rubber vulcanizers, antioxidants, explosives (blasting caps), and glazes.

Sources

Food is the main source of tellurium in the general population, particularly meats and dairy products that typically average ~4 mg Te/kg. The estimated daily Te intake from the diet is ~100–150 μg.[9,10] Ambient Te concentrations in air are low; anthropogenic sources include coal combustion and industrial plants (e.g., electrolytic copper-refining). Tellurium concentrations in surface water and drinking water are usually low (<1 ng/L),[11] whereas soil Te concentrations typically average ~10 ppb. Tellurium concentrations in ambient water are an order of magnitude lower than selenium as a result of usually low Te concentrations and a relatively higher affinity for sediment; dimethyltelluride occurs in water samples in the range of 0.01–0.1 μg/L as measured by purge-and-trap GC/ICP/MS.[12] Anthropogenic sources of organic tellurium compounds in the environment are not well documented, whereas the semiconductor industry, PVC/rubber production, municipal waste, and the use of inorganic Te during chemical synthesis are potential anthropogenic sources of inorganic Te.

ENVIRONMENTAL FATE

Organic tellurium compounds exist in the environment primarily as simple methylated tellurides (e.g., dimethyltelluride, dimethylditelluride, dimethyltellurenyl sulfide, diethyltelluride, trimethyltelluronium). Several bacteria and fungi species (*Pseudomonas* spp., *Rhodospirillum* spp., *Penicillium* spp., *Scopulariopsis* spp.) can produce organotellurium compounds (e.g., dimethyltelluride, dimethylditelluride).[12] The conversion of Te compounds to dimethyltelluride (DMTe) by mammals and the excretion of this compound in exhaled air, sweat, and urine result in detectable pungent odors.

DOSE EFFECT

The accidental instillation of 2 g sodium tellurite into the bladder of two patients with renal colic produced emesis, cyanosis (possible methemoglobinemia), hemolysis, dyspnea, coma, and death;[13] determination of the cause of death is unclear because of the lack of laboratory, clinical, and monitoring data in the 1946 case report. There are no reports of serious illness following inhalation of tellurium or tellurium compounds in industry.[14] In animal studies, inorganic and organic tellurium compounds demonstrate greater toxicity than elemental tellurium. During chronic rodent studies published in the 1930s and 1940s, administration of diets containing 25–50 ppm inorganic Te as Na_2TeO_4 for 100 days was associated with some growth retardation and hair loss;[15] slight growth retardation occurred following administration of diets containing up to 1,500 ppm elemental Te for up to 21 days.[16] The significance of these reports remains unclear because of the potential reduction in food consumption from malodorous Te-containing feed, small sample sizes, and the lack of statistical comparisons. Animal studies indicate that inhalation of TeF_6 at concentrations of 1 ppm Te for 4 hours produces pulmonary edema.[17] In rats feed tellurium compounds, oral tellurite administration is approximately twice as toxic as tellurate.[15]

TOXICOKINETICS

Absorption

Experimental data on the absorption of tellurium and tellurium compounds is limited. In a study of healthy adults, the fractional absorption of powdered elemental Te in three fasting volunteers was 10% ± 4% compared with 23% ± 9% following the ingestion of sodium tellurate (Na_2TeO_4) by four volunteers.[18] The fractional absorption of sodium telluride by a single volunteer was 21.5% as measured by atomic absorption spectrometry. No subject developed adverse effects during the study. Animal studies suggest the gastrointestinal tract absorbs ~10–20% of an oral dose of tellurites.[2] Absorption of tellurium compounds through tellurium-induced skin burns or rashes is sufficient to produce a garlic odor in the breath as a result of the formation of volatile dimethyltelluride from tellurium methylation. Organic tellurium esters may penetrate intact skin producing blue-black discoloration of the skin between the fingers.[19]

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Distribution

Tellurium distributes initially from the blood to the liver, kidney, lungs, thyroid, and spleen; ~90% of the total body burden of tellurium (i.e., ~500–600 mg) exists in the bone.[9] In rodent studies, tellurium binds primarily to hemoglobin and the remainder to plasma proteins.[20]

Elimination/Metabolism

The kidney excretes most of the absorbed tellurium dose; other excretion routes include the bile and exhalation of dimethyltelluride; the latter is associated with the characteristic garlic-like, malodorous breath. In rats, the biological half-life is biexponential with a range of 9–23 days for most organs and ~2 years for bone.[21] Although inorganic tellurium (i.e., tellurite, tellurate) probably follows similar metabolic pathways as selenite and selenate in animals, few data exist on the exact metabolic pathways. These complex pathways probably produce organotellurium compounds.[22]

Maternal–Fetal Kinetics

Animal studies with radioactive tellurous acid suggest tellurium crosses the placenta.[23] In lactating rats receiving intravenous tellurium, breast milk transfers small amounts of ^{123m}Te from the mother to the suckling rat.[24]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Tellurium is a nonessential metalloid that crosses the cell membrane of Schwann cells producing segmental demyelination and peripheral neuropathy in rats characterized by weakness and/or paralysis of the hind limbs.[25,26,27] Animal studies suggest organotellurium species (e.g., dimethyltelluronium compounds) produce demyelination by the inhibition of squalene epoxidase.[28] To date, neurological changes in workers exposed to tellurium have not been described. Tellurite compounds induce alterations of the red cell membrane leading to swelling, hemolysis, and shedding of cell fragments. These membrane perturbations involve the formation of a tellurium species, possibly HTe^-, that penetrates the cell membranes.[29] Autopsies of two patients receiving intravesical injections of sodium tellurite demonstrated black tellurium deposited in the mucosa of the urinary tract along, fatty changes of the liver, and congestion of the liver, lungs, and kidneys.[13] All tissue demonstrated the strong odor of garlic.

CLINICAL RESPONSE

Acute Toxicity

Tellurium and most tellurium compounds have relatively low toxicity; however, tellurite compounds are more toxic than elemental tellurium. The accidental instillation of sodium tellurite into the bladder of two patients with renal colic was associated with vomiting, stupor, dyspnea, cyanosis (methemoglobinemia), coma, and death within 6 hours.[13] The exact cause of death is unclear because of the lack of laboratory and clinical details in the 1946 case report. A 37-year-old woman developed weight loss, fatigue, and a strong garlic odor on the breath after eating Te-contaminated meat (800–1,000 μg/kg).[30] The onset of fever occurred 2 days after ingestion with nausea and vomiting developing 3 days later. Endoscopy revealed petechial gastric bleeding in the fundus with minimal focal irritation. Hair loss developed 2 weeks after consumption of the contaminated meat. Experimental studies suggest the strong garlic odor may persist for months after exposure based on the detection of garlic odor for 237 days after the ingestion of 15 mg sodium tellurite during experimental studies from the 19th century.[31]

Two children developed vomiting, black discoloration of the oral mucosa, and a garlic odor to the breath following the ingestion of an acidic metal-oxidizing solution containing tellurium; one of the children also had corrosive injuries to the esophagus.[32] They recovered without sequelae.

Occupational Exposure

Most Te exposures occur in the workplace. Tellurium hexafluoride is a colorless, irritating gas. A 30-minute exposure during a leak of TeH_6 was associated with garlic odor in the breath and sweat, metallic taste in the mouth, anorexia, lethargy, and a bluish-black discoloration underneath the skin of the face, neck, and fingers.[19] Pulmonary symptoms did not develop; the patients recovered without sequelae. To date, serious toxicity has not been associated with exposure to tellurium and tellurium compounds in the occupational setting.[14] The most common complaint of workers exposed to tellurium is a garlic-like odor on the breath and sweat.[33] Other symptoms associated with occupational Te exposure include dry mouth, metallic sensation

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in the mouth, decreased appetite, transient nausea, dry mouth, and lethargy.[30]

Reproductive Abnormalities

Epidemiological data on human reproductive abnormalities following human exposure to tellurium are limited; however, current evidence does not indicate tellurium is a human teratogen. The administration of high Te doses (500–3,000 ppm) in the diet of rats during the day 9–15 of gestation produced an increased incidence of hydrocephalus in the offspring;[34,35] however, maternal toxicity occurred at dietary Te concentrations of ≥300 ppm and no unique teratogenic abnormalities developed.[36] There are no studies demonstrating tellurium is teratogenic at doses commonly present in the workplace.

Carcinogenesis

Neither the IARC nor the US Toxicology Program lists tellurium or tellurium compounds as suspected carcinogens. Exposure of rats to sodium tellurite and sodium tellurate in drinking water (2 mg Te/L) for a lifetime (2 years) did not produce an excess incidence of tumors, despite some decrease in the longevity of female mice fed sodium tellurite.[37]

DIAGNOSTIC TESTING

SI Conversion Units

1 μg/L = 0.007837 μmol/L
1 μmol/L = 127.6 μg/L

Analytical Methods

Sensitive techniques for the determination of Te in biological and environmental samples include inductively coupled plasma/mass spectrometry (LOD, 0.01 μg/L),[38] graphite furnace/atomic absorption spectrometry (LOD, 0.3 μg/L),[39] and hydride generation/atomic absorption spectrometry (LOD, 0.03 μg/L).[40,41] Analysis of urine samples with hydride generation/atomic absorption spectrometry with derivative signal processing produces Te detection limits in the range of 1 μg/L.[42] The use of ion chromatography/inductively coupled plasma/mass spectrometry allows the speciation of inorganic Te compounds (e.g., tellurite (4+), tellurate (6+)) at detection limits of 0.01–0.08 μg/L.[43] For the identification and speciation of unknown tellurium metabolites, dual hyphenated techniques (liquid chromatography/inductively coupled plasm/mass spectrometry, liquid chromatography/electrospray ionization/tandem mass spectrometry) are recommended because sample matrix may seriously affect electrospray ionization.[22]

Biomarkers

Blood

Whole blood Te concentrations in the general population without occupational Te exposure are <1–5 μg/L.[44] The median whole blood Te concentration in a study of 99 healthy children was 0.12 μg/L (95% CI: 0.07–0.22 μg/L) compared with 0.06 μg/L (95% CI: <0.4–0.11 μg/L) in plasma samples as measured by inductively coupled plasma/mass spectrometry.[45] In a symptomatic child ingesting an acidic metal-oxidizing solution, the whole blood Te concentration was 200 μg/L.[32] A 37-year-old woman developed weight loss, fatigue, metallic taste in her mouth, a strong garlic odor, and gastrointestinal distress soon after eating Te-contaminated meat; her serum Te concentration 4 weeks after ingestion was 27.6 μg/L.[30]

Urine

The urine Te concentrations in 20 Italian subjects without occupational Te exposure were <1 μg/L.[46] In a convenience sample of 14 nonsmoking workers without occupational exposure to Te, the mean urine Te in 24-hour urine samples was 0.11 ± 0.05 (range, 0.07–0.18 μg/L).[38] Spot urine samples from two children (i.e., vomiting, garlic odor) symptomatic after ingesting a metal-oxidizing solution that contained Te concentrations of 56 μg/L and 260 μg/L.[32]

HEALTH SURVEILLANCE

Environmental Monitoring

The US OSHA PEL–TWA for tellurium and its compounds (excluding tellurium hexafluoride and bismuth telluride) is 0.1 mg Te/m^3 as a dust or fume. The recommended TLV–TWA of the American Conference of Governmental and Industrial Hygienists (ACGIH) is consistent with US OSHA standards. The ACGIH recommendation for Te and most Te compounds is formulated to reduce the likelihood of foul breath and the potential risk of central nervous effects, liver dysfunction, and cyanosis based on animal studies, whereas the TLV–TWA for TeF_6 is designed to reduce the

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TABLE 29.1. Regulations and guidelines for exposure to tellurium and tellurium compounds.

Exposure Limit	Recommended Level
OSHA	
PEL–TWA (8-hour)	
Tellurium and tellurium compounds[a]	0.1 mg/m^3 (as Te)
Tellurium hexafluoride	0.02 ppm
NIOSH	
REL–TWA (10-hour)	
Tellurium and most tellurium compounds[a]	0.1 mg/m^3 (as Te)
Tellurium hexafluoride	0.02 ppm (as Te)
REL–IDLH	
Tellurium and most tellurium compounds	25 mg/m^3 (as Te)
Tellurium hexafluoride	1 ppm (as Te)
ACGIH	
TLV–TWA (8-hour)	
Tellurium and most tellurium compounds[a]	0.1 mg/m^3 (as Te)
Tellurium hexafluoride	0.02 ppm
BEI	None
US EPA	
RfD	None
US federal drinking water guidelines	None
ATSDR	
MRL	None

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; BEI = biological exposure indices; IDLH = immediately dangerous to life and health; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = reference dose; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency.

[a] Except tellurium hexafluoride and bismuth telluride.

risk of pulmonary irritation noted in animal studies.[14] The exact tellurium ambient air concentration at which a garlic-like odor appears in workers varies substantially as a result of individual variation and the extent of skin contamination; some workers may develop garlic-like odor in their breath at this value.[33] Table 29.1 lists the regulations and recommendations regarding exposure to tellurium and tellurium compounds.

Biological Monitoring

There are inadequate data to determine specific blood or urine Te concentrations that limit the risk of adverse long-term health effects. Case reports suggest urine Te concentrations >25 µg/L or whole blood/serum Te concentrations of >50 µg/L are levels of concern.[47] Hydrogen telluride is excluded from this TLV–TWA because of its greater toxicity compared with other tellurium compounds. The likelihood of developing garlic odor substantially decreases when the urinary tellurium concentration is <1 µmol/mol creatinine.[48] The limited data available correlating urinary Te concentrations with the development of a garlic odor suggest these odors do not develop at urine levels of <1 µg/L.[33,49] Medical surveillance of workers should include a physical examination for conditions (e.g., caries, bronchiectasis, gingivitis, exposure to selenium) that also produce an objectionable breath.

TREATMENT

Treatment is supportive. There are no known antidotes or effective chelating agents for the treatment of tellurium poisoning.

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Chapter 30

THALLIUM

HISTORY

Sir William Crookes discovered thallium in 1861 while he was preparing selenium from flue dust obtained from a sulfuric acid factory. Shortly thereafter, he recognized the toxicity of thallium when he and his assistant developed signs of thallium toxicity following animal experimentation with thallium.[1] The name thallium derives from the Greek word, *thallos*; in Greek mythology, this word refers to the goddess of spring and the protector of new growth. By the end of the 19th century, thallium sulfate was a medicinal agent for the treatment of venereal disease, gout, dysentery, night sweats, and the diaphoresis associated with tuberculosis.[2] However, the prominence of gastrointestinal and neurological reactions resulted in the cessation of the medicinal use of thallium by 1912.[3] Raymond Sabouraud reported the association between thallium ingestion and cranial hair loss in 1897; subsequent clinical studies resulted in the use of thallium compounds (e.g., thallous acetate) to produce cranial alopecia as a preliminary step in the treatment of *Tinea capitis* and *Trichophyton rubrum* scalp infections.[4] Numerous cases of thallium poisoning in humans occurred following the introduction of thallium as a rodenticide and an insecticide in the 1920s.[5] In Germany, thallium acetate and thallium sulfate were reintroduced in the 1920s as a treatment for ringworm of the scalp; the latter compound was also a rodenticide. In spite of the dermatological use of thallium in reduced doses compared with earlier treatments for venereal disease, thallium poisoning continued to occur.[6] In 1930, 14 of 16 infants administered excessive thallium for the treatment of ringworm died of thallium poisoning.[7] Several case reports in the early 1930s document alopecia and lower extremities neuropathy (i.e., pain, paraesthesias) from thallium poisoning following the use of a thallium-containing depilatory (Koremlu).[8,9] Examination of a Koremlu sample by the Bureau of Investigation of the American Medical Association demonstrated that this commercial product contained 7% thallium acetate. An outbreak of thallium poisoning occurred in California during 1932 when a grain mixture containing thallium sulfate was inadvertently used to make tortillas.[10] Thirteen people died. The bait was a rodenticide used to control the ground squirrel population. By 1940, medicinal thallium use was abandoned in the United States;[11,12] however, the use of organic thallium to separate industrial diamonds from abrasives was associated with thallium toxicity in the workers during the 1950s.[13] The use of thallium as a depilatory paste continued until the 1950s in some countries.

In 1964, Hausman reported 52 cases of thallium poisoning that resulted from accidental and suicidal intentions as well as homicidal intent.[14] By 1965, federal US legislation had ended the use of thallium as a rodenticide. However, the use of thallium as a rodenticide continued in countries outside the United States, despite a World Health Organization recommendation against the use of thallium-containing rodenticides in 1973.[15] Industrial use of thallium continues along with sporadic cases of thallium poisoning. Most recent commercial uses of thallium include the manufacture of imitation jewelry, pigments, low-temperature thermometers, semiconductors, scintillation counters, and optical lenses. Thallium is a cumulative poison and

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known homicidal agent used by murderers,[16] including the English serial killer, Graham Young.[17]

PHYSIOCHEMICAL PROPERTIES

Thallium is a member of Group 13 (Group IIIA including aluminum, boron, gallium, indium) of the periodic table located between lead and mercury. Metallic thallium is a soft, malleable metal with a shiny appearance and physical properties similar to lead. Upon exposure to air, this blue-white, heavy metal forms a superficial layer of brownish-black thallous oxide (Tl_2O). Elemental thallium is highly reactive, readily forming monovalent thallous (Tl^+) and trivalent thallic (Tl^{+3}) salts; elemental Tl easily oxidizes in air to form superficial layers of insoluble thallium oxide (TlO_2). The electrical charge and ionic radius of Tl^+ are similar to those of potassium (K^+). Most of these salts are colorless, odorless, and tasteless. The monovalent compounds behave like alkali metals (e.g., potassium), whereas trivalent compounds resemble less basic metals (e.g., aluminum). The trivalent (thallic) ion in inorganic thallium compounds is less stable than the monovalent thallium ion, whereas the latter ion is less stable in organic compounds. Thallium salts do not hydrolyze at pH ≥7 to form insoluble hydroxides, resulting in enhanced toxicity compared with other metal salts that form insoluble salts at physiological pH. There are 26 artificial thallium radioisotopes with masses ranging from 191–210 and physical half-lives ranging from 2.1 msec (^{201m}Tl) to 3.8 years (^{204}Ti). The natural radioisotopes are ^{205}Tl (70.48%) and ^{203}Tl (29.52%).

Table 30.1 lists the identifying information and physical properties of metallic thallium and the common thallium compounds. Most thallium salts are water-soluble, but these salts readily hydrolyze in alkaline environments (pH >7) to form insoluble hydroxides.[18] The water-soluble thallium salts include thallium acetate ($TlC_2H_3O_2$), thallium carbonate (Tl_2CO_3), thallium nitrate ($TlNO_3$), thallium oxide (Tl_2O), and thallium sulfate (Tl_2SO_4), whereas insoluble compounds include elemental thallium as well as thallous iodide (TlI), thallium sulfide (Tl_2S), and thallic oxide (Tl_2O_3). Although thallous compounds are generally much more water-soluble than thallic compounds, animal studies indicate both thallic and thallous compounds are potent toxins.[19]

Chemical properties favoring thallium use as a homicidal agent include the insidious onset of nonspecific symptoms, the lack of taste, color, and smell, and the absence of routine testing for the presence of thallium. Urine heavy metal screens do not typically detect the presence of thallium.

EXPOSURE

Production Processes

The principal mineral ores containing thallium are crookesite [Cu_7(Tl, Ag)Se_4] and lorandite ($TlAsS_2$), but the commercial production of thallium usually occurs as a by-product of cadmium production or through the recovery of thallium from the flue dust from the smelting of other metals (copper, lead, zinc). Thallium is present in the pyrites used to produce sulfuric acid; sufficient amounts of thallium are present in the waste of sulfuric acid production to recover thallium commercially. Recovery of thallium occurs primarily by electrolysis and, to a lesser extent, by precipitation or reduction. Thallium is usually present in the form of thallous sulfate.

Uses

Currently, the semiconductor industry uses most of the production of thallium (i.e., primarily as thallous salts) with the remainder used in the pharmaceutical industry for cardiac imaging and the manufacture of highly refractory optical glass.[20] Commercial uses for specific thallium compounds include the following: acetate (separation of ores by flotation using solutions with high specific gravity); carbonate (fungicide, artificial diamond production); chloride (catalyst for chlorination); chromate (pigments); nitrate (manufacture of signals at sea, photocells, fireworks, and low melting glass); oxide (production of artificial gems and highly refractive glass); selenite (semiconductors); sesquioxide (ceramics, yellow-green glass, optical fibers, semiconductors); and sulfate (chemical intermediate pharmaceutical industry, semiconductors, low range thermometers, photoelectric cells, textile fiber production, rodenticide). Uses for thallium in chemical production include oxidation of hydrocarbons and olefins, epoxidation, and polymerization. Although most industrial countries no longer permit the use of thallium as a rodenticide, its use still occurs in developing countries as an inexpensive way to control rodents. Thallium toxicity occurred following the mistaken use of thallium chloride as homeopathic medicine.[21]

Sources

Thallium is a stable, nonvolatile, heavy metal that exists in the environment mostly combined with other elements (e.g., halogens, oxygen, sulfur). Although thallium is ubiquitous in nature (e.g., sulfide ores of heavy

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TABLE 30.1. Identifying information and physical properties of metallic thallium and thallium salts.

Physical Characteristic	Tl	$TlC_2H_3O_2$	Tl_2CO_3	TlCl	$TlNO_3$
Synonym	Metallic thallium	Thallium acetate, thallous acetate	Thallium carbonate	Thallium chloride, thallous chloride	Thallium nitrate
CAS RN	7440-28-0	563-68-8	6533-73-9	7791-12-0	10102-45-1
Valence	0	+1	+1	+1	+1
Molecular weight g/mol (%Tl)	204.38 (100)	263.43 (77.59)	468.78 (87.20)	239.85 (85.22)	266.39 (76.72)
Color	Bluish-gray	White	Colorless to white	White	Colorless
Physical state	Solid hexagonal crystalline	Deliquescent crystals	Crystalline solid	Crystalline powder[a]	Crystalline solid
Melting point (°C)	303.5	131	272	430	206
Density (g/mL)	11.85 (20°C)	3.76 (137°C)	7.11 (20°C)	7.00	5.55 (20°C)
Water solubility (g/L)	Insoluble	Very soluble	Very soluble (40.3,15°C)	Very soluble (2.9,16°C)	Very soluble (95.5,20°C)
Odor	Odorless	Odorless	Odorless	Odorless	Odorless

Physical Characteristic	Tl_2SeO_3	Tl_2SO_4	Tl_2O_3	$TlCl_3$
Synonym	Thallium selenite	Thallium sulfate, dithallium sulfate	Thallic oxide, thallium sesquioxide	Thallium trichloride
CAS RN	12039-52-0	7446-18-6	1314-32-5	13453-32-2
Valence	+1	+1	+3	+3
Molecular weight g/mol (%Tl)	535.72 (76.30)	504.83 (80.97)	456.78 (89.49)	310.74 (65.78)
Color	Gray	Colorless	Black	Yellow
Physical state	Metallic lamina[b]	Crystalline solid	Powder	Crystalline powder
Melting point (°C)	340	632	717	25
Density (g/mL)	No data	6.77 (20°C)	10.18	ID
Water solubility (g/L)	Slightly soluble	Very soluble (48.7 at 20°C)	Insoluble	Soluble
Odor	Odorless	Odorless	Odorless	Odorless

Abbreviation: CAS RN = Chemical Abstracts Service Registry Number; ID = insufficient data.
[a] Turns purple after exposure to sunlight; [b] Decomposes in smoke.

metals, Jurassic coal, iron/lead/zinc ores), the thallium concentration in nature is usually low (<2 mg Tl/kg).[22] Relatively high concentrations of thallium occur in granite, shale, and manganese nodules.[23] As a trace contaminant of materials, thallium enters the environment primarily from the emissions from coal-burning and ferrous/nonferrous smelting. Exposure of the general population occurs mostly through the ingestion of thallium-containing food.

Air

Emissions from cement factories, coal-burning power plants, and smelting operations are the primary source for thallium release into the air.[24] Thallium volatilizes during the combustion of coal or raw materials for cement production; then, Tl condenses as ash particles. About one-third of these particles are small enough to reach the lower respiratory tract.[25] Data on Tl concentration in ambient air are limited with thallium concentrations in unpolluted air typically <1 ng/m^3. In six US cities, the typical Tl concentration in ambient air was ~0.4 ng/m^3,[26] whereas the geometric mean thallium concentration in air around Genoa, Italy, was ~15 ng/m^3.[27] Thallium concentrations near a point source (coal-burning plant) averaged ~700 ng/m^3.[26]

Soil

Thallium typically exists as a trace mineral (<1 mg/kg) in the soil, primarily in rock formations (granite, shale) and potassium feldspar- and mica-containing soil.[28] In a study of 244 French arable soil samples, the median thallium concentration was 0.29 mg/kg with a 90th percentile concentration of 1.54 mg/kg and a range up to 55 mg/kg.[29] The highest thallium concentrations in these soil samples were not associated with anthropogenic sources, whereas silty or clay-silty soils

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derived from limestone, marl, or granite contained relatively high thallium concentrations. In a study of soils from the industrialized Euroregion Neisse (German–Poland–Czech Republic border area), the median Tl concentration in soil was 0.5 mg/kg.[30] High thallium-containing minerals usually contain sulfur (hutchinsonite, lorandite, vrbaite) or selenium (e.g., crookesite); these minerals are rare in the earth's crust. Thallium concentrations in the soil near point sources are higher including stream sediment near a metal industry (5 mg/kg)[31] and a Michigan lake (mean = ~13 mg/kg) contaminated by air pollution.[26] Natural weathering processes and/or mining activities of thallium-rich sulfide minerals substantially increase the Tl concentration in the soil. Soil from thallium-rich pyrite processing areas near industrial sources in South China contained Tl concentrations up to 5–15 mg/kg.[32] The water-soluble fraction of thallium in these soils is small (i.e., 0.1%).[33]

Water

Typically, the thallium concentration in water samples is low. In a study of seawater samples from the Northern Atlantic Ocean, the thallium concentration ranged from 0.01–0.017 μg/L as measured by neutron activation analysis.[34] Thallium was relatively evenly distributed in seawater samples collected from the Atlantic and Pacific Oceans at depths up to 3,500 m; the range was 0.0012–0.0016 μg/L ($n = 24$).[35] In a study of 476 groundwater samples obtained from boreholes in Norwegian crystalline bedrock, the thallium concentration ranged from 0.001–0.25 μg/L as measured by inductively coupled plasma/mass spectrometry. Similar total thallium concentrations (i.e., 0.001–0.036 μg/L) occurred in water samples from the US Great Lakes.[36] The median Tl concentration in water samples from Lake Superior ($n = 26$) was 0.0012 μg/L (range, 0.0009–0.0014 μg/L) compared with 0.0094 (range, 0.0059–0.0117 μg/L) in Lake Erie ($n = 18$) and 0.0057 μg/L (range, 0.0045–0.008 μg/L) in Lake Ontario ($n = 47$). The Tl concentration did change significantly with water depth; however, the Tl concentration was substantially higher in the harbor draining St. Claire River (range, 0.023–0.036 μg/L; $n = 8$). The mean Tl concentration in 178 dissolved river water samples from a summary of 4 Japanese studies was 0.007 ± 0.152 μg/L compared with 0.025 ± 0.104 μg/L in 178 particulate samples from the same area, as measured by ICP/MS.[37] For 25 dissolved and particulate lake water samples, the mean Tl concentrations were 0.011 ± 0.020 μg/L and 0.036 ± 0.105 μg/L, respectively. The mean Tl concentrations in 31 dissolved and 24 particulate water samples from coastal seawater were 0.008 ± 0.006 μg/L and 0.003 ± 0.003 μg/L, respectively.

Substantially higher thallium concentrations exist in water samples from areas near natural and anthropogenic sources of thallium.[33] Water samples from a river surrounding a base metal sulfide mine in northeastern Canada contained thallium concentrations ranging from 2.5–80.3 μg/L.[38] A survey of tap water from over 3,000 US homes revealed an average concentration of 0.89 μg Tl/L in the 0.68% of the samples that were positive for thallium.[26] Substantially higher thallium concentrations (e.g., 17–40 μg/L) may occur in water samples from domestic wells near water sources contaminated by thallium.[39] The major sources of thallium include runoff from the following industries: mining, refining and ore processing, iron and steel manufacturing, and nonferrous metal production.

Diet

The most frequent exposure of the general population to thallium occurs following ingestion of thallium-containing food. In contaminated areas, most terrestrial food contains <1 mg Tl/kg fresh weight with typical thallium concentrations in edible plants ranging from 0.03–0.3 mg/kg.[22] Plants grown in high-thallium soils can accumulate thallium above typical Tl concentrations. Cereal grains and green cabbage grown in soil contaminated by thallium emissions from a German cement plant contained average thallium concentrations of 9.5 mg/kg and 45 mg/kg, respectively.[40] The concentration of thallium in farm animals correlates with Tl concentrations in fodder. Bioconcentration of thallium occurs in water-dwelling organisms. Experimental studies revealed thallium bioconcentration factor in muscle from juvenile Atlantic salmon ranging from 27–1,430;[38] however, biomagnification of thallium either in aquatic or terrestrial food chains is unlikely.

The average daily Tl intake from the diet of the general population is <5 μg Tl, whereas the US EPA daily reference doses are as follows: insoluble thallium, 0.07 μg/kg; thallium sulfate, 0.08 μg/kg; and thallium acetate, 0.07 μg/kg.[41] Green vegetables are usually the major source of thallium in the diet, whereas thallium concentrations in red meat range from 50–70 μg/kg.[42] Typical thallium concentrations in milk range from 10–30 μg/kg with an estimated mean total dietary Tl exposure of 0.024–0.27 mg/kg in toddlers aged 1.5–4 years; the estimated adult daily Tl dose was smaller (0.011–0.012 mg/kg).[43] Smoking may contribute to Tl intake with estimated consumption of 1.1–2.4 ng/cigarette.[44] Typically, the urinary Tl excretion is higher in smokers than nonsmokers.[26]

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ENVIRONMENTAL FATE

Air

Because thallium is nonvolatile, anthropogenic sources (cement plants, coal-fired power-generating plants) release fly ash containing thallium into the air.[22] Thallium chloride is a major form of thallium in the ash from cement plants. Oxidation of thallium in the air occurs slowly. Although thallous chloride is photosensitive, photochemical reactions do not account for a significant part of Tl elimination from the atmosphere.

Soil

Elevated Tl concentrations occur primarily on the upper surfaces as a result of wet and dry deposition of thallium-contaminated fly ash. The fate of thallium in soil depends on pH (i.e., increasing water solubility in acidic conditions) and the soil type with increased retention in soils that contain large amounts of iron or magnesium oxides, organic matter, or clay. The uptake of thallium in plants increases as the soil pH decreases.

Water

In some markedly acidic soil, thallium will leach into groundwater or surface water. Most thallium in seawater and well-oxidized freshwater exists in the trivalent form, whereas the thallous ion is the predominant species in other freshwater. Hydrolysis of thallium in freshwater precipitates thallium as a hydroxide or an oxide that settles in organic-rich sediment. There is no direct evidence that thallium is transformed in the environment into other compounds.

DOSE EFFECT

Signs of acute thallium intoxication may appear at doses as low as 4 mg Tl/kg.[45] The typical adult and prepubescent children's Tl dose (i.e., depilatory dose) as thallium acetate used as a preliminary step in the treatment of fungal infections of the scalp was 8 mg Tl/kg (range, 4–10 mg Tl/kg body weight) with toxicity reported in ~5% of the patients.[4,46] Severe poisoning occurs with doses of >0.8–1 g thallium salts in adults and >8 mg thallium salts/kg in children. The average lethal adult dose is 1–2 g (10–15 mg/kg) soluble thallium salt. In a case series of three workers poisoned by surreptitious addition of thallium acetate to their beverages, the perpetrator kept careful records of the thallium doses.[47] The administration of 0.93 g thallium in two or three divided doses caused death, whereas the third victim survived the administration of 0.31 g after developing vomiting, diarrhea, weakness, paresthesias, and hair loss. The acute, surreptitious ingestion of an estimated 1.5 g thallium in drinking water by a husband and wife was associated with the acute onset of mild nausea and vomiting followed by the development of a painful neuropathy. Later, lower extremity muscle weakness, eczematous rash, alopecia, Mees lines, and diarrhea occurred.[48] Administration of Prussian blue began 3 weeks after exposure. At 1-year follow-up, hyporeflexia, lower extremity weakness, and hypoesthesias persisted. Survival occurred after the ingestion of 1.3 g thallium sulfate, whereas the intentional ingestion by adults of 3.2 g thallium sulfate[49] and of 4–8 g Tl as thallium nitrate[50] resulted in death. The ingestion of 10 g thallous malonate (8 g Tl) produced terminal cardiac failure in a 26-year-old man presenting 6 hours after ingestion, despite the use of hemodialysis and hemoperfusion.[51] In animals, the toxicity of water-insoluble thallium(III) oxide by oral and parenteral routes is somewhat lower than that of water-soluble thallous(I) compounds.[22]

TOXICOKINETICS

Absorption

Most thallium compounds are water-soluble; the gastrointestinal tract absorbs these thallium compounds rapidly.[52] Limited animal and human data suggest that Tl absorption following ingestion is almost complete.[53] Dermal absorption occurs after the application of ointments, but no data are available to accurately quantify the extent of dermal absorption of thallium salts. Percutaneous absorption of organic thallium was the suspected cause of gastrointestinal symptoms, malaise, myalgias, and alopecia in workers with reportedly no significant airborne Tl exposure.[13] The absorption of thallium following nasal insufflation of thallium sulfate-containing illicit drugs was sufficient to produce thallium toxicity (hypertension, alopecia, paresthesias).[54] Although there are little quantitative data on Tl absorption following inhalation, absorption probably would be sufficient to cause toxicity depending on the severity of exposure based on case reports of thallium toxicity in workers exposed to water-soluble thallium salts (e.g., carbonate, sulfate).[55]

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Distribution

The volume of distribution of thallium is relatively large. In a study of nine patients undergoing myocardial scintigraphy with tracer amounts of ^{201}TlCl, the mean steady-state volume of distribution was 4.23 ± 0.67 L/kg.[56] Following an overdose, the distribution of thallium was similar at ~1–5 L/kg; Tl distribution occurs primarily intracellularly, where thallium mimics the movement of potassium.[52] Analysis of blood thallium concentrations following fatal ingestion of thallous malonate revealed a red blood cell/plasma ratio of 9.52. Thallous ions accumulate in tissues with high concentrations of potassium.

Thallium distributes rapidly into cells based on radionuclide studies with ^{201}TlCl; 5 minutes after the intravenous injection of 2–5 mCi ^{201}TlCl, 5–8% of the injected activity remained in the blood of 11 patients.[57] Based on data from tracer studies in animal[58] and postmortem studies in humans,[51] thallium distributes primarily to the kidney, soft tissue (muscle), scalp hair, the heart, and, to a lesser extent, the brain and liver. Case reports suggest thallium distributes more slowly to the central nervous system than blood. In a patient with severe thallium poisoning, the CSF thallium concentration increased from 1,200 µg/L on day 1 to 2,100 µg/L on the day of death (day 3), whereas the serum thallium concentration decreased from 8,700 to 7,200 µg/L.[59] Depending on the time since ingestion, large amounts of thallium may be present in the large intestine. Thallium is soluble at physiological pH; unlike lead and arsenic, thallium does not form complexes in bone. Because of its rapid accumulation in cells, whole blood Tl concentrations do not reflect the Tl concentration in tissues.[22]

Elimination

Thallium elimination follows a two-compartment model in human pharmacokinetic studies. In a study of nine patients undergoing myocardial scintigraphy with ^{201}TlCl, the mean terminal plasma half-life of thallium was 51.8 ± 14.9 hours.[56] The major portion of thallium remains in the gut following an acute overdose, probably because of enterohepatic recirculation; elimination occurs primarily via the feces.[60] However, following the ingestion of small doses of thallium, the kidney excretes most of the body burden of thallium with a daily urinary loss of about 3% of the total body burden of thallium.[53,61] During the first month after admission for severe thallium intoxication (respiratory failure, areflexic paralysis of all extremities, visual loss), the elimination half-life of thallium averaged ~2–4 days (range, 3–8 days); treatment with Prussian blue and potassium began midway through this period.[60,62] Thereafter, the elimination half-life increased considerably. Without treatment, the biological half-life of thallium is ~10–15 days based on limited data.[63,64] Compared with laboratory animals, the excretion of thallium in humans is slower, occurring primarily via the kidney and substantially less in the feces. Thallium does not accumulate in the body.

Maternal–Fetal Kinetics

Thallium does cross the placental barrier and produces alopecia and nail abnormalities in a fetus exposed in the last trimester.[65] Excretion of thallium in human milk occurs after the administration of ^{201}Tl to breastfeeding mothers.[66] In a lactating mother receiving 111 MBq (3 mCi) for evaluation of a residual brain tumor, the estimated dose to the breastfeeding infant was 0.00072–1.92 mSv depending on the age of the child.[67]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

Thallium is a nonessential heavy metal. The exact mechanism of thallium toxicity remains unclear; however, animal models and *in vitro* experiments suggest that thallium causes lipoperoxidation and interferes with mitochondrial function by competing with potassium ions in essential enzymes.[68] Potential mechanisms include: 1) modification of the Na^+/K^+ ATPase pump and alteration of resting membrane potential across the active cells;[69] 2) inhibition of energy production from glucose (i.e., pyruvate kinase-catalyzed conversion of ADP to ATP);[70] and 3) inactivation of riboflavin and reduction in the activity of the Krebs cycle.[71] Like other heavy metals, thallium has an affinity for sulfhydryl groups of mitochondrial membranes; therefore, thallium inhibits sulfhydryl-containing enzymes involved in respiration and protein synthesis (e.g., keratin). Inhibition of the sulfhydryl-containing enzyme, cysteine, inhibits keratinization resulting in alopecia. Succinic dehydrogenase, protease, and monoamine oxidase are all thiol enzymes that are reduced in the corpus striatum of thallium-fed experimental animals.[72] The interaction of thallium with sulfhydryl groups produces free radicals and increases lipid peroxidation in the brain. The increased rate of lipid peroxidation depletes glutathione,

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leading to the accumulation of lipid peroxides and the formation of lipofuscin granules in the kidney, liver, and brain.

Sharing similar ionic radii, thallium displaces potassium throughout the body and interferes with oxidative phosphorylation by inhibiting Na^+/K^+ ATPase.[73] The affinity of the Na^+/K^+ ATPase enzyme is over 10 times greater for thallium than potassium.[11] Axonal mitochondria accumulate thallium, resulting in necrosis.[74] Deficiencies of riboflavin produce a clinical picture similar to thallium poisoning including dermatitis, alopecia, and neuropathy. Another potential mechanism of action for thallium toxicity is the interference of riboflavin homeostasis by the formation of insoluble complexes that sequester riboflavin intracellularly.[75]

Pathological Changes

Microscopic examination of the peripheral nerves following thallium intoxication demonstrates primarily axonal degeneration with preservation of most overlying myelin, particularly in the small sensory nerves.[76] Secondary myelin degeneration may occur. Electron microscopy demonstrates damage to small and unmyelinated fibers with denervation of the epidermis and loss of epidermal nerves.[77] Medium-sized nerves are selectively damaged; decreased density of large myelinated fibers also occurs. Examination of the brain reveals edema and necrosis of the neurons and glial cells. Electron microscopic changes are most prominent in the mitochondria with marked swelling, dilation of intermembrane spaces, distortion of the endoplasmic reticulum, and destruction of cristae and membranes.[78]

Biopsies of acneiform pustules of the face and hyperkeratotic lesions of the feet demonstrate gross follicular plugging with eosinophilic keratohyalin granules in adjacent layers of the epidermis along with the disintegration of the hair shafts, atrophy of the hair bulb, dystrophic cuticles, and cystic dilation of the follicles.[79] Polarized light microscopic examination of hair roots during the first week after thallium exposure demonstrates dark zones around the hair root as a result of the accumulation of gaseous inclusion bodies that refract light; thallium is typically not deposited in the skin as analyzed by the rhodizonate staining test.[80] The alteration of hair shaft diameter and disorganization of the cortex appear as dark zones under transmitted-light microscopy. Multiple dark zones may occur following poisoning by successive doses of thallium. Histological examination of crusted eczematous lesions from a patient with thallium poisoning demonstrated marked parakeratosis, mild epidermal atrophy and vacuolar degeneration of the basal layer, and dilated hair follicles filled with keratin and necrotic sebaceous debris.[48]

Postmortem

Autopsies of patients dying of thallium poisoning demonstrate mucosal hemorrhages of the intestine, heart, lungs, and endocrine glands, degenerative changes in the renal tubules and glomeruli, fatty infiltration of the heart and liver, and central nervous system fatty degeneration of the ganglion cells with preservation of the anterior horn cells and deterioration of the myelin sheaths and axons.[81] Nerve biopsies from patients with thallium poisoning reveal demyelination characterized by focal beading of the myelin along with an axonopathy characterized by prominent fusiform dilations and loss of axons.[82] Pathological changes of muscle fibers include central nucleation, splitting of fibers, and necrosis.[20] Case reports suggest distal peripheral degeneration of motor and sensory axons occurs following thallium poisoning with relative preservation of proximal fibers.[47] Postmortem examination of a 32-year-old man with thallium poisoning demonstrated widespread loss of peripheral nerve fibers and chromatolysis of spinal neurons, particularly long distal fibers (i.e., lumbar sensory > cervical sensory).[83]

CLINICAL RESPONSE

The differential diagnosis of thallium poisoning includes heavy metal poisoning (arsenic, lead, mercury, selenium), adverse drug reactions (isoniazid, hydralazine, phenytoin), botulism, alcoholic peripheral neuropathy, musculoskeletal pain, connective tissue diseases, Guillain–Barré syndrome, and thiamine deficiency. The presentation of chronic thallium intoxication is similar to the presentation of acute thallium poisoning. However, symptoms of chronic thallium poisoning begin insidiously with symptoms peaking within 2–3 weeks followed by gradual resolution or death.[65]

Acute Toxicity

The classic presentation of acute thallium poisoning is the initial development of mild gastroenteritis (nausea, vomiting, diarrhea, epigastric pain) followed by polyneuritis (prominent paresthesias/pain, ptosis, dysphagia, tremor, confusion, encephalopathy, cerebellar symptoms, choreiform movements) within 2–5 days and subsequently dermatological abnormalities (alopecia, loss of lateral third of eyebrow,

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acneform/eczematous lesions, scaling of palms and soles, Mees' lines) ~2–3 weeks postexposure.[84,85,86] Peak alopecia occurs ~3–4 weeks after acute ingestion with some sparing of axillary, pubic, and facial hair (e.g., eyelashes).[2,87] The absence of alopecia does not exclude the diagnosis of thallium poisoning.[88] Nonspecific autonomic effects include tachycardia, hypertension, fever, salivation, fatigue, and sweating. Hematemesis is rare; coma and death may occur following massive overdoses of thallium acetate or thallium sulfate.[2,89] In severe cases, cranial neuropathies may develop.

Central Nervous System

Although symptoms of peripheral neuropathy often dominate the clinical presentation, CNS symptoms also occur including optic neuritis, encephalopathy, extrapyramidal signs, and cerebellar dysfunction.[90] The central nervous system features of acute thallium poisoning include disorientation, irritability, poor concentration, headache, lethargy, tremor, ataxia, coma, convulsions, psychosis, thirst, insomnia, visual illusions, ophthalmoplegia, and cerebral edema with central respiratory failure. Cranial nerve abnormalities and cerebellar signs are less common than clinical features of peripheral neuropathy. Although recovery from neurological abnormalities occurs after cessation of thallium exposure, the improvement is variable; some central nervous system abnormalities may persist including psychosis,[2] ataxia, tremor, intellectual impairment (poor performance IQ, reasoning skills, memory impairment),[91,92] and visual loss.[93] The latter case report documents persistent visual loss 3 years after thallium poisoning.

Peripheral Nervous System

Within ~2–5 days after acute, severe thallium exposure, symptoms of a painful, rapidly progressive peripheral neuropathy begin; by the second to third week, these symptoms dominate the clinical picture. Neurological examination may detect a stocking-glove type of polyneuropathy involving a combined motor and sensory neuropathy that is primarily a distal axonopathy manifest in the lower extremities.[55,94] Involvement of the upper extremities occurs infrequently; cranial nerve palsies following thallium poisoning are rare. Hyperesthesia of the palms and soles may be particularly severe. Unlike Guillain–Barré syndrome, stretch reflexes are preserved until late in the course of toxicity; prominent sensory changes precede the distal motor weakness. Leg cramps may be severe. Peripheral nervous system abnormalities (e.g., motor weakness, foot drop, visual loss) usually improve, but weakness and sensory disturbances may persist for at least several years, primarily in the lower extremities.[95]

Cardiorespiratory System

Severe cases of Tl toxicity may exhibit myocardial necrosis with dysrhythmias and cardiac failure.[96] Death usually results from respiratory or cardiac failure. Intractable hypotension, elevated pulmonary wedge pressures, and bradycardia may dominate the clinical picture. Acute respiratory distress syndrome may develop within the first 48 hours of hospitalization after a large Tl ingestion based on case reports documenting normal pulmonary capillary wedge pressures with diffuse interstitial and alveolar inflammation.[97] Postmortem examination confirmed the latter with hyaline membrane formation. Variations in blood pressure occur as a result of autonomic dysfunction.

Eye

Early signs of ocular involvement include blepharitis, conjunctivitis, diplopia, ptosis, nystagmus, bilateral facial palsy, facial hyperesthesias, and hyperemia of the optic disc. The severity of visual impairment depends on dose; early ocular signs may be transient.[98] Late ocular signs of thallium poisoning include optic atrophy, visual loss, and a central scotoma. In a case report of two women with severe thallium poisoning including visual abnormalities, severe asymmetrical vision impairment persisted in both women along with central scotomata and impaired color discrimination at 2-year follow-up.[99]

Skin

Nonspecific dermal signs begin within the first week after ingestion including scaling of the palms and soles, acneform lesions and dark pigmentation of the hair roots, and black, tapered, dystrophic anagen roots.[79,100] The cortex appears disorganized and the hair shaft may display intermittent, dark transverse bands. Severe acne may develop on the nose, cheeks, and nasolabial folds manifested by necrotic lesions and follicular plugging along with blue-gray lines on the gums.[101] Other dermatological abnormalities include crusted eczematous lesions, palmar erythema, dry scaly skin with hyperkeratosis, anhydrosis, glossitis, stomatitis, and discoloration of the hair. Approximately 2–4 weeks after thallium exposure, the most characteristic dermatological sign is the development of scalp and facial hair loss, primarily in the scalp and temporal parts of the eyebrows.[75]

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Pubic and axillary hair along with eyelashes are relatively spared during thallium intoxication. Crusted eczematous lesions and dry scaly skin may appear on the trunk and the distal portions of the extremities as a result of generalized anhidrosis and destruction of sebaceous glands. Impaired growth of the nails occurs along with the appearance of white stripes (Mees lines) across nails ~1 month after exposure. Alopecia and nail changes (e.g., Mees lines) usually resolve completely after cessation of thallium exposure.[102] The hair loss stops ~2–3 months after Tl exposure ceases.[103] The appearance of new hair begins ~2 months later; hair regrowth is complete within 2 months.[48]

Environmental Exposure

In a study of 1,265 residents living near a thallium-emitting cement production plant, the primary route of thallium exposure was the consumption of Tl-contaminated vegetables and fruits grown in private gardens near the plant.[104] The reference group included 31 residents of a small German city (Steinfurt) and 10 residents of a large urban area (Dusseldorf). Although an exposure-response relation existed between urinary thallium concentrations and a variety of complaints (neuralgias, sleep disorders, weakness, tiredness, headache, fatigue, neurasthenia, joint pains, paresthesias), skin alterations, and gastrointestinal dysfunction did not correlate to urine Tl concentrations.

Occupational Exposure

Although thallium is a potent toxin, industrially related thallium toxicity is relatively uncommon with most cases occurring before the 1960s. Chronic percutaneous Tl exposure was associated with the onset of abdominal pain, alopecia, fatigue, irritability, myalgias, and weight loss in 12 of 15 workers using organic thallium salts to separate industrial diamonds from abrasives.[13] A 29-year-old specialty glass worker developed alopecia, abdominal pain, diarrhea, weight loss, fatigue, myalgias, and paresthesias of the extremities following the initiation of a new glass production process requiring thallium carbonate.[55] After cessation of his exposure to Tl-containing dust, his symptoms gradually improved; however, his complaints of gastrointestinal discomfort and extremity numbness remained over 2 years after his thallium exposure ceased. A survey of workers with Tl exposure from the production of Tl–Mg–Al alloys (5% Tl) for anodes in magnesium seawater batteries; routes of exposure included fumes from furnaces, percutaneous contact with the alloys, and dust generated during brushing the alloy.[105] Examination of medical records did not detect differences between 86 Tl-exposed workers and 79 unexposed workers, despite Tl concentrations up to 236 μg/L in spot urine samples from the exposed workers as measured by colorimetric methods. Medical history and physical examination of 128 Tl-exposed German cement plant workers with urine Tl concentrations up to 6.3 μg/L did not reveal Tl-associated adverse effects as measured by statistical differences in diagnostic codes between the two groups.[106]

Reproductive Abnormalities

There are few data on the teratogenicity of thallium. Existing animal data suggest that thallium may affect fetal cartilage or bone formation, but teratogenic effects are limited compared with maternal toxicity.[107] Thallium crosses the placental barrier resulting in Tl toxicity during maternal toxicity. A review of thallium intoxication during pregnancy indicated a wide variety of fetal effects ranging from normal development to severe toxicity in infants born to mothers poisoned with thallium.[108] There were insufficient data to formulate prognostic factors for the fetal outcome of pregnant women poisoned with thallium including the severity of maternal toxicity. Relatively low birth weight and alopecia occurred in neonates born to mothers who developed thallium poisoning during pregnancy; however, other congenital abnormalities were not detected.[22] The ingestion of 750 mg thallium sulfate 60 days before delivery produced alopecia and nail abnormalities characteristic of thallium intoxication in a neonate.[109] A follow-up study of 297 children living near the Tl-emitting cement plant did not detect a causal relationship between thallium and the occurrence of congenital malformations in the children investigated based on retrospective community health surveys and comparisons with general rates of congenital malformations in control populations.[40] The authors noted the difficulty in estimating the maternal thallium exposures retrospectively. In a study of 1,106 Chinese women without occupational thallium exposure, the median thallium concentrations in the group of women with adverse pregnancy outcomes ($n = 73$) and the referent group were not statistically different as measured by inductively coupled plasma/mass spectrometry.[110] The mean Tl concentration in umbilical cord samples from the adverse outcome group was 0.40 ± 0.38 μg/L compared with 0.41 ± 0.33 μg/L in the referent group. The latter group consisted of 106 women randomly selected from the women with normal pregnancy outcomes.

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Although the transplacental transfer of thallium does occur, many strains of mice and rats demonstrate either no or only slight teratogenic effects following Tl exposure. In rodents, fetal thallium concentrations are lower than maternal Tl concentrations.[111]

Carcinogenesis

Neither the IARC nor the US National Toxicology Program lists thallium or soluble thallium salts as potential carcinogens; however, little data are available regarding the carcinogenic potential of thallium and thallium salts, primarily as a result of the difficulty of conducting carcinogenic studies because of the severe toxicity of thallium.

DIAGNOSTIC TESTING

SI Conversion Units

1 mg = 4.893 μmol
1 μmol = 0.2044 mg

Analytical Method

A commonly used method to analyze blood thallium concentrations is direct aspiration atomic absorption spectrometry, whereas furnace atomic absorption analysis, inductively coupled plasma/mass spectrometry, and neutron activation analysis are sensitive methods for very low concentrations (μg/kg) of thallium in small samples.[112] Inductively coupled plasma/atomic emission analysis and isotope dilution mass spectrometry are accurate and precise methods for multi-analyte analyses in biological and environmental samples at μg/kg (ppb) concentrations.[20] Urine specimens should be collected in pre-cleaned polyethylene or polypropylene containers; blood samples are typically collected in BD Vacutainer® Plus tubes with Royal Blue Hemogard™ using Terumo® Venoject needles. These tubes contain sodium heparin and Na_2EDTA specifically for trace metal analysis.

Biomarkers

Blood

Measurement of thallium in blood reflects recent exposure (i.e., several days) because of the rapid distribution of thallium intracellularly. The Tl half-life in the blood following the ingestion of 38 mg Tl as a soluble thallous salt was ~2 days.[53] Most internal thallium resides in the red blood cell; whole blood Tl concentrations are approximately twice the serum Tl concentration.

General Population

About 80% of 320 specimens of whole blood from asymptomatic children aged 1–5 years residing in Newark, New Jersey, were below the Tl limit of detection (<5 μg Tl/L); 1.6% of the sample ranged between 21–40 μg Tl/L as measured by atomic absorption spectrophotometry.[113] The highest recorded thallium concentration in this sample was 80 μg/L. In a study of 418 Italian subjects without occupational Tl exposure, the mean Tl concentration was 0.39 ± 0.05 μg/L (range, 0.1–1.1 μg/L); for 360 serum samples, the mean Tl concentration was 0.18 ± 009 μg/L (range, <0.05–0.4 μg/L) as measured by electrothermal/atomic absorption spectroscopy and neutron activation analysis.[114] The mean whole blood Tl concentration in 47 young Taiwanese adults was 1.9 ± 1.67 μg/L with a maximum of 4.76 μg/L.[115] The authors suggested the relatively high Tl concentrations reflected environmental exposure from thallium in commercial products (incense sticks, candles, mosquito coils) and fish consumption.

Toxicity

Generally, serum Tl concentrations of >200 μg/L are associated with toxicity, whereas serum Tl concentrations of >300 μg/L indicate severe poisoning. A 10-year-old boy was admitted with scalp alopecia, abdominal pain, lower extremity paresthesias, and seizures 2 weeks after drinking a bottle containing thallium; his admission serum thallium concentration was 296 μg/L.[103] He survived without sequelae. A 7-year-old survived thallium poisoning with intensive care and a whole blood thallium concentration of 358 μg/L at admission (i.e., ~1 week after ingestion); in the same case series, a 5-year-old girl with a whole blood thallium concentration of 289 μg/L at admission died later.[84] A 39-year-old man was admitted to an intensive care unit with hair loss, nystagmus, facial/bulbar weakness, mild upper extremity weakness, and flaccid paralysis of the lower extremities with absent reflexes; his illness began 20 days before admission.[62] His admission serum thallium concentration was 2,068 μg/L. After a prolonged hospital course including 3 months on the respirator, he was discharged with visual impairment and difficulty walking more than a few steps with aid. Survival with severe neurological impairment (flaccid extremities, ataxia, intellectual impairment) occurred in a patient with an admission serum Tl concentration of 5,750 μg/L.[91]

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Urine

Urine is the best fluid to measure chronic Tl exposure; large sample size also allows pre-concentration prior to analysis. Limited data correlate urine thallium concentrations with potential clinical effects.

General Population

The urine Tl concentration in the general population is typically <1–1.5 μg Tl/L or <1 μg Tl/g creatinine.[106,116] Based on a sample of 776 participants (≥40 years of age) in the 1999–2000 National Health and Nutrition Examination Survey (NHANES III), the geometric mean urine thallium concentrations were 0.165 μg/L with a maximum of 0.86 μg/L (95th percentile, 0.440 μg/L).[117] The geometric mean Tl concentrations in a representative sample of 2,848 individuals age 6 years and older from NHANES IV data were 0.144 μg/L (95% CI: 0.41 μg/L).[118] In a convenience cohort of 273 British residents without occupational Tl exposure, the 95% upper limit of urine thallium was 0.36 μg/L compared with 0.41 μg/L for 565 workers without known thallium exposure.[119] The mean Tl concentration in urine samples from 496 Italian subjects without known sources of Tl exposure was 0.42 ± 0.09 (range, 0.06–0.82).[114]

In a study of 1,265 residents living near a thallium-emitting cement production plant, the mean Tl concentration in 24-hour urine samples was 2.6 μg/L with a range up to 76 μg Tl/L; the mean Tl concentration in the two referent groups was 0.2 μg/L (urban) and 0.4 μg/L (rural).[104] Urine thallium concentrations of <5 μg/L present in the general population living near point sources of thallium are not associated with causing adverse effects, whereas clinical effects occur in patients when thallium concentrations exceed 500 μg/L.[22] There are few data on the risk of thallium exposure resulting in urine Tl concentrations of 5–500 μg/L.

Toxicity

Urinary thallium concentrations following thallium intoxication are frequently reported in the range of 2,000–4,000 μg/L with potentially fatal cases associated with urine thallium concentrations exceeding 5,000 μg/L.[97] Painful paresthesias of the lower extremities, acne, gastrointestinal distress, stomatitis, scalp alopecia, and urinary retention developed in two patients after drinking thallium-contaminated water.[77] A few weeks after presentation, the urine thallium concentration was 11,325 and 14,520 μg/L. Both patients survived with partial improvement in sensory symptoms 6 months after presentation.

Hair

Examination of scalp hair roots showed that black pigmentation was present in 95% of cases after 4 days.[11] Little quantitative data are available to use hair analysis as an indicator of Tl exposure. Thallium may be incorporated into hair; therefore, external contamination complicates the interpretation of thallium concentrations in hair. Normal concentrations of thallium in hair typically range from 5–10 ng/g.[20] Most hair samples from the scalp, and to a lesser extent, from the chest and legs are positive in cases of thallium poisoning; however, hair from the eyebrows often does not contain thallium following Tl exposure.

Bone

Typically bones from individuals without exposure to thallium contain non-detectable concentrations (<0.01–0.05 μg/g tissue) of thallium. Analysis of the skull and thigh bones from a victim of thallium poisoning 29 years after death revealed thallium concentrations of 2.63 μg/g and 1.76 μg/g, respectively, as measured by laser ablation in combination with inductively coupled plasma sector field/mass spectrometry.[120]

Abnormalities

Blood

A slightly depressed serum potassium concentration and mild hypochloremic alkalosis probably reflect thallium-induced renal tubular dysfunction.[4] Lymphopenia, neutrophilia, and thrombocytopenia were associated with a fatal case of chronic thallium poisoning.[121] Laboratory abnormalities detected in a case series of 10 family members poisoned by Tl-contaminated cake included normochromic, normocytic anemia, thrombocytopenia, hyponatremia, hypokalemia, hypomagnesemia, and hypermagnesemia; the hypokalemia was attributed to the administration of Prussian blue.[85] Unlike lead poisoning, thallium intoxication does not alter coproporphyrinogen III or protoporphyrin IX concentrations.[122]

Imaging

Thallium is radiopaque in concentrated form; the radiographic appearance of thallium in the gut following Tl exposure is inconsistent depending on the amount of thallium present.[60] A hazy abdominal opacity on X-ray may correspond to thallium in the liver; however, the absence of radiopaque material in the gastrointestinal tract does not exclude the ingestion of a fatal

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Tl dose.[123] A week or more after exposure, laboratory evidence of renal, liver, or muscle dysfunction may become apparent including hypointense lesions in T1-weighted images and hyperintense lesions in T2-weighted images of the corpus striatum during brain MRI.

Electrocardiogram

Electrocardiographic abnormalities include T wave inversion, ST-segment depression or elevation, prolonged QT interval, heart block, and both atrial and ventricular dysrhythmias.

Electrophysiology

Electromyography and nerve conduction studies of patients with peripheral neuropathy secondary to thallium intoxication demonstrate diffuse axonal degeneration of sensory and motor fibers, particularly in the distal lower extremities. Although abnormalities in nerve conduction studies, visual evoked potentials, and brainstem auditory evoked potentials improve along with symptoms, abnormalities may persist at least several years after cessation of exposure.[99] Manifestations of these electrophysiological abnormalities include marked reduction in CMAP amplitudes with mild slowing of motor and sensory nerve conduction velocity and relatively normal distal latencies, particularly in the lower extremities.[124] In an adolescent with severe peripheral neuropathy from thallium intoxication, weakness and sensory disturbances persisted for years after poisoning, primarily in his feet.[95] Electrodiagnostic studies demonstrated bilateral improvement in voluntary activity of distal lower limb muscles along with increases in the response amplitudes of median and sural nerves when compared with earlier studies. An electrophysiological investigation of a thallium-intoxicated patient with optic atrophy revealed a conduction block of the retinal nerve fibers (reduced visual evoked potentials) and lesions near the retinal bipolar cells (diminished amplitude on multifocal electroretinography).[125]

Neuropsychological Testing

Case reports suggest thallium intoxication produces temporal lobe dysfunction on neuropsychological testing (i.e., deficits in memory recall, reversed digit span, memory recognition, similarities, proverb reasoning, verbal fluency) correlating with hypointense lesions in T1-weighted images and hyperintense lesions in T2-weighted images of the corpus striatum on the brain MRI.[126] Slow improvement occurred over 1 year including resolution of the lesions. These patients also display anxiety, depression, and emotional lability.

TABLE 30.2. Regulations and guidelines for exposure to thallium. (Adapted from Lauwerys and Hoet).[127]

Exposure Limit	Value
OSHA	
PEL–TWA[a] (8-hour)	
Soluble Tl	100 μg/m^3
NIOSH	
REL–TWA (10-hour)	100 μg/m^3
IDLH	15,000 μg/m^3[b]
ACGIH	
TLV–TWA (8-hour, with skin notation)	20 μg/m^3
US EPA	
RfD (chronic oral exposure)	NA
MCL	None

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; IDLH = immediately dangerous to life and health; MCL = maximum contaminate level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = reference dose; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency; NA = not available.
[a] As metallic Tl; [b]soluble thallium compounds only.

HEALTH SURVEILLANCE

The US PEL–TWA for thallium and soluble thallium salts is 0.1 mg Tl/m^3 with a skin notation. Table 30.2 outlines the regulations and guidelines for thallium and thallium compounds. In a study of 128 cement production workers exposed to thallium, spot urine samples contained Tl concentrations ranging from <0.3 (LOD) to 6.3 μg/g creatinine; history and physical examination of these workers did not detect any clinical features characteristic of thallium intoxication.[106] Urinary Tl concentrations of 100 μg/L in asymptomatic workers roughly correlate to workplace exposures at the threshold limit value of 0.1 mg Tl/m^3 based on a study of workers manufacturing thallium-containing seawater batteries.[105] The recommended action level for occupational Tl exposure was 50 μg/L; however, there are few data to substantiate this value.[127]

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TREATMENT

Decontamination

The usual gastrointestinal decontamination measures (activated charcoal, lavage) may be used within the first 1–2 hours after exposure; however, the delayed presentation of thallium intoxication usually results in the arrival at health care facilities long after decontamination measures would be effective. *In vitro* studies suggest activated charcoal binds thallium, and thallium undergoes hepatic recirculation; hence, at least a single dose probably is beneficial. A cathartic may be necessary for severe thallium poisoning when constipation complicates the administration of activated charcoal and/or Prussian blue. The presence of radiopaque material in the gastrointestinal tract suggests the need for whole bowel irrigation; however, there are insufficient clinical data to guide the use of this modality. Because of potential skin absorption, clothing in direct contact with thallium compounds should be removed and the skin washed with soap and water.

Enhancement of Elimination

Prussian Blue

Prussian blue is the crystal blue lattice of soluble potassium ferric hexacyanoferrate; this compound reduces thallium gastrointestinal absorption and increases fecal excretion by exchanging thallium for potassium.[128] This exchange disrupts the enterohepatic circulation of thallium, creating a gradient between the intestinal tract and the blood. The gradient favors the movement of thallium into the intestines. In animal studies, the administration of Prussian blue reduced Tl half-life from 4 days to 2 days.[129] The affinity of Prussian blue for thallium depends on the particle size and the form (i.e., colloidal or soluble form vs. non-colloidal or insoluble form). Small particle size and high solubility enhance the affinity of Prussian blue for thallium;[130] however, these characteristics vary between different batches of Prussian blue. The administration of this compound causes few side effects except constipation as a result of the poor absorption of the Prussian blue–thallium complex from the gastrointestinal tract. Experimental studies in rats indicate Prussian blue reduces brain thallium concentrations and overall mortality during acute thallium intoxication.[131,132] This compound is commercially available in Europe and the United States as insoluble Radiogardase™ (HEYL Chemisch-pharmazeutische Fabrik Gmb H & Co., Berlin); pathology labs use Prussian blue for nonmedicinal purposes. Although there are insufficient data to determine if the insoluble form of Prussian blue is as effective as the soluble form, the insoluble form of Prussian blue (Radiogardase™) is approved by the US FDA for the treatment of thallium poisoning.[128] Prussian blue (Radiogardase™) is available through the Radiation Emergency Assistance Center in Oakridge, Tennessee (www.orau.gov/reacts/prussian.htm) or the US FDA. Prussian blue is 35–40% cyanide by weight; however, *in vitro* studies suggest long-term storage over 10 years does not increase cyanide release despite some water loss.[133]

The capacity of Prussian blue to improve clinical outcomes during thallium intoxication remains unproven in the absence of controlled human trials.[60] Several authors recommend the use of Prussian blue in thallium poisoning, particularly when administered *early* in the clinical course.[96] The usual daily dose is 250 mg colloidal (soluble) Prussian blue/kg divided into four oral administrations. The recommended adult dose of insoluble Prussian blue (Radiogardase™) is 3 g orally three times daily. The pediatric dose for 2–12-year-old children is 1 g three times daily. A mild cathartic (e.g., 50 mL 15% mannitol containing the Prussian blue dose or 50–100 mL 15% Sorbitol) helps prevent constipation. An alternative to a cathartic is a high fiber diet should be added to each dose to prevent constipation. Inadequate data are available to determine the optimum duration of Prussian blue treatment.

Severe poisoning with protracted vomiting may require the placement of a duodenal tube to administer the Prussian blue.[134] The administration of 50 mg Prussian blue/kg produced a statistically significant increase in the 5-day survival of mice receiving 70–85 mg Tl/kg; however, the addition of 200 mg *N*-acetylcysteine/kg did not affect 5-day survival.[135] The patient should be monitored for the development of hyperkalemia. *In vitro* studies suggest thallium excretion increases in an alkaline environment,[136] but no human studies are available to confirm the efficacy of alkalinization.

Multi-dose Activated Charcoal (MDAC)

The administration of serial doses of activated charcoal is an alternative to Prussian blue when the latter is unavailable; however, human data on the clinical efficacy of MDAC during thallium intoxication are limited.[88] *In vitro* and rodent studies suggest activated charcoal effectively binds thallium ions;[137,138] however, inadequate data are available to assess the efficacy of serial doses of activated charcoal or the combination of MDAC and Prussian blue on the outcome of thallium intoxication.

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Extracorporeal Methods

Although thallium is a small molecule with no significant protein binding, the large volume of distribution and intracellular distribution of thallium theoretically limit the effectiveness of these methods. Forced diuresis increases thallium excretion by 60% in animal models;[139] however, this method is limited by the relatively small amount of thallium cleared by the kidney after a Tl overdose. There are limited data on the effect of hemodialysis on thallium clearance. In a severe case of thallium poisoning (serum thallium = 5,240 μg/L ~ 4 hours post-ingestion), the reported Tl clearance rate from the blood ranged from 96–150 mL/minute.[140] A case report of thallium poisoning demonstrated that hemofiltration did not remove clinically significant amounts of thallium.[91] Hemoperfusion may enhance thallium clearance when combined with hemodialysis.

In severe poisoning, the early use (i.e., within the first day) of the combination of hemodialysis or hemoperfusion is a therapeutic option, although the clinical effectiveness of this treatment remains unproven. In a 32-year-old woman who was normotensive 7 hours after the ingestion of 100 mg thallium sulfate, the thallium clearance was 150 mL/minute at a blood flow rate of 200 mL/minute. The estimated amount eliminated by the combination of 4 hours of hemodialysis and hemoperfusion was only ~7% of the estimated ingested dose.[141] The estimated mean thallium clearance from hemoperfusion and hemodialysis was 139 mL/minute and 49 mL/minute, respectively. In a patient hypotensive from severe thallium intoxication, the thallium clearance values during two different times were 50.2 and 60.4 mL/minute at a blood flow rate of 100 mL/minute.[51] The use of hemodialysis for 120 hours eliminated 143 mg (~7%) of an estimated 2 g-thallium overdose by a 56-year-old woman.[142] During the first few days following a thallium overdose, thallium concentrations are relatively high; therefore, measures to enhance elimination should be initiated as soon as possible.

Despite the relatively low dialyzability of thallium and limited clinical data to support the use of dialysis, the Extracorporeal Treatments in Poisoning (EXTRIP) workgroup recommended the use of hemodialysis in severe thallium poisoning.[143] Indications included history or clinical features suggestive of thallium intoxication or serum thallium concentration of >1 mg/L. Treatment recommendations included initiating hemodialysis as soon as possible (i.e., within 24–48 hours) and continuing hemodialysis until the serum Tl concentration is <0.1 mg/L or a minimal duration of 72 hours.

Potassium Chloride

In general, the potassium concentration should be kept in the normal range without additional supplementation. The role of potassium *alone* in the treatment of thallium poisoning is controversial. Potassium may inhibit the resorption of thallium from the renal tubule and displace thallium from intracellular stores. Some animal studies suggest potassium supplementation increases the excretion of thallium; however, the amount excreted is relatively small.[73] Potassium chloride supplementation (40–65 mEq/day in adults) and diuresis increase thallium excretion, but the redistribution of thallium to the brain may enhance toxicity. Case reports have not documented the efficacy of this regimen. The combination of *peritoneal dialysis* and potassium chloride diuresis removed only 30–35 mg of thallium (6% of the estimated dose) daily.[144] Consequently, potassium-enhanced diuresis has very limited use in thallium intoxication; other measures (e.g., activated charcoal, hemodialysis, charcoal hemoperfusion, Prussian blue) are better techniques to enhance thallium elimination.[145,146]

Chelating Agents

Thallium does not respond to traditional chelation therapy in the absence of clinical data to support the use of chelating agents (diethyldithiocarbamate, $CaNa_2$ EDTA, BAL, penicillamine). Diethyldithiocarbamate causes redistribution of thallium to the central nervous system, resulting in a worsening of neurological symptoms.[147] Case reports on the effectiveness of DMSA to remove thallium are limited and conflicting; there are inadequate experimental data to determine the efficacy of chelating agents.[131] The effectiveness of combined therapy (e.g., D-penicillamine, Prussian blue) as a means to increase Tl removal from critical target organs without redistribution of thallium following the use of chelating agents remains to be confirmed in human studies.[148]

Supplemental Care

Severe stomatitis may develop following thallium poisoning; therefore, mouthwashes and gargles are preferable to tooth brushing.[149]

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Chapter 31

TIN

METALLIC AND INORGANIC TIN

HISTORY

Tin smelting dates back to the Neolithic age. Along with copper and gold, tin has been used in metallurgy for over 5,000 years. Bronze, the tin–copper alloy, was invented ~2,500 BC.[1] The Romans coated metal with tin. Initially, tin was the main constituent of food containers because the storage of food and drinks in these vessels did not alter flavor or taste. During the Napoleonic wars, the preservation of foods by sealing them in tin cans was developed; by the middle of the 19th century, the practice of packaging food in tin cans was widespread in the United States. Medicinal use of tin and inorganic tin compounds (stannous chloride, tin oxide) began several centuries ago with the oral administration of these relatively insoluble compounds as anthelmintics.[2] Tin compounds were believed to possess anti-staphylococcal properties because French tin miners in Beauve seldom developed furuncles.[3] During the 1940s, a benign pneumoconiosis was attributed to workers chronically inhaling dusts and fumes from processes involving the bagging and smelting of tin oxide.[4]

PHYSIOCHEMICAL PROPERTIES

Tin is a member of Group 14 (Group IVA germanium, lead) of the periodic table that forms two primary oxidative states, stannous (Sn^{2+}) and stannic (Sn^{4+}). At pH >6, stannous compounds are strong reducing agents. Stannous chloride and stannous sulfate are strongly acidic, whereas potassium and sodium stannate are strongly alkaline; the irritant properties of these compounds are sufficient to cause skin and mucous membrane irritation. In nuclear medicine, these compounds function as reducing agents for ^{99m}technetium.[5] Stannous compounds easily oxidize at pH >6. Tin forms a highly toxic hydride, stannane (SnH_4). Table 31.1 lists the identifying information and physical properties of tin and common tin compounds. Elemental tin is a lustrous white, soft, odorless, malleable metal with very high density (i.e., 7.3). This metal has a highly crystalline structure that exists in two allotropic forms under normal pressures depending on temperature. Below ~13°C, tin appears as a gray material with a cubic structure, whereas above this temperature, tin is a white material with a tetragonal structure. At 200°C, tin becomes brittle, and below −40°C, tin crumbles into a gray amorphous powder. Tin exists in the environment primarily as colloidal complexes rather than ionized forms; typically, a transparent film of SnO_2 covers elemental tin. The affinity of divalent and tetravalent inorganic tin for nitrogen and sulfur ligands is low, limiting the toxicity of inorganic tin.

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TABLE 31.1. Identifying information and physical properties of tin and inorganic tin compounds. (Adapted from ATSDR).[6]

Physical Characteristic	Tin	Tin Chloride	Tin Oxide	Tin Fluoride
Formula	Sn	$SnCl_2$	SnO_2	SnF_2
Synonym	Metallic tin, silver matt powder	Stannous chloride, tin dichloride	Stannic oxide, tin oxide, stannic anhydride	Stannous fluoride
CAS RN	7440-31-5	7772-99-8	18282-10-5	7783-47-3
Valence	0	+2	+4	+2
Molecular weight (g/mol)	118.69	189.60	150.71	156.71
Color	Silver–White	White	White	White
Physical state	Solid	Solid	Solid	Solid
Melting point (°C)	231.9	246	1,630	213
Density (g/mL, 20°C)	5.769 (gray) 7.265 (white)	3.9	6.95	4.57 (25°C)
Odor	Odorless	Odorless	Odorless	Odorless
Water solubility (g/100g)	Insoluble	90 (20°C)	Insoluble	30 (20°C)
Vapor pressure (mmHg)	8×10^{-3} (1,224°C)	25 (427.9°C)	~0	NA

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.

EXPOSURE

Production Processes

Tin comprises ~0.0006% of the earth's crust; the major producers of tin include Indonesia, China, and Peru. Although nine minerals contain tin, the only commercially important tin ore is cassiterite (~75% tin as SnO_2).[6] Tin ores contain a variety of metal contaminants including antimony, arsenic, bismuth, cadmium, cobalt, copper, iron, lead, nickel, sulfur, tungsten, and zinc. Prior to smelting, gravity or magnetic separation processes concentrate tin. The smelting process is the primary source of exposure to dusts and fumes of tin oxide.[1] Imports or recovery of tin from scrap materials are the main sources of tin consumed in the United States.

Uses

In tin smelters, feed mixing during sintering and reduction in blast furnaces convert ores to an impure alloy of tin and lead; dry refining prior to electrolytic separation yields pure tin as a cathode deposit. Workers at these smelters are potentially exposed to a variety of substances including antimony, arsenic, cadmium, lead, ^{210}polonium, and sulfur dioxide. Mortality studies at these facilities have not detected a significant increase in lung cancer in the workers.[7] The principal use of tin is in the production of containers for food and aerosols. Stannous and stannate compounds are used for electroplating. Tin is a component of solder (lead/tin alloy) and coating for copper wire. Tin alloys include brass, pewter (91% tin, 7% antimony, 2% copper), bronze (copper/tin), dental material (silver/tin/mercury), aircraft components (titanium/tin), and nuclear reactor parts (zirconium/tin).[6] Inorganic tin compounds provide strength to glass and glass coatings, act as catalysts and stabilizers during PVC production, and are involved in the formulation of perfumes, soaps, fingernail polish, and colors. Stannous fluoride, stannous pyrophosphate, stannous hexafluorozirconate, and pentafluorostannite are toothpaste additives for the prevention of cavities. Tin oxide is a small portion of the sintered alloy, indium-tin oxide, used for transparent conductive films on liquid-crystal and plasma displays. A tin plate is a small gauge, steel strip, or sheet coated with pure tin that lines ~80 billion food cans yearly; most of these containers now have lacquered linings.[8]

Sources

For the general population, the diet accounts for >99% of tin exposure with the remainder resulting from the inhalation of tin in ambient air based on analyses of balance studies from the 1950s and 1960s.[9,10]

Air

Anthropogenic and natural sources contribute about equal amounts of tin to the atmosphere. Release of tin into air results from natural (e.g., dust from windstorms, human activities) and anthropogenic (e.g., smelting, refining, coal-burning power plants) sources. Fly ash from coal-burning power plants contains 7–19 μg Sn/g.[11] The concentration of tin in ambient air is usually

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low. Elemental tin is infrequently detected in ambient air, except near-point sources. Tin appears in the atmosphere in the form of particulates with the tin concentration generally <0.1 μg Sn/m^3 based on data collected before 1970.[6, 12]

Soil

The average concentration of tin in the earth's crust is about 2–3 ppm.[6] Most of the deposition of tin occurs in landfills and, to a lesser extent, in sewage sludge and fly ash. The mean tin concentration in US soil is ~0.9 mg/kg soil with a range up to 200 mg/kg in areas without tin deposits and up to 1,000 mg/kg in areas with large tin deposits.[13]

Water

Releases of inorganic tin into water result from industrial production; natural waters contain only trace amounts of tin. The concentration of tin in seawater was 0.2–3 μg/L; the mean tin concentration in surface water in Maine was 0.038 μg/L.[14]

Diet

Food is the primary source of tin exposure secondary to the use of tin-lined food containers; the amount of tin consumed daily depends on the portions of fresh and canned foods in the diet. Estimates of the daily intake of tin range from 1 mg (diets consisting mainly of fresh meats, vegetables, and cereals) to 38 mg (diets with high proportion of canned foods) in the older medical literature using different analytical and study methods.[9,15] The estimated daily tin intake in the United States during the 1980s was ~4 mg.[16] Later estimates of daily tin intake were up to an order of magnitude lower depending on the use of tin containers. The estimated mean daily Sn intake based on analysis of a market basket representative of the Northern Italian diet was 1.57 mg with a range of 0.01–4.44 mg.[17] Using duplicate diet samples over 24 hours, the median daily tin intake in 95 Japanese adults was 5.6 μg with a 75% of 15.3 μg and a maximum of 2,291 μg as measured by ICP/MS.[18] In a Japanese study of 296 preschool children aged 3–6 years, the median daily dietary intake of tin was 4.2 μg with a range of 0.4–>3 μg depending primarily on the amount of canned foods in the diet.[19] Although the median daily tin intake differed significantly between canned food consumers (GM = 30.2 μg) and non-consumers (GM = 3.3 μg), urinary tin concentrations between the two groups were similar as measured by inductively coupled plasma/mass spectrometry (ICP/MS). The mean estimated daily tin intake in the French diet was 2.32 mg as measured by duplicate diet samples and ICP/MS.[20]

Tin concentrations in fresh cereals, meats, and vegetables typically range from 0.1–1.0 mg/kg (ppm) depending on a variety of factors including pH, valence, solubility, adsorption to surrounding material, and the presence of complexation; however, tin concentrations up to 500 mg/kg may occur in food stored in unlacquered tin containers.[13,21] In a market basket study representative of the Northern Italian diet, cereals and tubers accounted for an estimated 97% of the daily tin exposure.[17] Tin concentrations of fruits and fruit juices, nuts, dairy products, fish, poultry, eggs, and beverages not packaged in metal cans are generally <2 mg/kg.[6] The inner surface of most cans now contains a protective lacquer coating rather than tin to reduce the corrosive effects of acidic foods. Dissolution of unlacquered tin by acidic foods can increase tin concentrations to by >200 mg/kg.[22] Foods from cans with lacquered inner coatings usually contain tin concentrations of <12–25 mg/kg.[9]

ENVIRONMENTAL FATE

Air

The deposition of metallic tin occurs by gravitational settling; washout mechanisms are relatively unimportant because the vapor pressure of tin is negligible. Theoretically, airborne particles of tin may travel long distances before deposition depending on a variety of physical and environmental factors including the type of emitting source, size, density, degradation during transport, adsorption processes, and meteorological conditions.[23]

Soil

Tin is relatively immobile in the soil as a result of adsorption to soils.

Water

Tin exists in water as stannous (Sn^{2+}) and stannic (Sn^{4+}) ions. Elemental tin is nondegradable, but this metal undergoes ligand exchange, oxidation–reduction, and precipitation reactions. In anaerobic (reducing) environments, tin occurs primarily as stannous tin; however, Sn^{4+} is more stable in the environment than Sn^{2+}. The presence of alkaline conditions encourages the formation of SnS and $Sn(OH)_2$. Methylation of inorganic tin by microorganisms can transform tin into organometallic forms,[24] but the biomethylation of inorganic tin

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probably accounts only for small amounts of organic tin in the environment compared with anthropogenic sources.[25] In extremely anaerobic conditions, microalgae can convert inorganic tin to stannane (SnH_4).[26] *In vitro* studies suggest inorganic tin may bioconcentrate up to several thousand folds in invertebrates and fish.[6]

DOSE EFFECT

Adverse gastrointestinal effects may occur following ingestion of inorganic tin at concentrations of ≥700 ppm; case reports and volunteer studies indicate elemental tin concentrations of 1,400 mg Sn/L produce acute gastrointestinal symptoms.[27] Typically, tin concentrations of <700 mg Sn/L do not produce gastrointestinal effects depending on the amount of liquid ingested; however, the ingestion of canned tomato juice containing 477 mg Sn/L was associated with 113 cases of gastroenteritis.[28] Other studies did not detect adverse gastrointestinal effects at tin concentrations exceeding 700 ppm.[8] There is little evidence that the consumption of foods containing inorganic tin up to 200 ppm causes clinically significant acute adverse gastrointestinal effects.[8]

TOXICOKINETICS

Absorption

Although human data are limited, experimental studies suggest the lungs and gastrointestinal tract absorb inorganic tin poorly. In a balance study of eight volunteers receiving diets with low (0.11 mg/day) and high (~50 mg stannous chloride) tin content, the average tin absorption was 50% and 3%, respectively.[29] Animal studies indicate ~1–5% of an inorganic tin dose is absorbed by the gastrointestinal tract.[30,31]

Distribution

Animal tests indicate inorganic tin is distributed into all tissues except the testis.[32] The highest tin concentrations appear in the liver, kidney, and bone with lesser amounts in other tissues. The clearance of tin from bone is slower than other compartments; therefore, bone is the main site of deposition of tin.[1,33] A majority (i.e., ~80%) of tin in the blood exists in the erythrocytes.[31]

Elimination

The results of animal and human studies on the elimination of tin from the body are somewhat inconsistent, primarily as a result of methodological differences. Excretion of tin absorbed into the body probably occurs primarily by the kidney with smaller amounts of tin excreted in the bile;[31,34] the tin concentration is substantially higher in urine than bile. Clearance of tin from the bone displays the longest half-life with a biological half-life of ~400 days.[30]

Maternal–Fetal Kinetics

Inorganic tin does not easily cross the placenta. The very low inorganic tin concentrations in the fetus during chronic feeding studies in rodents and the lack of developmental effects suggest the placenta restricts the passage of inorganic tin into the fetus.[31]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Although tin is an essential trace element in animals,[35] the specific biological actions of tin are unknown. In rodents, tin binds to 5-aminolevulinate hydrolyase (ALA dehydratase) and thereby inhibits ALA dehydratase activity.[36] The simultaneous injection of selenium prevents the binding of tin to ALA dehydratase.

CLINICAL RESPONSE

Acute Toxicity

Inorganic tin is relatively nontoxic; however, inorganic tin compounds may produce upper respiratory tract or gastrointestinal irritation. Although the corrosive properties of inorganic tin salts produce gastrointestinal disturbances in high doses, poor oral absorption limits systemic toxicity. Nausea, vomiting, diarrhea, and abdominal pain develop soon after the ingestion of food or drink contaminated with tin.[37]

Environmental Exposure

Environmental exposure to tin is not typically associated with toxicity in the general population as a result of relatively low elemental toxicity and limited exposure. Sensitization to inorganic tin is rare. In a series of 2,206 patients skin tested at a Danish dermatology clinic, five patients (four women, one man) tested positive to 1% $SnCl_2$ patch test.[38] This reaction was nonirritant.

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Occupational Exposure

Exposure to tin oxide fumes may cause metal-fume fever manifested by vomiting, myalgias, bronchitis, and pulmonary infiltrates. Workers in glass bottle factories where the combination of stannic chloride and water produces HCl commonly complain of cough, dyspnea, chest pain, and wheezing;[39] however, pulmonary function test results usually remain normal. Inhalation of dust or fumes from stannic oxide for 15–20 years produces a benign pneumoconiosis known as stannosis;[40] case series indicate these workers develop dense radiopacities on chest X-rays without evidence of pulmonary dysfunction despite the gross radiological abnormalities.[41] Massive fibrosis following exposure to tin oxide dust typically does not occur in workers with stannosis.[42] A case report associated the development of interstitial pneumonia with chronic exposure to indium-tin oxide dusts, but tin was a relatively small (10%) component of this oxide.[43,44] Inorganic tin is a rare cause of allergic dermatitis in the occupational setting.[45,46] A case report described the development of chest tightness, dry cough, and wheezing in a chronic smoker 36 hours after her flooded office was sprayed with a fungicide containing tributyltin oxide.[47] During a challenge test with the carpet solution 7 months after exposure, she had a 19% fall in FEV_1 1 hour after exposure. The authors opined that tributyltin oxide was the likely etiology of the patient's respiratory symptoms.

Reproductive Abnormalities

Inorganic tin is not usually associated with abnormalities in fetal development. In a study of lactating mothers of premature and full-term infants, the tin concentrations in successive milk samples did not display any pattern indicative of biological regulation and potential human requirements.[48]

Carcinogenesis

Neither the IARC nor the US NTP lists tin or tin compounds as suspected carcinogens. There are few epidemiological data on the carcinogenicity of these compounds. Most chronic animal studies on inorganic tin compounds are negative (e.g., stannous chloride) including organotin compounds (e.g., tributyltin).[6,49]

DIAGNOSTIC TESTING

SI Conversion Units

1 μg/L = 0.008424 μmol/L
1 μmol = 118.7 μg/L

Analytical Methods

Techniques for analyzing tin concentrations in biological or environmental samples usually involve the determination of tin as a total metal rather than a specific tin species.[6] Older methods involved flame/atomic absorption spectrometry; however, low sensitivity and loss of tin oxide during combustion limit the usefulness of these techniques. Newer techniques improve the sensitivity and reduce the loss of tin oxide with combustion. The most common and simplest method for the detection of tin is flame atomic absorption spectrometry, but graphite furnace/atomic absorption spectrometry, inductively coupled plasma/mass spectrometry, and inductively coupled argon plasma/atomic emission spectrometry are more sensitive (<0.1–1 μg Sn/L) for quantitation of tin in biological and environmental samples.[50,51]

Biomarkers

Based on recent mass spectrometry studies and neutron activation analysis, the average whole blood tin concentration in the general population is low (few μg/L), depending on tin exposure in the diet. The mean whole blood total tin concentration in a master mixture of equal aliquots from 2,500 healthy UK residents during the early 1970s was ~5 ± 2 μg/L (ppm, wet weight) as measured by spark source/mass spectrometry with thermal ionization.[33] In whole blood samples from 14 Italian adults, the tin concentration was below the limit of detection (2 μg/L) in all samples as measured by radiochemical activation analysis during the late 1970s,[52] whereas the median tin concentration in a study of 99 healthy French children was 0.96 μg/L (95% CI: 0.41–4.03 μg/L).[53] The corresponding median plasma tin concentration in the latter study was 1.8 μg/L (95% CI: <1.0–4.7 μg/L). About 80% of whole blood tin resides in the erythrocytes; therefore, plasma tin concentrations are extremely low. Twenty-four-hour urine tin concentrations in the general population range from ~1–20 μg/L.[54] Collection of the urine for tin confirms excessive exposure to tin.

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Abnormalities

In symptomatic workers from glass bottle factories exposed to stannic chloride aerosolized HCl, pulmonary function tests usually remain normal.[39] The high atomic weight of tin produces prominent radiopaque lesions on chest X-rays, but little tissue reaction (fibrosis) occurs as a result of the inhalation of tin.[55]

HEALTH SURVEILLANCE

Table 31.2 lists regulatory levels and guidelines for elemental tin and inorganic tin compounds. The ATSDR determined a intermediate-duration minimal risk level of 0.3 mg/kg/day based on a NOAEL of 32 mg Sn/kg/day as stannous chloride for hematological effects (reduced hemoglobin content and cell volume) in a 13-week study of rats.[56] The ACGIH derived an 8-hour TLV–TWA of 2 mg/m^3 for elemental tin and tin oxides to minimize the risk of mild pneumoconiosis (i.e., stannosis).

TREATMENT

The treatment of elemental tin and inorganic tin toxicity is supportive. Decontamination measures are usually unnecessary. Exposure usually results in gastrointestinal tract irritation or mild upper respiratory tract irritation that responds to removal from exposure and symptomatic care. Systemic toxicity is rare; the presence of serious abnormalities in vital signs or persistent clinical symptoms suggests exposure to another etiology.

TABLE 31.2. Regulatory levels and guidelines for elemental and inorganic tin exposure.

Exposure Limit	Value
OSHA	
PEL-TWA (8-hour)	
Inorganic compounds[b]	2.0 mg Sn/m^3
Tin oxide[d]	
(total dust)	15 mg Sn/m^3
(respirable fraction)	5.0 mg Sn/m^3
NIOSH	
REL-TWA (10-hour)	
Inorganic compounds[b]	2.0 mg Sn/m^3
Stannous oxide	2.0 mg Sn/m^3
IDLH	100 mg Sn/m^3
ACGIH	
TLV–TWA (8-hour)	
Elemental tin	2.0 mg/m^3
Tin oxides and inorganic compounds[a,c]	2.0 mg/m^3
US EPA	
Stannous chloride	
Direct food substance, GRAS	<0.0015%
Food additive	<20 ppm
FAO/WHO	
Tolerable weekly intake	14 mg/kg body weight
ATSDR	
MRL (intermediate-duration oral)	0.3 mg/kg/day (as stannous chloride)

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; FAO = Food and Agriculture Organization; GRAS = generally recognized as safe; IDLH = immediately dangerous to life and health; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency; WHO = World Health Organization.
[a] Except hydride and indium tin oxide; [b] Except tin oxides. [c] inhalable particulate matter [d] maritime industry only

ORGANIC TIN

HISTORY

Although the first organotin compound was synthesized by Lowig in 1852, the first commercial application did not occur until the issuing of patents for the use of organotin compounds as stabilizers of transformer oils (1932) and vinyl plastic (1940). The commercial use of organotin compounds has expanded rapidly over the last 40 years as biocidal agents, catalysts, and heat stabilizers for polyvinyl chloride polymers.[57]

In France, a diethyltin preparation (Stalinon) was sold as a treatment for acne, anthrax, furunculosis, and osteomyelitis; this product was withdrawn from the French market in 1960 following the outbreak of a fatal neurological disease associated with the Stalinon use in 1954. Of the ~1,000 people ingesting this drug during the outbreak, 217 developed the illness, and 102 died. Triethyltin iodide, which is 10 times more toxic than diethyltin, contaminated up to 10% of the tin present in

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Stalinon.[3] The most common symptom was headache that appeared after a 4-day latent period. Vertigo, urinary retention, vomiting, photophobia, and abdominal pain were also common symptoms. Paresthesias, headaches, and visual abnormalities persisted for years in some patients; complete recovery occurred in only ~10% of the severe cases.[58]

Organic tin compounds (e.g., tributyltin, triphenyltin) are endocrine disruptors in marine animals, particularly mollusks.[59] In the 1970s, the use of organotin (i.e., tributyltin) in antifouling paints was associated with the decline of coastal marine mollusks as a result of the phenomenon of the superimposition of male sexual characteristics (e.g., penis) on female gastropods (i.e., imposex). In 2008, the International Maritime Organization banned the application of TBT-based points.

PHYSIOCHEMICAL PROPERTIES

Organic tin compounds form covalent bonds between at least one of three carbon atoms and a tin atom; the number of covalent carbon-tin bonds (mono, di, tri, tetra) characterizes organotin compounds. Stannic compounds are covalent; the ionic form of Sn^{4+} does not exist naturally. Almost all commercially important organotin compounds possess a tetravalent structure. For industrial compounds, the most important organic constituents are methyl, butyl, octyl, and phenyl groups, whereas the most important anions are carboxylate, chloride, fluoride, hydroxide, oxide, and thiolate.[60] Table 31.3 lists some physiochemical properties of methyl-, butyl-, dimethyl-, and dibutyltin compounds.

Tributyltin compounds are organic derivatives of Sn^{4+} that possess different chemical properties than inorganic tin compounds depending on the chemical group covalently bonded to Sn. Tributyltin compounds are lipophilic and possess relatively low water solubility. Tributyltin oxide is a mild oxidizing agent with an octanol/water partition coefficient (log K_{ow}) of 3.19–3.84.[61] The vapor pressure of tributyltin compounds is very low; little loss of tributyltin oxide occurs from solution over 60 days, even though 20% of the water evaporates.[62] Triphenyltin compounds (e.g., hydroxide, acetate, chloride) are triphenyl derivatives of tetravalent tin. At ambient temperature in the neutral pH range (3–8), triphenyltin acetate and triphenyltin chloride hydrolyze to triphenyl hydroxide in a few minutes.[63] Triphenyl compounds are generally lipophilic, and their water solubility is low (few mg/L).[63] Table 31.4 lists the identifying information and physical properties of trimethyltin and similar covalent compounds. Tetrabutyltin (tetrabutylstannane, CAS RN: 1461-25-2) is an odorless to slightly yellow oily liquid that is insoluble in water.

EXPOSURE

Production Processes

The manufacturing of organotin compounds involves chemical processes. Comproportionation reactions (i.e., two differently charged ions of the same element reacting to form two equally charged ions) between tin tetrachloride and organotin compounds produce mono-, di-, and tri-organotin derivatives. Processes using Grignard reagent or organic-aluminum compounds form tetraalkyl and tetraaryltin compounds.

Uses

The major uses of organotin compounds include PVC heat stabilizers, biocides, catalysts, agrochemicals,

TABLE 31.3. Identifying information and physical properties of monomethyl-, dimethyl-, monobutyl-, and dibutyltin compounds. (Based on Snoeij et al.).[60]

Physical Characteristic	Methyltin Trichloride	Dimethyltin Dichloride	Butyltin Trichloride	Dibutyltin Dichloride
Formula	CH_3Cl_3Sn	$C_2H_6Cl_2Sn$	$C_4H_9Cl_3Sn$	$C_8H_{18}Cl_2Sn$
Synonym	Trichloromethylstannane	Dichlorodimethylstannane	Butyltrichlorostannane	Dibutyltin chloride
CAS RN	993-16-8	753-73-1	1118-46-3	683-18-1
Molecular weight (g/mol)	240.08	219.67	282.17	303.85
Color	Colorless	Colorless	Colorless	White
Physical state	Solid	Solid	Liquid	Solid
Melting point (°C)	43	90	−63	43
Density (g/mL)	NA	NA	1.71 (25°C)	1.36 (24°C)
Odor	Odorless	NA	NA	NA
Water solubility	Soluble in cold water	Soluble in cold water	Miscible in water	Insoluble in cold water

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.

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TABLE 31.4. Some physiochemical properties of selected organic tin compounds. (Based on International Programme on Chemical Safety).[61]

	Trimethyltin Chloride	Tributyl Chloride	Triethyltin Bromide	Triphenyltin Hydroxide	Triphenyltin Chloride
Formula	C_3H_9ClSn	$C_{12}H_{27}ClSn$	$C_6H_{15}BrSn$	$C_{18}H_{16}OSn$	$C_{18}H_{15}ClSn$
Synonym	Chlorotrimethyl stannane	Chlorotributyl stannane	Bromotriethyl stannane	Hydroxytriphenyl stannane	Triphenylchloro stannane
CAS RN	753-73-1	1461-22-9	2767-54-6	76-87-9	639-58-7
Molecular weight (g/mol)	199.26	325.49	285.79	367.03	385.48
Color	Colorless	Colorless	Colorless	White	White
Physical state	Solid	Liquid	Liquid	Solid	Solid
Melting point (°C)	37.5	NA	−13.5	119	103.5
Density (g/mL, 20°C)	NA	1.20	1.630	1.54	NA
Odor	NA	NA	NA	Odorless	NA
Water solubility	Miscible with water	Insoluble in cold water	Very slightly soluble in cold water	1.2 mg/L (20°C)	40 mg/L (20°C)

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.

and glass coatings.[6] Mono- and di-substituted organotin compounds are stabilizers in plastics, whereas tri-substituted organotin compounds are primarily biocides. The concentration of organotin compounds in PVC is ~1–1.5%.[64] Octyl- and methyltin compounds are constituents of PVC in food packaging. Alkyltin chloride inhibits the dissociation of hydrochloric acid from polyvinyl chloride. When bound to the plastic, the organotin compounds do not produce toxicity. These compounds are also added to polyurethane foams and silicone to reduce odor and strengthen their structure. Tributyltin (TBT) and triphenyltin (TPT) compounds have been used as marine anti-fouling compounds, molluscicidal agents, wood preservatives, disinfectants, slimicides, and biocidal agents since the 1960s, but these uses have been gradually banned. TPT is an antifungal agent for rice, potatoes, sugar beets, hops, and celery.[65] Initially, many countries banned the use of TBT and TPT antifouling paints for boats of <25 m in size to reduce the effects of TBT on the aquatic ecosystem, particularly shellfish. The content of TBT is restricted to reduce the leaching of TBT from paint to <4–5 μg TBT/cm^2/day.[66] Tetra-*n*-butyltin has been used as a gasoline additive.

Sources

Organotin compounds are not typically part of the natural environment. Anthropogenic sources release organotin compounds into the environment; however, biomethylation of inorganic tin to methyltin compounds can occur naturally or anthropogenically as stabilizers in PVC products.[67] Butyltin compounds exist only as a result of anthropogenic sources; however, marine sources in the diet provide the main exposure to butyltin compounds based on the presence of these compounds in postmortem specimens of human livers.[68] The presence of tributyltin compounds in antifouling coatings is a significant source of these compounds in marine and freshwater environments. The only source of octyltin compounds is the use of these compounds as stabilizers in PVC products. These latter compounds do not usually appear in water or sediments. The use of antifouling paints is the major source of tributyltin in the coastal environment, whereas triphenyltin compounds enter the environment primarily from use as pesticides.

Air

Although little data on the volatilization of organotin compounds from water exist, *in vitro* testing of tributyltin in water indicates that this organotin does not partition into the air.[62]

Soil

The adsorption of trisubstituted organotin compounds to suspended particulate matter, low water solubility, and poor mobility result in the accumulation of these compounds and their degradation products in sediment. High concentrations of TBT (e.g., up to 14 μg/g sediment) may occur in the bottom sediment of ship channels, marinas, harbors, or ports.[69] In a study of sediments from Goteborg Harbor in Sweden, the TBT and TPT concentrations (dry weight) ranged from 17–366 ng/g and 1.5–71 ng/g, respectively.[70] Sediments

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under coastal waters may contain complex degraded organotin compounds (e.g., di-*n*-butyloctyltin chloride, di-*n*-butyl(2-methylhexyl)tin chloride).[71]

Water

Commercial applications (e.g., agriculture, antifouling coatings on ships, stabilizers in polyvinyl chloride plastic) account for the release of organic tin compounds into the water. In a Canadian study on organotin compounds in drinking water from houses with recently installed (i.e., <6 months) PVC pipes, the maximum organotin concentrations in water from these houses were 291 ng Sn/L for methyltin, 49.1 ng Sn/L for dimethyltin, 28.5 ng Sn/L for butyltin, and 52.3 ng Sn/L for dibutyltin.[72] However, the water in most of these houses contained no detectable organotin compounds.

In general, the concentration of TBT ranges from 1–10 ng/L in coastal waters and estuaries with higher concentrations (i.e., up to 1.3 μg/L) occurring in marinas and major ports.[61] Maximum concentration of TBT in marine water rarely exceeds 100 ng/L except in locally contaminated areas (e.g., newly industrialized countries).[73] Concentrations of tributyltin (TBT) up to 1.58 μg/L in seawater and up to 7.1 μg/L may occur in areas near pleasure-boating activities.[66] The actual TBT concentration is usually less and depends on the use of antifouling paints, the degree of tidal flushing, and the turbidity of the water. The TBT concentrations in freshwater marinas demonstrate seasonal variation with the highest concentrations occurring in late spring and the lowest in winter.[74] Sampling techniques may produce abnormally high organic tin concentrations, particularly if the samples contain paint particles or if the sample consists primarily of the surface microlayer.[61]

Diet

Exposure to organotin compounds occurs primarily following the ingestion of organotin-containing seafood and, to a lesser extent, contact with consumer products that contain organotin compounds.[6] The estimated daily intakes of tributyltin (TBT) and triphenyltin (TPT) compounds from the Japanese diet during the early 1990s as measured by the duplicate portion method were 2.2–4.7 μg and 0.7 μg, respectively, whereas the market basket method results were 6.7–6.9 μg and 1.3–5.4 μg, respectively.[75] In a study of organotin intake from fish consumption in Finland, the estimated average daily intake of organotin compounds (dibutyltin, tributyltin, triphenyltin, dioctyltin) was 3.2 ng/kg bodyweight.[76] Domestic wild fish (e.g., herring, pike, perch) accounted for 61% of the total organotin intake compared with 35% for imported fish (e.g., salmon, rainbow trout, tuna, herring, shrimp) and 4% for farmed fish (e.g., rainbow trout).

Butyltin and phenyltin accumulate in the marine food chain, resulting in elevated tin concentrations in marine organisms (e.g., crabs, fish, oysters). The concentration of butyltin compounds is usually low (ng/g range).[77] The highest concentrations (i.e., 100–1,500 ng/g) of butyltin compounds in marine food occur in cultured fish and molluscs, particularly in Asia.[78] Butyltin compounds can accumulate in the liver and kidney of higher trophic animals including marine predators (dolphins, sharks, tuna). The concentration of total butyltin compounds ranged up to 980 ng/g wet weight in samples collected from deepwater fish near Japan,[79] up to 2,610 ng/g wet weight in river otters near Puget Sound in Washington,[80] and up to 2,200 ng/g wet weight liver in dolphin caught off the coast of Italy.[81] Accumulation of these compounds is about an order of magnitude higher in liver and kidney than subcutaneous fat.

Triphenyltin and tributyltin compounds are found mostly in seafood, particularly in marine fish. The presence of TPT in coastal and pelagic (open-ocean) fish from Tokyo fish markets suggests limited biomagnification of these compounds may occur in the food chain. Biological monitoring of Japanese coastal fish indicates decreasing concentrations of organotin compounds as a result of the restrictions on the use of these compounds in marine paint. In 1989, ~60% of the coastal fish contained triphenyltin at concentrations ranging up to 2.6 μg/g wet weight in muscle, whereas 30% of the samples were positive in 1995 with a range up to 0.25 μg/g wet weight in muscle.[63] The mean TPT concentration in pelagic fish was 0.048 μg/g, and freshwater fish were relatively uncontaminated.

ENVIRONMENTAL FATE

Most organotin compounds are sparingly soluble in water, resulting in the partition of these compounds into soils and sediments. The low vapor pressures, low water solubilities, and high affinities of soil and organic sediments significantly limit the mobility of commercial organotin compounds in environmental media.[82] Progressive elimination of organic groups from the tin cations results in the degradation of organotin compounds in the environment depending on temperature, light, and pH. Anaerobic environments may retain hydrophobic organotin compounds for

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years in sediment.[67] Photodecomposition by ultraviolet light is the most important degradation process in air, whereas biological processes are more important in soil and water.[83] Degradation of triphenyltin and tributyltin occurs by the cleavage of the tin–carbon bond through biological, chemical, and UV radiation, resulting in sequential dephenylation and debutylation, respectively. Biodegradation of the organotin compounds depends on environmental conditions (e.g., temperature, pH, tin, oxygen concentrations) and the type of microflora. Under favorable conditions, TBT degrades to DBT, then to MBT, and ultimately to inorganic tin.[84] Elevated temperatures, aerobic conditions, and intense sunlight enhance this degradation;[63] however, hydrolysis and photolysis of organotin compounds are limited under normal environmental conditions.[61]

Air

There are few data on the concentrations of organotin compounds in the air. Low vapor pressures and rapid photodegradation significantly limit the release of organotin compounds into the air.[67]

Soil

In general, the measured half-lives of dialkyltins in soils are ~120–150 days in laboratory tests, whereas methyltins and butyltins are more persistent in forest soils with half-lives ranging from 6 months–15 years.[64] Persistence of triphenyltin acetate and triphenyltin hydroxide depends on soil type and pH. The uptake of triphenyltin hydroxide by plants is extremely low because of the strong adherence of this compound to soil.[63] The half-life of this compound in sandy loam soils was 1–3 months with saturation of the soil increasing the half-life to 126 days.[85] Microorganisms degrade triphenyltin compounds into inorganic tin and carbon dioxide.

Degradation of organotin compounds in the soil is much slower (i.e., several years) in sediment than in water. In marine sediment, tributyltin occurs primarily in the upper layers, where the estimated half-life is ~2 years.[86] Based on a first-order multi-step kinetic model of the sequential degradation of tributyltin, the estimated half-lives of dibutyltin and butyltin are 1.9 and 1.1 years, respectively. These degradation products are typically present in the lower layers of marine sediment. The slow release of TBT into the aquatic system results in exposure of gastropods and filter-feeding organisms to substantial amounts of TBT.

Water

The low water solubility and the lipophilic nature of TBT promote TBT adsorption onto particles (sediment) depending on environmental conditions (quantity and physical characteristics of particles, temperature, presence of dissolved organic matter, salinity). The affinity for adsorption of organobutyltin compounds increases with increasing tin substitutions (i.e., TBT > DBT > MBT).[87] Bioavailability of organotin compounds depends primarily on pH and the presence of humic acids/dissolved organic carbon; the presence of dissolved organic carbon decreases organotin bioavailability, whereas neutral or slightly alkaline pH enhances bioavailability.

The persistence of organotin compounds depends on the interaction of several processes including fast and reversible adsorption/desorption, slow anaerobic biotic and abiotic degradation, and moderate to fast aerobic biotic degradation. The fate of TBT usually results from degradation rather than desorption.[88] In general, the half-life of tributyltin in water is several days to weeks, but tributyltin compounds can persist in sediments for several years depending on soil conditions.[61] Tributyltin has a relatively short half-life in water (~6 days under optimum conditions), but the half-life increases to almost 2 years in anaerobic environments like sediment.[89] *In vitro* studies indicate TBT degrades faster ($t_{1/2}$ = 28 days) in organic-rich sediment than sandy organic-poor sediment ($t_{1/2}$ = 78 days).[87] TBT undergoes photolysis with a fairly long half-life of ~3 months in sedentary waters, but the role of photodegradation in the removal of tributyltin is limited by the poor penetration of UV light into the water.[62] Consequently, the estimated half-life of TBT in surface (river) water was substantially less (3–13 days).[90] Direct photolysis results in the sequential loss of butyl groups; inorganic tin is the residual product. There is no evidence of biomagnification (i.e., uptake from the food chain) of tributyltin in marine ecosystems, but bioaccumulation (i.e., uptake from water, sediment phase, and food chain) may occur from the ingestion of organisms with high tissue concentrations of TBT.[91]

The hydrolysis of TPT compounds in water produces triphenyltin hydroxide and various hydrated oxides. The chloride in seawater reacts with hydrated cations to form the covalent organotin chloride that is less water-soluble than TPT.[63]

Food Chain

As a result of the lipophilicity of TBT, the TBT concentrations in organisms living in water containing TBT

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are greater than TBT concentrations in the surrounding water. Laboratory studies indicate the bioconcentration of TBT in mollusks and fish from surrounding water is up to 7,000 times.[92] Bioaccumulation of TBT in bivalves (i.e., up to 5 ppm) is especially high because of their limited metabolism of TBT;[61] the bioaccumulation is greater in cetaceans than pinnipeds.[93] Fish accumulate substantially less TBT than marine bivalves because of their greater ability to degrade TBT. Recent studies indicate TBT accumulation is greater in the liver and kidney than subcutaneous fat, perhaps as a result of the binding of TBT to proteins in the liver and kidney.[94] Evidence for the transfer (i.e., biomagnification) of TBT through the food chain is limited with biomagnification substantially less important than the bioconcentration of organotin from the water phase.[66,88] The biomagnification factor in harbor porpoises in Turkish coastal waters of the Black Sea was 0.8; this value is comparable to pinnipeds and lower than cetaceans.[95] The residues of organotin compounds in these studies are substantially higher in fish from coastal waters and developed countries than open-sea fish, particularly near developing countries.

Studies of TPT compounds (triphenyltin chloride) in experimental conditions revealed the bioconcentration factor (BCF) of daphnids did not exceed 300; the BCF in fish ranged from 257–4,100.[96] In these studies, the accumulation of organotin compounds did not correlate with fat content; in marine fish, the BCF was higher for TBT than TPT.

The biological half-lives of TPT in short-necked clams were ~30 days compared with 139 days for mussels from a busy Japanese port.[97] The biological half-lives of TPT and TBT compounds in a benthic predator (*Buccinum undatum*) that feeds predominately on live benthic bivalve molluscs and dead animals near the Netherlands were ~1 year with Sn concentrations ranging up to 625 ng/g dry weight and 40 ng/g dry weight, respectively.[98] The order of tissue accumulation for butyltin compounds was dibutyltin > monobutyltin > tributyltin. Studies of organotin compounds in freshwater demonstrated benthic organisms accumulate TPT from the sediment; at higher trophic levels, the net bioaccumulation of TPT compounds exceeds that of TBT compounds.[99] The accumulation of TPT compounds at higher trophic levels occurred via mechanisms different from traditional lipophilic compounds because TPT concentrations were greater in the liver and kidney than subcutaneous fat. Although biomagnification of TBT (tributyltin) compounds probably does not occur, examination of organotin compounds in mussels (*Mytilus edulis*), common whelks (*B. undatum*), and sediment from marine waters near the Netherlands suggests some biomagnification of TPT (triphenyltin) compounds may occur.[100] The TPT concentrations in whole-body homogenates of common whelks from the Eastern Scheldt of the Netherlands were 4–100 times higher than TBT concentrations.

DOSE EFFECT

In general, the toxicity is greater for trisubstituted organotin compounds than for monosubstituted and disubstituted organotin compounds. The toxicity of trialkyltin compounds decreases as the number of carbon atoms in the alkyl chain increases. TBT is toxic to microorganisms; susceptibility varies with different species. Algicidal tributyltin oxide (TBTO) concentrations also vary with species ranging from <1.5 to >1000 μg/L.[66] The estimated toxic dose in adults ingesting triethyltin iodide during the Stalinon epidemic in France was 70 mg triethyltin iodide over 8 days.[101] Subacute animal studies suggest Sn doses of 12–25 mg/kg for 30–90 days produce inflammation and hyperplasia of the bile duct with necrosis in the liver.[102]

TOXICOKINETICS

Absorption

Absorption is greater for organotin than inorganic tin compounds; organic tin compounds (e.g., dibutyltin, triphenyltin) are detectable in blood samples from the general population depending on exposure and individual kinetics of the specific compound.[103] Animal studies indicate the gastrointestinal tract absorbs triethyltin, trimethyltin, tributyltin, and dibutyltin well, but the absorption of triphenyltin depends on the species. Good absorption of triphenyltin occurs in rats and guinea pigs, but sheep and cows absorb this compound poorly.[1] Case reports suggest acute organotin intoxication can occur following the intentional ingestion of 60% triphenyltin acetate-containing molluscicide[104] and inhalation of vapor/dusts from triphenyltin acetate-containing fungicides.[105] Absorption of tributyltin compounds varies between 20–50% following ingestion compared with ~10% of a TBT dose applied to the skin.[66] Based on the limited data available on the dermal absorption of tin compounds, absorption of these compounds through the skin is not a major route of exposure.

Distribution

Limited diffusion of methyltin, butyltin, and octyltin occurs across the blood–brain barrier with relatively

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low concentrations in the brain.[64] In animals, the distribution of organic tin is similar to the distribution of inorganic tin.

Elimination

The liver transforms most organic tin compounds by dealkylation with inorganic tin being the residual compound. Analysis of urine samples from patients poisoned by dimethyltin-contaminated cooking oil suggests dimethyltin compounds may be methylated to trimethyltin compounds after absorption.[106] Renal excretion accounts for most tin eliminated by the body with smaller amounts of tin appearing in the bile;[31] however, the contribution of biliary excretion is relatively greater for organotin than inorganic tin compounds. The bile is the main excretory route for tributyltin and triphenyltin. The estimated biological half-life of TBT in mammals is ~23–30 days.[66,107]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Central Nervous System

Mechanism of Toxicity

The *lower* homologs of tetraalkyltin and trialkyltin compounds possess neurotoxic properties. The effects of tetraalkyltin compounds are similar to the effects of trialkyltin compounds because of the conversion of tetraalkyl tin compounds to trialkyltin compounds in the liver.[108] A molecular model for this neurotoxicity is not available. Like tri-organolead compounds, the main biochemical action of tri-organotin compounds is probably the inhibition of mitochondrial enzyme systems.[109]

Pathological Changes

Trimethyltin compounds produce necrosis of the hippocampus in both animals[110,111] and humans.[112] In rats treated with a single oral dose of 7 mg trimethyltin/kg, convulsions, irritability, hyperactivity, and impairment of spatial discrimination develop.[113] Histological studies of these rats reveal pathological changes in the limbic structures, particularly the pyramidal cells in CA1 and CA4. Localized neuronal damage occurs to a lesser extent in the pyriform cortex, the amygdaloid nucleus, brainstem, neocortex, spinal cord, retina, sensory neurons, and cochlea.[114,115] Exposure of rats to trimethyltin causes high-frequency hearing loss associated with cochlear damage.[116] Triethyltin compounds demonstrate less neurotoxicity than trimethyltin compounds. In contrast to the neuronal necrosis produced by trimethyltin in rats, exposure of rats to triethyltin causes cerebral edema and neuronal changes that often are reversible.[117]

Postmortem

The primary pathological features involve necrosis in the limbic system structures (e.g., amygdala) and cerebellar Purkinje's cells. Electron microscopy reveals many cytoplasmic lamellated inclusions (zebra bodies) along with vacuoles and granulo-membranous particles. The presence of zebra bodies reflects increased activity of lysosomes. Morphological changes also appear in the temporal cortex, basal ganglia, and pontine nuclei. The major nonneurological findings on the autopsies of patients dying after exposure to trimethyltin include tracheobronchitis, pneumonia, severe acute pulmonary edema, fatty degeneration of the liver, and shock kidney.[118]

The main pathological findings in a 48-year-old woman dying 6 days after the ingestion of TMT involved the nervous system including generalized chromatolysis of the neurons in the brain, spinal cord, and spinal ganglia.[119] Neuronal necrosis in the fascia dentata of the hippocampus and spinal ganglia probably resulted from TMT toxicity, whereas pre-terminal anoxic injury could not be excluded as a cause of recent necrosis in pyramidal cell layers (hippocampus, cerebral cortex, basal ganglia) and the Purkinje cell layer of the cerebellum. Electron microscopy demonstrated marked accumulation of lysosomal dense bodies and disorganization of the granular endoplasmic reticulum in the neurons, but no cytoplasmic zebra bodies were detected. In contrast to the localized neuronal alterations in the limbic system produced by TMT exposure, triethyltin exposure causes a diffuse edema of the myelin sheaths (i.e., intramyelinic edema) in the brain.[120]

Immune System

Various *in vitro* and rodent studies indicate dialkyl tin compounds[121] and tributyltin oxide[122] suppress cell-mediated immunity, but there are few data in humans to support the production of immunological abnormalities in humans following exposure to these organotin compounds. In animal studies, tributyltin and dibutyltin compounds produce less neurotoxic effects than trimethyltin or triethyltin compounds.[123] Studies in mammals indicate tributyltin oxide exposure produces adverse immune effects (leukopenia,[124] thymus-dependent immunity[125]). Dibutyl dichloride

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and tributyltin compounds are primary skin irritants that cause slightly delayed (1–2 hours) pruritic, erythematous skin lesions.[126]

CLINICAL RESPONSE

Acute Toxicity

Inhalation of tributyltin oxide may cause upper respiratory tract irritation. A case report attributed the development of asthma in a 52-year-old atopic patient with a 32-pack-year smoking history to exposure to a carpet deodorizer containing tributyltin oxide.[47] However, workers involved with the manufacture of dibutyl and tributyltin compounds have not demonstrated an excess incidence of respiratory abnormalities despite the presence of skin irritation.[126] A case report associated triphenyltin exposure with the development of nausea, vomiting, abdominal pain, general malaise, weakness, dizziness, and transient elevation of hepatic transaminases that resolved without sequelae.[127]

Tributyltin compounds are irritants of the skin and mucous membrane that may cause cutaneous lesions and irritation of the conjunctiva and nasal mucosa. Cutaneous burns develop within several hours *after* dermal contact with dibutyltin or tributyltin compounds (acetate, chlorides, laurate, oxides). The most prominent sign is inflammation of the hair follicles that progresses to minute pustules within 2 days. These lesions are more pruritic than painful. Both irritant effects and a contact dermatitis developed in painters applying formulations containing tributyltin oxide (TBTO) concentrations as small as 0.6% TBTO.[128] Recovery from these lesions is usually complete within 1–2 weeks. Triphenyltin hydroxide compounds present in pesticide formulations are moderately strong irritants, but these compounds do not produce strong hypersensitivity reactions based on patch testing of workers exposed to these compounds.[129]

Serious neurological abnormalities may occur after exposure to high doses of organotin compounds, particularly trimethyltin (TMT). Other organotin compounds (e.g., triethyltin (TET), triphenyltin (TPT)) are much less potent central nervous system toxins. Acute exposure to high TMT doses causes clinical signs of dysfunction of the limbic system and cerebellum along with hearing loss and mild sensory changes. Examples of limbic dysfunction include confabulation, retrograde and anterograde amnesia, aggressiveness, hyperphagia, and abnormal sexual behavior.[118] Additionally, short-term memory loss may develop 72 hours after TMT exposure that improves over the next 3 months.[130]

A 48-year-old woman developed tinnitus, lightheadedness, aggression, and episodes of unresponsiveness after the ingestion of an unknown amount of TMT; her clinical course progressed to multiorgan failure and death 6 days after ingestion.[119]

Environmental Exposure

Five family members developed mucous membrane irritation following the painting of the second story of their house with paint with a mildew control agent containing 25% bis(tributyltin) oxide.[131] Symptoms included headache, nausea, vomiting, sore throat, burning nose, watery eyes, and wheezing. On physical examination the day after painting, two children had wheezing; oxygen saturations by pulse oximetry and chest X-rays were all normal. Follow-up 5 days after the painting indicated all symptoms resolved without sequelae.

Occupational Exposure

Case reports associate neurological (headache, memory loss, poor balance, tinnitus, cerebellar dysfunction, leukoencephalopathy) and psychiatric (hallucinations, emotional volatility, temper tantrums, aggressive behavior, apathy) symptoms in workers following excessive exposure to dimethyltin (DMT) and trimethyltin (TMT). Clinical features of acute exposure to high TET doses include symptoms of increased intracranial pressure, generalized tonic-clonic seizures, and paralysis. In contrast to TET-induced effects from the Stalinon epidemic, trimethyltin exposure produces predominantly clinical signs of limbic system dysfunction (e.g., disorientation, confabulation, amnesia, aggressiveness, disturbances of sexual behavior), cerebellar signs (e.g., nystagmus, ataxia), hearing loss, and mild sensory disturbances. Mild exposure to TPT-containing agricultural fungicides produces nausea, vomiting, headache, vertigo, impaired vision, photophobia, weakness, paresthesias, convulsions, and transient loss of consciousness.[105]

Dimethyltin

Clinical features of DMT toxicity include aggressiveness, amnesia, ataxia, confabulation, disorientation, hearing loss, nystagmus, paresthesias, partial-complex/tonic-clonic seizures, and sexual dysfunction.[118] A 43-year-old tank cleaner developed disorientation, visual hallucinations, and agitation 3 days after cleaning a storage tank containing dimethyltin.[132] Within 2 days,

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he developed coma, respiratory failure, acute hepatorenal failure, and rhabdomyolysis. His urine contained dimethyl and trimethyltin. Ataxia, dysarthria, and retrograde amnesia persisted 19 months after dimethyltin exposure. Diffuse myalgias and partial-complex or grand mal seizures may complicate the clinical picture. Two chemists developed seizures while synthesizing dimethyltin chloride over 3 months; neither patient had a prior history of seizures; the seizures resolved after cessation of exposure.[133] Other symptoms during their intermittent exposure to dimethyltin chloride included memory impairment, poor vigilance, insomnia, anorexia, disorientation, and headache. The case report contained no airborne tin measurements or analyses of tin in biological specimens.

Trimethyltin

One day after cleaning a tank containing TMT for 4 days, a 43-year-old man complained of disorientation, hallucination, irritability, lightheadedness, and memory impairment.[134] He became comatose, requiring intubation within 3 days. Although he improved with intensive supportive care, memory impairment, moderate motor ataxia, disorientation, and difficulty speaking persisted 6 months later. Six chemical workers were exposed to variable amounts of vapor from a solution of 75% dimethyltin and 25% trimethyltin chloride during a maximum of nine 10-minute episodes. The normal vapor pressure of trimethyltin is substantially higher than that of dimethyltin.[112] After a latent period of 1–3 days, headache, tinnitus, deafness, memory loss, disorientation, psychosis, coma, and respiratory depression developed in the workers; one worker died. Neurological disabilities in the most severely affected workers persisted for at least 6 years including extrapyramidal hyperkinesias, memory impairment, and personality changes (e.g., aggressiveness). These workers did not have pulmonary sequelae. A case series of 22 chemical workers exposed to TMT chloride, DMT dichloride, and methyl chloride reported residual neurological and psychiatric symptoms (depression, irritability, marital difficulties, forgetfulness, loss of motivation, volatility) in four workers followed for ~3 years; three of these workers did not return to the workplace during the follow-up period.[135] The study did not correlate symptoms to urine tin concentration; no ambient air tin concentrations were measured.

Reproductive Abnormalities

Limited data are available on the developmental and reproductive effects of tin compounds. In experimental studies of rodents at doses of tributyltin oxide and tributyltin acetate that produce toxic effects in the mother, an increased incidence of fetal deaths and resorptions[136] occur along with an increase in the number of cleft palates and cervical ribs.[137] The relevance of these studies at tin concentrations currently present in the work environments or the general population is unclear because of the presence of maternal toxicity at these very large doses of tributyltin compounds. In a study of Wistar rats exposed to di-*n*-butyltin dichloride, the NOAEL for malformations was 1.7–5 mg/kg body weight, which was associated with substantial maternal toxicity.[138] This NOAEL was about 1/3 the value of the LD_{50} for this tin compound.

Carcinogenesis

Neither the IARC nor the US NTP lists organotin compounds as suspected carcinogens. Chronic feeding studies of rats using the organotin compounds, stannous octoate and sodium chlorostannate, did not demonstrate evidence of carcinogenicity.[49] An increased incidence of benign tumors at 50 mg TBTO/kg diet raises the possibility of carcinogenic effects, but the relevance of this data to humans is questionable.[66] A 2-year study of rats daily fed up to 2.5 mg tributyltin oxide/kg demonstrated an increased incidence of some tumors (pheochromocytomas, parathyroid, pancreatic, prolactinomas), but the high spontaneous incidence of these tumors and the lack of dose-response relationships limit conclusions regarding the significance of these tumors.[139] Although a 2-year rat feeding study with dietary concentrations of 0, 5, 20, and 80 ppm triphenyltin hydroxide detected an increased incidence of pituitary adenomas in females and an increase in testicular Leydig cell tumors at higher doses, the low survival rate limits conclusions regarding carcinogenicity.[63] The presence of Leydig cell hyperplasia and adenomas in rodent studies has limited relevance to human risks because of the hormonal mode of action in rodents.[140] TPT compounds probably are not genotoxic.[65]

DIAGNOSTIC TESTING

Analytical Methods

Atomic absorption spectrometry can separate organic tin compounds from inorganic tin following either liquid extraction or adsorption onto a solid matrix followed by re-extraction and/or concentration.[63] Other detection methods include gas chromatography

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with flame photometric or mass spectrometric detection[141,142] and normal-phase liquid chromatography with ultraviolet or fluorescence detection.[143–145] Methods to quantitate organic tin compounds include gas chromatography/mass spectrometry,[146] and ion-pair/reversed-phase chromatography/hydride generation-quartz furnace/atomic absorption spectrometry.[147] The latter technique allows the speciation of TBT, TPT, and DBT. Graphite furnace/atomic absorption spectrometry with liquid extraction or adsorption onto a solid matrix and then re-extraction and/or concentration can separate inorganic tin and quantitate organic tin compounds.[63]

Organotin compounds can also be separated from biological samples by capillary supercritical fluid chromatography and measured by inductively coupled plasma/mass spectrometry with detection limits near 12 pg.[148] Gas chromatographic methods require conversion of ionic alkyltin compounds either by *in situ* hybridization (sodium borohydride) or alkylation (sodium tetraethylborate).[149] Analytical methods for the speciation of organotin compounds include high-performance liquid chromatography coupled with atomic absorption spectrometry.[150] Limits of detection range from ~0.15–0.60 μg Sn/L, whereas the limits of quantitation range from ~0.5–2.0 μg Sn/L. Butyltin compounds are stable in ambient and refrigerated conditions for at least 1 month.[141]

Biomarkers

Blood

In a study of blood samples from 32 volunteers in central Michigan, the following percentage of butyl tin compounds were detectable: butyltin, 53%; dibutyltin, 81%, and tributyltin, 70%.[151] The concentration of these compounds ranged up to 0.027 μg organotin ion/mL (monobutyltin), 0.016 μg organotin ion/mL (dibutyltin), and 0.085 μg organotin ion/mL (tributyltin). Two days after exposure to triphenyltin acetate, a 36-year-old man was admitted to the hospital with dizziness, malaise, nausea, abdominal pain, and mild liver dysfunction; his admission plasma tin concentration was ~78 μg/L.[127]

Urine

Collection of the urine for tin confirms recent excessive tin exposure. In a study of 500 urine samples from participants in the National Health and Nutrition Examination Survey (NHANES) III, conducted from 1988–1994, 89% of the urine samples had detectable concentrations of tin (LOD, 0.1 μg/L). The 95% CI was 20.1 μg/L.[152] In a worker developing gastrointestinal distress, abdominal pain, urticaria, and mild liver inflammation after exposure to triphenyltin acetate, the peak urine tin concentration of 96 μg/L occurred 6 days after exposure.[127] Maximal excretion of tin occurred 4–10 days after a large exposure to trimethyltin that produced neurological symptoms in workers exposed to organic tin.[118] In these workers, peak urine tin concentrations ranged from 445–1,580 μg/L compared with a mean urine level of 36 μg/L in asymptomatic workers exposed to organotin compounds at the same plant.

Abnormalities

Abnormal laboratory values following excessive exposure to organotin compounds included elevated hepatic aminotransferase levels, severe hypokalemia, hyperglycemia, increased serum creatine kinase concentrations (rhabdomyolysis), elevated serum creatinine (renal dysfunction), sensorimotor polyneuropathy, and leukocytosis.[134] The electroencephalogram may demonstrate moderate slowing of background activity (4–6 Hz) with periodic paroxysmal generalized spikes following TPT exposure or sharp waves or prolonged bilateral theta activity localized to the temporal region following TMT exposure. The initial MRI images from a 43-year-old man with organotin encephalopathy were normal 1 day after exposure; however, by 12 days post-exposure, the MRI demonstrated high-intensity signals in white matter of the cerebral hemisphere, posterior rim of the internal capsule, corpus callosum, cerebral peduncle, and corticospinal tract.[132] At that time, he was comatose.

HEALTH SURVEILLANCE

There are limited data on the risk of adverse effects of organotin compounds in humans.[153] The estimated tolerable daily intake (TDI) for bis(tri-*n*-butyltin) oxide was 0.25–5 μg/kg based on the most sensitive adverse effect (reduced lymphoid function, reduced lymphoid weight) in animal studies and a safety factor of 100.[154] The ADI for TPT compounds in Japan is 0.5 μg/kg body weight based on a 500-fold uncertainty factor and an LOAEL of 0.3 mg/kg body weight for increased mortality and reduced serum immunoglobulin in a 2-year rat study.[63]

The ACGIH derived an 8-hour TLV–TWA of 0.1 mg Sn/m^3 for organic tin to minimize the potential for adverse effects on immune function and the central nervous system.[101] The TLV–STEL of 0.2 mg Sn/m^3 was established to minimize eye and upper respiratory tract

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TABLE 31.5. Regulations and guidelines for organic tin exposure. (Based on Fait et al.).[155]

Exposure Limit	Value
ACGIH	
TLV–TWA (8-hour with skin notation)	0.1 mg/m^3 (as Sn)
TLV–STEL (15-minute)	0.2 mg/m^3 (as Sn)
NIOSH	
REL–TWA (10-hour)[a]	0.1 mg/m^3 (as Sn)
IDLH	25 mg/m^3
OSHA	
PEL–TWA (8-hour)	0.1 mg/m^3
US EPA	
RfD (Bis(tributyltin) oxide)	3×10^{-4}/mg/kg/day
EFSA	
TDI – organotin (TBT, DBT, TPT, di-*n*-octyltin)	250 ng/kg body weight

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; EFSA = European Food Safety Authority; IDLH = immediately dangerous to life and health; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = reference dose; STEL = short-term exposure limit-15 minutes; TDI = tolerable daily intake; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency.
[a] Except cyhexatin.

irritation, headache, and nausea. Medical surveillance includes a comprehensive medical and work history with emphasis on the lungs, liver, kidneys, mucous membranes, allergies, and the central nervous system.[155] Table 31.5 lists the regulations and guidelines for organic tin exposures.

TREATMENT

Management of organotin toxicity is primarily supportive and preventative. There is a lack of clinical data to support the use of antidotes for the treatment of organotin poisoning. The administration of D-penicillamine did not increase urinary tin excretion in patients poisoned by trimethyltin.[3] BAL does not chelate organic metal compounds well. Animal studies suggest BAL[156] and meso-2,3-dimercaptosuccinic acid (DMSA)[157] may reduce the toxicity of dialkyltin compounds, but no data are available for humans. Plasmapheresis did not increase the tin elimination from workers poisoned with dimethyl and trimethyltin compounds.[112,118] Patients with triethyltin poisoning should be observed closely for the development of cerebral edema.

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Chapter 32

TITANIUM

HISTORY

In 1791, Rev. William Gregor discovered titanium oxide in a mill stream in south Cornwall, England, near the parish of Manaccan. Four years later, the chemist, Martin Klaproth, named the metal after the giants in Greek mythology (Titans); he changed the name of the black iron titanium oxide ore from manaccanite to the current name of ilmenite.[1] In 1908, the French metallurgist, A.J. Rosii, discovered the dense opacity of a relatively pure titanium dioxide; however, commercial production of the white pigment did not begin until after World War I. Although the pure metal was not isolated until 1910, commercial production of metallic titanium did not begin until after World War II following the development of an economic purification process. Leventhal published the first paper on the use of titanium for orthopedic implants in 1951. Subsequently, an alloy containing 90% titanium, 6% aluminum, and 4% vanadium replaced elemental titanium commercially. Later, a variety of other titanium alloys became available as alternatives to replace aluminum and vanadium in this alloy; the metals included niobium, molybdenum, zirconium, iron, and tin; however, these later alloys demonstrate less strength than the original Ti–Al–Vd alloy.[2] Research on titanium dental implants began in the early 1950s with the first titanium implant recorded in 1964–1965.[3]

PHYSIOCHEMICAL PROPERTIES

Titanium (CAS RN: 7440-32-6, atomic mass: 47.87 g/mol) is an odorless, silver-gray metal that possesses both metallic and nonmetallic properties that are similar to silica and zirconium. Titanium is a member of Group 4 (Group IVb) of the periodic table along with hafnium and zirconium. Titanium is a transition element that combines with other metals (calcium, iron, potassium) to form alkyl and aryl titanate compounds; elemental Ti rapid forms a 1- to 2-nm oxide layer following air exposure that reduces reactivity and protects the metal from further redox reactions. The most common oxidation states are titanic (4+) and titanous compounds (3+); less common bivalent compounds (2+) and oxy-compounds (titanyl chloride) also exist. Titanic compounds easily hydrolyze to titanium dioxide (TiO_2). Naturally occurring TiO_2 exists in three crystalline structures: anatase, brookite, and rutile with the latter crystalline form being the most stable. Rutile TiO_2 is birefringent with refractive indices in the UV and visible wavelengths (i.e., suitable for sunscreens).

Metallic titanium is highly resistant to corrosion and water-insoluble. Titanium tetrachloride ($TiCl_4$) is a colorless, light-yellow liquid that is water-soluble at 20°C and decomposes in hot water, whereas other common titanium compounds (elemental titanium, titanium dioxide) are insoluble in cold water. $TiCl_4$ is a corrosive liquid that reacts with air to produce a dense white fume composed of solid, hydrolyzed titanium particles and a hydrogen chloride mist. In the presence of water, $TiCl_4$ undergoes a vigorous exothermic reaction yielding heat and hydrochloric acid. Titanium dioxide (TiO_2; CAS RN: 13463-67-7, MW 79.87) is a white crystalline solid that occurs in two primary forms (i.e., anatase and the more thermally stable, rutile). Organic titanium compounds are rarely used commercially.

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EXPOSURE

Production Process

The major titanium ore is ilmenite (iron titanate, $FeTiO_3$, 53% TiO_2) with rutile ores (95–100% TiO_2) being much less abundant. Smelting ilmenite in an electric furnace produces titanium slag. The production process for TiO_2 previously involved the sulfate process; however, the chloride process using $TiCl_4$ as an intermediate is now more common. The treatment of titanium-containing ores in the presence of coke at high temperature (850–1,000 °C) releases $TiCl_4$. After the vaporized reaction, products are condensed and separated to produce pure $TiCl_4$; the oxidation of $TiCl_4$ under high temperature (1,200–1,370°C) and pure oxygen forms TiO_2. Chlorine gas is a by-product of this process that is recycled after separation from TiO_2. The primary particles are usually 0.2–0.3 μm in diameter; larger aggregates or agglomerates may appear. Ultrafine titanium dioxide has particle sizes in the range of 10–50 nm for use in sunscreens, catalysts, and plastics. These nanoparticles are typically coated with organic (e.g., esters, polyols, silanes, siloxanes) or inorganic (e.g., alumina, silica, zirconia) compounds to improve surface properties.

Uses

Because titanium is inert, corrosion-resistant, and 45% lighter than steel, this metal is a common constituent of welding rod coatings and alloys (e.g., Al, Sn, Mo, V) used in the aircraft and spacecraft industries. TiO_2 is the most common titanium compound (i.e., ~95% of titanium production); applications include constituents of white pigment and a coloring agent for many buildings and commercial and consumer products (e.g., teeth whiting). TiO_2 has replaced lead and zinc compounds as the white pigment in indoor paints; these pigments usually contain fine particles (i.e., >100 nm). Nanoscale TiO_2 particles (i.e., agglomerated particles <100 nm) are currently the most widely applied nanomaterial with various rods and shapes including anatase (7–10 nm), nanotubes (10–15 nm diameters × 70–150 nm length), and rutile (15–20 nm).[4] Applications of these nanoparticles range from sunscreens to cosmetic additives and surface coatings. Some of these nanoparticles produce inflammatory responses and reactive oxygen species in experimental studies; however, the exact properties and dose necessary to cause these effects remain unclear.[5] In a study of the nanoscale packing area of a plant producing TiO_2, the airborne particles range from 50 nm–several mm in diameter with 90% of the particles being <100 nm.[6]

TABLE 32.1. Commercial uses for titanium and titanium compounds. (Adapted from Valentin and Schaller).[7]

Substance	Uses
Elemental titanium (Ti)	Alloys, aerospace, chemical processing, dental amalgam
Titanium dioxide (TiO_2)	Pigments, paints, lacquers, printing ceramics, food additives, drug and cosmetic applications (nanoparticles)
Titanium tetrachloride ($TiCl_4$)	Polymerization (Ziegler type) catalyst, starting material for organic compounds
Titanous chloride ($TiCl_3$)	Polymerization catalyst
Organic titanium compounds	Cross-linking agents, catalysts

The ability of TiO_2 to effectively screen short-wave ultraviolet sunlight enhances its use in cosmetic products. Since the 1980s, TiO_2 and ZnO nanoparticles have been incorporated into sunscreens with the use of these nanoparticles becoming widespread by the 1990s. These formulations are highly effective UV radiation filters in transparent, light-textured products. The use of TiO_2 nanoparticle-dominated sunscreens requires the use of organic filters for broad-spectrum UV protection. Titanium is a constituent of dental amalgams. Table 32.1 lists common uses for titanium and titanium compounds.

Sources

Air

Ambient titanium concentrations in air are usually low (<0.1 μg/m^3) with concentrations ranging up to 0.5 μg/m^3 near industrial sources based on data collected before 1970.[8,9] Occupational Ti exposure results primarily from the inhalation of dust containing titanium production, particularly in the crushing and grinding of concentrates of rutile and the handling/production of $TiCl_4$.[10]

Soil

Titanium is the ninth most abundant metal in the earth's crust (i.e., 0.57% by mass). Typical Ti concentrations in soil average ~4.4% with a range of 0.3–10% titanium. Soils of the Canary Islands and the Hawaiian Islands particularly contain high Ti concentrations (i.e., up to 25%).

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Water

Although data on the titanium concentration in water sources are limited, available data suggest that concentrations in water supplies average ~2 μg/L with a range up to 15 μg/L, whereas Ti concentrations in some rivers range up to 107 μg/L.[11]

Diet

Food represents the primary source of titanium in the diet with a very minor contributions from drinking water and ambient air. Relatively high titanium concentrations occur in butter, corn oil and margarine, integument, milled grains, condiments (ground black pepper, cloves), and lettuce, whereas whole grains, some vegetables, fruit, and most fish and meat contain little titanium.[12] In a duplicate food sample study, corn oil margarine contained 1.8 μg Ti/g, whereas fresh corn contained no detectable titanium. Titanium concentrations in meat ranged from 0.1 μg/g in beef chuck and lamb chops to 1.84 μg/g in pork chops. The daily intake of titanium averages ~300 μg with little titanium accumulation in the body based on long-term balance studies from the 1960s;[13] the mean titanium body burden averages ~15 mg.

DOSE EFFECT

Titanium is probably not an essential element. TiO_2 is practically nontoxic following ingestion. The older medical literature suggests the ingestion of 450 g TiO_2 is not associated with any toxicity.[14] Titanium and titanium compounds (oxides, peroxide, salicylate, tannate) demonstrate extremely low toxicity in animal studies, but little data are available in humans to correlate systemic effects with specific doses of titanium compounds.

TOXICOKINETICS

Although some titanium absorption occurs following ingestion, the amount of titanium and titanium compounds absorbed into the body is small (<3%). *In vitro* and *in vivo* human studies indicate nanoparticulate titanium dioxide is poorly absorbed by the gastrointestinal tract, similar to micron-sized particles.[15] The highest titanium concentrations typically occur in the lungs, particularly in miners, whereas the lowest Ti concentrations of titanium usually exist in the brain.[16] Titanium dioxide nanoparticles probably do not penetrate the dermis (stratum corneum) following skin application.[17] The biological half-life in humans is probably ~2 years based on animal studies.[18] Elimination of titanium occurs primarily by renal excretion; however, the role of biliary secretion of titanium into the intestines remains undefined.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

The major finding on autopsies of workers exposed to fine titanium particles is Ti deposition in the lungs with little evidence of hyperplasia or fibrosis. Under light microscopy, titanium is birefringent and distinguishable from carbon. Moran et al. reported a series of six patients with birefringent foreign material and abundant black pigment in macrophages from various locations including fat, alveoli, and muscle.[19] X-ray analysis demonstrated the presence of titanium dioxide. Three of the patients had diffuse fibrosing interstitial pneumonitis with alveolar metaplastic changes and areas of bronchopneumonia; four patients died of sepsis. The source and amount of titanium exposure were not well defined. Postmortem examinations of drug addicts may demonstrate granulomatous reactions containing titanium and talc in the lungs, spleen, and liver.[20] A histological study of three workers exposed to titanium over 10 years revealed increased titanium deposition in the lungs along with cell necrosis and slight fibrosis;[21] however, co-exposure to silica, cigarette smoke, and tuberculosis could account for these changes and actual TiO_2 exposure was not reported. Other studies of lung tissue from titanium workers did not demonstrate evidence of pulmonary fibrosis despite large Ti deposits in the lungs.[22]

CLINICAL RESPONSE

Acute Toxicity

TiO_2 is practically nontoxic in ingestion as a result of very limited absorption by the gastrointestinal tract. Similarly, the bioavailability of TiO_2 nanoparticles appears low. In a study using gavage of rats with titanium dioxide nanoparticles, ICP/MS did not detect a significant increase in Ti concentrations in any tissues 24 hours after gavage including the small intestine, Peyer's patches, mesenteric lymph nodes, spleen, or liver; however, TEM demonstrated several nanoparticles in one cell from Peyer's patch.[23] Sections of the intestines did not reveal any nanoparticles.

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Environmental Exposure

Environmental exposure to titanium is not typically associated with toxicity in the general population as a result of its relatively low elemental toxicity. Currently, TiO_2 is considered an inactive ingredient additive in human food. Titanium is a rare cause of hypersensitivity reactions in the general population; typically, adverse reactions to TiO_2 result from surgical or dental implants.[24] Despite relatively high Ti concentrations, these reactions usually develop in malfunctioning implants made of metals other than titanium. The clinical significance of type IV hypersensitivity reactions in relation to peri-implant reactions remains unresolved because cutaneous dendritic cells differ from antigen-presenting cells in deeper tissues.[25]

The European Scientific Committee on Consumer Safety considers the use of TiO_2 nanoparticles in dermal preparations are safe at concentrations up to 25%;[26] currently, there is no clear evidence that engineered nanomaterials including TiO_2 nanoparticles penetrate intact or inflamed skin and enter the systemic circulation.[27] Similarly, the Therapeutic Goods Administration concluded that current evidence supports the safe human use of sunscreens containing TiO_2 and ZnO nanoparticles.[28] Using immune-competent hairless mice, 36-week studies of weekly topical applications of TiO_2 and ZnO nanoparticle-containing sunscreens did not detect a statistically significant incidence of histologically diagnosed malignant or benign skin lesions in the UV-exposed groups compared with controls (no UVR, no sunscreen).[29] Few to no transcriptional lesions were found in the TiO_2- or ZnO-treated groups. Some elevation of hepatic Ti concentrations occurred in the TiO_2-treatment groups.

Occupational Exposure

Titanium Tetrachloride

$TiCl_4$ is extremely irritating to the skin, mucous membranes, and lungs. In the presence of water, $TiCl_4$ produces heat and hydrochloric acid. Two workers accidentally splashed with liquid $TiCl_4$ developed burns over ~20% of their bodies in areas where the liquid was in direct contact with their perspiration.[30] The burns were more severe than initially recognized on admission, resulting in grafting over the affected skin. Inhalations of this compound may cause chemical bronchitis or pneumonitis.[31] A large exposure to $TiCl_4$ was associated with the development of diffuse endobronchial polyposis that resolved within 1 year of exposure.[32]

Titanium Dioxide

TiO_2 is biologically inert; this compound probably does not possess fibrogenic properties following exposure to micron-sized particles.[11] Epidemiological studies generally support the lack of clinical effects including pulmonary fibrosis following such exposure.[33,34] A clinically significant lung disease is uncommon in workers at plants producing titanium by the sulfate process.[35] A study of titanium production workers exposed to Ti concentrations of 0.2–2.8 mg/m^3 demonstrated a slight reduction of FEV_1. Pleural thickening occurred in 36 of 209 workers; however, asbestos exposure could not be eliminated as a cause of these findings.[36] A single case study associated the development of fibronodular pulmonary infiltrates with titanium exposure based on a positive lymphocyte transformation test.[37] This hypersensitivity lung disease, which was suggestive of sarcoid, occurred in an aluminum smelter worker following titanium exposure for 13 years; however, exposure to a variety of metallic fumes prevented the determination of a direct causal relationship between hypersensitivity pneumonitis and titanium exposure. Similarly, the development of pulmonary alveolar proteinosis in a painter, who did not wear respiratory protection while painting, was associated with very high titanium concentrations on lung biopsy.[38] The specific exposure of this heavy smoker was not well defined. A case report associated the development of bronchiolitis obliterans in a 58-year-old Taiwanese diabetic with a 3-month exposure to heated electrostatic polyester powder paint containing TiO_2 nanoparticles.[39] The powder paint contained highly crystalline titanium dioxide and silicon dioxide with particle sizes ranging from 100–300 nm (i.e., above the nanoparticle range). The lung biopsy contained similar particles.

Titanium Ethanolate

A case report associated a large, accidental exposure to titanium ethanolate and hydrogen chloride in a chemistry laboratory with the development of a metal fume-like syndrome including low-grade fever, dyspnea, myalgia headache, and fatigue.[40] The symptoms resolved within 24 hours without any complications or sequelae.

Reproduction

No data are available on the genetic effects of titanium; however, there is no experimental evidence to suggest that titanium is a teratogen.

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Carcinogenesis

Neither the IARC nor the US National Toxicology Program lists titanium or titanium compounds as human carcinogens. The IARC categorizes TiO_2 as possibly carcinogenic to humans (Group 2B) with sufficient evidence of carcinogenicity in animals and inadequate evidence of carcinogenicity in humans; the particle size was not specified.[41] A lifetime (2-year) study of $B_6C_3F_1$ mice exposed to TiO_2 at concentrations of 0–250 mg/m^3 revealed unique squamous cell carcinomas only at Ti concentrations that saturated the normal pulmonary clearance mechanism.[42] No excess tumors occurred at concentrations five times higher than the current permissible exposure limits. Substantial interspecies, route, and sex differences occurred with intratracheal studies in hamster and female mice negative.[43,44]

Epidemiological studies on workers exposed to engineered nanomaterials including TiO_2 nanoparticles are very limited by short duration of nanoparticle use, resulting in few exposed individuals and relatively short exposures.[27] There is little epidemiological evidence that occupational exposure to titanium dioxide is carcinogenic including lung and kidney cancers;[45] however, none of the studies assessed the impact of particle size (fine or ultrafine) or the potential effect of the coating compounds on the risk of lung cancer. A study of 969 workers exposed to $TiCl_4$ between 1956 and 1985 did not demonstrate a statistically increased incidence of lung cancer or a dose-response relationship between exposure to $TiCl_4$ and lung cancer.[46] The statistical power of the study was sufficient to exclude a 3-fold increase in the risk of cancer. A retrospective cohort mortality study among 4,241 titanium dioxide workers employed for at least 6 months did not detect increased mortality from bladder cancer, lung cancer, or any other cause, when compared with the general US population.[47] Similarly, the standardized mortality ratio (SMR) for all causes including lung cancer was not elevated in a cohort of European titanium workers with median cumulative exposure of 1.98 mg/m^3/year (interquartile range, 0.26–6.88 mg/m^3/year).[48] Examination of individual cancers revealed a slightly increased lung cancer risk compared with the general population and a suggestive dose-response relationship but no overall excess risk for kidney cancer. The SMR for lung cancer was 1.23 (95% CI: 1.10–1.38) based on a fixed effects statistical model. The SMRs varied from 0.76 (95% CI: 0.39–1.32) in Finland to 1.51 (95% CI: 1.26–1.79) in Germany. The heterogeneity between countries was of borderline significance ($P = 0.05$). Evaluation of the data using a random effects model yielded a SMR of 1.19 (95% CI: 0.96–1.48).

A mortality study of 3,607 titanium dioxide production workers followed from 1935–2006 did not demonstrate any increased mortality from all malignant neoplasms (SMR = 0.93, 95% CI: 0.82–1.06) or lung cancer (SMR = 0.98, 95% CI: 0.78–1.21).[49] Poisson regression modeling did not detect any significant trends with increasing exposure. A meta-analysis of 24,312 TiO_2 production workers from three industry-based cohort mortality studies using Cox regression coefficients for exposure-response models derived from random effects modeling did not demonstrate clear evidence of an association between occupational TiO_2 exposure and lung cancer.[50] The summary standardized mortality ratios were 1.10 (95% CI: 0.91–1.32) for lung cancer mortality and 0.92 (95% CI: 0.82–1.03) for all-cancer mortality.

Case-control studies do not indicate an increased risk for either lung or kidney cancer. A population-based, case-control study of 484 patients with bladder cancer suggested a weak association with titanium dioxide among several other occupations and chemicals;[51] however, other studies have not detected a similar association. In a case-control study of 857 cases of lung cancer, 33 cases and 43 referents were classified as exposed to titanium dioxide.[52] The odds ratio for lung cancer was 0.9 (95% CI: 0.5–1.5) with no apparent trend for increasing dose or frequency. The odds ratio for lung cancer following medium to high exposure for at least 5 years was 1.0 (95% CI: 0.3–2.7).

DIAGNOSTIC TESTING

SI Conversion Units

1 μmol/L = 47.87 μg/L
1 μg/L = 0.02089 μmol/L

Analytical Methods

The use of high-temperature reducing flame is important to increase the sensitivity of analytical methods because titanium poorly atomizes.[10] Atomic absorption spectrometry (AAS) has a detection limit of ~0.07 μg Ti/m^3 for environmental samples, whereas the detection limit of x-ray florescence is ~0.011 μg Ti/m^3 and proton-induced x-ray emission spectrometry is 0.001 μg Ti in ambient air samples. The use of inductively coupled plasma/optical emission spectrometry (336.121 nm) after acid digestion allows the detection of titanium in food samples in the 2–7 μg/L (ppb) range.[53] The detection limit of neutron activation analysis is ~10 times lower (0.007 μg Ti/m^3) than the sensitivity of AAS. The

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limits of detection and quantitation for Ti in biological samples using inductively coupled plasma/mass spectrometry (ICP/MS) are 0.9 μg/L and 1.8 μg/L, respectively.[54] Using ultrasonic nebulization and a desolvating membrane, the LLOQ for titanium in serum was 0.002 μg/mL as measured by ICP/MS.[55] The use of double-focusing sector field ICP/mass spectrometry or ICP/MS allows detection of serum titanium in the ng/L range.[56]

A range of polyatomic and isobaric interferences, particularly from ^{48}Ca, complicate the interpretation of studies using graphite furnace atomic absorption spectrometry (GF/AAS) and quadrupole inductively coupled plasma/mass spectrometry, resulting in overestimation of titanium concentration. Inductively coupled plasma/optical emission spectrometry (ICP/OES) uses emission lines from the analyte to avoid any specific analytical interferences. In an analysis of whole blood and serum samples from patients with hip replacements, the limit of detection for serum titanium at 336.1 nm was 0.6 μg/L with a limit of quantitation of 1.9 μg/L.[57]

Biomarkers

Titanium ions associate with plasma proteins, resulting in higher titanium concentrations in plasma and serum than in whole blood. In an analysis of 16 matched serum and whole blood samples, the average serum Ti concentration was 3.7 μg/L (range, 0.6–15.6 μg/L) compared with 2.2 μg/L (range, 0.5–9.0 μg/L) for whole blood as measured by inductively coupled plasma/optical emission spectrometry. Regression analysis indicated that the best fit for the whole blood concentration was 0.58 serum Ti + 0.12.

Blood

The typical baseline serum Ti concentration in humans without titanium implants is <1 μg/L, whereas values in patients with titanium hip and/or knee implants range from 2–6 μg/L.[58] In the older medical literature, the reported Ti concentrations were much higher. Eight patients underwent insertion of a proximally porous-coated modular titanium-alloy femoral stem with a cobalt-alloy femoral head and a titanium acetabular socket. The mean serum titanium concentrations peaked ~3 years after insertion at ~2.9 μg/L; at 10-year follow-up, the mean serum Ti was ~1.8 μg/L (18 times higher than baseline) as measured by high-resolution sector field/inductively coupled plasma/mass spectrometry.[59] All hip implants were well functioning. A cross-sectional study of 95 of 199 patients with well-functioning, unilateral titanium alloy implants reported median whole blood Ti concentrations of 1.2 μg/L (IQR: 1.0–1.5 μg/L, 95th percentile: 2.2 μg/L) and 1.7 μg/L (IQR: 1.4 μg/L, 95th percentile: 2.56 μg/L) for plasma Ti.[60] The mean implant time was 8.4 years with a range of 5.3–11.9 years. The analytical method was high resolution/inductively coupled plasma/mass spectrometry with a limit of detection of 0.77 μg/L. The Ti concentrations were not correlated to the UCLA activity scale. In a retrospective cross-sectional study of titanium concentrations in 67 patients with total hip arthroplasty using modular neck titanium implants, the mean serum titanium concentration was 3.0 μg/L (range, 0.8–21.0 μg/L) compared with 0.9 μg/L (range, 0.1–4.5 μg/L) in 23 controls without implants.[61] The mean follow-up at the time of blood sample collection was 9 years (range, 7–13 years); complications were not reported.

In a study of Ti concentrations in eight patients with failed titanium alloy cementless total knee arthroplasties, the serum Ti concentrations were substantially higher than controls.[62] The mean serum Ti concentration in 21 patients with loose prostheses containing femoral stems composed of a titanium–aluminum–vanadium alloy was 8.08 μg/L (range, <2.11–17.2 μg/L) compared with 4.10 μg/L (range, <2.11–7.92 μg/L) in 21 controls (no implants) and 4.42 μg/L (range, <2.11–7.05 μg/L) in 12 patients with similar, normal-functioning prostheses. The analytical method was graphite furnace Zeeman atomic absorption spectrometry.

Urine

In a pooled urine sample from the general population and hospitalized patients collected in the 1950s, the Ti concentration averaged ~10 μg/L as measured by spectrographic analysis of ashed samples.[63] This value differed substantially from later studies using more sensitive analytical methods. The mean Ti concentration in urine samples from 20 controls and 17 dental health care workers without occupational Ti exposure was ~1,100 μg/L (maximum = ~2,000 μg/L) with no statistically significant difference between the workers and the control group.

HEALTH SURVEILLANCE

Titanium dioxide is the only titanium compound with exposure standards. The US OSHA PEL-TWA for TiO_2 is 15 mg/m^3. The recommended NIOSH REL-TWA guideline for exposure to airborne respirable TiO_2 pigment particles is 2.4 mg/m^3 compared with 0.3 mg/m^3

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for nanoscale TiO_2 particles. The ACGIH recommends a TLV–TWA of 10 mg/m^3 to maintain normal pulmonary clearance and minimize the potential for respiratory tract irritation.[64] There are no commonly accepted biological exposure indices for titanium or titanium compounds; urine is probably the most suitable specimen for evaluating Ti exposure.

TREATMENT

Treatment is supportive. $TiCl_4$ is an acid-corrosive that requires immediate removal from the eye. Excess liquid should be wiped away; then, the eye should be irrigated because the combination of moisture and $TiCl_4$ causes an exothermic reaction. Any solid particles of $TiCl_4$ should be removed from the eye, and the eye should be irrigated copiously for 30 minutes. All symptomatic patients following exposure to liquid $TiCl_4$ should have an ophthalmology consultation. Serious eye injuries require mydriatic agents, topical antibiotics, topical steroids, and ascorbate under the direction of an ophthalmologist.[65]

TiO_2 is poorly absorbed from the gastrointestinal tract; therefore, the decision to use decontamination measures depends on the ingestion of other substances that require decontamination measures. Inhalation of $TiCl_4$ may produce irritation of the lungs. Measures to evaluate lung function (ABGs, pulse oximeters, chest x-rays, pulmonary function tests) should be performed as indicated by the clinical condition of the patient.

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Chapter 33

TUNGSTEN

HISTORY

The Swedish chemist Axel Fredrik Cronstedt discovered tungsten in 1758, naming the mineral tungsten (Swedish for heavy stone); Carl Wilhelm Scheele first discovered tungsten in the form of tungsten trioxide in 1781; however, he was unable to isolate the element. Two years later, the Spanish chemists Jose and Fausto de Elhuyar isolated tungsten after reducing tungstic acid in wolframite ore. In the early 1900s, the oral administration of tungsten power (25–80 g) as a substitute for barium during radiographic examinations was administered without observed adverse effects.[1] Hard metal is a powder metallurgy process that combines tungsten carbide with cobalt as a binder. The hard metal industry began in Germany after World War I with the development of armaments, radiotherapy screens, and cutting edges for dies, tools, and drills. In the 1940s and 1950s, case reports and case series documented an excess of respiratory abnormalities in workers with prolonged exposure to dusts from the grinding and processing of hard metal including cough, sputum production, bronchitis, bronchospasm, emphysema, and pulmonary fibrosis. Although symptoms were mild in most workers, a few developed severe pulmonary fibrosis and respiratory insufficiency. Bech et al. described six hard metalworkers with mild respiratory changes suggestive of early pulmonary fibrosis; he used the term, *hard metal disease* to denote the pulmonary abnormalities of workers exposed to dust from hard metal processes.[2] Animal studies in the 1950s suggested tungsten was relatively benign, whereas cobalt was intensely irritating to lung tissue, particularly when combined with tungsten carbide.[3,4] Bronchoprovocation tests of hard metalworkers in the 1980s implicated cobalt as the cause of hard metal-induced asthma rather than tungsten.[5] In the late 1990s and early 2000s, clusters of acute lymphocytic leukemia developed in children in Fallon, NV (16 cases), Elk Grove, CA (6 cases), and Sierra Vista, AZ (12 cases). The number of leukemia cases far exceeded the national incidence of this disease. All three of these clusters occurred in communities with active or inactive tungsten mines along with high natural tungsten concentrations in the soil as a result of environmental conditions (e.g., geothermal waters, evaporative concentrations in rivers, and precipitation of tungsten-containing minerals in sediment). Although tungsten concentrations in drinking water and urine of the children of Fallon were substantially higher than typical background concentrations, there was no dose-response or clear causal relationship between tungsten concentrations and the development of acute lymphocytic leukemia.[6]

PHYSIOCHEMICAL PROPERTIES

Tungsten (wolfram, W) is a hard, brittle, grayish-white, transition metal that belongs to Group 6 (Group VIB) of the periodic table along with seaborgium (a synthetic radioactive element produced by nuclear bombardment), molybdenum, and chromium. Elemental tungsten is highly resistant to acids and oxidation in air at ambient temperatures; however, above 400°C tungsten oxidation occurs. Being extremely dense (specific gravity = 19.3), tungsten has the highest melting point

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(3,410°C) of all elements with the exception of carbon, the lowest coefficient of expansion (4.5×10^{-6}/°C), and the lowest vapor pressure of all metals along with good thermal and electrical conductivity. Pure polycrystalline tungsten is brittle; therefore, tungsten alloys contain transition metals (cobalt, nickel) to improve tensile properties and mold the metal to the shape required for commercial applications. Additionally, tungsten has the highest tensile strength at temperatures of >1,650°C. Tungsten is a good electron conductor.[7] Tungsten carbonyl is volatile (vapor pressure 0.1 mmHg at 20°C), whereas tungsten hexafluoride is a gas at room temperature.

Hexavalent is the highest and most stable tungsten oxidation state in the environment with lower valence states being relatively unstable; oxidation states range from 2− to 6+. In nature, there are five stable isotopes: ^{180}W (0.12%), ^{182}W (26.5%), ^{183}W (14.3%), ^{184}W (30.6%), and ^{186}W (28.4%). Table 33.1 list the identifying information and physical properties of

TABLE 33.1. Identifying information and physical properties of elemental tungsten and tungsten salts.

Physical Characteristic	Tungsten	Tungsten Oxide	Tungsten Trioxide	Tungsten Carbide
Formula	W	WO_2	WO_3	WC
Synonym	Wolfram	Tungsten dioxide	Tungsten blue, tungstic oxide, tungstic acid, tungsten oxide	Tungsten monocarbide
CAS RN	7440-33-7	12036-22-5	1314-35-8	12070-12-1 (carbide), 11130-73-7 (monocarbide)
Valence	0	+4	+6	+4
Molecular weight (g/mol)	183.85	215.84	231.85	195.85
Color	Silver–gray to tin–white	Blue	Canary yellow	Gray
Physical state	Solid	Solid	Solid	Solid
Melting point (°C)	3,410	1,500–1,700 (decomposes)	1,472	2,785
Density (g/mL)	18.7–19.3 (20°C/4°C)	10.82 (calculated)	7.2	15.6
Odor	odorless	odorless	NA	NA
Water solubility (mg/L)	Insoluble	Insoluble	Insoluble	Insoluble (<0.1, 20°C)
Vapor pressure (mmHg)	1.97×10^{-7} at 2,327°C	NA	NA	7.5×10^{-3} at 3,204°C

Physical Characteristic	Tungsten Chloride	Tungsten Hexafluoride	Ammonium Paratungstate	Sodium Tungstate, Dihydrate
Formula	WCl_6	WF_6	$W_7H_{24}N_6O_{24}$	$W_2NaO_4 \cdot 2H_2O$
Synonym	Tungsten hexachloride	Tungsten fluoride	APT	Disodium tungstate, dihydrate; sodium tungsten oxide; tungstic acid, disodium salt, dihydrate
CAS RN	13283-01-7	7783-82-6	12028-06-7 (anhydrous)	10213-10-2 (dihydrate); 13472-45-2 (anhydrous)
Valence	+6	+6	+6	+6
Molecular weight (g/mol)	396.56	297.83	1779.16	329.85
Color	Purple	Colorless	White	White or colorless
Physical state	Solid	Gas	Solid	Solid
Melting point (°C)	275	2.3	NA	692
Density (g/mL)	3.52	12.173	NA	3.25
Water solubility (g/L)	Decomposes	Decomposes in water (60°C)	270.2 (soluble)	732 (very soluble, 21°C)
Vapor pressure (mmHg)	43 (215°C)	Gas at room temperature	NA	NA

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NA = not available.

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elemental tungsten and common tungsten compounds. Tungstate shares a common tetrahedral structure with phosphate, vanadate, and molybdate along with insulin-like effects.[8]

The chemical properties of tungsten and molybdenum are similar; tungsten forms a variety of compounds with different stereochemistry and oxidation states (ammonium paratungstate, tungsten carbide, tungsten trioxide). Most of the commercial compounds involve the 6+ oxidation state, although other oxidation states (2+, 4+, 5+) also exist. The lower valence states are relatively unstable compared with hexavalent tungsten. This metal easily forms complexes (e.g., oxyhalides). Similar to molybdenum, tungsten is an amphoteric metal that readily polymerizes as an acid anhydride and condenses with other acids (e.g., phosphoric) to form heteropolyacids. In acid solutions, tungsten forms condensed complex ions of polytungstates (e.g., ammonium paratungstate hydrate, $(NH_4)_{10}(H_2W_{12}O_{42})\cdot 4H_2O$), whereas these tungsten species depolymerize in alkaline solutions at room temperature. Polymerization of tungstate anions begins in mildly alkaline solution and progresses as the pH decreases. In acidic solutions (pH = 4.0–5.9), sodium tungstate polymerizes to sodium paratungstate ($N_{10}W_{12}O_{41}$) and sodium metatungstate ($N_6W_{12}O_{39}$).[9] *In vitro* studies suggest a stable protective oxide layer forms on the surface of implanted tungsten in tissues when the pH is <7.4, whereas the presence of a pH of >7.4 facilitates the corrosion of tungsten implants.[10]

Insoluble tungsten compounds (i.e., <10 mg W/100 mL water) include tungsten carbide, carbonyl, oxide, silicide, and sulfide, as well as tungstic acid. The tungstate ion (WO_4^{2-}) is the most water-soluble and most frequently encountered tungsten compound in biological systems. Other water-soluble tungsten compounds (W^{5+}, W^{6+}) include the oxyhalides (chloride, fluoride, oxychloride).

Experience with implanted tungsten coils suggests that tungsten is biodegradable *in vivo* following prolonged implantation. In a study of 46 children following a mean of 39.3 months (range, 2–72 months) after intraarterial implantation of pure tungsten coils (99.9%) for embolization of aortopulmonary collaterals, radiographical examination of the coils demonstrated loss of radiopacity.[11] Approximately 60% of the coils were no longer visible within 2 years after implantation. Assuming a loss of visibility as a biomarker of complete biodegradation and an exponential trend in the reduction of radiopacity, the authors predicted that almost all of the coils would dissolve within 10 years.

EXPOSURE

Production Process

Tungsten typically does not occur in the earth as a free element; underground mines produce ores containing ~0.3–1.5% WO_3; benefaction facilities usually concentrate the content of WO_3 to 60–75% by gravity separation.[7] Tungsten miners are exposed to a variety of potential carcinogens including cigarette smoke, silica, radon, and diesel fumes, particularly exhaust from pre-2000 engines.[12] In the soil, tungsten exists almost exclusively as oxo-rich tungstate minerals including wolframite (iron-manganese tungstate, $(Fe,Mn)WO_4$), scheelite (calcium tungstate, $CaWO_4$), and less commonly ferberite (iron tungstate, $Fe\ WO_4$) and hubnerite (manganese tungstate, $MnWO_4$). Tungsten production typically involves the following: 1) reduction of tungsten trioxide with hydrogen or carbon; 2) aluminothermic reduction of tungsten trioxide; 3) hydrogen reduction of tungstic acid or the corresponding anhydride; or 4) hydrogenation of tungsten trioxide or ammonium paratungstate. Production of elemental tungsten results from the digestion and reduction of tungstate ores with ammonium paratungstate being the main intermediate. After pretreatment with acid leaching (hydrochloric acid) or roasting with soda ash in an autoclave (aqueous sodium carbonate at ~200°C and >11.9 atm), tungsten is extracted as sodium tungstate. A liquid ion-exchange process converts the sodium tungstate to ammonium tungstate; then, to crystalline ammonium paratungstate after evaporation of the solvent. Arsenic frequently coexists with tungsten in polymetallic sulfide ores (e.g., wolframite, scheelite).[13]

The stepwise reduction of ammonium paratungstate with hydrogen or carbon either in tube or in rotary furnaces produces tungsten metal powder. The mixing of finely powdered tungsten with carbon black in an electric furnace at high temperatures filled with hydrogen as a catalyst produces tungsten carbide. Tungsten carbide prepared from oxygen-containing tungsten compounds is also a source for the production of tungsten carbide. Cobalt-tungsten carbide hard metals are composites of metallic cobalt powder and tungsten carbide particles alone or in combination with other carbides. Typically, the tungsten carbide (WC, W_2C) concentration ranges from 50–97% with small amounts of other metallic carbides (chromium, molybdenum, nickel tantalum, titanium) along with 3–16% cobalt depending on the desired properties. Cobalt is a binding agent for tungsten carbide in wear-resistant tools formed from cemented (sintered) tungsten carbide. The manufacturing process consists of the following

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three steps: 1) production of cobalt and tungsten carbide powders; 2) mixing, pressing into desired shape (pre-sintering), heating to 1,500°C (sintering); and 3) finishing sintered product into desired shape by grinding and sharpening. The highest exposure to dust from the production of hard metals occurs during step 2, particularly powder-processing operations. The smelting of wolframite concentrates with charcoal or coke in an electric arc furnace forms ferrotungsten, an alloying material in steel production.

Typical tungsten alloys used for military applications contain tungsten concentrations exceeding 90% by weight along with transition metals (nickel, cobalt, and/or iron). These alloys are formed by liquid-phase sintering as a result of combining elemental tungsten powder and small amounts of transition metals that are heated from 1,100–1,500°C. These temperatures exceed the melting points of the transition metals, but not tungsten. Consequently, this sintering process produces a two-phase microstructure consisting of nearly pure tungsten microparticles embedded in a solid matrix composed of tungsten and variable amounts of transition metals depending on the temperature of the process and the amount of transitional metals.

Uses

Tungsten uses include the following: tungsten carbide, 65%; alloy additives, 16%; elemental tungsten, 16%; and tungsten chemicals, 3%.[7] The addition of tungsten to ferrous and nonferrous alloys increases hardness and tensile strength. Consequently, tungsten possesses a prominent place in the space and nuclear industry as a result of the frequent presence of tungsten as a component of alloys (e.g., steel, hard metal). Heavy metal tungsten alloy-based munitions ("green bullets") are alternatives to depleted uranium and lead in military applications.[14] Typically, these munitions contain 91–93% tungsten in combination with 3–5% nickel and either 2–4% iron or 2–4% cobalt. Tungsten concentrations in shots for hunting waterfowl typically range from 20–70% along with bronze, iron, nickel, and tin, whereas kinetic-energy penetrators usually contain >90% tungsten.[15] In addition, cemented tungsten carbide has replaced diamonds in most applications requiring a hard surface (e.g., rock drills, high-speed tool bits, grinding wheels, cutting tools). Tungsten wires, electrodes, contacts are common constituents of electrical and electronic applications.

Elemental tungsten is an electron emitter, a connector for aluminum layers in semiconductors, and a component of welding electrodes (e.g., thoriated tungsten), turbine blades, X-ray and electron tubes, lasers, rocket nozzles, high-speed rotors (e.g., gyroscopes), counterbalance weights, and consumer products (golf clubs, fishing weights, hunting munitions, lamp/light bulb filaments).[16] Tungsten disulfide is a solid lubricant, whereas deposition of tungsten coatings involves carbonyl, chloride, and fluoride salts of tungsten. Tungsten compounds (e.g., oxides, sulfides, hexachloride) are stable catalysts for a variety of chemical processes. Uses for sodium tungstate include the fireproofing of textiles, manufacture of tungsten-based catalysts, and production of colorants for printing inks, cigarette filters, waxes, glasses, and textiles. In Zucker diabetic fatty rats and streptozotocin-induced diabetic rats, the administration of oral sodium tungstate reduces blood glucose concentrations by a mechanism independent of the insulin receptor.[17,18] Ammonium paratungstate is a precursor of high-purity tungsten oxides, tungsten, and tungsten carbide powders, whereas tungsten trioxide is a source of tungsten metal and tungsten carbide powders. Table 33.2 lists occupations with potential exposure to tungsten or tungsten compounds; actual exposure varies with changes in the composition of products, production processes, and improvements in ventilation. Sodium tungstate is an experimental drug for the treatment of diabetes and obesity.[19,20]

Sources

Environmental sources for tungsten include alloy fabrication, municipal waste combustion, ore processing,

TABLE 33.2. Occupations with potential exposure to tungsten or tungsten compounds. (Adapted from Agency for Toxic Substances and Disease Registry).[7]

Alloy makers	Melting, pouring, casting workers
Carbonyl workers	Metal sprayers
Ceramic workers	Ore-refining and foundry workers
Cemented tungsten carbide workers	Paint and pigment makers
Cement makers	Papermakers
Dye makers	Pen-point makers
Dyers	Petroleum refinery workers
Flameproofers	Photographic developers
High-speed tool steelworkers	Spark-plug makers
Incandescent-lamp makers	Textile dryers
Industrial chemical synthesizers	Tool grinders
Ink makers	Tungsten and molybdenum miners
Lamp-filament makers	Waterproofing workers
Lubricant makers	Welders

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and tungsten carbide production. Although limited data are available, the exposure of the general population to tungsten is probably very low. The daily intake of tungsten averaged ~10 μg in four health volunteers given controlled diets and followed for 5 days.[21]

Air

Windblown dusts release tungsten to the atmosphere in very low tungsten concentrations (<10 ng/m^3); the unusually high density of tungsten limits the dispersion of tungsten to nondetectable concentrations (<1.5 ng W/m^3) unless near industrial sources or related to fallout from tungsten-containing explosives.[16,22] Occupational exposure to respirable particles of tungsten primarily occurs in scheelite and wolframite milling operations and near powder metallurgy operations that utilize tungsten or hard metal.[23] Tungsten oxide fibers are by-products of the reduction stage of the raw material used to produce tungsten carbide.[24] Air sampling of particulate matter in six US cities (Cincinnati, Denver, St. Louis, Washington, Chicago, Philadelphia) during winter of 1969–1970 demonstrated average tungsten concentrations of ~1 μg/m^3 (range, 0.1–2 μg/m^3).[25] During the late 1970s, a study of particulate emissions from five copper smelters in Arizona demonstrated a mean tungsten concentration of 15 ± 2 ng/m^3 (0.015 ± 0.002 μg/m^3).[26] Analysis of emissions from the stack of coal-burning facilities demonstrated tungsten concentrations ranging up to ~23 μg/m^3.[27]

Soil

Tungsten is the 18th most abundant metal in the Earth's crust, with tungsten concentrations in surface soils usually <2.5 mg/kg dry weight, but some areas (e.g., Alaska) exceed 24 mg/kg.[27,28] Higher tungsten concentrations in soil occur near point sources of tungsten. In a study of soil during the Gulf War (1990–1991), maximum tungsten concentrations (126 mg/kg) occurred in surface soil (<5 cm) near the Saudi Arabian–Kuwait border.[29] In surface soil 300 km from the border, the tungsten concentration was 3.25 mg/kg. The dissolution of tungsten in soil caused acidification, whereas high tungsten concentrations (i.e., >1%) produced a reduction in soil microbes and an increase in the fungal biomass.

Water

Tungsten is not usually detectable in US surface water or groundwater, except near mineral formations containing tungsten. Tungsten concentrations in drinking water are usually <0.1 μg/L; however, areas with tungsten formation (Nahanni River Basin in Northwest Territories of Canada, Iceland) may have elevated tungsten concentrations in groundwater and surface water. A study of surface water and groundwater down to 60 m from the Ethiopian Rift Valley demonstrated a median tungsten concentration of 0.11 μg/L with a range of <0.002–3.81 μg/L.[30] Higher tungsten concentrations (i.e., up to ~550 μg/L) occurred in nearby lakes. In Fallon, Nevada, several studies were conducted in the early 2000s by the US Agency for Toxic Substances and Disease Registry because of concerns about tungsten concentrations in drinking water. The mean tungsten concentration in samples from 76 private and municipal water supplies was 19.9 μg/L.[6] In samples from the private residential wells, the mean tungsten concentration was 37.5 μg/L with a range of 0.25–337 μg/L. Only trace amounts of tungsten (i.e., ~0.1 μg/L) are typically present in seawater.[7]

Diet

There are few data on the amount of tungsten in food or the daily tungsten intake from the diet. The estimated daily tungsten intake of four healthy adults fed diets with variable amounts of calcium ranged from 8–13 μg.[21] In a study of Danish onions grown commercially without known contamination, the mean tungsten concentration was 16.7 μg/kg fresh weight (n = 64; range, 6.3–39 μg/kg).[31] Certain plants (e.g., tomatoes) may exclude tungsten, whereas other plants (e.g., eucalyptus trees, rye grass, and *Calluna vulgaris* or heather) accumulate tungsten.[32,33] In a study of trace elements in Italians, beverages contributed significantly to the daily tungsten intake.[34] Mean tungsten concentrations in common beverages were as follows: wine, 1.7 ± 1.4 μg/L; beer, 7.4 ± 6.5 μg/L; tea infusion, 0.31 ± 0.51 μg/L; instant coffee, 1.8 ± 0.3 μg/L; and mineral water, 1.1 ± 1.2 μg/L.

Environmental Fate

Tungsten is a lithophilic element that occurs primarily in terrestrial rather than atmospheric or aquatic environments with very low concentrations in air and water.

Air

In the atmosphere, tungsten exists in the particulate phase because of the low vapor pressure of tungsten and tungsten compounds with the exception of tungsten carbonyl and tungsten hexafluoride. Windblown dusts naturally contain tungsten; anthropogenic processes

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may release tungsten into air including the production and use of tungsten carbide, processing of tungsten ore, and hard metal fabrication. There is no current evidence that insoluble or soluble particulate-phase tungsten reacts with carbon dioxide or other compounds in the atmosphere.[27]

Soil

Following distribution to soil, tungsten exists as either soluble ions (e.g., tungstate ion, WO_4^{2-}) or insoluble (e.g., tungsten trioxide) tungsten species. Potentially, tungsten can form soluble complexes with a variety of inorganic and organic ligands. Monomeric tungstate is stable only at pH ≥6.2; tungstate is the main soluble species in alkaline environments.[22] In acidic environments, polymerized tungstate species may predominate. Although tungsten hexacarbonyl may occur in gas from municipal landfills,[35] the presence of methylated tungsten and other organic tungsten species is not well-documented.

The mobility of tungsten in soil is low to moderate as a result of tungsten binding to clay minerals and organic matter based on *in vitro* studies of tungsten alloys.[36] The adsorption coefficient (Kd) for tungsten increases with decreasing pH; consequently, soil mobility of tungsten decreases in an acidic environment. Soluble tungsten compounds (e.g., tungstates) may leach into groundwater. There are inadequate data to determine the extent of conversion of tungsten between different anions and the bioavailability of tungsten in various forms to plants and animals; typically, the tungsten concentration in edible plants is low (i.e., <0.1 ppm).[37]

Water

Tungsten naturally enters waterways through erosion (i.e., weathering of rocks and soils) and anthropogenic sources (mining, tungsten manufacturing processes). Elemental tungsten and metal alloys occur in water as insoluble solids, whereas tungsten compounds exist as insoluble solids or ions adsorbed to suspended sediment. Dissolution of elemental tungsten in aqueous solution probably occurs through a stepwise anodic oxidation of the metal to the W^{6+} oxidation state through the formation of less stable, lower oxidation states (W^{3+}, W^{4+}, W^{5+}).[32] *In vitro* studies suggest that this dissolution is typically associated with a reduction of local pH and dissolved oxygen concentration in the presence of other metals (e.g., cobalt, iron, and nickel in ammunition-grade tungsten alloy).[36] The extent of tungsten dissolution into more soluble polytungstate ions also depends on the presence of these metals. Iron enhances the dissolution of tungsten, whereas cobalt reduces the rate and amount of dissolution. Under neutral, mildly alkaline conditions (i.e., pH >6.2), tungsten exists in water primarily as the soluble tungstate ion, whereas other polyanions predominate under acidic conditions. Tungsten easily forms complexes including heteropoly acids from phosphorous oxides (e.g., phosphotungstic acid), arsenic, silicon, and vanadium.[7] Tungsten also combines with a large number of organic ligands; however, there are few data on the extent of these ligands in water or soil.

DOSE EFFECT

The poor solubility of tungsten limits its toxicity. The administration of oral W doses of 25–80 g to patients as a substitute for barium in radiological studies did not produce observable toxic effects.[1] Based on animal studies, soluble tungsten compounds (e.g., sodium tungstate) are much more toxic following acute exposure than elemental tungsten and insoluble tungsten compounds.[38,39] Subchronic animal studies indicate tungsten carbide dust is relatively inert following intratracheal instillation[4] with elemental tungsten producing slightly more local inflammation compared with tungsten carbide.[40] Preclinical studies on repeated oral exposure of sodium tungstate indicate body weight reduction, and nephrotoxicity may occur at daily doses of 125–250 mg/kg; however, rodent studies with molybdate suggest rats and humans may handle tungstate differently.[41]

TOXICOKINETICS

Sparingly soluble tungsten compounds have limited *in vitro* bioavailability suggesting primarily fecal excretion after oral exposure, whereas soluble tungsten compounds (sodium tungstate, tungsten oxides) are absorbed following oral or pulmonary routes with excretion primarily via the kidney.[41] The dermal bioavailability of tungsten and tungsten compounds is very minimal.

Absorption

There are few data on the kinetics of tungsten in humans following inhalation or oral exposure. The gastrointestinal absorption of soluble tungsten (e.g., sodium tungstate) is rapid and relatively good (i.e., >50%) based on animal studies,[42] whereas the oral absorption of elemental tungsten and tungstic acid is low. *In vitro* studies of elemental tungsten particles using comprehensive

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artificial gastric juice formulations (NIOSH, ASTM, USP) and static dissolution technique indicate limited gastrointestinal absorption of elemental tungsten as a result of the short residence time in the stomach and the relatively long mean dissolution half-times varying from 60 ± 2 days (NIOSH) to 381 ± 84 days (USP).[43] In a 5-day study of four healthy volunteers fed a controlled diet that included 10 μg W/day, the balance study indicated ~60% of the tungsten was adsorbed as measured by neutron activation analysis; the species of tungsten in the diet was not reported.[7,21] Animal studies with ^{187}W suggest the gastrointestinal tract does absorb substantial (40–50%) soluble tungsten compounds containing the tungstate ion (WO_4^{2-})[44] with peak plasma tungsten concentrations occurring ~1–4 hours after the oral gavage of rodents with sodium tungstate.[45]

Distribution

Following the absorption from the gastrointestinal tract, distribution of tungsten occurs relatively rapidly, primarily to the bone, spleen, liver, and kidneys.[46] In contrast to ingestion, the highest tungsten concentration appears in the lungs and kidney following inhalation of insoluble tungsten compounds (e.g., tungsten oxide).[47] In rats administered sodium tungstate, most serum tungsten (i.e., ~80%) is bound to albumin with little binding to transferrin as measured by size exclusion chromatography/inductively coupled plasma/mass spectrometry and matrix-assisted laser desorption ionization/time-of-flight analysis.[18] Biokinetic modeling based on animal studies suggests that the kinetics of tungsten are similar to those of uranium rather than molybdenum with total transfer from plasma to all destinations in ~17 days.[48] These models predict that ~75% of the tungsten leaving the plasma passes directly into the bladder with ~5% deposited in the kidneys. At least a few tenths of 1% of the absorbed tungsten is retained in bone for an extended period.

Elimination

Following ingestion, elimination of insoluble forms of tungsten occurs primarily in the feces. Excretion of absorbed tungsten occurs rapidly (1–2 days) in the urine with animal studies indicating an initial plasma elimination half-life of 2–4 hours for soluble forms of tungsten (sodium tungstate) based on a two-compartment model.[42,49] However, animal studies indicate that bone is a repository for tungsten with a biological half-life exceeding 3 years.[44]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Although molybdenum is an essential element for several enzymes (e.g., aldehyde oxidase, mitochondrial amidoxime reductase, nitrate reductase, sulfite oxidase, xanthine dehydrogenase) in human and animal eukaryotes, tungsten is an essential element only for prokaryotes (i.e., microscopic, single-cell organisms including anaerobic bacteria, and cyanobacteria), probably as a result of the lower reduction potential of tungsten compared with molybdenum.[50] Elemental tungsten is relatively inert with low toxicity; data associating tungsten with human toxicity involves alloys of tungsten including elements other than pure elemental tungsten.

Mechanism of Toxicity

Tungsten Carbide

Hard metal disease is a giant cell interstitial illness of workers exposed to dusts from the manufacturing or grinding of tungsten carbide-containing tools or drill;[51] however, this disease probably results from exposure to the cobalt binders in combination with tungsten carbide (see chapter on Cobalt) because animal studies indicate that tungsten is relatively inert.[3] Tungsten may enhance the toxic effects of cobalt on the lungs based on animal studies that demonstrate pulmonary fibrosis in rats following the intratracheal instillation of tungsten carbide and cobalt in combination, but not in rats exposed to tungsten carbide or cobalt alone.[52] *In vitro* radiotracer studies indicate that solubility of tungsten in hard metal dust in blood and lung tissue is very low compared with cobalt; however, the low affinity of tungsten for proteins results in relatively high mobility of dissolved tungsten.[53] Additionally, *in vitro* studies indicate that markedly high tungsten concentrations (60,500 μg/L compared with 0.4 μg/L in human serum) in culture medium for 12 days do not inhibit the growth of human fibroblasts, vascular smooth muscle, or endothelial cells on the tungsten coils.[54] In contrast, *in vitro* studies indicate the specific tungsten alloy (91% W, 6% Ni, 3% Co) produces large amounts of reactive oxygen species, local cytotoxicity, inhibition of caspase-3, and DNA damage.[55] Other tungsten alloys without cobalt do not cause similar cellular reactions.

Elemental Tungsten

There are no human studies demonstrating tungsten **alone** causes respiratory disease; the interstitial lung

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disease associated with the cemented tungsten carbide industry probably results from the cobalt binders rather than exposure to tungsten.[56,57] Tungsten carbide is relatively inert with minimal reactivity with oxygen; however, *in vitro* studies indicate tungsten is a good electron conductor that may contribute to the formation of interstitial fibrosis by altering the ionic state of metallic cobalt, thereby increasing the cobalt solubility, the transfer of cobalt ions to the carbide surface with increased oxygen reduction, and the generation of active oxygen radicals.[58,59]

Histological examination of 10 rabbits implanted 4 months earlier with tungsten coils in their subclavian artery did not demonstrate inflammation in or near the subclavian artery.[60] Additionally, there was no evidence of degeneration or necrosis in the peri-subclavian fatty tissue and no lymphadenopathy along the subclavian artery. The explanted coils had massive corrosion; the mean serum tungsten concentration increased from 0.48 ng/mL at implantation to 14.6 ng/mL at explantation. In experimental studies, sodium tungstate antagonizes the metabolic action of molybdenum as a metal carrier for certain enzymes (xanthine oxidase, sulfite oxidase, aldehyde oxidase) in the body.[61] A high-tungsten and low-molybdenum diet reduces the activity of these molybdenum-dependent enzymes; however, the role of molybdenum in any toxicity related to tungsten is unclear, as small amounts of supplemental molybdenum reverse any tungsten-related effects in these animal models.[62] The presence of nickel or cobalt in tungsten alloys probably accounts for the development of dermatitis in tungsten carbide workers rather than any hypersensitivity to tungsten. Studies of metallic tungsten, tungsten carbide, and tungsten disulfide nanoparticles suggest these substances are relatively inert; however, exposure to tungsten carbide or tungsten disulfide may cause some oxidative stress.[63,64]

Pathological Changes

Retained tungsten may persist in tissues depending on a variety of factors including size, surface area, pH, oxygen tension, and duration of retention. Analyses of electrochemical equilibria data in aqueous solutions suggest a pH of <7.4 enhances the formation of protective oxide layers on the surface of tungsten particles (i.e., passivation), whereas alkaline environments (i.e., pH >7.4) facilitate corrosion of the particles.[65] Biopsies of lungs from workers with hard metal disease may demonstrate only tungsten carbide because of the greater cobalt solubility compared with tungsten solubility. Tungsten carbide is a constituent of coatings on cautery tips. A 44-year-old woman presented with radiographic findings suggestive of microcalcifications associated with ductal carcinoma *in situ*.[66] Twelve years earlier, she had a benign lump removed in the same area of her breast. Histological examination of core samples demonstrated small fragments of refractile, non-birefringent material with focal foreign body giant cell reactions and black granule-containing macrophages. Analysis of the material confirmed the presence primarily of tungsten and smaller amounts of calcium, carbon, oxygen, and sulfur. The authors concluded that the most likely source of this material was the tungsten carbon coating of a cautery tip left in the breast 12 years earlier.

Postmortem Examination

Postmortem examination of workers with hard metal pneumoconiosis indicates that tungsten remains detectable in the lung for extended periods of time following exposure to hard metal dust.[67]

CLINICAL RESPONSE

Acute Toxicity

Elemental and water-insoluble tungsten compounds have minimal physiological activity. Water-soluble tungsten compounds may cause gastrointestinal symptoms; however, these gastrointestinal effects are not well documented in the general population or the work environment. A 19-year-old recruit in a French artillery regiment drank 250 mL of a mixture of beer and wine that he rinsed in a hot 155 mm gun-barrel containing tungsten and other chemicals.[68] Shortly thereafter, he developed nausea, seizures, and obtundation followed by acute tubular necrosis and anuria. His renal failure gradually resolved without reported sequelae. Analysis of the drink by inductively coupled plasma (ICP)/emission spectrometry revealed very high concentrations of tungsten (1,540 mg/L) in the beverage; however, exposure to aromatic nitrogen compounds in this drink may have contributed to or caused toxicity. The species of tungsten was not reported. Clinical studies do not support the use of sodium tungstate as a pharmaceutical agent for weight loss.[69]

Environmental Exposure

An exploratory study of urine tungsten concentrations in 2,465 randomly selected participants in the 1999–2000 National Health and Nutrition Examination

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Survey (NHANES) suggested an association between urine tungsten concentrations and peripheral artery disease.[70] The adjusted odds ratio for peripheral artery disease comparing the 75th to the 25th percentile of patients based on the urine tungsten concentration was 2.25 (95% CI: 0.97–5.24). The results must be interpreted cautiously because of multiple comparisons (nine metals), the wide confidence interval that included zero, and the use of an estimated 25th percentile because 30% of the urine tungsten concentrations in the selected population were below the lower limit of quantitation.

Percutaneous coil embolism is a medical procedure that uses tungsten coils to occlude leaking blood vessels. Favorable properties of tungsten for this application included high radiopacity, thrombogenicity, and ease of use; however, prolonged use caused corrosion despite the purity of the tungsten (>99.9%). In a study of 21 patients with tungsten coils implanted for aneurysms and fistulas, the mean tungsten load was 220 mg (18.5 mg/kg) with a range of 50–520 mg (4.9–45 mg/kg).[71,72] As a result of corrosion of the tungsten coils, follow-up studies demonstrated elevated tungsten concentrations after implantation in some, but not all, of these patients.[73] Studies following these patients for up to 3 years did not report adverse effects from the elevated tungsten concentrations. No further adverse effects or clinical studies have been reported in the medical literature over the subsequent decade since the original studies were published.

Occupational Exposure

There are few data associating tungsten exposure alone with chronic diseases. Pneumoconioses probably do not develop in workers exposed only to elemental tungsten or insoluble tungsten compounds. A mortality study of 5,054 workers employed at a titanium dioxide plant for at least 6 months found mortality rates similar to the general population with no increased mortality from nonmalignant or malignant respiratory disease.[74]

Carcinogenesis

Human

Neither the International Agency for Research on Cancer (IARC) nor the US National Toxicology Program (NTP) lists elemental tungsten or tungsten compounds as carcinogenic in humans; however, the IARC lists cobalt metal with tungsten carbide as a probable human carcinogen (Group 2A). The NTP lists cobalt–tungsten carbide as reasonably anticipated to be a human carcinogen.

A childhood-leukemia cluster occurred in Fallon, Churchill County, Nevada, where a hard metal manufacturing facility is located. Airborne particulate samples collected by 10 portable, high-volume particulate air samplers in Fallon during March, April, and November demonstrated higher ambient air tungsten concentrations in Fallon compared with four nearby towns.[75] The samples contained tungsten and cobalt air concentrations reported as significantly (P = 0.001–0.002) higher in Fallon (range, tungsten = 0.1–40.9 ng/m^3; range, cobalt = 0.04–7.5 ng/m^3) than surrounding towns (range, tungsten = 0.02–0.16 ng/m^3; range, cobalt = 0.04–0.58 ng/m^3). The environmental tungsten concentrations in Fallon were over an order of magnitude below current workplace standards. Both arsenic and tungsten contaminated drinking water in Churchill County. In a study of 307 tap water samples from households in this area, the median total tungsten concentration was 2 ng/mL (mean = 26 ng/mL; range, <1–610 ng/mL), whereas the median total arsenic concentration was 27 ng/mL (mean = 93 ng/mL; range, <3–2,196 ng/mL).[76] A cross-sectional case comparison study found no relationship between leukemia occurrence and urinary tungsten concentrations.[77] Additionally, there was no statistically significant association (odds ratio = 0.78, P = 0.57) between tungsten exposure from drinking water and leukemia observed in a sample population from Churchill County, Nevada. The leukemia cluster at Fallon exhibited similar age and immunophenotype profiles as most childhood leukemia cohorts consistent with an infectious pattern affecting the timing and incidence of the cluster.[78]

Animal

In a study of male F344 rats implanted with 4 (110 mg) and 20 pellets (550 mg) of military weapons-grade tungsten alloy pellets (91.6% tungsten, 6% nickel, 2.9% cobalt) in their hind legs, all 92 rats developed high-grade pleomorphic rhabdomyosarcomas within 16–20 weeks that rapidly metastasized to the lungs.[15] All of the positive controls (280 mg nickel) also developed similar tumors that required euthanasia, but the rate of tumor development was slower in controls than in weapons-grade tungsten alloy tumors. No tumors occurred in the rats implanted with tantalum (negative control) within the 1-year study. In this study, the role of tungsten in the carcinogenic effect of tungsten alloy pellets was unclear because of the known carcinogenic effect of the intramuscular administration of nickel and cobalt. Subsequent rodent studies suggest differential species responses and synergy between the three-component tungsten alloys rather than tungsten

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alone. A 24-month rodent study examined groups of 20 male B6C3F$_1$ mice implanted with pellets containing one or two metal components of military-grade tungsten ammunition in the quadriceps after using an identical amount of the biologically inert tantalum (Ta) to replace the remaining components.[79] Sarcomas developed in 20% (n = 4) of the CoTa-implanted mice, 5% (n = 1) of WCoTa-implanted mice, and 5% (n = 1) of the WTa-implanted mice. These values were substantial below 80% of F344 rats developing rhabdomyosarcomas in the previous study. Another 24-month study examined groups of 20 male B6C3F$_1$ mice demonstrated the formation of rhabdomyosarcomas in the quadriceps of the high-dose WNiCo group, but not in the WNiFe group.[80] In contrast to the rat model, the rhabdomyosarcomas in the WNiCo group did not metastasize or exhibit aggressive growth patterns.

Subsequent studies confirmed that the tungsten/nickel/cobalt alloy, but not specifically tungsten, is carcinogenic. In a study of male F344 rats implanted intramuscularly with pellets of tungsten/nickel/cobalt, tungsten/nickel/iron, or pure tungsten, metastatic rhabdomyosarcomas formed around only tungsten/nickel/cobalt pellets between 6 and 12 months; no tumors developed in the rats implanted with tungsten/nickel/iron, pure tungsten, or tantalum pellets (negative control).[81] Urine tungsten concentrations ranged up to ~2,000 ng/mL in the high-dose wing of the study. Examination of the pellets demonstrated progressive, deep corrosion in the tungsten/nickel/cobalt pellets, but not in the tungsten/nickel/iron or pure tungsten pellets. Microarray analysis of the tumors associated with the tungsten/nickel/cobalt pellets demonstrated significant changes in gene expression including upregulation of the biological process of the cell cycle and downregulation of those involved with muscle development and differentiation. An 8-month pilot study on sodium tungstate administration to streptozotocin-induced diabetic rats did not detect any pathological changes consistent with carcinogenicity.[82]

DIAGNOSTIC TESTING

SI Conversion Units

1 μmol/L = 183.8 μg/L
1 μg/L = 0.005440 μmol/L

Analytical Methods

Methods for the quantitation of tungsten in biological samples include inductively coupled plasma/atomic emission spectrometry (ICP/AES; LOD, 50 μg/L), inductively coupled plasma/mass spectrometry (ICP/MS; LOD, 0.02–0.3 μg/L) after pretreatment with nitric acid,[83] chelation ion chromatography (CIC) coupled with on-line detection by ICP/MS, neutron activation analysis (NAA; LOD, 5 ng/g), atomic absorption spectrometry (AAS), and UV/Visible spectroscopy (UV/VIS). The limits of detection for tungsten in urine samples using ICP/MS are about one to two orders of magnitude lower than AAS using both quadrupole (LOD, 0.36 ng/L) and sector field (LOD, 0.49 ng/L) instrumentation.[84] The use of ICP/MS without sample pretreatment allows detection of tungsten at 5 ng/mL (LLOQ, 10 ng/mL) with some matrix-related interferences.[85] High-pressure liquid chromatography/inductively coupled plasma/mass spectrometry coupled with specialized separation methods including matrix-assisted laser desorption ionization/time-of-flight, size exclusion chromatography, anion exchange chromatography, or electrospray ionization/mass spectrometry detection allows the speciation of tungsten biomolecule complexes (e.g., polyoxotungstates).[18,86]

Samples for ICP/AES and ICP/MS are typically wet-ashed with nitric acid at elevated temperatures and then diluted prior to analysis. Most analytical methods (e.g., ICP/AES, ICP/MS, Flame AAS, UV/VIS spectrophotometry, NAA) for determining tungsten in biological media are also applicable to the analysis of tungsten concentrations in environmental samples (e.g., soil, water, and air). Flame AAS is the NIOSH-recommended technique (Method 7074) for determining tungsten in air with detection limits of 50 μg of soluble tungsten (LLOQ, 0.25 mg/m^3) and 125 μg of insoluble tungsten per sample (LLOQ, 0.6 mg/m^3). Results reported for tungsten typically are total tungsten concentrations without speciation.

Biomarkers

Blood

General Population

In a study of 8 healthy and 16 untreated hypertensive volunteers during the 1970s, there was no statistically significant difference in the serum tungsten concentration between the 2 groups as measured by neutron activation analysis; however, there was wide variation in the tungsten concentrations between the healthy volunteers (mean = 5.8 ± 3.5 μg/L) and untreated hypertensive volunteers (mean = 11 ± 13 μg/L).[87] More recent studies indicate serum tungsten concentrations in blood samples

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TABLE 33.3. Blood tungsten concentrations in studies of patients presenting with corroding tungsten coils. (Data from Butler et al.).[94]

Study	Mean Exposure[a] (Range)	Number of Patients	Mean Serum Tungsten (Range, μg/L)	Mean Whole Blood Tungsten (Range, μg/L)	Reported Adverse Effects
Butler et al.[94]	16.7 (2–39)	10	10.7 (6.2–18.4)[c]	8.4 (4.7–15.1)[c]	None
Bachthaler et al.[73]	26 (15–38)	6[b]	NA	4.0 (1.3–7.2)	None
Peuster et al.[71]	16 (6–35)	8	6.43 (2.0–14.4)	NA	None

Abbreviation: NA = not available.
[a] Months; [b]The other 8 of 14 patients in this series had normal whole blood tungsten concentrations that were reported as <0.7 μg/L; [c]95% CI range.

from the general population without occupational exposure to tungsten are typically <0.5–1 μg/L with serum tungsten concentrations slightly lower than whole blood tungsten concentrations.[88] The tungsten concentrations from 355 Swedish urban adolescents were above the limit of detection ($n = 355$, LOD = 0.04 μg/L) in 79% of the serum samples with a maximum of 1.8 μg/L, whereas only 7% of whole blood concentrations in this same group had detectable tungsten concentrations ($n = 326$, LOD = 0.2 μg/L) with a maximum of 0.94 μg/L.[89] Similarly, only 6% of the whole blood samples from 130 northern German residents contained tungsten concentrations above the LOD (0.011 μg/L) with an upper 95th percentile of 0.017 μg/L as measured by inductively coupled/plasma mass spectrometry with an octopole-based collision/reaction cell.[90] In an Italian study of urban residents from Umbria, the mean serum tungsten concentration was 0.15 ± 0.004 μg/L (range, 0.05–0.40 μg/L) with a 95th percentile of 0.26 μg/L as measured by sector field/inductively coupled/plasma mass spectrometry (LOD, ~0.005 μg/L).[91] The arithmetic mean serum tungsten concentration in 218 Calabrian residents was similar (0.12 ± 0.003 μg/L).

Tungsten Coil Implants

Human A study of 19 patients followed a mean of 40 months after endovascular embolization of the spermatic vein with tungsten coils, the whole blood tungsten concentrations ranged from <1.0–4.8 μg/L.[92] Serum tungsten concentrations may increase soon after implantation in patients with large tungsten loads. The serum tungsten concentration was 4.95 μg/L in a sample drawn 3 months after the implantation of 225 cm of tungsten spirals (Mechanical Detachable Spirals, Balt, Montmorency, France) for a dural fistula.[93]

In a series of 10 patients with tungsten coils inserted during aortic aneurysm surgery, the mean whole blood tungsten concentration was 8.4 μg/L (95% CI: 4.7–15.1 μg/L) compared with 0.44 μg/L (95% CI: 0.37–0.51 μg/L) for a control group matched for age and sex.[94] Table 33.3 lists the mean and range of tungsten concentrations in three studies of blood samples from patients with corroding tungsten coils.

Animal Animal studies confirm the occurrence of increased blood tungsten concentrations following the retention of tungsten-containing material (e.g., coils, stents, and bullets).[95] In a study of 10 New Zealand white rabbits receiving tungsten coil implants in their subclavian artery, the mean serum tungsten concentrations increased from 0.48 μg/L (range, 0.2–1.8 μg/mL) before implantation to 12.6 μg/L (range, 9.9–22.0 μg/L) 4 months after implantation. Despite corrosion of the tungsten coils and elevated serum tungsten concentration, there was no histological evidence of local toxicity (i.e., peri-subclavian fat) or damage to any organs (heart, kidney, liver, lung, pancreas, spleen).

Overdose

A 19-year-old military recruit was transferred from a respirator to a tertiary referral center after the ingestion of a tungsten-containing liquid. He was acidotic with mildly elevated serum hepatic aminotransferases and hyperkalemic with moderate renal dysfunction requiring dialysis.[96] Renal biopsy demonstrated acute tubular necrosis. He was extubated the day after admission; no other seizures occurred. In admission blood samples at the tertiary referral hospital, the serum creatine phosphokinase was 1,287 IU/L and the serum tungsten concentration was 4,960 μg/L. Screening with high-performance liquid chromatography/diode array spectrophotometric detection and gas chromatography/mass spectrometry did not detect any other intoxicants in the wine. Two other military recruits vomited after drinking the wine; they did not develop any other sequelae.[97]

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TABLE 33.4. Urine tungsten concentrations in two studies of patients presenting with corroding tungsten coils. (Data from Butler et al.).[94]

Study	Mean Duration Exposure (Range, months)	Number	Mean Urine Tungsten (Range, µg/L)	Reported Adverse Effects
Butler et al.[94]	16.7 (2–39)	10	335 (209–539)[a]	None
Bachthaler et al.[73]	26 (15–38)	14	419.1 (2.0–837.7)	None

[a] 95% CI range.

Urine

General Population

Typically, urine tungsten concentration in the general population without occupational tungsten exposure is <1 µg/L.[88] The mean tungsten concentration in 24-hour urine samples from 14 German adults without occupational exposure to tungsten was 0.21 ± 0.09 µg/L with a range of 0.10–0.32 µg/L as measured by inductively coupled plasma/mass spectrometry.[83] In a study of 34 Northern Italian adults (mean age, 61.4 ± 12.4 years), the mean urinary tungsten concentration was 0.08 µg/L (95% CI: 0.02–0.26 µg/L),[98] whereas the mean urine tungsten concentration in 50 randomly selected central Italian adults was 0.77 ± 0.80 µg/L as measured by sector field/ICP/MS.[84] The values for the latter group were not normally distributed (geometric mean = 0.052 µg/L; range, 0.009–0.410 µg/L). The geometric mean of urine tungsten in representative samples of the US population collected in 2009–2010 during the National Health and Nutrition Examination Survey (NHANES IV) was 0.081 µg/L (95% CI: 0.075–0.087 µg/L); the corresponding creatinine-corrected value was 0.086 µg/g creatinine (95% CI: 0.080–0.093 µg/g creatinine).[99] NHANES data indicate the mean urinary tungsten concentration in smokers (mean = 0.10 µg/L, 95% CI: 0.091–0.111) is significantly higher than nonsmokers (mean = 0.08 µg/L, 95% CI: 0.076–0.084).[100] The mean tungsten concentration in 496 urine samples selected from participants in the NHANES III study and collected from 1988–1994 was 1.92 µg/L (1.92 µg/g creatinine) for all ages and sexes.[101] The upper 95th percentile was 3.31 µg/L (2.83 µg/g creatinine) with an LOD = 0.3 µg/L. The specimens represented a broad spectrum of the population (all ages and both sexes), but the sampling was not randomized. In a group of healthy patients consuming a normal diet, daily urinary excretion of dietary tungsten ranged from 2–13 µg as measured by neutron activation analysis, whereas the mean daily urinary excretion of tungsten in hypertensive patients was about 35 µg.[87]

Urinary tungsten concentrations in the general population vary with local sources of tungsten. During an investigation of a cluster of childhood leukemia in Churchill County, Nevada, a cross-sectional study of urine tungsten concentrations in the community demonstrated a geometric mean of 1.19 µg/L (95% CI: 0.89–1.59 µg/L) compared with the US National Exposure Report reference mean of 0.08 µg/L (95% CI: 0.07–0.09 µg/L).[102] The former value reflected a relatively high tungsten concentration in Church Hill drinking water (GM = 4.66 µg/L; 95% CI: 2.98–7.30 µg/L).

Tungsten Coils

Most follow-up studies of patients with tungsten coils implanted for embolization therapy have elevated urine tungsten concentrations compared with the population without occupational tungsten exposure.[73] In a series of 10 patients with tungsten coils inserted during aortic aneurysm surgery, the urine tungsten concentrations ranged from 290–539 µg/L compared with <1 µg/L in 10 age- and sex-matched controls.[94] Table 33.4 lists the mean and range of tungsten concentrations in two studies of urine samples from patients with corroding tungsten coils.

Abnormalities

Tungsten is radiodense, resulting in the presence of opacities following retention in tissues. Abnormalities in serum chemistries are not typically associated with exposure to elemental tungsten or tungsten compounds.

HEALTH SURVEILLANCE

Environmental Monitoring

The US OSHA PEL–TWA for exposure to soluble tungsten compounds in the construction and shipyard industries is 1 mg W/m^3 with a STEL of 3 mg W/m^3. OSHA established a PEL–TWA of 5 mg W/m^3 for elemental tungsten and its insoluble compounds with a STEL of 10 mg W/m^3 to reduce the risk of pulmonary fibrosis from other dusts (e.g., cobalt). ACGIH has similar guidelines for tungsten exposure as demonstrated

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TABLE 33.5. Guidelines and regulations for exposure to tungsten in workplace air.

Media	Value
	OSHA[a]
PEL–TWA (8-hour)[b]	5 mg W/m^3 (elemental/insoluble W)
	1 mg W/m^3 (soluble W)
	NIOSH
REL–TWA (10-hour)	1 mg W/m^3 (soluble W)
	5 mg W/m^3 (elemental W/insoluble W salts)
REL–STEL (15-minute)	3 mg W/m^3 (soluble W salts)
	10 mg W/m^3 (elemental W/ insoluble W salts)
	ACGIH
TLV–TWA (8-hour)	3 mg W/m^3 (elemental W/W salts)[c]

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; STEL = short-term exposure limit; TLV = threshold limit value; TLV–TWA = respirable particulate matter; TWA = time-weighted average.
These guidelines and regulations for exposure to tungsten and tungsten compounds assume these substances do not contain cobalt. For co-exposures to cobalt or nickel (e.g., tungsten carbide), separate guidelines and regulations apply, depending on cobalt and nickel concentrations nickel concentrations.
[a] In July 1992, the 11th Circuit Court of Appeals vacated PELs set by OSHA in 1989 for 212 substances including tungsten. Currently, OSHA does not have regulations for tungsten exposure except for the maritime and construction industries; [b]Shipyards, construction industries only; [c]As respirable particulate matter in absence of cobalt.

in Table 33.5. Analysis of data for the derivation of no-effect levels for tungsten compounds using criteria of the European Community Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) indicates derived no-effect levels (DNEL) for exposed workers similar to the above values. The long-term inhalation of DNEL for sodium tungstate (i.e., water-soluble tungsten compounds) was 1.3 mg Na_2WO_4/m^3 (1.7 mg W/m^3) compared with 7.3 mg WO_3/m^3 (5.8 mg W/m^3) for sparingly soluble tungsten compounds.[103] The World Health Organization has not issued any drinking water guidelines for tungsten.

Initial medical screening and annual medical examinations for workers directly exposed to soluble and insoluble tungsten compounds as well as elemental tungsten should include a chest X-ray and pulmonary function tests.

Biological Monitoring

Tungsten carbide and cobalt are the main constituents of hard metal alloys; these two metals are combined in the sintering process to form cemented carbides for composite materials in cutting and grinding tools. Multi-element analysis of biological specimens from workers with hard metal pneumoconiosis indicates that blood and urine tungsten concentrations do not correlate well to the presence of disease in affected workers.

The tungsten concentrations in biological media from hard metalworkers vary substantially between factories as a result of varying bioavailability and the variety of techniques used in the production of hard metal.[104]

Blood

In a study of Italian hard metalworkers (sintering, grinding, mold filling, manufacturing), blood and urine tungsten concentrations did not separate diseased workers from healthy workers with the tungsten concentrations in the diseased workers independent of age, duration of exposure, and tungsten dose.[105] The mean tungsten concentration in whole blood samples from 43 workers in this study was 1.2 ± 1.6 µg/L (range, 0.04–6.5 µg/L) with a median of 0.6 µg/L. In a study of 49 Italian workers in hard metal alloy industries, the geometric mean tungsten concentration in whole blood and plasma was 0.13 ± 2.20 µg/L and 0.18 ± 2.49 µg/L, respectively.[98] The highest blood tungsten concentrations occurred in 14 wet grinders (0.27 ± 1.83 µg/L and 0.46 ± 1.87 µg/L, respectively). A 37-year-old hard metal grinder developed hard metal disease while working at a small shop with poor ventilation; her admission blood tungsten concentration was 60 µg/L as measured by neutron activation analysis.[106] She had a restrictive lung defect and an eosinophilic interstitial fibrosis (BAL fluid, 30% eosinophils) that progressed to death 8 months later despite steroid use.

Urine

The mean tungsten concentration in urine samples from 78 Italian hard metalworkers was 6.7 ± 19.4 µg/L (range, 0.11–230 µg/L) with a median of 1.05 µg/L.[105] In a study of the hard metal manufacturing industry, the mean urinary tungsten concentration in 14 powder processing workers was 12.2 µg/g creatinine (95% CI: 8.0–16.5 µg/g creatinine) compared with 94.4 µg/g (95% CI: 11.2–177.5 µg/g creatinine) in 5 grinders.[107] The former were exposed primarily to tungsten metal, whereas the latter were exposed to tungstate (wet grinding) and tungsten oxide/carbide

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(dry grinding). On a group basis, air tungsten concentrations did not correlate to urine tungsten concentrations, probably as a result of variations in solubility and bioavailability of tungsten compounds. The maximum tungsten concentration during ambient air monitoring was 417 μg/m^3 with four samples from powder processing area ranging from 177–254 μg/m^3 and ~81 μg/m^3 in a sample from the dry grinding area. In a study of 36 Italian workers in hard metal alloy industries, the geometric mean tungsten concentration in end-of-shift urine samples at the end of the week was 7.06 ± 4.46 μg/L.[98] There were substantial differences between urine tungsten values and different parts of the hard metal process. The highest mean urine tungsten concentration (20.49 ± 2.38 ng/mL) occurred in wet grinders ($n = 13$), whereas the lowest mean end-of-shift urine tungsten concentration was 1.11 ± 6.04 μg/L in sintering ($n = 6$). The latter process involves exposure to tungsten carbide (airborne tungsten = 0.13 μg/m^3, $n = 1$), whereas wet grinders were exposed to tungstate (airborne tungsten = 6.54 μg/m^3, $n = 1$). Limited air monitoring suggested tungsten exposure of these workers was below current occupational standards, with the exception of wet grinders. The article did not report any symptoms associated with these tungsten concentrations. In a German study of 52 workers in a hard metal producing and processing plant, the urine tungsten concentration (median, 30.5 μg/L; interquartile range, 14.5–57.7 μg/L) as measured by high-resolution/inductively coupled/plasma mass spectrometry correlated with the airborne tungsten concentration ranging from 0.12–0.21 mg/m^3.[108] There was no correlation between the tungsten concentration in ambient air or urine and the tungsten concentration in exhaled breath condensate.

A 37-year-old hard metal grinder developed fatal hard metal disease while working at a small shop with poor ventilation.[106] Three other workers at the shop remained asymptomatic. The authors noted that blood and urine tungsten concentrations did not accurately predict the clinical course of hard metal disease.

TREATMENT

The treatment of exposure to tungsten is supportive. Serious toxicity as a result of exposure to tungsten or tungsten compounds has not been well-described. Decontamination measures following exposure to soluble tungsten compounds may be appropriate within the first 1–2 hours after exposure, but these measures are probably not necessary for exposures to elemental tungsten or insoluble tungsten compounds. There are few data on the efficacy of chelating agents following tungsten exposure; limited animal studies do not support the use of DMSA following large exposures to sodium tungstate.[109]

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Chapter 34

VANADIUM

HISTORY

The Spanish mineralogist del Rio first discovered vanadium (V) in 1813; he gave this element the name *panchromium* because of the color changes that occur during the transition of elemental vanadium to various oxidation states.[1] Nils Sefstrom purified vanadium in the oxide form during 1831; he named the compound after the Norse goddess of youth, love, beauty, and the dead, Vanadis (Freja, wife of Oden). Because of their hardness and ability to form alloys, vanadium-containing alloys (e.g., ferrovanadium) became popular components of hard steel alloys used in machines and tools. In 1911, Dutton first reported the development of dry cough and irritation of the eyes following occupational exposure to the fumes and dusts of vanadium oxide.[2] Case series in the 1930s and 1940s document the occurrence of conjunctivitis, rhinitis, sore throat, and cough following occupational exposure to vanadium pentoxide.[3,4] Although the use of vanadium compounds to treat syphilis and leishmaniasis was recommended in the 1920s and 1930s,[5] the medicinal use of vanadium preparations has been rare.

As the use (e.g., mordant in dyeing, catalyzer in chemical industry, accelerator for the drying of paint) of vanadium compounds expanded in the 1940s and 1950s, case reports associated exposure to vanadium dusts with greenish-black discoloration of the tongue and irritation of the skin, mucous membranes, and respiratory tract.[6,7] Workers developed vanadium poisoning while cleaning oil- or gas-fired boilers because vanadium is a natural component of fuel oils. Vanadium probably corrodes the oil-heated boilers by catalyzing the oxidation of sulfur dioxide to sulfur trioxide.[8] A vanadium-deficiency disease has not been defined in humans; however, vanadium is a prime candidate for essential status, in part because vanadium occupies position 25 in the periodic table. This position is near the positions (23–34) of the most essential trace elements in the periodic table. Haloperoxidases were the first vanadium-containing enzymes discovered in 1984.[9]

PHYSIOCHEMICAL PROPERTIES

Vanadium (V) is a transitional metal that is a member of the first transition series of the periodic table Group 5 (Group VB) that includes niobium, proactinium, and tantalum. Tables 34.1 and 34.2 list identifying information on elemental vanadium and vanadium compounds. Elemental vanadium is a soft, silvery-gray, nonvolatile, refractory (high-melting point) element that reacts with oxygen, nitrogen, and carbon to form oxidation states varying from 1− to 5+; the most common valences are +3, +4, and +5. Elemental vanadium does not occur naturally. This metal oxidizes easily above temperatures of >660°C forming brownish-black trioxide, blue-black tetroxide, or reddish-orange pentoxide depending on the temperature.

The most stable oxidation state is the quadrivalent salt (VO^{2+}, vanadyl). Trivalent vanadium (V_2O_3) is a strong reducing agent that dissolves in acid to form a green hexa-aquo ion. Pentavalent salts include metavanadate (VO_3^-), orthovanadate ($H_2VO_4^-$), and pyrovanadate ($V_2O_7^{4-}$). The metavanadate form is the most common state in extracellular body fluids, whereas

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TABLE 34.1. Identifying data on vanadium and vanadium compounds. (Adapted from Table 3.1, Agency for Toxic Substances and Disease Control).[10]

Compound	Synonyms	Chemical Formula	CAS RN	NIOSH RTECS Number
Vanadium	Vanadium-51	V	7440-62-2	YW1355000
Vanadium pentoxide	Vanadic anhydride, divanadium pentoxide, vanadium oxide, vanadic acid	V_2O_5	1314-62-1	YW2450000
Vanadyl sulfate	Vanadium oxysulfate, vanadium oxide sulfate, vanadium oxosulfate	$VOSO_4$	27774-13-3	YW1925000
Sodium metavanadate	Vanadic acid, monosodium salt	$NaVO_3$	13718-26-8	YW1050000
Sodium orthovanadate	Vanadic (II) acid, trisodium salt; sodium vanadate; sodium vanadate oxide; trisodium orthovanadate	Na_2VO_4	13721-39-6	YW1120000
Ammonium metavanadate	Ammonium vanadate; vanadic acid, ammonium salt	NH_4VO_3	7803-55-6	YW0875000

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances.

TABLE 34.2. Physiochemical data for vanadium and vanadium compounds. (Adapted from Table 3.2, Agency for Toxic Substances and Disease Control).[10]

Compound	Molecular Weight (g/mol)	Color	Density (g/mL)	Melting Point (°C)	Water Solubility (g/L)
Vanadium	50.94	Light gray or white luster	6.11 (18.7 °C)	1880–1900	Insoluble
Vanadium pentoxide	181.88	Yellow to rust brown crystals	3.36 (18 °C)	690	8
Vanadyl sulfate	163	Blue powder	No data	No data	Soluble
Sodium metavanadate	121.93	Colorless crystals	No data	No data	211 (25 °C) 388 (75 °C)
Sodium orthovanadate	183.91	Colorless	No data	850–856	Soluble
Ammonium metavanadate	116.98	White-yellow crystals	2.33 (20 °C)	200 (decomposes)	Slightly soluble

the quadrivalent form predominates intracellularly.[11] Vanadium pentoxide is the most common commercial and environmental form of vanadium; this compound exists as a yellowish to red-brown crystalline powder that is sparingly soluble in water. There are few data on the odor-warning properties of vanadium compounds; VCl_4 and VCl_3 may release a pungent odor (i.e., Cl_2) following decomposition at room temperature.

Like molybdenum, vanadium participates in biological processes in both anionic (vanadates) and cationic (VO^{2+}) forms. The chemical reactions of the former resemble phosphate, whereas the latter behaves as complexes in coordination to biogenic ligands and compounds similar to other transition metal ions. Below pH 3.5, vanadium exists as vanadyl (VO^{2+}). In basic solutions, vanadium exists as orthovanadate (VO_4^{-3}), which is chemically similar to phosphates (PO_4^{3}).[12] Neutral solutions contain vanadium primarily as $H_2VO_4^-$. In high concentrations, vanadium polymerization occurs; the tetramer ($V_4O_{12}^{4-}$) form is the main polymer in these solutions.[13] Further polymerization can produce an isopolyanion, $V_{10}O_{28}^{6-}$. The chemical similarity of vanadium to phosphorus helps explain the effect of vanadium on phosphorylation reactions in the body. Some VO_3^- enter cells via anion transport systems where glutathione reduces pentavalent vanadate to quadravalent vanadyl. Vanadyl is relatively nonreactive as a result of its complexing with proteins and other small molecules. Vanadium generally does not combine with organic compounds. Synthetic vanadium compounds are experimental drugs for the treatment of diabetes (vanadyl acetylacetonate, bis(maltolato)oxyvanadium (IV), the ethylmaltol analog, bis(ethylmaltolato)oxyvanadium (IV)),[14] and cancer (vanadyl sulfate).[15]

EXPOSURE

Production Processes

Commercial vanadium-containing ores include carnotite (potassium uranyl vanadate), patronite (impure vanadium sulfide), roscoelite [$K(V^{3+}, Al, Mg)_2AlSi_3O_{10}(OH)_2$], vanadinite [$Pb_5(VO_4)_3Cl$], and phosphate rock.[16] Sources in the United States include uranium-

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bearing minerals in Colorado and some Western US phosphatic shales and phosphate rocks. Extraction methods for elemental vanadium in these ores involve calcium reduction, electrolytic refining, solvent extraction from uranium ores, and thermal decomposition. Extraction of some of these ores produces vanadium-rich alloy (e.g., ferrovanadium).[17] Other sources of vanadium include crude petroleum deposits (e.g., Venezuelan crude oil),[8] slag from the production of ferrous alloys, and by-products of the processing of some nonferrous ores (aluminum, titanium, uranium). After these vanadium-containing materials are crushed, dried, and finely ground, sodium salts are added to produce sodium metavanadate ($NaVO_3$) during the roasting process. The mixing of sulfuric acid with sodium metavanadate produces a precipitate that dries in the form of vanadium pentoxide. High vanadium concentrations (i.e., up to 50%) occur in flue-gas deposits from oil-fired furnaces, particularly oil from Iraq, Iran, Kuwait, Venezuela, and the Mexican Gulf. Petroleum from the United States generally contains very small amounts of vanadium.[18]

Uses

Uses of vanadium include the following: 1) production of steel and nonferrous alloys for ball bearings, springs, and automobile parts; 2) catalyst for the production of sulfuric acid and the conversion of naphthalene to phthalic anhydride during the formation of plastic; 3) manufacturing of semiconductors, photographic developers, and coloring agents; 4) production of brown to green colors in ceramics; and 5) ferrous alloys for aircraft engines. Of these uses, ferrovanadium as a steel additive accounts for ~80% of vanadium production, particularly in rust-resistant and high-speed tool steels.[16] Vanadium pentoxide provides ultraviolet-filtering properties in some forms of glass. Pure vanadium seldom is the preferred industrial form of vanadium because elemental vanadium readily reacts with carbon, nitrogen, and oxygen at temperatures above 300 °C. The vast majority of vanadium is used as ferrovanadium or vanadium carbide in the production of high-resistance carbon steels. The addition of the vanadium compounds improves the hardness, malleability, and fatigue resistance of the steel. Nonferrous alloys containing vanadium are used in jet aircraft, space technology, and the atomic energy industry. Important applications of vanadium oxides and vanadates as catalysts include the following processes: petroleum cracking, purification of exhaust gases, and the oxidation of ethanol. Vanadium is a constituent of scale dust from boilers burning V-containing crude oil. Samples of scale dust may contain 5–15% vanadium pentoxide as well as other compounds (e.g., calcium oxide, copper, iron oxide, nickel oxide, potassium oxide, sodium oxide, silica, sulfate, phosphate).[19] Elemental vanadium, sodium metavanadate, and vanadyl sulfate are constituents of some commercial supplements including weight-training supplements and multivitamins.

Sources

Air

Exposure of the general population to vanadium *in air* results primarily from the combustion of petroleum, coal, and heavy oils during the generation of electricity and heat. During the burning of oil fields in Kuwait, air particulate matter in Bahrain contained 11–42 ng V/m^3.[20] Vanadium concentrations in coal, crude oil, and carbon fossils average ~15–100 μg/g (ppm), 600 μg/g (ppm), and 1,500 μg/g (ppm), respectively.[21] Vanadium is usually the most abundant trace metal present in petroleum. Vanadyl ion (VO^{2+}) in the form of organometallic complexed with porphyrins is the most common form of vanadium in petroleum as measured by high-resolution continuum source/atomic absorption spectometry with a graphite furnace or conventional electrothermal/atomic absorption spectrometry.[22] Natural gas contains very small amounts of vanadium (<0.05 ppm). Additional industrial sources of vanadium in the metallurgy industry include discharges from furnaces roasting vanadium slag, vanadium pentoxide smelting furnaces, and crucibles that melt ferrovanadium alloys. Anthropogenic sources account for ~$^2/_3$ of the atmospheric vanadium (i.e., vanadium oxides), particularly from residual fuel oils (1–1,400 ppm).[16] Continental dust, marine aerosols, and, to a lesser extent, volcanic emissions account for the rest of the vanadium in the atmosphere.

Ambient air concentrations of vanadium typically are low depending in part on urbanization and industrialization. Marked seasonal and geographic variation occurs in the ambient concentration of vanadium. These variations result from climatic conditions (e.g., cold weather, atmospheric inversions) and the burning of residual fuel oils during the production of electricity and heat. In 1973, the highest vanadium concentrations in the United States occurred in the northeast where the consumption of fossil fuel during the production of electricity and heat was high. The median vanadium concentration in these cities was 620 ng/m^3 (range, 150–1,400 ng V/m^3) compared with a mean of 11 ng/m^3 in other urban areas.[23] The concentration of vanadium

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in ambient air in rural areas is usually much lower than in urban areas. Typically, the vanadium concentration ranges from 1–2 ng/m^3 in *remote* rural areas to 50–60 ng V/m^3 in rural areas with sources of vanadium.[16] In a 3-year sampling period in southeast Chicago and east St. Louis, Illinois, average vanadium concentration of fine particles (<2.5 μm) in inhalable particulate matter was 3.0 ng/m^3, whereas the mean vanadium concentration in coarse particles (2.5–10 μm) was 3.7 ng/m^3 and 3.0 ng/m^3, respectively.[24] Average vanadium concentrations in fine and coarse particulate matter collected from a rural site (Bondville, Illinois) were 0.8 ng/m^3 and 1.2 ng/m^3, respectively. In sampling ($PM_{2.5}$ fraction) from rural Vermont, the geometric mean seasonal vanadium concentration was 0.82 ng/m^3 with maxima occurring during the winter and spring months and minimum concentrations observed during the summer months.[25] The authors attributed the variation to the operation of northeastern oil-fueled power plants based on factor analysis. Average vanadium concentrations in air samples collected from a rural forest in Denmark ranged from 11.5 ng/m^3 in 1979 to 4.4 ng/m^3 in the early 2000s.[26] Emissions from adjacent European cities contributed to the vanadium load.

Soil

Vanadium is a widely distributed trace metal that is the 22nd most abundant element in the earth's crust with an average concentration of ~100 mg/kg (ppm) in soil; vanadium concentrations in typical soil are similar to nickel and zinc. The actual content of vanadium depends on the type of parent rock. The soil types that contain the highest concentration of vanadium are tundra podzols and clays. Elemental vanadium does not exist in nature because of its propensity to react with other elements, particularly oxygen.[16] The largest releases of vanadium to the soil result from the weathering of rocks rather than from anthropogenic sources (e.g., super-phosphate fertilizers, 0.05–2 g V/kg; basic slag, 1–5 g V/kg).[27] Basic rocks contain higher vanadium concentrations compared with neutral and acidic rocks. The bioavailability of vanadium in soil is limited because of the binding of vanadium to soil.[28]

Water

In water, vanadium is converted from trivalent to pentavalent oxidation state. Natural releases of vanadium from the erosion of soil and the weathering of rock far exceed the deposition of vanadium from anthropogenic sources in the air. The former process involves the release of vanadium into water following the conversion of the less water-soluble trivalent form to the more water-soluble pentavalent form. Most samples from drinking water supplies contain levels of vanadium below detectable limits. When detected, the vanadium concentration in drinking water is usually 1–6 μg/L with a range of up to 20–100 μg/L.[17,29] The vanadium concentration in fresh surface water depends on geographical difference in leachates and effluents from natural and anthropogenic sources. Typically, surface water contains vanadium concentrations of <3 μg/L with a range of up to 70 μg /L.[30] In the US STORET database for 2007–2008, 3,387 of 3,625 surface water samples contained detectable vanadium concentrations ranging from 0.04 (LOD)–104 μg/L.[31] Concentrations may range up to 220 μg V/L in freshwater in rivers in the Colorado Plateau, where vanadium exists in naturally occurring uranium ores.[27] Some water with high mineral content may contain concentrations up to 10 μg V/L in conjunction with other elements (e.g., fluorides, arsenic). Groundwater sampling in California indicates that the primary vanadium sources in groundwater are leachates of V-rich rocks (mafic and andesitic) in volcanic areas, particularly under aerobic and alkaline conditions; anthropogenic sources contribute substantially smaller amounts of vanadium to groundwater.[32]

Diet

Even though most foods contain low vanadium concentrations (<1 ng/g),[33] food is the major source of vanadium exposure for the general population; the form of vanadium in foods is primarily inorganic tetravalent (vanadyl) and pentavalent (vanadate) compounds including vanadium pentoxide, sodium metavanadate, ammonium metavanadate, sodium orthovanadate, and vanadyl sulfate. The daily requirement for vanadium is probably small (<10 μg) with the highest vanadium sources in black pepper, dill seed, wild mushrooms (0.05–2 μg/g), ground parsley (1.8 μg/g), shellfish (e.g., oysters), freeze-dried spinach (0.5–0.8 μg/g), and some prepared foods.[34] The estimated daily dietary intake for the US population is ~10–60 μg V.[35] In the National Human Exposure Assessment Survey (NHEXAS) study of Midwestern US diets, the estimated daily vanadium dietary intake was 0.34 μg/kg body weight,[36] whereas the estimated daily vanadium intake for adults living near a hazardous waste incinerator with elevated vanadium concentrations in the soil was ~29 μg.[37] The estimated mean daily V intake based on analyses of market basket representatives of the Northern Italian diet was 12.2 μg with a range of 3.3–17.9 μg.[38] Cereals and tubers accounted for 37% of the daily intake compared with 23% for fruits and vegetables. The estimated

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intake for meats, fish, and eggs was 18%, whereas beverages accounted for 15% of the intake. The latter was the highest percentage of the daily intake of all trace elements except boron.

In general, seafood contains higher concentrations of vanadium compared with terrestrial animal food sources. Beverages, fresh fruit and vegetables, cereals, liver, fats, and oil contain smaller amounts (<1–10 ng V/g). The processing of food tends to raise vanadium concentrations.[39] The mushroom, *Amanita muscaria*, contains about 100 times the vanadium concentration (100 ppm) found in other plants and mushrooms.[40] Following the major oil contamination of the marine environment during the Gulf War, the mean vanadium content of edible seafood ranged from ~0.48–1.48 μg/g dry weight.[41] In a study of six fish species in the Adriatic Sea, samples of anchovies contained up to 90 μg V/kg (ppb) fresh weight compared with 79 μg/kg (ppb) fresh weight for red mullet and 45 μg/kg (ppb) fresh weight for mackerel.[42] Sole, angler, and hake had substantially lower vanadium concentrations (<4 μg/kg fresh weight). Wines may contain vanadium. In a study of 68 samples of California and French red wines, the V concentration ranged from 7–90 μg/L with somewhat smaller V concentrations in white wine samples.[43] Vanadium is not listed on the US Food and Drug Administration GRAS (Generally Recognized as Safe) list for addition to food.

Drinking water is a relatively small source of vanadium for the general population with typical vanadium concentrations of <1 μg/L in drinking water; drinking water provides an estimated ~2 μg of the daily vanadium intake in adults.[17,36] In the National Human Exposure Assessment Survey (NHEXAS) of several personal, environmental, and biological media in the upper Midwest United States, the mean vanadium concentrations in standing (4 hours) and flushed (3 minutes running) tap water samples were 1.0 μg/L and 1.2 μg/L, respectively.[36]

Lifestyle

High vanadium concentrations exist in tobacco; typically, smoke from tobacco contains 1–8 ppm V.[33] In a Japanese study, the mean vanadium content in cigarettes was 1.11 ± 0.35 μg/g (ppm); the mean vanadium concentration in mainstream smoke was 0.33 ± 0.06 μg/g.[44] Vanadium is a contaminant of some human albumin solutions in concentrations up to ~600–700 μg/L.[45] Health supplements contain vanadium, particularly those for patients with diabetes. Typical daily intakes of elemental vanadium in the following salts from these supplements are 30–150 mg vanadyl sulfate (9–47 mg V) and 125 mg for sodium metavanadate (52 mg V); however, there are currently inadequate clinical data to determine the efficacy of vanadium supplements for the treatment of diabetes.[46]

ENVIRONMENTAL FATE

The global recycling of vanadium involves the release of vanadium from natural and anthropogenic sources to the air, water, and soil; the transport of vanadium particles in water and air include: wet and dry deposition; absorption; and complexing.[16]

Air

Vanadium enters the air as an aerosol of simple or complex vanadium oxides from anthropogenic sources and as mineral particles of less-soluble trivalent forms from natural sources. Vanadium residence time in the atmosphere is inversely related to particle size. The particle size of vanadium is typically smaller from oil-fueled power plants than from natural sources; thus, the residence time in the atmosphere of discharges from power plants is probably longer than from natural sources. In a Turkish study of urban dust samples, vanadium deposition rates ranged from 20.5–84.9 μg/cm^2/day with an arithmetic mean deposition rate of 45.3 μg/cm^2/day.[47] The authors considered vanadium concentrations in dust as a measure of air pollution from residual oil and coal combustion (i.e., depending on vanadium content).

Soil

Compared with other metals, vanadium is moderately mobile in neutral and alkaline soils, but the mobility of vanadium in acidic soil is relatively low. The weathering of rock may release vanadium into air or water and also precipitate vanadium with polyvalent cations or organic complexing agents. In addition to adsorption to particulate matter, vanadium typically exists in solution in fresh water as the tetravalent vanadyl ion (VO^{2+}, $VO(OH)^{+}$) in reducing conditions or the pentavalent vanadate ion ($H_2VO_4^-$, HVO_4^-) in oxidizing conditions.[48] Both vanadate and vanadyl species adsorb or complex well on mineral or biogenic surfaces.

Water

Relatively small amounts of vanadium are transported via water compared with the sedimentation process. In fresh water, vanadium exists as the vanadyl ion (VO^{2+}, $VO[OH]^{+}$) in reducing environments, whereas pentavalent vanadate (acidic solution, VO^{+}; alkaline

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solution, VO_4^{3-}) dominates under oxidizing conditions. Transport of vanadium in water occurs primarily in suspension and to a much lesser extent in solution. In water, trivalent and tetravalent vanadium rapidly oxidize to the pentavalent form of vanadium. Consequently, most of the vanadium in fresh water enters seawater adsorbed to colloids or in suspended form. Removal of vanadium dissolved in seawater results from precipitation as hydrated ferric trioxide or by biochemical processes in organic matter. In general, marine plants and invertebrates accumulate much higher vanadium concentrations than terrestrial plants and animals, with bioconcentration more common among lower terrestrial plant phyla than higher, seed-producing phyla, depending on water-soluble vanadium concentrations in the soil, pH, and growing conditions.[16] Although data are limited, human studies do not suggest biomagnification of vanadium in the food chain.[49]

DOSE EFFECT

The toxicity of vanadium compounds depends on a variety of factors including the route of administration and the inherent toxicity of the particular compound. In general, the toxicity of vanadium compounds is low; vanadium toxicity is least following ingestion and greatest following parenteral administration. Inhalation is a route of exposure that produces intermediate toxicity. The toxicity of vanadium increases with higher valences; the pentavalent compounds are usually the most toxic. Acidification tends to reduce the toxicity of vanadium compounds.[50]

Ingestion

Human

Historically, vanadium compounds (e.g., sodium metavanadate) were administered for the treatment of anemia, tuberculosis, diabetes, and syphilis in doses of 1–8 mg sodium metavanadate.[17] Vanadyl sulfate ($VOSO_4$) is a common supplement used to improve performance in weight-training athletes at doses up to 60 mg/day. A 12-week, double-blind, placebo-controlled clinical trial involving 31 weight training athletes did not detect any hematological abnormalities at doses of 0.5 mg $VOSO_4$/kg/day;[51] however, there was no evidence that the use of vanadium improved endurance or physical performance. Loose stool, abdominal cramps, and occasional nausea are common complaints associated with the ingestion of therapeutic doses of vanadyl sulfate.[52] The daily administration of 100 mg $VOSO_4$ for 4 weeks[53] and 125 mg sodium vanadate for 2 weeks[54] to noninsulin-dependent diabetic patients was well tolerated, except for some mild gastrointestinal complaints. The daily ingestion of ammonium vanadyl tartrate of 50–100 mg as a cholesterol-lowering agent for up to ~10 weeks was associated with abdominal cramps, loose stool in all six volunteers; some of the subjects complained of fatigue, lethargy, and a blue-green tongue.[55] Daily doses of 125 mg diammonium vanadotartrate for 5 months produce gastrointestinal side effects in a few subjects,[56] whereas no overt evidence of toxicity occurred in five medical students receiving up to 125 mg diammonium oxytartratovanadate for 6 weeks.[57]

The estimated ingestion of 10–15 g ammonium metavanadate was associated with the development of gastrointestinal symptoms, green tongue, and *focal* neurological lesions (right-sided facial paresis, hemiparesthesia).[58] MRI revealed a high-intensity signal lesion in the left parietal cortex with slight edema in the adjacent subcortical white matter. All clinical symptoms were resolved within 10 days.

Animal

In a study in mice, the toxicity of vanadium trioxide was six times less than vanadium pentoxide.[59] The exposure of rats to 34–155 mg vanadyl sulfate/kg/day in drinking water was not associated with any significant changes in hematocrit, hemoglobin, leukocyte count, or platelet count.[60]

Inhalation

Vanadium pentoxide (V_2O_5) is a potential respiratory irritant. An 8-hour exposure of 1 mg V_2O_5/m^3 to two healthy volunteers produced a cough for 8 days, but no alteration in the pulmonary function tests or chest X-ray; exposure of two volunteers to 0.1 mg V_2O_5/m^3 produced mucous and slight cough that increased 2 days after exposure and resolved within 4 days.[61] Exposure of 24 workers to V_2O_5 at an average concentration of 0.3 mg/m^3 (range up to 5 mg/m^3) was associated with a productive cough, irritation of the nose, throat, and eyes, rhinitis, and green tongue that cleared within several days of cessation of exposure.[62] Low-dose exposure to vanadium causes an increase in nasal inflammatory cells on nasal smears accompanied by symptoms of nasal irritation.[63] Exposure to respirable vanadium dust concentrations of 0.1–139 μg/m^3 was associated with increased adjusted polymorphonuclear cell counts from nasal lavage in nonsmokers but not in smokers.[64] However, large interindividual variations in the polymorphonuclear cell counts occurred, and

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no dose-response effect was demonstrated. Prolonged exposure to high concentrations of vanadium dust in the range of 5–150 mg V/m^3 causes atrophic rhinitis and a persistent inflammation of the bronchi.[17]

Parenteral

Patients with syphilis tolerated doses ranging up to 600 mg V_2O_5 over 13–23 days. Based on clinical experience in the early 1900s, single intravenous doses of 10 mg V_2O_5 were considered safe with renal "irritation" and anorexia being the limiting adverse effects. The administration of 20 mg as sodium tetravanadate was associated with lacrimation, hypotension, throat constriction, vomiting, and apnea.[65]

TOXICOKINETICS

Absorption

The absorption of vanadium compounds depends on their solubility and the route of entry. Inhalation of dusts and fumes is the major route of vanadium exposure for workers. Although the rates of absorption are not well defined, soluble vanadium compounds including V_2O_5 are well absorbed following instillation into the lungs. In contrast, therapeutic doses of vanadium salts (e.g., ammonium vanadyl tartrate) are poorly absorbed that from the gastrointestinal tract;[55] animal studies suggest the amount of vanadium absorbed by the gastrointestinal tract is <1–2%.[66] Dietary vanadium exists either as vanadyl or vanadate, with the latter being absorbed ~3 times more effectively by the gastrointestinal tract than the former; thus, conversion of vanadate to vanadyl in the acid milieu of the stomach contributes to the low vanadium absorption in animal studies.[67] Vanadium remains in the vanadyl form in the alkaline medium of the duodenum. The skin probably is a minor route of exposure as a result of the low lipid/water solubility of elemental vanadium.[16]

Distribution

Following transport in plasma, the distribution of vanadium from the blood is rapid ($t_{1/2}$ ~1 hour) with the highest vanadium concentrations initially appearing in kidney, liver, and lungs. Transferrin reversibly binds vanadyl and vanadate in blood at two metal-binding sites; however, the binding of vanadium to transferrin is most likely in the vanadyl form because this complex is more stable than the vanadate complex.[68] Therefore, ~90% of the vanadium in the blood resides in the plasma, primarily as vanadyl bound to transferrin and albumin.[69] *In vitro* studies suggest that vanadium circulates as a polyvanadate (i.e., isopolyanions containing pentavalent vanadium) in the blood, whereas these studies suggest NADPH-dependent reduction of polyvanadate may form tetravalent vanadyl cations in the tissues (microsomes).[70]

Following the IV administration of 47.6 μg vanadium to five healthy adults, the volume of distribution at steady state was ~54 L.[71] In animal studies, the vanadium concentration in the brain is ~5% of the vanadium concentration in the blood.[72] The total amount of vanadium in the human body is small with the total body vanadium burden averaging ~100 μg.[33] Based on animal studies, the bones and teeth retain the highest vanadium concentrations; these tissues provide a major sink for retained vanadium.[9] Vanadium does not accumulate in the brain of animals or humans.

Elimination

Most ingested vanadium is eliminated unabsorbed in the feces. The kidneys are the principal route of vanadium elimination after absorption with minor amounts (i.e., <10%) excreted via the feces. Following occupational exposure to vanadium dust, urine vanadium concentrations increase significantly compared with unexposed control groups.[73] The excretion of vanadium is relatively rapid; animal studies indicate that the kidney excretes ~40–60% of the vanadium dose within 1–3 days of ingestion.[74] The biological half-life of vanadium in the urine is 20–40 hours.[75] Animal studies indicate that vanadium elimination from the body following inhalation of vanadium oxides is biphasic with an initial rapid rate of elimination (10–20 hours) and a longer terminal phase (40–50 days).[76] In a study of five healthy volunteers receiving a single, intravenous vanadium dose of 47.6 μg in a commercial 20% albumin solution, the serum elimination half-life followed a three-compartment model with half-lives of 1.2 hours, 26 hours, and 10 days.[71] The terminal phase accounted for ~80% of the vanadium dose. About 52% of the vanadium dose appeared in the urine within 12 days of administration.

Maternal-Fetal Kinetics

The vanadium concentrations in human breast milk ranged from 0.11–0.69 μg/g (ppm) in a review of sample of lactating women in Nigeria, Zaire, Guatemala, Hungary, the Philippines, and Sweden.[77] The estimated daily vanadium intake for infants in the United States

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was as follows: milk-based powder formula, 0.05 μg; soy-based powder formula, 3.5 μg; and hypoallergenic powder formula, 2.8 μg.[78]

HISTSOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

The specific biochemical function of vanadium in animals and humans has not been identified. Although vanadium is not unequivocally accepted as an essential trace metal for humans, it is probably an essential trace element.[79] Features favoring essentiality include rapid excretion, ubiquity in the biosphere, homeostatic regulation with accumulation, and the ability to catalyze the chelation of biologically active compounds.[35] The vanadate ion is one of the most potent inhibitors of the Na^+/K^+ ATPase pump. Recent research suggests that vanadium may help regulate the Na^+ pump. The vanadium-containing haloperoxidases (bromoperoxidases, chloroperoxidases, iodoperoxidases) catalyze the two-electron transport of a halide by hydrogen peroxide. Studies from the 1970s suggested vanadium deficiency produced impairment of reproduction, skeletal abnormalities, and biochemical changes (plasma cholesterol), but the findings were inconsistent and confounded by the ingestion of unbalanced diets. Later studies using balanced diets also demonstrated some biochemical abnormalities (hepatic glycogen and lipids, bone copper, fecal bile acids, plasma cortisol and glucose, thyroid peroxidase activity) in vanadium-deficient guinea pigs.[80,81]

In biological systems, vanadium complexes act as catalases, peroxidases, and nitrogenases involved in a variety of cellular processes including redox processes. There are at least the following three known types of vanadium-containing proteins: vanadium haloperoxidase, vanadium nitrogenase, and the vanadium transport proteins (vanabins).[82] In its lower life forms, vanadium reacts with hydrogen peroxide to form a pervanadate that catalyzes the oxidation of halide ion and stimulates the phosphorylation of receptor proteins.[34] Thyroid peroxidase is the most recognized haloperoxidase in animals. These findings in lower life forms along with recent animal data suggest vanadium is an essential trace element in higher animals including humans.[67]

In vitro and animal studies indicate that vanadate and other vanadium compounds increase glucose transport activity and improve glucose metabolism.[79,83] The action of vanadium is probably distal to the receptor, perhaps related to the translocation of glucose through the plasma membrane. Inhibition of phosphotyrosine phosphatase and protein tyrosine kinase activation is probably involved in the action of vanadium on glucose homeostasis.[84] The enhancement of glucose uptake, glucolysis, and glycogen synthesis by vanadate is less than that of insulin; however, vanadate produces greater simulation of lactate and glucose oxidation than insulin.[85] Both vanadyl and vanadate compounds mimic the action of insulin in isolated cell systems, and these compounds produce dramatic decreases in blood glucose levels in animal models of both types of diabetes mellitus.[86] Additionally, the administration of vanadyl sulfate to streptozotocin-diabetic Wister rats provides some protection against the destructive action of streptozocin on the pancreatic β-cells.[87] Relatively large doses (100 mg vanadyl sulfate/kg/day) are necessary to lower plasma glucose in animal studies.[88] Some laboratories reported toxic effects (e.g., decreased weight gain and renal function, increased mortality) in Sprague–Dawley rats following administration of vanadium doses in the range of 25–75 mg/kg/day.[89] Other laboratories did not detect significant toxic effects of vanadium at doses (i.e., >100 mg/kg/day) that reduced plasma glucose levels in diabetic Wister rats.[90] Peroxovanadium compounds are the most potent inhibitors of insulin receptor tyrosine kinase described to date.[91]

In addition to the insulin-mimetic effects of vanadium compounds, vanadium affects signal transduction mechanisms and proto-oncogene expression *in vitro*.[92] At concentrations of >5 μM, orthovanadate is cytotoxic to proliferating cells, including primary culture and tumor cell lines.[93] These studies suggest that orthovanadate may possess antineoplastic properties.

Mechanism of Toxicity

The systemic effects of vanadium probably result from its oxidizing ability.[63] This metal also inhibits oxidative phosphorylation,[94] but the role of this mechanism in toxicity is unclear. Vanadium acts as a phosphate analog that interferes with a variety of phosphate-containing enzymes including phosphatases, phosphate-transfer enzymes, protein kinases, ribonucleases, phosphatases, and ATPases. Vanadate interferes with phosphate-containing enzymes (ATP phosphohydrolases, adenylate kinase, glyceraldehyde-3-phosphate dehydrogenase, ribonuclease) at relatively high (μmol–mmol) extracellular concentrations.[95] Based on *in vitro* data, vanadate probably is a noncompetitive inhibitor of Na^+/K^+ATPase (K_1 = 880 nM). This vanadium species is a more effective inhibitor of ATPases in concentrations of >50 μM, whereas vanadyl is an effective inhibitor in very low concentrations (10 nM).[96]

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Pathological Changes

Human

Postmortem examination of a 24-year-old woman dying after the ingestion of ammonium vanadate demonstrated pulmonary congestion, erosive gastritis, and greenish discoloration of the oral mucosa.[97]

Animal

Acute sodium vanadate poisoning in rats causes acute desquamative enteritis, mild congestion of the liver with fatty changes, and slight parenchymal degeneration of the renal convoluted tubules.[98] High V concentrations over a short duration (e.g., <1 hour at doses up to 0.693 mg V_2O_5/L) produce conjunctivitis, acute laryngotracheitis, bronchopneumonic changes in the lung, and fatty degeneration of the liver.[99] Following acute exposure to 5 mg V_2O_5/m^3, airflow limitation developed in the central and peripheral airways of monkeys without detectable changes in the parenchymal function. Significant increases in the total cell counts were recovered during bronchoalveolar lavage of the lung suggesting a role for pulmonary inflammation in the development of the decrease in flow.[100] In mice administered high doses (i.e., 20 mg V/kg) as ammonium metavanadate, severe necrosis of lymphoid tissue occurred along with pulmonary hemorrhage and acute renal tubular necrosis.[101] The mitochondria probably are an important target of vanadium toxicity. *In vivo* and *in vitro* data suggest that pentavalent vanadium-induced liver toxicity results from disruption of mitochondrial respiratory complexes I, II, and III and subsequent reactive oxygen species and ATP depletion in liver cells.[102] The outcome is cell death signaling via MPT pore opening and cytochrome c release. The oral administration of ammonium metavanadate (AMV) with a maximum dose of 20 mg V/kg/day to male C57BL/6N mice for 7 weeks resulted in marked lipid accumulation in hepatocytes, renal epithelial cells, and mucosal epithelial cells of the small and large intestines along with severe degeneration, necrosis, and loss of mucosal epithelial cells in the small intestine.[103]

CLINICAL RESPONSE

Acute Toxicity

Most clinical effects of vanadium compounds result from local irritant effects on the eyes, upper respiratory tract, and gastrointestinal tract rather than systemic toxicity. Ammonium vanadate is a corrosive that may cause erosive gastritis following ingestion.[58] A 24-year-old woman developed nausea, vomiting, diarrhea, abdominal pain, hypoglycemia, and renal failure after ingesting ammonium vanadate; she died the day after admission from acute respiratory failure.[97]

Environmental Exposure

The International Programme on Chemical Safety (IPCS) reviewed epidemiology studies on environmental vanadium exposure in 1988; they concluded that the data did not support a causal relationship between environmental V exposure and adverse effects.[17] Several studies have suggested environmental vanadium exposure is associated with impaired immunity,[104] cardiovascular morbidity/mortality,[105] and bipolar disorder;[106] however, the lack of adequate control of confounding factors (e.g., other metals, particulates) prevents the establishment of a causal relationship.

Occupational Exposure

Most clinically significant vanadium exposures occur when workers inhale vanadium pentoxide fumes. Exposure to vanadium dust is a well-documented cause of upper respiratory tract irritation characterized by rhinitis, wheezing, nasal hemorrhage, conjunctivitis, cough, sore throat, and chest pain.[3] These symptoms are prominent in boilermakers exposed to high concentrations of V_2O_5 fumes during the cleaning of the boilers with rhinitis and cough particularly prominent; hence the name "boilermakers" bronchitis.[107] Symptoms may be delayed a few days; recovery usually occurs within 2–5 days. Following more severe exposure, an acute bronchitis with dyspnea and expiratory wheezes may develop along with gastrointestinal symptoms and fatigue. Chronic effects are not consistently reported after exposure to vanadium, in part, because of the lack of persistence of vanadium in the lung.[16] Bronchitis and pneumonitis may occur after prolonged exposure, but chronic respiratory dysfunction is not usually associated with occupational V exposure.[108,109,110]

Case series indicate that asthma may develop after heavy exposure to vanadium compounds in vanadium refineries[111] and vanadium mines (mean spot urine vanadium concentration = 52.7 μg/g creatinine; $n = 12$);[112] however, cohort studies have not detected an increased prevalence of asthma to date. A prospective study of boilermakers measured the pulmonary function of 26 male boilermakers exposed for 4 weeks to a complex mixture of gases, vapors, and particles from the combustion of fuel oil. This exposure involved low vanadium concentrations (mean = 12.2 ± 9.1 μg/m^3).

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The study demonstrated a significant ($P < 0.01$) mean decrease in the FEV_1 of 140 ± 160 mL; however, there was no dose-response relationship between the vanadium concentration and the change in FEV_1 adjusted for age and smoking.[113] Similarly, there was no correlation between the vanadium concentration and airway responsiveness as measured by methacholine challenge.

Vanadium is a weak sensitizing agent for skin at high concentrations. A study associated the development of dry eczematous dermatitis in 9 of 36 workers who were exposed to vanadium concentrations averaging 6.5 mg V/m^3; only one worker had a positive patch test using 2% sodium vanadate.[1] A green discoloration of the tongue and a metallic taste suggest vanadium exposure. This discoloration usually resolves within a week of the cessation of V exposure depending on the absorbed dose of vanadium.[114] Although workers who were exposed to vanadium compounds have reported nonspecific symptoms (e.g., headache, palpations, weakness, tinnitus, and dizziness), neurological symptoms are not well documented in the medical literature. A Chinese study of steel workers with high (time–weighted average = 0.216 mg/m^3) and low (TWA = 0.013 mg/m^3) vanadium exposure reported some differences in mean scores on the WHO neurobehavioral core test battery between the two groups including error dot score, digit span, digit symbol, Benton visual retention, and correct/error pursuit aiming (but not total pursuit aiming).[115] Limitations of the study include a lack of baseline scores, lack of adjustment for smoking, alcohol, job types, and differences between groups in the Profile of Moods scores (e.g., statistically significant increased scores on anger-hostility, depression-dejection, fatigue-inertia, and vigor-activity in the highly exposed group), and confounding exposures (e.g., manganese, dusts, ammonia).

Reproductive Abnormalities

Although there are few data on reproductive abnormalities in humans, the lack of accumulation of vanadium in reproductive organs suggests vanadium does not cause reproductive abnormalities following exposure to vanadium concentrations that do not produce maternal toxicity. Gavage of male and female rats with sodium metavanadate before mating and during gestation and lactation did not produce any effects on fertility, reproduction, or parturition.[116] Animal studies indicate maternal toxicity occurs before the appearance of teratogenic effects. The no-observed-effect level (NOEL) for maternal toxicity and developmental toxicity for sodium orthovanadate were 7.5 mg/kg/day and 15 mg/kg/day, respectively, following administration at doses of 7.5 mg/kg/day, 15 mg/kg/day, and 30 mg/kg/day to mice via gavage on gestational days 6–15.[117] Both fetotoxicity (reduced fetal weight) and teratogenicity (increased incidence of cleft palate) occurred in Swiss mice following the intraperitoneal injection of sodium metavanadate ($NaVO_3$) at 2 mg/kg/day, 4 mg/kg/day, and 8 mg/kg/day during organogenesis.[118] Abnormalities in sperm count and sperm morphology as well as reduced fertility were detected in CD-1 male mice given 8.5 µg V_2O_5 /g body weight every 3 days for 20 treatments (i.e., 60 days).[119]

Carcinogenicity

The IARC lists vanadium pentoxide as a group 2B (possible) human carcinogen based on an increased incidence of bronchioloalveolar neoplasm in male/female mice and male rats, even though issues were raised regarding improperly characterized exposure data in the test group.[120] The US Toxicology Program does not list vanadium or vanadium compounds as suspected carcinogens. There is inadequate evidence for the carcinogenicity of vanadium or vanadium compounds in humans.

Vanadium is not clastogenic and is weakly mutagenic.[121] No data currently indicate vanadium is definitely carcinogenic, but the possibility of carcinogenicity remains because vanadium interferes with mitosis and chromosome distribution. *In vitro* studies indicate that vanadium pentoxide is not cytotoxic; however, this compound produces rapidly repairable DNA damage (single-strand breaks).[122] Although vanadium compounds have not been thoroughly tested for carcinogenic potential, some animal studies designed to test other toxicological endpoints did not demonstrate an excess incidence of tumors.[123,124] In a 2-year study of F344/N rats and $B6C3F_1$ mice exposed to vanadium pentoxide concentrations ranging from 0.5–4 mg/m^3, there was evidence of carcinogenicity in male and female mice.[125] This exposure caused more pronounced neoplastic response in mice than in rats. There was some evidence of carcinogenicity in male rats based on the incidence of alveolar/bronchiolar neoplasms, but the relationship between alveolar/bronchiolar neoplasms in female rats was equivocal. This exposure caused a wide range of nonneoplastic proliferative lesions in the lungs of rats and mice over the course of the study. *In vitro* studies suggest that some vanadium compounds (e.g., vanadocene dichloride, peroxovanadates with or without a heteroligand) possess some antitumor properties.[126]

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DIAGNOSTIC TESTING

SI Conversion Units

1 μg/L = 0.01963 μmol/L
1 μmol/L = 50.94 μg/L

Analytical Methods

Atomic spectroscopic techniques for the determination of vanadium in biological and environmental samples include atomic absorption spectrometry (AAS) with flame and graphite tube atomizers, X-ray fluorescence spectroscopy (XRF), inductively coupled plasma/optical emission spectrometry (ICP/OES), and inductively coupled plasma/mass spectrometry (ICP/MS). Neutron activation analysis (NAA) is a highly sensitive method for the detection of vanadium in biological samples with detection limits in the low- to sub-ppb range. Even though NAA is highly sensitive, disadvantages include high cost and limited availability. Atomic absorption spectrometry is inadequate for measuring vanadium in biological specimens, but electrothermal atomic absorption spectrometry is sufficiently sensitive to detect vanadium at concentrations present in the serum and urine of the general population.[127,128] The range of graphite furnace atomic absorption spectrometry (GFAAS) extends from 10–500 μg V/L at a sample volume of 20 μL. Usually biological and environmental samples are prepared by acid digestion with nitric acid to extract vanadium from the sample matrix. GFAAS and flameless atomic absorption spectrometry (FAAS) are sufficiently reliable and sensitive methods to detect vanadium at ppb in water and wastewater samples. Analytical techniques (liquid chromatography or capillary electrophoresis coupled with electrothermal atomic absorption spectrometry, inductively coupled plasma/atomic emission spectrometry, or inductively coupled plasma/mass spectrometry) are available for the speciation of vanadium into tetravalent and pentavalent forms.[129] The potential redistribution of vanadium species during analysis and the small concentration of this element in samples require separation/preconcentration techniques prior to direct determination.[127] Inductively coupled plasma/atomic emission spectrometry and direct current plasma/atomic emission spectrometry are sensitive methods for the detection of vanadium in air. Contamination-free sampling and sample handling, particularly preconcentration steps, are important quality control procedures.[130] The complexity of the matrices of biological and environmental samples requires techniques to reduce interference with analysis of vanadium concentrations; the main methods for matrix removal are liquid–liquid extraction and solid-phase extraction.[16]

Biomarkers

Before the middle 1970s, wide variation occurred in the measurement of vanadium concentrations in the urine and blood, particularly with the use of colorimetry. The concentrations obtained in these studies probably are too high for comparison with concentrations obtained in more recent studies.[131]

Blood

Limited data on the distribution of vanadium in blood suggest that the vanadium concentrations in plasma/serum and whole blood are similar.[132]

General Population

There is substantial variation in reported blood vanadium concentrations in the general population, probably as a result of variation in analytical techniques. Generally, the whole blood vanadium concentration in the general population without excessive vanadium exposure is <1 μg/L. After a literature survey, Sabbioni et al. estimated the normal value of whole blood and serum vanadium concentration in the general population as ~0.05 μg/L with a range of 0.022–0.937 μg/L depending on sampling techniques, population sampled, and association with environmentally polluted areas.[130] In a study of 52 randomly selected Taiwanese college students, the mean vanadium concentration in whole blood samples was 0.42 μg/L with a range of 0.01–1.20 μg/L. The mean vanadium concentration in the five smokers in this study was 0.47 ± 0.32 μg/L.[133] The median whole blood vanadium concentration in 11 urban adults without occupational exposure to vanadium was 0.056 μg/L with a range of 0.032–0.095 μg/L.[104] The mean V concentration in a study of 130 German residents without occupational V exposure was 0.052 μg/L with a range of 0.016–0.11 μg/L as measured by ICP/MS.[134] In a study of 99 healthy French children, the upper 95% of vanadium in whole blood was 0.35 μg/L compared with 0.41 μg/L in plasma as measured by ICP/MS.[135]

In a convenience sample of 74 Belgian volunteers, the mean serum V concentration was 0.031 ± 0.010 μg/L (range, 0.16–0.94 μg/L) as measured by neutron activation analysis in the 1970s.[132] Serum vanadium concentrations increase above these reference values in patients with renal failure, probably as a result

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of the transfer of vanadium from the purified dialysate water to the blood. In a study of 43 chronic hemodialysis patients, the mean serum vanadium concentration was ~24 ± 11 μg/L related to high vanadium concentrations in tap water (mean $V_{tap\ water}$ = 16.9 μg/L) as measured by a modified electrothermal atomic absorption technique.[136] No adverse effects were attributed to the serum vanadium concentrations. The mean vanadium concentration in 80 chronic dialysis patients was 18.4 ± 7.6 μg/L spectrometry before dialysis as measured by flameless atomic absorption spectrophotometry.[137] After the use of purified water in the dialysate, the postdialysis vanadium concentration decreased to 13.0 ± 5.3 μg/L.

Medical Use

Vanadium is a minor constituent of titanium–aluminum–vanadium alloy used in cementless hip prostheses. Whole blood and serum V concentrations in patients with these hip prostheses are typically higher than in the general population with higher values in symptomatic patients with damaged prostheses than in asymptomatic patients.[138] In a cross-sectional study of 129 consecutive patients attending routine follow-up after implantation of cementless total hip prostheses with titanium-alloy containing acetabular and femoral components, the mean whole blood V concentration in asymptomatic patients was 0.16 ± 0.35 μg/L compared with 0.77 ± 1.40 μg/L in symptomatic patients.[139] The mean duration of the implants was 4.9 years (range, 0.08–28.1 years). The serum V concentrations were slightly higher than the whole blood V concentrations. The mean serum V concentration in asymptomatic patients was 0.18 ± 0.49 μg/L compared with 1.21 ± 2.37 μg/L in symptomatic patients. The difference was not statistically significant as a group. A sensorimotor axonal neuropathy and bilateral sensorineural hearing loss developed in a patient with a broken ceramic-on-ceramic bearing couple and stem containing titanium alloy.[140] The whole blood V and serum V concentrations were 6.1 μg/L and 5.8 μg/L, respectively; the serum Al concentration was 11.5 μg/L. Two months after replacement of the damaged implant, the neuropathy resolved, whereas the sensorineural hearing loss remained unchanged.

Toxicity

A 24-year-old woman developed acute respiratory distress, renal failure, and cardiac arrest within 1 day of ingesting an unknown amount of ammonium vanadate; analysis of inferior vena caval blood detected a blood vanadium concentration of 6.22 mg/L as measured by inductively coupled/plasma mass spectrometry.[97] Initial reports suggested that blood vanadium concentrations decrease during recovery from manic-depressive illness;[141,142] however, subsequent reports have not confirmed a correlation between blood vanadium concentrations and various types of depression.[143,144] A 69-year-old man with a ruptured ceramic-on-ceramic prosthesis (titanium–aluminum–vanadium femoral component) developed a grayish-green tongue, a fistula secreting abundant grayish-black exudate, hypoacousia, and sensorimotor deficits in the lower extremities.[145] Prior to revision, the whole blood and serum vanadium concentrations were 6.1 μg/L and 5.8 μg/L, respectively. Three months after revision, the symptoms resolved except for the hearing loss. At that time, the whole blood and serum V concentrations were 2.6 μg/L and 1.9 μg/L, respectively. The mean serum V concentration in 21 patients with loose total hip prostheses containing femoral stems composed of titanium-aluminum-vanadium alloy was 1.30 μg/L (range, <0.81–1.60 μg/L) compared with <0.81 μg/L (i.e., <LOD) in 21 controls (no implants) and 1.74 μg/L (range, <0.81–2.58 μg/L) in 12 patients with similar, normal-functioning prostheses.[146] The analytical method was graphite furnace Zeeman atomic absorption spectrometry.

Urine

In the general population with typical vanadium exposure, the urine V concentration is usually <1 μg/g creatinine and <8 μg/24-hour urine volume.[147] After a literature survey, Sabbioni et al. estimated the normal value of urinary vanadium concentration in the general population as ~0.5 μg/L with a range of 0.212–0.800 μg/L.[130] In a study of 382 healthy Italians, the mean urine V concentrations were 0.8 ± 0.08 μg/L with a range of 0.05–1.44 μg/L.[148]

Abnormalities

Following exposure to V_2O_5, reductions in forced vital capacity and forced mid-expiratory flow rates may occur within 24 hours. Even following acute, high-dose vanadium exposure, symptoms and signs of respiratory irritation, including reductions of airflow on pulmonary function tests, return to normal within 2–4 weeks.[107,149] Hypoglycemia may complicate severe vanadium intoxication.[97] Serum electrolytes, creatinine, and urea were normal in workers chronically exposed to airborne vanadium concentrations of 0.01–0.5 mg/m^3, suggesting a lack of clinical evidence of renal dysfunction.[63]

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HEALTH SURVEILLANCE

Risk Assessment

ATSDR derived an acute-duration inhalation minimal risk level (MRL) for vanadium of 0.8 μg/m^3 based on a LOAEL of 0.56 mg vanadium/m^3 for lung inflammation in rats exposed to vanadium pentoxide 6 hours/day, 5 days/week for 13 days and dividing the human equivalent LOAEL concentration (0.073 mg vanadium/m^3) by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for animal to human extrapolation with dosimetric adjustments, and 10 for human variability).[16] The chronic-duration inhalation MRL for vanadium is 0.1 μg/m^3 based on a $BMCL_{10}$ (lowest lower bound on the benchmark concentration, 40 μg/m^3) for degeneration of epiglottic respiratory epithelium in rats exposed to vanadium pentoxide 6 hours/day, 5 days/week for 2 years. The minimal risk level (MRL) for intermediate-duration oral vanadium exposure of 10 μg/kg/day was based on a NOAEL for hematological and blood pressure effects in humans exposed to vanadyl sulfate for 12 weeks. The US EPA calculated a reference dose (RfD) of 7 μg/kg/day that was without appreciable risk of adverse effects over a lifetime based on gastrointestinal cramping and diarrhea observed in human studies.[150] The no observable adverse effect level (NOAEL) for reproductive toxicity (i.e., based on decreases in sperm count) in male mice administered sodium metavanadate for 64 days prior to mating with untreated females was 0.2 mg sodium metavanadate/mL drinking water.[151]

Environmental Monitoring

Vanadium concentrations near metallurgical industries usually average about 1 μg/m^3, whereas ambient air near industries producing vanadium metal or V compounds contains V concentrations of a few μg/m^3.[17] Very high V concentrations result from boiler-cleaning operations as a result of the high concentration (i.e., ~10–25%) of vanadium oxides in the dust. During these cleaning operations, concentrations of 50–100 mg V/m^3 are frequent, ranging up to 500 mg V/m^3. During an overhaul, 18 boilermakers worked both inside and outside the boiler; the time-weighted average exposures for the boilermakers before and during the overhaul were 1.20 μg/m^3 compared with 8.9 μg/m^3 during the overhaul work.[152]

The US OSHA PEL–Ceiling for respirable vanadium dust and fume, of vanadium pentoxide (V_2O_5), is 500 μg/m^3 and 100 μg/m^3, respectively. The ACGIH recommends an 8-hour TLV–TWA of 0.05 mg/m^3 inhalable particulate matter measured as vanadium to protect workers from airway inflammation after exposure to vanadium pentoxide. In a study of 18 boilermakers, the workers were exposed to median vanadium exposure before and during boiler work of 1.0 μg/m^3 and 12.7 μg/m^3, respectively, during a short-term partial-shutdown.[153] No significant change in any lung function parameter on spirometry occurred when comparing values before, during, and 2 weeks after exposure ceased. Table 34.3 outlines the regulations and guidelines for vanadium concentrations in food, water, and air. The lungs are the primary target organ of vanadium toxicity; therefore, preplacement and periodic medical examinations should carefully document the status of the pulmonary system including chest X-rays and pulmonary function tests. The reporting of upper respiratory tract symptoms is probably the most sensitive indicator of excessive V exposure; however, this sign is not specific to vanadium. Although vanadium is on the US EPA Drinking Water Contaminant Candidate List, it is currently not regulated by existing US national primary drinking water regulations.

Biological Monitoring

URINE

After adjusting for creatinine concentrations, urine vanadium concentrations are probably a more reliable measure of exposure for biological monitoring than blood vanadium concentrations.[154] Samples should be collected several days after pulmonary exposure begins because of the slow diffusion of vanadium through the lungs. The presence of vanadium in the urine documents exposure, but studies of workers exposed to vanadium do not demonstrate a close correlation between ambient air vanadium and urine V concentrations.[16] Marked reduction of urine vanadium levels occurs within 24 hours after cessation of exposure; however, elevated urine vanadium concentrations may persist up to 2 weeks following heavy, acute V exposure.[155] Patients with titanium alloy implants typically have urine V concentrations several-fold higher than reference values, particularly in symptomatic patients.[139] In a study of workers involved in the manufacture of vanadium pentoxide from slag rich in vanadium, the vanadium concentration in urine samples ranged from 3.0–769 μg/L compared with 0.066–53.4 μg/L in controls.[156] The estimated airborne exposure to vanadium was 0.016–4.8 mg/m^3 over a mean of 9.2 years.

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TABLE 34.3. Regulations and recommendations for exposure to vanadium and selected vandium compounds.

Description	Value
OSHA	
PEL-Ceiling (transitional)	
Vanadium pentoxide	
(respirable dust)	0.5 mg/m^3
(fume)	0.1 mg/m^3
ACGIH	
TLV–TWA (8-hour)	
Vanadium pentoxide (dust/fume)	0.05 mg/m^3
Ferrovanadium (dust)	1.0 mg/m^3
BEI (end of shift at end of workweek)	
Urine	50 µg/g Creatinine
NIOSH	
REL (15-minute ceiling)	
Vanadium compounds	0.05 mg/m^3
REL-TWA (10-hour)	
Elemental V and vanadium carbide	1 mg/m^3
IDLH	
Vanadium pentoxide (dust/fume)	35 mg/m^3
WHO	
TWA (24-hour)	
Air quality guideline	1 µg/m^3
US EPA	
RfD	
Vanadium pentoxide (oral RfD)	9 µg/kg/day
ATSDR	
MRL	
Acute-duration inhalation	0.8 µg/m^3
Chronic-duration inhalation	0.1 µg/m^3

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; BEI = biological exposure indices; IDLH = immediately dangerous to life and health; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = reference dose; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency; WHO = World Health Organization.

The ACGIH currently does not have a biological threshold limit for vanadium;[157] tentative recommended biological exposure limits include 50 µg V/g creatinine for a postshift urine sample with the provision that more data are necessary to validate this value.[158] In individuals without occupational vanadium exposure, the background urine vanadium concentration in morning specimens is usually low (<0.4–0.5 µg/L) as measured by electrothermal atomic absorption spectrometry.[159] The correlation between 8-hour TWA V concentrations and morning urinary vanadium concentrations in this study was poor. In a study of 20 workers exposed to low (0.36–32 µg V/m^3) air concentrations of vanadium during the overhaul of an oil-fired boiler, the urine vanadium concentrations ranged from 190–4,300 µg/g creatinine with a mean V concentration in end-of-week samples of 1,530 ± 530 µg/g creatinine.[160] The median V concentration was 1,520 µg/g creatinine. The study demonstrated that the correlation between the start-of-shift urine vanadium and airborne V exposure on the previous day was stronger than the correlation between the end-of-shift urine vanadium and V exposure on the same day.

Blood

The serum vanadium concentrations in workers exposed to vanadium typically exceed reference values in the general population by up to several orders of magnitude; however, clinical manifestations of illness are unusual other than respiratory tract irritation.[147] A study of 11 ferroalloy plant workers exposed primarily to ferrovanadium dust and V_2O_5 (slag dust) below 1 mg V/m^3 demonstrated a mean whole blood vanadium concentration of 1.82 µg/L (35.7 nmol/L) with 95% CI: 1.52–2.19 µg/L (29.8–43.0 nmol/L) as measured by neutron activation analysis; the mean vanadium concentration was 0.78 ± 0.09 µg/L (15.4 ± 1.8 nmol/L) in six unexposed controls.[154] In an occupational study of vanadium pentoxide production workers exposed to ambient air concentrations of vanadium ranging from 0.016–4.8 mg/m^3, the vanadium concentration in whole blood samples from workers and controls ranged between 3.11–217 µg/L and 0.032–0.095 µg/L, respectively.[132] The average vanadium concentration in whole blood from a convenience sample of volunteers with occupational exposure to vanadium was 33.2 µg/L with a range of 3.10–217 µg/L.[133]

TREATMENT

Treatment is supportive. Usually measures to enhance vanadium elimination from the body are unnecessary because of the lack of persistence of vanadium in the body and because of the dearth of well-documented cases of chronic vanadium toxicity. Little clinical data are available on methods to enhance vanadium elimination. Ascorbic acid was a recommended agent for the treatment of acute vanadium toxicity based on its ability to reduce the pentavalent vanadate ion to the less toxic tetravalent vanadyl ion.[161,162]

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Animal studies suggest ascorbic acid is the most effective agent to **prevent** vanadium poisoning; however, deferoxamine and Tiron (4,5-dihydroxy-1,3-benzenedisulfonic acid) were more effective chelating agents following vanadium intoxication in mice compared with Na_2Ca-ethylenediaminetetraacetate (EDTA) and Na_3Ca-diethylenetriaminepentaacetate (DPTA).[163] Based on pharmacological endpoints for these chelators, only deferoxamine reduced vanadium in tissue when administered 8 hours after the injection of sodium metavanadate.[164] The administration of ascorbic acid was associated with increased vanadium in the tissue and no increase in urinary vanadium excretion. Because vanadate is 90% protein-bound, hemodialysis probably would not significantly increase the clearance of this compound.[12]

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Chapter 35

ZINC

HISTORY

The use of zinc alloys dates back to the Babylonians over 5,000 years ago.[1,2] Industrial and ornamental applications of zinc included its use in Semitic bronze (23% Zn) and brass. By the late 1800s, an acute febrile reaction (chills, fever, myalgias, headache, nausea, vomiting) was recognized as an illness in brass workers inhaling zinc oxide fumes. This clinical entity has been given various names including spelter chill, zinc fever, brass founders' ague, smelter shakes, and metal fume fever.[3] References to the medicinal uses of zinc appeared in the Ebers' papyrus, written in ~1,500 BC. In this document, the topical use of zinc as calamine was recommended as a therapy to heal lesions around the eye;[4] zinc remains a popular constituent of topical skin and eye preparations. During the late 1700s and early 1800s in Western Europe, zinc oxide and zinc sulfate were treatments for convulsions, gleet (urethral discharge), and vaginal exudates; however, variability of chemical composition and lack of efficacy soon limited the use of these zinc compounds.

Zinc is an essential cofactor for enzymes that control many cell processes including DNA synthesis, normal growth, brain development, behavioral response, reproduction, fetal development, membrane stability, bone formation, and wound healing. Zinc deficiency produces growth retardation, anorexia, delayed sexual maturation, iron-deficiency anemia, and alterations of taste.[5,6] Zinc possesses less toxicity compared with other metals (e.g., lead, arsenic, cadmium, antimony) that contaminate zinc ores;[7] however, fatalities occurred after the accidental infusion of zinc[8] and inhalation of zinc chloride fumes in closed spaces.[9] Today, zinc oxide is the most common cause of metal fume fever.

PHYSIOCHEMICAL PROPERTIES

Zinc is a relatively soft, bluish-white heavy metal that belongs to Group 12 (Group IIB) of the periodic table. This divalent metal reacts readily with inorganic (oxides, phosphates, sulfates) and organic compounds; consequently, elemental zinc and organometallic zinc compounds do not occur naturally in the environment.[10] Although zinc is stable in dry air, the presence of moisture quickly results in the formation of zinc oxide or basic carbonate on the surface of the metal. This metal is frequently alloyed with other metals (copper, aluminum, titanium, magnesium) as a result of the poor strength of metallic zinc. Table 35.1 lists the identifying information and physical properties of zinc and zinc compounds.

Zinc is amphoteric (i.e., dissolves in strong alkalis and mineral acids to form hydrogen and soluble zinc salts). These amphoteric properties (i.e., ability to react as an acid or a base) produce a variety of nonconducting, nonmagnetic zinc salts excluding zinc chromate. Zinc is most soluble in weakly acidic solutions; therefore, the ingestion of acidic foods from vessels composed of galvanized iron may produce adverse gastrointestinal effects. Zinc chloride is an irritating, hygroscopic corrosive salt that forms hydrochloric acid and zinc oxychloride on contact with moist mucous membranes. The fumes of this zinc salt are white with an acrid odor. The pH of some concentrated solutions of zinc chloride in

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TABLE 35.1. Identifying information and physical properties of zinc and zinc compounds. (Adapted from Agency for Toxic Substances and Disease Registry).[11]

Physical Characteristic	Zinc	Zinc Acetate	Zinc Chloride	Zinc Chromate
Synonym	Zinc dust; zinc powder	Zinc salt of acetic acid, zinc diacetate	Butter of zinc, zinc dichloride, Tinning flux™	Zinc salt of chromic acid; basic zinc chromate, zinc chrome yellow
Formula	Zn	$Zn(C_2H_3O_2)_2$	$ZnCl_2$	$ZnCrO_4$
%Zn	100%	36%	40%	36%
CAS RN	7440-66-6	557-34-6[a] 5970-45-6[b]	7646-85-7	13530-65-9
NIOSH RTECS	ZG8600000	AK1500000[a] ZG8750000[b]	ZH1400000	GB3290000
Molecular weight (g/mol)	65.38	183.48	136.29	181.37
Color	Bluish-white	White	White granules	Lemon-yellow
Physical state	Solid metal	Granules	Solid	Solid
Boiling point (°C)	908	Not applicable	732	Not available
Melting point (°C)	419.5°C	237	290	316°C
Density (g/mL)	7.14 (25°C)	1.74	2.91 (25°C)	3.40
Water solubility (mg/L)	Insoluble	4.0×10^4 (25°C)	4.32×10^6 (25°C)	Sparingly soluble
Vapor pressure (mmHg)	1 (487°C)	Not available	1 mm Hg (428°C)	Very low

Physical Characteristic	Zinc Hydroxide	Zinc Oxide	Zinc Phosphate	Zinc Sulfate	Zinc Sulfide
Synonym(s)	Zinc dihydroxide	Calaminec, zincitec, zinc monoxide	Zinc ortho-phosphate, neutral or basic zinc phosphate, zinc acid phosphate	Acid zinc salt; zincum sulfuricum; sulfuric acid, zinc	Wurtzite (α), sphalerite (β), zinc monosulfide
Formula	$Zn(OH)_2$ (66% Zn)	ZnO (80% Zn)	$Zn_3(PO_4)_2$ (51% Zn)	$ZnSO_4$ (40% Zn)	ZnS (67% Zn)
CAS RN	20427-58-1	1314-13-2	7779-90-0	7733-02-0	1314-98-3
NIOSH RTECS	ZH3853000	ZH4810000	TD0590000	ZH5260000	ZH5400000
Molecular weight (g/mol)	99.40	81.38	386.11	161.44	97.44
Color		White–yellow powder	White	Colorless	Colorless
Physical state	Solid	Solid	Powder	Solid	Solid
Boiling point (°C)	No applicable	Sublimes	Not available	Not available	1,185
Melting point (°C)	Decomposes (125°C)	Decomposes (100°C)	900	100[c]	~1,700
Density (g/mL)	3.05	5.607 (20°C)	4.00 (15°C)	3.54 (25°C)	3.98 (20°C)
Water solubility (mg/L)	Poorly soluble	Poorly soluble (1.6 at 29°C)	Insoluble	Soluble (9.1×10^5 at 70°C)	Poorly soluble (6.9 at 18°C)
Vapor pressure (mmHg)	Not available	~0	~0 (20°C)	Not available	10-4 (~800°C)

Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances.
[a] Anhydrous; [b] Dihydrate; [c] Decomposes at 680°C.

soldering flux may be 2–3. The taste threshold of zinc in water is ~15 ppm Zn; a definite metallic taste develops at 40 ppm. Opacification of water begins when the zinc concentration in water exceeds 30 ppm. Water-soluble zinc salts include chloride, chlorate, nitrate, and sulfate, whereas carbonate, oxide, phosphate, silicate, sulfide, and organic complexes of zinc are relatively water-insoluble.

EXPOSURE

Production Processes

Elemental zinc occurs rarely in nature.[12] Most zinc production results from the processing of zinc sulfide (ZnS) ores including sphalerite, wurtzite, and marmatite; the more accurate chemical formula for these ores is (Zn, Fe)S because iron frequently replaces zinc

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in these sulfide ores.[10] Initially, the zinc in the ore is concentrated by crushing and grinding, followed by gravity or magnetic methods of separation or flotation and caustic-leaching to prevent loss of zinc during the concentration process. For ores that do not undergo caustic leaching, the production of metallic zinc results from electrolytic processing or smelting in the presence of zinc oxide, heat, coal, and sulfuric acid. Exposure of workers to zinc occurs during smelting, welding, galvanizing, or brass foundry operations. Heating zinc near its boiling point of 908°C in an oxidizing atmosphere produces fresh zinc oxide particles in the respirable range. The inhalation of large doses of zinc oxide causes metal fume fever. During the hot galvanizing process, workers may be exposed to concentrations of hydrochloric acid in ambient air sufficient to cause dental erosions.[13]

Uses

Zinc is the fourth most widely used metal after iron, aluminum, and copper.[10] Metallic zinc commonly provides a protective coating for other metals (e.g., iron, steel) using a variety of processes including zinc plating, zinc spraying, hot-dip galvanizing, electro-galvanizing, or continuous-line galvanizing; zinc is also a constituent of dye casting and alloys.[14] The majority of commercially produced zinc is consumed during the galvanizing of iron and steel or the manufacturing of brass. Zinc improves the structural durability of iron and steel alloys. In contrast to other US coins, US pennies have contained 97.6% zinc and 2.4% copper since 1982. Nickels are 25% copper and 75% nickel, whereas dimes, quarters, and half-dollars have a copper core with a surrounding nickel coating. The ability of the zinc ion to precipitate proteins increases the value of zinc as a component of antiperspirants, styptics, astringents, and mild antiseptics.

Zinc oxide is the most commonly used zinc compound, primarily as a vulcanization activator and accelerator that reduces rubber aging by neutralizing sulfur and organic acids formed by oxidation.[12] Zinc is a solubilizing agent in many drugs (e.g., insulin) and a constituent of dental cement for dentures.[15] Some manufacturers of zinc-containing denture adhesives withdrew these products because of concern that ingestion of large amounts of these adhesives could cause zinc-induced hypocupremia and possibly bone marrow suppression or neuropathies.[16] A causal link was not well-established; zinc-containing denture adhesives remain on the US market. Table 35.2 lists the common uses of various zinc compounds.

Zinc Chloride

Uses include soldering flux, dry battery cells, oil refining, dental cement, and taxidermy. Exposed workers include military personnel, rubber workers, textile finishers, embalmers, and dental cement makers. Zinc chloride is the primary ingredient in smoke bombs used to disperse crowds. During manufacturing processes, irritating substances (i.e., hydrochloric acid, zinc oxychloride) form in the airways of workers following the inhalation of zinc chloride.

Zinc Oxide Nanoparticles

Zinc oxide is a semiconductor with commercial applications in pharmaceutical and solar cell manufacturing, rubber formulation, vulcanizing, and white pigment/ceramic production. Workers exposed to zinc oxide

TABLE 35.2. Uses of zinc compounds. (Adapted from Knapp et al.).[17]

Compound	Uses
Zinc acetate	Wood preservative, mordant, glazes, reagent
Zinc carbonate	Pigment, feed additive, manufacture of porcelains, pottery, rubber
Zinc chloride	Deodorant, disinfectant, antiseptic, wood preservative, fireproofing, soldering flux, cement, batteries, smoke bombs
Zinc chromate(VI) hydroxide	Pigment in paint, oil, varnish, linoleum, rubber
Zinc gluconate	Suggested treatment for common cold
Zinc oxide	Pigments, dental cements, glass tires, glue, matches, white ink, reagent, photocopy paper, flame retardant, fungicide, catalyst in organic synthesis
Zinc phosphide	Rodenticide
Zinc stearate	Tablet and rubber manufacture, cosmetic and pharmaceutical powders, ointments
Zinc sulfate	Mordant, wood preservative, fertilizers, sprays, animal feed additive, rayon manufacturing, starting material for other zinc compounds, textile dying, phosphor in watches/TV screens, pigment

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during the heating of zinc-containing alloys include galvanizers, electroplaters, and welders. Zinc oxide nanoparticles have useful commercial uses involving antimicrobial, UV filtering, catalytic, and photochemical properties.[18] Zinc oxide absorbs UV light, particularly the UVA portion, whereas visible light is reflected and scattered.[19] Many sunscreens and cosmetics use nanoparticles of zinc oxide and titanium dioxide to reduce the white, chalky appearance of the older dermal preparations; these nanoparticles easily aggregate (i.e., 20 nm → 130 nm) to reduce the penetration of UV light between gaps in the UV absorption spectrum of normal-sized (i.e., 20 nm) ZnO nanoparticles.[20] Additionally, makeup, shampoo, toothpaste, and anti-wrinkle cream contain nanoparticles to reduce the weight and greasy feeling of these products. Zinc oxide nanoparticles typically do not penetrate the stratum corneum (horny) layer of the intact epidermis. ZnO nanoparticles are often coated with polymers (e.g., aluminum hydroxide, silica oxides) to reduce potential toxicity (e.g., reactive oxygen species) from other routes of exposure.[21]

Zinc Gluconate

Double-blinded, placebo-controlled studies suggest oral zinc lozenges shorten the duration of the common cold in healthy people when administered within 24 hours of the onset of symptoms;[22] however, the use of zinc does not reduce severity. Additionally, the use of zinc lozenges is associated with a high prevalence of adverse effects (e.g., nausea, bad taste).[23] The high degree of heterogeneity of the data indicates the need for cautious interpretation of these data. At concentrations of 0.1 mmol/L, zinc inhibited the *in vitro* replication of several viruses associated with the common cold by preventing the formation of viral capsid proteins and limiting intracellular adhesion.[24] The zinc ion blocks intracellular adhesion molecule 1 in the nasal epithelium, where the human rhinoviruses attach.[25] Evidence to support the use of zinc lozenges in the treatment of children is limited. Of eight double-blind, placebo-controlled clinical trials published before 2000, half the trials found zinc lozenges effective and half found no difference between placebo and zinc.[26] In some studies of children and adolescents with the common cold, the use of zinc lozenges was associated with an increased incidence of minor adverse effects (e.g., diarrhea, throat discomfort, bad taste, nausea) when compared with controls.[27] There is insufficient evidence to recommend the use of zinc supplements for the treatment or prevention of Alzheimer's disease.[28]

Zinc Sulfate

The World Health Organization and UNICEF recommend zinc supplementation during acute diarrheal illnesses in children from developing countries where zinc deficiency is common. Zinc sulfate was the most common zinc supplement given to children in Uttar Pradesh, India, with diarrheal illnesses; the use of zinc gluconate was less common.[29] Although there is insufficient evidence that zinc supplementation reduces death or hospitalization during acute diarrheal illnesses, zinc may shorten the duration of the illness. In a Cochrane review of studies in children aged >6 months with acute diarrhea, zinc supplementation reduced the duration of diarrhea by ~10 hours (mean difference = −10.44 hours, 95% CI: −21.13 to 0.25; n = 2,175).[30] There was moderate evidence that zinc supplementation decreased the duration of the illness beyond 6 days (RR = 0.73, 95% CI: 0.61–0.88; n = 3,865).

Sources

Zinc is a common constituent of the earth's crust. Typical background zinc concentrations in the environment include the following: fresh water, <0.1–50 μg/L; seawater, 0.002–0.1 μg/L; soil, 10–300 mg/kg dry weight; sediments, <100 mg/kg dry weight; and ambient air, <300 ng/m^3.[10] Risk assessment suggests there is no clear evidence that environmental zinc exposure causes adverse health effects.[31]

Air

Zinc release into the air is greater from anthropogenic sources than from natural sources. These anthropogenic sources include metallurgic industries (lead smelting, brass works), zinc-containing fertilizers and pesticides, mining, refuse incineration, coal and fuel combustion, corrosion of galvanized structures, and smelter operations.[32] Mildly irritating zinc ammonium sulfate is a zinc salt emitted during the combustion of fossil fuels.[33] The average zinc concentration in ambient air in the United States is usually <1 μg/m^3 with the arithmetic mean varying from 0.02–0.16 μg Zn/m^3 in urban areas.[12] In the early 1990s, the median zinc concentration in air samples collected across Minnesota was 0.012 μg/m^3 with a maximum of 0.187 μg/m^3.[34] In remote areas, the zinc concentration in ambient air is much lower (i.e., <0.003–0.027 μg/m^3), particularly in winter.[35] Average annual zinc concentration in the air near a smelter was ~5 μg/m^3 with a daily range up to 15.7 μg/m^3.[32] Inhalation of zinc from ambient air is a minor route of zinc exposure for the general population.

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Soil

The zinc concentration in cultivated US soils ranges from <5–400 mg/kg (mean = ~36 mg/kg) compared with <10–2,000 mg/kg (~51 mg/kg) in uncultivated soils;[12] however, natural zinc concentrations in the soil can vary by three to four orders of magnitude depending on the presence of zinc-containing ores and types/concentrations of zinc salts used in local commercial activities[10] Releases of zinc to the soil account for the major amount of zinc released from natural and anthropogenic sources to the environment. The major industrial zinc sources include mine tailing, coal and bottom fly ash, and discharges of waste. Zinc concentrations in soil from a reclaimed waste dump of phosphate ore mines averaged ~450–1,100 mg/kg; zinc concentrations were higher in vegetation grown on this land compared with control plots.[36]

Water

Erosion of soil particles containing natural trace amounts of zinc accounts for the major source of zinc in water. Concentrated releases of zinc into water usually result from discharges associated with zinc smelting and refining operations or cadmium and lead operations. Zinc concentrations in surface water are usually <50 μg/L; however, the zinc concentrations may range up to 50 mg/L near concentrated sources (e.g., mines).[37] In freshwater, zinc occurs in the following forms: zinc oxy ions, hydrated ions in complexes of organic matter (humic acid, fulvic acid), and adsorbed to solid particulate matter. Zinc concentrations are higher in sediment compared with water because zinc is transported in an adsorbed or precipitated state. The Zn concentration ranged from 1–2.9 g/kg in sediment from Hamilton Harbor compared with 6–48 μg Zn/L in the surrounding water.[38] In ultrafiltered samples from residential ground water collected in acid-washed Teflon tubing from eastern Long Island, New York, ~40% of the dissolved Zn fraction (<0.45 μm) resided in the colloidal fractionate (1 kDa–0.45 μm) with the remainder in the low molecular weight fractionate (<1 kDa).[39] The precipitation of zinc sulfate occurs under anaerobic conditions in the presence of sulfide ions. Zinc bioconcentrates moderately in aquatic organisms primarily in crustaceans and bivalve species rather than fish.[12]

Zinc concentrations in drinking water may exceed surface water concentrations as a result of water treatment and leaching from water lines. During the late 1970s, 77% of 1,577 US surface water samples contained zinc concentrations of 2–1,200 μg/L, whereas 380 drinking water samples contained zinc concentrations of 3–2,000 μg/L.[37] Higher concentrations in drinking waters are a result of water treatment and contamination from plumbing of the water distribution system. The zinc concentration in drinking water may increase in the distribution systems secondary to the leaching of zinc from piping materials, particularly in soft water with a low pH. Typically, zinc concentrations in Seattle drinking water ranged from ~10–100 μg/L with zinc concentrations in water standing in galvanized pipe ranging up to 1,300 μg/L.[40,41] The zinc concentration in drinking water from houses was ~10-fold higher in houses with galvanized plumbing than copper plumbing. Substantial variation in the concentration of trace metals typically occurs in the same water source over time.

Diet

Zinc is a ubiquitous, essential element. In plants, zinc does not bioconcentrate or biomagnify through terrestrial food chains.[12] The average daily zinc intake ranges from ~5–16 mg (~0.1–0.2 mg/kg body weight) with food and water providing the major sources of zinc intake.[10,42] In an urban Italian study, the mean daily intake of zinc was 3.65 mg with meat accounting for the main contribution of zinc.[43] The mean daily Zn intake in a market basket study of Northern Italian foods was 12.0 mg with a range of 7.5–19.8 mg; the contribution of various food groups was similar, except sweet foods.[44] In a study of diets from 250 Mumbai adults (170 vegetarian, 80 nonvegetarian),[45] the mean daily zinc intake was 6.3 mg compared with means ranging from 5.7–7.9 mg for Mumbai children (6–10 years) as measured by differential pulse anodic stripping voltammetry.[46] Typically, a person must consume a diet rich in high-protein sources to meet the recommended daily adult zinc allowance of 11 mg for men and 8 mg for women (12 mg for pregnant women). US federal regulations permit the addition of zinc chloride, zinc oxide, zinc stearate, and zinc sulfate as food additives; thus, these zinc salts have generally recognized as safe (GRAS) status. The bioavailability of zinc is not well defined because of limited information on factors that affect the mammalian uptake of zinc including speciation, composition of food ingested, body stores of zinc and related metals, physiological status, control mechanisms of zinc in the body, and nutrient-dietary interactions. In general, the absorbed dose is substantially less than the administered dose; diet usually accounts for almost all (i.e., >95%) of the total intake of zinc.[10]

Zinc concentrations in fresh edible potions of vegetables range from ~10–150 mg/kg.[10] In general, meat,

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dairy products, and eggs contain more zinc than plants, with liver being a rich source of zinc. Seafood (oysters, mussels), meat, dairy products, nuts, legumes, and whole grains also contain relatively high Zn concentrations. The average Zn concentration in meats, poultry, and fish is ~25 mg/kg (ppm).[47]

Lifestyle

A Turkish study did not detect a statistically significant difference ($P > 0.05$) in the mean plasma zinc concentrations between 32 smokers (i.e., at least ½ ppd for 1 year) and 26 nonsmokers; the mean plasma zinc concentration in the nonsmokers was 0.87 ± 0.14 µg/L compared with 0.88 ± 0.13 µg/L for the smokers as measured by atomic absorption spectrometry.[48] A Jordanian study of 56 smokers and 17 nonsmokers demonstrated mean whole blood zinc concentrations of 3.21 ± 0.44 mg/L (range, 1.70–6.48 mg/L) and 6.80 ± 0.26 mg/L (range, 5.16–9.00 mg/L), respectively, as measured by inductively coupled/plasma optical emission spectrometry. A majority of the smokers used >1 ppd.[49] Zinc does not equilibrate across the dialysis membrane; the strong affinity of plasma proteins for zinc causes zinc extraction from the dialysate.

ENVIRONMENTAL FATE

Air

Zinc exists in the environment primarily in the divalent state as an oxidized form (ZnO) bound to submicron particulate matter.[12] Zinc particles with small diameters and low densities suspended in the atmosphere may travel long distances from emission sources. Before deposition, zinc-containing particles/aerosols may undergo chemical transformation in the atmosphere to other zinc compounds (e.g., sulfide, ferrous zinc, phosphide, chloride, elemental zinc).[50] Dry and wet deposition removes zinc from the air with deposition to soil and surface waters.

Soil

Sorption is the dominant reaction of zinc in the environment as a result of the inability of zinc to volatilize from soil or water. In the soil, zinc remains adsorbed to soil; leaching is limited except at waste disposal sites. The relative mobility of zinc in soil and water depends on chemical species (solubility) and soil conditions (e.g., salinity, pH, humic acid concentrations, cation exchange capacity, pH, redox potential); under anaerobic conditions, zinc sulfide is the controlling species.[51] Zinc sulfide is insoluble; hence, zinc mobility in anaerobic soil is low. The mobility of zinc in soil increases at low pH under oxidizing conditions and limited cation exchange capacity (i.e., low calcium).[10] Adsorption of zinc to sediment occurs more readily at pH >7 and low salinity. The deposition of zinc in soil produces relatively small concentrations of the soluble and more mobile form (zinc sulfate). Most contaminated soils contain <1% soluble zinc; consequently, zinc remains primarily in immobile forms in these soils.[52]

Water

The balance between suspended (i.e., undissolved) zinc, dissolved zinc, and zinc adsorbed to suspended matter in waters depends on pH, redox potential, total organic carbon, and speciation. In a study of eight rivers polluted by mining operations, <10% of total zinc was sorbed on particles or colloids in acidic Norwegian river water (pH = 3.1 and 5.1) compared with 21% in water from six rivers with neutral pH.[53] As the pH decreases relatively, more zinc dissolves into the water phase. In surface waters, zinc partitions into sediments through sorption onto organic material, clay, and hydroxides (iron, aluminum, manganese). Zinc exists as a divalent form in aqueous solution that exhibits amphoteric properties. In acidic environments, zinc metals and compounds form hydrated divalent zinc cations, whereas zincate anions form in strong bases including the hydroxo-complexe $[Zn(OH)_3]^-$, $[Zn(OH)_4]^{2-}$, and $[Zn(OH)_4(H_2O)_2]^{2-}$.[12] However, the formation of anionic zinc species is unlikely at the pH of most natural waters. Biomethylation of zinc compounds in aquatic ecosystems is also unlikely because of the instability of alkyl zinc compounds in oxygen and water.

Complexing agents (e.g., humic acid) bind zinc in natural waters. The stability of these complexes depends on pH of the water and the chemical reactivity of the complex. The dissociation of the complex contributes to the amount of free zinc ions in solution; as the pH decreases, the dissociation rate increases with ~50% dissociation of the zinc-humic acid complexes at pH 5.5.[54] The mobility of zinc in anaerobic environments and the presence of sulfides are poor because of the precipitation of zinc in its insoluble form (i.e., zinc sulfide).[55] Consequently, severe zinc contamination occurs primarily near sources of zinc release. Because zinc is an essential metal, organisms naturally concentrate it. Many organisms regulate the internal concentration of zinc within certain limits; therefore, zinc tissue concentrations do not necessarily

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reflect ambient concentrations.[10] Bioaccumulation of zinc occurs to a moderate extent (i.e., ~50–1,000 times), particularly in crustaceans and bivalve animals; zinc does not concentrate in plants above zinc concentrations present in the soil.[56] Consequently, significant biomagnification of zinc in the food chain does not occur.[57,58,59]

DOSE EFFECT

Zinc gluconate tablets contain 14.3% zinc by weight, while zinc sulfate contains 40.5% zinc by weight.

Ingestion

Acute Toxicity

Ingestion of 1–2 g zinc sulfate (405–810 mg elemental Zn) produces emesis.[60] Emesis usually occurs when the concentration of zinc salts in fluid from galvanized zinc containers exceeds 675–2,000 ppm(mg/L). Gastrointestinal irritation (i.e., nausea, vomiting, abdominal pain) developed in 26 of 47 healthy volunteers after ingesting zinc sulfate tablets (2 mg Zn/kg/day) for 6 weeks.[61] The ingestion of 12 g elemental zinc over 2 days by a 16-year-old adolescent was associated with lightheadedness, slight ataxia, lethargy, and headache, but no gastrointestinal complaints occurred.[62] Severe nausea and vomiting occurred within 30 minutes of the ingestion of 4 g zinc gluconate (~570 mg elemental zinc) by a 17-year-old adolescent; he recovered within 7 hours.[63] No diarrhea, gastrointestinal irritation, neurological dysfunction, or hepatic inflammation developed.

Zinc chloride is an extremely soluble zinc salt that possesses corrosive properties. Ingestion of 1 g $ZnCl_2$/kg by a child resulted in minimal systemic effects.[64] Ingestion of 3 oz of solder flux (11% $ZnCl_2$) by a 24-year-old resulted in lethargy, vomiting, pharyngitis, esophagitis, mucous membrane irritation, and mild pancreatitis, but serious systemic effects did not occur.[65] Although the zinc chloride content varies between fluxes, most fluxes contain ~11% $ZnCl_2$. The intentional ingestion of a 35% solution of $ZnCl_2$ produced severe upper pharyngeal corrosion, subcutaneous emphysema of the upper chest, and severe corrosion of the stomach that resulted in gastric obstruction.[66]

Chronic Toxicity

The recommended daily allowance of zinc for adults is 15 mg compared with 3–5 mg Zn in infants. In groups with adequate copper intake, adverse effects do not occur with the daily ingestion of <50 mg zinc.[10] Long-term studies of the ingestion of zinc in humans have not detected signs of gastrointestinal irritation at doses below 4.3 mg/kg/day.[67,68] The daily ingestion of 440–660 mg $ZnSO_4$ for 10 months[69] and 1–2 g elemental Zn over several months[70] produced a copper deficiency (sideroblastic anemia, hypochromic microcytic anemia, neutropenia). The chronic ingestion of >425 pennies was associated with diarrhea, gastrointestinal bleeding, and a fatal bacterial and fungal sepsis.[71] The composition of the pennies was 97.6% Zn and 2.4% Cu. The daily ingestion of 850–1,000 mg zinc gluconate as a dietary supplement was associated with severe anemia and neutropenia that resolved with copper supplementation.[72] Nausea, vomiting, fever, severe anemia, and elevated plasma zinc concentrations were associated with home dialysis with water that contained ~6 mg Zn/L.[73] Following the ingestion of 4.3 mg Zn/kg/day as $ZnSO_4$ for 6 weeks by healthy volunteers, the mitogenic response of peripheral blood lymphocytes and the phagocytic activity of polymorphonuclear leukocytes were impaired, but no abnormalities developed in the number of lymphocytes or T cell and B cell subsets.[67]

Inhalation

Mild reduction in forced expiratory flow rates occurred following a 30-minute exposure to fumes from zinc oxide containing 77 mg Zn/m^3; pulmonary function tests did not demonstrate abnormalities in workers exposed to 8–14 mg Zn/m^3 for up to 8 hours.[74,75] Two volunteers developed symptoms of metal fume fever after exposure to zinc oxide fumes for 5 minutes and 12 minutes, respectively, at an estimated concentration of 600 mg/m^3.[76] In a study of 26 welders exposed to zinc oxide fumes ranging from 70–140 mg/m^3, 2 workers developed clinical features of metal fume fever.[77] Mild increases in body temperature (1.4 ± 0.3°F) occurred in 10 of 13 subjects exposed to zinc oxide concentrations of 5 mg/m^3 for 2 hours.[78] No cases of metal fume fever occurred in a study of 20 zinc foundry workers exposed to zinc oxide fumes at concentrations up to 36.3 mg/m^3 for <4 hours.[79]

TOXICOKINETICS

Absorption

Ingestion

Zinc absorption occurs via passive diffusion and a saturable carrier-mediated process (cysteine-rich intestinal

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protein) throughout the gastrointestinal tract; in rodent studies, the largest portion of zinc absorption occurs in the second part of the duodenum.[80,81] The amount of absorption depends on several factors including the amount of zinc, the type of food consumed (e.g., coingestion of calcium or phosphorus in dairy products decreases zinc absorption),[82] and the zinc requirements of the body. Based on isotope studies, a person with a normal diet absorbs an average of ~20–40% of the zinc present in the diet.[83] The body homeostatically regulates zinc absorption with zinc deficiency by increasing zinc absorption from the gastrointestinal tract; saturable transport mechanisms limit Zn absorption following excessive Zn intake.[84] The presence of trace metals (cadmium, copper, mercury) and phosphates in the diet reduces zinc absorption. Similar to other metals, zinc induces production of the metal-binding protein, metallothionein. This protein binds to zinc in the mucosal cells covering the gastrointestinal tract. By excretion of the metallothionein-zinc complex during the sloughing of these cells, metallothionein helps prevent the absorption of excessive amounts of zinc.[85] In a study of 12 healthy volunteers receiving 20 mg organic zinc (zinc gluconate) or inorganic zinc (zinc oxide) daily for 14 days, the time to maximum concentrations was ~1.5–2 hours with some rebound occurring 16–24 hours after the last dose.[86] The mean maximum Zn concentration at the end of 14 days of Zn gluconate was 1.25 ± 0.18 mg/L, whereas similar amounts of Zn oxide produced slightly lower values.

Inhalation

The amount of zinc absorbed by the lungs is not well defined. Elevated zinc concentrations in workers exposed to zinc oxide fumes suggest the lungs absorb zinc oxide, but some gastrointestinal absorption of particles cleared by the cilia cannot be excluded.[87]

Dermal

Data on the absorption of zinc through the skin are limited. Some absorption of zinc through damaged skin occurs in burn patients treated with zinc oxide dressings.[88]

Distribution

As one of the most abundant trace elements in the body, zinc is present in all human tissues and fluids; however, zinc does not accumulate in the body. The absorbed zinc dose distributes to muscle, bone, liver, pancreas, prostate, and kidney as well as other organs. Muscle and bone contain ~63% and 28%, respectively, of the total body zinc burden based on ^{65}Zn tracer studies in healthy adults.[89] The average amount of zinc in the adult body is ~1.4–2.3 g.[90] The prostate contains relatively high zinc concentrations, probably because of the presence of the zinc-containing enzyme, acid phosphatase. In the plasma, albumin binds ~$^2/_3$ of the zinc with the balance bound mostly to α_2-globulins.[91]

Elimination

Zinc elimination results primarily from fecal excretion (i.e., 70–80%) with relatively little zinc (i.e., 15–25%) appearing in the urine and sweat. Based on the elimination of radioactive zinc administered orally, daily zinc elimination averages ~1% of the absorbed dose in patients with alcoholic liver disease.[92] Fecal excretion of zinc increases as the intake of zinc increases.[93] Following parenteral or oral zinc administration, the biological half-lives range from 100–500 days.[60,89]

Maternal-Fetal Kinetics

Zinc concentrations are typically higher in maternal blood than cord blood. The geometric mean maternal and cord whole blood zinc concentrations in 148 mothers from Mumbai, India, were 6.33 ± 0.12 mg/L and 2.53 ± 0.13 mg/L, respectively, as measured by differential pulse anodic stripping voltammetry; the maternal whole blood/cord blood ratio was ~2.5.[94] A study of 56 mothers living in Singapore demonstrated a mean zinc concentration in maternal blood of 4.97 ± 1.15 mg/L compared with 1.58 ± 0.45 mg/L in cord blood.[95] Stages of lactation affect the zinc concentrations in human milk. In a French study of 82 lactating mothers, the peak zinc concentration (12.0 ± 4 mg/L) occurred 2 days postpartum and declined to 5.0 ± 1.4 mg/L 6 days postpartum as measured by flame/atomic absorption spectrometry.[96] Zinc concentrations in breast milk decline significantly in the months following birth.[97] Although plasma Zn concentrations in 41 lactating Polish mothers increased from the initiation of lactation to the formation of mature milk, the zinc concentration in their breast milk declined.[98] The mean maternal *plasma* zinc concentration increased from 0.51 ± 0.13 mg/L (0–4 days postpartum) to 0.76 ± 0.20 mg/L (10–30 days postpartum), whereas the zinc concentration in their *breast milk* decreased from 8.2 ± 2.8 mg/L to 1.4 ± 0.7 mg/L, respectively. In a study of 25 lactating Libyan women, the mean zinc concentration in their breast milk declined from 16.1 ± 2.7 to 4.95 ± 1.3 mg/L over the first 3 weeks of lactation.[99]

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HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

Zinc is a cofactor for >200 biologically important enzymes (e.g., alcohol dehydrogenase, carbonic anhydrase, carboxypeptidase), particularly enzymes involved in protein synthesis.[64] Adverse effects of zinc deficiency in humans include neurosensory changes, respiratory infections, diarrhea, impaired neuropsychological functions, growth retardations, delayed wound healing, immune disorders, dermatitis, and oligospermia. Causes of these deficiencies include poor dietary intake, long-term parenteral nutrition without supplementation, and enteral causes such as malabsorption.[100] Hypogonadal dwarf syndrome has been associated with zinc deficiency characterized by hypogonadism and growth retardation along with anemia, dysosmia, altered taste, poor wound healing, and hepatosplenomegaly. Acrodermatitis enteropathica is an inherited disorder of zinc deficiency manifested by alopecia, hypertrophic and ulcerated skin, chronic diarrhea, and muscle wasting. An abnormally low zinc concentration in breast milk has been associated with the development of zinc deficiency in breast-fed newborns characterized by acrodermatitis, irritability, and delayed growth.[101] Albumin-bound plasma zinc is the metabolically active zinc pool in the body. Zinc in bone is relatively inert, except during periods of calcium mobilization from bone.

Mechanism of Toxicity

Zinc chloride is a caustic agent that causes irritation of the alimentary and respiratory tracts. Excessive zinc intake interferes with copper absorption, probably by the induction of metallothionein; this protein has a higher affinity for copper than zinc. Consequently, more copper is bound to metallothionein and excreted into the feces.[102] Anemia may develop as a result of zinc-induced copper deficiency. Elevated Zn concentrations also reduce serum concentrations of high-density lipoprotein cholesterol while causing a transient elevation in serum low-density lipoprotein cholesterol.[67] Bone marrow aspirates demonstrate cytoplasmic vacuolization of myeloid and erythroid precursor elements; however, a variety of other conditions (e.g., nutritional deficiencies, myeloproliferative syndromes, acute alcohol intoxication, drug reactions, malignant hematological conditions) produce cytoplasmic vacuolizations.[103] High zinc concentrations impair lymphocyte and neutrophil function. Several case reports associate elevated serum zinc, very low serum copper, and low plasma ceruloplasmin concentrations with pancytopenia, myelopathy, and neuropathy; some of these patients improved with cessation of the use of zinc-containing denture pastes.[104,105,106] Publication bias and determination of the initial abnormality (i.e., low serum copper/ceruloplasmin vs. high serum zinc concentrations) limit conclusions regarding causation.

The exact mechanism of action of metal fume fever is unknown; however, an immune response to zinc oxide in the respiratory tract probably produces inflammation and the release of pyrogenic cytokines with zinc as a hapten and a zinc-protein conjugate as the antigen.[78,107] Experimental studies on the inhalation of zinc-coated steel fumes from metal inert gas brazing indicate acute inflammation occurs in humans 24 hours after exposure based on the increase in serum C-reactive protein.[108] *In vitro* experiments indicate zinc oxide exposure causes dose-dependent release of proinflammatory cytokines (e.g., pulmonary tumor necrosis factor-alpha, interleukin-6, interleukin-8) and pulmonary neutrophils.[77,109] In experimental studies of smoking and nonsmoking volunteers, smoking did not increase these inflammatory cytokines; however, there was a dose-dependent relationship between smoking and interleukin-1 when compared with the nonsmoking group.[110] Both divalent zinc and zinc oxide stimulate the formation of free oxygen radials as measured by the luminol-amplified chemiluminescence assay.[111] Exposure to zinc oxide fumes during welding was associated with an increase in pulmonary inflammation as defined by an increase in polymorphonuclear leukocytes recovered in bronchoalveolar lavage fluid.[75] In this study, 4 of 14 welders developed symptoms of metal fume fever. There were no clinically significant changes in airway reactivity or pulmonary function. Experimental studies indicate the development of clinical tolerance to the acute effects of zinc oxide inhalation in workers during recurrent exposure; these changes result in decreased pulmonary inflammation (i.e., reduced alveolar neutrophil and plasma IL-6).[112] The latter substance may act as a pyrogen and an anti-inflammatory agent. In experimental human studies, zinc toxicity was associated with impaired immune and inflammatory responses. Zinc oxide nanoparticles are relatively more toxic than other metallic oxide nanoparticles as a result of oxidative stress, inflammatory, and ion-shedding properties.[113] Although these properties potentially induce specific signaling pathways (e.g., necrosis, apoptosis), the clinical significance of the potential effects remains unclear.

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Pathological Changes

Zinc compounds can produce irritation and corrosion of the gastrointestinal tract following ingestion. Acute tubular necrosis and interstitial nephritis may occur. Inhalation of high zinc chloride concentrations and other constituents of smoke bombs in closed spaces produces a chemical pneumonitis and acute respiratory distress syndrome (ARDS). Typically, severe damage to the mucous membranes of the upper respiratory and tracheobronchial tracts manifests by edema, yellow-gray discoloration, and necrosis.[114,115] Two autopsies of workers dying following the detonation of smoke bomb material in a tunnel revealed pulmonary edema and severe inflammation of the mucosa in the upper respiratory tract.[116] Autopsies from patients dying within 20–30 days after inhalation of zinc chloride along with other constituents of these devices demonstrated extensive interstitial and intraalveolar fibrosis with obstruction of the pulmonary arteries and widespread occlusion of small vessels.[117] In these patients, the injury to venous vessels appeared more severe than other types of ARDS, including contracture of preacinar and intraacinar arterial and venous vasculature.[118] Zinc concentrations in all tissues were within the normal range; no zinc particles were present on examination of lung tissue at autopsy.

CLINICAL RESPONSE

Acute Toxicity

The principal adverse effects of excessive oral zinc exposure include nausea, vomiting, abdominal pain, anemia, and occasionally pancreatitis. Following the ingestion of large doses of zinc compounds, vomiting almost universally occurs together with abdominal pain and diarrhea. Hematemesis may develop in severe cases, particularly with corrosive compounds (e.g., zinc chloride). Zinc compounds produce more prominent gastrointestinal symptoms compared with elemental zinc. Lethargy, slight ataxia, and difficulty with writing developed following the acute ingestion of 12 g elemental Zn over 2 days without the appearance of gastrointestinal symptoms.[62] Zinc chloride is a corrosive, particularly in concentrations exceeding 20%; serious ingestions produce partial and full thickness burns of the oral mucosa, pharynx, esophagus, stomach,[17] and laryngotracheal tree[119] with the subsequent development of dense scarring and clinically significant strictures.[120] The corrosive actions of zinc chloride dominate the clinical presentation following ingestion; systemic zinc toxicity is rare in children following the ingestion of zinc chloride.[121] Both animal and human data indicate the liver is not a primary target organ for zinc toxicity.[122,123] Hypotension, diarrhea, vomiting, pulmonary edema, jaundice, hyperamylasemia, oliguria, anemia, and thrombocytopenia occurred after an intentional injection of zinc sulfate.[8]

Environmental Exposure

Most of the severe injuries following exposure to the smoke from the detonation of zinc chloride bombs occur in closed spaces; evaluation of patients following exposure to this smoke in open spaces reveals less severe respiratory symptoms that do not usually cause permanent pulmonary dysfunction.[124] Inhalation of high concentrations of zinc chloride smoke produces a biphasic respiratory syndrome characterized initially by mucous membrane irritation, cough, lacrimation, and dyspnea followed within 24 hours by persistent respiratory symptoms that may persist for several weeks.[125] In severe cases, acute respiratory distress syndrome (ARDS) may develop. During World War II, 10 people died and numerous other patients developed respiratory distress following the detonation of material from a smoke bomb in a tunnel.[116] This episode involved the inhalation of fumes from a smoke bomb in a closed space that produced high concentrations of zinc chloride (i.e., estimated 33,000 mg Zn/m^3) along with other constituents (calcium silicate, hexachloroethane, zinc oxide, an igniter). Most survivors complained of dyspnea, retrosternal chest pain, stridor, rhinitis, and lacrimation. No toxic changes appeared in the kidney or liver. In the survivors of an intense exposure to the smoke from zinc chloride smoke bombs, delayed sequelae included the development of emphysematous blebs[126] and a progressive acute respiratory distress syndrome beginning several weeks after exposure.[117] Greater pulmonary damage typically occurs following exposure to zinc chloride than at similar concentrations of zinc oxide.

Skin lesions are unusual following exposure to elemental zinc and zinc compounds, in spite of the long history of the use of these compounds to treat skin lesions. In an experimental study, no skin irritation developed in volunteers following the application of 25% zinc oxide ointment to the skin for 48 hours.[127] Zinc chloride and zinc acetate are more irritating to the skin than zinc sulfate and zinc oxide.

Similar to acute overdose, the chronic ingestion of excessive amounts of zinc compounds produces a

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variety of gastrointestinal symptoms along with hematological effects including copper deficiency, varying degrees of anemia,[128] and neutropenia.[72,129] Current clinical data do not indicate that chronic ingestion of zinc compounds causes increased susceptibility to disease.

Occupational Exposure

Metal Fume Fever

Metal fume fever (brassfounder's ague, metal shakes, zinc fever, zinc chills, Spelter's shakes) is an acute influenza-like illness associated with the inhalation of metallic oxides in the workplace. Typically, metal fume fever is a benign, self-limited illness that resolves within 12–48 hours following cessation of exposure.[130,131] Exposure to high ambient air concentrations of freshly oxidized zinc oxide fumes (i.e., 77–600 mg/m^3) over several hours is the most common cause of metal fume fever;[12] aerosolized zinc oxide powder does not produce similar symptoms.[131] Other causes of this illness include exposure to fumes of aluminum, antimony, copper, iron, magnesium, manganese, and nickel in welding, galvanizing, or smelting operations. The onset of symptoms begins ~4–10 hours following exposure to zinc oxide fumes, typically in the evening after exposure to the fumes. Fatigue, chills, fever, headache, myalgias, cough, dyspnea, leukocytosis, thirst, metallic taste, and salivation characterize this usually mild illness. Resolution of symptoms occurs ~36–48 hours after the onset of illness. Although some patchy infiltrates may occur in more serious cases,[132] the chest X-ray is usually clear. Tolerance develops in workers following recurrent exposure; however, this tolerance may dissipate over the weekend ("Monday Morning Fever"). The reduction in pulmonary function and the radiographic abnormalities usually resolve following cessation of exposure. A cross-sectional study of 11 zinc-coated steel welders, 10 nonwelders with indirect exposure to welding fumes, and 17 controls did not detect a statistically significant difference in airflow on pulmonary function tests between the three groups.[74] The highest exposure to welding fumes was 5.1 and 8.0 mg/m^3 as measured by PAS-6 samplers. A volunteer study of galvanized mild steel welders detected clinically minimal changes in pulmonary function following exposure to zinc fumes; there was no statistically significant correlation between cumulative zinc exposure and pulmonary function.[75] The diagnosis of metal fume fever is primarily clinical with diagnostic testing usually normal in uncomplicated cases.

Hypersensitivity Reactions

Zinc may act as a sensitizer in the occupational setting. Some,[133] but not all,[134] older studies of workers associated zinc oxide exposure with the development of a pruritic, pustular rash; however, the role of personal hygiene and other factors cannot be excluded as causative factors of these rashes. A case report suggests that urticaria and angioedema may develop following exposure to zinc fumes at a zinc-smelting plant.[135] Rare case reports associate the galvanizing of metals in heated zinc with the development of hypersensitivity to zinc and occupational asthma. A galvanized metalworker with chest tightness, dyspnea, and wheezing had a positive immediate reaction to a skin test for zinc sulfate.[136] During workday monitoring, the forced expiratory volume in one second (FEV_1) fell to a maximum of 24% from the baseline at the end of the day; bronchial responsiveness increased the following day. Inhalation challenges with zinc sulfate produced immediate decrease of 23% from the baseline in the FEV_1. There was no documented elevated body temperature to suggest metal fume fever; symptoms requiring intermittent use of an inhaler persisted 3 months after leaving work. A smelter developed recurrent symptoms of bronchiolitis (fever, cough, dyspnea) 3 years after beginning exposure to zinc fumes; the symptoms resolved spontaneously after cessation of exposure. The lack of tolerance, the late emergence of symptoms, and a marked increase of CD8 T cell lymphocytes in bronchoalveolar lavage suggested hypersensitivity pneumonitis.[107]

Reproductive Abnormalities

Zinc is an essential element for normal fetal growth and development; however, there is no clear evidence that zinc supplementation improves pregnancy outcomes in healthy mothers eating well-balanced diets.[137] The weight of the evidence indicates zinc is not genotoxic or teratogenic; however, zinc deficiencies may cause preterm births and increased perinatal mortality.[138] Studies of mothers given zinc supplements (aspartate, citrate, sulfate) during their pregnancy have not demonstrated reproductive abnormalities.[139] Pregnant women receiving capsules containing 0.3 mg zinc/kg/day as zinc sulfate during the last two trimesters did not exhibit any changes in maternal body weight gain, postpartum hemorrhage, or infection.[140] There are few animal or human data to indicate that zinc causes developmental abnormalities at concentrations that do not produce maternal toxicity.[141] A report listed the occurrence of three stillbirths and one premature delivery in a group of women

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taking 0.6 mg Zn/kg/day as zinc sulfate supplements during the third trimester of pregnancy. The clinical significance of this case report is questionable because the report did not include a comparison to controls or the total number of women observed. A case-control study of women giving birth to children with neural tube defects demonstrated a statistically significant ($P = 0.03$) increase in the zinc concentration of the mothers of children with neural tube defects compared with controls.[142] However, conditional logistic-regression analysis showed the increase in the risk of neural tube defects in women with elevated serum zinc concentrations was not statistically significant. Animal studies suggest exposure to high concentrations of zinc in the range of 100–200 mg/kg/day produces reduced fetal weight, alopecia, anemia, and increased fetal resorption; however, the effects of zinc are difficult to separate from the development of zinc-induced deficiencies of copper and iron.[143] The parenteral administration of single doses of 12.5–25 mg $ZnCl_2$ during days 8–11 of gestation in CF-1 albino mice produced skeletal anomalies without accompanying soft tissue defects.[144]

Carcinogenesis

Neither the IARC nor the US National Toxicology Program lists zinc or zinc compounds as suspected carcinogens. Limited data exist on the incidence of cancer in workers exposed to zinc. No statistically significant relationship between zinc exposure and the occurrence of cancer was demonstrated in a cohort of 4,802 male workers exposed at least 1 year during 1946–1975 to electrolytic zinc and copper refining plants based on death certificates; there was no adjustment for smoking.[145] The overall SMR for the cohort of zinc refinery workers ($n = 978$) was 82. An excess of lung cancer mortality was associated with living near an old lead-zinc mining and smelting area, but the lack of control of confounding variables including carcinogens (smoking, radon, arsenic) limits any conclusions regarding the contribution of zinc to the prevalence of lung cancer.[146]

DIAGNOSTIC TESTING

SI Conversion Units

1 μg/L = 0.0153 μmol/L
1 μmol/L = 65.38 μg/L

Analytical Methods

Atomic absorption spectrometry using a furnace atomizer is the routine technique for determining zinc in biological materials based on sensitivity and cost; however, neutron activation analysis and inductively coupled plasma/atomic emission spectroscopy are more sensitive analytical techniques in blood (NIOSH Method 8005) and urine (NIOSH Method 8310), particularly for multielemental analysis in the sub-ppm range.[12]

Lower limits of detection for graphite furnace atomic absorption spectroscopy, anodic stripping voltammetry, and inductively coupled plasma mass spectrometry are ~6 ng/L in water samples and 10 μg/kg in solid samples.[10]

Sample preparation usually involves acid digestion with concentrated acids. Because zinc is a ubiquitous trace element, inaccuracies may result from the failure to institute proper procedures to prevent the contamination of biological samples with exogenous zinc (e.g., anticoagulants, evacuated tubes, preservatives, rubber stoppers, sampling and filtration equipment, inadequate reagent purity, atmospheric deposition).[147] Some anticoagulants (e.g., citrate, EDTA, oxalate) effectively chelate metallic ions; therefore, the presence of these anticoagulants in collection tubes artificially reduces the plasma zinc concentration.[10] Variability in the concentration of trace metals in rivers reflects the unique chemistry of the river as much as the input of trace metals from anthropogenic sources.

Biomarkers

Blood

Typical whole blood Zn concentrations are 4–7 mg/L compared with 0.6–1.2 mg/L in plasma or serum. Average whole blood concentrations of zinc exceed mean plasma zinc concentrations by a ratio of ~6–8 because of the relatively high zinc content in erythrocytes compared with serum or plasma.[148] In a study of 1,000 Swedish adults in their 70s, the mean whole-blood/serum Zn ratio was 8.56 as measured by inductively coupled plasma/sector field mass spectrometry.[149] The median ratio in this group was similar (8.70) to the mean. The mean whole-blood/plasma Zn ratio in an Italian study of healthy subjects without excessive zinc exposure was 6.87; the mean whole blood Zn concentration was 6.34 mg/L (range, 4.08–7.59 mg/L) compared with 0.92 (range, 0.59–1.21 mg/L) in plasma.[150]

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General Population

There are no simple measures of the total body Zn burden. Although plasma zinc concentrations are usually low in severe zinc deficiency, plasma zinc concentrations do not necessarily reflect total body zinc burden because the plasma contains relatively small amounts of the total body zinc burden.[151] In healthy adults, the plasma Zn concentration is <1.5 mg/L; lower zinc concentrations (e.g., 0.8 mg/L) occur in elderly patients confined to a hospital.[152] A study of 12,741 French adults revealed a statistically significant (but clinically small) difference in the serum zinc concentrations between women (mean, 0.84 mg/L, 95% CI: 0.60–1.09 mg/L) and men (mean, 0.88 mg/L, 95% CI: 0.63–1.12 mg/L; $P < 0.0001$).[153] In a study of 66 Greek children (mean = 7.53 ± 3.31 years) and their parents, the mean serum zinc concentrations were similar (i.e., ~1 ± 0.2 mg/L) between the two groups.[154] The mean zinc concentration in whole blood from a convenience sample of Spanish medical personnel was 6.95 ± 1.08 mg/L as measured by square wave voltammetry; there were no anthropogenic sources of zinc, and zinc concentrations increased with age.[155] A Spanish study suggests smoking does not significantly alter the serum zinc concentration as measured by inductively coupled plasma/mass spectrometry.[156]

Toxicity

The initial serum zinc concentration in a child after ingesting two mouthfuls of soldering flux containing 22% $ZnCl_2$ was 9.5 mg/L.[17] The patient developed lethargy and frequent episodes of vomiting along with a markedly inflamed gastric antrum. Five hours after the ingestion of 4 g zinc gluconate by a 17-year-old adolescent, the serum Zn concentration was 4.97 mg/L.[63] This patient developed severe nausea and vomiting, but the patient recovered within 7 hours without sequelae. Following the intentional ingestion of ~190 g $ZnCl_2$ by a 20-year-old woman, the plasma Zn concentration 1 hour later was 39.1 mg/L; she was agitated, complaining of retrosternal chest pain.[157] The presence of stridor required 11 days of intubation. Endoscopy revealed ulcerative and necrotic lesions in the gastric fundus. She recovered after a prolonged hospitalization.

Postmortem

In a Polish study of 50 postmortem samples from cases without excessive Zn exposure, the mean blood concentration of zinc (sample site not reported) was 6.81 ± 1.21 mg/L with a median of 7.00 mg/L as measured by flame atomic absorption spectrometry; the range was 4.02–8.68 mg/L.[158] The liver contained the highest mean postmortem zinc concentration with a mean of 39.6 ± 16.1 mg/L (range, 16.0–78.8 mg/L).

Urine

In a study of 683 healthy Italians without occupational zinc exposure, the mean urinary Zn concentration was ~0.45 mg/L (range, 0.27–0.85 mg/L).[150] In a Japanese study of >275 workers at an aluminum alloy fabricating plant without occupational exposure to zinc, the geometric mean zinc concentration in 24-hour urine samples was ~0.5 mg.[159] The urinary zinc concentrations remained consistent over the 13-year study period. There are limited data on the correlation between urinary zinc concentrations and zinc exposure. The amount of zinc in 24-hour urine collections from healthy subjects typically ranges from ~300–600 µg. Various factors (e.g., sickle cell disease, burns, diuretics) increase Zn excretion.[160] Depletion of zinc stores produces a reduction in urinary zinc excretion in *healthy* subjects.[161] Although zinc may interfere with results from urine drug of abuse screens, the urine zinc concentration required to alter these results is extremely high. The addition of zinc to urine samples in concentrations 5,000 times higher than controls produces false-negative results on enzyme multiplied immunoassay technique (EMIT)-based drug abuse testing; self-administration of 200 mg zinc gluconate orally did not alter the results of ELISA-based drug testing.[162]

Abnormalities

Metal Fume Fever

Following the development of zinc oxide-induced, metal fume fever, leukocytosis occurs; pulmonary function tests may demonstrate temporary reductions in lung volumes and carbon monoxide diffusing capacity. These changes along with the increase in bronchiolar leukocytes do not usually produce chronic pulmonary disease.[163] About 20 hours after exposure to zinc oxide fumes at concentrations of 77–153 mg Zn/m^3, bronchoalveolar lavage demonstrated elevated polymorphonuclear leukocytes and lymphocytes (i.e., T helper cells, T suppressor cells, activated killer T cells).[75] The leukocytosis lasts ~12 hours after the fever resolves.[164] Although mild elevations of serum zinc concentrations may occur within 24 hours following exposure to zinc oxide fumes,[165] the zinc concentration in the blood is usually normal during the course of acute metal fume fever.[166] Case reports associate an acute, temporary reduction in expiratory flow rates in workers exposed to zinc oxide fumes during the heating of zinc wires[167] and the soldering of galvanized metal.[168]

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Zinc Compounds

Oral

Sideroblastic anemia, myelodysplasia of the bone marrow, copper deficiency, and neutropenia are characteristic of chronic zinc intoxication.[169] Elevated serum glucose, alkaline phosphatase, and amylase concentrations along with depressed serum calcium concentrations may occur in cases of zinc intoxication.[62,65] Following low daily $ZnSO_4$ doses (i.e., 0.5 mg Zn/kg), no alterations of serum glucose, plasma insulin concentrations, or glucose tolerance occur in healthy volunteers.[170] Low plasma copper concentrations frequently occur following the chronic ingestion of excessive amounts of zinc compounds.[171] Routine blood chemistries and physical examinations revealed no hepatorenal disease among 12 workers exposed to zinc oxide fumes for 4–21 years during the production of brass alloys.[87]

Inhalation

Exposure to high concentrations of zinc chloride in confined spaces produces pulmonary edema, pneumonitis, diffuse alveolar damage, and pulmonary fibrosis. Initial abnormalities on high-resolution CT scan of the lungs involve patchy or diffuse ground-glass opacities with or without consolidation.[172] Clinical symptoms do not always correlate to pathological changes on chest radiographs, particularly in the first 48 hours after exposure. Most patients demonstrate a reduction of FEV_1, FVC, total lung capacity, and D_{LCO} with normal FEV_1/FVC ratios consistent with a restrictive impairment. These impairments typically improve, but pulmonary fibrosis may occur. In a case series of 13 soldiers exposed to zinc chloride during a combat exercise, lung diffusion capacity and total lung capacity 4 weeks after exposure declined from baseline values of ~16% and ~4%, respectively; these values returned to baseline 2–6 months postexposure.[173]

HEALTH SURVEILLANCE

Risk Assessment

The estimated safe amount of zinc is 0.15 mg/kg based on a safety factor of 3 in a study demonstrating depression of erythrocyte copper-zinc superoxide dismutase following the ingestion of ~60 mg Zn daily for several weeks.[174] The ATSDR derived a minimal risk level (MRL) of 0.3 mg Zn/kg/day for intermediate oral exposure based on the development of reduced erythrocyte superoxide dismutase activity (a sensitive measure of copper status) and decreased serum ferritin concentrations in women receiving a 10-week course of zinc gluconate (50 mg Zn/day).[175] Dietary studies of women indicate a lowest observable adverse effect concentration (LOAEL) of 1 mg Zn/kg/day with a threshold concentration of 50 mg Zn/day.[176] The US EPA also adopted 0.3 mg/kg/day as an oral reference dose (RfD).

Environmental Monitoring

The US OSHA PEL–TWA for zinc chloride fumes is 1 mg/m^3, whereas the STEL is 2 mg/m^3. These concentrations are designed to reduce the risk of damage to the eyes, respiratory tract, and skin. European countries permit similar zinc chloride exposures. The US OSHA limit for zinc oxide fumes is 5 mg/m^3 (fume or respirable fraction) as a PEL–TWA and 10 mg/m^3 as a STEL to reduce the incidence of metal fume fever. Table 35.3 lists various regulatory and recommended concentrations of zinc in air and water. The maximum contaminant level (MCL) for US drinking water is 5 mg Zn/L.

Biological Monitoring

There are no well-defined biological exposure limits for zinc.[177] Blood and urine zinc concentrations do not correlate well to zinc concentrations in ambient air;[178] limitations of this correlation include the natural diurnal variation in blood and urine zinc concentrations.[179] Zinc concentrations tend to peak during the morning, whereas the nadir occurs in the late evening.[180]

Blood

In a study of 20 Chinese zinc foundry workers, serum zinc concentrations did not correlate to airborne exposure of zinc ranging up to 36.3 mg/m^3 over <4 hours (mean air sample concentration = 3.16 mg/m^3).[79] The serum zinc concentrations for these workers averaged ~0.75 mg/L (11.5 μmol/L) during an 8-hour shift. In an Egyptian study of 61 workers in the galvanization process of an iron and steel manufacturing company, the mean serum zinc concentration was 0.88 ± 0.43 mg/L compared with 0.77 ± 0.14 mg/L in 50 administrative controls ($P < 0.001$) from the same factory.[181] The mean serum copper concentration was significantly lower in workers than in controls. Although the incidence of metal fume fever in the workers was ~25%, there was no significant difference in pulmonary function of chest X-ray abnormalities between the two groups.

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TABLE 35.3. Guidelines and regulations for zinc compounds.

Exposure Limit	Value
Air	
OSHA	
PEL–TWA (8-hour)	
Zinc oxide	
(fume)	5 mg Zn/m^3
(total dusts)	15 mg Zn/m^3
(respirable fraction)	5 mg Zn/m^3
Zinc chloride (fume)	1 mg Zn/m^3
Zinc stearate	
(total dust)	15 mg Zn/m^3
(respirable fraction)	5 mg Zn/m^3
ACGIH	
TLV–TWA (8-hour)	
Zinc oxide (fume, dusts)	2 mg Zn/m^3 [a]
Zinc chloride (fume)	1 mg/m^3
Zinc stearate	3 mg Zn/m^3 [a], 10 mg Zn/m^3 [b]
TLV–STEL (15-minute)	
Zinc oxide (fume, dusts)	10 mg Zn/m^3 [a]
Zinc chloride (fume)	2 mg Zn/m^3
NIOSH	
REL–TLV (10-hour)	
Zinc oxide (fume/dust)	5 mg Zn/m^3
Zinc chloride (fume)	1 mg Zn/m^3
Zinc stearate	
(total dust)	10 mg Zn/m^3
(respirable fraction)	5 mg Zn/m^3
REL–STEL (15-minute)	
Zinc oxide	
(dust)	15 mg Zn/m^3
(fume)	10 mg Zn/m^3
Zinc chloride (fume)	2 mg Zn/m^3
IDLH	
Zinc oxide (fume/dust)	500 mg Zn/m^3
Zinc chloride (fume)	50 mg Zn/m^3
Water	
US EPA	
Secondary MCL – public water	5 mg Zn/L
Ambient water quality criterion	5 mg Zn/L
NAS	
Drinking water standard	5 mg Zn/L

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; IDLH = immediately dangerous to life and health; MCL = maximum contaminate level; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average; US EPA = US Environmental Protection Agency; US FDA = US Food and Drug Administration.

[a] Respirable particulate matter; [b] Inhalable particulate matter.

URINE

Occupational studies suggest urine is the best medium to monitor exposure to zinc. Urine zinc concentrations probably more closely reflect zinc exposure than plasma or whole blood because homeostatic mechanisms increase urine zinc concentrations following excessive zinc exposure; however, neither sample closely correlates to zinc exposure. In a study of 20 Chinese zinc foundry workers, urinary zinc concentrations correlated with airborne zinc exposure ranging up to 36.3 mg/m^3 over <4 hours (mean air sample concentration = 3.16 mg/m^3).[79] Concentrations of zinc in serum and urine for these workers averaged 11.515 µmol/L (0.75 mg/L) and 3.6705 µmol/L (0.24 mg/L), respectively, during the period of an 8-hour shift. Examination of these workers did not detect evidence of metal fume fever or pulmonary abnormalities. In patients with symptoms of acute zinc chloride poisoning, the urinary zinc concentration may exceed normal concentrations by three times.[182]

TREATMENT

Decontamination

Zinc chloride and zinc acetate are mild-to-moderate corrosive agents; contamination of the eyes or skin with these substances requires immediate irrigation with copious amounts of saline, particularly if the concentration of these substances exceeds 10–25%. The usual measures for gastrointestinal decontamination (ipecac or lavage, charcoal, cathartics) are usually unnecessary, especially if vomiting has occurred or the patient ingested the substance >1 hour before arrival at the medical facility. Case reports suggest that whole-bowel irrigation is an effective adjunct to other decontamination measures for radiopaque tablets (e.g., zinc sulfate) that pass beyond the pylorus.[183] However, there are no clinical studies that confirm the efficacy of whole bowel irrigation.

Chelation

Case reports suggest calcium disodium ethylenediaminetetraacetate ($CaNa_2EDTA$) is potentially an effective zinc chelator based on the successful clinical use of this compound to normalize zinc concentrations.[64,65] Clinical data confirming the efficacy of chelation in humans are very limited. Chelation with $CaNa_2ETDA$ and BAL that began 74 hours after the ingestion of zinc chloride by a 16-month-old toddler was

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associated with clinical improvement within 24 hours; however, no significant excretion of zinc appeared in the urine.[119]

Animal experiments suggest some polyaminecarboxylic acids (diethylenetriaminepentaacetic acid (DTPA), cyclohexanediaminetetraacetic acid (CDTA)) are more effective chelators of zinc than $CaNa_2$ EDTA;[184,185] however, clinical data to confirm the efficacy of DTPA and of CDTA are lacking. Other potential zinc chelators based on experimental data include *N*-acetylcysteine; in rats, this compound increases urinary zinc excretion.[186] D-penicillamine increased mortality in animal models and probably is not an effective chelator of zinc.[65]

Supplemental Care

Treatment for the ingestion of zinc compounds is primarily supportive with careful attention to fluid and electrolyte balance. Symptomatic patients should be evaluated endoscopically for esophageal and gastric burns if the patient ingested a corrosive zinc salt (chloride, acetate) that exceeded a concentration of 20–25% Zn. H_2 receptor antagonists and/or sucralfate may be helpful for superficial burns of the upper gastrointestinal tract. Treatment of copper deficiency with oral or intravenous copper may be necessary following chronic zinc intoxication. Patients with chronic zinc intoxication should be evaluated for copper deficiency, particularly if anemia and leukopenia are present.

After acute inhalation of corrosive zinc compounds (e.g., zinc chloride-containing smoke bombs), careful attention should be directed to the adequacy of oxygenation as measured by pulse oximeter or arterial/venous blood gases. Support includes artificial ventilation, high-dose steroids, antibiotics, and positive end-expiratory pressure; however, few data exist to guide management with these modalities. Complications include pneumothorax, pneumomediastinum, and acute respiratory distress syndrome (ARDS). Case reports suggest high-dose steroids and venovenous extracorporeal life support may improve survival from ARDS.[187] The treatment of metal fume fever in otherwise healthy workers is supportive (rest, hydration, antipyretics, nonsteroidal anti-inflammatory drugs); patients with cardiopulmonary disease may require stabilization in the hospital. Peppermint oil and milk are ineffective home remedies for metal fume fever.

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Chapter 36

ZIRCONIUM

HISTORY

Zirconium was known in Biblical times as the golden gemstone, zircon. The name zirconium is derived from the Arabic word *zargun* for this gem. In the Middle Ages, colorless zircon was considered an inferior diamond. The German chemist, Martin Klaproth, discovered zirconium in 1789 after analyzing the gem. Isolation of zirconium did not occur until the work of the Swedish chemist Jöns Jacob Berzelius in 1824. Commercial production of pure zirconium did not develop until the 20th century as a constituent of ceramic pigments, glass, chemicals, foundry equipment, and metal alloys. In the late 1940s, the corrosion resistance and poor neutron absorption of zirconium lead to the prominent use of this metal inside nuclear reactors and nuclear submarines. In the 1950s and 1960s, several case series associated the use of organic zirconium-containing deodorants (e.g., sodium zirconium lactate, zirconium oxide) with the development of axillary granulomas.[1] The US Food and Drug Administration subsequently banned the use of aerosolized zirconium preparations;[2] however, some deodorants continued to contain lower zirconium concentrations (i.e., <20% Zr anhydrous weight) in combination with aluminum.

PHYSIOCHEMICAL PROPERTIES

Elemental zirconium (Zr, CAS RN: 7440-67-7, atomic mass: 91.22 g/mol) is a bluish-black, amorphous powder or a hard, shiny, grayish-white, heavy metal that is a member of Group 4 (Group IVb) of the periodic table with titanium and hafnium. Because elemental zirconium is highly reactive, zirconium commonly occurs in nature as zirconium dioxide (ZrO_2), zirconium silicate (zircon, $ZrO_2.SiO_2$), or complex zirconates (ZrO_3^{2-}). Zirconium is a passive metal that develops a protective oxide film following exposure to air or water, similar to titanium, chromium, niobium, and tantalum. The most common valence is the tetravalent oxidation state. This metal forms alloys with most metals except mercury including alkali and alkaline earth groups. Zirconium does not form covalent bonds with carbon; therefore, zirconium does not interact well in biological systems or easily form organic compounds. Zirconium exists naturally in five stable isotopes with ^{90}Zr being the most common (51%).[3] There are 28 artificial isotopes (78–110) with ^{93}Zr being a by-product of a fission reaction and the longest lived ($t_{1/2}$ = 1.53×10^6 years). ^{95}Zr is one of the most prevalent fragment products in uranium fission with a half-life of 64 days.

Zirconium possesses high density (SG = 6.5107 at 25 °C), heat resistance (MP = 1,852 ± 2°C), and corrosion resistance along with poor water- and acid-solubility. When mixed in air with oxidizing agents, zirconium powder is flammable. Water-insoluble zirconium compounds include zirconium oxide, zirconium acetate, zirconium hydroxide, and zirconium silicate, whereas zirconyl chloride ($ZrOCl_2$) and zirconium lactate are water-soluble. Zirconium carbide and zirconium oxychloride are slightly water-soluble. Following exposure to water, zirconium tetrachloride decomposes into zirconyl chloride and hydrochloric acid. The physical ability to capture neutrons is a desirable property for the use of zirconium in the nuclear industry.

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EXPOSURE

Uses

Elemental zirconium is a component of furnace bricks, high-temperature textiles, optical lens-grinding powders, and metal alloys for nuclear, aerospace, and medical (e.g., orthopedic, dental implants) applications.[4,5] The nuclear industry accounts for most of zirconium production. Additional commercial applications of metallic zirconium include a scavenger in the steel industry, a "gas getter" in vacuum tubes, ceramic colorant, and a constituent of photoflash bulbs. Experimental applications for zirconium phosphate nanoparticles include drug delivery to cancer cells.[6] Zirconium tetrachloride salt is a tanning agent and a textile water repellent, whereas cubic zirconia is a sparkling artificial gem composed of zirconium oxide. Water-soluble zirconium salts were components of cosmetics, deodorants, and topical ointments, but the formation of granulomas following absorption through damaged skin limited their use.[7] In 1977, the US FDA declared zirconium an unsafe constituent of drugs and cosmetics;[2] aluminum zirconium compounds were considered safer antiperspirant components and remained on the market.[8]

Sources

Zirconium compounds are common constituents of minerals throughout the universe including S-type stars, the sun, moon, and the earth's crust (i.e., ~10–300 ppm).[9] Zirconium is substantially more abundant in the soil than copper and zinc. In surface waters, Zr concentrations typically occur in the very low ppb range (e.g., 0.1–20 ppb). Zircon ($ZrO_2 \cdot SiO_2$) and baddeleyite (ZrO_2) are the most abundant commercial zirconium ores. Most commercial production of zirconium occurs as a by-product of titanium ores (rutile, ilmenite). Potential occupational exposures to zirconium include the preparation of zirconium-containing alloys, zirconium casting and refining operations, and the use of zirconium-containing substances (e.g., grinding powder, enamels, porcelain, abrasives). A Japanese study of ambient dose rate and activity concentration of natural radionuclides in raw materials, products, and aerosols including radon in an unshaped refractory, a shaped refractory, and an electrocast refractory plant processing zirconium ores did not detect radiation doses exceeding current workplace standards.[10] The annual maximum effective dose for workers was 0.43 mSv. The typical daily dose of zirconium in the diet is about 4 mg.

ENVIRONMENTAL FATE

Most zirconium compounds are water-insoluble; thus, these compounds do not easily enter living organisms. The low water solubility and the strong affinity of Zr for soil constituents limit soil mobility; however, speciation and physicochemical properties (organic content, pH, texture) of the soil affect Zr mobility.[11] At the pH present in the environment, insoluble hydrous zirconia forms from water-soluble zirconium compounds released by industry. These compounds are deposited in sediment as inert compounds. Zirconium oxide and hydroxide are poorly water-soluble and precipitate at low pH. In general, the translocation of zirconium from soil to plants is low with most Zr accumulating in roots.[11]

TOXICOKINETICS

Most zirconium compounds are water-insoluble with limited absorption. The low oral toxicity of zirconium probably results from poor absorption of zirconium by the gastrointestinal tract.[12] In a ^{95}Zr tracer study of 13 healthy adults followed for 100 days, the total fraction absorption of Zr in citrate-buffered and zirconium oxalate solutions was 0.1% and 0.7%, respectively.[13]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Zirconium is not an essential component of any known biological process. The use of organic zirconium salts (e.g., $NaZrC_3H_5O_3$, sodium zirconium lactate) as a deodorant was associated with the development of dusky, red–brown, discrete papular granulomatous reactions in the axilla.[14,15] These lesions occurred primarily in the central portion of the axillas. In rabbit studies, intradermal and subcutaneous injections of sodium zirconium lactate produced acute inflammatory reactions and granulomas characterized by histiocytes and some giant cells along with macrophages containing a foamy, granular substance.[16] A daily 20-minute exposure of 44% sodium zirconium lactate mist to six albino rabbits for 6 weeks was associated with the development of bronchiolar abscesses, lobar pneumonia, and peribronchial granulomas.[17]

CLINICAL RESPONSE

Environmental Exposure

Subcutaneous granulomas develop from repeated use of deodorant sticks and lotions for poison ivy that contain

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zirconium lactate and zirconium dioxide,[1,18] probably as a result of hypersensitivity reactions.[19] Although these reactions typically involved sodium zirconium lactate or zirconium oxide, a case report associated the development of an acute hypersensitivity reaction with exposure to aluminum zirconium complex.[20] This 27-year-old woman developed axillary granulomas following the use of aluminum zirconium complex characterized by a caseating necrotic lesion with multinucleated giant cells, lymphocytes, and plasma cells, as well as acute inflammation with abscess formation in the mid dermis and subcutaneous tissues.

Podoconiosis is a noninfectious (nonfilariasis) disease of barefoot workers living in tropical regions of the North African Rift Valley, Central America, and Northwest India with volcanic soils; persistent contact with irritant volcanic soils causes an inflammatory reaction, fibrosis, and obstruction of lymphatic flow.[21] The disease manifests as chronic, bilateral, asymmetric lower limb swelling (i.e., elephantiasis) with pruritus, burning, oozing, mossy papillomata, and rigid toes. Epidemiology studies suggest the volcanic soils in areas with podoconiosis contain higher zirconium and beryllium concentrations than control areas without this disease.[22] The abnormal inflammatory reaction appears to be genetically determined. The etiology of the disease remains unclear; however, the presence of zirconium is a suspected contributing factor to predispose patients to the dermal dehydration and cracking of lower extremity skin necessary to facilitate entry of mineral particles and microorganisms into the lymph.[23] The role of beryllium sensitization and lymphoid granuloma formation also remains unclear.

Occupational Exposure

Minimal toxicity has been associated with the use of zirconium in industry. Rare case reports associate zirconium exposure with pulmonary disease; however, most epidemiological studies do not detect excessive pulmonary disease in zirconium workers. A case report associated the development of a slowly progressive pulmonary fibrosis in a worker who spent 39 years grinding and polishing lenses containing zirconium oxide, aluminum oxide, and silica; confounding exposure to fibrosing silica limits conclusions regarding the causal role of zirconium exposure.[24] Lung biopsy did not detect pulmonary granulomas, and lymphocyte proliferation studies did not document evidence of lymphocyte activation. A 25-year-old with a history of atopic dermatitis worked as sorter and tile glazer for 3½ years; her exposure included clay, quartz, wollastonite, and zirconium silicate with no regular use of protective respiratory devices. She subsequently developed dry cough and dyspnea.[25] Lung biopsy demonstrated granulomatous interstitial pneumonia with mild fibrosis consistent with hypersensitivity pneumonitis. Analysis of pulmonary particles revealed primarily clay minerals and silicates including zirconium silicate. Limited epidemiological studies of zirconium workers have not detected an increased incidence of pulmonary diseases. A study of 22 workers exposed for 1–5 years to fumes from a zirconium-reduction process did not demonstrate any clear relationship between zirconium and pulmonary diseases including pneumoconioses.[26] No significant increase in radiographic abnormalities appeared in a study of 136 workers exposed for an average of ~4 years to dust containing ~10% zircon (zirconium silicate).[27] A study of 32 workers exposed to respirable zirconium dust in the range of 0.67–3.2 mg/m^3 for a mean of ~5 years did not demonstrate pulmonary abnormalities based on questionnaires, pulmonary function tests, and chest x-rays.[28]

Zirconium oxychloride is a potential upper respiratory irritant as a result of the hydrolysis of this water-soluble compound to hydrochloric acid. Animal studies suggest exposure to high zirconium tetrachloride concentrations may produce significant respiratory irritation;[29] however, no human data are available to confirm adverse pulmonary effects in workers inhaling this substance.

Carcinogenesis

Neither the IARC nor the US Toxicology Program recognizes zirconium or zirconium compounds as suspected carcinogens. Little data exist on the carcinogenicity of zirconium in animals; the kinetics of zirconium in the body does not favor the role of zirconium as a carcinogen.

DIAGNOSTIC TESTING

SI Conversion Units

1 μmol/L = 91.22 μg/L
1 μg/L = 0.01096 μmol/L

Analytical Methods

Analytical techniques for quantifying zirconium include atomic absorption spectrometry (LOD, 44 μg/L),[30] inductively coupled plasma/mass spectrometry (LLOQ, 0.7 μg/L),[31] quadrupole/inductively coupled plasma/mass

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spectrometry (LLOQ, 0.008 μg/L),[32] and inductively coupled plasma/atomic emission spectrometry (LLOQ, 50 μg/L).[33,34] The latter technique lacks the sensitivity of ICP/MS. Using ultrasonic nebulization and a desolvating membrane, the LLOQ for zirconium in serum was ~0.015 μg/mL as measured by ICP/MS.[35] A 13-year follow-up study of 178 workers exposed to zirconium compounds typically of <10 mg/m^3 did not detect any significant abnormalities on chest radiographs or pulmonary function tests.[36] Zirconium oxide is radiopaque.

HEALTH SURVEILLANCE

The US OSHA PEL–TWA for zirconium compounds is 5 mg Zr/m^3 with a STEL of 10 mg Zr/m^3. The American Conference of Governmental and Industrial Hygienists recommends similar values to prevent pulmonary irritation.[29] NIOSH recommends an IDLH value of 500 mg Zr/m^3.

TREATMENT

Treatment is supportive. Because of the low toxicity of these compounds, recommendations for decontamination and treatment should be based on the presence of toxins other than zirconium.

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Medical Toxicology of Occupational and Environmental Exposures

Volume 2

Radiation: Risk Assessment, Diagnostic Tests, and Therapeutics

DONALD G. BARCELOUX

Edited by Robert B. Palmer

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Volume 2

Radiation: Risk Assessment, Diagnostic Tests, and Therapeutics

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To my grandchildren, Sophia, Henry, Hayden, and Brody
You bring so much joy to our family. I wish you a bright future and the treasured gifts of a loving family, loyal friends, meaningful work, and faith to guide your journey.

Grandpa

To my daughter Abigail, and my wife Karen
Thank you for the things too numerous to list.

Dad/Rob

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FOREWORD

The multivolume *Medical Toxicology of Occupational and Environmental Exposures* covering metals, radiation, and cancer is the eagerly awaited third instalment in the seminal series of medical toxicology textbooks written by Dr. Donald Barceloux. The first two books focused on natural substances and drugs of abuse, respectively, and have quickly established themselves as reference works in their respective fields. The comprehensive coverage of topics coupled with a consistent and easy-to-follow organization of content have made them indispensable companions of physicians and researchers alike.

The newest volumes in the series, created by Dr. Barceloux and edited by Dr. Robert Palmer, is a worthy successor to the first two books. Once again, the focus is on naturally occurring and man-made toxic threats that all medical toxicologists will have heard of but few will have had first-hand experience with. This is precisely what makes this work so valuable. The first volume literally comprises an A–Z of all there is to know about the clinical toxicology of metals and metalloids, from aluminum to zirconium. Chapters on well-known toxic metals such as arsenic, lead, and mercury are almost textbooks in their own right covering their subjects in a breadth and depth rarely seen in other publications. But who would know where to look for information on the toxicokinetics of rare earths, or whether tellurium is a human teratogen?

There is an ongoing debate on whether radiation is a subject that toxicologists should concern themselves with, or whether it would best be left to physicists, radiologists, and oncologists. The second volume takes a pragmatic view: if it induces a toxic response, then it is of relevance to anyone involved in the prevention, diagnosis, and treatment of human exposures. Consequently, the chapters in the section on radiation provide a comprehensive summary on what is known about potential health effects of all forms of radiation, and what may be done to prevent them.

The final volume on cancer departs from the familiar substance-based approach of the rest of the book in that it starts from the point of view of the risk assessor, looking at the mechanism of chemical carcinogenesis and then providing an organ-centered overview. This is a useful approach since carcinogenicity is as much governed by the cascade of molecular events elicited by carcinogens as it is by human physiology, biokinetics, and organ response.

In contrast to standard textbooks on clinical toxicology, *Medical Toxicology of Occupational and Environmental Exposures* is not only aimed at those working in the treatment of the poisoned patient. As the most comprehensive source of information in its field, it will equally be an invaluable reference for occupational physicians and hygienists, those working in environmental health and indeed anyone concerned with the human health risk assessment of exposure to metals, radiation, and chemical carcinogens. It is a truly interdisciplinary work that will stand the test of time.

Professor Martin F. Wilks, MD, PhD, ERT, FRCP (Edin), FBTS, FEAPCCT

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PREFACE

This volume, *Radiation*, along with *Cancer* and *Metals and Metalloids* in the three-volume *Medical Toxicology of Occupational and Environmental Exposures* is a continuation of the *Medical Toxicology Series* that began with *Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals* and *Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants*. The *Medical Toxicology Series* provides in-depth, evidence-based coverage of the most important human toxins. Similar to the rest of the *Medical Toxicology Series*, the goal of this volume is the creation of a comprehensive and convenient reference that answers questions regarding medical toxicology issues. This volume presents the basic and clinical science associated with the various types of ionizing and nonionizing radiation.

The reader will recognize the similarities between the template in this volume and the templates in the other two books of the *Medical Toxicology Series*. This organizational consistency allows easy location of the appropriate information necessary for decisions regarding the sources, effects, regulation, and management of toxic exposures throughout the *Medical Toxicology Series*. General sections headings in this volume include, but are not limited to, physical properties, current and past exposure, dose effect, toxicokinetics, histology/pathophysiology, clinical response, dosimetry, health surveillance, and treatment.

Medical toxicology is a field often dependent on relatively weak scientific evidence (case reports, case series, retrospective analyses), resulting in the increased risk of perpetuating equivocal statements and even folklore. This volume provides the relevant evidence base to determine the clinical consequences and safety measures important for protection from radiation exposure in the workplace and environment. References are documented to validate the information and provide sources for further inquiry. Although this unique volume provides a medical toxicologist's perspective on radiation exposures, the coverage contains input from a variety of disciplines including other clinical specialties, public health physicians, and basic scientists.

The choice of topics in this volume reflects our desire to expand communication between medical toxicologists and related fields. Our hope remains that this interdisciplinary, evidence-based approach will increase communication between traditional clinical settings and fields aligned with medical toxicology including those in laboratories, academic settings, and regulatory agencies. We anticipate this approach will encourage more inquiry into the pathophysiology, clinical effects, biomarkers, treatment, and prevention of illnesses related to radiation exposures.

Robert B. Palmer, PhD, Editor
Donald G. Barceloux, MD, Author

November 18, 2025

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I thank the following colleagues for their contributions to the quality, depth, and accuracy of *Medical Toxicology of Occupation and Environmental Exposures: Radiation*.

John Wiley & Sons' Staff

Dr. Andreas Sendtko, Senior Managing Editor, Physical Sciences Books, whose dedication and patient guidance guaranteed the accuracy of the printing process and the quality of these books.

Bob Esposito, former Senior Editor, made our *Medical Toxicology Series* a reality by believing in the importance of a highly detailed, structured series covering the expanding field of Medical Toxicology.

Michael Leventhal, Commissioning Editor, helped smooth the production process from submission to printing.

Summers Scholl, Executive Editor, whose contributions were essential to informing our medical audience of the key constituents of the *Medical Toxicology Series*.

Pomona Valley Hospital Medical Center

I admire the dedication and perseverance of the physicians, nurses, and the Emergency Department staff in times complicated by COVID-19 and variants, difficult medical problems, and complex social issues. In particular, I appreciate the support of the physician staff including Howard Friedman; Ivan Schatz; Richard Dorosh; Ken Nakamoto, past Vice President of Medical Affairs; Ken Moore, former Medical Director Emergency Department; and James Kim, Medical Director, Emergency Department.

UCLA Emergency Department Colleagues

I appreciate all our colleagues who shared their expertise and clinical experience at UCLA Conferences, especially Gregory W. Hendey, MD, Department Chair; Steven Lai, MD, Assistant Program Director, Olive View-UCLA; Richelle J. Cooper, MD, UCLA Emergency Department Research Director; Lynne B. McCullough, MD, UCLA ED Medical Director; Pamela Dyne, MD, Associate Program Director, Olive View-UCLA; Cynthia Koh, MD; Eric A. Savitsky, MD; Luis Lovato, MD, Informatics; David A. Talan, MD, former Chairman, Department of Emergency Medicine, Olive View-UCLA Medical Center, and Matthew Waxman, MD.

UCLA Librarians

Writing this book series was not possible without the support of the UCLA Biomedical Library, especially Juan Jaime, Access Services Manager, UCLA Science Libraries.

DONALD G. BARCELOUX, MD

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REVIEW PANEL

The critical reviews and clinical insights of the distinguished Review Panel were much appreciated as an invaluable method to validate the scientific basis of *Medical Toxicology of Occupational and Environmental Exposures: Radiation*.

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VOLUME 2

RADIATION: RISK ASSESSMENT, DIAGNOSTIC TESTS, and THERAPEUTICS

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A

RADIATION PHYSICS

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Chapter 37

RADIATION PHYSICS

HISTORY

Even though high-energy radiation has always permeated the universe, the discovery of electromagnetic waves did not occur until 1900.[1] Roentgen produced X-rays artificially from the bombardment of metal in evacuated tubes with electrons in 1895.[2] He named the radiation that penetrated screens of various thicknesses X-rays to denote the unknown nature of the radiation. The following year, Henri Becquerel detected radioactivity in the natural environment while investigating the role of phosphorescence of a glass tube.[3] Physicists and physicians began using X-rays to examine the bones, lungs, and other organs of patients. In 1903, Einstein determined the origin of energy transferred by radiation and the equivalency of matter and energy. Victor Hess discovered cosmic radiation in 1912 during a high-altitude balloon flight.[4] Currently, the average annual ionizing radiation dose in the United States from natural and artificial sources is similar (i.e., ~3 mSv).[5] Figure 37.1 displays the natural and artificial sources of radiation exposure in the United States.

PHYSICAL PROPERTIES

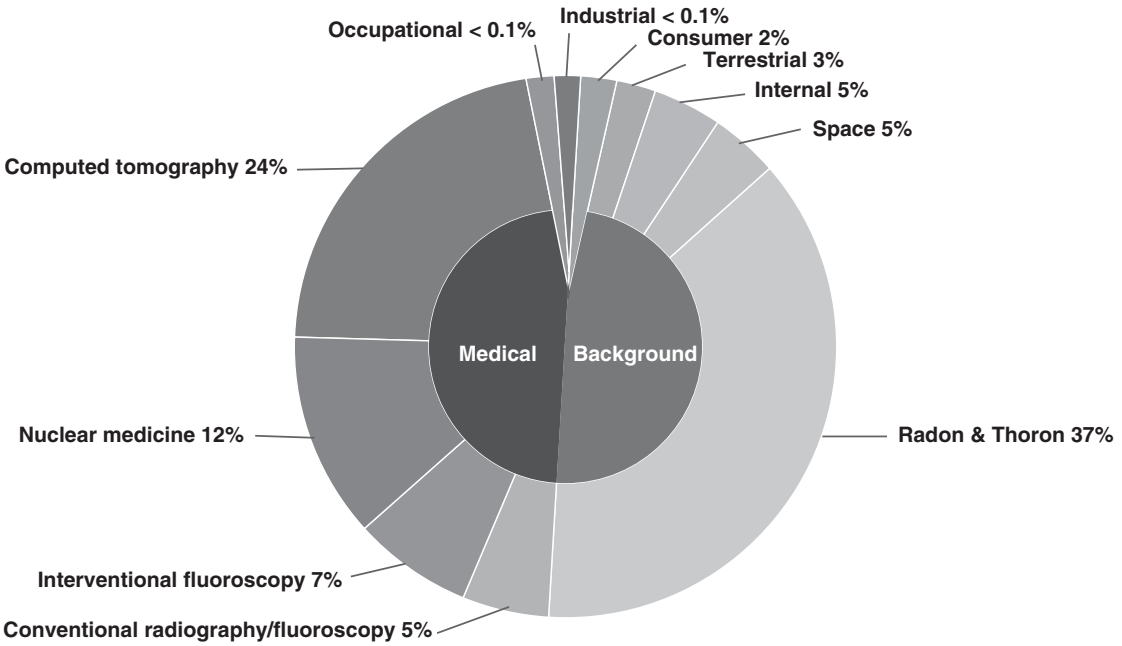
Radiation involves the transfer of energy from a source through a vacuum or a medium. Our senses detect some forms of radiation (e.g., visible light, sound, heat), whereas the wavelengths of some electromagnetic radiation are below (e.g., radio wave, microwave, radar) or above (e.g., X-rays, γ-rays, some UV light) those detectable by our inborn senses. Hence, our senses do not detect the hazardous forms of radiation in the ionizing portion of the electromagnetic spectrum. The two types of ionizing energy are: 1) electromagnetic radiation carried by discrete bundles of energy (photons) traveling as an electromagnetic wave, generated by the movement of electrical charges through an oscillating electromagnetic field or by nuclear decay; and 2) subatomic particles released from high-speed interactions of subatomic particles or from decay of atoms. Gamma-rays and X-rays from cosmic or human sources characterize the first form of radiation, whereas α-and β-particles characterize the latter form. Gamma-rays originate from radioactive decay of nuclei or galactic sources, whereas X-rays are released from electron orbitals. The biological effects of radiation depend on several factors beside the type of radiation, including the amount of energy transferred to living tissue, the geometry of the applied radiation, and the sensitivity of tissues to radiation damage.

Electromagnetic Waves

Photons comprised of electromagnetic waves possess no mass or electrical charge. Electromagnetic waves travel through the vacuum of space at the speed of light (3×10^8 m/second), whereas most other waves (e.g., sound) require a medium (gas, liquid, solid) to propagate. Wavelength (λ) is the distance of one full cycle of the oscillation of the electromagnetic wave as measured between adjacent troughs or peaks, whereas frequency is the number of cycles per second. Energy in electromagnetic radiation varies directly with frequency

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Average Annual Radiation Dose

Sources	Radon & Thoron	Computed Tomography	Nuclear Medicine	Interventional Fluoroscopy	Space	Conventional Radiography/ Fluoroscopy	Internal	Terrestrial	Consumer	Occupational	Industrial
Units											
mrem (United States)	228 mrem	147 mrem	77 mrem	43 mrem	33 mrem	33 mrem	29 mrem	21 mrem	13 mrem	0.5 mrem	0.3 mrem
mSv (International)	2.28 mSv	1.47 mSv	0.77 mSv	0.43 mSv	0.33 mSv	0.33 mSv	0.29 mSv	0.21 mSv	0.13 mSv	0.005 mSv	0.003 mSv

FIGURE 37.1. Sources of radiation exposure in the United States. (National Council on Radiation Protection and Measurements).[5]

and inversely with wavelength; the higher the frequency, the greater the energy and the smaller the wavelength. Longer wavelength waves (e.g., radio waves) carry less energy than shorter ones. Shorter wavelength means higher frequency (e.g., γ-rays, X-rays), which transmits higher energy and greater penetration of tissue.

In SI units, the unit of energy is the joule (J); the energy (E) in a photon in joules is related to the frequency as defined by Equation 37.1.

$$E\ (\mathrm{J}) = hf \qquad \text{(Equation 37.1)}$$

where

h = Planck's constant (6.62607015 x 10^{-34} J/Hz or J-seconds),
f = frequency (Hz).

Wavelength (λ) and frequency (f) are inversely related as defined by Equation 37.2.

$$f = c/\lambda \qquad \text{(Equation 37.2)}$$

where

λ = wavelength,
f = frequency,
c = speed of light in a vacuum (299,792,458 m/second).

Both joules and electron volts are units of energy. The small amount of energy in photons necessitates the use of electron volts (eV). An electron volt is the energy acquired by an electron accelerating through a potential difference of 1 V; this value is equivalent to 1.602×10^{-19} J. Energy in electron volts (or joules) is directly related to frequency and inversely related to wavelength as determined by substituting Equation 37.2 into Equation 37.1 and rearranging it into Equation 37.3.

$$E\ (\mathrm{eV}) = hc/\lambda = 12{,}400/\lambda = 1.24\times10^{-6}/\lambda \qquad \text{(Equation 37.3)}$$

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where

E = energy (electron volts, eV),
h = Planck's constant (4.136×10^{-15} eV × second),
c = speed of light (2.99792458×10^{8} m/second),
λ = wavelength (angstroms, 10^{-10} m).

Electromagnetic radiation interacts with biological tissues in the following three ways: 1) *transmission*, where the radiation passes through the tissue without interacting; 2) *reflection*, where the radiation deflects off the air/tissue interface back into space; and 3) *absorption*, where the radiation passes the outer layer and deposits the energy in the tissues. The frequency and wavelength determine the amount of energy released in the tissues. Injury to tissues results from the absorption and transfer of large amounts of energy to atoms and molecules in the path of the radiation.

Particulate Radiation

The second form of ionizing radiation is associated with high-velocity particles that are either electrically charged (e.g., α- or β-particles) or electrically neutral (e.g., neutrons). Linear accelerators, betatrons, and cyclotrons produce beams of particulate radiation by accelerating electrically charged particles, whereas fission in a nuclear reactor or the interaction of a charged particle and a target (e.g., accelerating deuterons into tritium) produce neutrons. The rate of ionization depends on charge, mass, and velocity. The higher the charge and the lower the velocity, the greater the potential for ionization. Emitted particles have very high energies; their energy is related to the mass of the particles by the Einstein Theory of Relativity, as displayed in Equation 37.4.

$$E \text{ (energy)} = mc^2 \qquad \text{(Equation 37.4)}$$

where

m = mass,
c = speed of light.

Whenever the nucleus emits an α- or a β-particle with a high-energy photon, the mass of the nucleus decreases by the amount (i.e., E/c^2) defined by Equation 37.4. Because of the equivalence of mass and energy, the mass of particles is usually expressed as energy (e.g., million electron volts, MeV) rather than units of mass.

Figure 37.2 displays the photon family of electromagnetic waves; photons are quanta of light or other electromagnetic radiation that have energy proportional to their frequency, but no mass. The non-photon family of elementary particles has charge *and* mass as displayed in Table 37.1. Each elementary particle exists in the following two states: matter and antimatter. The positron is the antimatter state of the electron. Although these two states are stable when separated, the collision of the two states annihilates both particles and transforms the matter into neutrinos and photons. In addition to photons, stable particles include electrons, protons, muon neutrinos, and electron neutrinos. Other members of the hadron family (mesons, hyperons) are extremely short-lived particles studied through the operation of high-energy accelerators. Electrons are the only important member of the lepton family of particles from a medical perspective. Although neutrinos are common, they do not contribute significantly to the medical effects of radiation.[1] The emission of neutrons usually occurs during the operation of nuclear reactors. Table 37.2 lists the physical characteristics of electromagnetic waves and particulate radiation.

Atomic Structure

All matter consists of elements (e.g., hydrogen, oxygen, lithium) composed of characteristic atoms. These atoms contain an extremely tiny nucleus (positively charged protons and electrically neutral neutrons of equal mass) and a relatively large surrounding area containing negatively charged, relatively low-mass (i.e., 1/2000 the mass of a proton) electrons. Consequently, atoms are mostly empty space. The nucleus contains most of the mass in an atom with each element described by the total number of protons and neutrons (*mass number*). Hence, the element and the mass number (e.g., uranium-238) characterize most atoms. The various species of atoms are called nuclides. Table 37.3 lists the terms used to define the structure of an atom.

There are 92 natural elements, ranging from hydrogen to uranium. For each element, the atomic number characterizes a specific number of protons along with a variable number of neutrons; the lightest element is hydrogen (one proton, hydrogen-1). An *isotope* is a nuclide of an element that possesses the same number of protons but different numbers of neutrons. Isotopes are different species of the same element. Hydrogen has the following three isotopes: hydrogen-1 (elemental hydrogen – 1 proton); hydrogen-2 (deuterium – 1 proton, 1 neutron); hydrogen-3 (tritium – 1 proton, 2 neutrons). Many isotopes are stable isotope species (i.e., atoms of a chemical element with the same atomic number but a different atomic mass or mass number) that do not undergo radioactive decay.

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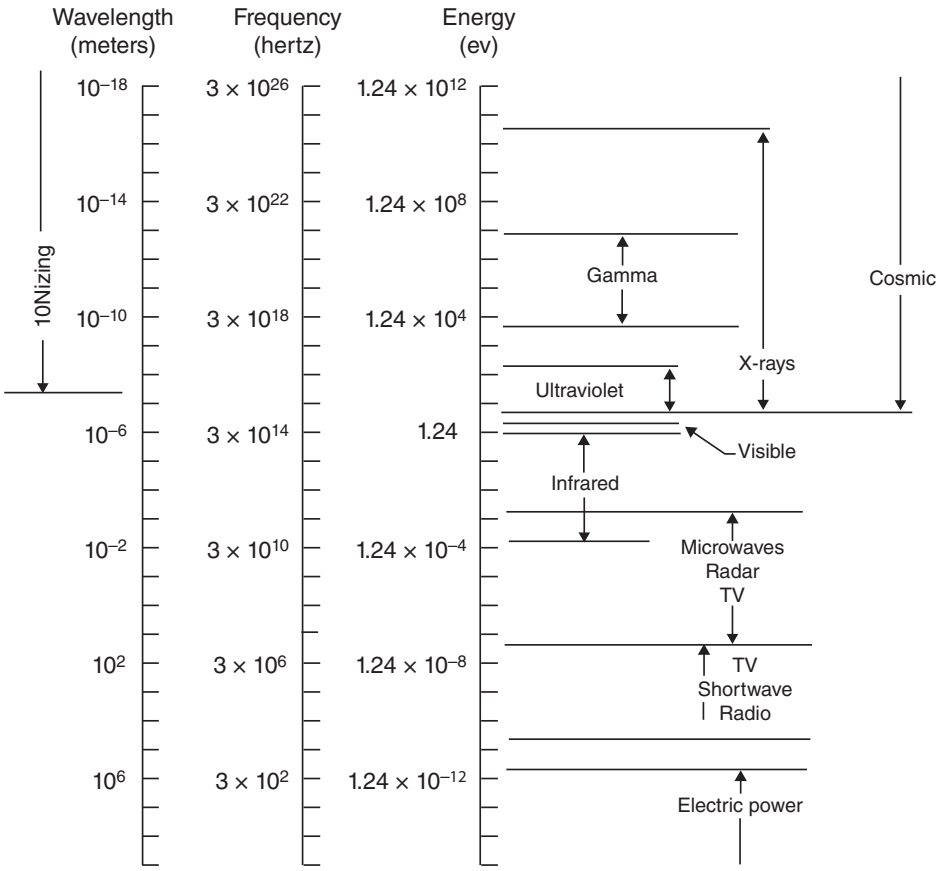


FIGURE 37.2. The electromagnetic spectrum. The wavelength is inversely proportional to the frequency and energy. Ionizing radiation represents the portion of the electromagnetic spectrum with energy exceeding ~10 eV. (Mettler and Upton).[6]

TABLE 37.1. Mass and charge of particulate radiation.

Particle	Mass (AMU)[a]	Charge
Electron (beta minus or negatron)[b]	0.000548756	−1
Positron (beta plus)	0.000548756	+1
Proton	1.008	+1
Neutron	1.009	0
Deuteron (heavy hydrogen)	2.015 (1 proton/1 neutron)	+1
α-particle	4.034 (2 protons/2 neutrons)	+2

[a] AMU: The definition of an atomic mass unit is 1/12 the mass of an atom of carbon-12; the rest mass of a proton and neutron averages 1 AMU; [b] β-Particles are high-speed electrons emitted from the nuclei of decaying radioisotopes with the negative charge and small mass of an electron.

ELECTROMAGNETIC SPECTRUM

The electromagnetic spectrum emitted by natural and man-made sources ranges from the low frequencies and energy of radio waves to the high frequencies and energy of γ-rays and X-rays. Figure 37.2 demonstrates the electromagnetic spectrum. The frequency of electromagnetic waves in the electromagnetic spectrum is directly proportional to the amount of energy in the photons; thus, the greater the frequency, the higher the energy of the waves. The wavelength is inversely proportional to the amount of energy in the electromagnetic

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TABLE 37.2. Ionizing radiation characteristics.

Name (Symbol)	Charge	Mass[a] (Composition)	Energy (eV)	Range (Air/Tissue)	Potential Hazard Source
Alpha particle (α)	+2	4 (2 protons +2 neutrons)	4–8 MeV	Few cm/50 μm	Internal
Beta particle (β)	±1	$\sim 2 \times 10^{-3}$ (1 electron)	0–3 MeV	≤Several m/few mm	Internal/external
Neutrons (n)	0	1	0–5 MeV	Many m/many cm	External
Gamma ray (γ-ray)	0	0	0–3 MeV	Many m/many cm	Internal/external
X-ray	0	0	0–0.5 MeV	Many m/many cm	Primarily external

[a] Atomic mass unit.

TABLE 37.3. Atomic structure terminology.

Term	Definition
Nucleus	Protons and neutrons
Atom	Nucleus and electrons
Molecule	Combined atoms
Elements	Atoms with same number of protons
Nuclides	Species of atom
Isotope	Nuclides of same element with different numbers of neutrons
Radionuclides	Unstable nuclides
Radioactivity	Emission of radiation
Decay	Transformation of radionuclide from unstable to stable atom

wave. The electromagnetic spectrum includes *non-ionizing* radiation (e.g., electric power, radio waves, microwaves, infrared, visible light, UVA, UVB, and UVC bands of UV radiation) and *ionizing* radiation (cosmic rays, X-rays, γ-rays). *Ionizing radiation* has sufficient energy to create charged particles (i.e., ions) by removing negatively charged electrons from the atom. This process creates: 1) a negatively charged electron; and 2) a positively charged atom. Human senses detect only the visible portion of the electromagnetic spectrum, except for the heat-generating absorption of infrared photons. Some nonionizing radiation (e.g., microwaves, ultrasound) can affect tissue by generating heat.

Ultraviolet (UV) radiation penetrates tissue poorly; therefore, UV light produces injury to the skin only by direct chemical interaction with molecules in the skin that possess high UV absorbance. Radiation with wavelengths shorter than visible light possesses the ability to displace electrons from their orbital shells; this portion of the electromagnetic spectrum produces ions in tissue.

Both γ-rays and X-rays possess sufficient energy to produce ionization and the formation of hydroxyl free radicals capable of damaging DNA and other biomolecules. Gamma-rays are photons emitted by unstable, radioactive nuclei; often these photons accompany the emission of β-particles from the same nuclei. X-rays are produced outside the nucleus when an electron transitions from a high-energy orbital to a lower energy state. Both X-rays and γ-rays travel great distances, easily penetrating cells of the body; however, man-made X-rays generally have somewhat lower energy (0.15 MeV) and comparatively less ability to penetrate tissue.

IONIZATION

Ionization occurs when electromagnetic radiation interacts with tissues to produce a loss or gain of electrons; this process involves sufficient energy to displace orbital electrons in atoms with a subsequent break in the chemical bonds holding the molecules together and the formation of free radicals (i.e., an atom or a molecule with a single unpaired electron in one orbit). The biological effect is the disruption of cellular molecules (primarily DNA) and consequent tissue damage. Typically, this reaction involves water or oxygen; the former usually involves the formation of hydroxyl radicals (i.e., OH, a highly reactive, oxidizing species). Radiation capable of causing ionization is called *ionizing radiation*. Direct radiation damage involves the deposition of a relatively large amount of energy (i.e., 33 eV) into a DNA sequence sufficient to disrupt the C=C bond and break the DNA strand. This type of reaction occurs most commonly with high linear energy transfer (high LET) from an α-particle. Indirect radiation damage results primarily from the interaction of a low linear energy transfer (low LET) photon with a water molecule, producing a free radical. The loss of an electron from the energy transfer causes the formation of an ion with high chemical reactivity and the capability to cause DNA strand breaks and cellular damage.

All forms of ionizing radiation penetrate matter and release energy by colliding with atoms and molecules. Ionization begins in a picosecond (10^{-12} seconds) with energy absorption, excitation, ionization, and free radical formation depending on the amount of energy deposited in the tissues. Disruption of biologically

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important molecules (nitroxides, oxygen, thiols) occurs within a second; DNA damage (chromosomal aberrations, delayed cellular division, disruption of signal transduction, reduced cell proliferation, alteration of gene expression) follows in seconds to hours. The physiological effects (e.g., decreased growth factor, increased cytokines) develop in minutes to years. Cancer is a very late somatic effect. The physical and chemical reactivity of nonradioactive and radioactive isotopes of a given element are identical, except that the radioactive isotopes emit ionizing radiation.[7]

Indirect Ionization

Indirectly ionizing radiation passes through matter without interacting with electrons until the path is sufficiently long to produce a chance collision with components of an atom; this type of radiation includes both electromagnetic waves (X-rays and γ-rays) and some uncharged particles (neutrons and uncharged mesons). In contrast to directly ionizing particles, these uncharged particles do not lose energy to the surrounding medium until a chance collision occurs with an elementary particle in the atom. X-rays and γ-rays produce ionization indirectly by interacting with orbital electrons (Compton Effect or photoelectric effect) or nuclear forces (pair-production). At low energies (<0.05 MeV), the photoelectric effect predominates when the X-rays displace tightly bound electrons from the inner shell of the atoms. For photons with higher energies (0.1–10 MeV), the photon ejects the electron; however, the photons retain sufficient energy to continue exciting and ionizing molecules until the energy in the photon is sufficient only for photoelectric interactions. Photonuclear reactions occur when high-energy photons (>1.02 MeV) convert to a positron–electron pair that subsequently reacts with cellular processes.

Once freed from the atom, the ejected electrons then deposit energy in other atoms through electrical interactions with orbital electrons. Neutrons represent a special case where the main interaction is the collision of the neutron with the nucleus of an atom, typically hydrogen, carbon, or nitrogen. The kinetic energy of this collision displaces some nuclei, resulting in ionization of the tissue. Some very high LET particles may result from the fission process when neutrons interact with some nuclei.

Direct Ionization

Directly ionizing radiation includes free neutrons and all charged particles (e.g., α- and β-particles, electrons, positrons, deuterons, negative pi mesons, accelerator particles). This type of radiation produces ionization in all matter through which it traverses through its electrical interactions with orbital electrons of the atoms. The impulses of these charged particles act at a distance through the electrical forces between the charged particles and the electrons in the orbit of the atom. The amount of kinetic energy transferred to the tissues by this interaction depends on the velocity, charge, and mass of the particle.

$$\text{Kinetic energy} = \tfrac{1}{2} m v^2 \qquad \text{(Equation 37.5)}$$

where

m = mass,
v = velocity.

This energy transfer is measured by *linear transfer energy*. As the charged particles penetrate the medium, they lose kinetic energy until they stop. Consequently, higher initial kinetic energy of the charged particle causes relatively deeper penetration of the charged particle into the medium. Heavy, highly charged particles (e.g., α- and β-particles) lose energy rapidly in tissue, resulting in limited penetration.

Linear Energy Transfer

Linear energy transfer (LET) is the average amount of energy deposited along the path of the radiation through the tissue; the LET measured in keV/μm tissue is directly proportional to the amount of damage produced by the radiation. High-LET radiations include α-particles (LET >3.5 KeV/μm). This densely ionizing, high-LET radiation causes greater damage to the tissue than sparsely ionizing, low-LET radiation (γ-rays, X-rays) with track average LET ranging from ~0.2 to 3.5 keV/μm. LET increases with the square of the charge on the particle. Table 37.4 lists the characteristics of radiation quality as measured by the type of linear transfer energy.

TABLE 37.4. Characteristics of radiation quality as measured by linear transfer energy.

Low LET (γ-rays, X-rays)	High LET (α-particles, neutrons)
Sparsely ionizing	Densely ionizing
Modified by radical scavengers	Unaffected by radical scavengers
Dose rate dependent	Dose rate independent
Dose-response linear quadratic	Dose-response linear

Abbreviation: LET = linear transfer energy.

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TABLE 37.5. Approximate relative biological effectiveness of ionizing radiation along with selected distances at which the radiation type penetrates selected media. Photon energy is measured in the half-value layer, reflecting the depth that absorbs one half of the incident radiation. The other radiation types are measured by the depth of penetration. (Adapted from Mettler and Upton).[6]

Radiation Type	Relative Biological Effectiveness	LET (keV/μ)	Air (cm at 1 MeV)	Water (cm at 1 MeV)	Concrete (cm at 1 MeV)	Lead (cm at 1 MeV)
γ-/X-rays[a]	1.0	0.3–10		9.6	5.0	0.9
β-particles	1–2	0.5–15	315	0.40		0.034
Neutrons	2–5	20–50				
α-particles	3–20	80–250	0.5	0.0072	—	—

Abbreviation: LET = linear energy transfer.
[a] Penetration measured in half-value layer rather than distance.

In general, the LET categorizes the relative biological effectiveness of different particles by the equilibration of the same biological effect for a given dose of relatively light particles (protons, helium ions) with different masses and charges. LET is a reasonable measure of radiation quality, but this quantity does not determine the total amount of damage because some high-LET radiation (α-particles) penetrates tissue poorly; therefore, this type of particle causes damage only in the area immediately adjacent to the α-particle. *Relative biological effectiveness* (RBE), as displayed in Table 37.5, is a general term that approximates the LET by comparing experimental ionizing radiation to X-rays and γ-rays (RBE ≅ 1). The RBE usually results from localized deposition of energy; this value may vary slightly between different tissues. Temperatures in tissue increase little (e.g., <0.002°C), even following the absorption of lethal doses of ionizing radiation).[6]

RADIOACTIVITY

The stability of a nuclide depends on the number of protons and neutrons, their configuration, and intra-atomic forces.[8] Typically, equal numbers of protons and neutrons produce stability. A *radionuclide* is an unstable atom that contains an excess of mass (protons, neutrons) or energy; radioactive materials emit ionizing radiation to reach nuclear stability. Elements with an atomic mass number of >200 are radioactive. Unstable atoms restore stability by emitting a particle (α or β) and/or energy in the form of electromagnetic waves (γ-ray, X-ray) during the process of radioactive decay. Activity (i.e., decay rate) is the number of disintegrations (or transformations) per unit time that occur in radioactive material, whereas specific activity refers to activity/mass (i.e., Bq/g or Ci/g). By convention, the curie (3.7×10^{10} disintegrations/second) is the conventional unit of activity, whereas the Becquerel (1 disintegration/second) is the metric (SI) measure of activity. Radioactive isotopes have identical chemical and physical properties (e.g., density, melting point, solubility) as nonradioactive isotopes of the same element; these nuclides chemically react identically within the body (e.g., the function of radioactive iodine and stable iodine is the same). Figure 37.3 displays the penetrating properties of radioactive particles and photons.

Alpha Particles

An *α-particle* is an energized helium nucleus (two protons, two neutrons, no electron shell) emitted by the heaviest nuclides in the periodic table (e.g., uranium, radium, plutonium) during their transformation to a stable nuclide. The emission of an α-particle reduces the atomic number by 2 and the atomic mass by 4. *Radioactive decay* is the process of a radionuclide converting to a stable nucleus; however, intermediate progeny may be more unstable (i.e., have a shorter half-life) than the parent form. When an unstable radionuclide spontaneously emits radiation, it is *radioactive*. The energy of an α-particle is relatively low (i.e., ~4–8 MeV) and unique to the α-particle compared with β-particles; the latter emits energy on a continuous spectrum with a maximum energy characteristic of the radionuclide. Alpha particles are easily shielded because they travel only a few centimeters in air; these particles are unable to penetrate paper or a few microns of epidermis.

Beta Particles

Radionuclides with excess neutrons usually emit negatively charged β-particles that convert neutrons to protons. Carbon-14 is a radionuclide that contains 6 protons and 8 neutrons in contrast to the stable nuclide carbon-12 (6 protons, 6 neutrons). Carbon-14 restores stability by emitting a β-particle and transforming into nitrogen (7 protons, 7 neutrons). Beta particles demonstrate a wide range of energies, depending on the specific radionuclide. These particles usually travel a few

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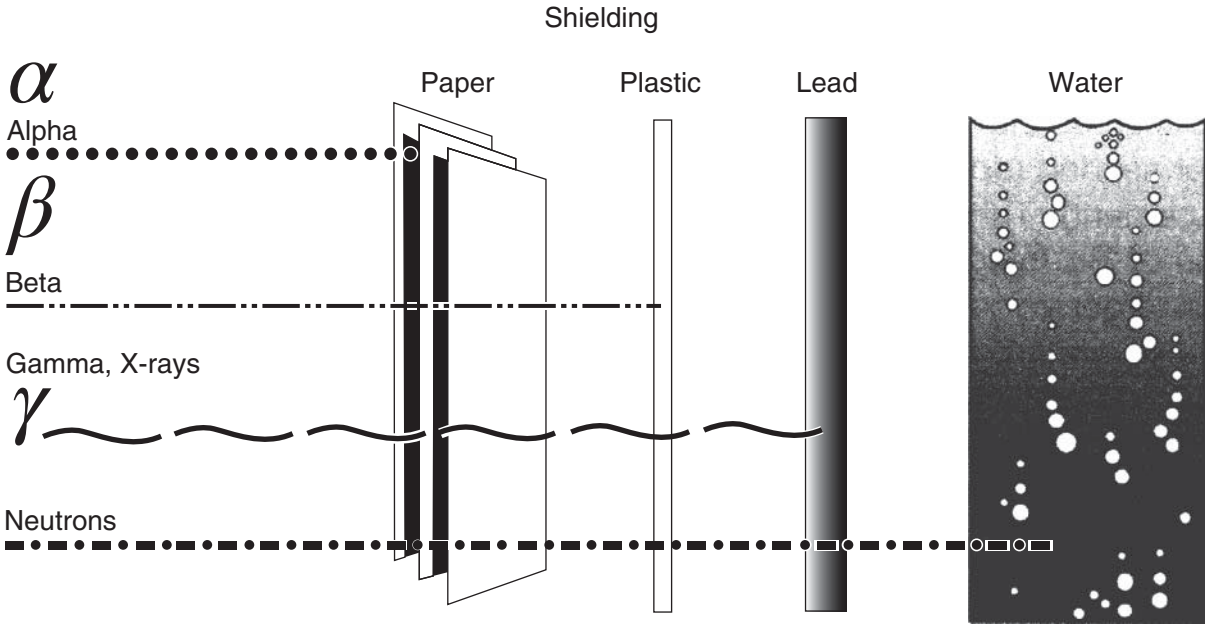


FIGURE 37.3. Materials able to stop the penetration of α-particles, β-particles, γ-rays, X-rays, and neutrons. (Adapted from REAC/TS).

meters in air and penetrate a few millimeters into tissue. Consequently, plastic provides an effective shield from β-particles. Radionuclides with an excess of protons emit a positive charged electron called a *positron* that converts a proton to a neutron. Fluorine-18-deoxyglucose (FDG) is a positron-emitting radionuclide used for whole-body PET/CT medical imaging. Frequently, this transformation requires the release of energy.

Gamma- and X-rays

Gamma- and X-rays are photons (i.e., pure electromagnetic energy) that possess no mass. Electromagnetic energy emitted from *inside* the nucleus is called a *γ ray*. *Gamma radiation* travels many meters in air; lead is required to shield objects from γ-rays. *X-ray radiation* is electromagnetic energy emitted from *outside* the nucleus (e.g., radiation produced by bombarding high-energy electrons in an X-ray machine on a target). Some radioactive materials also emit X-rays. The penetration and shielding requirements (concrete, lead, steel) are similar for X-rays and γ-rays, as displayed in Figure 37.3.

Neutrons

Neutron radiation consists of neutral particles emitted from inside the nucleus, usually during fission reactions, with the exception of the decay of a few beryllium radionuclides. Neutrons exist at a wide range of energy levels and may travel extremely long distances in air. This type of radiation can induce radioactivity (neutron activation) when absorbed into the nuclei by stable elements (e.g., Al, Cl, N, Na, P, S); neutrons are the only type of radiation capable of creating radioactivity in other matter. Neutron radiation penetrates deeply; protection from this type of radiation requires special shielding (e.g., paraffin, water).

Positrons

Radioactive decay involving the emission of a positron (positive electron) is equivalent to converting a proton to a neutron. Conceptually, positrons are antiparticles of electrons; the interaction of an electron with a positron releases energy as two 511 keV photons at an angle of 180° to each other. Neutron-deficient nuclides (i.e., atoms with excess protons) typically emit positrons. The emission of a positron and neutrino converts a proton to a neutron; this reaction requires at least 1.02 MeV of energy.

RADIATION UNITS

Because the physical nature of radioactivity limits the application of ordinary measurements of mass, length, and weight, special units are necessary to describe the

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amount of radiation received by an individual. The International System of Units (SI) is usually preferred over the MKSA (meter-kilogram-second-ampere) system.[9] The major advantage of the SI system is the facilitation of international communication (the SI system is accepted by almost every country including the United States); the coherence and simplicity of this system do not require conversion factors for units derived from base and supplementary units.[10]

Exposure

The radiation dose measures the amount of radiation exposure. The absorbed dose is a quantifiable measure (milligray, mGy) whereas the equivalent dose (millisievert, mSv) and effective dose (mSv) are calculated for individual organs and the whole body, respectively, for use in radiological protection. Radiation exposure is synonymous with irradiation, typically defined as the amount of ionization per unit air mass resulting from X-rays or γ-rays. Measures of exposure quantify the amount of radiation in the environment rather than the actual dose received by an individual. In the older MKSA system, the roentgen (R) quantified the amount of ionization produced in air in terms of charge/mass of air (C/kg). This measure applies **only** to electromagnetic waves with energies 10 keV–3 MeV (e.g., X-rays, ~0.15 MeV; γ-rays, 0.01–3 MeV) in air; the roentgen does not apply to charged particles or other media (e.g., water). The roentgen approximates the old unit of absorbed dose (rad) only for γ-rays and X-rays; the roentgen typically overestimates the rad by a few percent.[11]

There is no SI equivalent to roentgen in the SI system. In this system, radiation fields can be specified by the *fluence* as defined by the number of particles or electromagnetic waves (photons) per unit area (e.g., per cm^2). The fluence rate (old term, flux) expresses the number of particles or photons/cm^2/second.

Absorbed Dose (D)

The absorbed dose is the fundamental radiation quantity that describes the deposition of energy delivered by ionizing radiation into an absorbing medium defined at a specific point or averaged over a mass of tissue. The absorbed dose (energy/unit mass, J/kg) usually refers to the average radiation dose transferred from the environment to the body (D) or a specific tissue (D_T); however, the absorbed dose throughout an organ or tissue is often nonhomogeneous, particularly when comparing the dose of specific internal organs. In general, the absorbed dose reflects the radiation risk to an organ or tissue only when the variation in uniformity is <50%.[6]

The transfer of energy by a photon results from: 1) the interaction of the photon with an atom that sets an electron in motion; and/or 2) the absorption of the kinetic energy from the high-energy photon into the surrounding tissue through excitation and ionization.[12] In SI units, the *gray* measures the latter effect in dimensions of energy per unit mass; the gray (Gy) is equivalent to the deposition of 1 J of energy/kilogram of tissue. The old metric equivalent of the gray is the rad. A rad (100 ergs/g) equals one centigray (cGy); 100 rad is equivalent to 1 gray.

Table 37.6 lists the units and conversion factors for the SI system and the old metric system, whereas Table 37.7 provides the conversion factors for SI (Gy, Sv, Bq) and conventional (rad, rem, Ci) units. The gray is an important unit for understanding and comparing the biological effects of radiation.

The unit for describing radiation fields is the *kerma* (**k**inetic **e**nergy **r**eleased in **ma**tter); this value is particularly suitable for high-energy photons and neutrons. This unit measures the initial stage of the energy transfer by summing all initial kinetic energy in a specific volume or mass released by the interaction of charged ionized particles, photons, and uncharged ionizing particles. The kerma measures the transfer of energy over a specific area, whereas the gray measures the absorption of energy over the whole path of the electron. Typically, the rad and kerma are interchangeable with the notable exception of calculating the doses for adult atomic bomb survivors; the organ dose/tissue kerma dose ranges from 0.4–0.7 for γ-rays and 0.12–0.55 for neutron radiation.[13] The absorbed dose may be smaller than the kerma for a given photon interaction because some energy may be lost through the emission of charged particles. Although the kerma is quantified by the gray, the kerma is equivalent to the absorbed dose only if: 1) the direction, energies, and number of charged particles are constant throughout the area; and 2) there is negligible production of secondary ionizing radiation (e.g., X-rays). Significant differences between the kerma and absorbed dose occur at the interface of two different materials (e.g., bone, soft tissue) and very high-energy radiation. Japanese atomic bomb survivors sustained multiple radiation exposures in addition to γ-rays and neutrons from the blast, including radioactive fallout from black rain and neutron activation in soils.

The equivalent dose (Sv, rem) is the absorbed dose (Gy, rad) times a quality factor (Q). For X- and γ-rays, the equivalent and absorbed doses are similar.

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TABLE 37.6. SI and conventional radiation units.

Quantity (Symbol)	SI Units (Symbol)	Name (Symbol)	Conventional Unit (Symbol)	SI Unit Equivalent	Comment
Average energy/ ion pair	Joule (J)		Electron volt (eV)	1.602×10^{-19} J	
Power (P)	Joule/second (J/s)	Watt (W)	Watt (W)	equivalent	
Exposure (X)	Coulomb/kilogram (C/kg)		Roentgen (R)	1 C/kg = 3,876 R	Amount of radiation directed at a medium
Absorbed dose (D)	1 Joule/kilogram (J/kg)	Gray (Gy)	rad	0.01 Gy	Energy deposited in tissue
Dose equivalent (H_T)	Joule/kilogram (J/kg)	Sievert (Sv)	Roentgen equivalent man (rem)	0.01 Sv	Absorbed dose weighted for radiation quality
Effective dose equivalent (H_E)	Joule/kilogram (J/kg)	Sievert (Sv)			Dose equivalent weighted for radiation sensitivity of tissue
Collective effective dose equivalent	Joule/kilogram (J/kg)	Man Sievert (man-Sv)			Effective dose equivalent applied to a population
Fluence (ϕ)	$1/m^2$		$1/cm^2$	$10^4/m^2$	Number of particles (irradiance) from all angles crossing a unit area
Fluence rate (ϕ)	$1/m^2$ s	m^{-2}/s	cm^{-2}/s	$10^4/m^2$ s	Number of particles (irradiance) from all angles crossing a unit area per unit time. Flux is the old term for fluence
Kerma	Joule/kilogram (J/kg)	Gray (Gy)	rad	0.01 Gy	Mean kinetic energy transferred from charged particles to uncharged particles in a given mass
Linear energy transfer (LET)	Joule/meter (J/m)		Kiloelectron volt/ micrometer (keV/μm)	1.602×10^{-10} J/m	
Radioactivity (A)	1/second (1/s)	Becquerel (Bq)	Curie (Ci)	3.7×10^{10} Bq/second	Nuclear transformation rate

TABLE 37.7. Conversion table for units of radiation dose.

Unit	Symbol	Value	Conversion Factor
Gray	Gy	1 J/kg	100 rad
Sievert	Sv	1 J/kg	100 rem
Becquerel	Bq	1 disintegration/ second	2.7×10^{-11} Ci
Rad	Rad	100 erg/g	0.01 Gy
Rem	Rem		0.01 Sv
Curie	Ci	3.7×10^{10} disintegrations/ second	3.7×10^{10} Bq

Dose Equivalent (H_T)

The dose equivalent is a derived quantity used in radiation protection to calculate whole-body effective dose to an organ or tissue. The dose equivalent applies to reference models of stochastic effects using population group averages for radiation protection rather than risk assessment for individuals. The biological effectiveness of a given absorbed dose (Gy) varies depending on the type of ionizing radiation and a variety of other factors including the susceptibility of a given tissue. To compare all ionizing radiation doses in terms of potential biological damage, the ICRP developed dose coefficients (equivalent and effective dose/Bq intake) for formulating radiation protection guidelines using the process outlined in Figure 37.4. The primary purpose of the equivalent and effective dose is the summation of radiation doses from external and internal (i.e., absorbed radionuclides) sources to compare the stochastic risks of whole-body radiation exposure with dose limits, reference levels, and constraints; hence, these values apply

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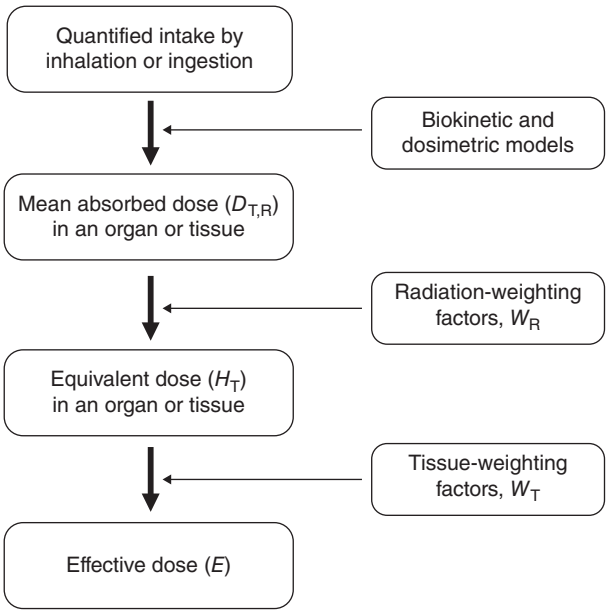


FIGURE 37.4. International Commission on Radiological Protection (ICRP) process for developing dose coefficients (equivalent and effective dose) based on modeling the absorption of the external radiation dose and adjusting the absorbed dose with radiation- and tissue-weighting factors. This method allows the summation of radiation doses received from external sources and intake of radionuclides. (Adapted from Harrison and Streffer).[15]

to radiological protection rather than determination of radiation-induced effects in epidemiology studies.[14] Calculation of the absorbed dose in Gy involves the use of biokinetic models to determine the total number of radioactive transformations within specific body regions and dosimetric models (e.g., anthropomorphic and mathematical phantoms) to determine energy deposition of important organs and tissues from transformations occurring in those regions. The dose equivalent normalizes the risk of a given absorbed radiation dose by accounting for the difference in the relative biological effectiveness of densely and sparsely ionizing radiation by using the Q or Quality factor as determined in Equation 37.6. However, the basis of the Q factor was a mathematical relationship to linear energy transfer (LET) rather than the relative biological effectiveness (RBE) of a radiation type.

$$\text{Dose Equivalent } (H_T) = (\text{absorbed dose}) \times (\text{quality factor}) \times (\text{distribution factor}) \quad \text{(Equation 37.6)}$$

Hence, Equation 37.6 did not account for the varying sensitivities of different tissues to the effects of ionizing radiation. Subsequently, the ICRP replaced the Q factor and the distribution factor in Equation 37.6 with the radiation weighting factor (w_R) by combining all factors other than absorbed dose to easily compare different types of radiation. The radiation-weighting factors adjust for the varying effectiveness of different radiation types/absorbed doses (Gy) to cause stochastic effects at low doses and dose rates. Thus, Equation 37.7 allows the comparison of radiation risks for people exposed to different radiation sources in different portions of their bodies.

$$H_T \text{ (sievert)} = D \text{ (gray)} \times w_R \text{ (no dimensions)} \quad \text{(Equation 37.7)}$$

TABLE 37.8. Radiation weighting factors related to external or internal ionizing radiation. (Adapted from Mettler and Upton).[6]

Radiation Type	Energy Range	Weighting Factor (w_R)
Photons	All	1
Electrons/muons	All	1
Neutrons	<10 keV	2.5[a]
	10–100 keV	2.5–7.5[a]
	>100 keV–2 MeV	7.5–20[a]
	>2–20 MeV	20–7.5[a]
	>20 MeV	7.0–2.5[a]
Protons/charged pions		2
α-particles, heavy nuclei		20

[a] Ranges represent a continuous function of neutron energy rather than discrete values.

Table 37.8 lists the radiation weighting factors symbolized as w_R for each type of ionizing radiation. The dose equivalent is designed to protect individuals from radiation; therefore, the dose equivalent is the basic unit in radiation protection. The dose equivalent is a better measurement of radiation risk than the absorbed dose.[16]

For X-rays, γ-rays, and β-particles, the rad and the rem are equivalent to the gray (Gy) and the sievert (Sv), respectively. 1 Gy = 100 rad and 1 Sv = 100 rem. Alpha particles cause 20 times greater biological damage than an equal absorbed dose of γ-rays or β-particles; therefore, the quality factor for α-particles is 20. The dose equivalent (sievert) is not a measured quantity; the sievert normalizes the damage caused by different types of ionizing radiation. Table 37.6 demonstrates the conversion factor for the older unit of absorbed dose (rem).

Effective Dose Equivalent (H_E)

Typically, the body does not receive the equivalent dose in a uniform manner; therefore, the *effective dose equivalent* (effective dose) was created by the ICRP to equate

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the radiation risk to a specific part of the body relative to the risk of whole-body radiation for the purpose of setting radiation protection limits (i.e., annual radiation exposure to ionizing radiation or radionuclides for workers and the public). Consequently, the effective dose is a derived rather than a physically measurable quantity. This quantity includes multiple factors including radiation types, tissue radiosensitivities, population characteristics, and biological endpoints.[17] The ICRP recommends the use of the abbreviated term *effective dose* to describe the effective dose equivalent as the product of the equivalent dose (H_T) and the weighting factor (w_T) summed over all tissues, as displayed in Equation 37.8. The tissue weighting factors adjust for the contribution of individual organs and tissues to the age- and sex-averaged overall detriment from cancer and hereditary effects. The effective dose is a broad risk measure for developing a fatal malignancy irrespective of the type and energy of the radiation or the distribution of the radiation in the body. The effective dose provides a measure of the risk of radiation-induced adverse effects for protection purposes rather than an assessment of individual doses or an estimation of the hypothetical number of cancer cases in the exposed population.[15,18] Consequently, the effective dose applies to reference models rather than predictions of future cancer risks in individuals.

$$\text{Effective Dose } (H_E) = \sum H_T \times w_T \quad \text{(Equation 37.8)}$$

where

H_E = effective dose (Sv),
H_T = dose equivalent of a tissue,
w_T = tissue weighting factor for the type of ionizing radiation and tissue (dimensionless).

For evaluation of the effective dose from the incorporation of radionuclides, the ICRP uses the *committed effective dose* (E_t), where t is the integration time in years following the intake of the radionuclide. Because the sensitivity of organs in the body to ionizing radiation varies, the biological effect of an absorbed dose differs depending on the time of delivery (equivalent doses received over a long period of time are less harmful than the same dose delivered at one time) and the tissue receiving the absorbed dose. The effective dose provides the basis for radiation protection assessments; only organ weighting factors recommended by the International Commission on Radiological Protection (ICRP), as listed in Table 37.9, should be used for assessing radiation risk of radionuclides.[16] The effective dose does not provide information on the risks of specific cancer types or deterministic effects. The ICRP values apply to reference values rather than risks in an individual or population with no assessment of uncertainties related to individual characteristics.[15]

TABLE 37.9. International Commission on Radiological Protection recommendations on tissue weighting factors (w_T). These values are averaged across all ages and genders; consequently, these values do not necessarily apply to radiosensitive subpopulations (e.g., children, young women). Additionally, the values reflect the observed late stochastic effects rather than short-term adverse tissue reactions, which are important in the use of therapeutic radiotherapy. (Adapted from Wrixon).[18]

Tissue Group	Tissue Weighting Factor (w_T)	Group w_T Value
Adrenal glands, bone marrow (red), breast, colon, extrathoracic region, gallbladder, heart, kidneys, lung, lymph nodes, muscle, oral mucosa, pancreas, prostate[a], small intestine, spleen, stomach, thymus, uterus[a]	0.12	0.72
Gonads	0.08	0.08
Bladder, esophagus, liver, thyroid gland	0.04	0.16
Bone surface, brain, salivary glands, skin	0.01	0.04
Total		1.00

[a] When present.

The effective dose accounts for different radiosensitivities to the development of malignancy in various tissues by using the committee-selected weighting factors listed in Table 37.9. Weighting factors include substantial uncertainties including the linearity of the dose-response at low radiation doses.

The effective dose equivalent is the amount of radiation required to produce the same risk as the application of ionizing radiation to the whole body rather than specific parts or organs within the body.[19] Because the quality factors are approximations used for radiation protection, these factors contain built-in biases to protect radiation workers.[11] Consequently, epidemiology studies using effective dose equivalents may underestimate the true risk of a given exposure depending on the accuracy of the quality factors. Effective dose equivalents were not calculated for studies completed before 1977, when the old system did not calculate weighted risks.

The effective dose originally reflected the risk of fatal cancer within the first two generations of offspring in the working population. The incidence of curable cancer is not considered in the risk calculation;

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hence, extrapolation of these risk factors to the general population does not account for the difference in ages between the general population and the working population. Additionally, the effective dose equivalent does not include the development of curable cancer or the appearance of hereditary harm beyond the second generation of offspring in the general population. Frequently, the effective dose equivalent is abbreviated as the dose or the effective dose and reported in units of the sievert; this value has the same dimension (J/kg) as the gray.

Collective Effective Dose Equivalent (Man Sievert)

For epidemiological purposes, the *collective effective dose equivalent* is a measure of the total radiation to a specific population. The unit is the man sievert (man Sv) calculated by multiplying the effective dose equivalent by the number of people exposed to the effective dose equivalent. Similar to dose uniformity, collective dose implies linearity between radiation dose and adverse effects with no threshold. Additionally, this concept applies only to low radiation doses (e.g., background radiation), as adverse effects differ dramatically when the radiation dose received by the population is applied to one person.

Radioactivity (Becquerel)

Radionuclides decay occurs by the emission of radiation in the form of particles and photons. *Activity* is a measure of decay in units of disintegrations per second. The *Becquerel* corresponds to one disintegration of the radionuclide/second. The radioactivity of plutonium-239 is expressed in millions of Becquerels (i.e., megabecquerel, MBq); the activity of 1 g of this radionuclide is 2,000 MBq because it emits 2,000 α-particles each second. The emission rate of a particle is equivalent to its activity **only** when each disintegration involves that particle. Many radionuclides eject α-and β-particles in addition to photons; hence, the number of α- or β-particles released by the radionuclide would be less than the activity of the radionuclide.

The time required for a radionuclide to lose half of its activity is called the *physical half-life*. The physical half-life is unique to every radionuclide, varying from milliseconds to millions of years; the physical half-life is constant throughout the life of the radionuclide. The physical half-life of uranium-238 is 4,470 million years. The *biological half-life* is the time required to eliminate ½ the dose of the radionuclide from the body. Biological half-lives are shorter for radionuclides (iodine, cesium, tritium) that deposit in soft tissue compared with radionuclides (plutonium, radium, strontium) primarily entering bone. The effective half-life is a measure of the transit time of the radionuclide in the body as defined by Equation 37.9:

$$1/\text{effective}\ t_{1/2} = 1/\text{biological}\ t_{1/2} + 1/\text{physical}\ t_{1/2} \quad \text{(Equation 37.9)}$$

The effective half-life is always shorter than the biological half-life or the physical half-life. This value accounts for the situation where a radionuclide with a long physical half-life is eliminated quickly or absorbed slowly.

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B

IONIZING RADIATION

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Chapter 38

COSMIC RADIATION AND RADON

COSMIC RADIATION

HISTORY

Human exposure to ionizing radiation began with the beginning of evolution. In September 1859, telegraph systems failed in Europe and America as auroras filled the sky from a geomagnetic storm that released high-energy particles during a solar flare. Victor Hess used three ionization chambers to detect increasing radiation as he ascended to 5,300 m during a historic balloon flight in 1912. Later, Robert Millikan's discovery of his law of motion of a particle entering the earth's atmosphere and falling toward the earth, along with his studies of ionization chambers, convinced him that the radiation penetrating the atmosphere was electromagnetic from above rather than below. He called this radiation cosmic rays in a paper published in 1925.[1] In the same year, Arthur Compton correctly determined that cosmic radiation was primarily composed of charged particles. These investigations helped demonstrate the extraterrestrial source of cosmic radiation and the variation of this radiation with latitude. Only since the 20th century has human activity (e.g., uranium mining, air travel, nuclear technology) added to the natural burden of radiation.[2] The development of commercial supersonic aircraft during the 1960s with cruising altitudes of 19 km required monitoring of the effective radiation dose of flight crews and passengers. The first commercial supersonic airliner, the Russian Tupolev-144, descended to lower altitudes when the effective dose rate exceeded 300 μSv/hour.[3] By the early 1990s, natural radiation sources represented ~87% of the annual effective dose rate (2.5–3.6 mSv) compared with 13% for artificial (human) sources.[4]

PHYSICAL PROPERTIES

Cosmic radiation refers to high-energy extraterrestrial particles striking the earth's surface and particles (e.g., radionuclides) formed by the interaction of extraterrestrial particles with the atmosphere. The sources of these particles are galactic (outside the solar system) and solar (from the sun). Galactic particles are mostly protons (i.e., ~85%) with energy fluence up to 10^{20} electron volts (eV), whereas protons with energies $<10^6$ eV comprise 99% of solar particles. The two mechanisms of irradiation from natural sources are internal and external. Cosmic rays and terrestrial γ-rays are the main external causes of natural radiation, whereas ingestion of radionuclides from cosmic and terrestrial origins is the major internal source of natural radiation.[5] Terrestrial γ-ray flashes presumably result from the collision of atoms in the atmosphere and electrons accelerated to near the speed of light by lightning; these events last a few milliseconds with energies up to 20 MeV and are not related to cosmic radiation.[6] High-energy protons are the main constituent of those extraterrestrial particles that originate from the sun (i.e., solar particles) and sources outside the solar system (i.e., galactic particles). Solar and galactic particles are primarily high-energy muons and electrons; these secondary particles produce an absorbed dose similar to β- and γ-radiation generated by terrestrial radionuclides.[7]

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TABLE 38.1. Estimated annual worldwide effective dose rate. (United Nations Scientific Committee on the Effects of Atomic Radiation).[8]

Source	Average Annual Worldwide Dose (mSv)	Typical Annual Range of Individual Doses (mSv)
Natural sources		
Inhalation (radon gas)	1.26	0.2–10
External terrestrial	0.48	0.3–1
Ingestion radionuclides	0.29	0.2–1
Cosmic radiation	0.39	0.3–1
Total natural sources	2.4	1–13
Human sources[a]		
Medical imaging (excluding radiotherapy)	0.6	0–several tens
Atmospheric nuclear testing	0.005	Higher doses near test sites
Occupational exposure	0.005	~0–20
Total human sources	0.6	0–several tens

[a] Contributions from nuclear power plants and radiation accidents (e.g., Chernobyl) are too small and geographically localized to affect the total dose of radiation.

EXPOSURE

The estimated annual worldwide effective dose rate for natural radiation is 2.4 mSv with a typical range of 1–13 mSv; some populations may receive up to 10–20 mSv.[8] Radiation doses for nuclear medicine are substantially higher in developed countries. Table 38.1 displays the estimated annual worldwide effective dose rates for natural and human sources of radiation.

Cosmic Rays

On the earth's surface, the major variation in the energy delivered by cosmic radiation results from changes in altitude (i.e., doubling every 2,000 m) and latitude (i.e., doubling between the equator and pole). The atmosphere attenuates the energy of cosmic rays with the intensity decreasing linearly ~1.5 μSv/km at 16 to 80 km above the earth's surface.[9] The solar cycle accounts for ~10% of the variation in the radiation from cosmic rays.[10] Galactic cosmic rays reach their maximum intensity during the least active portion of the solar cycle and their minimum intensity during maximum solar activity. The magnetic fields of the earth also provide a partial shield against the charged particles.

Cosmic radiation entering the earth's atmosphere consists of protons (86%), α-particles (11%), and electrons (2%), with heavier nuclei accounting for the remainder; the energy spectrum of cosmic radiation ranges from 10^8 to over 10^{20} eV.[11] With the exception of high-energy radiation (i.e., $>10^{15}$ eV) that probably originates in supernovas, most cosmic radiation is created in our galaxy.[12] Our atmosphere attenuates radiation from galactic (i.e., outside the solar system) and solar particles (i.e., radiation from the sun) by >1,000-fold times.[5] The amount of cosmic radiation modulated by our atmosphere also depends on the geomagnetic field of the earth with minimum dose rate and intensity at the equator and maximums near the geomagnetic poles. Table 38.2 compares the composition of cosmic radiation at 12 km above the minimum and maximum locations of the earth's geomagnetic field where there is no significant solar radiation.

TABLE 38.2. Contribution of various components of cosmic radiation to the ambient dose equivalent comparing geomagnetic equator (minimum) with polar latitude (maximum), assuming an altitude of 12 km and solar minimum. (Modified from European Radiation Dosimetry Group (EURADOS), European Commission).[9]

Component	Equator (% of Total)	Polar Latitude (% of Total)
Muons	5	3
Photons	8	5
Protons	12	14
Neutrons	37	64
Electrons / Positrons	38	14

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Although no deflection of cosmic radiation occurs at the geomagnetic poles, the atmosphere deflects most extraterrestrial particles with an energy of $<2\times10^{10}$ eV within the first several hundred g/cm of atmospheric thickness at the geomagnetic equator. The galactic radiation flux is relatively constant over time; however, strong disturbances of local magnetic fields caused by solar flares produce ~3-fold variation in total galactic particle density. This change in the galactic particle flux occurs over the 11-year cycle of solar flares, varying inversely with the intensity of the solar flares. Modeling solar events is complicated by the large uncertainties (e.g., >5-fold) involved in determining their contribution. Typically,[13] the estimation requires retrospective use of ground-level neutron monitors and rarely on-board measurements.

Cosmic rays interact with the atmosphere producing pions (π mesons), protons, neutrons, and low-Z nuclei; neutral pions decay to high-energy photons that generate electrons and more photons, whereas charged pions decay to muons. Muons are the dominant particle at low altitudes (<6 km), whereas electrons and neutrons are the primary components at higher altitudes as demonstrated in Figure 38.1. Variation in the intensity of the radiation flux also occurs at different locations on the earth. The earth's magnetic field strongly influences the cosmic neutron flux with neutron fluence rates at sea level near the equator at 20–25% of the polar rate, primarily changing between 50° and 20° latitude. The contribution of neutrons is greater (i.e., ~75%) at the poles compared with ~50% at the equator. At sea level, muons comprise ~70% of the dose equivalent, photons/electrons contribute ~15%, and neutrons ~10%; charged pions and protons account for ~1–2% of the dose equivalent at sea level.[11]

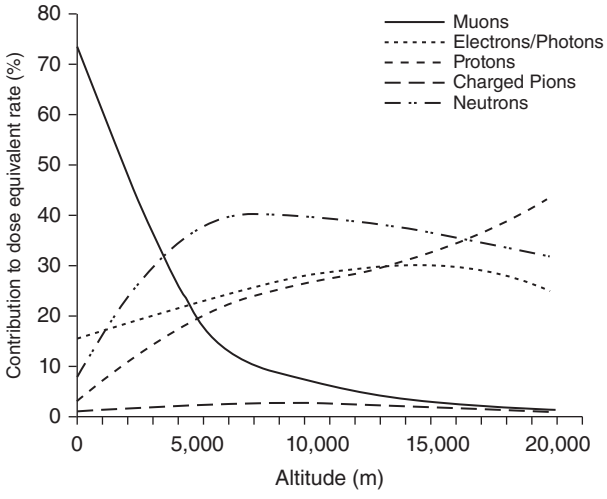


FIGURE 38.1. Components of dose equivalent rate from cosmic rays at various altitudes. (United Nations Scientific Committee on the Effects of Atomic Radiation).[11]

Cosmic Radionuclides

Although cosmic rays produce at least 14 radionuclides in the atmosphere, ranging from ^{3}H to ^{81}Kr, only 4 cosmic radionuclides contribute significantly to the cosmic radiation dose in the general population including ^{3}H, ^{7}Be, ^{14}C, and ^{22}Na. Radiocarbon decays naturally in the atmosphere with a half-life of 5,700 ± 30 years.[14] Fossil fuels are millions of years old and contain stable carbon isotopes (^{12}C, ^{13}C) rather than ^{14}C. The introduction of carbon from the combustion of coal and oil along with alterations in CO_2 cycling between terrestrial, oceanic, and atmospheric carbon reservoirs reduce the specific activity of carbon in airborne carbon dioxide because fuels contain little ^{14}C.[12] Alterations of the ^{14}C/C ratio impair the ability of radiocarbon dating techniques to accurately determine the age of substances.[15]

Primordial (Terrestrial) Radionuclides

The ubiquitous radionuclides of terrestrial origin involve radionuclides with half-lives comparable to the age of the earth and their decay products; irradiation from this material consists primarily of γ-radiation from the ^{238}U series, ^{232}Th series, and ^{40}K. Ingestion of these radionuclides results in internal irradiation. Inhalation exposure to primordial radionuclides mainly involves ^{222}Rn from the ^{238}U series; the effective dose from inhaling ^{220}Rn is substantially less than ^{222}Rn because of the short half-life (i.e., 55 seconds) of the former decay product of the ^{232}Th series. The contribution of other primordial radionuclides (e.g., ^{87}Rb, ^{138}La, ^{147}Sm, ^{176}Lu, ^{235}U) to effective dose rates is small.[11]

DOSE EFFECT

Total background radiation exposure for the general US population is 2–3 mSv with annual occupational limits of 50 mSv in the United States and 20 mSv in Europe. The absorption of 1 Sv (1,000 mSv) during a radiation incident produces nausea, vomiting, diarrhea, skin vesicles, and increased cancer risks.[16] The population-averaged value for the cosmic effective dose equivalent depends on the altitude, time spent indoors, shielding, and duration of aircraft flights.[5] The estimated annual dose equivalent in the US population is ~0.25–0.26 mSv. Table 38.3 lists the estimated annual US

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TABLE 38.3. Estimated total annual dose equivalent rate (mSv/year) for a US resident from natural background radiation. (Adapted from National Council on Radiation Protection and Measurements).[7]

Source	Bronchial Epithelium	Soft Tissues	Bone (Surface)	Bone (Marrow)
Cosmic	0.27	0.27	0.2	0.27
Terrestrial	0.28	0.28	0.28	0.28
Cosmic radionuclides	0.01	0.01	0.01	0.03
Inhaled radionuclides	24	—	—	—
Ingested radionuclides[a]	0.35	0.35	1.1	0.50
Total (mSv/year)	25	0.9	1.7	1.1

[a] Excludes cosmic radionuclides.

dose equivalent rate from cosmic radiation for various tissues. As displayed in this table, inhaled radionuclides (i.e., radon) dominate the exposure to cosmic radiation, affecting primarily the lungs.

Cosmic Rays

Cosmic rays contribute ~30–50% of the total radiation dose from external environmental sources. In the United Kingdom, the annual effective dose equivalent (effective dose rate) is 0.3 mSv with muons accounting for 0.28 mSv and neutrons contributing 0.02 mSv.[5] The variation in this dose rate is much smaller in the United Kingdom than in the United States because the United Kingdom is relatively flat compared with the United States. The annual world population average effective dose rate from charged particles (primarily muons) and photons is 0.28 mSv, whereas the global average effective dose rate for neutrons is 0.10 mSv accounting for altitude and latitude effects.[11] The composition and intensity of the radiation flux and the effective dose rate from cosmic rays vary with altitude, latitude, and solar cycle, as displayed in Figure 38.2. Although solar events may double the effective dose rate during short periods, the overall effect on annual exposure rates for airplane crews is minimal.[17] The galactic effective dose equivalent rate (effective dose rate) is ~2 times greater over the geomagnetic pole than the geomagnetic equator.[18] Shielding structures (e.g., airplanes, houses) do not affect the absorbed radiation dose because muons penetrate these structures easily.

Environmental Exposure

Passengers receive more cosmic rays flying in an airplane than standing on the ground, especially during polar flights; however, an occasional airplane flight contributes a very small amount of radiation compared with natural background sources. The typical cruising altitude of commercial flights exceeds 10,000 m, whereas the effective dose rate can range up to 7 μSv/hour (i.e., >150-fold greater than exposure to cosmic radiation at

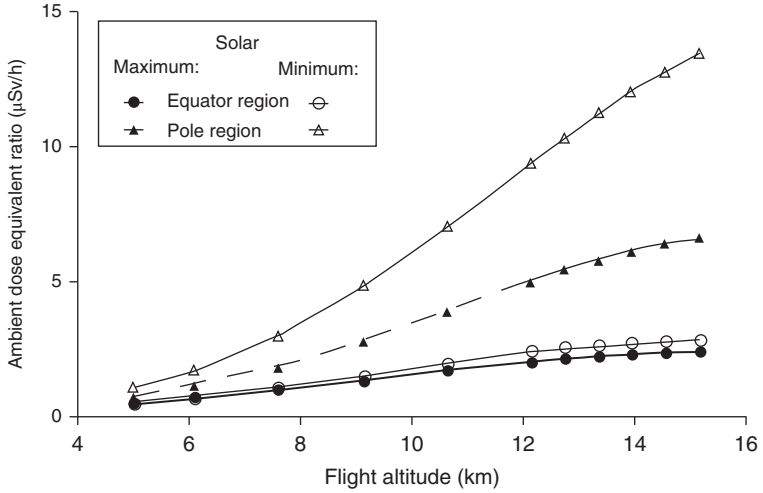


FIGURE 38.2. Ambient dose rates (μSv/hour) as a function of altitude, solar maximum/minimum, and polar/equatorial regions. One kilometer equals 3,280.84 feet. (Di Trolio et al.).[19]

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sea level).[20] The average dose equivalent rate for cosmic and terrestrial radiation on the ground in the United States is ~0.06 μSv/hour compared with a dose equivalent rate of 6 μSv/hour from cosmic rays at 35,000 ft, ranging from 2–10 μSv/hour, depending on altitude, latitude, and solar activity.[18] The sun typically emits particles with energies too low to contribute to the annual effective dose rate even during flight; however, rare, unpredictable solar events may produce high-energy particles that can increase the dose equivalent rate by ~10-fold on aircraft at 41,000 ft (0.1 mSv/hour).[21] The effective radiation dose from spending a 10-day vacation in a high mountain region is the same dose of cosmic radiation a passenger receives flying from London to New York.

Occupational Exposure

The effective radiation dose rates from aircraft flights depend on altitude, geomagnetic latitude, and the solar cycle. Table 38.4 lists the estimated dose equivalents from cosmic radiation during various air routes to and from selected US airports. Frequent flyers (e.g., business/government personnel) and most crewmembers receive annual dose equivalents near 1 mSv (~200 hours exposed to ~5–6 μSv/hour), whereas some crewmembers flying frequent polar routes may receive radiation doses several times higher depending on the duration of the flights.[7] Flight times in the United States typically are ~900 hours compared with ~600 hours for European crewmembers. Except in unusual circumstances, airplane crewmembers typically receive an effective annual dose rate of <10 mSv with exposure conditions much more uniform than in the nuclear industry. Estimates of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) for the annual effective dose rate of airplane crewmembers range from a few mSv (1.2–5 mSv) up to ~6–7 mSv, depending on flight routes and hours.[22] The higher values in Europe apply to Denmark, Finland, and Germany. Use of more recent radiation weighting factors reduces these doses by ~30%.

Astronauts in low earth orbit receive radiation from galactic cosmic radiation, solar energetic particles, electrons, and protons in the earth's radiation belts, and, to a lesser extent, neutrons and protons resulting from the interaction of cosmic radiation with the earth's atmosphere. The typical whole-body dose equivalent

TABLE 38.4. Dose equivalents from galactic cosmic radiation received during flights. (Adapted from Friedberg et al.).[18]

Origin–Destination	Peak Altitude (ft / m)	Airtime (hours)	Block Time (hours)[a]	Single-Flight Dose Equivalent (μSv)[b]	Annual Flight Crew Exposure[c] (mSv)
New York–San Juan	37,000 / 11,278	3.0	3.5	13	3.5
Chicago–New York	37,000 / 11,278	1.6	2.0	8.5	4.0
New York–Chicago	39,000 / 11,887	1.8	2.3	12	5.0
Lisbon–New York	39,000 / 11,887	6.5	6.9	41	5.6
London–New York	37,000 / 11,278	6.8	7.3	49	6.4
New York–Seattle	39,000 / 11,887	4.9	5.3	36	6.5
Tokyo–New York	41,000 / 12,497	12.2	12.6	91	6.9
New York–Tokyo	41,000 / 12,497	13.0	13.4	99	7.0
Athens–New York	41,000 / 12,497	9.4	9.7	93	9.1
Chicago–San Francisco	39,000 / 11,887	3.8	4.1	26	6.0
San Francisco–Chicago	41,000 / 12,497	3.8	4.1	29	6.7
Chicago–London	37,000 / 11,278	7.3	7.7	56	6.9
London–Chicago	39,000 / 11,887	7.8	8.3	62	7.1
Honolulu–Los Angeles	40,000 / 12,192	5.1	5.6	25	4.2
Washington, DC–Los Angeles	35,000 / 10,668	4.7	5.0	24	4.6
Tokyo–Los Angeles	37,000 / 11,278	8.8	9.2	46	4.7
Los Angeles–Tokyo	40,000 / 12,192	11.7	12.0	62	4.9
London–Los Angeles	39,000 / 11,887	10.5	11.0	80	6.9
Denver–Minneapolis	33,000 / 10,058	1.2	1.5	4.7	3.0
Seattle–Portland	21,000 / 6,401	0.4	0.6	0.1	0.2

[a] Block time represents the time from leaving blocks before takeoff and reaching blocks after landing; [b] Estimated dose equivalent for airtime; [c] Estimated yearly workplace dose to flight crew based on 950 block hours for the same flight.

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TABLE 38.5. Estimated annual effective dose from ingestion of radionuclides from the uranium and thorium series. (Modified from United Nations Scientific Committee on the Effects of Atomic Radiation).[11]

Radionuclide	Committed Effective Dose (μSv)			
	Infants	Children	Adults	Age-Weighted
^{238}U	0.23	0.26	0.25	0.25
^{234}U	0.25	0.28	0.28	0.28
^{230}Th	0.42	0.48	0.64	0.58
^{226}Ra	7.5	12.0	6.3	8.0
^{210}Pb	40.0	40.0	21.0	28.0
^{210}Po	180.0	100.0	70.0	85.0
^{232}Th	0.26	0.32	0.38	0.36
^{228}Ra	31.0	40.0	11.0	21.0
^{228}Th	0.38	0.30	0.22	0.25
^{235}U	0.011	0.012	0.012	0.011
Total	260.0	200.0	110.0	140.0

Committed effective dose/year with weighting factors for age (infants, 0.05; children, 0.30; adults, 0.65).

received by an astronaut during a mission ranges from 1–10 mSv. Although no large solar events have occurred during these missions, radiation from solar flares may increase this dose by 100-fold.[1] Typical daily dose rates at the ~300 km altitude of the International Space Station range from ~35 μGy at the solar maximum to ~140 μGy at the solar minimum.[17]

Cosmogenic and Primordial Radionuclides

Radiation doses from cosmogenic radionuclides are substantially less than those from primordial radionuclides. The estimated annual committed effective dose rates (committed effective dose equivalent or effective dose rates) for the main cosmic radionuclides are as follows: ^{3}H, 0.01 μSv (0.00001 mSv); ^{7}Be, 0.03 μSv (0.00003 mSv); ^{14}C, 12 μSv (0.012 mSv); and ^{22}Na, 0.15 μSv (0.00015 mSv).[11] For external exposure to γ-radiation from terrestrial (primordial) radionuclides, the estimated population-weighted average annual effective dose rate is 0.48 mSv (indoors, 0.41 mSv; outdoors, 0.07 mSv). Results for individual countries typically range from 0.3—0.6 mSv, with outdoor rates lower than indoor rates depending on the percentage of wood-frame construction. External dose rates may increase by 10–100-fold in areas of thorium-containing monazite sand deposits (e.g., Madras and Kerala, India; Guarapari, Brazil), radium-containing hot springs, and volcanic soils. The concentration of ^{40}K in the soil is highly variable (i.e., 0.3–4.5%) with this radionuclide comprising 0.0118% of naturally occurring potassium.[12] The estimated annual effective dose rate from the ingestion of ^{40}K is 0.165 mSv for adults and 0.185 mSv for children. The concentrations of uranium and thorium radionuclides in food vary significantly because of differences in agricultural practices, climatic conditions, and baseline background values. Table 38.5 lists the estimated annual effective dose rate for the ingestion of uranium and thorium series radionuclides by the general population including infants and children; the values are given in μSv (0.001 mSv) based on UNESCAR calculations.

The inhalation of short-lived progeny of ^{222}Rn and ^{220}Rn provides the main exposure pathway for the lungs because of pulmonary energy deposition by α particles and smaller amounts of β-particles and γ-rays. The effective dose rates for these two radionuclides in outdoor air are highly variable secondary to diurnal and climatic changes with the values much smaller than indoor values. The estimated annual effective dose rate for outdoor exposure is 0.095 mSv compared with 1.01 mSv for indoor exposure.[11] Inhalation of these radionuclides from the uranium and thorium series is dominated by ^{210}Pb and ^{210}Po with these two radionuclides accounting for 70% and 20%, respectively, of the total committed effective dose rate of ~0.12 mSv.

CLINICAL RESPONSE

Environmental Exposure

The risk of developing terminal cancer from exposure to cosmic radiation is sufficiently small to complicate the detection of increased mortality in epidemiology studies.[23] Table 38.6 demonstrates the size of a cohort necessary to detect a statistically significant increase in the incidence of leukemia-related deaths from cosmic radiation. These data assume a power of 90% and an α of 0.05. These data indicate a cohort size of 1 million persons is necessary to detect a 60% increase (risk ratio = 1.6) in leukemia-related deaths at an excess annual dose rate of 20 mSv; the estimated annual effective dose rate from natural background radiation is ~2.5 mSv.[7]

Most aircraft passengers are occasional flyers; these individuals absorb negligible amounts of cosmic radiation during flight compared with total radiation exposure.[20]

Occupational Exposure

Epidemiological data demonstrate no clear relationship between annual flight duration, corresponding doses of cosmic radiation, and an excess risk of radiation-related cancers. Some studies report an increased incidence

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TABLE 38.6. Risk ratios, mortalities, radiation doses necessary to document a significant increase in leukemia mortality, given various sizes of control and exposed populations in a cross-sectional study. (Adapted from National Council on Radiation Protection and Measurements)[7]

Length of Observation (person-years)	Required Risk Ratio[a]	Required Annual Mortality/ Million Exposed (Total/Excess)[a]	Excess Dose Rate (mSv/year)[a]
1,000	124	8,700/8,600	4,300
10,000	15	1,070/1,000	500
100,000	3.3	230/160	80
1,000,000	1.6	110/40	20

[a] Expected leukemia mortality is 70/year/1 million persons with a lifetime risk factor coefficient of 2/year/million persons exposed to 1 mSv/year.

of certain types of cancer among flight crews, whereas other studies fail to demonstrate similar associations. Cohort studies of aircraft crews suggest excess risks of melanoma and nonmelanoma skin cancer, whereas the association with breast and brain cancers is weak. Other risk factors (e.g., lifestyle) and study biases potentially account for the excess risk of these cancers (e.g., skin cancers).[19,24] Increased incidence of skin cancers among airline cabin crews is the most consistent positive finding in epidemiological studies of pilots and cabin crews. A UK study of flight crewmembers did not detect an elevated incidence of skin cancers or a trend of increasing skin cancer rates with flight time.[25] In this study of 19,494 flight crews and air traffic control officers (controls), the standardized incidence ratio for skin melanoma was 1.87 (95% CI: 1.45–2.38) for members of the flight crew compared with 2.66 (95% CI: 1.55–4.25) for air traffic controllers (controls) based on cancer rates in the general UK population. The elevated SIR resulted from lifestyle (i.e., easily sunburned skin, sunbathing to obtain a tan) based on reviews of medical records and postal questionnaires (50% response rate). The overall incidence of cancer was relatively low in both groups, primarily due to lower prevalence of smoking in these groups compared with the general UK population.

Although some studies report a higher incidence of breast cancer among female cabin crews,[26] most other studies failed to demonstrate an association between breast cancer incidence and cumulative estimates of cosmic radiation, sleep rhythm disruptions, or time zones crossed.[27,28] Neither cosmic radiation nor circadian rhythm disruption explain the elevated breast cancer risks in the suggestive studies. Increased nulliparity, height, and alcohol intake among female cabin crewmembers compared with the general population may account for some of the differences in the studies.[29] In a pooled cohort study of 93,771 airplane crewmembers from 10 countries followed for a mean of 21.7 years (2.0 million person-years), the overall mean mortality rate was strongly reduced in male cockpit (SMR = 0.56, 95% CI: 0.54–0.58) and female cabin crews (SMR = 0.73, 95% CI: 0.69–0.77).[30] The mortality from radiation-related cancers was also reduced in male cockpit crews (SMR 0.73, 95% CI: 0.62–0.85) but not in cabin crews (SMR ≅ 1). Mortality from female breast cancer (SMR = 1.06, 95% CI: 0.89–1.27), leukemia, and brain cancer was similar to that in the general population. The study suggested increased mortality from malignant melanoma, particularly in male cockpit crews (SMR = 1.57, 95% CI: 1.06–2.25). Interpretation of these studies is complicated by the healthy worker effect; airplane crewmembers typically have lower rates of hypertension, obesity, and smoking along with increased physical activity when compared to the general population. Additionally, some studies suggest diagnostic scrutiny may have a stronger influence on melanoma incidence than overall UV radiation.

DOSIMETRY

Analytical Methods

The complexity of particles and energy in cosmic radiation complicates the quantitation of effective dose rate during flight; instruments designed to measure this radiation are bulky and have limited accuracy. Consequently, validated computer models are available to estimate the effective dose rate of aircraft crews and passengers with accuracy of 20% within the measured median.[3] The International Commission on Radiation Protection and Measurements recommends the use of validated computer models to retrospectively estimate individual radiation doses from airplane flights instead of measurement devices (e.g., dosimeters).[3] These programs divide the route of the flight through the atmosphere into cubes with the mean effective dose rate in each cube dependent on the altitude, geomagnetic latitude, and solar modulation. Decreasing solar activity allows more galactic radiation to reach the atmosphere, resulting in increased high-altitude

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radiation doses.[31] Typically, changes in the standard flight path do not significantly alter the estimated mean effective dose rate.[32] The cosmic radiation field in the aircraft is relatively uniform; consequently, the exposure of individual passengers and crew is similar.

Abnormalities

Cytogenic studies indicate that some cell damage occurs in astronauts and cosmonauts as a result of cosmic radiation present in the thin atmospheres of their orbiting vehicles.[33] A study of peripheral lymphocytes from seven astronauts demonstrated an elevated incidence of chromosome-type aberrations but not chromatid-type aberrations when comparing blood samples before and after space flights; one astronaut had several multi-chromosomal-type aberrant cells (rogue cells).[34] The frequency of the chromosome-type aberrations was correlated to the estimated dose of cosmic radiation. All 16 astronauts tested within 1 month of long-term space flights (i.e., >3 months) had a higher frequency of chromosome exchanges than their preflight yield.[35] There was a trend of declining exchanges with time after space flight; however, this trend was not present in all astronauts. Studies of 36 cosmonauts demonstrated similar results with an increased incidence of chromosomal aberrations (dicentrics, centric rings) in post-space flight evaluations; this cytogenic damage decreased over 1.5–2 years after the flights, but the values did not return to preflight values.[36] The mean dose of space radiation was 110 mGy. The evidence of chromosomal aberrations in airplane flight personnel is less consistent. A study of 59 female cabin attendants, 31 station ground personnel, and 56 female clerks did not detect a statistically significant difference in the frequency of dicentric chromosomes between the 3 groups.[37] Similarly, the frequency of chromosome translocations in peripheral blood lymphocytes of 83 airline pilots and 50 control personnel did not differ statistically; however, the frequency of translocation in the pilots correlated to flight years ($P = 0.01$) with rate ratios of 1.06 (95% CI: 1.01–1.11) for a 1-year incremental increase in flight and 1.81 (95% CI: 1.16–2.82) for a 10-year incremental increase in flight years.[38] Positive studies included an 8-fold increase in dicentric chromosomes in 18 Concorde pilots (mean effective dose rate, 11–37 mSv/year) compared with 10 controls[39] and statistically increased relative risks of translocations (adjusted OR = 5.1, 95% CI: 1.5–17.3) and gaps/breaks (adjusted OR = 7.8, 95% CI: 2.4–24.9) in 48 male airplane crewmembers working long-haul flights.[40] The control group contained 48 ground staff.

HEALTH SURVEILLANCE

Risk Assessment

There is little direct evidence that exposure to typical natural ionizing radiation doses in the environment (i.e., <100 mSv) produces adverse health effects; however, excess cancer is *assumed* to occur as a result of low-level radiation exposure because a threshold dose for cancer development is not generally accepted for protection purposes.[4] Risk estimates for natural radiation are extrapolated from high-risk groups (e.g., Japanese atomic bomb survivors, workers in nuclear facilities, patients exposed to high radiation doses). The values obtained from these risk estimates depend on several factors including 1) the type of mathematical model (linear, quadratic, linear-quadratic) chosen, 2) the dose rate effectiveness factors used to extrapolate acute dose to chronic exposure, 3) the type of health effect (cancer deaths, cancer incidence, genetic, miscarriages), and 4) the age of the population. The International Commission on Radiological Protection (ICRP) uses an estimate of 0.05 cancer deaths per Sv for the general population. Using the ICRP estimate, the expected annual cancer deaths in a population of 30 million exposed to an annual effective dose equivalent of 2.5 mSv would be 3,750.

Environmental Monitoring

The ICRP recommends setting reference levels for occupational exposure to cosmic radiation within a range of 1–20 mSv, primarily in the 5–10 mSv range, as an effective annual dose rate.[3] The selected reference value represents the upper limit of the dose level with the actual level reduced as low as reasonably achievable given prevailing social and economic factors. The main action to reduce radiation exposure in aviation is the adjustment of flight schedules for the highest-exposure worker by altering flight times and routes (i.e., latitude, altitude). Shielding the aircraft fuselage is not practical because of the added weight necessary to reduce radiation exposure. Several limitations restrict the overall effectiveness of these measures to reduce radiation exposure including increasing the number of workers exposed to radiation (if flight time increases) and increasing the risk of accidents, flight distances, time, and costs due to rerouting.

Other ICRP recommendations for aircraft crews include 1) an educational program to inform the flight crew individually about cosmic radiation, 2) assessment of the radiation dose using a validated computer model, 3) keeping records of the individual and cumulative dose of the crew; these records should be kept

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for the lifetime of the individual, and 4) adjusting the flight roster when appropriate based on selected dose reference level in consultation with the crewmember.[20] For frequent flyers, the Commission recommends self-assessment of the individual's dose and adjustment as needed. Pregnant frequent flyers may also need to adjust their flight exposure based on their assessment of exposure. Frequent flyers (i.e., >500 hours/year) should be managed similarly to aircraft crews. Occasional flyers do not usually require measures to protect them from cosmic radiation.

Medical Screening

The IRCP recommends annual assessment of the effective radiation dose rate for aircraft crewmembers based on validated computer models of individual flight times and routes. Although real-time alert systems are not recommended, the IRCP recommends the occasional use of on-board ambient monitoring to verify dose calculations of cumulative radiation exposure. Aircraft crews undergo routine medical evaluations for reasons other than cosmic radiation exposure; exposure to cosmic radiation does not require any specific additional medical examinations. After a woman becomes pregnant, working conditions should be adjusted to ensure the additional radiation dose to the embryo/fetus during the rest of the pregnancy does not exceed a total dose of 1 mSv.

RADON

PHYSICAL PROPERTIES

Radon is a colorless, odorless, tasteless, nonirritating, chemically inert, noble gas emitted from rocks (e.g., granite) containing uranium; this substance is the heaviest noble gas in the uranium decay series. Radon has an atomic number of 89. Air pressure inside houses is usually lower than outside air pressure; therefore, soil gas containing radon tends to enter dwellings. Most of the natural radiation dose from radon results from the emission of α-particles during the decay of radon to polonium, lead, and bismuth. When discussing radiation exposure, the term "radon" commonly encompasses all radon isotopes and their short-lived decay products produced by the radioactive decay of the uranium and thorium series. Although there are 25 radon isotopes, only 3 of them occur naturally. ^{226}Ra is an intermediate decay product (fifth progeny) of the ^{238}U series; ^{226}Ra decays directly to radon (radon-222, ^{222}Rn). ^{219}Rn (actinon) is a relatively rare, short-lived radon isotope formed from ^{235}U decay. The physical half-life of ^{219}Rn is 4 seconds. Radioactive decay of the ^{232}Th with emission of an α-particle produces ^{220}Rn (thoron); radioactive decay of the ^{238}U series does not result in the formation of ^{220}Rn.

^{222}Rn is the most stable radon isotope with a physical decay half-life of 3.82 days compared with ^{218}Po. Figure 38.3 displays the decay scheme of ^{222}Rn that ultimately produces the stable isotope ^{206}Pb. Radon progeny are decay products of ^{222}Rn outlined in the heavy boxes on Figure 38.3. These progenies emit primarily α-radiation in the following proportion: ^{214}Pb – 52%, ^{214}Bi – 38%, and ^{218}Po – 10%.[41] The diffusion of radon is limited with 90% of radon decaying before traveling 5 m in air, 5 cm in water, or 2 m in soil.[42] The immediate progeny of radon are positively charged, radioactive isotopes of solid elements that rapidly form particles with water molecules. These particles are small (i.e., ~0.001 μm), highly mobile, and attach to aerosol particles that are ubiquitous in air.[43] The progeny of ^{222}Rn settle on the pulmonary surface after attaching to aerosol particulates.

EXPOSURE

The radioactive decay of the ^{238}U series causes the slow, continuous formation of radioactive gaseous (radon) that subsequently produces α-emitting, reactive solids (termed radon progeny, radon progeny). Radon is a relatively inert noble gas that emanates primarily from soil and, to a lesser extent, from water. The adverse health effects of radon result from its decay products (radon progeny). Both radon and its progeny emit α- and β-particles as well as γ-radiation; however, most toxicity ensues from α-radiation emitted from airborne particles (dust, water droplets) containing radon progeny rather than from the original gaseous radon. Deposition of these radon progeny in the lungs results in irradiation of the pulmonary lining with α-radiation and an increased lung cancer risk.

Potential occupational sources for ^{222}Rn include underground mines, oil or natural gas extraction, and cement or phosphate production.[45] Calibration of measuring instruments is the only commercial application of radon in the United States; radon is no longer used in radiology or cancer radiotherapy.

Sources

Radon is a ubiquitous, radioactive gas in soils and, to a lesser extent, some building materials that results

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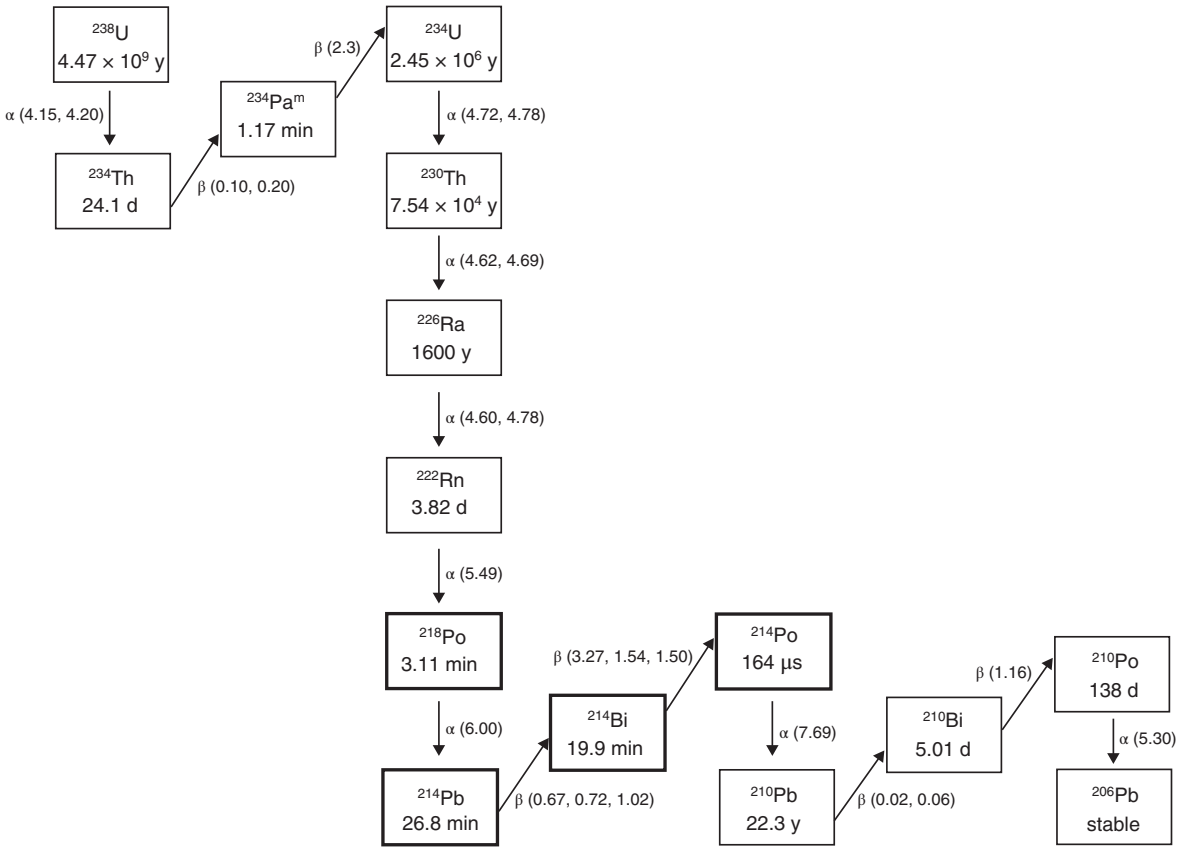


FIGURE 38.3. Principal decay scheme for ^{238}U to stable ^{206}Pb including radon and radon progeny (bold outline) with associated half-lives. *Abbreviations:* α = alpha particle, β = beta particle, d = days, min = minutes, µsec = microseconds, y = years. (Samet).[44]

from the decay of the ^{238}U series and specifically the decay of ^{226}Ra following the emission of an α-particle. ^{222}Rn contributes ~50–70% of the absorbed radiation dose from the natural environment,[46] whereas overall radon exposure represents 37% of the total effective dose of ionizing radiation in the general population compared with 48% from medical procedures and 15% from background cosmic and terrestrial radiation.[47] The quantity of ^{226}Ra in earth materials is not a direct determinate of the amount of ^{222}Rn present in the air; however, the content of ^{226}Ra in the ^{238}U series is an indicator of the potential for radon production in the soil and bedrock. Although the amount of ^{220}Rn from the ^{232}Th series and ^{222}Rn from the ^{238}U series produced in the environment is similar, the short physical half-life (56 seconds) and poor aerosolizing properties of ^{220}Rn limit environmental concentrations and adverse health effects of ^{220}Rn. Typically, the average airborne ^{220}Rn concentration is 5-fold lower than ^{222}Rn; uranium mines do not usually contain clinically significant amounts of ^{220}Rn.[42] US Mine Health and Safety Administration data indicate uranium and vanadium mines contain the highest median potential alpha energy concentrations (PAECs) as measured in WL units.[48] Potential radon exposure in the occupational setting includes phosphate production, tourist caves, and waterworks. Phosphate rock commonly contains uranium, radium, and thorium impurities with uranium concentrations in US deposits ranging from 10–400 ppm.[49]

High natural background radon concentrations occur in several areas around the world including Brazil (Guarapari, in the Atlantic coast state of Espirito Santo; Pocos de Caldas, Araza, and Tapira in the Minas Gerais State), China (Yangjiang County, Gaungdong Province in south China), India (Kerala region in southwest India), and Iran (Ramsar in coastal city in northern Iran).[50] A typical classification system for separating radon exposure based on an annual effective dose involves 1) *low*, ≤5 mSv, 2) *medium*, 5–20 mSv, 3) *high*, 20–50 mSv, and 4) *very high*, >50 mSv.[51] The upper bound of the low category represents twice the mean background natural radiation, whereas the high category begins at the upper guideline for occupational exposure. Breathing air containing 300 Bq/m^3 for 1 year

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corresponds to an effective annual radiation dose of 5 mSv. The Committee on the Biological Effects of Ionizing Radiation (BEIR VII) considers cumulative linear energy transfer (LET) radiation below 100 mSv as a low dose, whereas medium- and high-level categories are not typically relevant to environmental studies.[52]

Soil adjacent to a house is the primary radon source rather than drinking water or building materials.[53] The entry of radon into structures is highly variable depending on primarily 1) a constant input rate (~80% of the total input in calm weather) from the diffusion of ^{222}Rn through floors and walls, and 2) a variable rate resulting from the indoor-soil pressure differentials.[54] The amount of radon emanating from building materials depends on the amount of ^{226}Ra present in the material and the radon fraction released from the material. In a study of building materials and radon, the emanating radon fraction from building materials averaged 4% of the total radon dose with a range of 0.3–12%.[53] In poorly ventilated masonry buildings, the percent of the total dose of radon contributed by the cement blocks ranged up to 20%.[55] The radon in soil gas diffuses through rocks and soil into subsurface air pockets with radon concentrations exhibiting a diurnal cycle. Minimum levels occurred at sunset, whereas maximum concentrations arose at sunrise.[56] Radon enters the house through cracks and pores caused by the pressure differential between the soil and the house. The ventilation rate controls radon transport within the structure.[57]

Concentrations

The amount of radon diffusing from soil into homes depends on the following factors: porosity of the soil, occupant activities, tightness of the house construction, local ^{226}Ra concentration, pressure differential between the inside and outside of the house, humidity, wind conditions, and the home temperature compared with the soil. Typically, the amount of indoor radon is an order of magnitude greater than outdoor radon concentrations as a result of differences in ventilation and dispersion.[5] In well-ventilated houses (2 air exchanges/hour), the level of radon decay products is ~30% of the radon concentration in contrast to ~50% without significant ventilation.[43] Reducing the ventilation rate from 1 air exchange/hour to 0.5 air exchanges/hour increases the annual effective radon dose equivalent to 2.83 mSv from 1 mSv.[58] The construction of tight, energy-efficient buildings with increased weather stripping and subsequent reduced ventilation can increase indoor radon levels by a factor of ~50%.[59] However, the differential in radon levels between floors in the same home is small compared with the differential between the same floor in different homes.[53,60] The main driving force for the migration of radon from cellars to the upper floors of a home is called the stacking effect.[61] This effect results from the development of a pressure differential across vertical walls separating air masses with different temperatures. Heating a structure and opening windows to decrease the indoor–outdoor pressure differential strongly influence the diurnal cycle of radon levels.

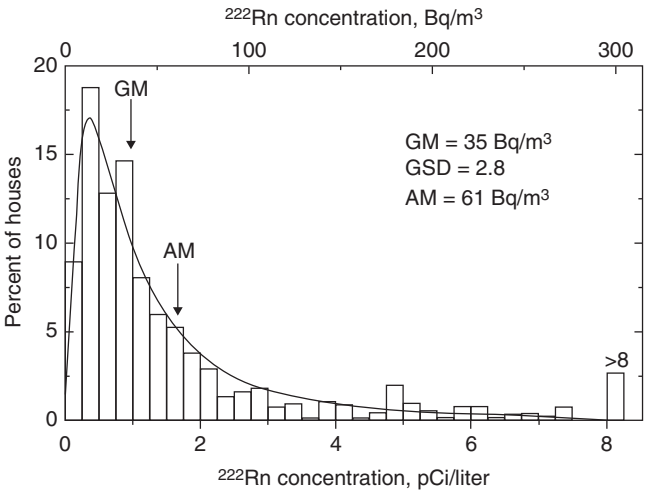


FIGURE 38.4. The probability distribution of ^{222}Rn in 552 US homes with the associated geometric mean (GM), geometric standard deviation (GSD), and arithmetic mean (AM). (Redrawn from Nero et al.).[62]

The radon level in homes follows a log-normal pattern with most homes containing relatively low radon levels and a small number with moderate-to-high radon levels.[62] Radon levels in homes in the United Kingdom and the United States vary by >2 orders of magnitude; radon exposure at work and home is usually similar unless the work involves underground exposures.[53,63] Figure 38.4 demonstrates the probability distribution of radon in a convenience sample of 552 US homes, where the geometric and arithmetic means were 35 ± 2.8 Bq/m^3 and 61 Bq/m^3, respectively. In a UK study by the National Radiological Protection Board, the mean indoor and outdoor radon concentrations were 22.3 Bq/m^3 and 3.5 Bq/m^3, respectively.[64] A collaborative analysis of radon data from 13 case-control studies of residential radon and lung cancer demonstrated a mean radon concentration of 104 Bq/m^3 in 7,148 homes of lung cancer patients compared with 97 Bq/m^3 in 14,208 control homes.[65] The estimated radon concentration for each individual was calculated as a time-weighted average of the measured radon concentrations in all the homes occupied over the past

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5–34 years (based on a latent period of 5 years) with weights proportional to the length of time the individual had lived in each home. Radon concentrations are not constant within a building. Typically, radon concentrations are highest in basements with concentrations declining as the elevation increases from ground level.

A study of US homes indicated that the average radon concentration was 55.5 Bq/m^3 (1.5 pCi/L), with 1–3% of the homes demonstrating levels of >296 Bq/m^3 (>8 pCi/L).[63] This study demonstrated a geometric mean of 33.3–103.6 Bq/m^3 (0.9 ± 2.8 pCi/L). In the Reading Prong area of eastern Pennsylvania, the highest indoor radon concentration was 74,000–111,000 Bq/m^3 (2,000–3,000 pCi/L).[66] The highest average radon level in a UK study occurred in Devon and Cornwall, with ~5% of the homes exceeding 400 Bq/m^3. In California, only 0.8% of 310 homes surveyed for radon exceeded the recommended radon limit of 148 Bq/m^3 (4 pCi/L), whereas the radon level did not exceed 740 Bq/m^3 (20 pCi/L) in any house.[67] In an analysis of two national Swedish studies of radon and cancer, the mean radon concentrations in these dwellings were 113 Bq/m^3 in 1990 and 90 Bq/m^3 in 2008, with 8% of the studied population living in houses with >200 Bq/m^3.[68]

ENVIRONMENTAL FATE

Radon acts as a carrier of α-particle decay energy from the ground to the biosphere. In the atmosphere, aerosols absorb the short-lived progeny (^{214}Bi, ^{214}Pb, ^{214,218}Po). The direct source of radon and its decay products is the presence of ^{226}Ra in building materials, soils, water, and natural gas. The 3.82-day half-life of ^{222}Rn allows the diffusion of this noble gas into air or water over substantial distances.

Soil

The crystalline structure in radioactive rocks (e.g., granite, shale, phosphate) tightly binds the radon released by the radioactive decay of ^{238}U and ^{226}Ra. Heavily fractured rocks containing uranium allow radon to be released into the atmosphere. The southwest portion of England contains the highest radon concentration in that country, even though the risk of lung cancer in that area is comparatively low.[69] Most soils including granite contain 1–4 ppm uranium, whereas phosphate-rock formations in Florida comprise up to 120 ppm uranium.[70] In the United States, the Reading Prong area of Pennsylvania, New York, and New Jersey also possesses unusually high uranium concentrations. Underground uranium mines possess the highest radon risk from exposure to radon progeny, silica dust, diesel fumes, and cigarette smoke. Significant radon concentrations may also occur in iron ore, fluorspar (fluorite), gold, lead, potash, tin, and zinc mines.

Water

Radon levels are relatively low in surface water compared with groundwater; the radon concentrations in groundwater range from 200–600 pCi/L (~7–22 Bq/L). Radon diffuses through groundwater with the mechanical flow of the water. Because the water solubility of radon is low and the half-life is short, most radon decay occurs before the release of radon gas from groundwater. Radon concentrations in large aquifers average ~240 pCi (8.8 Bq) ^{222}Rn/L water; however, water in private wells may demonstrate radon concentrations two to three times higher.[71] In a German study of 582 public drinking-water samples, the radiation dose from ^{222}Rn ranged from <1.3–1,800 Bq/L, with a median of 7.3 Bq/L and a 95th% of 140 Bq/L.[72] Hence, groundwater is not a significant radon source (i.e., usually <10% of the annual effective dose of radiation) compared with radon release from soil, unless the radon concentration in well water is ≥300 Bq/L water.[73] Radon gas can transfer from water to air during water treatment. The geometric mean of the annual average airborne radon concentration of workers in water treatment plants was 3.4 pCi/L (126 Bq/m^3) with a maximum of 133 pCi/L (4,921 Bq/m^3).[74] Radium concentrations in the oceans do not contribute significantly to the radon burden in air because the radium concentrations in groundwater are three to four orders of magnitude less than soil concentrations.[42]

Air

Radon release from ^{226}Ra in soil is the dominant radon source in the atmosphere.[57] The rate of emanation is highly variable depending on several factors including temperature, humidity, barometric pressure, wind, soil moisture, and soil composition. Although most radon in groundwater decays before reaching the surface, the emanation of radon from groundwater is the second-largest radon source. An estimated 20% of the radon in the tailings from uranium and phosphate mines is released into the atmosphere; emanation rates of radon near these tailings range up to 1,000 pCi (37 Bq)/m^2/second. Negligible radon amounts reach the stratosphere. People working in caves (e.g., park service employees) may receive radon doses similar to underground miners; however, the casual visitor does not receive significant radon doses.[75]

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DOSE EFFECT

Estimation of the delivered dose of radon and radon progeny requires very complex mathematical models with the dose depending on multiple assumptions including time spent indoors/outdoors, aerosol kinetics and concentrations, size and distribution of particles, house ventilation, and the respiratory rate. The lungs exhale most of the radon reaching the tracheobronchial tree; hence, the short-lived decay products of radon (radon progeny, formerly "radon daughters") are the most clinically important component of the radiation dose following inhalation of radon.[76] Longer-lived radon progeny (e.g., ^{210}Pb, ^{210}Po) contribute minimal radiation doses to lung tissue because of the likelihood these progenies are eliminated by cellular or mucociliary transport prior to radioactive decay. Figure 38.5 displays the short- and long-lived radon progeny with their associated half-lives.

In epidemiology studies, the benchmarks for radon exposure are year-long measurements of contemporary radon concentrations with α-track detectors; temporal fluctuations result from differences in climate, environment, lifestyle, and structure of the homes. The estimated mean radon levels in US homes range from ~1–1.5 pCi/L (~37–56 Bq/m^3); this value correlates to ~20 WLM over a lifetime of 70 years.[77] An estimated 8.5 million US homes exceed the US action level of 148 Bq/m^3 (4 pCi/L) based primarily on short-term testing (i.e., ~98%).[78] In a study of 98 Minnesota homes from 1983–2000, the median radon concentration was 120 Bq/m^3.[79] Although median radon concentration within each house varied little year-to-year with no consistent temporal trends, annual radon doses varied by 3–110% (median = 26%) between individual sites. Climate, wind exposure, radon concentration, and building attributes (heat/ventilation systems, house structure) contributed to the variation. The daily radon dose derived from drinking water averages 3.7–22.2 Bq ^{222}Rn; these values represent ~2% of the daily US indoor dose. For the average individual in the United Kingdom, the estimated annual effective dose equivalent from radon decay products is ~0.8 mSv within a range of 0.1–100 mSv.[5]

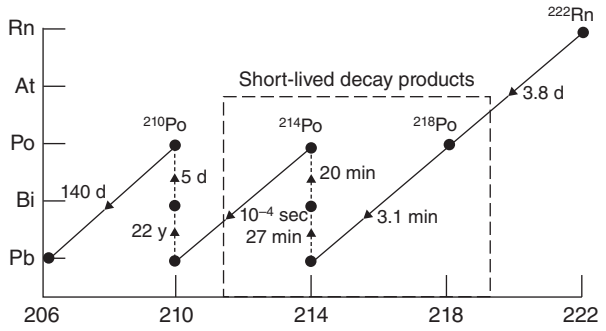


FIGURE 38.5. Short-lived decay products of ^{222}Rn to ^{210}Pb and subsequent conversion to stable ^{206}Pb. ^{214}Po and ^{214}Bi contribute negligible radiation doses because of their very short half-lives. (Kendall and Smith).[76]

Depending on assumptions about equilibrium, an annual radon dose of 1.3 pCi/L (~48 Bq/m^3) correlates to a pulmonary dose of 3.1–4.6 rem (31–46 mSv).[80] Using the ICRP weighting factors for radiation quality and tissue sensitivity, the NCRP action level of 200 Bq ^{222}Rn/m^3 air corresponds to an annual effective dose equivalent of 10 mSv.[64] The ICRP concluded that average annual radon concentrations of 200 Bq/m^3 and cumulative occupational concentrations of ~50 working level months (WLMs) are associated with a significantly increased lung cancer risk.[81] The radon dose for children may be higher than for adults because of differences in lung anatomy and minute ventilation rates.

TOXICOKINETICS

Absorption

Inhalation is the primary route of exposure to radon and its progeny. Radon is an inert gas that diffuses across alveolar membranes; however, the lungs exhale most inhaled radon before decay and emission of α-particles.[82] Radon progeny (daughters) attach to the surface of aerosol particles before depositing on the lining of the respiratory tract through impaction, diffusion, and sedimentation. Most deposition occurs in the tracheobronchial portion of the lung with the first bifurcation of the bronchi being the primary site.[57] Systemic radon absorption is minimal; therefore, sites other than the lung receive little radiation with the exception of the stomach and skin, depending on the amount of contact with radon progeny.[83]

Most radon absorption following ingestion of water occurs rapidly in the stomach and small intestine with ~1–3% crossing the epithelial lining in the large intestine.[84,85] Absorption is more complex for radon decay products than radon, occurring primarily in the small intestines with several absorption phases involving minutes to several hours.[86] Although data on the dermal absorption of radon are limited, experimental studies suggest dermal radon absorption is small; however, radon decay products may expose the skin to substantial α-radiation.[57]

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Distribution

The distribution of radon following inhalation depends on the physical properties of radon and its progeny. Although the radioactive decay of radon progeny is relatively short-lived, radon progeny contribute most of the radiation dose to the respiratory tract following radon exposures; these progeny are sufficiently long-lived to create complex toxicokinetic processes that govern transport and distribution, particularly because radon progenies are inhaled from the natural environment along with radon. The mucociliary mechanism transports radon particles to the trachea and the gastrointestinal tract. Radon concentrations in body organs can reach 30–40% of the systemically absorbed radon dose following chronic exposure; however, radon absorption is much lower from the gastrointestinal tract than the lungs.[87] The stomach wall receives the vast majority (i.e., ~95%) of the ingested radon dose depending on radon loss from the stomach; the estimated effective dose for 1 Bq radon in drinking water is 1×10^{-5} assuming a half-time of 20 minutes in the stomach.[88]

Elimination

Radon is an inert gas that does not interact chemically with cell constituents. The lungs eliminate most inhaled radon before significant radioactive decay occurs.[57] The biological half-lives of radon progeny in the lung range from ~6–60 hours, while the half-life in the upper airway near the carina is ~0.16–4.8 hours.[89,90] The urinary excretion of ^{210}Pb in uranium miners after cessation of radon exposure suggests the slow release of radon progeny from bone.[91] Experimental studies in humans indicate the lungs exhale >90% of an absorbed dose of radon from water within 100 minutes; ~1% of the absorbed dose remained in the body after 10 hours.[92] Except for slight differences in tissue solubility, ^{133}Xe and ^{222}Rn share similar kinetics; ^{133}Xe elimination studies are consistent with the rapid excretion of radon from the body. No radioactivity remained in the bodies of 5 volunteers exceeding 0.75 μCi 24 hours after the ingestion of a few mCi of ^{133}Xe.[93]

Maternal-Fetal Kinetics

Rodent studies suggest ^{222}Rn easily crosses the placenta to produce similar maternal and fetal radon concentrations, whereas all short-lived progeny do not diffuse through the placenta.[94]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Radon does not accumulate in the respiratory tract; consequently, radon toxicity results primarily from inhalation of α-radiation during the radioactive decay of radon progeny ^{218}Po, ^{214}Bi via β-, and γ-decay, and the essentially instantaneous decay of ^{214}Po to ^{210}Pb. The β- and γ-radiation from radon progeny is small compared with the α-radiation from radon progeny. The dose of α-radiation is much higher in the upper than lower bronchial epithelium; consequently, bronchogenic carcinoma is a common sequelae of radon exposure.[95] The ionizing radiation from α-particles penetrates bronchial epithelium to a depth of ~70 μm (5 cell diameters), resulting in DNA breakage, repair mistakes (deletion, insertion, rearrangement), chromosomal changes, gene mutations, genetic instability, apoptosis, dysfunctional regulatory genes, and ultimately malignancy.[96] Radon releases high linear energy transfer (LET) particles that produce indirect intranuclear damage via free radical formation. These reactive oxygen species alter p53 stability and damage individual DNA bases leading to point mutations and mispairing during DNA replication. Cigarette smoke strongly enhances the carcinogenic effects of radon in a supra-additive but sub-multiplicative relationship.[97] Both tobacco smoke and ionizing radiation induce oxidative stress via the formation of reactive oxygen intermediates. Subsequent base DNA damage, and potentially base excision repair errors, altered gene expression, and genomic instability.

Radon exposure is not associated with a specific histological subtype of lung cancer, with squamous cell carcinoma and adenocarcinoma being the most common subtypes in the East German study of 240 miners from the Wismut cohort; almost all miners in this group were smokers.[98] Early reports suggested small cell bronchogenic cancers accounted for most radon-induced lung cancers in miners exposed to radon progeny.[99] Subsequent studies of uranium miners indicate the incidence of small cell bronchogenic cancer may exceed the incidence in the general population; however, all types of lung cancer occur in uranium miners including squamous (epidermoid) carcinoma, small (oat) cell carcinoma, large cell carcinoma, adenocarcinoma, carcinoid tumors, and bronchial gland carcinomas.[60] Frequently, the tumor site is the upper airway near the carina, although the exact original location is often difficult to determine when the lung tumor is advanced. The sequencing of DNA exons of the p53 tumor suppressor gene in lung cancer from uranium miners suggests the lung cancer mutational spectrum

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of radon-induced cancer differs from the direct DNA sequencing of lung tumors associated with smoking.[100]

CLINICAL RESPONSE

Radon exposure is the second-most common cause of lung cancer in the United States behind tobacco smoking, whereas radon is the most common cause of lung cancer in never-smokers.[101] The US EPA estimates 5,000–20,000 annual cases of lung cancer occur in the United States from exposure to radon progeny whereas other reviews suggest the number of new lung cancer cases ranges from 3,000–33,000 cases.[102,103] The attributable risk of radon-induced lung cancer mortality varies between countries depending on radon distribution, exposure, and treatment. The estimated population attributable fraction for lung cancer induced by residential radon exposure was 8.3% in Switzerland and 5.0% in Germany.[104] The National Radiological Protection Board estimates ~1,500 UK deaths occur from radon exposure;[105] however, the risk of developing lung cancer from radon exposure is at least an order of magnitude below that of chronic smoking.[106]

Environmental Exposure

There is no evidence that radon exposure increases nonrespiratory mortality based on Cox proportional hazards regression models using ecological data from the American Cancer Society Cancer Prevention Study II on radon exposure (mean county-level residential radon concentration = 53.5 ± 38.0 Bq/m^3).[107]

Occupational Exposure

Diffuse interstitial fibrosis occurs in the lungs of some uranium miners; however, multiple potential etiologies for these diseases exist in uranium mines including silica, diesel exhaust, and tobacco smoke.[108] In a cohort of 58,690 German uranium miners followed from 1946–2008, 2,336 deaths were attributed to nonmalignant respiratory diseases including 715 deaths from chronic obstructive pulmonary disease (COPD) and 975 deaths from silicosis or other pneumoconiosis.[109] The relative risk of death did not correlate to cumulative radon doses. The mean estimated cumulative radon exposure was 280 WLM with a median of 33 WLM and a maximum of 3,224 WLM. Compared with the US population, standardized mortality ratios (SMRs) for interstitial pulmonary fibrosis were highly elevated in white (SMR = 3.95, 95% CI: 2.41–6.11, $n = 20$) and American Indian (SMR = 8.70, 95% CI: 4.17–16.0, $n = 10$) miners.[110] The SMR for pulmonary fibrosis in never-smokers was 4.1 (95% CI: 1.7–8.5). Pulmonary fibrosis is a common result of exposure to several types of agents (smoking, γ-radiation, silicosis, diesel exhaust). Misclassification of pulmonary disease and the cause of death also remains problematic because of the difficulty in differentiating pulmonary fibrosis from obstructive lung diseases and pneumoconiosis. The exact contribution of radon progeny to the development of diffuse pulmonary fibrosis remains unclear.

Carcinogenesis

The US National Toxicology Program (NTP) lists ionizing radiation including ^{220}Rn and ^{222}Rn as known to be a human carcinogen; the International Agency for Research on Cancer (IARC) classifies ^{222}Rn and its decay products as Group 1 (human) carcinogens based on increased lung cancer in uranium miners. Although most studies of uranium workers have not detected elevated risks of leukemia,[111] analysis of leukemia rates in Czech uranium miners provided some evidence for an association of cumulative radon exposure with an increased leukemia risk. However, coexposure to γ-radiation and other radionuclides confounded the results. Most case-control studies of children and adults have not detected an increased risk associated with residential radon exposure. Currently, there is no convincing evidence of nonpulmonary solid tumors associated with exposure to radon or radon progeny.

Residential

The results of ecological and observational studies associating documented radon exposure in homes with an increased lung cancer incidence are inconsistent, potentially resulting from potential recall bias, exposure misclassification, and wide variation in radon concentrations in homes and between geological areas, confounding from differences in smoking rates, and limited statistical power.[112] Most studies suggest a positive association; however, only a few of these studies demonstrated a statistically significant increase in lung cancer risk.[113,114] More recent analyses of pooled case-control study data indicate a consistent, relatively small increased risk of lung cancer with long-term radon exposure; the health implications of this excess risk are substantial because of the size of the population exposed to radon.

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Lung Cancer

A meta-analysis of 17 case-control studies demonstrated a positive dose-response relationship between residential radon exposure and lung cancer risks.[115] The pooled odds ratio ranged from 1.07 (95% CI: 1.04–1.11) for exposure to 50 Bq/m^3 to 1.24 (95% CI: 1.11–1.38) at 150 Bq/m^3 and 1.43 (95% CI: 1.19–1.72) at 250 Bq/m^3. Pooling studies restricted to women and excluding men increased the estimated odds ratio. In a prospective Danish cohort of 52,692 persons exposed to low to medium radon levels (median = 35.8 Bq/m^3) followed for ~10 years, the adjusted incidence rate ratio (IRR) for lung cancer was 1.04 (95% CI: 0.69–1.56) for all participants exposed to 100 Bq/m^3.[116] For nonsmokers, the IRR was 1.67 (95% CI: 0.69–4.04) with a dose-response trend. None of the associations were statistically significant. In a study of pooled data from 7 North American case-control residential studies involving 3,662 lung cancer cases and 4,966 controls, the estimated OR after radon exposure at a concentration of 100 Bq/m^3 5–30 years before the index date was 1.11 (95% CI: 1.00–1.28).[117] The estimate was compatible with extrapolation of the miner data to the residential radon concentrations determined by long-term α-track detectors; the downward extrapolated estimate was 1.12 (95% CI: 1.02–1.25). A Swedish case-control study of 586 women and 774 men with lung cancer demonstrated cancer risks consistent with the estimates based on data in miners.[118] The relative risk of residential exposure to radon concentrations of >10.8 pCi/L (>400 Bq/m^3) was 1.8 (95% CI: 1.1–2.9).

A population-based case-control study of 292 cases of small cell and nonsmall cell lung cancers in Swedish women demonstrated a statistically significant increased risk (RR = 2.2, 95% CI: 1.2–4.0) for women exposed to radon concentrations of >150 Bq/L air.[119] Radon exposure was based on the measurement of samples and locations near areas commonly associated with radon exposure and the measurement of samples from 10% of the residences rather than direct radon measurements. Smoking was not a major confounder in this study; however, a detailed smoking history was not available for the study participants. Another Swedish study of pathologically mixed lung cancer cases in 210 women with average radon concentrations of >150 Bq/m^3 (4 pCi/L) revealed a statistically marginally increased RR of 1.7 (95% CI: 1.0–2.9).[120] A systematic review of residential radon exposure and small cell lung cancer suggested lung cancer risks following radon exposure are greater for small cell lung cancer than nonsmall cell lung cancer;[121] a hospital-based case-control study also suggested the presence of *GSTT1* and *GSTM1* deletions increases susceptibility to lung cancer following radon exposure.[122]

Nonpulmonary Cancer

Ecological studies on cancer incidence and radon in drinking water have not clearly demonstrated an association between nonpulmonary tumors and residential radon exposure;[123] however, methodological limitations (limited sample size, exposure assessment, confounding) restrict conclusions regarding causation and dose effect at naturally occurring radon concentrations.[124] An ecological study of the incidence of monocytic leukemia, myeloid leukemia, and other childhood cancers suggested a positive association between regional estimates of radon exposure and these cancers;[125,126] however, a French study of acute childhood leukemia involving 2,763 cases and 30,000 population controls did not detect an increased acute leukemia risk with radon exposure, irrespective of the acute leukemia subtype or age group.[127]

Although a meta-analysis of 6 case-control studies on childhood leukemia reported an elevated overall odds ratio of 1.37 (95% CI: 1.02–1.82) comparing the highest and lowest residential radon exposures,[123] the evidence for an increased risk of childhood cancers (i.e., leukemia, lymphoma, central nervous system) from residential radon exposure is weak and inconsistent, primarily resulting from the uncertainty in the radon dose estimates. Residential radon exposures in Norway and Switzerland are relatively high compared with other European countries. A cohort study based on Norwegian population registers containing 712,674 children <16 years of age was followed from 1967–2009; the study identified 437 cases of childhood leukemia along with 427 cases of central nervous system cancers.[128] The geo-coded radon exposures did not detect significant differences in geometric mean radon concentration between leukemia cases (89.1 Bq/m^3), CNS cancers (100.2 Bq/m^3), and the overall cohort (91 Bq/m^3). After adjustment for confounders, the hazard ratio for childhood leukemia and estimated radon exposure was not significant, whereas the hazard ratio for childhood CNS cancers was borderline significant (17% increase/100 Bq/m^3) following exposure before 5 years of age. The association was not significant for CNS cancer when comparing high (>200 Bq/m^3), medium (100–199 Bq/m^3), and low (<100 Bq/m^3) estimated radon exposures. Similarly, a prospective, census-based cohort study of Swiss children of <16 years of age did not detect elevated adjusted hazard ratios for overall childhood cancers (0.93, 95% CI: 0.74–1.16), all childhood leukemias (0.95, 95% CI: 0.63–1.43), or childhood CNS tumors (1.05, 95% CI: 0.68–1.61) when comparing children with estimated radon exposure below the median (<77.7 Bq/m^3) and ≥90% (≥139.9 Bq/m^3).[129] A study of childhood

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lymphoma using the Texas Cancer Registry ($n = 2{,}147$), US Census data, and the Texas Indoor Radon Survey did not demonstrate evidence of increased adjusted incidence rate ratios of overall lymphoma or lymphoma subtypes (Hodgkin, Non-Hodgkin, Burkitt) and estimated residential radon exposures with the exception of diffuse large B cell lymphoma (aIRR = 1.73, 95% CI: 1.03–2.91; $n = 315$).[130] The adjusted incidence of the latter lymphoma subtype did not display a dose-response relationship with estimated residential radon exposure.

Workplace

Lung Cancer

The lung is the primary target organ of radon exposure with excess lung cancer risks known in underground miners from the Erz Mountains in Bohemia and Saxony since the 16th century.[131] The tracheobronchial region of the lung absorbs radiation doses at least an order of magnitude greater than other organs in the body. Epidemiology studies of underground uranium,[132] hard-rock,[133] iron,[134] and niobium[135] miners associated exposure to radon progeny with increased risks of lung cancer; animal studies support this association.[136] The minimum latency period for radon-induced lung cancer in these studies is ~10 years,[57] whereas the usual latency period averages 20–30 years. Several factors (e.g., older age at the time of exposure, high radon doses, heavy smoking) may reduce the length of the latency period.[95] Some conditions (e.g., dusty conditions and diesel exhaust) that contribute to the development of lung cancer are not usually present in the home environment. In the East German Wismut cohort of 59,001 former male employees, the highest risks occurred in the youngest age group (<55 years of age) 15–24 years after exposure; duration of exposure did not modify the relative risk.[137] The highest exposures were associated with a strong inverse exposure-rate effect, whereas this effect was not observed in workers with cumulative exposures below 100 WLM.

Nonpulmonary Cancer

Epidemiological studies of underground miners clearly indicate an increase in the risk of lung cancer from exposure to radon decay products; however, there is little evidence of an increased risk of other diseases.[102] Generally, the radiation dose received by the bone marrow is at least 30–40 times below pulmonary levels.[138] Some mortality studies suggest a positive correlation between radon exposure and leukemia, primarily acute myelogenous leukemia.[139] Studies of Czechoslovakian and Canadian uranium miners revealed no evidence of cancers other than lung cancer in miners exposed to radon concentrations much higher than residential exposures.[140,141] Similarly, a follow-up study (mean duration ~30 years) of a French cohort of uranium miners detected an increased risk of lung cancer mortality (SMR = 1.43, 95% CI: 1.22–1.68; $n = 159$); however, there was no increased risk of leukemia, multiple myeloma, pancreatic cancer, or stomach cancer.[142] The average cumulative exposure was 36.6 working level months (WLM). The presence of confounders of radon exposure (mostly high-LET) and leukemia in uranium miners includes the presence of external γ-radiation (mostly low-LET) and other radionuclides from the ^{238}U series. Examination of data from the East German Wismut Uranium miner cohort through 2013 demonstrated a positive, but statistically non-significant dose-response for nonchronic lymphocytic leukemia mortality (non-CLL, $n = 120$) in the low-LET radiation exposure group with an ERR/Gy = 2.18, 95% CI: −0.41 to 6.37).[143] The ERR/Gy for non-CLL in the high-LET radiation exposure group was 16.65 (95% CI: −1.13 to 46.75). A statistically significant excess occurred for the subgroup of myeloid leukemia (ERR/Gy = 26.02, 95% CI: 2.55–68.99; $n = 99$) in the high-LET radiation exposure group, presumably mostly radon progeny. Leukemia mortality did not demonstrate a dose-response relationship to occupational radon dose in the Wismut cohort.[144] The association of radon with kidney cancer is weak. An increased risk of kidney cancer death (SMR = 2.0, 95% CI: 1.22–3.09; $n = 20$) was observed in this cohort; however, this increased risk was not associated with cumulative radon exposure. In the Czech uranium minor study, the relative risk of the incidence of kidney cancer was not significantly elevated (RR = 1.13, 95% CI: 0.62–2.04; $n = 66$) comparing cumulative lifetime radon exposure of the upper 10% (180 WLM) with the lower 10% (3 WLM).[145] A pooled analysis of 11 uranium miner studies by the BEIR VI Committee did not demonstrate excess cancer risks at sites other than the lung.[102]

DOSIMETRY

Units

Measurements of cumulative radon exposures in mines are typically expressed as working level months (WLM), which assumes 170 working exposure hours/month. In homes, the conversion factor is 1 WL = 200 pCi/L, assuming the equilibrium factor is 0.5. The conversion of pCi/L to Bq/m^3 is independent of the equilibrium

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factor; therefore, 1 pCi/L = 37 Bq/m^3. Thoron (^{220}Rn) does not typically contribute to radon radiation unless the thoron sources are close to the surface or part of the house construction because the half-life of 54.5 seconds limits the underground diffusion of thoron gas. In contrast, ^{222}Rn can diffuse into homes from several meters away from the structure.

History

In early uranium mining operations, when mines had little ventilation and radon gas was in near equilibrium with its progeny, the safe working level (concentration) of radon gas was estimated at 100 Bq/m^3. Recognizing that radon progeny, rather than radon itself, accounted for most of the lung radiation dose, the safe working level was redefined in terms of radioactive energy per air volume to avoid measuring the activities of all progeny separately. This new "working level" (WL) was defined as the concentration of radon progeny at equilibrium (i.e., no progeny loss due to ventilation) assuming the parent radon 1 L of air releases 1.3×10^5 MeV (2.08×10^5 J/m^3) of α-energy during complete decay. Converting radon gas concentrations to the modern WL requires the use of equilibrium factors to account for equilibrium between parent radon and radon progeny (daughters) due to variations in ventilation.

The working level (WL) is a combination of radon progeny in 1 L of air that releases 1.3×10^5 MeV (2.08×10^5 J/m^3) of α-energy during decay. Converting radon gas concentrations to WL requires the use of equilibrium factors to account for the equilibrium between parent radon and radon progeny (daughters). In modern mines, the concentrations of radon progeny are usually expressed in WL with a conversion factor of 1 WL = 300 pCi/L assuming an equilibrium factor of 0.33. Some organizations (e.g., US Environmental Protection Agency) use an equilibrium factor of 0.5 for mine data, resulting in 1 WL = 7,480 Bq/m^3. Table 38.7 displays the conversion factors for converting the traditional units of radon concentration in air (pCi/L) to radon progeny (WL) and duration of exposure to radon progeny over time (WLM/year) as expressed in nominal months (1 nominal month = 170 hours).

TABLE 38.7. Conversion of radon exposure into traditional units of activity, energy, and exposure.

Radon Air Concentration (Activity, pCi/L)	Radon Progeny Air Concentration (Energy, WL)	Progeny Concentration over Time (Full-Time Exposure, WLM/Year)
Indoors		
1	0.005	0.25
4	0.02	1
200	1	50
Outdoors		
0.2	0.0013	0.06
1	0.007	0.3
150	1	50
Mines		
4	0.013	0.16
300	1	12

Abbreviations: pCi = picocurie (2.2 radioactive decays/minute); WL = working level; WLM = working level month.

Radioactivity

The picocurie per liter (pCi/L) is the unit of measure for radon concentrations in the air, whereas the working level unit describes the potential α-decay energy concentration of the combined radon progeny. The pCi represents ~2.2 decays per minute with typical indoor radon concentrations typically ranging from 1–2 pCi/L (37–74 Bq/m^3). One becquerel/m^3 represents 60 decays per minute per cubic meter. When sampling a cubic meter of air at the same location, Bq/m^3 will always be numerically larger than the corresponding pCi/L; however, when sampling a liter of water, 1 pCi/L represents 0.037 Bq/L. Table 38.8 displays the conversion factors for converting traditional units of radon activity (Ci), concentration (pCi/L), and exposure (WLM) to SI units.

TABLE 38.8. Physical quantities and units used to quantify radon and radon progeny with conversion factors for traditional to SI units.

Quantity	SI Unit (Symbol)	Traditional Unit (Symbol)	Conversion Traditional to SI Units
Activity	Becquerel (Bq)	Curie (Ci)	1 Ci = 3.7×10^{10} Bq
Concentration	Bq/m^3	pCi/L	1 pCi = 37 Bq/m^3
Exposure	J-s/m^3	Working level (WL)	1 WLM = 12.97 J-s/m^3 = 0.0036 J-hours/m^3
Exposure rate	J/m^3	WLM	1 WLM/year = 4.11×10^{-7} J/m^3
PAEC	J/m^3	WLM/year	

Abbreviation: PAEC = potential α-energy concentration; WLM = working level month.

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Working Level

The working level (WL) measures intensity and duration of radiation exposure from radon progeny; the definition of this unit is any combination of radon progeny in 1 L of air that results in the emission of 1.3×10^5 MeV of α-particle energy. At equilibrium, 1 WL = 100 pCi/L; however, rapid dispersion of radon progeny in indoor air usually prevents the attainment of equilibrium. For general calculations, 1 WL for *indoor* radon progeny equals ~200 pCi/L (50% equilibrium), ~300 pCi/L (33% equilibrium) for an underground *mine*, and ~150 pCi/L (67% equilibrium) for *outdoor* area.[146] The WL assumes that all α-activity is the same, whereas a small portion of unattached radon progeny possess greater biological impact.

Working Level Month

The working level month (WLM) was designed for epidemiological studies of miners as a measure of cumulative exposure (i.e., intensity × duration). The working level month (WLM) is equivalent to the exposure of 1 WL for 170 hours. None of these units directly measure the absorbed radiation dose; the latter depends on biological factors including the pattern and extent of breathing, the characteristics of the inhaled aerosol, physiological parameters in the lung (mucous thickness and clearance), exposure duration, and the location of target cells.[60,147] The conversion coefficient for annual indoor home exposures to radon adopted by the International Commission on Radiological Protection (ICRP 65) is 1 WLM = 4 mSv assuming 7,000 hours indoors and an equilibrium factor of 0.4, whereas at work, assuming 2,000 annual work hours and a similar equilibrium factor, the annual radon exposure is 5 mSv.[148] Assuming different occupational and residential durations of radon exposure, 1 WLM ≅ an average annual residential exposure of 230 Bq/m^3.[149]

Analytic Methods

Residential radon concentrations are difficult to predict using models based on soil porosity, foundation type, location, building materials, ventilation rates, water supply, or entry points for soil gas. Most US detectors provide an initial rapid screening measurement to detect the maximum radon concentrations in the home. Although the US EPA offered a proficiency program certifying accuracy (≤25% at 4 pCi/L) and precision (coefficient of variation ≤10%) for radon testing until 1998, the accuracy of these tests at radon concentrations in most homes (1–2 pCi/L) is probably less (e.g., ~50%).[150,151] The length of monitoring depends on the analytical procedure. Screening tests should be performed in the lowest portion of the house with the windows and doors closed for at least 12 hours. Ventilation of the room being tested should be minimized, usually during the coolest months of the year. Because the radon concentration varies with time of day, season, and location in the home, the results should be considered a screening technique indicating the potential for excessive radon exposures.[152] Screening measurements usually provide overestimates of the actual radon exposure.

The two categories of devices used to measure air radon and radon progeny include 1) passive devices (e.g., activated charcoal absorption) and 2) continuous monitor devices. The former monitors average radon concentrations over time, operates without power, and requires laboratory analysis to obtain results, whereas the latter measures radon gas in relatively small increments (e.g., <1 hour), typically requires power to operate, and supplies continuous readings for either radon or radon progeny. Some passive devices (e.g., activated charcoal absorption) allow adsorbed radon to undergo radioactive decay during the measurement period, whereas others (e.g., α-track detection) use a small piece of plastic or film enclosed in a container with a filter-covered opening to permit the passage of radon but not radon progeny.

Commercial devices for quantitating radon concentrations in homes include activated charcoal detectors, α-track detectors, continuous monitors, Electret ion chambers, and electronic integrating devices. All these devices measure short-term radon exposures (i.e., few days to a few months), whereas the latter three devices are suitable for long-term monitoring (i.e., months to years). The simplest, least expensive method of detecting indoor radon is a canister filled with 20–50 g of charcoal that adsorbs radon passively over 2–7 days; subsequently, a γ-ray detector measures the radiation level in the material. The solid-state nuclear track detector records the decay of radon progeny on a special polycarbonate plastic film that records the number of α-particles striking the film. A caustic solution accentuates the submicron damage caused by the α-particles; an automated counting unit or a microscope tabulates the amount of radon. These solid-state detectors remain in place for 1–12 months. The scintillation cell method continuously measures the radon concentration by detecting the number of α-particles emitted by radon and radon progeny trapped in a particulate filter on a continuous pump. A photomultiplier tube generates an electrical signal when the α-particles produce scintillations inside the scintillation cell. Long-term testing methods (solid-state detectors, Electret ion detectors) are the most accurate methods of screening homes for elevated radon concentrations.

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Biomarkers

The ionizing radiation dose determines the biological effects following exposure; these effects are not unique to radon and radon progeny. Although the presence of radon progeny in tissues indicates exposure to radon, ingestion of food- or water-containing radon-producing radionuclides (e.g., uranium and thorium) also produces these decay products. Additionally, the short half-lives of many decay products determine the presence of these radionuclides after exposure. Measurements of radon in blood or urine are not practical biomarkers because of the 3.8-day half-life of radon, whereas analysis of long-lived radon progeny (e.g., ^{210}Pb, ^{210}Po) in biological samples suggests radon exposure. However, these radionuclides are not unique biomarkers of radon exposure because a variety of sources emit them. Consequently, estimation of radon exposure typically involves the analysis of environmental samples.

In vitro studies demonstrate a significant increase in the frequency of dicentrics, excess acentric fragments, and centric rings with increasing **radon** doses, whereas total acentric rings plus double minute and chromatid breaks/cell were not significantly elevated.[153] Epidemiological evidence for chromosomal abnormalities following residential radon exposure is conflicting; however, studies of uranium miners have not demonstrated excess dicentrics or translocation despite radon exposures substantially higher than residential radon exposure.[154] These studies detected no significant difference between miners and controls in the frequencies of chromosome- and chromatid-type aberrations; additionally, the frequency of translocations did not correlate to the estimated radon dose. In a German study of chromosomal aberrations in peripheral lymphocytes of Wismut uranium miners in East Germany and Ruhr coal miners, the frequencies of chromosomal aberrations and sister chromatid exchanges were attributed to age, diagnostic radiation, illnesses, medications, and lifestyle rather than radon exposure.[155] Cells with multiple chromosome aberrations (rogue cells) occur in different populations, primarily following radiation exposure. Several studies have associated rogue cell formation with radon exposure;[156] however, the etiology of rogue cells remains unclear.

HEALTH SURVEILLANCE

Risk Assessment

Although epidemiological studies clearly indicate radon is a human carcinogen, animal studies demonstrate substantial variation in the sensitivity of animal species to radon-induced cancer with rats and dogs being relatively sensitive and hamsters and mice being relatively insensitive up to doses exceeding 10,000 WLM. Consequently, the wide variation in animal responses and insufficient data on the mechanisms of interspecies variation seriously limit animal-to-human extrapolation in risk assessment.[57]

Models

Relative Risk

Most analyses of cancer risk from radon use the linear excess relative risk (ERR) model where the excess risk is the product of the risk coefficient measuring the unit increase in ERR per unit increase in cumulative exposure (e.g., unit/100 WLM) and the lifetime cumulative radon progeny exposure without a threshold. The relative risk is then 1 + ERR. The ERR per unit of exposure varies with age, time since exposure, and time since exposure ceased.[157] Table 38.9 lists the features of the risk models for radon-induced lung cancer developed by the NCRP, ICRP, and BEIR IV Committee based on uranium miner data published before and during the 1980s. These studies typically used cohort designs with retrospective assessments of radon exposure. The BEIR VI Committee updated the risk data from recent studies of uranium miners by developing 2 preferred risk models (exposure-age-concentrations, exposure-age-duration) after evaluating data from ~60,000 miners in 11 cohort studies (8 uranium and remainder fluorspar, iron, and tin). The Committee retained the linear, non-threshold relationship between lung cancer risk and radon exposure after excluding cumulative radon exposures exceeding 3,200 WLM; however, the Committee acknowledged that threshold and curvilinear relationships could not be excluded at low radon concentrations. Both the relative and absolute excess risk models fit the available epidemiological data. The predicted lung cancer risk depends on the model chosen and the assumptions accepted by the expert groups. The relative risk model (ICRP, BEIR IV) assumes that the risk from radon is a multiple of the background cancer risk with the risk varying by age, sex, and smoking history.

Relative risk models are usually easier to use; this type of model forecasts the most conservative risk estimates, particularly in older age groups that have a high mortality rate from underlying lung cancer.[102,159] The ICRP model uses a constant relative risk model, which forecasts the highest risk of lung cancer. The US EPA uses a constant relative risk model with relative risks ranging from 1–4% per WLM and with adjustments for

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TABLE 38.9. Characteristics of risk models created by the National Council on Radiation Protection and Measurements (NCRP), International Commission on Radiological Protection Publication 50 (ICRP 50), and Committee on the Biological Effects of Ionizing Radiation IV (BEIR IV) for radon-induced lung cancer. (Adapted from Samet).[158]

Characteristic	NCRP	ICRP 50	BEIR IV
Model type	Attributable risk	Relative risk	Relative risk
Time-dependence after exposure	Risk declines exponentially	Time-independent	Risk declines as time increases
Lag interval (years)	5	10	5
Age at exposure	Increased risk for childhood exposure	3-fold increased risk for exposure at ≤20 years of age	No adjustment
Age at risk	Risk starts at age 40 years	Age-related relative risk is constant	Lower risk for ages ≥55 years
Dosimetry adjustment	Increased risk for indoor exposure	Decreased risk for indoor exposure	No adjustment
Risk coefficient	10×10^{-6}/year/WLM	ERR: 1.9%/WLM age ≤20 years; 0.64%/WLM age ≥21 years	ERR: 2.5%/WLM modified by time since exposure

Abbreviation: ERR = excess relative risk.

minute ventilation (15.3 L air/minute). Analysis of data from the cohort of Eldorado uranium workers indicates that the increased risk of lung cancer following exposure to radon decay products is linear with increasing exposure.[160] The increased risk of lung cancer mortality in the cohort ($n = 618$) using a simple linear model was 5.5%/WLM (95% CI: 3.7–7.8%). The risk of lung cancer mortality for cumulative exposure of <100 WLM was relatively small. Smoking data were unavailable for the cohort. The relative risk of developing lung cancer from radon exposure diminishes with increasing time since the exposure ceased. In miners, shorter durations and higher radon exposure rates have a lower risk of developing lung cancer than the same total radon exposure over a longer period of time.[161]

Absolute Risk

Differences in study population characteristics (e.g., time since exposure, age attained) complicate the comparison of individual study results. Lifetime excess absolute risk (LEAR) allows the comparison of different risk models for different populations with the same exposure scenario. The attributable risk model (NCRP) assumes that excess risk is additive to the background level of risk; the risk is independent of smoking and age before 40 years. The NCRP model usually predicts the lowest excess risk because the additive model assumes the risk of developing lung cancer decreases over time.[162] Absolute risk models tend to overestimate risk at lower ages and underestimate risk at higher age groups. The validity of this model is better in the age group >40 years and with longer latency periods.[95] The minimal latency period for the BEIR VI and NCRP models is 5 years, whereas the ICRP model uses 10 years. The updated ICRP lifetime excess absolute risk based on occupational exposure studies is ~0.0005/WLM (14×10^{-5}/mJh/m^3).[149] This value depends on the background mortality rates. Using lung cancer rates of Euro-American males instead of ICRP reference rates, the estimated absolute risk is higher (LEAR = ~0.0007/WLM (20×10^{-5}/mJh/m^3).

Uncertainties

Radon is ubiquitous in all environments on earth. The key areas of controversy include whether the same risk factors derived from the higher radon exposure level present in mines apply to radon exposure in homes including the following: 1) the duration of radon exposure may modify (e.g., by cellular repair processes) the risk factors for lung cancer, 2) the use of different detectors in mines and homes, 3) equilibrium conditions, and 4) the presence of other carcinogens (e.g., arsenic, γ-radiation, thoron);[43] additionally, substantial diurnal and season–season variation in indoor radon concentrations occurs with changes in weather patterns and occupant behavior (temperature preferences, window opening).[44] Figure 38.6 displays the uncertainties associated with lung cancer mortality risks from high-dose miner data to low-dose residential radon exposures. Dosimetric modeling can correct some, but not all, problems when extrapolating high-dose miner data to the general population. Current comparative estimates suggest relatively similar types of radon progeny doses in homes and mines.[163]

Smoking

Smokers account for ~85% of radon-induced lung cancer cases.[164] Although the large majority of lung cancers occur in smoking miners, an increased incidence also occurs in nonsmoking miners with epidemiology

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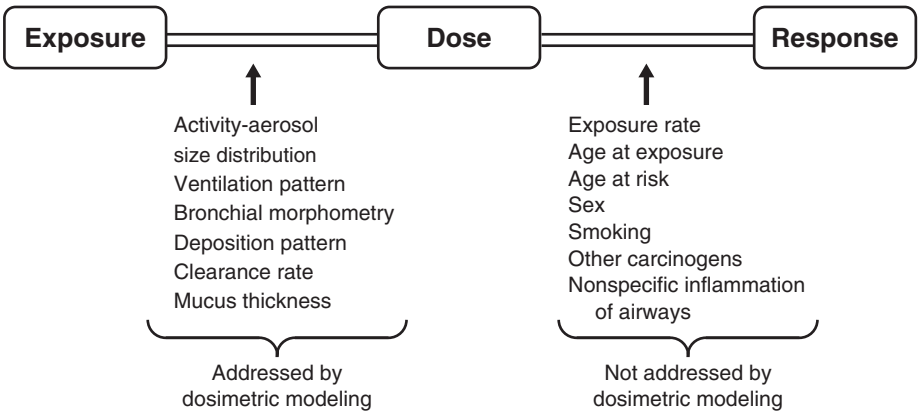


FIGURE 38.6. Sources of uncertainty when extrapolating high-dose radon data to low-dose radon data. Models estimating radon-associated lung cancer risks initially extrapolated data from earlier epidemiology studies on uranium miners exposed to relatively high radon doses to lower indoor radon concentrations. More recent epidemiology studies on the exposure of miners to low radon doses similar to residential exposures and analyses of pooled data from residential case-control studies of lung cancer risks improved the estimation of lung cancer mortality risks associated with radon exposure. (Adapted from Samet et al.).[44]

data suggesting radon exposure causes a relatively greater portion of lung cancer cases in nonsmokers than smokers.[165] Many analyses suggest the contribution of smoking to the risk of developing lung cancer after radon exposure is more (but not completely) multiplicative than additive.[42,166] Reanalysis of the mining data by the BEIR IV and VI committees suggests that the effect of smoking and radon exposure is more than additive but less than multiplicative with a wide confidence interval (ERR/WLM = 3.0, 95% CI: 0.3–29.2).[83] Increased radon-induced lung cancer risks persist after controlling for smoking habits. In a European study of 1,046 lung cancer cases and 2,492 controls in three uranium mining cohorts with detailed radon exposure data and smoking status, time since exposure was the major modifier of the effect of radon exposure on lung cancer risk.[167] The excessive relative risk for lung cancer remained elevated after adjustment for smoking (ERR = 0.0079/WLM, 95% CI: 0.0044–0.0141). The predicted lifetime lung cancer excess mortality of smokers is much greater in the ICRP and BEIR VI models using multiplicative models compared with the NCRP model using the additive model.[168] Smoking information was available in some uranium miner studies evaluated by the BEIR VI Committee. The average increased lung cancer death rate in the studies with smoking information was 0.0053/WLM (95% CI: 0.002–0.0138), similar to the overall average of the 11 studies. The average increased radon-induced lung cancer death rates/WLM were elevated in never-smokers (0.0102/WLM, 95% CI: 0.0015–0.018/WLM) compared with the combined group of current and ex-smokers (0.0048, 95% CI: 0.0018–0.0127); however, the difference was not statistically significant. In a nested case-control lung cancer mortality study of 704 deceased German miners and 1,398 controls matched for birth year and attained age, the crude ERR/WLM was 0.0025 (95% CI: 0.0013–0.0046).[169] The smoking-adjusted ERR/WLM using conditional logistic regression was similar (0.0023, 95% CI: 0.0011–0.0046) assuming smoking was a multiplicative factor. Smoking history was reconstructed retrospectively with questionnaires and company records. A case-control study of 308 Chinese women with lung cancer found no difference between radon concentrations in the homes of the lung cancer cases and the control group regardless of smoking status.[170]

Occupational Exposure

Initial estimates of radon health effects were derived from excess lung cancer mortality occurring in cohort studies of uranium miners frequently exposed to radon doses of >100 WLM in their early work years (i.e., before 1970); the radon exposure was usually estimated retrospectively in working level months (WLM). Risk estimates for lung cancer deaths vary substantially between studies and mines. The estimated relative excess of lung cancer mortality in several studies differed by an order of magnitude (i.e., 0.0027–0.03 cases/WLM).[158,171] Overall excess relative risk (ERR) estimates of lung cancer mortality in 5 analyses of pooled cohorts involving ~300,000 miners and ~6,000,000 person-years ranged from 0.0049–0.0160/WLM with the highest ERR in the combined cohort with the lowest radon exposure.[149] Variation in cohort characteristics potentially accounts

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for the differences in ERR including background lung cancer rates, radon exposure levels, attained age, duration of work, and follow-up time.

In an analysis of pooled data from 11 cohort studies involving ~60,000 miners, the Committee on the Biological Effects of Ionizing Radiation (BEIR VI) estimated an overall, average excess lung cancer death rate of 0.0044/WLM (95% CI: 0.002–0.01/WLM).[102] The estimated size of the increased risk of lung cancer-related deaths varied by a factor of 10 between the 11 studies. Using the exposure-age-concentration BEIR VI model, the highest ERR was ~0.077/WLM for a miner with an attained age below 55 years after 5–14 years of exposure to a low radon dose (<0.5 WLM). The average increased lung cancer rate/WLM of 0.0021 (95% CI: 0.0018–0.0024) for an East German uranium miner (Wismut) cohort, nearly as large as the combined pool in the BEIR VI assessment and was ~1/2 the average BEIR VI rate. Smoking data were not available for miners in the East German cohort.

Lung cancer mortality risk (i.e., estimated excess relative risk or ERR/WLM) for a 30-year-old miner with 20 years of exposure to cumulative radon doses lower than older studies ranged from 0.004 (95% CI: <0.01–0.04) in the Port Hope uranium processor cohort[172] to 0.042 (95% CI: 0.022–0.067) in the French/Czech pooled miner cohort.[173] The excess relative risk (ERR) of lung cancer/WLM in a subcohort of 26,766 German uranium miners hired before or after 1960 was 0.013 (95% CI: 0.007–0.021) with a linear relationship to radon exposure; the mean age at first employment was 21 years (range, 13–68 years), and the mean duration of employment was 10 years (range, 0.5–30 years).[174] The mean cumulative exposure was 17 WLM with a maximum of 334 WLM. A study of Swedish iron mine workers employed from 1923–1996 and followed from 1958–2000 identified 122 lung cancer cases. The excess relative risk (ERR/kBq-year/m^3) was 0.046 (95% CI: 0.015–0.077) and 0.022/WLM.[175] Quartz exposure confounded the risk estimates, accounting for <20% of the excess. The average cumulative radon exposure was 65 WLM over 14.6 years. Statistically significant excess deaths were attributed to squamous cell and small cell lung cancers, but not adenocarcinoma lung cancer.

Residential Exposure

Earlier residential studies used ecological designs to compare average radon concentrations and average lung cancer rates in different geographic regions. The inability to control confounding variables (e.g., smoking, other carcinogens) and accurately estimate cumulative radon exposures resulted in biased, potentially misleading estimates of true radon-related lung cancer risks. Although most case-control studies have insufficient power to detect increased lung cancer risks from radon exposure, 3 studies derived pooled estimates from similar residential studies of radon-induced lung cancer risks by collating and comparing individual information from 13 European studies,[176] 7 North American studies,[177] and 2 Chinese studies.[178] The average radon exposure was 30 years with a minimum lag time of 5 years prior to diagnosis and adjusted for smoking.

Thresholds

Analysis of European data from 7,148 persons with lung cancer and 14,208 age- and sex-matched controls demonstrated an excess relative risk of lung cancer mortality after controlling for confounding; these data suggested a statistically significant excess risk of lung cancer mortality following time-weighted, average annual radon exposures of ~200 Bq/m^3 for 5–34 years. There was no evidence that the excess relative risk varied with age, sex, or smoking history. The dose-response relationship was linear without evidence of a threshold including residents with radon exposures of <200 Bq/m^3.[176] Figure 38.7 displays the best-fitting straight line and the 95% confidence intervals for the European pooled study with an x-intercept of 0 Bq/m^3 (i.e., no threshold). A New Jersey study of 561 lung cancer cases and 740 local controls suggested an increased lung cancer risk for residential exposures exceeding 75 Bq/m^3 (excess odds ratio = 0.05, 95% CI: −0.14 to 0.56); however, the excess was not statistically different from controls.[179] Some studies suggest the linear no-threshold model is not the best fit for lung cancer risk at radon levels below 400–800 Bq/m^3.[180] A follow-up study of *nonsmoking* miners in the Colorado Plateau study did not detect any cases of lung cancer in workers with cumulative radon exposures below 465 WLM (1 WLM is equivalent to an annual exposure to 200 Bq radon progeny from mines/m^3).[165]

Relative Risk/Odds Ratio

Direct comparisons of lung cancer risks from radon exposure during occupational and residential exposures are complicated by differences in radon exposure and the inverse exposure-rate effect at the higher radon concentrations in uranium mines, particularly during earlier years. Uncertainties extrapolating lung cancer risk from radon exposures in miners to residents of homes with radon exposure include age, different radon concentrations, and exposure misclassification associated with retrospective analyses reflecting differences in ventilation

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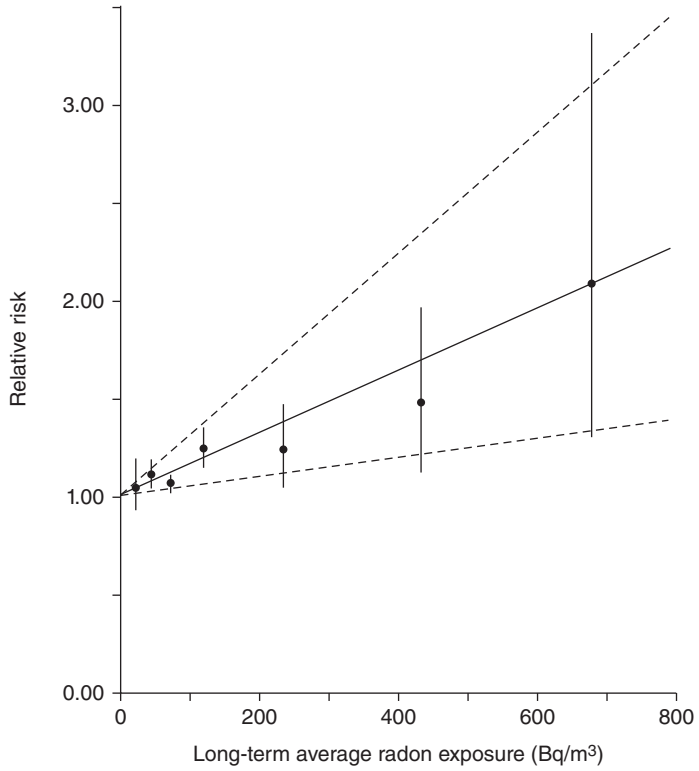


FIGURE 38.7. Relative risks and 95% confidence intervals (dotted lines) for long-term radon exposure with the solid line representing the best-fitting straight line based on pooled data from 13 European studies by Darby et al.[65] The risk at 0 Bq/m^3 represents the background lung cancer rate, set at 1.00. (Zeeb and Shannoun).[181]

and activities during radon exposure.[182] Case-control studies of residential exposure indicate an increased relative risk of lung cancer from long-term radon exposure depending on several factors including age at exposure, age attained, and cumulative radon dose.

Although organs other than the lung (e.g., kidneys, bone marrow) receive low radiation doses following residential radon exposure,[76] there is no clear evidence that residential radon exposure increased the rates of nonpulmonary cancers including leukemia.[183] Positive studies are typically ecological studies subject to a substantial number of biases. The Iowa Radon Leukemia Study reported excess rates of leukemias associated with radon exposure including chronic lymphocytic leukemia (CLL);[184] however, this type of leukemia is not usually associated with radiation exposure.

Excess Relative Risk/Excess Odds Ratio

Excess relative risk (ERR) for lung cancer in a population exposed to radon is the ratio of lung cancer rate in the exposed population to the lung cancer rate in the unexposed population minus one (i.e., the background rate). Theoretically, the ERR should be the same as the attributable risk; however, in practice, the ERR is calculated from an observed effect (e.g., lung cancer), whereas the attributable risk is calculated from an estimated or observed exposure (e.g., radon). Excess relative risks for residential exposures are usually expressed as radon concentrations (pCi/L, Bq/m^3), whereas occupational exposures are expressed as radon progeny concentrations (WL, WLM). Typically, summary risk estimates are somewhat lower for uranium miners than residential studies. The ICRP model yields a risk lung cancer coefficient of ~0.035/Sv as an effective dose equivalent, whereas the NRPB model estimates a risk coefficient of 3×10^{-10}/Bq-h/m^3 as an integrated radon concentration. The overall joint estimate of the excess risk of lung cancer in the European, American, and Chinese pooling studies based on radon measurements in residences was 0.01/100 Bq/m^3 consisting of 0.08/100 Bq/m^3 (95% CI: 0.03–0.16/100 Bq/m^3) for the European pool, 0.11/100 Bq/m^3 (95% CI: 0–0.28/100 Bq/m^3) for the American pool, and 0.13/100 Bq/m^3 (95% CI: 0.01–0.36/100 Bq/m^3) for the Chinese pool.[181]

Individual residential studies of residential radon exposure demonstrate substantial variability in alculating the ERR. Using conditional likelihood regression to

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estimate the excess risk of lung cancer due to prolonged residential radon exposure demonstrated an excess odd ratio (EOR) of 0.18 (95% CI: 0.02–0.43)/100 Bq/m^3 after adjustment for attained age, sex, study, smoking factors, residential mobility, and completeness of radon measurements.[177] The estimated EOR was compatible with an EOR of 0.12 (95% CI: 0.02–0.25)/100 Bq/m^3 predicted by downward extrapolation of the miner data. In a similar study of pooled data from 13 European studies of prolonged (e.g., 25 years) residential radon exposure and lung cancer, the excess relative risk of lung cancer/100 Bq/m^3 was 0.08 (95% CI: 0.03–0.16; $P = 0.0007$) after controlling for confounding.[176] In the prospective Cancer Prevention Study II cohort of 1.2 million participants using ecological radon data, 3,493 lung cancer deaths occurred during the first 6 years of follow-up.[185] Categorizing the cases by radon exposure evaluated at the beginning of the study demonstrated an increased lung cancer mortality risk of 0.15 (95% CI: 0.1–0.31)/100 Bq/m^3 with the risk increasing to 0.34 (95% CI: 0.07–0.68)/100 Bq/m^3 for initial radon exposures exceeding the USEPA guideline recommending an upper limit of 148 Bq/m^3.

Biological Monitoring

Although models have been developed to estimate exposure to radon and radon progeny using long-lived radon progeny (^{210}Pb, ^{210}Po) in teeth, bone, and blood, numerous uncertainties limit the accuracy of these models including the spatial distribution of radon decay progeny and the ubiquitous presence of radon, ^{238}U, and ^{226}Ra.[186,187] Consequently, these models are not useful biomarkers of exposure for quantifying exposure to radon and radon progeny. Epidemiological studies of uranium and lead-zinc miners exposed to radon demonstrate an increased incidence of structural chromosomal abnormalities compared with the general population. In a study of US uranium miners, the correlation between chromosomal aberrations and radon dose was variable.[188] The prevalence of deletions and dicentrics plus rings correlated poorly with radon dose, particularly in the miners exposed to >3,000 WLM. Pericentric inversions and translocations consistently increase with radon dose. The frequency of total chromosomal aberrations persists for years after cessation of radon exposure in uranium miners.[189] In a study of 70 workers from a lead-zinc mine, total structural chromosome aberrations decreased significantly from 5.08/200 metaphases in 1995 to 3.28/200 metaphases in 1997, when the mine closed.[190] These values were significantly different from the control group of local inhabitants never employed in the mine (1.43/200 metaphases). Sister chromatid exchanges correlated more closely to heavy metal concentrations than radon concentrations; the latter exposure was high in some portions of the mine (3,000–5,000 Bq/m^3). The interactions of radon with genotoxic substances (e.g., arsenic, cigarette smoke, crystalline silica dust, diesel exhaust particulates, heavy metals) complicate studies correlating radon exposure with intrachromosomal aberrations (pericentric inversions, centric rings, acentric fragments), interchromosomal aberrations (translocations, dicentric/acentric fragments), and sister chromatid exchange between two sister chromatids. Consequently, these genotoxic effects are not exclusively attributable to radon exposure, limiting the usefulness of chromosomal aberrations as biomarkers of radon exposure.

The exfoliated-cell micronucleus assay is a noninvasive, cytogenetic technique for monitoring the mutagenic and carcinogenic potential of chemical exposure. Chromosomes or fragments from chromosomes remain in the cell cytoplasm when DNA fails to incorporate into a progeny nucleus. These DNA fragments form micronuclei in the cell cytoplasm. Use of this cytogenic technique on the sputum of uranium workers is not an effective technique for determining exposure to radon or cigarette smoking.[191] Direct measurements of radon and radon progeny in biological media (serum, urine, teeth, hair) are not practical markers of radon exposure.[57,83]

Environmental Monitoring

Radon exposure should be kept as low as reasonably achievable (ALARA) with regulations and guidelines setting upper exposure limits. The ICRP recommends an upper limit of radon exposure of 200 Bq/m^3 (5.4 pCi/L) for buildings on which remedial action is economically feasible. Using the ICRP model, the National Radiological Protection Board calculated that a lifelong exposure to an average radon concentration of 200 Bq ^{222}Rn/m^3 air corresponds to a lifetime risk for the general population of 3% (10% for smokers, 1% for nonsmokers).[192] For new buildings, their recommendation is 100 Bq/m^3 (2.7 pCi/L). The World Health Organization (WHO) endorses an upper average annual radon limit of 100 Bq/m^3 (2.7 pCi/L air) for remedial action. In 2014, the ICRP reduced the upper reference radon level for homes to 300 Bq/m^3 in response to a doubling of the ICRP detriment-adjusted nominal risk coefficient for lung cancer in a mixed adult population of nonsmokers and smokers to 8×10^{-10}/Bq h/m^3 for ^{222}Rn

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gas in equilibrium with its progeny (5×10^{-4}/WLM).[193] The reference value of 300 Bq/m^3 corresponds to an annual effective radiation dose of ~10 mSv. Considering the prevailing social and economic circumstances, the Commission recommended reducing the radon level in homes as low as reasonably achievable in the range of 100–300 Bq/m^3. Although 1,000 Bq/m^3 was the recommended entry point for applying occupational radiological protection requirements in 2010,[81] the Commission recommended replacing this value with a specific graded approach that included reducing radon concentrations to levels as low as reasonably achievable below the reference level set for dwellings (<10 mSv/year). The upper value of the range of existing exposure situations should not exceed 20 mSv/year, regardless of whether the worker is occupationally exposed to radon or not.

As outlined in Table 38.10, the action level for remedial action recommended by the US EPA is 4 pCi/L (150 Bq/m^3).[194,195] At this action level, the risk of

TABLE 38.10. Residential and occupational regulations and guidelines for radon.

Source	Focus	Description	Regulation	Guideline
		Public		
National Council for Radon Protection	Indoor Residential Air	Limit		2 WLM/year
World Health Organization (WHO)	Indoor air Water	Remedial action Upper limit		≥100 Bq/m^3 (≥2.7 pCi/L) 100 Bq/L (2,700 pCi/L)
US Environmental Agency	Indoor residential air	Action level	≥4 pCi/L (0.2 WL)	
International Commission on Radiological Protection (ICRP)	Indoor residential air	Action levels (Radon level) (Effective dose)		 100–300 Bq/m^3[c] 3–10 mSv/year
		Workers		
American Conference of Governmental Industrial Hygienists (ACGIH)	Occupational exposure	Limit		4 WLM/year
National Institute for Occupational Safety and Health (NIOSH)	Underground miners	Annual limit		1 WLM/year[b]
International Commission on Radiological Protection (ICRP)	Occupational exposure	Action levels (Radon level) (Effective dose) Annual limit		 300–1,000 Bq/m^3[c] 3–10 mSv/year 14 mJh/m^3[d] 35 mJh/m^3[e]
Occupational Safety and Health Administration (OSHA)	Adult workers[a]	Annual limit 40-hour workweek average	4 WLM/year 100 pCi/L	
US Nuclear Regulatory Commission (USNRC)	Licensee workers	^{222}Rn with progeny without progeny	 4 WLM/year[f] 10,000 μCi[f]	
US Department of Energy (DOE)	Occupational exposure	DOE workers	10 WLM/year	
Mine Safety and Health Administration (MSHA)	Mining – underground miners	Radon progeny Annual limit Maximum	 4 WLM/year 1 WL	

Abbreviations: WL = working level; WLM = working-level month.
[a] Except DOE, MSHA, and USNRC workers; [b] As low as reasonably possible; [c] Assumes 7,000 indoor hours/year in homes or 2,000 hours/year at work with an equilibrium factor = 0.4; [d] 5-year average; [e] Single-year maximum; [f] ^{220}Rn with progeny – 12 WLM (20 μCi) and without progeny – 20,000 μCi.

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developing lung cancer is slightly above the lung cancer risk for the general population; however, further reduction of radon may be costly and difficult to complete.[196] The risk of developing lung cancer at this level increases by ~50%, which is approximately equivalent to the lung cancer risk from smoking 1/2 pack of cigarettes/day or receiving 200 chest X-rays/year. This EPA guideline is a recommendation rather than a strict boundary between safe levels and levels producing substantial lung cancer risks.[162] Hence, the decision to use mitigating measures at radon levels near 4 pCi/L depends on a risk-benefit analysis. The original regulations for radon exposure in uranium mines allowed an exposure of 12 WLM of radon progeny/year; however, the regulatory level decreased to 4 WLM of radon progeny/year in 1971.[146] Statistically significant, excess lung cancer mortality occurred in a Czechoslovakian cohort of miners at cumulative radon exposures of <50 WLM,[197] whereas excess lung cancer deaths appeared in US and Canadian miners at cumulative exposures of >100 WLM.[198] Although the US EPA recommends 4 pCi/L as the current action level for all occupied buildings as displayed in Table 38.10, the EPA does not exclude an increased lung cancer risk for indoor radon concentrations of <4 pCi/L (148 Bq/m^3).[199] The EPA encourages cessation of smoking as a mitigating factor for radon-associated risks.

TREATMENT

Remedial Methods

There are no methods to reduce radon absorption or body burden. Dietary supplements are not recommended for the prevention of radon-induced lung cancer.[200] The US Surgeon General and the US EPA recommend testing all homes for radon concentrations; substantial variation occurs in radon concentrations during short-term tests as a result of diurnal and seasonal variations. Soil beneath a dwelling is the most common residential radon source. Simple, inexpensive methods to reduce radon exposure include avoiding areas (e.g., basements) of high radon concentrations, venting basements and crawl spaces to the building exterior, and improving house ventilation. Radon concentrations remain low in well-insulated, well-sealed dwellings following the construction of effective vapor barriers that prevent radon diffusion into the dwelling.[201] Other methods to reduce radon concentrations include natural, heat recovery or forced ventilation, covering exposed earth, sealing cracks and openings, drain-tile or sub-slab suction, block wall ventilation, prevention of house depressurization, and basement pressurization.[202,203] Smoking substantially potentiates the radon-induced lung cancer risk; consequently, the most effective way to reduce radon-induced lung cancer is to reduce smoking prevalence.[204] Table 38.11 compares smoking and radon risks along with guidelines for repeat measurements and remedial action timelines.

The goal of remediation is the reduction of indoor radon concentrations to the outdoor concentration (i.e., 0.4 pCi/L in the United States) and lower if possible. Properly designed active soil ventilation systems (e.g., suction on perimeter drain tiles) are usually the most effective technique (i.e., 90–99% decrease) when a complete loop of drain tiles exists. Sub-slab suction is the next most effective method based on a study by the US EPA.[205] Ventilation of block wall cavities produces less predictable results. Heat recovery ventilation is moderately effective (i.e., ~50% reduction). The actual reduction in the radon concentrations varies between houses as displayed in Table 38.12; testing with different types of remedial measures may be necessary to achieve permanent reductions in the radon concentration. The effectiveness of each remedial

TABLE 38.11. Approximate comparable radon and smoking risks with suggested guidelines for remediation. (Adapted from Birrer).[196]

Concentration pCi/L (WL)	Comparable Radon Concentration	Comparable Smoking Risk	Recommended Duration Repeat Concentration	Remedial Action Timeline
0.2 (0.001)	Average outdoor concentration (AOC)		None	None
1 (005)	Average indoor concentration (AIC)		None	None
2 (0.01)	10 times AOC	>lung cancer mortality risk in nonsmoker	None	None
10 (0.05)	10 times AIC	>5 times nonsmoker risk	1 year or 1 week each season	Within several years
20 (0.1)	100 times AOC	>1-pack/day	<3 months	Within several months
100 (0.5)	100 times AIC	>2-pack/day	<3 months	Within several months
200 (1)	1000 times AOC	>4-pack/day	<7 days as soon as possible	Within several weeks

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TABLE 38.12. Estimated reduction of indoor radon concentrations using radon mitigation techniques. Sealing of entry routes requires the combination of other mitigation techniques with the sealing. (Adapted from Choi and Mazzone).[202]

Technique	Media	Estimated Indoor Radon Reduction
Basement pressurization	Air	50–99%
Block-wall suction	Air	50–99%
Drain-tile suction	Air	50–99%
Natural ventilation	Air	Variable
Passive sub-slab suction	Air	30–70%
Sub-membrane depressurization	Air	50–99%
Sub-slab suction	Air	50–99%
Sump-hole suction	Air	50–99%
Activated charcoal	Private well water	85–99%
Aeration	Private well water	95–99%

technique should be confirmed by comparing measurements using the same method. Carbon filtration is an effective technique (i.e., 95–99% reduction) to remove radon from water. The outcome of radon mitigation techniques depends on several factors including climate, soil conditions, building type, and source.[206] Empirical evidence for screening individuals with low-dose CT imaging similar to high-risk lung cancer groups (current smokers or former smokers having quit within the past 15 years and aged 55–80 years with ≥30-pack year smoking history) is insufficient to recommend CT screening at this time for specific radon exposures; however, the US Preventive Services Task Force recommendations have been reviewed.[207,208]

Initiating Remedial Measures

Table 38.11 outlines a timeline for repeat radon measurements and remedial actions following elevated radon concentrations during screening based on recommendations by the US EPA. The decision to perform remedial action depends on a variety of factors, including 1) presence of children, 2) amount of time spent in areas of high radon concentrations, 3) percent of time spent at home, 4) anticipated length of ownership, and 5) associated risk factors for the development of lung cancer (smoking, occupational exposure to lung carcinogens).[196]

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Chapter 39

IONIZING RADIATION INCIDENTS

PHYSICAL PROPERTIES

Alpha Particles

Alpha-emitting radionuclides release α-particles (two protons, two neutrons) from their nucleus along with a characteristic amount of energy. These particles rapidly decay while acquiring electrons from the surrounding environment to become inert ^{4}He; the typical lifetime of an α-particle is a few picoseconds. Alpha particles possess high linear energy transfer; therefore, these particles cause substantial damage at short range compared with β-particles. Because the relatively heavy α-particles travel at a comparatively low speed, they spend more time near the atoms and exert more impulses on the orbital electrons. Consequently, α-particles are particularly hazardous at short range because of the large amount of radiation imparted locally. The main determinant of tissue penetration is the energy of the particle. For charged particles (e.g., α- and β-particles) with the same energy, the depth of penetration depends on the size of the particle and its charge.

Alpha particles are the main source of radiation exposure for uranium miners breathing radon gas and workers ingesting radium or thorium isotopes while producing radio-luminescent dials. The internal absorption of the α-particles in these workers increases the risks of lung and bone cancers. An α-particle requires at least 7.5 MeV of energy to penetrate the keratin layer of the skin; therefore, α-emitting particles are hazardous only if ingested or inhaled. Table 39.1 compares the physical characteristics of the types of ionizing radiation involved in incidents related to the release of ionizing radiation.

Beta Particles

Beta particles are high-speed, negatively charged electrons released during the radioactive transformation of a neutron into a proton. The energies of the β-particle released from radioactive decay form a spectrum of energies ranging up to a maximum (E_{max}) characterized by the specific transformation involved. Hence, most β-particles emitted during the transformation do not possess the maximum potential energy (E_{max}). The difference between the maximum energy and the energy of the β-particle results from the emission of a neutrino from the nucleus. However, the neutrino does not interact with matter; therefore, the neutrino does not produce ionization or damage to the tissue.

Gastrointestinal absorption of β- and α-particles produces internal damage. The energy of the β-particle determines its ability to penetrate the skin and cause external damage. The maximum potential energy (E_{max}) for tritium is 0.018 MeV; this value is lower than the energies of electrons hitting most television screens. These β-particles are too weak to penetrate human skin in contrast to the high-energy β-particles from ^{32}P that penetrate up to 8 mm into the body.[1] Skin burns from high-energy β-particles were a major contributing factor to mortality in workers exposed to radiation exceeding 1 Gy at the Chernobyl accident in 1986.[2]

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TABLE 39.1. Physical characteristics of radiation commonly emitted from radioactive sources. The exact depth of radiation penetration in human tissue depends on a variety of factors including wavelength, mass, tissue composition (melanin, water), interactions of radiation with tissue (absorption, scattering), and the angle of observation (anisotropy).

Physical Character	α-particles	β-particles	γ-rays	X-rays	Neutrons
Symbol	α	β	γ	X	n
Composition	2 protons, 2 neutrons	1 electron	Electromagnetic wave	Electromagnetic wave	Free neutrons
Mass (amu)	4	0.0005	0	0	1
Charge	+2	±1	0	0	0
Energy (MeV)	4–8	0–3	0–3	0–0.5	0–5
Range (air)	Few cm	≤several meters	Many meters	Many meters	Many meters
Range (skin, soft tissue)	50 μm	Few mm	Many cm	Many cm	Many cm
Hazard	Internal	Internal-external	Internal-external	Mostly external	External

Gamma Rays

Gamma rays are "pure" electromagnetic waves (i.e., no mass/charge) that are emitted from radioactive nuclei; γ-rays often accompany the release of β-particles. Although γ-rays have the same range of energies as β-particles, a specific radionuclide releases discrete energy rather than the range of energies up to the maximum (E_{max}) that occurs with β-particles. Beta particles ultimately stop in the tissue and combine with an atom, whereas γ-rays travel at the speed of light through tissue until they lose energy due to the ejection of an electron during a chance encounter with an atom. The depth of penetration depends on the interaction of the γ-rays with the atoms in the tissue. The probability that a γ-ray will penetrate through tissue depends on the thickness and composition of the medium in addition to the energy of the γ-ray.

Gamma rays are indirect ionizing radiation with tissue damage resulting from electrons ejected by chance collisions rather than directly from interaction with the tissues. As with all indirectly ionizing radiation, some radiation will penetrate any shield depending on the amount of activity and the strength of the shield, whereas a β-shield will stop all β-particles within the maximum range.

X-Rays

Although X-rays and γ-rays are "pure" electromagnetic radiation, the origins of these two types of radiation differ. X-rays are photons emitted from electron shells or decelerating charged particles (e.g., electrons), whereas γ-rays originate from the atomic nucleus or particle annihilation. The emission of X-rays typically occurs when electrons in excited atomic shells transition to lower energy states. The deceleration or deflection of electrons in an electromagnetic field close to the nucleus produces a continuous X-ray spectrum characteristic of the corresponding element (e.g., tungsten). The classification of medical X-rays involves peak applied voltage (kVp) that varies from ultra-soft (5–20 kVp) to very hard X-rays (>250 kVp) produced by betatrons and linear accelerators.[3]

Neutrons

Other than the production of neutrons from the decay of ^{252}Cf (californium-252), exposures to neutrons occur from human activity through nuclear reactions (e.g., nuclear-fission reactors, high-energy accelerators). Neutrons are uncharged; therefore, these particles do not interact easily with tissue. In contrast to the interaction of X-rays and γ-rays with orbital electrons, neutrons interact with the atomic nucleus. They are indirectly ionizing particles that produce damage in the tissue by striking atomic nuclei (primarily hydrogen) and producing mostly highly charged, slow-moving recoil protons. The energy from recoiling atoms possesses high linear energy transfer that causes comparatively more tissue damage than β-particles or γ-rays. The nuclear absorption of a neutron results in the release of a substantial amount of energy (~7 MeV), usually in the form of a high-energy photon; this release complicates the development of effective shielding to attenuate neutrons.[1] Hence, complex designs for shielding are necessary to attenuate both neutrons and γ-rays.

EXPOSURE

Radiation from natural sources has existed on earth since the beginning of evolution; the three main sources of natural radiation are: 1) internal radiation from potassium-40 and other natural radionuclides, 2) terrestrial radiation from radium and other radioactive elements in the earth's crust, and 3) cosmic radiation

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originating in outer space. The importance of radiation during our evolution is unclear.[4] Radiation from human sources is new to our environment, including medical irradiation, low-level radioactive waste from nuclear reactors and medical applications, flying at high altitude, and fallout from nuclear testing and nuclear incidents (i.e., accidental and intentional releases). The biological effects of human and natural radiation sources are similar, depending on the cumulative absorbed dose. Minor sources of artificial radiation include nontobacco consumer products (e.g., color television sets, luminescent material, smoke detectors), nuclear power production, fallout from nuclear weapons testing, and radionuclides in the minerals of building materials and phosphate fertilizers exclusive of radon. These sources produce exposure pathways involving either *direct exposure* to ionizing radiation during and immediately after the release (e.g., nuclear detonation, medical irradiation) or continuing internal and external *radioactive contamination* from deposition of radionuclides. The former pathway includes primarily high-energy photons (γ- and X-rays) and/or neutrons, whereas radionuclides typically emit high-energy α-particles, β-particles, and/or photons (γ-rays, X-rays). Persons with direct exposure to ionizing radiation are not radioactive and do not represent a hazard to other people; however, people contaminated by radionuclides continue to expose themselves and adjacent people to continuing ionizing radiation until the completion of decontamination.

Background Radiation

In France, the United States, and the United Kingdom, the natural radiation dose in different regions, including radon, ranges from ~1.5–6 mSv.[5] The estimated US annual per-capita effective radiation dose from natural and human sources increased from 3.0 mSv in 1980 to 5.6 mSv in 2006.[6] The recent increase in medical radiation results primarily from the increased use of CT scanning, particularly in patients receiving relatively high annual radiation doses (>20 mSv). The actual effective absorbed dose received by a particular individual depends on their lifestyle and geographic location. Skiing or climbing far above sea level increases the natural radiation dose 2–3 fold compared with similar activities at sea level.[7] Natural radiation doses in certain geographic locations (e.g., Kerala, India; Brazil) may exceed US exposures 10–100 fold;[8] the difference results primarily from radon exposure.

For the average individual in the United States, radiation from occupational exposure, nuclear power production, and miscellaneous environmental sources including nuclear fallout contributes negligible amounts to their overall radiation exposure. Radiation exposure during adulthood limits the biological effects of human sources compared with the lifetime radiation exposure from natural radiation.[9] Although *low* doses of natural radiation are not conclusively linked to elevated cancer rates, this type of exposure produces biological effects (e.g., increased frequency of chromosomal aberrations in lymphocytes).[10,11]

Consumer products account for relatively small amounts of radiation. The major source of population exposure to X-rays from television was color television receivers manufactured before 1970; current estimates of the average annual effective dose are <5 μSv/year.[12,13] The emission of X-rays from color television sets and video display terminals was below the limit of detection for many instruments. The estimated average annual effective dose for X-ray emission from airport luggage inspection systems is <0.01 μSv; most personnel scanning systems use magnetic metal detectors and nonionizing radiofrequency radiation rather than ionizing radiation.[12,14] In a study of stray radiation from baggage X-ray equipment, none of the surveyed equipment presented a health hazard to the public or operators; the annual dose equivalent for workers near this equipment was below the occupational limit of 5 mSv.[15] In a study of a Taiwan airport using dosimeters, the calculated annual effective radiation doses were as follows: 1) export conveyor, 0.12 mSv; 2) outward face of X-ray scanning chamber, 0.39 mSv; and 3) X-ray image monitor, 0.16 mSv.[16] The estimated mean effective dose using tissue-weighting factors of the International Commission on Radiological Protection (ICRP) for a 10-year-old child using a phantom was 3.39 ± 0.33 μSv/scan.

Table 39.2 lists examples of the approximate effective radiation dose from external radiation and medical

TABLE 39.2. Comparison of radiation exposures. The values in the tables are approximations used only to compare different types of ionizing radiation exposures. The actual value of the individual exposures listed varies depending on several factors.

Exposure	Effective Dose (mSv)
Transatlantic flight	0.08
Diagnostic chest X-ray	0.1–0.2
Annual background radiation	3–6
Barium study	6
Cardiac angiography	8–10
Mild acute radiation sickness	2,000
Acute LD_{50} for single radiation dose	4,500

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procedures compared with the radiation dose required to produce radiation sickness.

Radiation Incidents

Classifications of significant radiation accidents include: 1) whole body dose ≥0.25 Sv, 2) skin dose ≥6 Sv, 3) external radiation absorbed dose ≥0.75 Sv, or 4) internal contamination ≥½ the maximum permissible body burden as defined by the International Commission on Radiological Protection.[17] Funded by the US Department of Energy, the Radiation Emergency Assistance Center/Training Site Registry of Oak Ridge Associates Universities in Oak Ridge, Tennessee, maintains a list of significant radiation injuries; the data indicate ~20 significant radiation accidents occur annually with ~5 fatalities, primarily as a result of total body irradiation. Except for the Chernobyl accident, radiation devices accounted for most fatalities. These latter accidents usually involve unsuspected exposure to radioactive sources from radiotherapy machines. Overexposure to radiation also occurs due to operator error or failure of the radiation device.

Conceptually, radiation accidents include the following three categories: 1) external, 2) internal or external contamination, and 3) a combination of an external source plus contamination with a radionuclide. External radiation results from exposure to an external radiation source (e.g., X-ray machine, particle accelerator, radioactive material). These accident types do not involve direct contact between the patient and the radiation source; hence, the radiation exposure ceases when the person leaves the radiation source (e.g., γ- or X-rays). Contamination occurs following the release of radioactive dust, gases, or liquids that deposit radioactive *dirt* either externally on the skin or internally (e.g., open wound, lungs, gastrointestinal tract, or urinary tract). A contaminated patient remains radioactive until the radioactive material physically decays or the body eliminates the radioactive material (e.g., radionuclide). Consequently, the excretions and lavage fluids from contaminated patients pose a radiation hazard.

Increasing public concern exists over nuclear terrorism from an attack on a nuclear power facility or the intentional/unintentional use of a nuclear weapon. Besides unintended radiological/nuclear accidents, potential radiation incidents involving the deliberate detonation of radioactive material include: 1) deliberate destruction of nuclear power facilities (Israel's 1981 attack on Iraq's Osirak nuclear power facility, Hamas' 2014 targeting of Israel's Dimona nuclear power plant); 2) detonation of radiological exposure devices by terrorists including a nuclear bomb or sophisticated nuclear weapon; 3) release of radioactive material in a conventional explosive device ("dirty bomb"); and 4) detonation of an improvised nuclear device stolen from a nuclear facility.[18]

Explosions

Nuclear explosions produce the following types of energy (percentage of total energy): 1) heat (~35%), 2) shock or bomb blast (~50%), and 3) radiation (~15%). Heat and intense light cause flash, flame, retinal burns, and flash blindness from temporary depletion of retinal pigment, whereas blast waves cause fractures, lacerations of internal organs, pulmonary hemorrhage, and acute respiratory distress syndrome.

Hiroshima and Nagasaki

On August 6, 1945, a unique uranium gun-type atomic (fission) bomb ("Little Boy") exploded with a force of ~15 ± 4 kilotons of TNT (trinitrotoluene) 576 m above the city of Hiroshima, virtually destroying all buildings in a 5-square mile area. Civilian causalities included 78,150 dead, 13,983 missing, and 37,424 injured.[19] Three days later, a ~22 ± 2 kiloton plutonium implosive device ("Fat Man") detonated 507 m above Nagasaki. Total civilian causalities exceeded 49,000 with few survivors within 1 km of the hypocenters; most of the deaths resulted from projectiles, percussive forces, and thermal injuries rather than radiation injuries; <10% of the energy released by the bomb formed ionizing radiation, primarily neutrons and γ-rays. A study of the effects of the bomb blast on the Japanese population confirmed that most of the initial deaths resulted from the immediate effects of thermal burns and trauma secondary to blast injuries.[20] The estimated intensity of the heat ranged from 3,000–4,000°C at the hypocenter to 573°C at distances of 1,000–1,600 m from the hypocenter. All persons within 4 km of the hypocenter without shielding suffered some degree of burns.[20] Additional injuries resulted from the compression and suction phases of the blast that reached up to 6–8 tons/m^2. An estimated 5% of cancer deaths among A-bomb survivors resulted from radiation exposure after the atomic bomb explosions in Hiroshima and Nagasaki, based on 63 years of follow-up.[21]

The 1950 Japanese National Census estimated that these two atomic bombs exposed ~280,000 persons directly to ionizing radiation. The Hiroshima weapon was a unique bomb that fired one block of uranium-235 into a gun assembly composed of steel. The Nagasaki weapon imploded a shell of plutonium-239 into a shell of depleted uranium-235. Although differences in the

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construction of the bombs initially were thought to result in greater exposure to neutron radiation at Hiroshima than Nagasaki, reevaluation of dosimetry at Hiroshima (DS86) decreased the neutron radiation dose to 10% of the T65DR estimates.[22] The current estimates of neutron radiation are too small to predict accurate estimates of the relative biological effectiveness of neutron radiation from that data.[23] In contrast to the unique detonation of the bomb at Hiroshima, the bomb type used at Nagasaki was tested several times in the Nevada Desert.

Initial Radiation For >90% of the survivors, the radiation dose was <0.01 Gy (10 rads) with a range up to ~3 Gy.[19] The estimated mean lethal dose of whole-body radiation required to kill 50% of humans within 60 days is 3.25–4 Gy without supportive care and 6–7 Gy with intensive supportive care.[24] In comparison to this dose, an increased incidence of malignancy generally occurs after exposure to radiation doses ~30 times higher (i.e., >0.3 Gy) than the radiation dose of most survivors.[25] Within the fireball above the cities, there was a dynamic mass of fission products that emitted delayed radiation from neutrons and γ-rays. Prompt radiation from high-energy γ-rays produced by neutrons from fission reactions ≤1 second after the nuclear explosion preceded the bomb-induced shock wave.[22] The survivors were exposed to radiation from the air proportional to the amount of shielding material, radiation scattered from the earth, and radiation reflected from buildings, depending on their orientation to these sources. An in-air tissue absorbed dose for γ-rays was estimated from thermoluminescent bricks and tiles of these cities; for neutrons, estimates were based on radiation-induced radioactivity of ^{60}Co in iron reinforcement bars within concrete buildings.[26]

President Harry Truman approved a directive to the National Academy of Sciences/National Research Council to undertake a long-range, continuous study of the biological and medical effects of the atomic bomb. In 1947, the Atomic Bomb Causality Commission (ABCC) was formed to study Japanese survivors; this organization was restructured in 1975 to the Radiation Effects Research Foundation (RERF). Early observations detected cataracts, leukemia, and birth defects, resulting in an initial focus on the blood, growth and development, and ocular effects. In 1955, the Francis Committee developed a unified study program to follow mortality and cancer incidence in a fixed sample of ~120,000 atomic bomb survivors and control subjects (Life Span Study). This cohort included ~1/2 of all survivors with high radiation exposure alive 5 years after the bombing.[21] Over 60% of these survivors received radiation doses of <100 mGy. Later, cohorts of survivors exposed *in utero* (*in utero* cohort) and children of exposed and nonexposed parents (F_1 cohort) were added. Although there were no direct measurements of radiation from the two bombs, calculations of individual radiation doses (γ-rays, neutrons) were calculated from the distance from the hypocenter, external shielding (terrain, buildings), and body self-shielding corrected for orientation, position of the organ doses, and age. The ABCC initially released estimates of radiation-related risks of cancer among Japanese survivors of the atomic bomb blasts based on their estimates (Tentative 1965 Dose Revised, T65DR) of the radiation dose. No risk estimates were available for cohort data from 1945–1950. After a reassessment of the individual doses by Japanese and American scientists, the individual doses were revised in the Dosimetry System 1986 (DS86). The DS86 system reduced some but not all biological ambiguities (i.e., epilation data, somatic mutations, cytogenetic abnormalities) present in the previous systems. The current dosimetry system (DS02) includes estimated radiation doses for 15 organs.[27] Some survivors in the Life Span Study received whole-body radiation doses approaching lethality (i.e., >2 Gy); however, the mean whole-body radiation dose for survivors receiving >0.005 Gy was ~0.2 Gy.[21] Although the cancer mortality data per absorbed dose is still higher in Hiroshima than Nagasaki, the difference is no longer statistically significant.[28]

The three different forms of estimating the dose of an individual include: 1) free-in-air kerma, 2) the shielded kerma, and 3) the organ-absorbed dose. The free-in-air kerma is the kinetic energy released at a point in air over bare ground, whereas the organ-absorbed dose is the radiation absorbed by a specific organ. The shielded kerma is the dose delivered to the skin of an individual; this value adjusts the free-in-air KERMA for the shielding of building structures. The DS86 data reduce the shielded KERMA dose somewhat, and risk estimates using the new shielded KERMA data are 40% higher; however, the DS86 organ dose and risk estimates based on that data do not differ significantly from the T65DR estimates.[29,30]

Figure 39.1 demonstrates the free-in-air absorbed doses adjusted for shielding of the houses (i.e., shielded kerma) and distance from the hypocenter. The hypocenter is the location on the ground vertically below the epicenter (i.e., the point in the air where the atomic bomb detonated). The actual absorbed dose equivalent required to calculate risk must be adjusted by the experimentally derived *R*atio of the in-*A*ir *T*issue dose to the *A*bsorbed dose (RATA) in critical organs based on the orientation of the individual to the hypocenter. This value converts the shielded KERMA into an average organ-absorbed dose.

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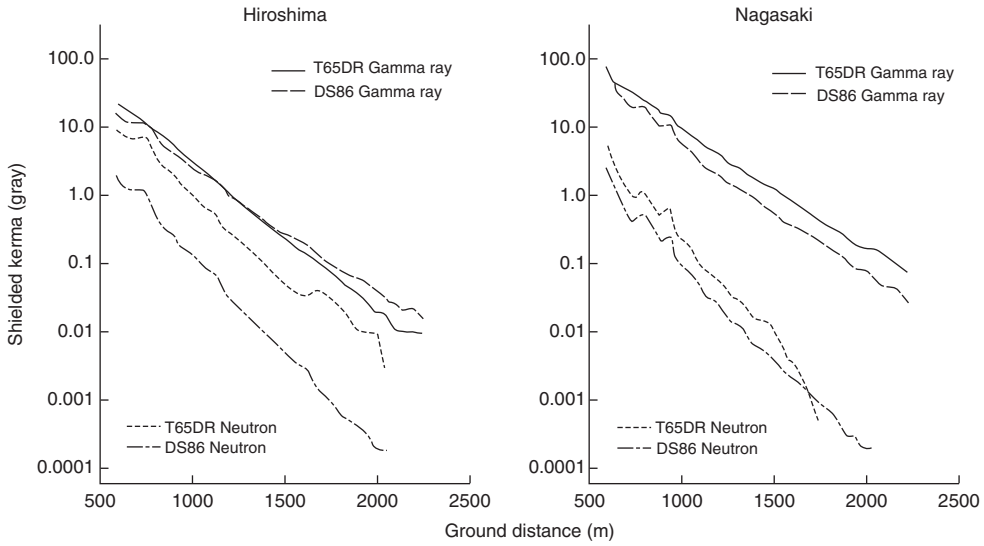


FIGURE 39.1. Shielded kerma (Gy) by city, ground distance from the hypocenter, and dosimetry system. (Shimizu).[29]

Fallout Atomic bomb-induced radioactivity and radioactive fallout from these two atomic bombs were additional sources of radiation exposure for the survivors. These radiation sources were the primary sources of radiation exposure for the early workers entering the bombed areas and the residents of areas receiving only fallout.[31] The radioactive fallout was deposited by yellow-brown clouds at a distance that minimized exposure to neutron radiation. The radioactive fallout was called black rain. This source dominated the radiation exposure in areas including the Nishiyama district near Nagasaki, where the inhabitants were shielded from the atomic blast by Mt. Kompira. The Nishiyama district received most of the fallout from the atomic bomb that exploded over Nagasaki. Although the average dose secondary to external radiation from fallout averaged ~0.3–1.3 Gy (30–130 rads), the only clinical abnormality detected was leukocytosis 2 months following the explosion.[32] Increased ^{137}Cs in the soil and agricultural products accounted for most of the internal radiation dose. These inhabitants did not develop thyroid nodules or thyroid malignancies as the Marshallese of Bikini did when large amounts of neutron-activated ^{131}I in coral debris produced much higher internal radiation doses.[33] In 1969, the average residual dose of external radiation for males and females in Nagasaki was 2.9 μGy (0.29 mrad) and 1.9 μGy (0.19 mrad), respectively.[32] These levels were ~500 times lower than the maximum annual dose limit recommended by the International Commission of Radiological Protection (ICRP) at that time.

Unfortunately, the exact compositions of fission products from the explosion were not directly measured. Based on experimental irradiation of soil from Hiroshima and Nagasaki, the following five radioactive species (half-lives) were most abundant: ^{28}Al (2.3 minutes), ^{56}Mn (2.58 hours), ^{24}Na (15 hours), ^{46}Sc (84 days), and ^{60}Co (5.3 years). Immediately following the detonation of the atomic bombs, the external dose rate primarily resulted from ^{56}Mn (0.94 rads/hour) and ^{24}Na (0.92 rads/hour); however, by 10–15 days post-explosion, the main source of radiation was ^{46}Sc.[31] The estimated cumulative radiation dose from the fallout in Hiroshima calculated over a lifetime was 0.13 Gy (13 rads).

Induced Radioactivity The cumulative radiation dose from soil activated by neutrons and γ-radiation for a person present at the hypocenter and residing there permanently was ~0.8 Gy (80 rads) in Hiroshima compared with ~0.3 Gy (30 rads) in Nagasaki.[26] At 500 and 1000 m from the hypocenter, the radiation dose decreased to 18% and 0.07% of the value at the hypocenter, respectively. These estimations did not consider the following: 1) β-radiation, 2) fallout of fission products, 3) internal doses from inhaled or ingested radionuclides, and 4) shielding.

Weapons

Hypothetical Attacks

Detonation of a nuclear weapon creates the following phenomena that contribute to physiological effects in humans and animals: 1) thermal wave, 2) blast wave, 3) initial γ- and neutron radiation, 4) radioactive fallout, 5) atmospheric disturbances, and 6) electromagnetic

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pulse.[34] A nuclear explosion produces over 200 radionuclides that possess different yields and half-lives as well as different physical and biological characteristics.[35] Individuals receive an **external** dose from the radioactive fallout passing overhead (cloud shine) and the ionizing radiation (neutrons, γ-rays). For most survivors, most of the external dose results from the deposition of radionuclides on the surface. The **internal** dose of radiation results primarily from the ingestion of radioactive material in food and water. Computer models indicate inhalation of radionuclides does not contribute significant amounts of radiation compared with the external dose except for ^{131}I irradiation of the thyroid.[35] These models also predict that the average American family surviving a nuclear explosion in their home would receive an internal dose that represents ~2% (0–0.17 Sv) from ingestion compared with a 48-hour external dose of 0.15–4.6 Sv over 48 hours postexplosion.

Based on nuclear testing at the Nevada Test Site, the most important radionuclides comprising the internal radiation dose are ^{137}Cs and ^{90}Sr with lesser contribution from ^{131}I and ^{89}Sr.[36] Although prediction of a radiation dose of a particular individual during a major nuclear attack is difficult, models (e.g., PATHWAY for calculation of time dependent ingestion) are available to estimate the average internal dose in certain locations given certain assumptions. These variables include the availability of food and water, actual nuclear war scenario, fallout pattern, climatic conditions, shielding from radiation, and transportation. These models can predict the internal dose from multiple explosions over a short period of time or fallout derived from prior nuclear explosions.

Weapons Testing

Between 1945 and 1980, >500 nuclear tests were conducted that released radioactive debris into the atmosphere. The deposition of nuclear debris was less in the Southern Hemisphere than in the Northern Hemisphere where the tests occurred. Nuclear testing began in the Pacific at Bikini atoll and continued until 1958. The large-scale atmospheric testing of nuclear devices occurred primarily between 1952–1958 and 1961–1962 (Christmas Island, Johnson Island). These nuclear explosions carried radioactive materials into the stratosphere where the mean retention time was ~1–5 years.[37] Deposition of radioactive debris was doubled in the mid-latitudes compared with the equator and polar regions as a result of the preferential air exchange between the stratosphere and troposphere in the mid-latitudes and air circulation in the troposphere.[38] Table 39.3 displays the yields of atmospheric nuclear testing from 1945–1980 in millions of tons (megatons) released into the atmosphere. In 1963, the annual average effective dose rate from atmospheric nuclear testing peaked in the Northern Hemisphere at 125 μSv, whereas the dose rate in the Southern Hemisphere peaked at 59 μSv in 1962.[39]

TABLE 39.3. Nuclear fission and fusion yields in megatons (Mt) from atmospheric nuclear tests by 5-year intervals, 1945–1980. (Modified from UNSCEAR).[38]

Interval	Tests	Fission Yield	Fusion Yield	Total Yield
1945–1950	9	0.2	0.0	0.2
1951–1955	83	39.0	23.7	62.7
1956–1960	172	41.8	46.6	89.4
1961–1965	179	90.2	166.8	257.0
1966–1970	29	12.3	8.4	20.7
1971–1975	25	3.1	2.2	5.3
1976–1980	7	2.9	1.9	4.8

In 1954, misjudgments in weather patterns and bomb yield resulted in the exposure of the residents of Rongelap, Ailinginae, and Utirik atolls in the Northern Marshall Islands to radioactive iodides. The estimated external γ-doses in air for evacuated inhabitants of Rongelap, Ailinginae, and Utirik were 1.9 Sv, 1.1 Sv, and 0.11 Sv, respectively, whereas the estimated mean doses of whole body external γ-radiation were ~10% of the external γ-doses in air.[40] Epidemiological data indicate that the highest radiation doses produced adenomatous thyroid nodules in the Rongelap inhabitants. In a study of 168 of the 253 exposed inhabitants ~40 years after the incident, no significant differences were found in the incidence of thyroid nodules or the mean nodule count between the three groups of exposed residents in Rongelap and Utirik and a comparison patient population.[41] Papillary thyroid carcinoma is the most common histological type of sporadic and radiation-associated thyroid cancer; this type of cancer is relatively benign. To date, there has been no mortality in the Marshallese population associated with the 1954 incident.

The fallout from nuclear explosions results in exposure to internal radiation from the ingestion of radionuclides incorporated in food and external radiation from radionuclides deposited on the ground. Epidemiological studies of radiation exposure in inhabitants near the Nevada Test Site have not detected definite evidence of excess cancer risks from fallout exposures; however, risk estimates do not exclude small increases in leukemia and thyroid cancer risks.[42] From 1962–1980, comparatively smaller nuclear weapons testing transported radioactive material only into the

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troposphere; radioactive fallout occurred over days to weeks. Atmospheric testing of nuclear weapons ceased in 1980. Underground testing of nuclear devices generally causes few serious effects on the environment.[37]

Long-lived radionuclides (strontium-90, carbon-14, cesium-137) produce the greatest exposure to ionizing radiation following large atmospheric nuclear tests, whereas γ-emitting radionuclides (ruthenium-106, zirconium-95) are important sources of ground contamination following nuclear explosions in the troposphere. The 1977 UNSCEAR Report estimated the collective dose commitment from nuclear explosions before 1976 at ~800–1,600 million man rad including carbon-14 exposure.[43] At that time, the estimated exposure from natural sources of radiation (~300 million man rad) exceeded the radiation dose from fallout by three to five times; hence, the collective effective dose equivalent commitment from all nuclear testing in the atmosphere is similar to the amount of radiation received by the population from natural sources over 3 years. Consequently, the increased risk of cancer from fallout for the general population is relatively small compared with the underlying cancer risk in the absence of exposure to fallout near the site of detonation.

Radiological Dispersal Devices (RDDs)

RDDs refer to any device used for intentional dissemination of radioactive material without a nuclear detonation. These "dirty bombs" potentially produce radioactive material (dust, shrapnel), distribution of radioactive contamination, blast injury (burns, blunt trauma, penetrating wounds), and panic; however, mass causalities associated with nuclear explosions usually do not occur. Following the detonation of a RDD, most fatalities and injuries would probably result from the trauma associated with the explosion depending on the dispersion pattern, type/quantity of radioactive material released, and device design.[44] Although some persons close to the explosion may require decontamination from external and, less commonly, internal contamination, the contamination level does not usually produce the severe radiation exposure necessary to require medical intervention.[45] Potential radioactive isotopes contained in RDDs include ^{137}cesium, ^{241}americium, ^{60}cobalt, and ^{192}iridium, with ^{252}californium, ^{238}plutonium, ^{210}polonium, ^{226}radium, and ^{90}strontium being much less common.

Power Plants

Production

The nuclear fuel cycle includes: 1) mining and milling, 2) enrichment and fabrication, 3) reactor operation, and 4) reprocessing. The transportation of nuclear material and disposal of waste also represent potential sources of radiation exposure. Although the concentration of radionuclides in effluent is small, some radioactive material is released into the environment at each step. Fuel fabrication and transportation of nuclear fuel usually produce little radiation exposure. Overall, recent environmental monitoring suggests the normalized collective effective dose equivalent commitment for radionuclides in the effluents of nuclear fuel cycle installations is ~4 man-sievert (S)/gigawatt (GW) of electricity produced.[37] The man-sievert is a calculated measure designed to optimized radiological protection with units of J/kg. Based on the current annual nuclear production of 190 GW/year, the annual per caput dose estimate is 0.15 μSv; this value represents ~0.01% of the annual dose from background radiation.

Plant Accidents

Accidents involving the release of radiation may occur at any point in the nuclear fuel cycle, including transportation and processing phases. Additionally, these accidents may be associated with the release of hazardous materials (e.g., hydrogen fluoride, sulfuric acid, chlorine, ammonia, sodium hydroxide, hydrazine). Most accidents at a nuclear power plant involve trauma (superheated steam burns, crush injuries, electrical injuries, blunt trauma from falls, heat illness) rather than significant radiation exposure. Accidental radiation exposure most often occurs during outages (e.g., during refueling) when there is inadequate shielding between a worker and a reactor, an activated metal, or spent fuel rods.

Large-scale nuclear accidents occur when enough fissionable materials (uranium-235, plutonium-239) meet in an environment containing a large neutron flux. Then a nuclear reaction develops, and the core material becomes *critical*. The intense heat from this *criticality* accident causes the fuel rod assemblies to melt and the reactor to explode from excessive steam pressure. A nuclear explosion does **NOT** happen because the reactor fuel contains only 3% ^{235}U in contrast to nuclear bombs that contain up to 90% ^{235}U.

Nuclear power plants contain large quantities of radionuclides; the potential for serious radioactive contamination of the environment exists when the superheated steam is released from the reactor core. The potential health consequences of such a release depend on the characteristics of the individual radionuclides (e.g., chemical and physical properties, biological behavior in the food chain, physical and biological half-lives, decay form). Important radionuclides released from such an environment include: 1) krypton and xenon

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gases (primarily external radiation because of half-lives in hours except the ~11-year half-life of ^{85}Kr), 2) potential release of large amounts of volatile ^{131}I, 3) minimal internal hazard of tritium resulting from a 10-day half-life, 4) ^{137}Cs (a potassium analog with a 30-year half-life), and 5) ^{90}Sr (nonvolatile calcium analog that accumulates in bone with a half-life of several years).

Windscale-1, United Kingdom From a health perspective, ^{131}I was the most important radionuclide released during the fire at the Windscale reactor in the UK on October 10, 1957, especially in the contamination of infant milk.[46] The physical half-life of ^{131}I is ~8 days; however, this isotope is rapidly absorbed and concentrated in the thyroid. The absorbed dose from ingestion of radionuclides (e.g., ^{137}Cs, ^{131}I, ^{89}Sr, ^{90}Sr) far exceeded the dose inhaled from these radionuclides. The age-corrected collective effective dose equivalent for the British population was ~1,200 man-sievert.[47] Risk estimates suggested up to 30 excess cancer deaths resulted from the environmental contamination, with ~½ resulting from ^{210}Po exposure.[48]

Three Mile Island-Unit 2, United States The Three Mile Island plant contains two pressurized water reactors. Figure 39.2 is a schematic diagram of one of these units. Although the actual release of radioactivity from this plant was minimal, the accident dramatized the possibility that enormous amounts of heat and radioactivity could be released from nuclear reactors following a major loss of reactor coolant. At 4 a.m. on March 10, 1979, a slow reactor coolant leak began from the pressurizer within the containment building. Contributing to the accident were the block valves that carried auxiliary feed water to the steam generator. Inadvertently, these valves were closed, resulting in a blockage in the transfer line and the failure of the condensate pumps. The lack of heat removal by the secondary loop dramatically increased the temperature and pressure of the reactor. As designed, the reactor shut down within 1 second and no nuclear explosion occurred; however, the inability of the operators to control continuing heat formation by the decay of fission products led to the accident.

Unknown to the operators, the pilot-operated relief valve stuck open and water continued to pour out of the primary coolant system, ultimately causing spillage of radioactive coolant onto the floor of the containment vessel. Because vibrations developed in the primary coolant pumps, the operators decided to shut off the circulation pumps rather than allow an automatic increase in the amount of water in the coolant system through the high-pressure injection system. These operators mistakenly believed high water levels in the pressurizer meant the primary loop was filled with coolant. In fact, the primary loop contained radioactive, superheated steam. Consequently, the core overheated and steam voids developed throughout the system. Approximately 10 hours after the accident began, a hydrogen explosion occurred in the containment building; however, no explosion ever occurred in the nuclear reactor. Release of radioactive iodine and noble gases followed the inadvertent pumping of radioactive coolant from the floor of the containment building to an auxiliary building.

Exposure Only noble gases and a limited amount of radioactive iodine escaped from the containment building.[49] Up to 3.7×10^{17} Bq (10 MCi) of the radioactive noble gases were released into the environment. The major noble gas was ^{133}xenon (half-life of 5.3 days) and to a lesser extent ^{135}xenon (half-life of 9.2 hours). Approximately 2.6×10^{15} Bq (10 KCi) of ^{131}I escaped from the core; that amount represented ~0.01% of the total amount of ^{131}I in the reactor core.

Dose The highest radiation dose measured outside the containment building was 10.2 mSv.[50] Based on field dosimetry, the Ad Hoc Inter-Agency Dose Assessment Group from the Nuclear Regulatory Commission, the Department of Health, Education, and Welfare, and the Environmental Protection Agency estimated the average collective dose for the population within 50 miles to be 33 man-sievert (3,300 person-rem).[51] The estimated average likely and average maximum whole-body γ-radiation doses for individuals living within 5 miles of the plant were 0.09 mSv (9 mrem) and 0.25 mSv (25 mrem), respectively. These values represent a fraction of the yearly dose received by persons in the United States from natural background radiation.[52] The maximum dose to an individual near the plant assuming no shelter was 0.83 mSv (83 mrem).[50] The population surrounding the plant received no significant internal dose from the ingestion or inhalation of radionuclides released into the environment.[53]

Health Consequences Conservative estimates of the cancer risk from the radioactive gases based on a linear, no-threshold model suggest few adverse reactions would occur.[54] The task force of the President's Commission estimated 0.7 excess cancer deaths with a 50% probability that no deaths would occur.[53] These risk estimates indicate the resulting deaths from this type of radiation exposure could not be detected in an epidemiology study of the exposed population. Increased cancer incidences in the TMI cohort are generally small and nonsignificant statistically. A cancer incident study for the period 1975–1985 did not detect any definite effects

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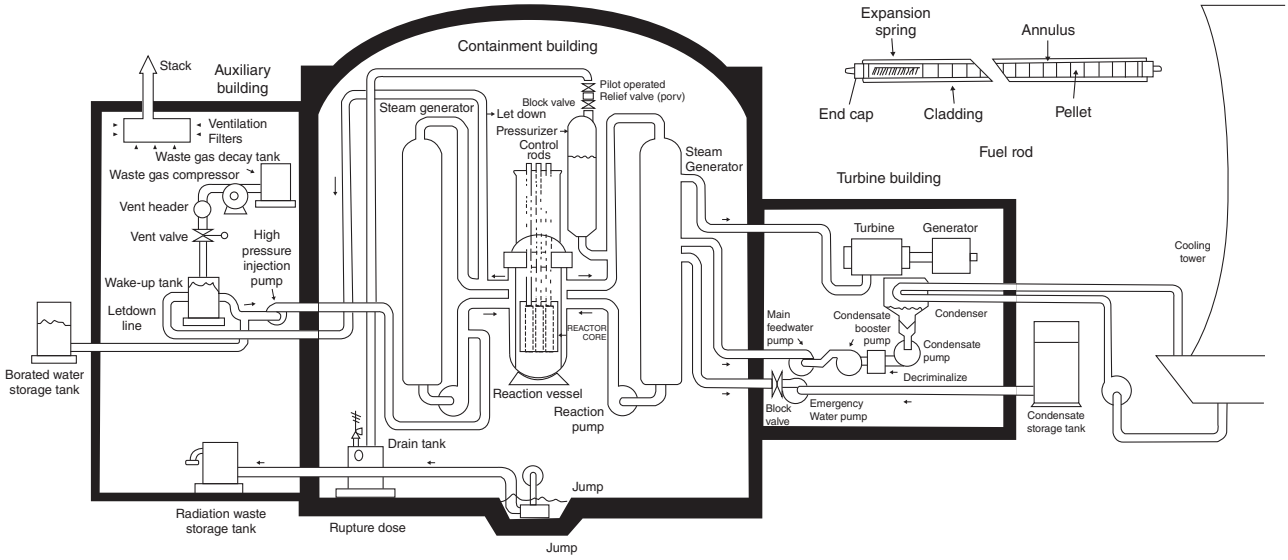


FIGURE 39.2. Schematic diagram of the Three Mile Island reactor. (Shapiro).[1]

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of exposure to the 1979 accident when analyzing the cancer types and population subgroups most susceptible to radiation.[55] Odds ratios for childhood cancers and childhood leukemia demonstrated no clear evidence of statistically significant increases in cancer risks. The confidence intervals were wide with no dose-response relationship between radiation exposure and cancer incidence. A retrospective cross-sectional study of records from 26,357 thyroid cancer patients and 2,611 patients within the Three Mile Island (TMI) area using data from the Pennsylvania Cancer Registry 1985–2008 demonstrated a higher proportion of papillary thyroid cancer ($P < 0.001$) and a lower proportion of follicular thyroid cancer ($P < 0.001$) in the TMI area population.[56] However, the incidence of thyroid cancer in the TMI group was not statistically different from the rest of the state. Using the same data, the risk of all malignant neoplasms was similar (RR = 1.00, 95% CI: 0.97–1.01) between the TMI cohort exposed to higher maximum radiation and the rest of the cohort after adjusting for age, gender, education, smoking, and background radiation.[57] In the higher exposure group, the leukemia risk in men (RR = 1.15, 95% CI: 1.04–1.29) but not women was elevated.

Chernobyl-Unit 4, Ukraine The world's most serious accident at a nuclear power plant occurred at Unit 4 of the Chernobyl nuclear power plant in Ukraine on April 26, 1986. Plant operators were performing a low-power engineering test without appropriate safety system operations when they lost control of the reactor. The subsequent steam explosion blew the 1,000-ton cover off the top of the reactor, and the hot, highly radioactive pieces of the reactor core started fires in nearby buildings. The design of the reactor at Chernobyl was a boiling-water, graphite-moderated reactor that was not in current operation outside the Soviet Union. The reactor had a positive void coefficient at low power that results in multiplication of both neutrons and power following water loss. Furthermore, the containment building provided much less protection than other types of reactor designs.[58] As a result of numerous violations of operating procedures listed in Table 39.4, a prompt critical reactivity excursion occurred that melted the uranium oxide leading to a steam explosion.

This explosion blew off the roof and released ~3–5% of the fission products in the nuclear reactor core as well as all of the noble gases and ~40–60% of the volatile nuclides.[59] The release of radioactive material from the Chernobyl reactor was ~200 times greater than the combined radioactivity released from the two atomic bombs dropped on Nagasaki and Hiroshima.[60]

The explosion and resulting fire vaporized the reactor core and destroyed parts of the reactor turbine buildings. A radioactive plume rose 10 km above Chernobyl. Over the next 10 days, 5,000 tons of material including boron carbide, dolomite, clay-sand mixtures, and molten lead were dropped without successfully suppressing the fire. Finally, the injection of liquid nitrogen into the passages below the reactor core cooled the reactor sufficiently to stop the evaporation of fission products.[1] Twenty-five percent of the release of radioactive material occurred instantaneously, with the rest of the release spreading over the 10-day period before the fires were extinguished.[2] The amount of radioactivity released over the 10 days required to extinguish the graphite fires exceeded previous releases from reactor accidents by several orders of magnitude.

Exposure The explosion and subsequent fire released primarily short-lived radioiodine and long-lived radionuclides including 1,760 petabecquerel (10^{15} Bq) ^{131}I, 85 PBq ^{137}Cs, and 35 PBq ^{134}Cs, along with similar amounts of noble gases as a plume traveling into adjacent parts of Russia, north into Belarus, west into Ukraine, and, to a lesser extent, over Europe and the Northern Hemisphere (e.g., Finland, Norway, Sweden, Austria, Bulgaria).[61,62] The Chernobyl nuclear power plant was

TABLE 39.4. Operator procedure violations during the Chernobyl-4 nuclear power plant incident. (Royal).[50]

Violation	Consequence
Power level below specified procedures	Large positive void reactivity coefficient, resulting in difficulty controlling reactor and overall positive power coefficient
Improperly positioned control rods	Unauthorized configuration resulted in ineffective emergency protective system
Authorized levels of coolant flow exceeded by operating all eight main circulation pumps	Reduced voiding with coolant temperature near saturation
Reactor scram signal blocked from loss of both turbine generators	Lost automatic scram protection at the start of ill-fated test
Reactor scram on water level and steam pressure in the drum separator was blocked	Lost reactor protection system based on thermal parameters
Emergency core cooling system turned off	Lost ability to reduce severity of the accident

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located 10 km south of the border with Belarus. The release lasted ~2 weeks (April 26, 1986–October 5, 1986) with highly variable aerosol characteristics and meteorological conditions causing extremely heterogeneous contamination of the surrounding areas. The most heavily contaminated areas were in Belarus, the Russian Federation, and Ukraine. Initially, the exposure to ionizing radiation consisted primarily of ^{131}I, whereas contamination during later phases resulted mainly from ^{137}Cs, ^{134}Cs, and ^{90}Sr.

For the patients hospitalized with acute radiation syndrome, the primary sources of radiation were external whole-body γ-radiation and extensive high-energy β-radiation to the skin. Contamination by radionuclides did not contribute significantly to the high radiation doses received by these hospitalized patients.[63] Many of the emergency personnel sustained extensive β-irradiation to the skin when highly contaminated water penetrated the porous canvas material of their protective clothing. Sodium-24 analysis indicated neutron exposure was minimal, and lung radionuclide surveys indicated internal contamination did not contribute significantly to the total radiation dose except in two cases.[64]

The initial evacuation of 45,000 people from Pripyat, located 2–4 km from the Chernobyl reactor, was delayed up to 36 hours to select the safest escape route, assemble buses, and reduce radioactive dust by spraying polymers on the ground surfaces.[2] Keeping people indoors during the initial 24 hours when most of the radioactivity was released also reduced their radiation exposure. Winds and rainfall governed the spread of the radioactive material; the deposition of radionuclides was heterogeneous. High radionuclide concentrations were deposited by rainfall in the area near the Chernobyl reactor.

An additional 70,000–90,000 people living within 30 km of Chernobyl were evacuated during the first 2 weeks when the graphite fires continued to release a radioactive plume. The initial cause of radiation exposure for the population surrounding Chernobyl during 1986 was the many short-lived radionuclides consisting primarily of ^{131}Iodine (8 day half-life) and to a lesser extent ^{132}I, ^{103}Ru, ^{95}Nb, and ^{95}Zr.[65,66] In the regions near Chernobyl that were not evacuated, the amount of internal radiation (inhalation of radionuclides from the radioactive plume, ingestion of contaminated food or water) was approximately equal to the amount of external radiation (radioactivity from the plume and fallout).[67] However, most of the short-lived radionuclides decayed by 1987 and the vast majority (>70–99%) of the subsequent radiation exposure resulted from the dispersion of ~70 PBq of long-lived ^{137}Ce with a half-life of ~30 years. This amount of ^{137}Cs corresponds to 22 kg spread mostly across the Northern European Hemisphere.[68] Cesium deposits on plants and enters vegetation through the roots. Rich sources of ^{137}Cs included meat, milk, potatoes, mushrooms, and berries.

DOSE Acute radiation sickness developed only among the reactor staff and firefighters. Eight medical attendants on the scene developed acute radiation sickness including one physician who later died. Because most environmental monitors were destroyed and most personal dosimeters were inadequately designed to detect high doses of radiation, estimation of the actual radiation dose depended on biological dosimetry including onset of vomiting, blood lymphocyte count, and the analysis of the distribution of cytogenic abnormalities. More than 100 workers received an estimated radiation dose of >1 Sv and the 20 most heavily exposed workers received 6–16 Sv (i.e., substantially >50% lethal dose of 4.5 Sv).[69] Because of the magnitude of the accident, complete decontamination on the scene was impossible; therefore, cleanup personnel received some irradiation. The average estimate of the radiation dose received by the cleanup personnel during the first 3 months after the explosion was ~300 mGy based on limited biological dosimetry. The overall average yearly estimated dose for these workers based on information from the Russian Obninsk Registry was 170 mGy in 1986, 130 mGy in 1987, 30 mGy in 1988, and 15 mGy in 1990.[70]

From the standpoint of individual risk, the radiation dose received outside the region of Chernobyl was not significant except for the average dose of external radiation for people living 3–15 km from Chernobyl (0.35–0.55 Sv), whereas the remaining evacuees received a dose of ~0.03–0.06 Sv.[71] The estimated collective effective dose equivalent commitment was ~600,000 man-sievert (S) divided between the USSR (40%) and the rest of Europe (57%). Countries outside the immediate area of Chernobyl (i.e., Russia, Ukraine, Belarus) receiving the largest first-year radiation doses were Bulgaria (0.76 mSv), Austria (0.67 mSv), Greece (0.59 mSv), and Romania (0.57 mSv). The North American and Southern Hemisphere countries received minimal radiation amounts from the Chernobyl accident compared with background radiation. After 1986, the radiation dose in the areas outside Chernobyl resulted almost exclusively from the deposition of long-lived radionuclides, primarily ^{137}Cs. Table 39.5 outlines the contribution of specific long-lived radionuclides to the annual external radiation dose (i.e., short-lived and long-lived radionuclides) from the Chernobyl release normalized to the unit deposition of ^{137}Cs.

The average estimated external radiation dose received by the most heavily contaminated residents of

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TABLE 39.5. Percentage of relative long-lived radionuclides to the total external dose in the Ukraine population caused by the release of short- and long-lived radionuclides from Chernobyl by year. (Likhtarev).[65]

	^{106}Ru	^{144}Ce/^{144}Pr	^{125}Sb	^{134}Cs	^{137}Cs
1986	6.0	1.0	0.5	11.2	9.5
1987	15.8	2.2	1.9	34.6	38.3
1988	12.2	1.3	2.2	33.4	50.6
1989	8.1	0.7	2.3	28.9	59.9
1990	5.1	0.4	2.2	24.1	68.3
1991	3.0	—	2.1	19.4	75.3
1992	1.7	—	1.8	15.3	81.1
1993	1.0	—	1.6	11.8	85.6
1994	0.5	—	1.3	9.0	89.1
1995	—	—	1.1	6.7	91.8
1996	—	—	0.9	5.0	93.9
1997	—	—	0.8	3.7	95.4
1998	—	—	—	2.8	96.6
1999	—	—	—	2.0	97.4
2000	—	—	—	1.5	98.1

TABLE 39.6. Estimated 50-year cumulative radiation dose from cesium isotopes released from Chernobyl as a mean value/inhabitant of all ages. (Adapted from Mole).[72]

Country	Estimated Cumulative Dose (mSv)
Bulgaria, Poland, Romania, Yugoslavia	3.5–4.2
Albania, Austria, Western Germany, Hungary, Italy, Sweden, European USSR	0.9–1.9
Turkey, rest of Europe	0.09–0.8
Asia, excluding Turkey	0.008–0.09
United States, Canada	0.004–0.005

the Ukraine from 1986–2000 was ~40 mSv.[65] Table 39.6 lists the estimated cumulative radiation dose from cesium compounds released from the Chernobyl accident in the country.[72]

Acute Health Effects The Chernobyl accident accounted for ~$^1/_3$ of reported cases of acute radiation sickness reported worldwide. About 134 of the Chernobyl workers and rescue personnel developed acute radiation sickness with 28 short-term deaths within 2 months of the disaster, primarily from bone marrow failure in plant employees and rescue workers receiving whole-body doses of >6.5 Gy.[73] One person died on the scene from trauma and another died several hours later from thermal burns. Extensive skin burns from β-irradiation occurred in 19 of these deaths. No cases of acute radiation sickness occurred in evacuated persons or the general population. Internal contamination was relatively minor clinically. Although incidences of spontaneous abortion in a Norwegian study increased from 7.2% in the 12 months before the accident to 8.3% after the accident, there was no dose-response association between adverse perinatal health effects and radiation dose based on average external radiation doses in Norwegian municipalities.[74] Additionally, studies of Norwegian municipalities did not detect any associations between radiation doses and birth defects typically associated with excessive radiation exposure (e.g., small head circumference, congenital cataracts, anencephaly, spina bifida, low birth weight).[75]

Chronic Health Effects Medically significant radiation doses for individuals were limited to the 30 km zone surrounding the Chernobyl reactor.[76] Estimates on the effect of the radiation released from Chernobyl vary widely depending on the type of model (e.g., absolute vs. relative) used to extrapolate the risk of developing cancer from high-dose exposures to the low radiation levels present in the area around Chernobyl. Instead of reporting only the upper bounds of risk estimates, recent risk evaluations included the zero-risk base commensurate with the possibility that the risk of low radiation doses may be zero.[54] Except for studies of the cohort of 25,000 people living near Chernobyl at the time of the accident, conventional epidemiological techniques are relatively insensitive to the detection of radiation-induced, excess cancer incidence (e.g., leukemia) from the current radiation exposure of the general population.

Demonstrating an increased cancer risk at relatively low annual radiation doses (5–10 mSv) requires a very large database (>100,000 person years).[77,78] Based on an average radiation dose of 0.4 Sv, this cohort may experience up to 25 additional cases (i.e., a 100% increase) in the incidence of leukemia from 1988–1998. The estimated Finnish population-weighted mean effective dose for the first 2 years post-Chernobyl was ~0.4 mSv, with the upper 20% receiving ~1 mSv.[79]

The most common malignancies associated with excessive radiation include leukemias and cancers of the thyroid, breast, and lung. No excess leukemia risk was detected in children during the first 7 years after the Chernobyl accident. In a 15-year follow-up study of 12,000 Belarusian children (median age, 7.9 years; 142,968 person-years at risk), the standardized incidence ratio (SIR) was not significantly increased statistically for nonthyroid solid cancer (SIR = 83, 95% CI: 0.61–1.11), leukemia (SIR = 1.78, 95% CI: 0.71–3.61, $n = 6$), or lymphoma (SIR = 0.66, 95% CI: 0.26–1.33, $n = 6$).[80]

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The major medical consequence of the radiation released from Chernobyl is a significant increase in childhood thyroid cancer in Ukraine, Belarus, and the Bryansk region of the Russian Federation, resulting from the consumption of radioiodine-contaminated milk during May and June 1986.[81,82] By 10 years after the accident, an estimated 1,000 cases of thyroid cancer had resulted from the ingestion of the radioiodine-contaminated milk with an estimated potential of 3,000–6,000 total cases based on ecological studies.[61] By 2005, 6,448 thyroid cancers were associated with children under 18 years of age exposed to radiation from the Chernobyl incident; the majority of the cancers occurred in children <14 years of age. No significant epidemiology studies support an increased thyroid cancer risk for children born after 1986 or for adults exposed during the incident.[83]

The initial latency period appears relatively short (i.e., 4–5 years); the thyroid tumors were unusually aggressive with papillary carcinomas being the vast majority of primary tumor types.[84] However, by 20 years, the clinical course of sporadic and post-Chernobyl thyroid cancer in pediatric patients of comparable age appeared similar with an overall disease-specific mortality rate of ≤1%, despite a high recurrence rate.[85] A prospective analytical cohort study of Ukrainian residents <18 years of age at the time of the incident underwent 4 screenings from 1998–2007; the last 3 screenings detected 65 incident thyroid cancer cases.[86] The excess relative risk (ERR) model described the dose-response relationship better than the excess absolute risk model with an ERR/Gy of 1.91 (95% CI: 0.43–6.34). The ERR/Gy varied significantly with the state (oblast) of residence; the ^{131}I-related thyroid cancer risk persisted throughout the first two decades of observation. There is also a dose-related increase in hypothyroidism in the ^{131}I-exposed cohorts, primarily subclinical and antibody-negative. In a study of 10,827 Belarus residents exposed to radiation from Chernobyl as children (mean = 8.2 ± 5.0 years at exposure), the mean estimated ^{131}I dose was 0.54 ± 0.23 Gy (range, 0.001–26.6 Gy). The excess odds ratio/Gy for hypothyroidism was 0.34 (95% CI: 0.15–0.62), varying significantly with age at exposure, residency, presence of goiter, and age at examination. There was no association between antibody-positive hypothyroidism and the radiation dose.

The association between thyroid cancer in adults and radiation exposure from Chernobyl is not definitive. Consistent evidence of an increased incidence of radiation-related cancers in the Baltic cohort of Chernobyl cleanup workers has not been observed, with the possible exception of thyroid cancer. In a cohort study of 17,040 men from Estonia, Latvia, and Lithuania participating in the environmental cleanup of the Chernobyl Nuclear Power Station from 1986–1991 and followed from 1986–2007, 756 cancer cases were reported.[87] The study detected no increased proportional incidence ratios (PIR) for leukemia or radiation-related cancer sites combined. The PIR for thyroid cancers in men was elevated at 2.76 (95% CI: 1.63–4.36); however, conclusions regarding causation were limited by the effect of thyroid screening among cleanup workers. An excess of esophageal cancers was also detected (PIR = 1.52, 95% CI: 1.06–2.11). Up to 9 years after the incident, studies of cleanup workers at Chernobyl did not detect a greater prevalence of nodular thyroid disease in those workers with the highest radiation exposure when compared with less-exposed workers.[88] Most,[89,90] but not all,[81] of the initial studies on thyroid-cancer rates in contaminated areas of the Ukraine and Russian Federation did not detect excessive cancer rates in adults during the first 9–10 years after the incident. An observational study of 99 of the most severely exposed Chernobyl workers (whole-body exposure, 0.3–8.7 Gy) followed for 12–14 years did not detect any clinically overt thyroid cancer.[91] Twenty-four of these workers reported ingestion of up to 200 μg of iodine daily before and after the accident. To date, studies of cancer rates in the contaminated areas around Chernobyl have not detected increased rates of leukemia in children or adults.[82,92] In a study of 99,024 Russian liquidators living in Russian territory near Chernobyl, the incidence of thyroid cancer increased from 1992–1998 (i.e., after the latent period) compared with the male Russian population with an SIR of 4.33 (95% CI: 3.29–5.6).[93] However, the increased rate was not correlated to the external radiation dose (ERR/Gy = −2.23, 95% CI: −4.67 to 0.22).

Studies of children in Ukraine and Belarus suggest an excess risk of benign thyroid tumors in children after exposure to radiation from the Chernobyl accident.[94,95] A study of 11,613 children aged ≤18 years residing in Belarus at the time of the accident suggested an excess risk of thyroid follicular adenoma following external radiation from Chernobyl.[94] The excess odds ratio/Gy was 2.22 (95% CI: 0.41–13.1) with a linear dose response. The odds ratio decreased significantly with increasing age at exposure ($P < 0.01$) with the highest estimated radiation risk for children ≤2 years. The mean follow-up period was ~3 years with 53% of the original cohort studied in follow-up.

Fukushima Daiichi Nuclear Power Plant Complex, Japan On March 11, 2011, the magnitude 9.0 Tohoku-Pacific Ocean Earthquake occurred 130 miles off the eastern Japanese coast, resulting in a tsunami that

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caused widespread damage at the Fukushima Daiichi Nuclear Power Plant Complex. The damage included the disabling of the cooling system and the subsequent development of fires and explosions in several nuclear reactor units. Subsequent events at the site resulted in the overheating of multiple reactors, core meltdown, and the contamination of surrounding land and coastal waters following the release of radionuclides, particularly ^{137}Cs. The radiation dose to workers and the general public during the Fukushima release was substantially smaller than the massive radiation release at Chernobyl. To date, there have been no confirmed radiation-induced deaths among workers exposed during these events.[96] Only ~30 workers received >100 mSv; these radiation levels were substantially below the radioactivity necessary to produce the acute radiation syndrome. However, this radiation level is sufficient to increase the lifetime incidence of cancer by ~1%. Radiation exposure of local residents was minimal as a result of prevailing winds blowing toward the ocean and establishment of protective measures including evacuation of persons within 20 km of the Fukushima plant, monitoring of food/water, and distribution of stable iodine pills or syrup. Monitoring of these releases in the United States indicated radioactivity levels were below a level of public health concern (i.e., <1% of the EPA Protective Action Guides).

Consumer Products

Blood

Graft-vs.-host disease is a rare, almost invariably fatal complication of blood transfusion in immunocompetent patients. Irradiating blood products with a γ-radiation dose of 15–50 Gy (1,500–5,000 rads) is currently the standard of care for the inhibition of lymphocyte proliferation and the prevention of graft-vs.-host disease.[97,98] Although some decrease in the expected survival times of less mature red cells may occur, mature red cells are highly resistant to these radiation levels. Additionally, most platelet functions, including formation of platelet proteins, are not altered by these levels.[99] The effect of radiation doses of ~50 Gy on neutrophils is more controversial; however, chemotaxis, superoxide production, and bacterial killing capacity remain intact.[100,101] Irradiation of blood products increases the potassium concentration and reduces the sodium concentration.[102] The mean potassium concentration in 20 units of plasma-reduced blood (Hct = 0.55–0.77) was 49 mEq/L (range, 39–65 mEq/L) 4 days after irradiation with 15 Gy, whereas the mean plasma potassium concentration in nonirradiated blood was 55 mEq/L at the expiration date 35 days after blood collection.[103] Plasma sodium concentrations fell concomitantly.

Food

In general, effective vaccines for the prevention of foodborne diseases in humans or animal hosts are unavailable. Irradiation of food is a safe method to substantially reduce foodborne illnesses and extend the shelf life of produce by delaying ripening.[104] Food irradiation technology uses three techniques: high-energy γ-radiation from radioactive ^{60}Co or ^{137}Cs, high-energy electrons (β-rays) emitted from an electron gun, and high-energy X-rays produced by an electron beam hitting a thin metal foil target.[105] The latter penetrates foods to a much greater depth than the few cm of an electron beam. The radiation dose required to kill simple organisms with small amounts of DNA is much higher than that required for more complicated organisms. Ionizing radiation doses of 1,000 Gy inhibit the sprouting of potatoes, reduce insects in cereal, delay the ripening of some fruits, and eradicate *Trichinella* in pork, whereas radiation doses of 50,000 Gy are necessary to eliminate viruses and bacteria in food. Intermediate doses in the range of 3–10,000 Gy reduce bacterial loads and eliminate nonspore-producing pathogens (*Salmonella*, *Yersinia*, *Campylobacter*).[106] The actual radiation dose required to sterilize food varies with the specific pathogen and the characteristics of the food.

Concerns regarding the ingestion of irradiated food include the possibility of increased chromosomal damage and the potential for vitamin loss; however, most nutritional studies, feeding trials, and toxicity studies indicate no significant health risk associated with the consumption of irradiated food.[107] These studies indicate the nutritional changes are less than those caused by pasteurization or canning. Although irradiation temporarily increases free radical formation in food, overall chemical changes in irradiated food are relatively small. Irradiating food with doses of γ-or X-rays up to 10,000 Gy at energies levels of <5 MeV does not affect the safety of food.[108,109] At energy levels of <10 MeV, this process does not produce radioactive particles (e.g., ^{24}Na) in food.[110]

DOSE EFFECT

Typically, low-LET radiation doses are categorized into low (0–0.1 Gy), medium (0.1–1 Gy), and high (>1 Gy) doses. At radiation doses of >1 Gy, acute radiation syndrome occurs; however, quantifying the health

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effects of lower radiation doses (i.e., <0.1–1 Gy) is a complicated task similar to understanding the effects of chemical carcinogens at doses below the range of current experimental and epidemiological data. The two broad categories of health effects occurring after radiation exposure are: 1) stochastic (e.g., genetic damage, cancer) and 2) deterministic (e.g., cataracts, acute radiation sickness, vascular fibrosis). The latter broad category is also known as tissue reactions. The extrapolation of high- to low-dose data several orders of magnitude below verified data produces uncertainty in dose-response relationships near zero dose.[111]

Figure 39.3 schematically represents the extrapolation of radiation-induced stochastic effects (e.g., cancer, genetic abnormalities) from known data points to doses below the radiation doses known to cause effects. Stochastic effects assume no threshold with effects (e.g., cancer) occurring at low radiation doses near zero. Although linear and curvilinear models in the low-dose range fit the high-dose data, the difference occurs in the estimation of low-dose radiation effects. For deterministic effects (tissue reactions), curves shift to the right to account for a threshold effect. Table 39.7 outlines the NCRP estimation of acute gastrointestinal symptoms, acute deaths, and excess cancer mortality associated with specific levels of whole-body radiation.[112]

For philosophical and regulatory purposes, deterministic effects assume a threshold exists where low radiation doses do not cause effects. The data from humans exposed to high doses includes the survivors from Nagasaki and Hiroshima, patients exposed to radiation for medical purposes, and workers in earlier times who received radiation doses exceeding current standards. Examples of radiation-induced cancers include **lung cancer** in uranium miners, **bone cancer** in dial painters and patients with tuberculosis or ankylosing spondylitis

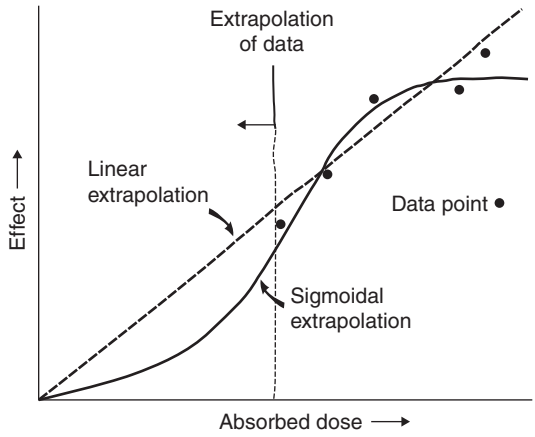


FIGURE 39.3. Schematic representation of the uncertainty of radiation-induced stochastic effects below known data points (<0.25 Gy). Extrapolation of the data below known data points to zero dose may be linear or sigmoidal. (Loken).[113]

ingesting radium, **thyroid cancer** in children receiving radiation for enlarged thymus or *Tinea capitis*, **breast cancer** in patients treated with fluoroscopy for tuberculosis and women receiving radiation treatment for postpartum mastitis, **leukemia** in patients treated with radiation for ankylosing spondylitis, and **solid tumors** and **leukemia** in the survivors at Nagasaki and Hiroshima. In the atomic bomb survivor cohort, significant dose-responses were observed for mortality from several solid tumor sites including esophagus, stomach, colon, lung, breast, ovary, urinary bladder, multiple myeloma, and central nervous system tumors (e.g., brain).[114]

Factors

The radiation dose as measured by the absorbed dose (mSv) received by a patient depends on several factors

TABLE 39.7. Estimated dose-response of acute symptoms, acute death with/without medical care, and excess risk of fatal cancer in healthy, noninjured adult emergency workers exposed to whole-body radiation based on National Council on Radiation Protection and Measurements data. Acute deaths typically occur 30–180 days after exposure. Gastrointestinal (GI) symptoms include nausea and vomiting beginning within 4 hours of exposure. The lifetime excess risk of death from cancer is the cancer mortality above the 24% of the general population likely to die from cancer. (Adapted from NCRP).[112]

Acute Whole-Body Dose (Sv)	Acute GI Symptoms (%)	Deaths *Without* Medical Care (%)	Deaths *With* Medical Care (%)	Lifetime Excess Risk of Fatal Cancer (%)
0.1	0	0	0	1
0.5	0	0	0	4
1	5–30	>5	0	8
1.5	40	<5	<5	2
2	60	5	<5	16
3	75	30–50	15–30	24
6	100	95–100	50	>40
10	100	100	>90	–

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TABLE 39.8. Shielding required to reduce the energy of specific photons by 50% (half-layer value) for water, concrete, and lead in centimeters. (Mettler).[17]

Photon (MeV)	Water (cm)	Concrete (cm)	Lead (cm)
0.1	4.2	1.7	0.015
0.2	5.0	2.3	0.065
0.4	6.5	3.0	0.27
0.6	7.8	3.6	0.5
0.8	8.8	4.0	0.7
1.0	9.6	5.0	0.9
2.0	14.0	7.0	1.3
5.0	23.0	11.0	1.5

including: 1) distance between the source and the patient, 2) time in the field of radiation, 3) extent of shielding between the patient and the source, and 4) the radiation amount and quality. Distance probably is the most effective way to reduce the radiation dose because the absorbed dose varies as the inverse square of the distance between the patient and the radiation source. Hence, doubling the distance decreases the radiation dose to $^1/_4$ of the previous value (1\distance^2). The amount of time spent in the radiation field is directly proportional to the absorbed dose. Doubling the amount of time in the field also doubles the absorbed dose. The reduction of the absorbed dose resulting from the interposition of shielding between the patient and the source of radiation depends on the density of the shield.

Lead is the usual metal used to shield patients, as a result of its high density. The half-value layer (HVL) and the tenth-value layer (TVL) measure the effectiveness of the shielding; these values represent a reduction of the absorbed dose by 50% and 90%, respectively.

Table 39.8 lists the amounts of different shielding types necessary for a 50% reduction in the radiation delivered by photons. As seen in Table 39.8, the effectiveness of shielding also depends on the energy of radiation source. Unfortunately, shielding during most radiation accidents is not very effective because the very high energy of the radiation emitted during these accidents easily penetrates the shielding.[115]

Stochastic Effects

Stochastic effects result from modification of an irradiated cell rather than cell damage. Tumors, teratogenic abnormalities (primarily mental retardation), and genetic effects are the classic examples of stochastic effects. The occurrence of these delayed effects is probabilistic; the expression of these effects depends on the number of cells initially modified and the size of the cell population. Increasing the dose increases the chance a cancer will appear; however, larger doses do not enhance the disease's severity. Consequently, only a small fraction of people exposed to a specific radiation dose will develop stochastic effects because cellular repair and defense mechanisms reduce the number of modified cells. Although a DNA repair mechanism may operate well, especially in the absence of cell division, safety concerns dictate the acceptance of the absence of threshold for effects related to low radiation doses. Therefore, stochastic effects potentially can occur at substantial distances from the radiation source.

Deterministic Effects (Tissue Reactions)

Deterministic (nonstochastic) effects result from radiation-induced cellular destruction, acceleration of normal physiological process of programmed cell death (apoptosis), and the resulting organ dysfunction. The severity of the health effect depends on several factors including total radiation dose, delivered dose rate (e.g., fractionated doses are typically 4-fold less potent than the same single radiation dose), radiation type, and tissue volume radiated.[116] Deterministic effects manifest within hours to days in response to radiation doses of >0.25–1 Sv as a direct result of the termination of cell division and excessive cell death; late deterministic effects (e.g., cataracts) may occur years after radiation exposure. The appearance of effects from the destruction of irradiated cells depends on cell loss sufficient to impair function; hence, there is a threshold below which these acute effects do not manifest. Deterministic effects are predictable in an individual depending on the radiation dose, whereas stochastic effects (e.g., cancer) develop in a few individuals exposed to the same radiation level. Teratogenic effects from *in utero* exposure may display deterministic or stochastic characteristics. Some deterministic effects (e.g., fibroatrophy, vascular fibrosis, cataracts, infertility, growth retardation, hypothyroidism) are delayed; however, the expression of these changes is not related to age as occurs with cancer. The amount of radiation-induced damage depends on the sensitivity of the organ as well as the absorbed dose.

The incidence and latency period for early prodromal symptoms of the acute radiation syndrome are dose-related. Vomiting occurs in 50% of patients within 3 hours of exposure to 2 Gy, whereas reduction of the lymphocyte count begins within 48 hours of acute exposure to 1–2 Gy. The LD_{50} for uniform low-LET radiation is ~3 Gy for cancer patients compared with ~4.5 Gy for

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TABLE 39.9. Approximate dose-effect relationship of whole body ionized radiation. (Adapted from Mettler and Voelz).[118]

Dose[a] (Gy)	Prodrome[b]	Clinical Features	Prognosis[c]
0.05–0.1	Absent	None	Survival
0.15–0.2	Absent	Chromosomal aberrations in cultured blood lymphocytes; reduction of sperm count with nadir at 45 days after exposure. No symptoms	Survival
0.5	Absent	Minor reduction in leukocytes and platelets	Survival
1	Mild, <48 hours	Detectable bone marrow depression (Hematopoietic syndrome begins), nausea/vomiting in ~10%	Survival highly likely (>90%)
2	Mild–Moderate, <24 hours	Nausea/vomiting in ~50% with marked reduction in leukocytes and platelets	Survival likely
2–3.5	Moderate		Probable survival
3.5–5.5	Severe, <8–12 hours	Moderate–severe bone marrow damage; slight GI damage (Nausea/vomiting ~90%, diarrhea ~10%)	50% mortality within 6 weeks
5.5–7.5	Severe	Pancytopenia; moderate gastrointestinal damage	100% morality from bone marrow failure within 30 days absent treatment
7.5–10	Severe	Marked gastrointestinal and bone marrow damage, hypotension	Rare survival at lower end of exposure with best medical care; death typically within 1–2.5 weeks
10–20	Immediate	Nausea/vomiting in all patients; severe gastrointestinal damage, pneumonitis, altered mental status	Death is certain within 1–2 weeks
20–30	Immediate	Cardiovascular/CNS syndrome (nausea/vomiting, hypotension, shock, convulsions, fever)	Death is certain within 1–5 days

[a] Whole-body absorbed dose in Gray (Gy); [b] Onset of symptoms is dose and dose-rate dependent; NA – not applicable; [c] Without therapy.

previously healthy patients receiving supportive care.[117] Survival is unlikely when the radiation dose exceeds 8 Gy. Low-LET radiation doses of 10–50 Gy usually cause a fatal gastrointestinal syndrome within several weeks, whereas doses of >50 Gy produce a fatal neurological syndrome within several days. Neutrons have a higher linear energy transfer (LET) compared with X- and γ-rays by a factor of 2–3.

The constellation of clinical signs and symptoms of the acute radiation syndrome follows a predictable pattern based on the inherent sensitivity of these cells. After absorbed doses of <1 Gy, tissue damage is not usually severe; most cells initially survive; however, malignant transformation may occur much later.[118] Generally, the larger the dose, the more severe and the sooner symptoms appear. Table 39.9 outlines the features of the acute radiation sickness based on whole-body radiation dose.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

The biological effects of ionizing radiation depend on several factors including total dose, dose rate, volume and type of tissue irradiated, specific anatomical part irradiated, and individual susceptibility (i.e., associated trauma and disease, metabolic polymorphisms, altered DNA repair capacity, hormonal imbalance, suppressed immunity). Maximum sensitivity of cells to ionizing radiation occurs during the mitotic phase of the cell cycle; therefore, rapidly dividing tissues (e.g., lymphocytes, myeloblasts, endothelial cells) are very sensitive to the effects of ionizing radiation. Similarly, embryos are much more sensitive than adults.

Biological Response

During passage through tissue, ionizing radiation transfers virtually all its energy to electrons that subsequently lose their energy by ionizing the irradiated medium. Directly ionizing particles (α, β) are charged; they deposit their energy by electrical interactions with nearby orbital electrons. Low-LET, indirectly ionizing radiation (i.e., γ-rays, X-rays) liberates orbital electrons that interact with other atoms to produce ions. The deposition of energy by neutrons is more complex. For neutrons with energies below 20 MeV, 90% of the absorbed energy in tissue results from protons that recoil

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from elastic collisions with neutrons.[9] As the energy of the neutron exceeds 20 MeV, inelastic scattering (i.e., emission of photons after the collision) and the spallation process (i.e., fragmentation of the nucleus with emission of particles and nuclear fragments) become more dominant processes.

Although the physical interaction that causes the formation of ions occurs in femtoseconds (10^{-13}–10^{-14} seconds), chemical events produce tissue damage following the initial ionization of atoms and molecules within the tissues. The most important initial radiochemical reactions occur in water because the average cell contains 70% water. Several important reactive species form from the radiolysis of water by ionizing radiation including: 1) aqueous electrons (e_{aq}), 2) hydroxyl free radicals, and 3) hydrogen free radicals. Initially, ionizing radiation produces aqueous electrons that subsequently form free radicals. The free radicals are uncharged (neutral), highly reactive atoms, or molecules with unpaired electrons. These highly oxidizing compounds readily react with cellular components (e.g., DNA) to destroy chemical bonds and disrupt cellular processes. This indirect reaction of free radicals with DNA is probably a more important cause of biological damage than the direct interaction of electrons with DNA, cellular membranes, or protein synthesis.

Biological damage from ionizing radiation results from direct and indirect effects. The former involves cellular DNA damage (double-stranded, single-stranded, base damage); the most critical cause of radiation-induced cell death is DNA double-strand breaks. Indirect effects involve the interaction of ionizing radiation with free or bound intracellular water to form reactive oxygen species (free radicals). Approximately $^2/_3$ of biological damage from high-energy photons released by X- and γ-rays results from the generation of free radicals and proinflammatory chemokines/cytokines (e.g., transforming growth factor-β, tumor necrosis factor, IL-1, IL-6), whereas direct DNA damage accounts for the remaining damage.[119] The covalent bonds in DNA molecules in the chromosomes are the primary molecular target with repair or miss repair of critical DNA lesions determining sensitivity of somatic and germline cells to ionizing radiation. The major types of damage to the chromosomes include alterations of DNA bases, single- and double-stranded chromosome breaks, formation of DNA adducts, chromosomal aberrations, aneuploidy (i.e., abnormal number of chromosomes), and altered DNA methylation. Double-stranded breaks in the chromosomes are not repaired easily; therefore, this type of damage and the subsequent loss of the associated gene products coded by the affected segment of DNA are important mechanisms of radiation-induced cell damage.[120] These molecular changes produce functional changes in the signaling pathways critical to cellular function including dysregulation of DNA repair mechanisms, alterations in cyclin-dependent kinases and cell cycle progression, posttranslational modifications of proteins, suppression of apoptotic rates, changes in secretory factors that stimulate DNA replication and transcription, and alteration of gap-junction mediated intercellular communications.

Radiation-induced, chemical-induced, and spontaneous cancers share a similar complex, multistep process. Animal experiments suggest low-dose radiation (i.e., ≤0.1 Gy) affects primarily initiation, whereas high-dose radiation (≥1 Gy) also enhances later stages (promotion, progression).

Tissue Sensitivity

Radiosensitivity of specific tissues depends on mitotic activity and regenerative processes. For low-LET radiation, the most sensitive stages to cell death are mitosis and late G_1. The survival of cells decreases with increasing radiation doses. All cells die at radiation doses of several hundred Gy; at radiation doses of 1–2 Gy, most cells will not divide.[121] Tissue susceptibility to ionizing radiation depends directly on the cellular proliferation rate and inversely on the degree of cell differentiation, as defined by the law of Bergonie and Tribondeau in 1906.[122] Cell survival is relatively lower with high- than low-LET radiation. In contrast to low-LET radiation, cell survival is relatively independent of the dose rate for high-LET radiation. Radiation-induced cancers are pathologically indistinguishable from cancers in the same tissues caused by other carcinogens. Although radiation causes a wide variety of tumors as determined from epidemiological studies on the survivors of the atomic bombs dropped on Hiroshima and Nagasaki, susceptibility of individual tissues to radiation-induced cancer varies widely.[123] Table 39.10 lists the relative sensitivities of different tissues to radiation-induced cancer.

Latency

The acute expression of tissue damage depends primarily on the kinetics of cell loss rather than functional deficiencies in irradiated, viable cells for deterministic effects. Tissues with rapid cell turnover (e.g., epithelium of the gastrointestinal tract, blood cells) react earlier than tissue with long-lived cells (e.g., thyroid, central nervous system). For low doses, the latency period prior to the appearance of gross tissue injury is dependent on the dose, whereas the latency

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TABLE 39.10. Relative susceptibility of various tissues to radiation-induced cancer based on increased incidence/unit dose. (Adapted from Mettler and Upton).[123]

Relative Susceptibility	Tissues
High	Bone marrow (leukemia except CLL), female breast, salivary glands, thyroid (females > males)
Moderate	Bladder, colon, liver, lung, ovary, skin, stomach
Low	Bone, brain, connective tissues, kidney, larynx, nasal sinuses
Very Low/Absent	Cervix, CLL, esophagus, gallbladder, Hodgkin's disease, lymphatic system and myeloma, melanoma, muscle, pancreas, prostate, testes, uterus

Abbreviation: CLL = chronic lymphocytic leukemia.

period is dose-independent for high radiation doses.[124] Table 39.11 summarizes the effects and doses associated with acute radiation injuries to some human organs.

Pathological Changes

Lethal radiation doses produce widespread destruction of tissues in radiosensitive organs (i.e., high metabolic rate, rapidly proliferating cells including the lining of the small bowel, bone marrow, salivary gland) and superficial dermal tissue exposed to the highest radiation dose. Organs with less radiosensitivity (i.e., slowly proliferating cells) include blood vessels, connective tissues, liver, and kidney. The pathological effects of radiation result primarily from disruption of cell reproduction along with some cell death. Cells sensitive to radiation include: 1) rapidly dividing cells, 2) undifferentiated cells, and 3) cells dividing at the time of radiation exposure.[125] Cells relatively resistant to radiation include liver, kidney, muscle, cartilage, nervous tissue, and the nonmarrow portion of the bone. Radiosensitive cells (e.g., immature spermatogonia, oocytes, lymphocytes) undergo degenerative changes within minutes of exposure to radiation doses of ~1 Sv; however, most pathological evidence of destruction becomes apparent only after the dying cells fail to divide and regenerate.

Cell necrosis usually occurs during or shortly after mitosis, particularly in rapidly dividing cells that populate the skin, gastrointestinal tract, and hemopoietic organ systems.[126] The extent of damage revealed by autopsy depends on the period of survival following exposure to the lethal radiation dose and the ability of surviving stem cells to replace lost cells. Radiation-induced injury ranges from immediate inhibition of mitosis in the epidermis and germinal epithelium of the gastrointestinal tract to degenerative changes in the lens and vessels months to years later. Exposure to high radiation doses causes a gradual reduction in the patency of the capillaries and the number of capillary beds. These changes are nonspecific including hypocellular bone marrow, loss of follicles in the spleen, prominence of nuclear fragments, and atrophy of the villi and glands in the gastrointestinal tract.[127]

Thyroid

Early radiation-induced alterations of the thyroid include vacuolization and eosinophilic granulation in the follicular cell cytoplasm, nuclear pyknosis, phagocytosis, and stromal edema with high radiation doses producing severe degenerative changes including desquamation of the follicular epithelium, extrafollicular colloid, and Hürthle cells.[128] Chronic pathological changes include interstitial fibrosis, vascular damage (intimal thickening and hyalinization of arterioles and medium-sized arteries), and focal calcification in the internal elastic membranes.[129,130] Benign thyroid nodules commonly occur after radiation, particularly multinodular goiter; thyroid cancers primarily involve papillary thyroid carcinomas.[130]

Bone Marrow

The most dramatic changes occur in the blood following exposure to ionizing radiation, with lymphocyte depletion appearing within several hours of exposure. There is a dynamic balance between the depletion of hemopoietic elements and the regeneration of these elements depending on the life span of the marrow stem cells and the time since exposure. The marrow can regenerate at acute radiation doses up to 6 Gy.[131]

Central Nervous System

The lack of rapid cell turnover limits the pathological evidence of acute injury to the brain including aggregations of granulocytes along the blood vessels, cerebral edema, and some localized changes (e.g., damage to the granular cell layer of the cerebellum).[125] Pathological changes include disruption of the blood–brain barrier, meningeal inflammation, impaired capillary circulation, interstitial edema, petechial hemorrhages, and hypertrophy of perivascular astrocytes.[132] Neurological symptoms in a patient dying 49 hours after receiving an 8.8-Gy whole-body dose of neutron radiation resulted from vascular damage and impairment of the cerebral circulation rather than primary destruction of

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TABLE 39.11. Latency, threshold, cause, and target cells of acute radiation injury (deterministic effects) on some human tissues from single radiation doses and single-dose equivalents calculated from fractionated radiation doses. Before the expression of gross tissue damage from inhibition cell replication reflected in the threshold dose column, the latency period from this damage is dose-dependent at low radiation doses and dose-independent at high doses. Changes in organ function occur at radiation doses well below the listed threshold of clinically apparent tissue damage (e.g., the sperm count begins to decrease ~1½ months after a radiation dose of 1 Gy, reduction of absolute lymphocyte count within several hours after radiation exposure with a nadir in ~48 hours and duration up to several weeks). Oligospermia may begin after a radiation dose of 0.15 Gy and azoospermia 10 weeks after a radiation dose of 1 Gy. (Adapted from Hendry).[124]

Tissue (Effect)	Latency Period	Threshold Dose (Gy)	High Incidence Dose (Gy)	Cause	Target Cells
Eye (cataract)	>1 year	2[a]	10	Abnormal cell maturation	Fiber-forming lens, epithelial cells
Whole body growth, Retardation	Age[b]	≤7.5	—	↓Growth hormone[c]	Hypothalamic pituitary axis
Lung (pneumonitis)	$M = 3$ months (1–7 for 90% of patients)	8.2	>10	Reduced barrier and alveolar surfactant	Type II alveolar cells[d]
Ovary					
(Infertility)	<1 month	≤4 (↑ younger women)	~10	Ovarian failure	Oocytes
(Sex development)	Age[b]	~10	—	↓Estrogen	Ovary
				↓Gonadotrophin	Pituitary
Testes					
(Sexual development)	Age[b]	~10	—	↓Testosterone	Leydig cells Pituitary
				↓Gonadotrophin	
Thyroid					
(↓ Growth, Metabolism)	<1 year	≤7.5	—	Hypothyroidism	Follicular cells

Abbreviation: M = mean (90% range, 1–7 months).

[a] In 2007, the ICRP estimated the occurrence of lens opacities may occur after single, acute radiation exposures of 0.5–2 Gy or following protracted radiation exposures of 5–6 Gy based on their review of animal and epidemiology studies. The exact threshold is unclear because of the heterogeneity of the data, multiple lens opacity classification systems, and short follow-up periods; [b] Age-dependent; [c] High doses, cartilage and bone are affected at lower doses by effects on chondrocytes; [d] Possibly endothelial cell involvement.

neurons.[133] Only minimal amounts of neuronal damage and glial reactions occurred in this case; death resulted from cardiac failure, increased intracranial pressure, and cerebral anoxia. Within 4–5 months of exposure to an absorbed radiation dose of >15 Gy, focal necrosis, calcifications, gliosis, and demyelinization of the white matter can appear. Little direct damage to neurons occurs at doses of <60 Gy.[131]

Heart

Radiation reduces the number of capillary beds following exposure to doses of >15 Gy. Although little damage occurs in the nonproliferating cells of the myocardium, the subsequent reduction in blood flow can cause secondary myocardial necrosis, pericardial effusions, and myocardial fibrosis.

Intestines

The rapidly dividing epithelial cells in the mucous membranes of the mouth and oropharynx are radiosensitive, resulting in the development of painful oropharyngeal lesions that persist for weeks. Altered gastric emptying and reduced gastrointestinal motility produce vomiting, diarrhea, and abdominal cramps. Loss of the mucosal barrier and changes in the normal gastrointestinal flora allow systemic access and predispose the patient to sepsis. Poor gastrointestinal function results in rapid weight loss. Radiation-induced injuries range from loss of crypt cells at absorbed doses of 1 Gy to complete loss of villi and denudation of the entire epithelia during severe forms of the gastrointestinal syndrome. Damage to the capillary endothelium results in fibrosis of the muscular layer and the serosa. A 35-year-old man died from the gastrointestinal syndrome and multiorgan failure 82 days after receiving 16–25 Gy of γ-ray and neutron radiation, despite receiving peripheral blood stem cell transplantation on days 6 and 7.[134] Pathological findings included blood clots throughout the gastrointestinal tract, ablated mucosal epithelial cells, mucosal congestion and bleeding, dyskaryotic cells in the stroma, submucosal fibrosis, and smooth muscle degeneration.

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A few squamous cells appeared in the esophagus along with a few epithelial cells in the descending colon, sigmoid colon, and rectum; however, no remnants of epithelial cells remained in tissues from the stomach to the ascending colon, probably reflecting the position of the abdomen at the time of irradiation and resulting in differences in the radiation dose delivered to various parts of the gastrointestinal tract.

Liver

Damage to the sinusoidal endothelium in the lobules can produce obstruction of the central lobules, secondary loss of hepatocytes, and portal hypertension within 6 weeks of exposure.

Lung

Ninety days after exposure to doses of 10 Gy, acute pneumonitis appears as a result of the occlusion of capillaries and loss of endothelial cells. Depletion of type II pneumocytes and surfactants precedes the development of pneumonitis. Hypoxia and interstitial edema of the lungs may develop during severe radiation syndrome.[135]

Kidney

Reduction of the cells lining the tubules occurs acutely after acute radiation doses of 10 Gy. Occlusion of the capillaries leads to loss of nephrons 4–18 months following exposure. Eventually, damage to the glomeruli and secondary hypertension appear.

Skin

In contrast to the acute radiation syndrome, the severity of skin damage depends on the local radiation dose and depth of dermal penetration rather than the whole-body radiation dose. Alpha particles do not penetrate the horny layer of the skin (i.e., <0.1 mm); however, prolonged contact produces serious burns from the highly ionizing properties of α-particles (30,000 ion pairs/cm air). Beta particles can penetrate skin (i.e., 1–2 cm) causing more intense, localized dermal damage than α-particles. Although γ- and X-rays are weakly ionizing, they penetrate deeply (i.e., many cm) into the body, depending on the tissue density with dermal damage inversely proportional to the energy of the γ- or X-ray. Neutrons penetrate >2 cm into the skin where collisions with stable atoms produce protons, α- and/or β-particles, and γ-rays. The relative biological effectiveness of neutrons is greater than that of other forms of electromagnetic radiation.

Transient vasodilation, interruption of cell proliferation in the basal layer, and thinning of the prickle cell layer result after exposure to acute radiation doses of 3–9 Gy. Initial erythema probably results from the release of vasoactive amines, whereas the second erythematous phase develops 2–3 weeks after the radiation exposure, depending on the radiation dose and skin tolerance. Animal models suggest the repair of radiation-induced intracellular injury is complete within 6 weeks in the absence of permanent damage; subsequent dermal changes result from capillary damage, fibrosis, and local ischemia. This biphasic late phase of skin damage results from narrowing of the blood vessels from fibrosis and obliteration of the capillaries secondary to endothelial damage.[136] The resulting vascular damage leads to ischemic necrosis. The latter phase is associated with mauve or blue discoloration of the skin. Secondary ulceration occurs from infection or dehydration of the dermis in patients with severe moist desquamation. Ulceration of the skin, loss of hair follicles, and damage to sweat glands occur when radiation exposure exceeds 20 Gy.

CLINICAL RESPONSE

The clinical pattern of acute radiation syndrome (ARS) varies in intensity, duration, and onset, depending on the extent of dose-dependent damage to tissue.[137] Variations in radiation exposures include whole-body exposure (acute radiation sickness), localized exposure from handling highly radioactive sources, internal contamination from pulmonary, gastrointestinal, or dermal absorption of radioactive nucleotides, and external contamination of clothing and exposed skin. ARS results from acute exposure to whole-body radiation doses of >1 Sv characterized by dose-dependent dysfunction of the hematopoietic system, gastrointestinal tract, and central nervous system.[138] The biological effectiveness of γ- and β-radiation is the same; therefore, the gray (Gy) and the sievert (Sv) are equivalent measures of the biological effect of an absorbed radiation dose from these two types of radiation. ARS is a rare event that occurs following the accidental release of high γ-rays, X-rays, or neutron radiation doses at large nuclear facilities (e.g., power plants, research/medical facilities, commercial organizations), the detonation of nuclear bombs, or the improper disposal of nuclear material. The importance of the initial symptoms of ARS results from the positive association between onset of prodromal symptoms and the amount of radiation received by the victim. Because of the prognostic value of the early onset of prodromal symptoms, the

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initial clinical pattern is an important early prognostic indicator to help triage victims based on their ultimate outcome.

Deterministic Effects

Deterministic clinical effects (tissue reactions) occur when the radiation dose is sufficient to damage enough critical cells in an organ to cause dysfunction (e.g., neutropenia, bone marrow failure). The severity of injury is dose-dependent (i.e., dose determines the effect) with a threshold and delivered at relatively high dose rates (e.g., >~0.05 Gy/hour).[119] Generally, the threshold for acute radiation sickness is ~1 Gy. In contrast to deterministic effects, stochastic effects occur in a random, probabilistic association with no threshold (e.g., cancer, birth defects). The risk of a stochastic effect increases with dose, but not the severity of the effect. Although genetic hereditary effects occur in animals exposed to radiation, human studies have not observed these effects.[139]

Acute Radiation Sickness

Sufficiently high radiation exposure over a short time causes acute radiation sickness (acute radiation syndrome, multiple organ dysfunction syndrome, radiation sickness, radiation poisoning, ARS). Although the biological effect of radiation is dose-dependent, most radiation exposures do not irradiate the body uniformly; additionally, sensitivity of the tissues to radiation varies (e.g., abdominal radiation produces more acute effects than an equivalent radiation dose to the chest or an extremity).[137] Factors affecting the response to a radiation dose include total radiation dose, dose rate, radiation quality, fraction of the body irradiated, amount of shielding, and a variety of individual factors determining radiation sensitivity (e.g., demographic, dietary, genetic, age, sex, preexisting medical conditions). Acute radiation sickness occurs following whole-body or significant partial-body irradiation exceeding 1 Gy delivered at a relative high dose rate. Acute radiation sickness comprises four life-threatening syndromes (hematopoietic, gastrointestinal, neurovascular, cutaneous); the clinical pattern of these syndromes includes: 1) a prodromal phase within the first few hours, 2) a latent period that decreases with dose, 3) the manifest phase of the illness, and 4) death or a recovery period extending weeks to months.[118,140] The clinical features of ARS may present as a combination of multiorgan effects.

Figure 39.4 demonstrates the time sequence of the major events that comprise the acute radiation syndrome based on clinical signs and absorbed radiation dose. Although the clinical course following radiation exposure depends primarily on the absorbed whole-body dose, variation in the presentation of symptoms will occur due to various factors including the underlying health of the patient, the type of medical treatment, environmental conditions, and the extent of associated trauma.[141] Cells that replicate rapidly (e.g., intestinal crypt cells, lymphohematopoietic elements, spermatocytes) are the most radiosensitive.

Ionizing radiation shortens the life span primarily from the development of cancer rather than an acceleration of the aging process.[143] Classically, mortality from diseases other than neoplasms is not consistently associated with epidemiology studies of radiation exposure;[121] however, aging and radiation exposure share similar pathological mechanisms, including oxidative stress, inflammation, stem cell exhaustion, chromosomal damage, and apoptosis.[144] Epidemiological evidence from Nagasaki and Hiroshima suggests low to moderate radiation doses affect mortality associated with some noncancerous diseases (e.g., cardiopulmonary disease, stroke, digestive disease); these studies do not detect increased mortality from Alzheimer's disease, type 2 diabetes, or infectious diseases.[145]

Prodrome

Nonspecific prodromal symptoms appear promptly within 1–2 hours to several days of radiation doses of >1 Gy. Although symptoms of stress may appear, absorbed radiation doses of <0.15–0.5 Gy are not typically associated with prodromal symptoms.[146] Prodromal symptoms include nausea, vomiting, diarrhea, anorexia, fatigue, headache, dermal erythema, erythematous mucous membranes, and glandular swelling, with higher doses producing increased severity, more rapid onset, and longer duration. Prodromal symptoms may cause significant dehydration. The onset of nausea and/or vomiting within 12–24 hours indicates a medically significant exposure beginning with the appearance of nausea. Vomiting 2–5 hours following exposure indicates a potentially severe radiation exposure; most individuals (80–100%) with total-body radiation of >3.5 Gy vomit.[141] However, estimation of the radiation dose based on the onset of emesis alone is imprecise and may produce high false-positive rates.[147] Serious radiation exposures may also occur in the absence of vomiting.

At Chernobyl, nausea and vomiting appeared in the most severely exposed victims within 15–30 minutes following the explosion; the onset of vomiting also depends on the radiation dose rate.[148] Among the 126 victims manifesting one or more prodromal symptoms within

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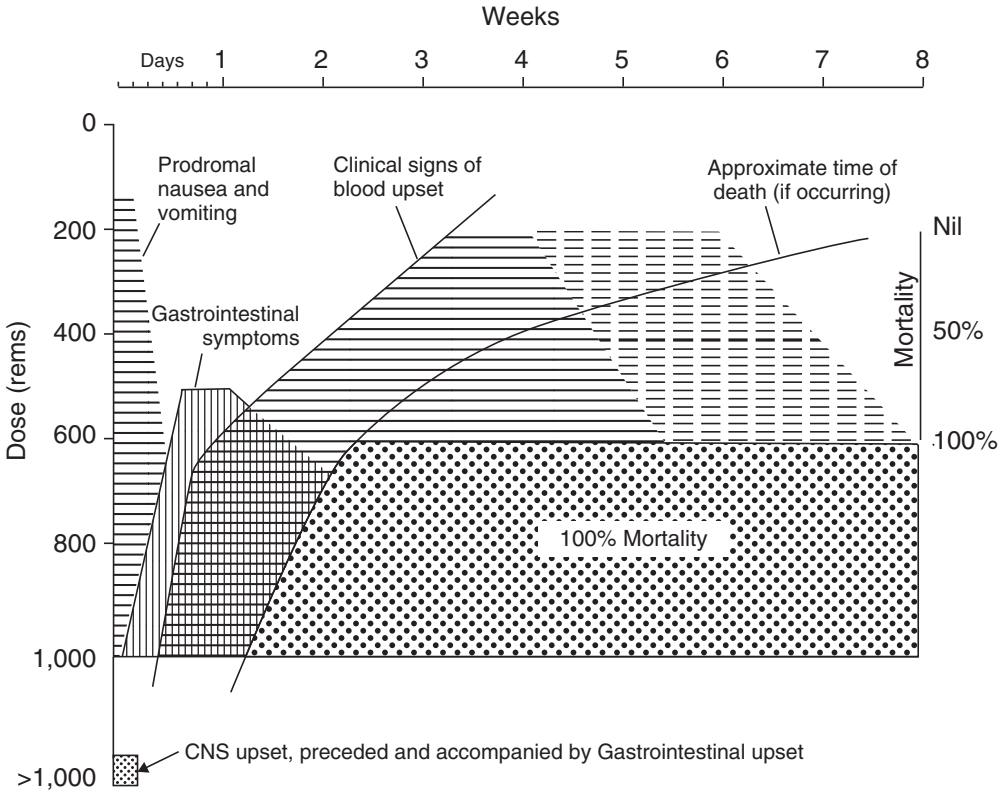


FIGURE 39.4. Schematic representation of time sequency for major clinical features of the acute radiation syndrome based on clinical signs and absorbed radiation dose. (Adapted from Llewellyn).[142]

36 hours of the explosion, 99 patients developed acute radiation sickness. The onset of bloody diarrhea within 1 hour of exposure, the appearance of mental confusion, ataxia, convulsion, and coma within 2–6 hours of exposure, or the development of hyperthermia, fever, chills, or hypotension within 24 hours of exposure in the absence of associated trauma or illness suggest a fatal outcome.[142]

Latent Period

The period between the cessation of prodromal symptoms and the onset of acute radiation syndromes depends on the absorbed dose.[149] For whole-body radiation doses of 2.5–4 Gy, the prodromal symptoms disappear within 24–48 hours before evidence for the hematological syndrome occurs 1–3 weeks later; the whole-body radiation dose causing death within 60 days in 50% of irradiation patients not receiving medical treatment is ~3.5 Gy.[116] Sepsis and gastrointestinal abnormalities develop within 7 days of the end of the prodromal period at doses of 4–6 Gy. Survival may occur in patients receiving aggressive supportive care following exposure to whole-body doses of 5–6 Gy. Supralethal doses of >15 Gy are associated with the appearance of cardiovascular dysfunction and mental status changes within hours of the radiation exposure.

Subsyndromes

Hematopoietic The hematopoietic subsyndrome results from the loss of critical hematopoietic stem and progenitor cell populations, resulting in life-threatening diffuse bone marrow suppression. The metabolic activity of the bone marrow is high, daily producing billions of cells that are immature and highly radiosensitive. Although changes in the bone marrow are detectable at ~0.2 Gy, clinically *apparent* findings do not occur until the absorbed dose exceeds 0.75–1.0 Gy. Clinically *significant* blood disorders develop following whole-body doses of >2 Gy from bone marrow suppression and the exponentially increasing death of bone marrow stem and progenitor cells. Stem cell damage in the bone marrow and the lymphatic tissue occurs following exposure to low- to mid-lethal doses of whole-body radiation (i.e., 2.5–5 Gy) along with depression of the production of blood elements. Clinical manifestations of bone marrow hypoplasia and aplasia include bleeding, infection, and poor wound healing.

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Maximal bone marrow depression occurs several weeks after exposure. The associated clinical conditions (i.e., hemorrhage, increased susceptibility to infection) develop 10 days to 6–8 weeks after radiation exposure, with pancytopenia and recovery of the marrow occurring earlier with radiation doses up to 6–7 Gy.[148] Hematopoietic recovery depends in part on the survival of foci of hematopoietic activity following nonhomogeneous radiation exposure, particularly relatively radioresistant stem or accessory cell irradiation during their noncycling (G_o) state. The nadir for the neutrophil count following radiation doses of ~1 Gy appears ~30–40 days postexposure, whereas the nadir for platelets at this dose occurs ~25–30 days after radiation exposure. Before decreasing, neutrophils and other granulocytes may transiently increase following radiation doses of <5 Gy. Figure 39.5 demonstrates the approximate time course of dose-related changes in granulocytes, lymphocytes, and platelets following whole-body radiation doses of 1–5 Gy. The occurrence of severe granulocytopenia within 7–10 days is a poor prognostic sign. The experience at Chernobyl suggests bone marrow recovery can occur following doses up to 9 Gy. Death from the hematopoietic syndrome may occur following radiation doses of 2–6 Gy 2–8 weeks after exposure when infection and/or bleeding results from neutropenia and thrombocytopenia, respectively. Mature red blood cells and platelets lack a nucleus and are radioresistant. The long lifespan of erythrocytes limits the effect of anemia during this time. Lung or kidney damage may appear months to years after radiation exposure from sclerosis of capillaries beds.

LYMPHOCYTE COUNT The earliest change in hematological indicators is the reduction of the total absolute lymphocyte count; these changes begin within several hours with a nadir in ~48 hours and duration up to several weeks.[137] Figure 39.6 displays Andrew's lymphocyte depletion curve; this curve associates the reduction in absolute lymphocyte counts during the first 2 days after acute radiation exposure with severity of the radiation-induced injury. Absolute lymphocyte counts of <1,000 cells/mm^3 4–7 days postexposure indicate serious irradiation (>1 Gy) and counts of <100 cells/mm^3 imply a probably lethal dose (>5–6 Gy).[150] Lymphocytes

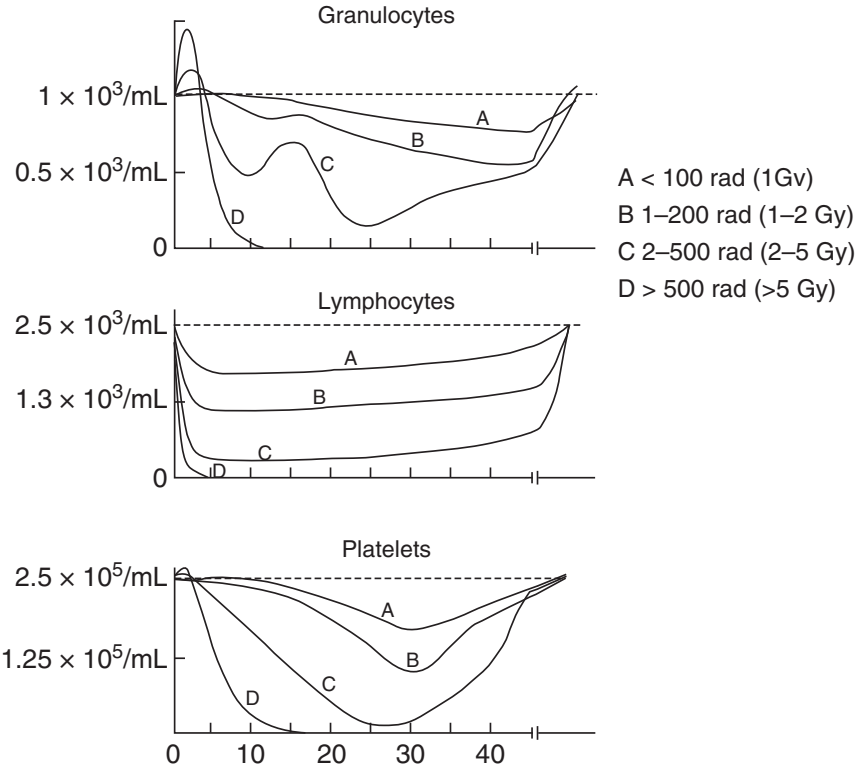


FIGURE 39.5. The time- and dose-dependent reduction of granulocytes, lymphocytes, and platelets following four progressively increasing whole-body radiation doses: A = <1 Gy, B = 1–2 Gy, C = 2–5 Gy, and D = >5 Gy. The dotted line represents the baseline value of these blood elements. The vertical axis represents the absolute count, whereas the horizontal axis represents time in days. (Adapted from Mettler and Upton).[123]

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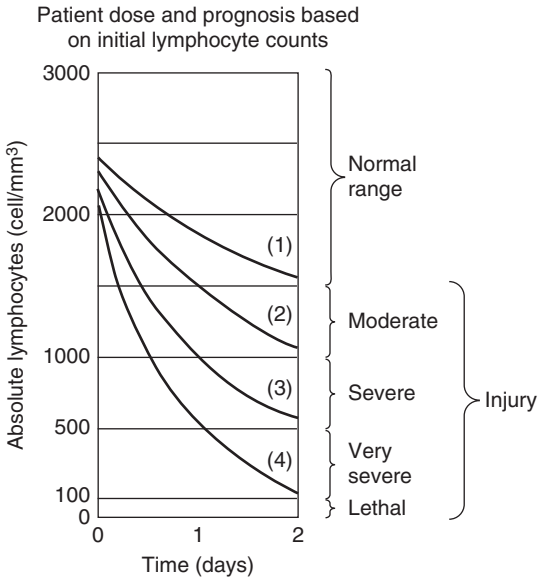


FIGURE 39.6. Andrew's lymphocyte depletion curve estimates the severity of the acute radiation syndrome based on the reduction in the absolute lymphocyte count within the first 2 days after exposure. The vertical axis represents the absolute lymphocyte count; the horizontal axis represents time after radiation exposure in days. The numbers on the curves represent the following whole-body radiation doses: 1) = 3.1 Gy, 2) = 4.4 Gy, 3) = 5.6 Gy, and 4) = 7.1 Gy. (Adapted from Goans).[152]

may decrease in trauma patients (e.g., burns) from the injury alone.[151]

FEVER AND INFECTION The presence of a temperature of >37°C within 5 hours after radiation exposure suggests a radiation dose of ≥2.5 Gy, whereas fever after the prodromal period typically occurs because of infection, dehydration, or other etiologies.[153] An agranulocytic fever appeared in 12% of patients exposed to 1–2 Gy at Chernobyl, whereas the incidence of fever was 70–80% at a dose of 4–5 Gy; the incidence of fever increases to ~100% at whole-body doses of >5–6 Gy.[148] Following radiation doses of <5 Gy, the source of most fevers in the patients was not identified; no deaths resulted in patients treated with broad-spectrum antibiotics. No infections developed in these patients past the period of agranulocytosis. Above the 5–6 Gy dose range, herpes simplex and cytomegalovirus infections exacerbated terminal bacterial infections; these viruses were the main causes of death in the patients dying after the period of agranulocytosis. These infections were resistant to the available antimicrobial agents; however, the effectiveness of antiviral agents has significantly improved since the Chernobyl accident in 1986.

GASTROINTESTINAL SUBSYNDROME Acute whole-body radiation exposures of >6 Gy produce clinical features of gastrointestinal syndrome secondary to necrosis of intestinal mucosal stem cells and disruption of the mucosal barrier. Massive apoptosis of the gastrointestinal epithelium followed by destruction of the mucosal epithelial barrier causes fluid/electrolyte loss, sepsis, and intestinal bleeding. When the dose of radiation exceeds 7 Gy, gastrointestinal symptoms and signs begin before the appearance of hematological abnormalities (e.g., pancytopenia). At radiation doses of >12 Gy, the mortality rate is greater for the gastrointestinal than the hematopoietic syndrome.[154] The initial prodromal symptoms of the gastrointestinal syndrome are similar to those of the hematopoietic syndrome; however, 5–26 days postexposure, severe diarrhea develops that progresses to bloody diarrhea and fluid/electrolyte loss as a result of damage to the gastrointestinal epithelium.[134] Abdominal distention, dehydration, hypovolemic shock, sepsis secondary to enteric bacteria, multiorgan failure, and death complicate the clinical picture. All patients developing the gastrointestinal syndrome after exposure to radiation doses of >11 Gy at Chernobyl had diarrhea between 5–8 days postexposure; all these patients died.

NEUROVASCULAR SUBSYNDROME The neurovascular syndrome following whole-body radiation doses exceeding 10 Gy is a less well-defined, fatal subsyndrome despite full supportive care; the clinical course is more compressed than other radiation syndromes. Patients receiving supralethal radiation doses of >20–50 Gy usually die within 48 hours despite supportive treatment.[155] These patients develop severe prodromal symptoms (nausea, vomiting, diarrhea, anorexia) within minutes to a few hours postexposure; the clinical course rapidly progresses to confusion, ataxia, convulsions, coma, sweating, hypotension, and multiorgan failure similar to septic shock. Manifestations of both cardiovascular dysfunction (shock, myocardial necrosis) and CNS dysfunction (papilledema, ataxia, absent deep tendon reflexes, cerebral edema, convulsions) are present in patients exposed to supralethal radiation doses.[133]

CUTANEOUS SUBSYNDROME The skin is an important immunological and external barrier to pathogens; compromise of this barrier enhances the severity of other radiation-induced injuries including mortality.[156] The depth of dermal damage, amount of edema, and destruction of underlying soft tissue and bone from external radiation exposure is dependent on the absorbed radiation dose. Skin damage may occur with or without the clinical features of acute radiation

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syndrome, depending on the absorbed radiation dose. The sensitivity of skin structures to radiation-induced damage starts with the most vulnerable are sweat glands, epidermis, hair follicles, and sebaceous glands.[157] Cutaneous radiation injury ranges progressively over the course of weeks to months from erythema and hair loss to scaly flaking skin (dry desquamation), weeping skin (moist desquamation), dermal edema, hyperpigmentation, subepidermal vascular damage, skin ulceration, skin atrophy, dilation of small skin vessels, fibrosis, and necrosis. Higher absorbed radiation doses to the skin produce earlier transient erythema and tissue necrosis in weeks to months. Whole-body radiation exposure to 3 Gy produces erythema 2–3 weeks after exposure with temporary hair loss, whereas an acute dose of 6 Gy causes an initial erythema within 1–2 hours with more permanent hair loss. The erythema usually resolves after a few hours; reoccurrence of erythema develops several days to weeks postexposure. The estimated absorbed dose thresholds for the cutaneous radiation syndrome are 10 Gy for dry desquamation, 15 Gy for moist desquamation, >25 Gy for skin necrosis, and >40 Gy for muscle-bone necrosis. In contrast to thermal and chemical burns, the appearance of radiation-induced skin damage is delayed; erythema appearing within a few minutes suggests a chemical or thermal injury. Table 39.12 describes the various clinical features associated with the cutaneous subsyndrome.

Dry desquamation of skin occurs ~2–4 weeks after external skin exposure to 10 Gy; vesicles appear 2–8 weeks after exposure to >15 Gy. Compartment syndrome may develop following severe radiation exposures. Local skin exposure to external radiation doses of >40–50 Gy causes necrosis and deep ulcerations. Following exposure to very high external radiation doses, skin necrosis, soft tissue, and bones can continue to spread from the initial site. Skin ulcerations occur initially following high radiation doses; although these ulcers may heal, recurrence of the ulcers is common due to vascular damage and subsequent ischemia. These ulcers may persist for years. Pigmentation varies from patient to patient with the final appearance of skin pigmentation occurring ~1 year after radiation exposure. Sebaceous glands and hair follicles display similar radiosensitivity with destruction occurring following acute radiation doses of 12–16 Gy; hair on the scalp and beard are particularly sensitive to radiation, particularly in children.

In a 15-year follow-up study of 22 survivors of the Chernobyl accident with cutaneous subsyndrome, all patients developed varying features of xerosis, cutaneous telangiectasias, subungual splinter hemorrhages, hemangiomas, lymphangiomas, epidermal atrophy, disseminated keratoses, extensive dermal and subcutaneous fibrosis with partial ulcerations, and pigmentary changes including radiation lentigo.[159,160] One patient developed two basal cell carcinomas in the irradiated skin during the late part of the follow-up period. Other radiation-induced diseases in this case series included dry eye syndrome, xerostomia, radiation cataract, and increased FSH levels suggesting impaired fertility. Two patients died during the follow-up period from myelodysplastic syndrome and acute myelogenous leukemia.

Local Radiation Injury

The initial clinical signs of radiation and thermal burns (i.e., erythema, desquamation, vesiculation) are similar, except for the dose-dependent delayed onset of radiation burns as listed in Table 39.12. The risk of death

TABLE 39.12. Clinical presentation of mild to very severe cutaneous subsyndrome. (Adapted from Radiation Emergency Medical Management (REMM, US Department of Health & Human Services).[158]

Sign/Symptom	Range	Mild	Moderate	Severe	Very Severe
Alopecia	2 days–8 weeks	Thinning	Visible, patchy	Complete, reversible	Complete, irreversible
Altered sensation	Hours–days	Pruritus	Slight–intermittent pain	Moderate, persistent pain	Severe, persistent pain
Desquamation	5 days–8 weeks	Absent	Patchy, dry	Moist, patchy	Moist, confluent
Edema	5 days–8 weeks	Asymptomatic, present	Symptomatic	Secondary dysfunction	Total dysfunction
Erythema	Few hours–30 days	Minimal, transient	<10 cm^2 or <10% BSA	10–40% BSA	>40% BSA
Onycholysis	2 days–8 weeks	Absent	Partial	Partial	Complete
Ulceration/Necrosis	5 days–8 weeks	Epidermis	Dermal	Subcutaneous	Deep tissue involvement
Vesiculation	5 days–8 weeks	absent–rare	Rare, hemorrhagic	Sterile bullae	Hemorrhagic bullae

Abbreviation: BSA = body surface area.

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following local skin irradiation is relatively small and dependent on burn depth reflecting the rapid decline in radiation dose rate with distance from the source. An estimated radiation dose of ~10,000 Gy to the legs resulted in bilateral leg amputations; however, initial pain or other symptoms of the acute radiation syndrome did not develop.[161] A 35-year follow-up study of four men irradiated with a skin dose of 200 Gy revealed no evidence of cancer, partly reflecting the reduction in the cancer incidence dose-response curve at very high doses.[162] At Chernobyl, radiation burns from β-irradiation were an important determinant of the prognosis for patients with acute radiation syndrome. The combination of radiation burns over 50% of the body and the hematopoietic system was inevitably fatal.[163]

Skin

Deep, localized skin exposure typically occurs while handling highly radioactive sources rather than from nuclear incidents. Frequently, these patients present weeks after exposure when edema, erythema, hyperpigmentation, desquamation, vesiculation, and pain occur. Radiation damage to the germinal cells in the basal layer of the epidermis produces four dose-dependent clinical stages characterized by: 1) transient erythematous reaction (an inflammatory response appearing within a few hours and disappearing within several days), 2) delayed main erythematous reaction with dry or wet desquamation (vesicles, bullae) depending on radiation dose, 3) late erythematous phase associated with dermal ischemia or necrosis after 8–16 weeks, and 4) delayed biphasic skin damage manifest by dermal atrophy after 26 weeks and skin necrosis and/or telangiectasias after 1 year.[164] An acute exposure to high-LET and neutron radiation estimated at 12.5 Gy produced the peak main erythematous reaction ~30 days postexposure.[165] Although the severity of the early erythematous reaction depends on total absorbed dose, dose fractionation, and the relative biological effectiveness of the radiation, the rate of radiation-induced skin damage depends on the regeneration of the basal cells in the epidermis and/or the clonogenic cells in the hair follicle canals rather than the dose.[166] Except for superficial injuries, the skin lesions usually evolve slowly, heal poorly, and recur sometimes years after the initial radiation exposure, as displayed in Table 39.13.

The presence of multiple/blunt trauma, steam burns, crush injuries, electrical injuries, and heat exhaustion complicates the initial evaluation for evidence of radiation-induced skin damage and the prodromal phase of the acute radiation syndrome. In the absence of these injuries, the presence of erythema within several hours suggests exposure to >2–8 Gy; however, this sign is neither sensitive nor specific. The intense heat of superheated steam produces blanching of the skin and third-degree burns that may be confused with radiation burns. Initially, radiation-induced burns are usually painless in contrast to thermal burns. Wet desquamation and second-degree thermal burns appear similar; the onset of these lesions at ~2–6 weeks marks the time when pain begins dominating the clinical picture.[167] Necrosis begins with ulcerations of variable depth ~2 weeks to several months postexposure following radiation doses of >25 Gy. The initial phase of dermal thinning at 16–26 weeks is associated with necrosis following exposure to high radiation dose. By 1 year, skin healing is usually complete with sequelae including hyperpigmentation, depigmentation, dry/atrophic skin susceptible to trauma, and telangiectasia. Healed radiation wounds have less strength than normal skin.

TABLE 39.13. Dermatological changes associated with acute absorbed radiation doses (Gy). (Adapted from Mettler and Voelz).[118]

Dose	Onset After Exposure	Clinical Features
3–4 Gy	2–3 weeks	Hair loss
10–15 Gy	Few hours (high dose) to 3 weeks (low dose)	Erythema with subsequent dry desquamation[a]
20 Gy	4–6 weeks	Moist desquamation (vesicles → bullae) with potential for ulceration
25 Gy		Ulceration with slow healing[b]
30–50 Gy	3 weeks	Blistering, necrosis
100 Gy	1–2 weeks	Blistering, necrosis

[a] Dose-dependent; [b] Skin necrosis and ulcerations may occur from ~16 weeks to >1 year at this radiation dose; the onset of necrosis and ulcerations occurs more quickly at higher radiation doses.

Dermal radiosensitivity depends, in part, on the depth of the basal layer; the depth varies with the location of the skin on the body. The thinnest areas (20–60 μm) exist on the trunk and face. Substantially more radiation damage may occur in these areas when the radiation dose includes low-energy photons and α- or β-emitters.[168] High doses (>100 Gy) of these types of radiation may produce direct cell death in the skin with clinical signs of acute epidermal necrosis occurring as soon as 2 weeks after exposure.

Muscle and Bone

Muscle, bone, and cartilage are relatively radioresistant; however, children in puberty or below the age of 6 years are less radioresistant than other children and adults.[169] In these young children, 10 Gy produces

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mild boney changes, whereas 10–20 Gy may cause asymmetric bone growth including spinal deformity, slipped capital epiphyses, aseptic necrosis of the hip, and hypoplasia of exposed bones.[170] Decreased bone activity can occur 4–19 months after fractionated doses of 20 Gy; necrosis of the bone results from fractionated doses exceeding 45 Gy. Osteonecrosis is rare in adults; complications include susceptibility to fractures from osteonecrosis with poor bone healing and reduced resistance to infection. Separating radiation-induced osteonecrosis from osteomyelitis is frequently difficult. The radiosensitivity of cartilage and bone is similar. Animal studies indicate muscle is extremely radioresistant with doses exceeding 500 Gy required to produce necrosis.[171] Atrophy and fibrosis of the muscle may occur from vascular insufficiency at lower fractionated doses (e.g., <50 Gy).[172]

Mucosal Surfaces

Alteration in the mucosa occurs in the pharynx, mouth, tonsils, nose, and tongue within a few days to 5 weeks after radiation exposure depending on the dose. Hyperemia of the oral cavity and pharyngeal edema develop within several days of exposure to 5–10 Gy followed by bleeding, ulceration, and necrosis.

Hair

Temporary hair loss (epilation) occurs at doses of >3–5 Gy beginning as early as 7 days after exposure; epilation typically starts 18–30 days postexposure. Hair loss may occur in the absence of radiation-induced erythema. An acute radiation dose of 7 Gy may produce permanent hair loss beginning 3 weeks after exposure.[123] Children are more susceptible to epilation than adults; the scalp and beard are the most sensitive portions of the body to hair loss after irradiation. In the range of 0.5–5 Gy, animal studies document a dose-related decrease in the diameter of the hair shaft.[173] The regrown hair in humans typically is slower-growing and finer than the original hair; occasionally, the color and curliness of the replacement hair differ from the original hair.

Chronic Sequelae

Deterministic radiation effects (tissue reactions) produce dose-dependent cell destruction, resulting in hypothyroidism, cataracts, skin atrophy, sterility, growth retardation, fibrosis, and chronic ulcerations. These biological effects occur uniformly in individuals exposed to identical radiation doses exceeding the threshold for the specific effect. The incidence and severity of these effects increase with increasing radiation doses. A follow-up Life Span Study of the cohort of atomic bomb survivors suggests acute radiation exposure exceeding 0.5–0.75 Sv may increase noncancer mortality for heart disease, stroke, digestive diseases, and respiratory diseases with an excess relative risk for overall noncancer and heart disease mortality of 14%/Sv (90% CI: 8–20%/Sv) and 17%/Sv (90% CI: 8–26%/Sv), respectively.[145] This study did not detect excess noncancer mortality in victims receiving <0.5 Sv. Studies of other radiation-exposed cohorts (e.g., patients) have not demonstrated similar excess relative risks of noncancer mortality, except for cardiovascular mortality; however, the risks per unit dose in these epidemiological studies vary over two orders of magnitude.[174] Consequently, the presence of confounding variables may account for the increased excess relative risk of cardiovascular mortality reported in the positive studies. The lungs are highly radiosensitive, particularly to chronic inflammation, fibrosis, and cancer. Inflammatory pneumonitis develops within 2–4 months and fibrosis ~4–6 months after radiation exposure, manifested by interstitial edema, inflammatory infiltrate, and epithelial loss.[175]

Cataracts

The latent period for radiation-induced cataracts is dose-dependent and highly variable with a range of 0.5–35 years and a mean of 2–3 years.[176] The dose-dependent occurrence of mild forms of lenticular opacities without visual impairment appeared in Japanese survivors at radiation doses of 0.6–1.5 Gy.[177] The incidence and severity of cataracts also increased with estimated dose in survivors at Hiroshima and Nagasaki.[178] The threshold for single exposures to γ-rays or X-rays following the therapeutic use is 2 Gy for single radiation doses and 5 Gy for fractionated radiation.[179] Almost all patients exposed to acute radiation doses of >7.5–8 Gy will develop cataracts. Fractionation doubles the threshold radiation level for cataracts. Confounding factors for cataract development include age, corticosteroid medications, diabetes mellitus, genetic predisposition, sex, smoking, and UV exposure.[180]

Radiation-induced cataracts are typically posterior subcapsular cataracts and occasionally involve cortical opacities; however, nuclear opacities are not usually associated with radiation injuries. A study of 873 Japanese atomic bomb survivors demonstrated an odds ratio for posterior subcapsular cataracts following 1-Sv exposure of 1.41 (95% CI: 1.21–1.64) and 1.29 for cortical cataracts (95% CI: 1.12–1.49) using the Lens Opacity Classification System II.[181] The odds ratio for nuclear cataracts in a survivor exposed to 1 Sv was not statistically different than the control group

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(<0.005 Sv) after adjustment for city, sex, age at the time of the bombings, and smoking. In contrast to senile cataracts that usually begin in the anterior pole of the eye, radiation-induced cataracts begin in the posterior pole of the eye. In a study of 8,607 Chernobyl cleanup workers with follow-up of 12–14 years, the prevalence odds ratio for 1 Sv and stage 1 posterior subcapsular cataracts was 1.52 (95% CI: 1.01–2.00).[182] The maximum likelihood central estimates of the dose threshold for stage posterior subcapsular cataracts were 0.35 Sv (95% CI: 0.19–0.66 Sv). The radiation exposure of 77% of the workers was below 0.2 Sv. These cataracts gradually enlarge, extending into the anterior pole. The classic presentation of radiation-induced cataracts is a localized lenticular opacity on the inner surface of the posterior polar capsule, with either punctate or aggregations of opacities in the subcapsular cortical layer of the posterior polar region.[183] These lenticular opacities increase slowly, and then their development typically stops. These opacities rarely progress following the cessation of radiation exposure.

Rodent studies suggest estrogen may accelerate the progression of radiation-induced lens opacification.[184] In these rodent studies, hormone supplementation experiments suggest estrogen is responsible for the enhancement of radiation-induced cataract formation by ovarian hormones; however, epidemiology studies associating female sex hormones with cataract formation are conflicting.[185]

Retinopathy

Radiation retinopathy developed in most survivors of the atomic bombings who received high radiation doses.[186] The ocular manifestations of radiation retinopathy and diabetic retinopathy are similar, including macular edema, microaneurysms, retinal hemorrhages, poor capillary perfusion, and nerve fiber layer infarcts. Substantial variation in the susceptibility to radiation-induced retinopathy occurs with a few patients developing radiation retinopathy below the currently accepted upper safe limit of a fractionated dose of 35 Gy.[187] Susceptible individuals include diabetic, hypertensive, and chemotherapy-treated patients.[188]

Carcinogenesis

The International Agency for Research on Cancer (IARC)[189] and the US National Toxicology Program[190] classify X- and γ-rays as Group 1 (human) carcinogens. Analysis of data from the Life Span Study of atomic bomb survivors indicates X-ray and γ-ray radiation causes cancer of the bladder, bone, brain and CNS, premenopausal female breast,[191] colon, esophagus, leukemia (excluding chronic lymphocytic leukemia),[192] kidney, lung, salivary gland, skin (basal cell), stomach, and thyroid (children, adult females).[30,193] These data are also suggestive of a positive association between these radiation types and cancer of the rectum, liver, non-Hodgkin lymphoma, multiple myeloma, ovary, pancreas, and prostate. In occupational studies, these cancers occur primarily in subcohorts with high-dose radiation exposure during early years of employment.[194] Cancers of the bone, soft tissue, skin, rectum, and soft tissue require relatively high doses, whereas some cancers (gallbladder, chronic lymphocytic leukemia, Hodgkin lymphoma, uterus) are not causally associated with X- or γ-radiation.[189] Only a small number of individuals irradiated with the same dose will develop cancer similar to the distribution of other stochastic effects including teratogenesis (predominantly severe mental retardation) and genetic abnormalities.[195] The cancer incidence increases with the radiation dose. The most sensitive tissues to radiation-induced cancer in the atomic bomb survivors were bone marrow, thyroid, and female breast.[9] Significant increases in mortality also occurred from cancers of the stomach, colon, bladder, esophagus, and lung.

Latent Period

Cancer is a multistage process involving: 1) *initiation* of irreversible DNA changes to create a cell with neoplastic proliferative potential, 2) *promotion* of initiated preneoplastic cells into expanded clones, 3) *neoplastic conversion* transforming preneoplastic cells into an autonomous variant able to proliferate, and 4) *malignant progression* of cells and progeny to accumulate changes allowing unrestrained growth, invasion of normal tissues, and metastasize to distant sites. A substantial latent period occurs between radiation-induced cell initiation and the clinical appearance of the tumor.

The latent period between radiation exposure and the clinical expression of the cancer depends on age and cancer site, as demonstrated in the Life Span Study of atomic bomb survivors under the age of 10 years at the time of exposure. In epidemiology studies of malignant breast tumors in atomic bomb survivors, female Japanese children exposed before 9 years of age had a longer latency period than Japanese women exposed during their twenties.[196] The increased leukemia incidence first occurred ~2–3 years after the bombing with peak incidence emerging 6–8 years after the bombing.[197] The minimal latency periods for bone cancer are 3–4 years and 4–5 years for thyroid cancer.[123,198] Although the minimum latent period for other solid

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TABLE 39.14. Estimated mean latent periods for acute radiation-induced tumors. (Mettler and Upton).[123]

Tumor Type	Mean Latent Period (years)
Bone	10–15
Brain	27
Breast, female	22
Colon	26
Larynx	24
Leukemia[a]	7–10
Lung	25
Pharynx	24
Salivary glands	20
Sarcoma	12
Skin, basal cell	24
Stomach	14
Thyroid	20

[a] Excludes chronic lymphocytic leukemia.

tumors is ~5–10 years, the mean latent period for solid tumors is typically 20–30 years.[118] The mean latent period for all tumors in survivors of Hiroshima and Nagasaki averaged ~15 years.[199] Table 39.14 lists the estimated mean latent period for the development of leukemia and solid tumors after acute whole-body radiation exposure.

Approximately 17% of radiation-induced leukemias occurred 22–33 years after the bombing.[200] For breast cancer, both age at exposure and age attained were important modifiers of the dose response.[201] Exposure of females before age 20 was associated with higher dose-specific excess relative risk of breast cancer compared with exposure at older ages; there was no consistent variation by exposure age for ages under 20. The relative risk declined with increasing age; the largest drop occurred at ~35 years of age.

Hiroshima and Nagasaki Survivors

Leukemia

Leukemia is the most common cancer detected in survivors of the atomic bombings in Hiroshima and Nagasaki; leukemia accounted for $\sim^1/_3$ of the initial cases of excess cancers.[202] The clinical, pathological, and genetic manifestations of radiation-induced leukemia and leukemia from other etiologies are similar, including cytotoxic drug-induced leukemias.[203] All types of leukemia appeared following radiation exposure except chronic lymphocytic leukemia.[204] The acute forms of leukemia account for the increased risk in children soon after the bombing, whereas adults also develop an increased risk for chronic myelogenous leukemia. Although the risk of developing leukemia decreased after 10 years, the risk did not return to baseline levels seen in controls 30 years after the bombing.[205]

The risk of developing leukemia varies with the radiation dose, age at radiation exposure, type of leukemia, and time elapsed since exposure. Most cases of radiation-induced leukemias demonstrate cytogenic abnormalities of chromosomes 5 and 7 with similar point mutations and base substitutions in the *N*- and *K-RAS* oncogene sequences.[206,207] Acute lymphoblastic leukemia is the common subtype in children, whereas acute and chronic myelogenous leukemias are the common subtypes in elderly patients.

Radiation from the A-bomb produced excess leukemias sooner than other radiation-induced cancers, particularly in children. In the Life Span Study cohort of 49,204 Japanese survivors, 204 leukemia-related deaths occurred from 1950–2000 with 94 deaths (46%) attributed to bone marrow doses of ≥0.005 Gy based on DS86 dosimetry.[208] Although the relative risk of radiation-induced leukemia is high, the absolute number of leukemia cases among survivors is relatively small because leukemia is a rare disease in the Japanese population. The updated DS02 dosimetry estimates decreased the curvilinear dose-response for leukemia by ~8% due to increased γ-ray dose estimates; however, the shape of the curve, estimated age-time patterns, and sex differences remain similar.[209] Table 39.15 displays the observed, estimated excess, and attributable risk associated with weighted bone marrow doses ranging from 0.005 Gy to over 2 Gy based on DS86 dosimetry. A few new cases of leukemia are occurring in this cohort currently.

Thyroid Cancer

Thyroid cancer was the first radiation-induced solid tumor recognized in Japanese survivors after the bombings in Hiroshima and Nagasaki; however, the mortality rates were not significantly increased among survivors because of the low mortality associated with thyroid cancer. These studies demonstrated a concave dose-response curve for the development of solid nodules in the Japanese cohort of atomic bomb survivors. Most,[210] but not all studies,[211] failed to detect a statistically significant relationship between radiation and the incidence of antibody-positive or antibody-negative hypothyroidism (autoimmune hypothyroidism). The common pathological types of radiation-induced thyroid cancer are papillary adenomas and carcinomas. Females and young children display a greater risk (2–4-fold for females) of developing thyroid cancer following irradiation than men.

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TABLE 39.15. Attributed leukemia-related mortality in the Life Span Study cohort of Japanese atomic bomb survivors 1950–2000 using DS86 dosimetry. (Adapted from RERF).[208]

Weighted Bone Marrow Dose (Gy)	Persons	Observed Deaths	Estimated Excess Deaths	Attributable Risk
<0.005	37,407	92	—	—
0.005–0.1	30,387	69	4	6%
0.1–0.2	5,841	14	5	36%
0.2–0.5	6,304	27	10	37%
0.5–1.0	3,963	30	19	63%
1.0–2.0	1,972	39	28	72%
>2	737	25	28	100%
Total	49,204	296	94	46%

Solid Tumors

Radiation-induced cancers typically become clinically apparent only after the atomic bomb survivors attain the age at which the specific cancers usually appear. In the cohort of Japanese survivors, ~260 nonleukemia-related cancer deaths from 1950–1985 are attributed to radiation doses of >0.01 Gy.[9] This number of deaths represents ~8% of the total deaths from cancers other than leukemia. The cancer rates in some solid tumors (e.g., pancreas, prostate, rectum, uterus) and chronic lymphocytic leukemia in the Life Span Study were similar in exposed and unexposed survivors.[212]

Environment Exposure

Most case-control studies of populations inhabiting areas with high natural radiation levels do not consistently demonstrate a statistically increased cancer incidence including residential radon studies.[9,213] However, some studies of natural radiation are positive. An increased incidence of thyroid nodules and chromosomal aberrations in peripheral lymphocytes occurred in a Chinese population exposed to high levels of background radiation (3–4 mSv γ-radiation/year).[10] Pooled data from two Chinese case-control studies of residential radon detected dose-related increases in the odds ratios of lung cancer mortality, particularly in residents inhabiting their home for over 30 years (OR = 1.33 at 100 Bq/m^3, 95% CI: 1.07–1.91).[214] Examination of cohorts exposed to highly contaminated releases from the Chernobyl accident indicates an excess incidence of thyroid cancer consistent with estimates of other populations exposed to radiation, primarily in children. The epidemiological evidence linking leukemia and nonthyroid solid cancers with environmental radiation exposures is inconclusive.

Nuclear Facilities

Most studies of various populations living adjacent to nuclear facilities involve thyroid disease and leukemia. Maternal radiation exposure was not related to the risk of developing central nervous system tumors in a case-control study of 338 children; the association with paternal exposure was inconsistent.[215]

Accidental Releases An increased rate of thyroid cancer occurred after the accidental nuclear release from the Chernobyl reactor; aging of the cohort and improved case ascertainment do not account for this increase with the estimated risks consistent with other radiation-exposed populations.[207] Iodine deficiency is a modifying factor in thyroid cancer risk. The current evidence of other cancer outcomes in this cohort is limited, with little indication of an increased risk of leukemia following exposure in fetuses, children, or adults. The most common late effect from exposure to thyroid radiation is the development of thyroid nodules; however, imprecise screening methods for thyroid nodules complicate the interpretation of epidemiology studies including the determination of nodule size and the occurrence of preexposure indolent nodules.[216] Although the mean accumulated thyroid dose from exposure to fallout from Chernobyl was 0.6–1.9 Gy in children and 0.2–0.4 Gy in adults, no significant increase in the incidence of thyroid nodules was detected within the first 5 years postexposure.[217] Current data do not support a causal relationship between increased childhood leukemia and releases from radioactive waste or the 1979 accident at the Three Mile Island nuclear power plant in Pennsylvania.[55] Retrospective analysis of the Pennsylvania Cancer Registry Dataset did not detect an increased thyroid cancer incidence in Dauphin County, where the power plant is located.[218] Nearby York County demonstrated a trend toward increasing thyroid cancer incidence beginning in 1995, ~15 years after the TMI accident,

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whereas nearby Lancaster County showed a significant increase in thyroid cancer incidence beginning in 1990.

Epidemiological data from studies of residents in contaminated regions of Belarus and the Russian Federation exposed to fallout from Chernobyl indicate a dose-dependent increase in the incidence of thyroid cancer, primarily in children. The main route of exposure for these children was the ingestion of ^{131}I-contaminated cows' milk and food. The most contaminated areas occurred in Belarus (e.g., Gomel) with several thousand children receiving a cumulative radiation dose of 2 Gy;[219] the increased incidence of thyroid cancer began ~5 years after the Chernobyl release, persisting into young adulthood consistent with studies of other radiation incidents.[220] In a population-based case-control study of 276 cases of thyroid cancer and 1,300 matched controls all aged <15 years living in contaminated areas of Ukraine and Russia after the Chernobyl accident, the estimated radiation dose and thyroid cancer risk demonstrated a significant dose-response relationship ($P < 0.001$). The odds ratio for a cumulative 1-Gy exposure varied from 5.5 (95% CI: 3.1–9.5) to 8.4 (95% CI: 4.1–17.3), depending on the applied risk model.[221] The risk of thyroid cancer was higher in iodine-deficient areas (RR = 3.2, 95% CI: 1.9–5.5) and lower in children receiving potassium iodide supplementation (RR = 0.34, 95% CI: 0.1–0.9). There is no convincing evidence of significant excess incidences of leukemia or other solid tumors following exposure to the Chernobyl release.

The radiation doses from the Fukushima Daiichi Nuclear Power Plant accident were extremely low; however, the relatively short physical half-life of ^{131}I complicates the determination of the actual dose. Most of the surrounding residents (i.e., 99.9%) probably received <1 mSv/year.[222] In a study of 300,476 Fukushima residents ≤18 years of age at the time of the accident, no thyroid cancers were attributed to the radiation exposure during screening four years after the incident.[223] The typical latency period for thyroid cancer is 4–5 years.

Nearby Residents

Thyroid Disease Evidence for an association between an elevated thyroid cancer risk and exposure to radiation from nuclear facilities is limited. Over 25,000 residents living near the Techa River in the southern Urals of the Russian Federation were exposed to external (γ-rays) and internal (^{137}Cs, ^{106}Ru, ^{90}Sr, ^{95}Zr) radiation released into the Techa River from the nearby Mayak plutonium production complex, predominately during the early 1950s. In a Russian study of 72,185 residents of Ozyorsk for at least 1 year while under the age of 15 years and exposed to fallout from Mayak Production Association (Mayak PA), the thyroid cancer incidence was elevated ~3–4 times the Russian rate and 1.5–2 times the local Chelyabinsk Oblast rates.[224] The Hanford Thyroid Disease Study did not detect an increase in thyroid cancer or other thyroid diseases with increasing thyroid radiation doses from Hanford facility ^{131}I releases.[225]

Leukemia Although studies of residents near nuclear installations have not demonstrated increased overall cancer mortality,[226] some ecological studies from the United Kingdom suggest the possibility of excess leukemia near some nuclear facilities including children near the Sellafield plant in Seascale, Cumbria (6–8-fold), Dounreay (5-fold),[227] Aldermaston (1.4-fold),[228] and Hinkley Point (1.8-fold).[229] Other studies of populations near nuclear facilities in the United States,[230] Scotland,[231] and La Hague, Normandy[232] did not detect statistically significant trends in mortality from childhood leukemia. Although these studies did not possess sufficient power to exclude the presence of an effect, they indicate the 6- to 8-fold increase in leukemia risk detected in the Sellafield plant in Seascale is probably an overestimate. These ecological studies of populations living near nuclear facilities and other potential sources of radiation do not contain *individual* estimates of radiation doses.

This increased leukemia incidence at these British facilities cannot be explained by the absorbed radiation dose from nuclear waste because the amount of radiation varies 1,000-fold between these four facilities, whereas the relative risk of leukemia fluctuates by less than 10-fold.[233] A case-control study of cases of childhood leukemia reported between 1950–1985 near the Sellafield plant suggests the effect of ionizing radiation on the fathers working at the nuclear facility may affect the incidence of leukemia and non-Hodgkin lymphoma in their offspring.[234] The excess leukemia cases occurred in Cumbrian children born in the area near the Sellafield plant rather than children moving to the area after birth. Data from parental questionnaires did not suggest an association between leukemia and radionuclides discharged from the Sellafield plant. This study did not detect any genetic abnormalities other than increased leukemia incidence. Although the number of leukemia cases was small, the effect was large with an exposure to radiation doses of >100 mSv associated with a 6–8-fold increase in the risk of developing leukemia in offspring. This magnitude of leukemia risk is inconsistent with data from the atomic bomb survivors because **no** increase in leukemia occurred in the cohort of 7,400 Japanese offspring of fathers exposed to radiation doses (0.3–0.6 mSv) four times greater than

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the fractionated radiation dose received by the workers at Sellafield. The relative risk of developing leukemia was <1 when the paternal dose was <0.1 mSv.

Interpretation of the significance of geographic clusters of disease (i.e., leukemia incidence at Sellafield) is limited because the small number of cases increases the sensitivity of the data to diagnostic, reporting, and classification biases.[235] Confounding from infectious agents,[236] genetic effects, chemical mutagens, drugs, and the ingestion of α-emitting radionuclides may influence the risk of developing leukemia.[233,237] A causal association between childhood leukemia and radiation exposure in the communities surrounding these nuclear facilities remains controversial.[238,239] The importance of the Seascale study lies in the strength of the association between paternal ionizing radiation and childhood leukemia. The increased risk detected by this study probably did not result from chance, but the etiology of the increased incidence of leukemia remains unknown;[240] the values published in this study depend on four cases of paternal exposure of 0.1–0.2 mSv and imply the sensitivity of the human genome to heritable mutations is several orders of magnitude greater than data from animal experiments and the atomic bomb survivor cohort.[241] The statistical significance of the association between childhood leukemia and paternal irradiation was relatively weak because the *P* value was 0.05 rather than 0.01 typically used for multiple comparisons.

A case-control study of children in Caithness near the Dounreay nuclear installation did not support an association between paternal exposure to external ionizing radiation before conception and childhood leukemia or non-Hodgkin lymphoma,[242] whereas a case-control study of 54 children with leukemia and non-Hodgkin lymphoma in West Berkshire and North Hampshire Districts found a statistically nonsignificant elevation (RR = 2.2, 95% CI: 0.6–6.9) in the number of children with fathers who were employed in the nuclear industry.[243]

Three case-control studies of populations residing near nuclear facilities did not demonstrate an increased cancer risk in the exposed group. The studies of residents near a French and a Scottish nuclear facility examined the risk of leukemia associated with environmental radiation exposures as determined by employment records and parental questionnaires.[242,244] Although both studies suggested an association between playing on beaches near nuclear facilities and leukemia, the small number of cases, potential systemic bias, and multiple hypothesis testing limit conclusions regarding causality.

Weapons Testing

Thyroid Cancer High radiation doses are a recognized cause of benign thyroid nodules and thyroid cancer. From June 1946 to August 1958, The US Department of Defense and the US Atomic Energy Commission conducted 66 nuclear weapons tests in the Northern Marshall Islands with 20 resulting in measurable fallout on one or more inhabited atolls. The largest aboveground thermonuclear test ever conducted by the United States was the Castle BRAVO test on March 1, 1954; the yield was 1,000 times greater than the Hiroshima atomic bomb. An unexpected wind shift resulted in the deposition of high levels of radioactive material on Rongelap and Utirik atolls. On March 3, 1954, inhabitants of these atolls were evacuated with the residents later returning to Utirik in June 1954 and to Rongelap in June 1957.[40] Adults of the northern Marshall Islands received an estimated external dose ranging from hundreds of mGy to over 1,000 mGy compared with 22–59 mGy for midlatitude atolls and 5–12 mGy for the southern atolls (control group).[245] Estimated adult internal thyroid doses were 760 mGy (Utirik community) and 7,600 mGy (Rongelap Island community), with young children on Rongelap during the Castle BRAVO test receiving ~3-fold the adult dose. Based on these doses, ~20% of the thyroid cancers and ~5% of leukemias were attributed to the fallout with a projected 170 lifetime excess cancers compared with ~10,600 spontaneous cancers during this time.[246] Although the prevalence of thyroid cancer in residents born before the Castle BRAVO test was elevated, the difference between the quartiles of exposure was not statistically significant. From 1954–1985, thyroid nodules appeared in 63% of children and 33% of adults living on the most heavily exposed atoll in Pacific test sites.[247] Similar excess incidences of thyroid nodules (i.e., estimated risk of 1,100 excess cases/10^6 person years-Gy) occurred in the inhabitants of other atolls in the Marshall Islands.[248] A cohort study of 3,122 schoolchildren exposed to an estimated mean thyroid dose of 170 mGy (range, 0–4,600 mGy) from Nevada Test Site fallout of 1951–1958 demonstrated a statistically significant excess of thyroid neoplasms (benign and malignant).[249] A relative risk of 3.4 occurred in subjects exposed to radiation doses of >400 mGy with an excess relative risk of 0.7% per mGy; although the dose-response slopes were positive, the dose-response was not statistically significant. In a case-control study comparing the risks of thyroid cancer mortality and incidence of residents near Nevada nuclear testing sites with US rates, the study suggested an increased thyroid cancer mortality for the 1950–1959 birth cohort (ERR = 12.0, 95% CI = 2.8–31); however, wide confidence intervals, the

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absence of a dose-response, and the generally negative results including thyroid cancer incidence rates limit conclusions regarding causality.

Leukemia In the latter part of the 1970s, several studies of residents of Utah and neighboring states downwind of the Nevada Test Site and test participants suggested an increased cancer incidence following radiation exposures of <50 mSv, primarily leukemia. The BEIR V Committee concluded that the most likely explanation for these excess observed cases of leukemia is a random overestimate of the risk coefficients.[9] Although the number of cases of leukemia is small, some case-control studies suggest a weak association between exposure to fallout from nuclear testing and leukemia incidents.[250,251] However, estimates of the number of cases attributable to these regions are small and lack a statistically significant association between estimated red bone marrow dose and leukemia mortality and incidence.

Several ecological studies of populations exposed to fallout from nuclear testing did not demonstrate statistically significant increases in childhood or adult leukemia. In an observational study of the leukemia incidence rates in Nordic children exposed to fallout from Soviet nuclear tests, no consistent, dose-related increase in leukemia risks during the first 15 years of life was detected in children born during the years of the highest fallout.[252] During the early, high-fallout time, the average estimated dose equivalent to fetal red bone marrow was ~0.14 mSv with little evidence of increased leukemia risk during the first 15 years of life (RR = 1.07, 95% CI: 1.0–1.4). An ecological study of ^{131}I exposure from nuclear testing in Nevada in the 1950s did not demonstrate a statistically significant increase in leukemia incidence during the first 15 years after fetal exposure when comparing cumulative high- (≥ 90 mGy) and low- (0–39.9 mGy) groups.[253] The relative risk for the high-dose group was 0.97 (95% CI: 0.91–1.03) with the low-dose group being the referent group. In a British study of 21,357 servicemen exposed to fallout during UK atmospheric nuclear weapons testing in the Pacific Ocean followed from 1952–1998, mortality and cancer incidence were similar between the exposed group and a control group of 22,333 unexposed servicemen based on film badge readings and potential exposure from job duty. Of the 4,808 men wearing film badges, 1,776 had detectable radiation doses with a mean of 9 mSv. The study suggested the possibility of a small increased leukemia incidence in the exposed group (RR = 1.41, 90% CI: 0.96–2.09; $n = 67$) excluding chronic lymphocytic leukemia (CLL) compared with controls that had leukemia incidence and mortality rates below the national averages. The difference between the two groups was not statistically significant. The relative risk for leukemia mortality in the exposed group excluding CLL was 1.83 (90% CI: 1.15–2.93).

Occupational Exposure

Epidemiological studies of occupational cohorts exposed to radiation complement the relative risks of adverse effects detected in other populations (e.g., Japanese A-bomb survivors), particularly in the low-dose and low-dose rate ranges (100–200 mGy); however, these studies frequently do not involve individual exposure data, resulting in significant uncertainties with variable estimates of cancer incidence, mortality, and large confidence intervals. These occupational cohorts include medical staff (e.g., radiologists), Chernobyl cleanup workers (liquidators), nuclear industry workers, and nuclear weapons test participants.[254] In 1944, the large excess of leukemia among US radiologists provided the first published evidence of the stochastic effects of low LET-radiation.[255] A mortality study compared the risk of death from acute myeloid leukemia and/or myelodysplastic syndrome in 43,763 radiologists (20% women) and a comparison group of 64,990 psychiatrists (27% women) graduating from medical school 1916–2006.[256] The mortality risk was elevated (RR = 1.62, 95% CI: 1.05–2.50) in radiologists graduating before 1940; however, the study did not detect excess mortality in radiologists graduating more recently. The authors opined that increased radiation protection and/or lifestyle changes possibly accounted for the difference in mortality between newer and older medical school radiology graduates.

In a study of the Rocketdyne cohort of 5,801 workers involved in radiation activities with exposure primarily to radionuclides, the SMRs for all cancers (0.88, 95% CI: 0.81–0.95), lung cancer (0.87, 95% CI: 0.76–1.00), and leukemia other than chronic lymphocytic leukemia (1.04, 95% CI: 0.67–1.53) were not statistically different than the general population.[257] There were no significant dose-response trends for any cancer as detected by Cox regression analyses. The mean cumulative dose of external radiation was relatively low (13.5 mSv) with a range up to 1,000 mSv as determined by a monitoring program for 2,232 workers. The estimated relative risk for all solid cancers for exposure to 100 mSv was 0.98 (95% CI: 0.82–1.17) compared with 1.06 (95% CI: 0.50–2.23) for all leukemias other than chronic lymphocytic leukemia.

The average cumulative whole-body exposure of monitored workers was 124 mSv at Sellafield, 32.4 mSv at the UK Atomic Energy Authority, and 7.8 mSv at

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the Atomic Weapons Establishment. Studies of cohorts from the Atomic Weapons Establishment[258] and Oak Ridge National Laboratory[259] detected a statistically significant positive correlation between radiation exposure and cancer mortality, primarily from an increased lung cancer mortality. Many workers at Sellafield accumulated radiation exposures of >50 mSv;[260] cancer mortality (SMR = 96, 95% CI: 90–103) was 4% below the England and Wales national rates and similar to data from the local UK county of Cumbria rates (SMR = 100, 95% CI: 94–107). A positive correlation occurred between leukemia incidence and cumulative radiation dose in exposed workers (2-year lag, $P = 0.009$). Mortality rates were significantly elevated above national rates for thyroid cancer (6 observed, 1.8 expected; $P = 0.01$). The estimated risk estimate for leukemia was four times higher than that for adult atomic bomb survivors with a confidence interval ranging up to ~20 times the estimate risk for atomic bomb survivors consistent with significant uncertainties regarding dose estimation. Leukemia-related deaths were not statistically significantly increased in the HARDTACK study of 1,010 navy veterans exposed to 5 rem for 1 year and unexposed navy controls (adjusted RR = 1.51, 95% CI: 0.23–9.69; $n = 3$); however, mortality from lymphopoietic cancer was significantly increased (RR = 6.44, 95% CI 1.96–21.24, $n = 6$).[261] The lack of increased mortality from cancers typically associated with radiation exposure, large confidence limits, and small case numbers suggest the presence of causal factor beside radiation.

Examination of 95,217 workers in the National Registry for Radiation Workers also demonstrated evidence for an association between radiation exposure and mortality from leukemia and multiple myeloma.[262] A statistically significant and dose-related increase in mortality from multiple myeloma also occurred in the cohort from Hanford;[263] however, this correlation ($P = 0.10$) was weaker in an updated analysis of this cohort.[264] Updated analyses of combined mortality data on workers at Hanford, Oak Ridge National Laboratory, and Rocky Flats Weapons Plant did not support a positive correlation between radiation exposure at Hanford and elevated risk of death from multiple myeloma.[265] The increased cancer risks with increasing age at Hanford and Oak Ridge indicated the possibility of significant dose uncertainties and the need for caution in interpreting the data.

The Atomic Weapons Establishment study reported excess prostate cancer deaths in exposed workers; however, internal contamination from radionuclides (e.g., tritium) accounted for at least some of the association. The elevated prostate cancer rates in the early Oak Ridge National Laboratory and the British Nuclear Fuels studies were not statistically significant or dose-related.[260] The lack of an association between radiation exposure and prostatic cancer in the Japanese atomic bomb survivors and the National Registry for Radiation Workers[262] suggests this association is coincidental.

In Utero Exposure

Although the risk of childhood cancer increases following exposure of the fetus or embryo to high radiation doses (i.e., >0.5 Gy), the risk of cancer in offspring following low radiation doses (i.e., <0.1 Gy) remains controversial.[266] Increased cancer mortality during the first year of life and after 9 years of age occurred in Japanese atomic bomb survivors exposed to radiation *in utero*;[267] however, only perinatal deaths correlated to the radiation dose received. The initial follow-up of the cohort of survivors of the atomic bomb irradiated *in utero* did not demonstrate an increased incidence of childhood cancer. The incidence of childhood leukemia in the subset of ~3,300 Japanese survivors exposed *in utero* at the time of the bombing did not increase significantly.[9] Only one leukemia-related death occurred in this subset of the Life Span Study during the first 15 years after prenatal radiation exposure, when the leukemia incidence peaked in radiation-exposed adults.[268] These results are inconsistent with the findings of the Oxford Survey of Childhood Cancers Study that suggested prenatal X-ray exposure was associated with an increased incidence of childhood cancer.[269] Interpretation of the Oxford Survey remains controversial because all childhood solid tumors increased at the same rate (i.e., ~40%), suggesting possible methodological problems (e.g., selection and recall biases). A 14-year follow-up study of the 1,630 members of the cohort of Japanese survivors exposed *in utero* detected two cases of childhood cancer.[270] Although this follow-up study suggested the cohort may have an increased risk of developing cancer during adulthood, the number of tumors detected was small (10 cases) and the tumor mix contained some cancers not typically associated with radiation exposure. During the first 42 years of follow-up, no cases of leukemia or breast cancer developed in the high-dose portion of this cohort; however, increase in the excess relative risk of solid cancers was dose-related, albeit with a wide confidence limit (ERR/Gy = 2.1, 90% CI: 0.2–6.0).[268] In a study of 8,000 offspring of female workers at the Mayak Nuclear Facility in Ozyorsk, Russia, 3,226 (40%) were exposed to *in utero* radiation with an estimated mean uterine γ-radiation dose of 54.5 mGy.[271] The risks of mortality from solid cancers and leukemia in this cohort born from

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1948–1988 were not statistically significant. For solid cancer mortality, the RR was 0.94 (95% CI: 0.58–1.49; ERR/Gy = −0.10; $n = 28$), whereas the RR for leukemia mortality was 1.65 (95% CI: 0.52–5.27; ERR/Gy = −0.8; $n = 6$). Updating the cohort through 2009 did not significantly alter the risk estimates or conclusions regarding solid cancer[272] and leukemia mortality.[273]

Reproductive Abnormalities

The risk of adverse heritable health effects in children conceived after their parents received radiation is very small compared with the baseline prevalence of genetic disease in humans. There is no convincing evidence that preconception exposure to environmental sources of radiation produces increased risks for congenital malformations, stillbirths, spontaneous abortions, neonatal mortality, or altered sex ratios; case-control studies for *in utero* exposure are inconsistent.[207]

Somatic Abnormalities

In all animal species, ionizing radiation produces breakage and rearrangement of the chromosomes of all diploid somatic and haploid germ cells (gametocytes, sperm, ova, embryonic cells, and stem cells). Human studies on the genetic effects of radiation indicate humans are less sensitive to radiation than mice.[9] These studies suggest the amount of radiation necessary to double the natural incidence of a genetic or somatic anomaly (i.e., the doubling dose) is ~1.56 Sv; this doubling dose is ~4 times greater in mice than humans.[274] The genetic effects of radiation are expressed as mutations in the offspring induced by parental irradiation. Potential adverse outcomes of these mutations in the offspring include: 1) serious complications of pregnancy (stillbirth, perinatal death, major congenital defects), 2) premature death, 3) induction of proteins with structural or conformational changes, and 4) sex chromosome aneuploidy. Studies of these endpoints for offspring exposed *in utero* in Hiroshima and Nagasaki suggest a positive correlation with radiation exposure; however, the differences between exposed and nonexposed persons were not statistically significant.[274] Dose-related increases in radiation-induced chromosomal aberrations (e.g., translocations, fragments, dicentrics) persisted for at least 20 years in some of the peripheral lymphocytes and bone marrow of Japanese atomic bomb survivors.[275] No clinically significant effects (mental retardation, microcephaly, leukemia) have been associated with these chromosomal aberrations.[276,277]

In Utero Exposure

Potential adverse outcomes from *in utero* radiation exposure include fetal or neonatal death, malformations, growth retardation, functional impairment, and cancer. The development of these abnormalities depends on the radiation dose received by the fetus, the stage of fetal maturation at the time of exposure, and other less well-defined modifying factors.[278] Several sources provide information concerning the effects of prenatal radiation exposure including studies of atomic bomb survivors in Hiroshima and Nagasaki,[279] pregnant women exposed to fallout from nuclear weapons testing near the Marshall Islands, and women exposed to diagnostic and therapeutic irradiation during pregnancy.[280]

Although studies of pregnant patients exposed to medical radiation suggest the human fetus is radiosensitive, animal studies do not support high radiosensitivity of animal fetuses. A study of atomic bomb survivors 40 years after *in utero* radiation exposure indicates the fetus was not more radiosensitive than adults; the frequency of translocation frequencies in blood lymphocytes did not increase with dose, except for a small, statistically significant increase (i.e., <1%) at radiation doses <0.1 Sv.[281] Additionally, rodent studies suggest cells with chromosome aberrations do not persist because fetal stem cells are less radiosensitive and their progeny replace the preexisting cell population during postnatal growth.[282]

Follow-up of 77,000 pregnant women in Nagasaki and Hiroshima did not detect a significant increase in adverse pregnancy outcomes (congenital malformations, stillbirths, perinatal deaths) within 1 week of birth; however, the data was not sufficient to exclude a small effect.[283] In the F_1 cohort of individuals born to Japanese parents exposed to radiation, there was no increased frequency of cytogenetic numerical or structural abnormalities compared with children born to unexposed Japanese mothers.[284] Other molecular studies of this cohort have not demonstrated discernible effects of parental radiation.[285] Additionally, studies of these cohorts have not demonstrated an increased prevalence of multifactorial diseases (e.g., diabetes, hypertension, ischemic heart disease) in the offspring of parents with radiation exposure.[286]

Occupational studies provide little information on fetal risks, except for a study of 3,000 offspring of radium dial painters; the deposition of radionuclides in the mother's skeleton exposed their children to radon progeny.[277] Fractionated radiation doses reduce the severity and incidence of congenital abnormalities compared with the same dose delivered in a single exposure.

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Embryotoxicity

Although trauma and nutritional status confound embryotoxicity data from Hiroshima and Nagasaki, examination of this data indicates substantial fetal loss following exposure to high radiation doses. Among 30 pregnant women exposed to radiation within 2,000 m of the hypocenter, which was sufficient to produce acute radiation sickness, fetal death occurred in 7 pregnancies (23%), 6 offspring (20%) died in the neonatal period or early infancy, 5 progenies (17%) developed congenital defects, and 12 offspring (40%) were normal.[287] Comparative data on expected pregnancies revealed a reduction in the expected number of fetuses exposed to radiation at <4 weeks of gestational age.[288] Live births from mothers exposed to radiation before the 15th day of gestation did not display any congenital abnormalities.[289] These data suggest high radiation doses cause fetal demise rather than birth defects. In general, the spontaneous risks of pregnancy are two orders of magnitude greater than the extrapolated risks associated with diagnostic radiation. Data on the effects of low radiation levels on fetal demise are limited, in part because of the high rates of spontaneous miscarriage compared with the small risks of miscarriage associated with these radiation levels. Doses of low-LET ionizing radiation below 0.1 Gy probably do not increase the incidence of fetal demise.[290]

Congenital Malformations

Major anatomical malformations occur in animal species after irradiation during the period of organogenesis, including abnormalities of the central nervous system, eyes, skeleton, and, to a lesser extent, the viscera, extremities, and other organs.[291] However, these data suggest a threshold may exist for major malformations.[292] Radiation exposure does not produce unique congenital malformations. Although genetic effects appear in every species experimentally exposed to radiation, human epidemiology studies have not unequivocally linked existing radiation exposure with congenital abnormalities. Because of the causal link between central nervous system damage and *in utero* radiation exposure during the atomic bombing, case-control studies focus on the development of central nervous system malformations. In a case-control study of 672 congenital malformations near the Hanford nuclear facility, 2 defects (tracheoesophageal fistula, congenital dislocation of the hip) were statistically associated with employment at the Hanford facility.[293] Available data do not suggest a significant risk of congenital malformations following *in utero* exposure to current limits for pregnant or potentially pregnant workers.[294,295]

Postnatal Abnormalities

Data from Japanese atomic bomb survivors document a reduction in live births in the subset of fetuses exposed to radiation at <4 weeks of gestational age.[277] Analysis of these births indicates excess cases primarily of small head size and mental retardation (−21 to −29 IQ points) following radiation exposure at 4–17 weeks and 8–15 weeks, respectively. In Hiroshima, the thresholds for small head size and excess mental retardation were 0.10–0.19 Gy and 0.2-0.4 Gy, respectively.

Seizures Examination of the data from the cohort of Japanese children exposed to radiation *in utero* demonstrated an increased incidence of seizures for those members of the cohort exposed after the seventh week of gestation. The incidence of nonfebrile seizures was related linearly to *in utero* doses of >0.1 Gy.[296] When the 22 cases of severe mental retardation were eliminated from the analysis, the increase in seizures unrelated to fever was only suggestive of a statistically significant increase. Hence, the association between unprovoked seizures and cases without overt evidence of brain damage remains unproved.

Intelligence Mental retardation with microcephaly was the most frequent congenital abnormality detected in the children of Japanese mothers exposed to radiation doses exceeding 0.5–1 Gy in Hiroshima and Nagasaki and mothers exposed to pelvic irradiation during the vulnerable period of organogenesis. Seven of eleven children from Japanese mothers exposed within 1200 m of the atomic bombs developed microcephaly with mental retardation.[297] No mental retardation occurred in 194 children exposed *in utero* at a distance greater than 1200 m from the hypocenter.

The maximum time of vulnerability to the development of mental retardation (i.e., five times greater risk) occurs during the 8–15th week following fertilization (10–17th week after the first missed menstrual period).[298] A small excess of mental retardation cases occurred after exposure during the 16–25th week following fertilization. Exposure to radiation earlier than the 8th week or after the 25th week did not increase the incidence of mental retardation.[299] Irradiation of a gravid uterus at 6 months of gestation with 7.5 Gy of X-ray therapy and 1.34 Gy of cervical irradiation with radium did not produce any detectable physical or mental abnormalities in the male offspring.[300] The period between the 8−15th week

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after fertilization corresponds to the time when the cortical neurons proliferate and then migrate from areas near the ventricles to the cortex.[301] The risk of mental retardation is ~40–43%/Gy during the 8–15th week, whereas the risk is ~four times less during the 16–25th week.[298] Epidemiology data are too limited to define the dose-response curve or determine the presence of a threshold. Significant increases in the incidence of mental retardation occur after doses exceeding 0.5 Gy; the data do not exclude a threshold of 0.2–0.4 Gy.[9]

A reduction in intelligence and school performance occurred in the cohort of 1,600 Japanese children exposed *in utero*.[9] This decrease in intellectual function was detected primarily during the 8–15th week post-conception. The effects of these factors were less for Japanese children exposed *in utero* during the 16–25th week with negligible effects from exposure during the other gestational periods. The data on intelligence scores fit a linear model with a reduction in scores ranging from 21–29 IQ points/Gy.

Microcephaly Permanent reduction in the size of the head (i.e., >2 standard deviations below the mean) with normal intelligence occurred three times more commonly than microcephaly with severe mental retardation.[288] The most vulnerable period occurs from the 6–11th week after fertilization up to the 18th week. The minimal radiation dose associated with a significant increase in risk of microcephaly was 0.1–0.19 Gy; at doses of 0.19 Gy, 11.1% of the exposed children had microcephaly compared with 4.1% of controls. At doses of radiation above 1.5 Gy, 38.5% of the exposed children had microcephaly, mostly with severe mental retardation.[302]

Parental Exposure

Little epidemiological evidence provides a causal association between preconception paternal radiation exposure and childhood leukemia or other cancers.[303] In a case-control study of 672 congenital malformations near the Hanford nuclear facility, the risk of congenital malformations in children born to parents employed at the Hanford nuclear facility was elevated, but the association was not statistically significant and unrelated to parental radiation exposure.[293] Although the number of cases was small, data on neural tube defects demonstrated a statistically significant relationship to parental preconception radiation exposure. The increased rate of neural tube defects was not explained by paternal radiation exposure or exposure to radioactive waste from the plant.[304] The odds ratio of neural tube defects ranged from 0.8–4 in children of men exposed to 0.1 Sv.

Males

The radiosensitivity of the testes germ cells depends on maturation, with type A spermatogonia being the most sensitive; later stages of spermiogenesis are highly resistant to radiation.[176,305] Although plasma testosterone concentrations remain normal after irradiation with doses of 0.1 Gy, plasma concentrations of follicle-stimulating hormone begin decreasing; oligospermia develops after radiation doses exceed 0.15 Gy. Because mature spermatogonia are relatively resistant to radiation doses of <3 Gy, the sperm count remains normal for 45 days after acute exposure; then, azoospermia occurs ~10 weeks after radiation doses of >1 Gy. Libido and potency are usually unimpaired because Leydig cells are relatively resistant to radiation-induced damage. Recovery from sterility following radiation doses of 2–4 Gy may require several years; case reports document the birth of normal offspring after extended periods of apparent radiation-induced sterility.[306] Radiation doses of >3–6 Gy are associated with permanent sterility.[121,307] Figure 39.7 demonstrates the dose-related reduction in the sperm count following single high-dose X-ray exposure to the testes.

Females

In contrast to males, ovarian irradiation is associated with decreased production of hormones and a reduction in the release of ovum. Females are born with a full complement of maturing ova that do not undergo further cell division; the ovary contains follicles at various stages of development. Based on animal studies, altered fertility including temporary sterility results from depletion of the radiosensitive mature and intermediate follicles. The period of sterility begins after single radiation doses of 1.5–6 Gy and fractionated doses of 1.5–12 Gy. Fertility returns after the maturation of the more radioresistant, immature follicles. Permanent sterility can occur after single radiation doses of 2–3.2 Gy[308] or fractionated doses of 20 Gy over 5–6 weeks.[307] The threshold for permanent sterility decreases with increasing age.[309] Disruption of the hypothalamic-pituitary-ovarian axis is a potential complication of cranial irradiation that can cause amenorrhea and infertility. In a study of endocrine function in 10 postpubertal, premenopausal women followed for a mean of 7 years after receiving cranial radiotherapy for brain tumors, 7 women developed oligomenorrhea, and 5 women had low serum estradiol concentrations.[310] Five women also had hyperprolactinemia. The mean total fractionated radiation doses delivered to the hypothalamus and pituitary were 53.6 Gy, with a range of 39.6–70.2 Gy.

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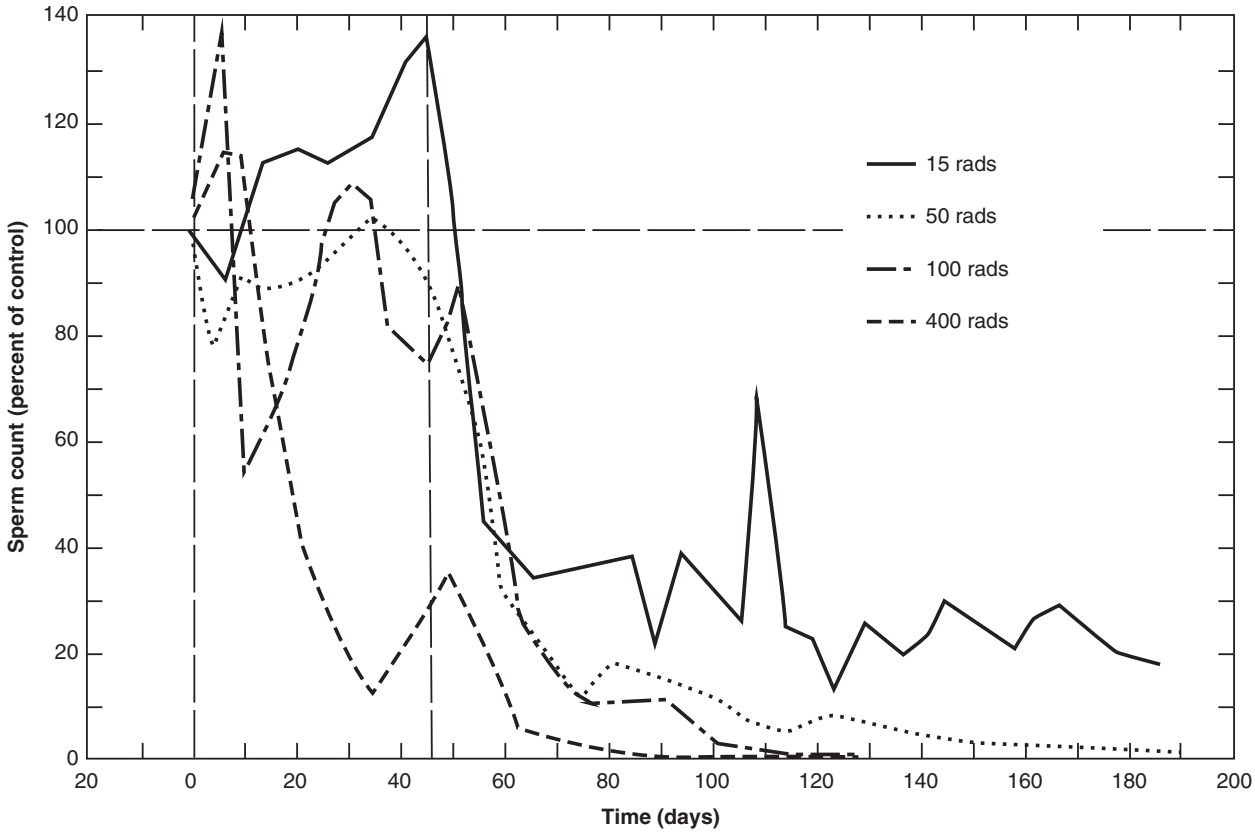


FIGURE 39.7. Dose-related reduction in sperm counts of normal men irradiated with a single high-intensity X-ray (maximum kilovolt during exposure, 190 kVp) ranging from 15–400 rads (0.15–4 Gy). (Lushbaugh).[307]

DOSIMETRY

Analytical Methods

Instruments are necessary to detect the presence of ionizing radiation because human senses do not recognize ionizing radiation. Radiation detection instruments typically detect either α-particles, radionuclides, or some combination of β-particles, γ-rays, and/or X-rays. Detection of the extremely short range of α-particles requires delicate instrumentation with thin windows to allow the passage of the α-particle to the detector. In most areas outside the defense industry, the use of instruments with β- and γ-detection capabilities is sufficient. Most portable instruments are either gas detectors that use a gas chamber as the detection media or scintillation detectors that are solid-state detectors. The two general categories of radiation sensing devices are: 1) contamination and radiation exposure survey instruments and 2) dosimetry devices. The former instruments typically measure radiation exposure rates (i.e., contamination). Contamination survey instruments measure the presence of radioactive material in counts per minute (CPM) or exposure rates rather than the cumulative radiation dose from dosimetry devices.

Incident managers and responders deploy radiation monitoring equipment depending on availability, training of responders, size and type of incident, and activities of the responders. Table 39.16 displays the usefulness of common devices for the detection of radioactive contamination, depending on the specific needs or mission.[311] No single device measures all types of radiation (e.g., α/β particles, γ-rays, X-rays, photons, neutrons); consequently, no single device is useful in all situations. These devices provide a variety of data including radiation energy (keV, MeV), exposure to γ-rays and X-rays (roentgen or milliroentgen/hour), accumulated radiation dose (Gy or rad), current dose rate (Gy/hour, rad/hour), and counts/minute or second.

Survey Instruments

Contamination survey meters (e.g., Geiger-Müeller counter) display environmental radiation in real time.

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TABLE 39.16. Mission-oriented detector uses. In routine radiation emergency responses, the hot zone is the area bounded by 0.01 R (roentgen)/hour line. The roentgen is a measure of ionizing radiation that produces one electrostatic unit of positive or negative ionic charge in one cubic centimeter of air under standard conditions. Entering this zone entails the use of appropriate personal protective equipment (PPE) while being properly monitored for radiation exposure. (Adapted from REMM).[311]

Mission	Alarming Dosimeter	Personal Radiation Detector	(Some) Survey Meters	Radioisotope Identification Device	Backpack	Mobile System	Aerial System	Portal Monitor	Sensor Networks	Medical Instru-mentation[a]
Confirmation of nuclear yield										
	●	○	●	○	○	○	●	○	○	–
Activities inside the area bounded by the 0.01 R/h line										
Location of ground zero	–	–	–	–	–	–	●	–	○	–
Worker safety	●	○	●	○	–	–	–	–	–	–
Area survey	●	–	●	–	–	–	●	–	○	–
Radiation monitoring at shelters	●	○	●	–	–	–	–	–	–	–
Establish evacuation routes	●	●	●	○	○	○	●	–	○	–
Activities outside the area bounded by the 0.01 R/h line										
Worker safety	●	○	●	○	–	–	–	–	–	–
Area survey	●	○	●	○	○	●	●	–	○	–
Cumulative dose determination[b]	●	–	–	–	–	–	–	–	–	○
Population monitoring at medical facilities	●	○	●	○	–	–	–	–	–	○
Radiation monitoring at shelters	○	●	●	○	○	○	–	○	–	–
Internal personnel contamination detection	○	○	●	●	–	–	–	–	–	●
External decon-tamination monitoring[c]	●	○	●	●	○	○	○	○	–	–

Abbreviations: ● Useful = the device was designed or intended for this application without modification. ○ Marginal = the device provides useful data in the noted application with modifications to the normal mode of operation. The data should be interpreted cautiously because use of the device may create a potentially unsafe condition for the user. – Not Useful = Although the device detects nuclear radiation, technical performance characteristics limit the usefulness of the collected data. Use of the device may create grossly unsafe conditions for the user.
[a] Includes nuclear medicine diagnostics and γ-imaging cameras; [b] Current systems do not provide retrospective dosimetry as the calculation assumes the exposure occurs after the device begins measurements; [c] Includes facilities, personnel, vehicles, and material.

These devices measure and locate the presence of radioactive materials (i.e., contamination) on personnel or equipment in counts per minute (CPM) within specific boundaries, assess the extent and magnitude of a contaminated area, verify the boundaries of the hot and cold zones, and evaluate the effectiveness of decontamination measures. These devices detect only a percentage of the total energy released by radioactive material, as radioactive decays or disintegrations per minute (DPM). Consequently, DPM as measured in becquerels or curies is always greater than the CPM. An efficiency factor converts CPM to DPM, as determined

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TABLE 39.17. Conversion table for converting SI units (sieverts) to traditional units (rem).

SI Units (sieverts)	Traditional Units (rem)
1 microsievert (μSv)	0.1 millirem (mrem)
10 microsievert	1 millirem
1 millisievert (mSv)	100 millirem
10 millisievert	1 rem
1 sievert (Sv)	100 rem

by Equation 39.1.

$$\text{DPM} = \text{CPM} \div \text{efficiency factor}$$
$$(\%\ \text{of total energy measured by device}) \quad \text{(Equation 39.1)}$$

The sensitivity of these instruments requires the determination of background radiation levels in the cold zone. Using this type of instrument on samples obtained by rubbing the area with moderate pressure (smear, wipe/swipe test) allows the determination of removable contamination. Moist wipes remove an estimated 20–30% of removable contamination compared with ~10% for a dry wipe. During routine surveys, the radioactivity is quantified in a 300–400 cm^2 area using a S-shaped pattern and analyzed by high-efficiency laboratory equipment, including liquid scintillation counters for α-, β-, and auger electron emitting radionuclides (^{3}H, ^{14}C, ^{32}P, ^{33}P, ^{35}S, ^{36}Cl, ^{51}Cr, ^{86}Rb, ^{125}I), auto-γ-counters for γ-emitters (^{51}Cr, ^{57}Co, ^{125}I), or gas-flow proportional counters for α- or β-emitters (^{14}C, ^{32}P, ^{33}P, ^{35}S, ^{45}Ca).

In contrast to contamination survey instruments, *radiation exposure survey meters* locate and measure radiation at incident scenes in biological equivalents (e.g., mrem or mSv/hour). The usefulness of this type of survey instrument includes: 1) locating the radiation source, 2) assessing the integrity of the object, 3) establishing the boundaries of control zones, and 4) controlling personnel exposure. Most radiation exposure survey instruments have rotating or movable β-shields that allow the detection of β- and γ-radiation in milliroentgen/hour (mR/hour) or roentgen/hour (R/hour) recorded in the biological equivalent of mrem/hour or rem/hour. Table 39.17 provides the conversion values for changing biological equivalents from SI units (sieverts) to traditional units (rem).

Radiation exposure survey equipment are not typically as sensitive as contamination survey instruments due to limitations on the type of radiation detected. Uses for the radiation exposure survey instruments include location of radiation sources, establishment of control zone boundaries, and evaluation of radiation exposure in personnel. Pancake-style detectors (CPM) are preferred for contamination surveys, whereas radiation exposure surveys typically use side window GM or "hotdog" style detectors (mR/hour). Radioisotope identifiers are radiation exposure survey instruments that identify and quantitate γ-emitting isotopes; many of these instruments also have neutron detection capability. These instruments help identify illicit sources of radioactive material by separating the illicit sources from naturally occurring radioactive materials (e.g., bananas, cat litter, ceramics, fertilizers). Traditional analog instruments often use a range multiplier switch that changes the display in multiples of 10. Personal radiation detectors are pocket-sized devices that alert the user to the presence of elevated radiation levels; however, most of these instruments are not dosimetry devices able to measure cumulative radiation doses.

Geiger–Müeller Meter

Geiger counters detect localized areas of contamination and identify sources of small amounts of radiation.[312] The detector is an argon- or helium-filled, cylindrical tube with a long, 900-V, positive, central wire connected via a meter to the walls of the tube. The detectors usually have a window at the end or side of the detector to allow the entrance of α- or β-particles. Depending on the window thickness, the Geiger survey meter can detect X-rays, γ-rays, α-particles, or β-particles. Additionally, these instruments can detect radioactive materials (e.g., ^{14}C, ^{45}Ca, ^{60}Co, ^{51}Cr, ^{137}Cs, ^{32}P, ^{22}Na, ^{35}S); however, these meters are relatively insensitive to α-particles and low-energy β-particles including detecting small amounts of ^{3}H, ^{63}Ni, ^{14}C, or ^{125}I. Radiation entering the tube ionizes gas molecules with electrons attracted to the positively charged wire and enters the electric circuit. The meter records the flow of electrons (i.e., ionizing events) as counts per minute. For charged particles (e.g., electrons), the counting efficiencies for particles that enter the halogen-filled counting tube are 90–100%. The Geiger survey meter is a pulse counter like the proportional counter; however, in contrast to the latter, the pulse height is relatively independent of the applied voltage and independent of the radiation energy. Consequently, these devices are highly sensitive survey instruments rather than dosimeters.

Measurement of α- and β-particles depends on the thickness of the detector tube and the ability of these particles to penetrate the detector wall and ionize gas molecules. For high radiation levels, an ionization chamber should be used initially because the output of the Geiger counter becomes nonlinear at high radiation doses. At very high radiation levels, the Geiger counter becomes unresponsive and fails to register any radiation. Prior to each use of the Geiger counter, the batteries

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should be tested in the "BAT" or "BATT" position and the X1 position with a small radioactive "check" source. Typically, the halogen tubes of the Geiger counters last 6 months to 2 years. Following radiation accidents, the patient must be removed from the radiation field because the Geiger counter cannot distinguish between contamination and an external source of radiation. The end of the Geiger counter should be covered with clear plastic or a surgical glove to prevent contamination of the tip of the counter.

Ion Chamber Meter

These meters measure current flow from ion pairs produced in the detector tube, primarily from γ- and X-rays expressed in mR or R/hour. Ion pairs form during interaction of the ionizing radiation with gas molecules in the chamber; the electrons are attracted to the anode forming an electric current proportional to the amount of energy deposited in the chamber. These meters are particularly useful for measuring the high radiation levels during the operation of nuclear reactors, accelerators, X-ray machines, and radiotherapy instruments. The optimum operation of the ion chamber and the counting efficiency depend on proper air pressure in the chamber and the use of voltage sufficient to collect all free electrons (i.e., saturation current). These instruments measure excess radiation above background levels, but not specifically particle contamination.

Gas-Flow Proportional Counter

For a proportional counter, the voltage between the anode and chamber wall, the magnitude of the output pulse from the chamber, and the total energy absorbed in the sensitive volume are proportional. Consequently, this type of meter can separate α- and β-radiation because the output depends on the type of radiation and voltage. Proportional counters are simple pulse counting devices rather than instruments capable of measuring radiation exposure (e.g., ion chamber). Liquid scintillation detectors are more sensitive instruments to detect removable contamination than proportional counters.

Scintillation Detectors

The absorption of ionizing radiation and its conversion to light is the process called scintillation. The variety of scintillation detectors includes noble gases (e.g., helium, xenon), inorganic crystals (e.g., GeLi, NaI-Tl), organic crystals (e.g., anthracene), and organic liquids or solids. In contrast to Geiger counters, the number of light photons produced in scintillation detectors is proportional to the absorbed energy. Liquid scintillation counting involves the assay of a radioactive sample by dissolution in a chemical solution (scintillation fluid or cocktail). These sophisticated instruments quantify radioactivity and measure removable radioactive contamination, particularly α- and β-emitters (e.g., ^{14}C, ^{45}Ca, ^{36}Cl, ^{32}P, ^{33}P, ^{22}Na, ^{35}S) and some γ-emitters (e.g., ^{51}Cr, ^{125}I). This method offers counting efficiencies near 100% and simple sample preparation.

Personal Dosimeters

Personal dosimeters detect radiation exposure over the time the badge is worn. The dosimetry devices include self-reading dosimeters (e.g., pencil or pocket ion chamber dosimeters), electronic dosimeters with digital displays of total dose (mR, mrem), film badges, and thermoluminescent dosimeters. The latter requires off-site, specialized equipment to retrieve the exposure data. The two most common types of personnel dosimeters are the thermoluminescent dosimeter (TLD) and the film badge. Active devices provide immediate feedback on the amount of radiation or radioactivity in the environment, whereas passive devices require special, offsite processing facilities. Previously, passive electronic dosimeters using gas-filled and solid-state detectors were common personnel monitoring devices. The use of these types of monitoring devices (i.e., pencil or pocket dosimeters) is limited by the confounding influence of external factors that reduce accuracy. Active electronic dosimeters using small battery-powered instruments are more accurate than passive electronic dosimeters that require off-site reading; however, cost currently limits their use.[313]

The self-reading and electronic dosimeters allow the determination of need to leave the hot zone (i.e., >75% of full scale on low-range dosimeter scale of 0–200 mR). Self-reading dosimeters (e.g., pocket ion chambers, direct reading dosimeters, pencil dosimeters) measure the accumulated radiation dose in mR or R; typically, the dose includes only γ- and X-rays. Radiation exposure during an incident is not uniform. The dose measured by the dosimeter on the torso may not reflect the dose received by other parts of the body. When working close to radiation exposure (e.g., removing radioactive shrapnel), personal dosimeters on the finger may measure the radiation exposure more accurately than a badge on the torso.

These instruments are usually read every 15–30 minutes in highly contaminated zones. Electronic dosimeters display the same data on a digital display, typically with an audible chirping noise. Personnel dosimeters are worn either around the collar or near the waist. They provide a single measure of the radiation

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received by the patient at a **single** location where the dosimeter was worn; the whole-body dose depends on the direction of the beam and the extent of shielding by the body. The choice of personal dosimeters is usually a compromise between several factors including ease of handling, convenient size and shape, adaptability, clear display, resistance to deterioration, precision, accuracy, and appropriate dose range.

During a radiation accident, both pocket or pencil dosimeters and either a film badge or thermoluminescent dosimeters (TLD) typically are worn. The former two devices provide an immediate assessment of the absorbed radiation dose, whereas the latter two devices allow a slightly more accurate determination of dose after dosimeter processing. If the patient is contaminated, the film badge or TLD should be protected from contamination. Both film badges and TLDs accumulate background radiation requiring periodic replacement.

Thermoluminescent Dosimeters (TLD)

Thermoluminescence involves the release of visible light from certain heated crystals that previously stored energy from ionizing radiation. The peak light intensity is proportional to the radiation dose. Thermoluminescent dosimeters (e.g., lithium fluoride crystals) measure accumulated radiation dose; these dosimeters are typically more sensitive than film badges. Thermoluminescent dosimeters are relatively insensitive to humidity and heat. These dosimeters have replaced film badges as the most common method to monitor personnel for exposure to β- and γ-radiation. Although α-particles cannot be measured directly by TLD, their presence can be identified by their associated low-energy γ-emissions. Typical monitoring intervals are 1 month, although the exact interval depends on the history and probability of exposure to medically significant radiation levels. The major advantage of these devices is their small size and variety of forms including the ability to measure thermal neutrons with changes in the composition of lithium fluoride crystals. Ionizing radiation interacts with thermoluminescent crystals (e.g., lithium fluoride) to raise electrons from the valence band to the conduction band. Heating these crystals after exposure to radiation produces a glow or thermoluminescence. Factors to consider in the use of TLD devices include the sensitivity and range of the dosimeter, glow peak temperatures, and fading of the stored thermoluminescent signal over time. The small size of the TLD device favors its use for monitoring the exposure of extremities to radiation.

Film Badges

Photographic film is the oldest and still the most common personal dosimeter *worldwide* because of its low cost, ease of use, and simplicity. These badges typically contain photographic film that darkens with radiation exposure depending on the photon energy and radiation dose. Detection of radiation results from the interaction of the ionizing radiation with silver halide (e.g., silver bromide) grains to produce reduced silver. The amount of free silver determines the latent image on the developed film. Problems associated with the use of film badges include energy dependence, light leakage, external contamination, heat and humidity artifacts, and pressure spots on the developed film.[313] Specially designed film holders with several different filters (e.g., aluminum, cadmium, copper, lead, tin) allow the detection of β-particles along with γ- and X-ray radiation, as displayed in Figure 39.8. The use of special neutron track film allows monitoring the amount of fast neutron irradiation (0.5–10 MeV) by counting the number of proton recoil tracks; below this range the recoil protons do not form recognizable tracks. The film provides a permanent visual record of the exposure conditions during the time of use. Movement blurs the image, whereas radioactive contamination appears as blotches or hot spots.

Optically Stimulated Luminescence

Optically stimulated luminescence dosimeters are relatively new devices for measuring occupational radiation exposure by evaluating the light emitted by irradiated objects (e.g., teeth, ceramic prostheses, cellphones, and other electronic devices); this method is more sensitive (i.e., several mGy–several Gy) than film badges or thermoluminescent dosimeters. Certain crystals luminesce following exposure to ionizing radiation and stimulation with specific frequencies of laser light; the luminescence and the number of trapped electrons are proportional to the radiation dose. A laser beam scans the exposed detector material, resulting in simulation of molecules with trapped electrons that subsequently emit light

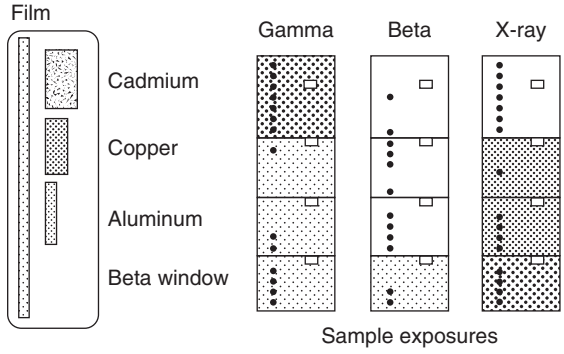


FIGURE 39.8. Composition of typical film badge with sample radiation exposures from β-particles, γ-rays, and X-rays.

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with a different frequency than the laser. The radiation dose is related to the intensity of the second type of light. Like film, reading the detector does not destroy the material. Newer devices use aluminum oxide with results stored for up to 1 year after exposure. The major disadvantage is the poor stability of the signal over time.

Neutron Detectors

As uncharged particles, neutrons are difficult to detect with energies ranging six orders of magnitude (0.25–14 MeV), whereas photons range from 20 keV (X-rays)–5 MeV (γ-rays). Neutrons interact differently with different elements depending on their energies. Determination of the presence and flux of a neutron requires indirect measures based on the energy released from their interactions with matter (e.g., capture, fission, scatter). Methods to determine exposure to neutron radiation include: 1) analysis of ^{24}Na in blood, 2) estimation of ^{32}P in the hair, 3) neutron activation of metal objects (e.g., belt buckles, metal buttons, shoe nails, coins, watches, pens, hair clips, jewelry, film badge inserts), and 4) quick sort method. The physical half-life of ^{24}Na is 15 hours; therefore, the analysis of blood within the first several days postexposure is sensitive to neutron radiation doses exceeding 0.1 Gy. Hair samples help determine the amount of local neutron radiation; origin of the hair samples requires clear markings. The quick sort method involves a Geiger counter survey of the abdomen based on the number of counts per second done at least four hours postexposure.[314] The choice of detectors (boron trifluoride, proton recoil counters, fission chambers, neutron foils, neutron rem counters) depends on the energy of the neutrons involved in the sample. Track-etch detectors use the chemical etching of damage to solid foil by neutron radiation to produce visible changes using either a microscope or the unaided human eye. This type of detector (inorganic crystals, glasses) allows the determination of mixed neutron and γ-radiation because β- or γ-radiation does not produce track damage. More sensitive organic polymers are necessary to record particles with transfer energy of <4 MeV/mg/cm^2.

Accident Reconstruction

History

An accurate history helps reconstruct the radiation event and calculate the absorbed dose. This information facilitates appropriate triage of patients with serious radiation-induced injuries and improves determination of the prognosis and treatment of irradiated patients.

TABLE 39.18. Important aspects of the history of an irradiated patient.

Item	Information
Patient	Name, phone number
Company	Name product, manufacturer
Medical history	Physical injuries, treatment
External irradiation	Precise location and position in relation to source, location of shielding
Internal contamination	Route of contamination, particle size, radionuclide chemistry
Skin contamination	Location, dose rate, decontamination procedures
Rate of exposure	Time, duration of exposure
Dosimeter	Type, location on body, present location of dosimeter
Postexposure symptoms	Onset, duration of nausea, vomiting, diarrhea, anorexia
Laboratory	Timed CBC, complete metabolic panel, PT, PTT, lithium heparin tube, HLA typing
Witnesses	Names, present location, and phone number
Current radiation levels	Evaluation of potential for continued irradiation

Table 39.18 outlines aspects of the history important for the estimation of absorbed dose.

Following the detonation of a nuclear device, radiation exposure results from the high, short duration (prompt) radiation dose near the detonation device and a lower dose rate from residual radiation (fallout) with the total absorbed dose dependent on location and duration of exposure. The dangerous fallout zone where persons are at risk of ARS reaches a maximum size 1–2 hours postexplosion before shrinking in size. Sheltering in place during the first day markedly reduces the radiation exposure.[315] Most persons exposed to fallout carried downwind by atmospheric winds do not develop ARS. In general, the greater the absorbed radiation dose, the sooner the onset of postexposure vomiting occurs. Typically, the onset of vomiting begins within 1–2 hours following exposure to 2–4 Gy, whereas exposure to 4–6 Gy causes vomiting within <1 hour. However, postexposure vomiting is a nonspecific sign that does not occur in all patients exposed to these radiation doses. Hence, postexposure vomiting is a less reliable measure of radiation exposure than lymphocyte count or cytogenetic dosimetry.

Biomarkers

The assessment of chromosomal aberrations in peripheral lymphocytes is a commonly used biological

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dosimeter for uniform, whole-body exposure; however, no single biodosimetry method provides all the data needed in a timely manner following a nuclear explosion.

Lymphocyte Count

The red marrow is highly sensitive to radiation with reduced production of granulocytes, lymphocytes, and platelets following a time- and dose-dependent course. Significant radiation exposures presenting ≥2 weeks postexposure demonstrate some evidence of lymphopenia, leukopenia, and thrombocytopenia with anemia appearing later. Figure 39.5 displays the variation of these elements with time and radiation dose. The most sensitive laboratory indicator of acute radiation poisoning is the exponential decrease in the lymphocyte count (lymphocyte depletion kinetic assay, LDK) within the first 12–48 hours after radiation exposure.[316]

The Andrew's lymphocyte depletion curve estimates the severity of radiation-induced damage based on the reduction of peripheral lymphocytes within the first 48 hours after radiation exposure, as displayed in Figure 39.6.[152] The early medical literature recommended measuring the absolute lymphocyte count as soon as possible, then every 2–3 hours to accumulate 3–4 data points for generating the LDK curve. Subsequent medical literature suggests the use of two lymphocyte counts; however, absolute lymphocyte counts vary with several factors (e.g., age, gender, race);[317] accuracy of data points on these curves increases with the number of serial blood counts. Table 39.19 displays the correlation between absorbed dose (Gy) and absolute lymphocyte count six days after acute radiation exposure.

An early fall in the lymphocyte count may occur in patients with severe burns or major trauma; therefore, a significant decrease in the absolute lymphocyte count should be interpreted cautiously, particularly in the presence of nonradiation-induced injuries. Significant decrements in the lymphocyte count may not occur following whole-body radiation exposure <1–2 Sv.

TABLE 39.19. Correlation of absolute lymphocyte count and absorbed dose (Gy) six days postexposure.

ARS Stage	Absorbed Dose (Gy)	Lymphocyte Count (10^9/L)
Preclinical	0.1–1.0	1.5–2.5
Mild	1.0–2.0	0.7–1.5
Moderate	2.0–4.0	0.5–0.8
Severe	4.0–6.0	0.3–0.5
Very severe	6.0–8.0	0.1–0.3
Lethal	>8.0	0.0–0.05

TABLE 39.20. Estimated absolute lymphocyte counts from 0–8 days after an acute radiation dose up to 8 Sv. The assumed mean baseline absolute lymphocyte count is 2.50×10^3/mL (2,500 cells/mL).

Dose (Sv)	12 Hours	24 Hours	Day 2	Day 4	Day 6	Day 8
0	2.45	2.45	2.45	2.45	2.45	2.45
1	2.30	2.16	1.90	1.48	1.15	0.89
2	2.16	1.90	1.48	0.89	0.54	0.33
3	2.03	1.68	1.15	0.54	0.25	0.12
4	1.90	1.48	0.89	0.33	0.12	0.044
5	1.79	1.31	0.69	0.20	0.06	0.020
6	1.69	1.15	0.54	0.12	0.03	0.006
8	1.48	0.89	0.33	0.044	0.006	<0.001

Table 39.20 provides a dose-dependent estimation of the absolute lymphocyte count during the first 8 days after radiation exposure ranging from 0–6 Sv. The LDK assay provides preliminary estimates of whole-body radiation doses ranging from 0.5–10 Gy up to ~8 days after radiation exposure.[318]

Granulocyte Count

The white blood cell counts may follow a predictable, dose-dependent time course with the granulocyte count increasing during the first few days after moderate radiation exposure followed by dose-dependent decline. Data from radiation accidents indicate a transient increase in the granulocyte count ("abortive rise") followed by a slow decline over the next 10–15 days. This pattern suggests a reversible hematological syndrome, whereas a rapid decline 4–6 days after radiation exposure indicates an irreversible hematological syndrome and a poorer prognosis.[319] Hematological recovery may not occur until 60–80 days after radiation exposure, particularly when partial-body shielding preserves some red marrow. The neutrophils/lymphocytes ratio is a potential adjunct to the LDK assay during early triage; however, use of this ratio requires knowledge of baseline values, particularly in burn and trauma patients.[315] The efficacy of this ratio needs further validation.

Cytogenetic Biodosimetry

The applicability of assays of cytogenetic damage in peripheral blood lymphocytes depends on the stability of the chromosomal damage. Classification of chromosomal aberrations includes unstable (dicentrics, acentric rings, and fragments) and stable (insertions, reciprocal, and nonreciprocal translocations) aberrations. Unstable aberrations usually involve loss of genomic material that contributes to underestimation of the ionizing radiation dose, whereas stable aberrations are transmissible through cell divisions and

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provide estimation of the radiation dose for a much longer time than unstable aberrations.[320] Dicentric, premature chromosome condensation fragments, and micronucleus frequencies decrease with lymphocyte turnover; hence, these assays are more appropriate for recent exposures.[318] For chronic or distant radiation exposures, the assay of choice is the detection of stable translocations by fluorescence *in situ* hybridization (FISH). The two standard assays for the detection of chromosomal abnormalities are: 1) the chromosome aberration assay that recognizes chromosome breakage and rearrangement and 2) sister chromatid exchange assay. The predictive value of the latter assay for subsequent health effects is unclear; therefore, the former assay is the most common method to confirm the absorbed radiation dose. Chromatid-type aberrations usually result from chemical stress, whereas chromosome aberrations are more specific to ionizing radiation. Although ionizing radiation produces biochemical changes in the body, the lack of specificity, variable dose-effect relationship, and persistent changes limit the use of these biochemical changes as markers of the absorbed radiation dose.[321]

No one technique adequately covers all exposure scenarios (e.g., recent/homogeneous events, recent/heterogeneous events, old events, mass causality events); thus, evaluation of the absorbed radiation dose requires the integration of clinical and biological data.[322] The use of calibration curves for micronuclei and dicentrics covers similar events; however, the latter remains the most accurate and practical. Other more recently developed techniques used primarily in research include analysis of premature chromosome condensations, FISH translocations, specific fluorescent probes for protein changes (BP53, H2AX, MR11), and genetic mutation rates (glycophorin A, HLA, HPRT). The introduction of fluorescent *in situ* hybridization allows measurement of stable translocations for biodosimetry present in patients with distant (i.e., years) radiation exposures.[323] Disadvantages of cytogenetic techniques include low throughput and the expertise required to analyze the tests.

Dicentric Chromosome Assay Since the 1960s, the gold standard for biological dosimetry has been the detection of dose-dependent, radiation-specific, aberrant chromosomes with 2 cm (dicentrics) in an irradiated person's peripheral blood. A dicentric chromosome forms from the fusion of two unstable, centromere-containing fragments of a chromosome following double-stranded breaks induced by radiation directly or indirectly during aberrant repair processes. The production of dicentrics occurs almost exclusively from ionizing radiation with a relatively low frequency in the healthy population (i.e., ~1/1,000 cells). Lymphocytes and fibroblasts are the typical cells used to evaluate absorbed radiation doses; lymphocytes are usually preferred test media because of their shorter culture times and lower risk of contamination.[324] The dose-related chromosomal aberrations involve both arms of one or several chromosomes in contrast to chemicals that produce chromatid-type aberrations comprising only of one arm of the chromosomes.[325] After ionizing radiation-induced irreversible chromosomal breaks, these chromosomes rejoin in a variety of ways in a dose-related relationship. The sensitivity for this assay ranges from 0.1–5 Gy, depending on the number of metaphases analyzed with upper range limited by a nonlinear dose-response relationship caused by cell cycle arrest, depressed lymphocyte production, and cell death.[326] Radiation doses of >5 Gy impair cell proliferation resulting in fewer cells reaching metaphase and scorable cells. Ideally, the dicentric assay should be performed within a few days of radiation exposure.

The conversion of dicentrics to absorbed radiation dose involves the use of calibration curves established *in vitro* by irradiating blood samples at defined doses and dose rates. Lower limits of sensitivity in the range of 50–250 mGy require the analysis of 500–1,000 metaphases.[327] Consequently, this test is time-consuming, requiring 48 hours for the lymphocyte culture and a specialized biodosimetry staff; only two laboratories perform these tests (REAC/TS, Armed Forces Radiobiology Research Institute) with a turnaround time of ~1 week for analysis during small incidents. Thus, analysis of dicentric chromosomes helps determine the clinical outcome of radiation exposure and postincident reconstruction of the radiation dose, but its use for triage purposes is problematic. Reducing the scoring of metaphases to ≤50 significantly reduces the time requirements during large causality situations; however, this approach requires more validation because accuracy diminishes as the number of metaphases analyzed decreases.[328] Limitations to the accuracy of analyzing dicentric chromosomes include inhomogeneous radiation doses, low dose rates, and the relatively rapid elimination of lymphocytes with chromosomal aberrations.[329] Cytogenic assays assume the response of all individuals to radiation is the same; thus, this assay does not account for interindividual radiosensitivity.

Estimation of a radiation dose with cytogenic biodosimetry uses a standard 1,000 cell, 2-day count of cultured peripheral lymphocytes demonstrating chromosomes rejoined at 2 cm (dicentric) and no centromeres (acentric fragment). Prompt sampling of

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TABLE 39.21. Estimation of acute whole-body radiation doses from 50-cell and 1,000 cell counts of dicentric and acentric chromosomal aberrations. The latter is substantially more time-consuming. (Adapted from REAC/TS Accident registry (https://www.osti.gov/biblio/1060542).

Dose (Sv)	Aberrations/50 Cells	Aberrations/1,000 Cells
0	0.05–0.1	1–2
1	4	88
2	12	234
3	22	439
4	35	703
5	51	1024

the peripheral lymphocytes allows the detection of external radiation doses; however, this technique is not sufficiently sensitive to detect internal doses from fallout (unless very large) or determine radiation exposure in the preceding years.[330] The accuracy of these time-dependent assays depends on the analysis of blood samples withdrawn <24–48 hours after exposure, and the analysis of blood withdrawn within this period for dicentrics helps confirm the estimated radiation dose. Table 39.21 indicates the radiation dose estimated by the number of aberrations in 50- and 1,000-cell counts.

The distribution of the lymphocytes in the peripheral circulation and the extravascular pool is a significant confounding variable for the determination of the radiation dose.[331] An average lymphocyte spends ~2 minutes in the peripheral circulation; extravascular stores of lymphocytes are 30 times greater than the peripheral circulation.[332] Because lymphocytes distribute throughout the body, rapidly delivered doses of whole-body radiation can be determined from the analysis of 500 or more metaphases for dicentric chromosome aberrations.[333] For the partial body, exposure to high doses of radiation over $^1/_3$–$^1/_2$ of the body is necessary to produce cytogenic evidence of lymphocyte damage. Following nonuniform irradiation of the body, cytogenic dosimetry helps determine the delivery of substantial radiation doses to the remainder of the body. The nonrandom distribution (overdispersion) of dicentric aberrations and the presence of large numbers of metaphases with more than three dicentric chromosome aberrations are characteristic of high radiation doses dispersed in a nonuniform manner.

Premature Chromosome Condensation Assay Interphase chromatin condenses into distinct chromosomes in mitotic Chinese hamster ovary cells or following exposure to chemical agents allowing visualization of the chromosome aberrations in lymphocytes by conventional microscopes. In contrast to the dicentric chromosome assay, progression through mitosis is unnecessary.[315] Scoring for this assay involves counting the number of premature chromosome condensation (PCC) fragments above the normal 46 chromosomes (e.g., chromosomal breaks, dicentrics, rings, translocations). Results are faster from CHO cells than from chemical methods requiring stimulation by mitogens and culturing (i.e., 2–3 hours vs. 2 days, respectively). In an *in vitro* study using blood samples irradiated with ^{60}Co γ-radiation, the PCC ring assay was linear up to whole-body doses of 20 Gy.[334] Compared with the dicentric chromosome assay, the PCC ring assay was more accurate in the high-dose range of >6 Gy and less accurate in the lower-dose range (0–6 Gy). Neither assay identified partial-body exposures. The PCC assay also allows accurate discrimination between total- and partial-body exposures to low- and high-LET radiation.

DNA Damage Assays Adverse radiation-induced responses include double-stranded DNA breaks, base lesions, and delayed cell cycle progression.[315] The kinetics of the appearance and elimination of these changes complicate the use of these biomarkers for triage and prognosis. Micronuclei are unstable chromosome aberrations that form from the failure of chromosome segments to separate during mitosis and pass into the daughter nuclei. These unstable, extranuclear chromosome fragments have a half-life of ~1 year with reliable estimate of radiation exposure up to 6–12 months after exposure. The typical whole-body dose range for this assay is 0.3–5 Gy[315] and up to 6 Gy with modification for triage; the micronuclei assay is not sensitive to partial-body radiation exposure.[335] Culturing of the cells requires 72 hours with results within 1 week of exposure if the blood is drawn immediately. Scoring typically involves 1,000 binuclear cells with accuracy decreasing with smaller sample size. Scoring requires less skill than dicentric assays; however, micronuclei are not unique to radiation exposure.[336]

During the DNA repair process, phosphorylation of the H2AX protein occurs near double-stranded DNA breaks. The peak amount of phosphorylated H2AX protein occurs ~30 minutes after radiation exposure followed by a rapid decline to baseline concentrations in a few days. The need to draw blood immediately after exposure limits the usefulness of the γ-H2AX foci assay; however, results are available within 4–6 hours for microscopy (dose range, 0.5–5 Gy) and 2 hours for flow cytometry (dose range, 0.5–10 Gy).[322]

Fluorescence *In Situ* Hybridization (FISH)
Single-color FISH (sFISH) detects interexchanges (e.g., dicentrics, translocations), whereas multicolor FISH

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assesses induced translocations in different labeled chromosomes and whole genome analysis (M-FISH). Translocation frequencies in circulating lymphocytes persist for years, allowing analysis of radiation exposures in the distant past; however, background frequencies vary with age and individuals. Consequently, the lower limit of detection is ~0.5 Gy.[337] The detection of partial-body exposures also decreases with time as the translocation often are unstable. Accurate assessment of individual doses requires ~1,000 genome equivalent cells.[318]

Tooth Enamel by ESR

Electron paramagnetic resonance (EPR) is a nondestructive spectroscopic technique used to detect and/or identify paramagnetic systems (i.e., atoms, molecules, molecular ions) characterized by the presence of at least one unpaired electron. Placing a paramagnetic system in a magnetic field produces an energy split (Zeeman splitting), resulting in two low-lying Zeeman levels corresponding to the ground state. Spectroscopy is a sensitive measure of energy created by the production of radicals. For teeth, the main paramagnetic material involves carbon dioxide radicals with results estimating the cumulative ionizing radiation dose to the head above 0.5 Gy during the last several years to a few decades; EPR does not correlate well when the radiation exposure does not include the head.[338] Ionizing radiation produces carbon dioxide radicals from carbonate impurities in the main tooth enamel components (hydroxyl apatite). Using EPR techniques to measure the intensity of the radiation-induced signals, the absorbed radiation dose in the enamel correlates to the EPR values.[339,340] The sensitivity of EPR (i.e., ≤100 mGy) is below the sensitivity achievable with cytogenetic dose reconstruction techniques.[341] Depending on the photon energy spectrum and geometry of the radiation exposure scenario, the absorbed radiation dose in the enamel can be converted to air kerma using appropriate conversion factors. EPR techniques allow detection of natural background radiation, ^{133}Xe in fission products from the accidental release of noble gases, and ^{41}Ar in noble gases routinely released from nuclear facilities. ^{133}Xe emits β- (100 keV), γ- (81 keV), and X-ray (2 keV) radiation during decay, whereas ^{41}Ar emits β- (1,300 keV) and γ- (460 keV) radiation during decay. In a study of nuclear workers living near the Mayak nuclear facilities at Lake Irtyash in the Southern Urals, Russia, during peak releases of noble gases (i.e., 1950s), the average excess absorbed radiation dose above natural background radiation (0.7 ± 0.3 mGy) was 36 ± 29 mGy based on EPR of their tooth enamel.[342]

Optically stimulated luminescence (OSL) is an alternative technique for determining the radiation from teeth; the main advantage of this method is the use of simpler, more mobile equipment because spectral deconvolution needed for electron paramagnetic resonance (EPR)-based techniques is unnecessary for OSL. Use of OSL for acute triage is complicated by the substantial decrease in the signal from the teeth that remain in the mouth during the first 12 hours; consequently, the sample should be processed within the first 24 hours after radiation exposure.[343]

Sperm Counts

The sperm count is a sensitive biological indicator of radiation exposure based on human studies, including testicular biopsies obtained at various intervals after intratesticular tritiated thymidine injections.[344] Rapidly dividing, differentiating spermatogonia are substantially more sensitive to radiation than later-stage germ cells, resulting in a progressive loss of more mature differentiating cells (i.e., dose-related maturation depletion) following radiation exposure based on 67 men receiving a single radiation dose of 8–600 rads to the testes.[345] Depending on the radiation dose to the testes, dramatic declines in ejaculated sperm counts occur ~10 weeks after exposure, whereas azoospermia develops ~18 weeks after exposure, depending on the number of differentiating spermatogonia surviving and epididymal sperm storage. Higher radiation doses cause a more rapid onset of oligospermia or azoospermia by a direct reduction in cells in the later stages of sperm production (e.g., spermatids). Recovery of sperm production depends on the regeneration of spermatogonial stem cells and their ability to differentiate. In the latter study, the beginning of histological recovery (↑ germinal cells) ranged from 6 months for 20 rads to 7.5 months for 600 rads, whereas ↑ ejaculated sperms began at 6 months for 20 rads and 24 months for 600 rads. The initiation of sperm count recovery is dose-dependent following single, acute radiation doses with the recovery usually beginning ~7 months after exposure following a 1-Gy dose and full recovery requiring 2 years, whereas recovery begins 2 years after a 6-Gy dose and >5 years, if at all, to preirradiation levels.[344,346] Fractionation of the radiation dose (e.g., radiotherapy) reduces these timelines of recovery.[308]

Figure 39.7 demonstrates the dose-related changes occurring in sperm counts over time. Failure of the sperm count to decrease 45 days after radiation exposure suggests the testes were not exposed to radiation doses of >0.15 Gy, whereas temporary azoospermia suggests a testicular radiation dose of >0.3 Gy.[345] Characteristic changes in the blood associated with normal

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spermatogenesis during the first 2 months postexposure suggest a partial-body exposure. The absence of changes in the blood and the presence of oligospermia or azoospermia indicates exposure of the lower extremity to radiation doses exceeding 0.15 Gy. After the 18th day postexposure, the presence of epilation helps confirm the distribution of radiation in areas receiving more than 3 Gy.[347]

Dose Assessment

The amount and distribution of the absorbed dose are the most important determinants of subsequent health effects; therefore, this information has important prognostic value. Proper assessment of the absorbed dose requires an evaluation of the position and orientation of the patient relative to the source of radiation, the duration of exposure, and the characteristics (quality, strength) of the radiation.[348]

Dosimetry

Most of the absorbed dose usually occurs next to the radiation source, even though the duration of exposure is short. Information on personal and cytogenetic dosimetry confirms the reconstructed model. The presence of individuals or material between the radiation source and the patient is important primarily for low-energy radiation sources (e.g., neutrons, β-particles or low-energy γ-rays, X-rays). Personal dosimeters measure the radiation received only in one unique location; consequently, the values obtained by these dosimeters do not necessarily reflect radiation exposure to other parts of the body, depending on the radiation distribution at the time of the accident. Estimation of the radiation exposure should include adjustment for the accuracy of the dosimeter.[349] Other methods of radiation dosimetry involve biological dosimetry and theoretical calculations based on an analysis of radiation-induced changes in biological tissue (e.g., teeth, bone, blood). Serial measurements of lymphocyte counts are a particularly effective method of biological dosimetry.

Modeling

Depending on the reliability of the data, computer modeling of radiation exposure helps delineate the actual dose. The two most common methods are the Monte Carlo technique and the discrete ordinates method. Both methods require validation by dosimetry data and physical modeling.[345] Incidental alterations of the tissue (dental enamel, blood, hair) of the patient or personal belongings (film, coins, rings)[350] provide opportunistic dosimeters for the neutron spectrum and the radiation distribution.[351] Alteration of electron structure in some crystalline materials is detectable by measuring thermoluminescent signals.[352] Electron spin resonance can determine the number of free radicals produced during exposure to a radiation source and retained in specific tissues (e.g., bone, tooth enamel). The magnitude of the exposure is directly proportional to the signal from the electron spin resonance.[353]

Phantoms

Reconstruction of the accident from a single radiation source involves loading a phantom with thermoluminescent dosimeters by a health physicist to approximate the accident, particularly if the distance between the source and the patient is known and exceeds 2 m. The use of a phantom containing a skeleton and equivalent soft tissue density helps estimate the absorbed dose, especially when the accident involved several people or steep radiation gradients. Thermoluminescent dosimeters are placed in the phantom; direct calculations of the absorbed dose are recorded when the source of exposure is reactivated. Comparison of absorbed doses involves the use of the midline-tissue or whole-body doses. For most accidents involving γ-radiation, the absorbed dose in air or skin must be multiplied by 0.66 to obtain the midline tissue dose.[354]

The dosimetric data are superimposed on a CT scan of the affected portion of the body. The situation when the patient walks toward the source of radiation is more complex. Because of the inverse square law, exposure at great distances is considered a unidirectional, whole-body exposure. The rest of the exposure is calculated by estimating the radiation distribution and exposure time. Time-motion studies, interviews with the patient, and reviews of videotapes and emergency radio broadcast logs help define the sequence of events.

Abnormalities

Radiation-induced damage to specific organs results in the release of biomarkers including serum α-amylase from pancreatic or salivary gland injury and lactate dehydrogenase from hemolysis and tissue injury; however, the presence of these biomarkers is not unique to radiation-induced injuries. For patients hospitalized after radiation exposure at Chernobyl, the α-amylase level correlated to the severity of clinical manifestations of the acute radiation syndrome;[63] however, serum amylase is a very general estimate of radiation dose with very significant variability in normal values. The

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increase in serum creatine kinase also correlated with the amount of damaged skin and the severity of the β-radiation-induced dermatitis. Bone marrow biopsy is an important measure of the radiation dose and distribution, prognosis, and treatment of the patient. Magnetic resonance imaging (MRI) is an alternative method of evaluating bone marrow recovery based on the difference in intensity of the T_1-weighted images between fat and active hematopoietic elements; however, the time and expense involved with MRI limit the usefulness of this imaging procedure in nuclear incidents.[355] Rodent studies suggest high-resolution magic angle spinning (MAS) ^{1}H NMR provides detailed information about biochemical changes in the bone marrow through *ex vivo* analysis of chemical extracts of marrow including decreased total choline content, increased fatty acids in the bone marrow, and decreased creatine content caused by radiation-induced damage to metabolic pathways in the bone marrow.[356]

Certain baseline tests may help detect the onset of late complications from radiation exposure, depending on the irradiated areas. Examples include slit lamp examination of the cornea and lens, pulmonary function tests including lung volumes for the detection of fibrosis, and bone scans for activity in the bone marrow. Abnormalities in the bone scan typically appear 4–19 months postexposure.

HEALTH SURVEILLANCE

Every reasonable effort should be made to minimize exposure to ionizing radiation as far below the regulatory dose limits as practical given economic, societal, and other relevant needs. The synonym for this approach is as low as reasonably achievable (ALARA). Reduction of the external dose of radiation involves minimizing the time near the radiation source, maximizing the distance from the source (e.g., the dose decreases with the square of the distance from the source), using available shielding, and minimizing the quantity of radioactive material handled. Methods to reduce the internal dose of radiation include control of contamination, use of proper protective clothing, elimination of food, drink, and smoking in areas of contamination, and monitoring of personnel in contaminated areas.

Risk Assessment

Chronic Low-Level Radiation

Most epidemiology data supporting an association between radiation and cancer result from acute exposure to high doses of radiation above 0.2–0.5 Gy; therefore, risk estimates of radiation exposure must be extrapolated from relative high doses to the more continuous, lower radiation levels present in medical, occupational, or environmental settings. Significant uncertainties remain in estimating radiation risks and disease probability in the low-dose region (<0.2 Gy) from disparities in the accuracy of modeling assumptions (e.g., dose assessment, low-dose/low-dose rates, relative biological effectiveness factors) and the validity of extrapolating data from radiation-exposed individuals to a healthy population.[357] Cancer is a common disease that will affect 42/100 individuals in their lifetime. Following brief radiation exposure of 100 mSv, epidemiological studies have had difficulty detecting the predicted single excess cancer case in the lifetime of 100 exposed individuals (i.e., relative risk 1.001–1.04 for low-dose radiation 1–100 mSv).[96] Variability in risk estimates at lower radiation levels occurs because of inconsistent data, assumptions about the characteristics of the dose-response curve, uncertainties about the degree of exposure, use of cancer incidence vs. cancer mortality, and several modifying factors including differences in the dose rates and individual sensitivity (e.g., age, sex, genetic susceptibility, nutritional status). Although there is considerable evidence of teratogenic effects and limited data on *in utero* carcinogenic effects of high radiation doses, there is little direct evidence to support the causal association between intrauterine exposure and subsequent heritable genetic abnormalities.

Based on current risk estimates, epidemiological studies of persons exposed to low radiation levels help determine the upper risk limits and the potential for underestimating true risks; however, chances of detecting statistically significant increases in risk are low given the small number of expected cases at low radiation levels and the presence of confounding factors and bias.[358] For survivors of the atomic bombs in Hiroshima and Nagasaki, the lowest dose interval associated with an increased leukemia incidence was 0.2–0.49 Gy; therefore, the Japanese data do not elucidate the shape of the dose-response curve below this level. Studies that produced estimates of cancer risk following exposure to external ionizing radiation primarily involved medical treatment, nuclear releases, and occupational exposures. In general, the relative risks per unit dose are greater for Japanese atomic bomb survivors than comparable subsets of medically exposed individuals.[174] Although several factors may account for the difference in risk estimates, including the higher baseline cancer risks in radiation studies of patients than in Japanese atomic bomb survivors, cell sterilization probably accounts for most of the

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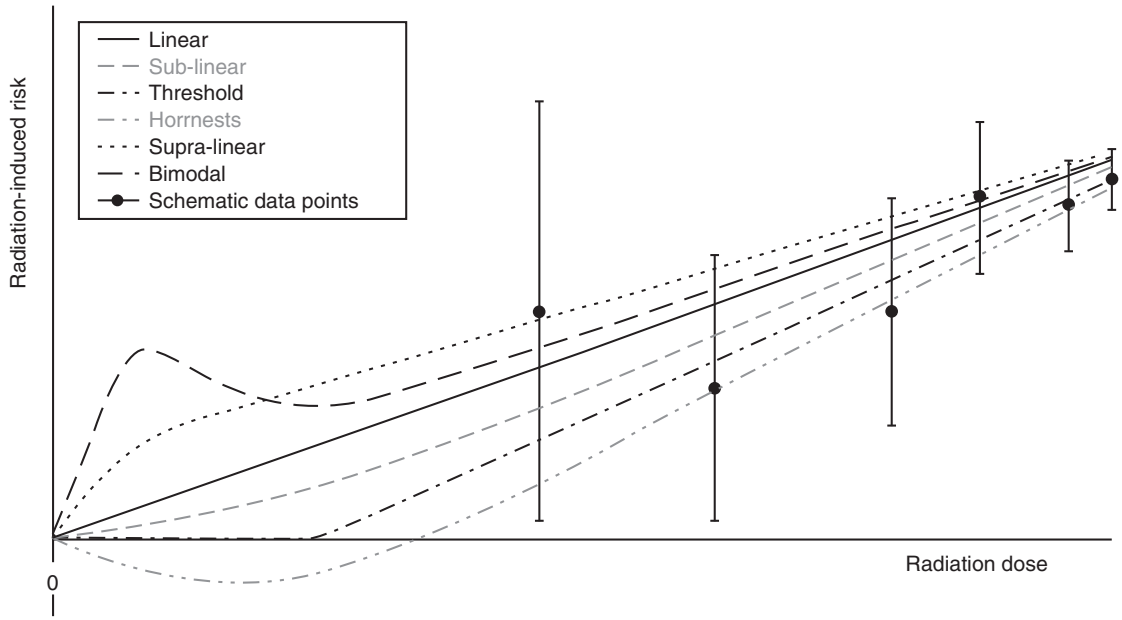


FIGURE 39.9. Several dose-response curves describe radiation-induced risks for stochastic health effects including linear, sublinear, threshold, supralinear, hormesis, and bimodal curves. The schematic data points on the graph are consistent with all the curves. For radiological protection, most organizations chose the linear curve. (Adapted from Wakeford).[254]

discrepancy between these two populations. Figure 39.9 schematically displays several dose-response curves that potentially fit low-dose exposure data. For radiological protection, most organizations chose the linear model.

Modeling

Because of data limitations, the determination of risks from cancer or genetic harm following exposure to low radiation doses (<0.1 Gy) present in environmental or occupational settings requires the use of mathematical models to extrapolate risk from high radiation doses observed following the detonation of atomic bombs and use of high-dose medical irradiation. The three most common models (i.e., linear, linear-quadratic, quadratic) adequately fit the data for exposure to radiation doses of >1 Gy; however, these models differ in the estimation of risk at lower radiation doses as displayed in Figure 39.10.

Dose-Response Curves

Quantitative animal data on dose-response relationships indicate the relationship between cancer and low-LET radiation is complex with tumor types primarily demonstrating linear or linear–quadratic relationships; a few studies suggest a low-dose threshold (e.g., thymic lymphoma, ovarian cancer) for tumors dependent on cell killing.[207] The linear model is the simplest and most conservative model for fitting epidemiological data to develop the dose-response curve for estimating radiation risk, particularly at high-LET radiation doses. Most risk estimates involving low-LET radiation (i.e., <0.1 Gy) by radiation protection organizations including the National Research Council's Committee on the Biological Effects of Ionizing Radiations (BEIR V,[9] BEIR VII[207]) use the linear no-threshold model for radiation-induced solid tumors and the linear-quadratic model for leukemia, bone cancer, and nonmelanoma skin cancers.[207] These models of radiation-induced cancer risks in the range of 0–0.1 Gy are based on mechanistic data with the risk estimate of an effect at low radiation doses usually lower for linear-quadratic than linear models.

Data from lifetime studies of A-bomb survivors are currently nearing completion as the number of survivors of the atomic bombing dwindles; therefore, models are necessary to extrapolate the future incidence of cancer based on data from cohorts followed for limited time. The dose-response relationships for individual tumor types differ in the Life Span Study of the atomic bomb survivors. For leukemia, the dose-response is curvilinear with statistically significant risk at doses exceeding 0.2 Gy, whereas nonmelanoma skin cancer risk is curvilinear with statistically significant excess risk above 0.5 Gy.[360] Most leukemia-related mortality in this

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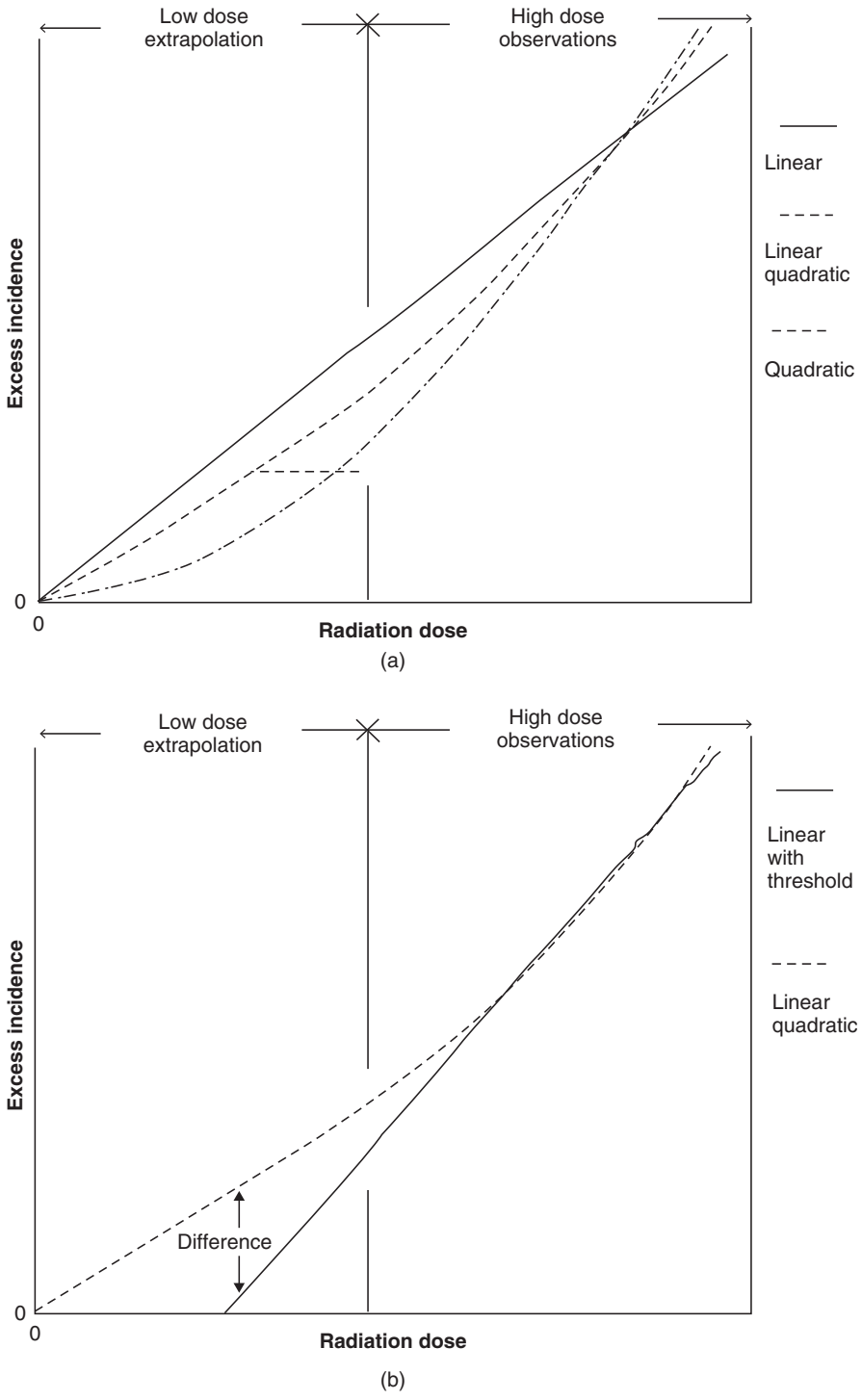


FIGURE 39.10. (a) Schematic representation of dose-response curves for three models (linear, linear-quadratic, quadratic) demonstrating the extrapolation of high-dose data for excess incidence to low-dose exposures. (b) Comparison of linear model with threshold to linear-quadratic model without threshold showing hypothetical difference between the two models at high- and low-dose exposures. Modeling of leukemia risk commonly uses the linear-quadratic function, whereas modeling of solid cancer risk usually uses the linear function. Estimating risk in the low-dose range involves extrapolation of data from higher levels. (Adapted from Richardson).[359]

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cohort occurred in the first 15 years after the atomic bomb explosion, with the risk of leukemia-related deaths decreasing to negligible levels after 50 years of follow-up.[361]

Although the actual shape of the dose-response curve for current environmental radiation levels depends on model type, the widespread prevalence of cancer requires additional assumptions about the effect of radiation on the spontaneous incidence of cancer, particularly the effect of age at exposure on cancer incidence and mortality. Children under the age of 10 years appear more susceptible to the induction of cancer than adults, especially leukemia and solid tumors of the breast, thyroid, and bone.[362]

Two main types of assumptions (excess absolute risk, excess relative risk) affect the age-related changes in the risk estimates for the dose-response curves of cancer incidence and mortality following low-dose LET radiation exposure. Excessive relative risk (ERR, Equation 39.2) expresses risk as a dimensionless function of the relative risk in the unexposed population, whereas excessive absolute risk (EAR, attributable risk, Equation 39.3) is independent of the baseline risk in the unexposed group expressed as excess cases or deaths/person-year. Figure 39.11 displays the difference in risk between the additive (absolute) risk model using excessive absolute risk (EAR) commonly applied to leukemia risk and the multiplicative (relative) risk model using excessive relative risk (ERR) commonly applied to solid cancers.

$$\text{ERR} = (\text{disease rate exposed population} / \text{disease rate unexposed population}) - 1 \quad \text{(Equation 39.2)}$$

$$\text{EAR} = \text{disease rate in exposed population} - \text{disease rate in unexposed population} \quad \text{(Equation 39.3)}$$

Although mechanistic considerations suggest the relative risk model more accurately predicts cancer risks from the atomic bomb data, mechanistic and epidemiological data are insufficient to determine the appropriate model. For cancer sites other than breast, lung, and thyroid, the BEIR VII committee recommends a weighed mean combining 70% of the excess relative risk (i.e., ERR) and 30% of the excess absolute risk (i.e., EAR).[207] Risk data on the US Caucasian population are sufficient for breast and thyroid cancers to directly estimate risks, whereas this ratio is reversed for lung cancer because of the high rate of smoking in Japan and the additive effects of smoking and radiation.[363]

Modifying Factors and Excess Risk

For purposes of protection, most governmental agencies use the linear no-threshold model to extrapolate the cancer risk from high-dose exposure data to the lower doses present in environmental and occupational settings. Although epidemiological data suggest the incidence of thyroid cancer, leukemia, and breast cancer best fits the linear no-threshold risk model,[359,364] experimental evidence suggests low-dose (<10 mSv) and low dose-rate (<100 mSv/day) radiation are less effective than single, high radiation doses in inducing cancer. Because of the effectiveness of cellular repair process at low and fractionated low-LET radiation doses, the linear extrapolation of animal data usually involves correction factors including the dose and dose-rate effectiveness factors (DREF, DDREF). The dose rate effectiveness factor (DREF) measures the difference between a single large acute radiation exposure and the same dose and type of radiation following a chronic radiation exposure fractionated over time. DDREF assumes the risk of a solid cancer at low acute doses or low dose rates of low-LET radiation differs from the risk at higher acute doses seen in the Japanese atomic bomb survivors. The risk reduction for these two factors (dose and dose-rate effectiveness factor, DDREF) is usually considered equal. For cultured somatic cells, the DDREF typically ranges 2–4-fold.[365]

Based on evidence from experimental data, the International Commission on Radiological Protection (ICRP),[366] Public Health England (formally, National Radiological Protection Board), the US Environmental Protection Agency, and UNSCEAR recommend reducing linear estimates derived from Japanese A-bomb survivors and other high-dose rate cohorts by a dose and dose-rate reduction factor (DDREF) of 2.0. BEIR V estimates did not reduce cancer risk estimates by a DDREF factor, whereas BEIR VII estimates on low-dose radiation used a linear model with a DDREF of 1.5 for solid cancer risk estimates. Leukemia risk estimates fit a linear-quadratic model rather than the linear no-threshold model reduced by the DDREF factor. This factor assumes the linear component of the dose-response does not depend on dose rate; however, some authors suggest some radiobiological animal data do not support this concept.[367]

Absolute Risk The absolute or additive risk model assumes the annual increased cancer risk appears after a latent period; then, the increased cancer rate remains constant. Consequently, the excess rate is constant and independent of the background cancer rate. The additive model is most applicable when radiation acts

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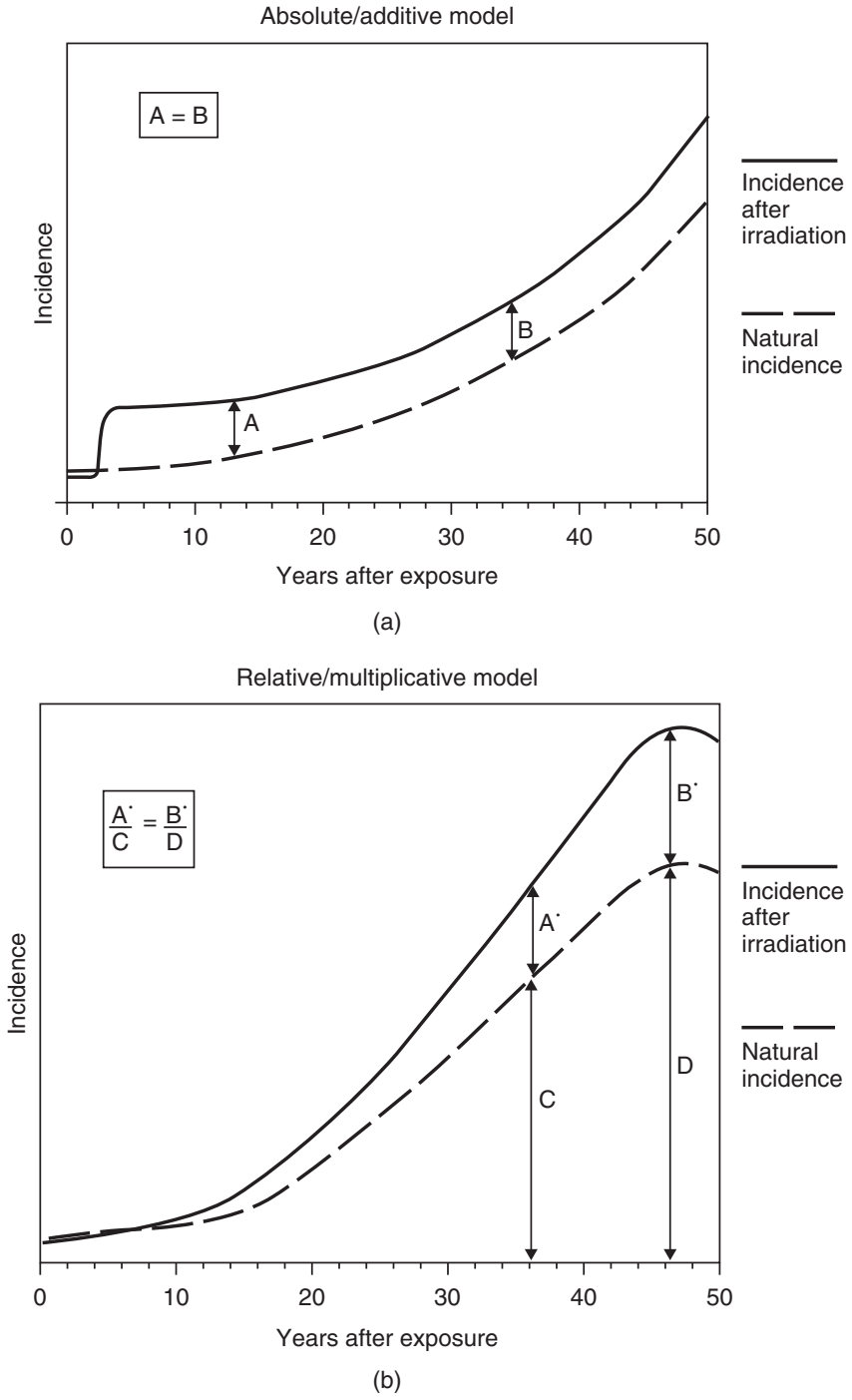


FIGURE 39.11. Schematic representation of the differences in incidence using the absolute (additive) model (a) and the relative (multiplicative) model (b). For the absolute model, the incidence increases with age after exposure with the natural incidence plus the radiation effect. The latter is constant with the radiation effect at 13 years after exposure (A) the same as at 35 years after exposure (B). For the relative model (b), the radiation effect increases with the natural incidence rate. The radiation effect at age 36 years (A′) is smaller than at age 46 years (B′) because the natural incidence is smaller at 36 years (C) than at 46 years (D). (Adapted from Richardson).[359]

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independently as one of many cancer-modifying factors after initiation (i.e., tumor promoter). The excess absolute risk (EAR) refers to the difference in the rate of disease occurrence between an exposed and unexposed population; absolute risk is expressed as the excess number of cancer cases per unit of population per unit of time per unit of absorbed dose. Although the lifetime absolute risk depends on the age at radiation exposure, the annual absolute risk does not depend on the age at observation once the latent period passes; this risk does not rely on the underlying cancer rate. Leukemia, bone cancer, and nonmelanoma skin cancers follow an absolute risk model. Most models now predict very few subsequent radiation-associated leukemia deaths among atomic bomb survivors.

Relative Risk Relative risk is the ratio of the occurrence rate in the exposed and nonexposed populations with the excess relative risk (ERR) equal to the relative risk minus 1; the ERR is a measure of the effect strength. The relative or multiplicative risk model assumes increased cancer risk follows the same pattern as the natural cancer incidence with the excess cancer rate increasing in direct proportion to the baseline cancer rate. This model implies that the cancer risk after the latent period depends on age and the spontaneous cancer incidence in the population studied. This model also suggests radiation initiates the first transformation steps in the multistage theory of cancer for solid tumors with other promotional steps necessary for tumor development.[29] All radiation, host biological sensitivity, and environmental factors affect the cancer risk equally, as would occur in the early stages of the multistage process of cancer (i.e., initiation). Both the EAR and ERR vary with factors other than radiation dose, including age at exposure, attained age (e.g., time after exposure), sex, and lifestyle (e.g., smoking). The radiation-induced excess risk of solid cancers follows a time-constant relative risk model (i.e., after a latent period, the excess cancer incident is proportional to the underlying cancer incidence rate in the nonirradiated population). The relative risk model implies radiation-induced cancer will increase as the natural incidence of cancer does with the excess relative risk diminishing as the age at exposure increases, particularly following exposure at a young age.

Although current epidemiology data indicate the relative risk model fits better than the absolute risk model, some modification of the relative risk model may be appropriate for diminishing risks.[207] Extrapolating risk data from Japanese atomic bomb survivors to other populations using the relative risk model requires modification when baseline cancer rates in the two population differ. Although the baseline cancer rate for solid tumors is similar in the United States and Japan, site-specific cancer rates are not similar; the baseline rate of stomach and liver cancer is relatively high in Japan, whereas breast, colon, lung, and prostate cancer rates are relatively high in the United States. Although the relative risk model predicts higher estimates of the cancer incidence following exposure to low-LET radiation than the absolute risk model, these cancers appear later in life; therefore, the loss of life expectancy is proportionally less.[368]

Figure 39.11 demonstrates schematically the differences in incidence between the two risk models. In the absolute risk model (a), the effect of radiation on the disease incidence remains constant to the natural incidence as the age after exposure increases (A = B). In the relative risk model (b), the effect of radiation on incidence increases as the age after exposure and the natural (spontaneous) incidence increase; however, the ratio of the radiation effect/natural incidence remains constant (A′/C′ = B′/D′). The BEIR V report does not use the dose rate effectiveness factor (DREF) to reduce risks at low levels of low-LET radiation.

Leukemia and some solid tumors (e.g., breast, thyroid, bone, lung) are clearly associated with excessive radiation exposure at doses of >0.1 Gy. The dose-response relationship between radiation exposure and breast cancer incidence was linear down to 0.5 Sv; data suggest this relationship may extend to lower radiation levels.[369] For most solid tumors, studies from atomic bomb survivors indicate the relative risk model best fits published data (i.e., persons irradiated at an older age have a greater cancer risk compared with persons irradiated at a younger age). The incidence of breast cancer and lung cancer in this population does not correlate well to the absolute risk model; the latter risk appears intermediate between the two models.

Validation of Models

As seen in Figure 39.10, the linear no-threshold model provides the most conservative risk estimates at low dose levels. Each of these models approximates the true dose-response relationship at low radiation doses; however, each model has limitations. Assumptions used in these models contain large safety factors to prevent underestimation of risk for regulatory purposes; therefore, these estimations do not necessarily imply a specific effect at a given dose. Technical difficulties (e.g., large number of subjects necessary to detect small increases in the incidence of cancer at low doses) prevent experimental validation of these models. Meta-analyses of various cohorts exposed to radiation

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provide alternative analytical methods to determine the effect of radiation on large populations; however, these methods are limited by the bias of publishing positive rather than negative results.[370] Despite the plausibility of low-dose radiation effects, the existence of conclusive evidence of biological harm in humans at radiation doses of <10–100 mGy remains controversial.

The validity of extrapolating high- to low-dose radiation is limited by the inverse square law; to preserve statistical significance and power, this law requires the sample size to increase by the inverse square as the additional risk becomes smaller. At an exposure of 0.1 Gy, a sample size of at least 100,000 workers and a similar group of age- and sex-matched controls are necessary to detect the difference in the cancer incidence.[371] Reducing the exposure to 0.01 Gy requires a sample size of 10 million to maintain statistical power. For low-LET radiation, the dose-response curve appears concave upward with a maximum peak that subsequently declines in response to increasing dose. This latter decline reflects the killing of radiation-initiated cells that eventually would produce tumors.

Interpretation of Risk

Interpretation of the significance of risk estimates and importance of these risks to specific populations is subjective. Table 39.22 lists several factors influencing the perception of acceptable risk.

Comparisons of estimated risks with known risks help explain the significance of the estimated risks. Almost 1 in 4 annual US deaths (i.e., ~600,000) result from cancer excluding basal cell carcinomas, squamous cell skin cancer, and *in situ* carcinomas except urinary bladder. Newly diagnosed cancer accounts for ~2¾-fold more persons (i.e., ~1,700,000).[373] If the lifetime risk of dying from cancer after an exposure to 0.01 Gy is 0.1% and the lifetime risk of cancer is 20%, then the total probability of dying from cancer increases by 0.5–20.1%. Another approach compares everyday hazards with estimated risks. Assuming the annual risk of a fatal accident in the United States is 6×10^{-4}, the risk of dying from a fatal accident over 40 years is 2% ($40\times6\times10^{-4}$) or the same risk as developing a fatal cancer after exposure to a radiation dose of 1 Gy.[372] The risk of developing a fatal cancer changes over time with more effective medical treatments. Estimates of the approximate annual risk of a fatal accident include: 1) lightning, 5×10^{-7}; 2) airplane crashes, 9×10^{-6}; 3) drowning, 3×10^{-5}; and 4) motor transportation deaths, 3×10^{-4}.[359]

TABLE 39.22. Perception of acceptable risk. (Adapted from Adelstein).[372]

More Acceptable	Less Acceptable
Voluntary	Involuntary
Immediate effect	Delayed effect
Certain risk	Uncertain risk
Ordinary	Catastrophic
Natural	Synthetic
Occupational	Environmental
Reversible	Irreversible
Clear benefit	Unclear or small benefit
Necessity	Luxury

Estimated Cancer Risks

Analysis of epidemiology data on radiation-induced effects on Japanese atomic bomb survivors and other medical, environmental, and occupational cohorts indicates radiation exposure causes excessive cases of leukemia and most solid cancers. At radiation doses of ≤0.1 Gy, statistical limitations complicate the evaluation of human cancer risks; hence, models are used to estimate risk in this range. For absorbed radiation doses ranging from 0.01–0.1 Gy, knowledge regarding fatal cancer risks is very limited because most epidemiological studies have insufficient power to separate small excess radiation-induced risks (i.e., <0.05/Sv) from background cancer risk factors.[374] There is no demonstrable risk of deterministic effects in this range. Linear-dose response functions fit most solid cancer data reasonably well, with the possibility of upper curve turning downward at high radiation doses. The highest risks for many cancers occur in persons exposed early in life with excess radiation-induced risks persisting throughout life, albeit at lower risk with increasing age.[375] Table 39.23 lists the estimated lifetime attributable risk of all solid cancers and leukemia incidence and mortality by the BEIR VII Committee for exposure to 0.1 Gy low-LET radiation. This model developed by the committee predicted ~1 in 100 persons would develop cancer (leukemia or solid tumors) in their lifetime following exposure to 0.1 Gy compared with 42 in 100 developing cancer in their lifetime without radiation exposure. This group primarily used Japanese atomic bomb survivor data for estimating cancer risks, except for combining data from the Japanese survivors and medically exposed persons for thyroid and breast cancers. These data do not account for the influence of smoking.

The fit for low-dose LET radiation data was closer for the linear-quadratic model than the linear model, whereas the linear-quadratic and linear models were not statistically different for all solid tumor data. The estimates for all solid tumors were reduced by a DDREF factor of 1.5 to account for the effect of low doses and

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TABLE 39.23. BEIR VII Committee estimates of lifetime attributable risk of incidence and mortality for all solid cancers and leukemia per 100,000 exposed persons following exposure to 0.1 Gy. (Adapted from BEIR).[207]

Estimate (Dose)	Solid Tumors All Males	Solid Tumors All Female	Leukemia Males	Leukemia Females
Excess cases (0.1 Gy)	800	1,300	100	70
Range excess cases (0.1 Gy)	400–1,600	690–2,500	30–300	20–250
Unexposed cases (baseline)	45,500	36,900	830	590
% Cases exposed/total exposed + unexposed	1.73	3.40	10.8	10.6
Excess deaths (0.1 Gy)	410	610	70	50
Range excess deaths	200–830	300–1,200	20–220	10–190
Unexposed deaths (baseline)	22,100	17,500	710	530
% Deaths exposed/total exposed + unexposed	1.82	3.37	8.97	8.62

dose rates; the linear-quadratic model does not require that reduction. The estimated risk of cancer mortality is age-dependent, with the risk of acute exposure to radiation during childhood being approximately twice that of an adult when comparing risks of all cancers at 5 and 30 years of age. Because of the imprecision of the Japanese data, the range of estimates for excess overall cancer deaths from solid tumors ranges from 200–830 for men and 300–1,200 for women.

These estimates depend partly on certain assumptions regarding the population (i.e., male/female), age at exposure, and cancer site (i.e., spontaneous cancer rate). Table 39.24 displays the magnitude of the effect of these variables on cancer mortality following a single, acute low-LET radiation dose of 0.1 Gy in males/females. The overall risk is greater for cancer incidence than cancer mortality because some cancers (e.g., thyroid) have a good prognosis. Thyroid cancer is not included in Table 39.24 because of the low mortality associated with this cancer.

Table 39.25 lists estimated mortality risks from two different low-dose radiation exposure scenarios using the BEIR VII data. Although most governmental and industrial organizations use similar models, their risk estimates differ slightly because of different assumptions (e.g., data sets, DDREF factors, and population composition). The mortality values (excess cases/100,000 person years) for leukemia from a single, acute low-LET radiation exposure of 0.1 Gy include 50 (ICRP, 1991), 56 (US EPA, 1999), 60 (UNSCEAR, 2000), and 95 (BEIR V, 1990). The BEIR VII models predict values of 70 for women and 100 for men (the estimated risks for men

TABLE 39.24. Lifetime attributable risk of cancer **mortality** in males/females for specific cancer sites following exposure to a single dose of 0.1 Gy at various ages in years. The values are based on a linear-quadratic model for leukemia and a linear model for all other tumors. The latter model, but not the former, includes a low dose and dose rate reduction factor (DDREF) of 1.5. The values in each cell represent the number of deaths/100,000 males and females exposed to a single low-LET radiation dose of 0.1 Gy at the age (years) indicated. These values are displayed in the format male/female unless the organ occurs in only one sex. Similar tables on cancer incidence are available in the BEIR VII report. Assuming a boy had a 0.01 Gy exposure from a barium enema at age 10, his lifetime risk of colon cancer is $0.01/0.1 \times 117 \times 100{,}000$ person-years = 11.7 per 100,000 or ~1 in 8,550. Linear extrapolation can be used on all tumors except leukemia because the latter follows a linear-quadratic model (Data from BEIR VII).[207]

Cancer Type	0	5	10	15	20	30	40	50	60	70	80
Leukemia	71/53	71/52	71/53	70/52	67/51	64/51	67/52	71/54	73/55	69/52	51/38
All solid	1028/1717	781/1295	641/1051	533/862	444/711	317/491	310/455	289/415	246/354	181/265	102/152
All Cancers	1099/1770	852/1347	712/1104	603/914	511/762	381/542	377/507	360/469	319/409	250/317	153/190
Stomach	41/57	34/48	30/41	25/34	21/29	16/21	15/20	13/19	11/16	8/13	4/8
Colon	163/102	139/86	117/73	99/62	84/53	61/38	60/37	57/35	49/31	36/25	21/15
Liver	44/24	37/20	31/17	27/14	23/12	16/9	16/8	14/8	12/7	8/5	4/3
Lung	318/643	264/534	219/442	182/367	151/305	107/213	107/212	104/204	93/183	71/140	42/81
Prostate	17	15	12	10	9	7	6	7	7	7	5
Bladder	45/59	38/57	32/43	27/36	23/31	17/23	17/23	17/22	17/22	15/19	10/13
Other	400/491	255/287	200/220	162/179	134/147	94/103	88/97	77/86	58/69	36/47	17/24
Breast, female	274	214	167	130	101	61	35	19	9	5	2
Uterus	11	10	8	7	6	4	4	3	3	2	1
Ovary	55	47	39	34	28	20	20	18	15	10	5

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TABLE 39.25. Lifetime attributable risk of death from solid tumors and leukemia after scenarios (a) lifetime exposure to 1 mGy/year and (b) 10 mGy/year, ages 18–65 years. The values are based on a linear-quadratic model for leukemia and a linear model for all other tumors. The latter model, but not the former, includes a low dose and dose rate reduction factor (DDREF) of 1.5. The values in each cell represent the number of deaths/100,000 males and females exposed to a low-LET radiation dose of (a) 1 mGy/year for a lifetime and (b) 10 mGy/year from age 18–65. These values are displayed in the format male/female unless the organ exists only in one sex. Assuming a woman received 10 mGy from a CT scan annually during adulthood (18–65 years), her chances of dying from leukemia would be 220/100,000 person-years or 1 in 455. The basis of this calculation is the linear-quadratic model; therefore, simple linear extrapolations cannot be used to calculate the leukemia risk of lower doses, because the dose-response curve deviates from linearity at low doses. Similar tables on cancer incidence are available in the BEIR VII report (Adapted from BEIR VII).[207]

Cancer Type	(a) 1 mGy/year for Lifetime	(b) 10 mGy/year Age 18–65 years
Leukemia	47/38	290/220
All solid	285/459	1,410/2,169
All cancers	332/497	1,700/2,389
Stomach	13/19	66/94
Colon	53/34	273/174
Liver	14/8	72/40
Lung	99/204	492/1,002
Prostate	6.3	32
Bladder	16/21	80/108
Other	85/98	395/449
Breast, female	53	193
Uterus	3.5	18
Ovary	18	91

and women were similar in BEIR V modeling). ICRP risk estimates including a DREF of 2 are between the Japanese survivor data and the combined data of American cohorts (Hanford, Rocky Flats, Oak Ridge).[376] The United Nations Scientific Committee on the Effects of Ionizing Radiation (UNSCEAR) uses a total cancer mortality risk coefficient for the average individual in the general population of 4.5%/Gy on the absolute risk model and 7.1%/Gy on the relative risk model. No reduction factors were applied to modify the risk when extrapolating from the high-dose Japanese data; however, the UNSCEAR Committee states the reduction factor (DDREF) should range from 2–10.

Leukemia

In a meta-analysis of 10 occupational and environmental studies on radiation exposure, the estimated ERR/Gy of leukemia (excluding chronic lymphocytic leukemia) resulting from long-term exposure to a whole-body absorbed dose of 100 mGy low-LET radiation was 0.19 (95% CI: 0.07–0.32). This calculation excludes 13 studies from the original number of studies and adjusts for publication bias.[377] Five of the original studies used leukemia incidence as the endpoint rather than leukemia mortality.

Hiroshima and Nagasaki Survivors Leukemia was the first cancer associated with atomic bomb survivors, beginning a few years after exposure followed by the appearance of an increased incidence of solid tumors 10 years after the bombings.[378] Excess risks of blood cancers were observed for leukemias (i.e., acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelocytic leukemia), but not chronic lymphocytic leukemia (CLL). The latter leukemia subtype has a low incidence in the Japanese population.[379] The risk of multiple myeloma and lymphomas was not clearly increased in this cohort.[380] There were 315 leukemia deaths in the Life Span Study cohort followed through 2002 with 98 (45%) excess deaths attributed to radiation exposure in the exposed survivors (>0.005 Gy).[209] The portion of excess deaths increased to ~86% at radiation doses exceeding 1 Gy. Radiation-related leukemia risk demonstrates a unique temporal pattern with higher excess deaths in the earlier years (i.e., peak ~10 years after exposure) among survivors exposed at a young age followed by a rapid decline with age. Figure 39.12 displays age-related differences in the excess leukemia deaths with the highest excess death rate occurring in young children. The dose-response relationship for leukemia demonstrated a linear-quadratic association. A small leukemia risk other than CLL remains in current survivors.[381] The estimated excess relative risk (ERR) for malignant lymphoma and multiple myeloma was not statistically significantly elevated. Table 39.23 lists the estimated lifetime attributable risk of leukemia incidence and mortality by the BEIR VII Committee for exposure to 0.1 Gy low-LET radiation.

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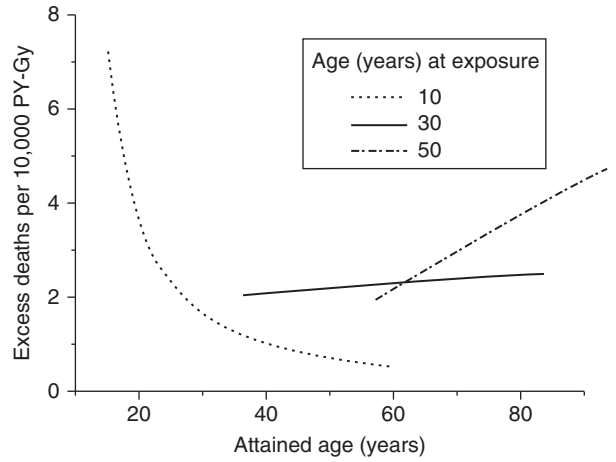


FIGURE 39.12. The estimated excess deaths from leukemia in atomic bomb survivors from Hiroshima and Nagasaki based on exposure at 10, 30, and 50 years of age (BEIRVII). [207]

The Life Span Study contains a subset of ~3,300 individuals exposed to *in utero* radiation. Only one leukemia-related death occurred in this cohort during the first 15 years after prenatal radiation exposure, when the leukemia incidence peaked in radiation-exposed adults.[268] There were only two leukemia-related deaths in this cohort studied up to age 55 years; consequently, the excess relative risk of cancer mortality from leukemia following *in utero* radiation exposure is currently not well defined in this cohort. In general, the relative cancer risks are higher for medical exposures than for Japanese atomic bomb survivors. In the Oxford Survey of Childhood Cancers case-control study of *in utero* radiation exposures from maternal diagnostic X-ray examinations, the excess relative risk coefficient for childhood cancers diagnosed before 15 years of age was ~50/Gy.[382] The excess absolute risk coefficient for incident cases was ~8%/Gy. Potential explanations for this difference include cell sterilization and higher underlying cancer incidence in the medical series.[383]

Environmental Exposure Most existing epidemiological studies of environmental radiation exposure are descriptive with ecological design using incidence, mortality, and prevalence data to estimate disease rates rather than individual measurements of radiation exposure. The former Soviet Union established the Chelyabinsk nuclear weapons production complex (PO Mayak) in the Southern Urals (Ozersk, Chelyabinsk Oblast) as part of their nuclear weapons program. The facility produced tritium, highly enriched uranium, plutonium, and plutonium warhead components. The facilities currently remain in operation. Site-specific risk estimates in the Mayak PA and Techa River cohorts have large uncertainties and highly variable unadjusted estimates that include ranges greatly exceeding the estimates detected in the Japanese cohort of atomic bomb survivors. The large variability in site-specific risk estimates primarily results from the small number of excess cases.

The Extended Techa River Cohort includes 29,873 people born before 1950 and living sometime between 1950–1960 near the Techa River downstream from the Mayak PA radioactive waste releases. In the summer of 1951, systematic measurements of radioactive contamination began in and around the Techa River with analysis of ^{90}Sr beginning in 1960 for teeth, 1976 for forehead bone, and 1974 for whole-body counting.[384] The average absorbed red bone marrow dose was estimated for each settlement ranging from 0.176–1.64 Sv.[385] The excess relative risk per gray for mortality from leukemia was 6.5 (CI 95%: 1.8–24), excluding chronic lymphocytic leukemia, with radiation exposure accounting for 63% of the leukemia-related deaths.[386]

Occupational Exposure Studies of workers in manufacturing, research, and the nuclear industry, including Mayak PA in the former Soviet Union, provide information on the risks associated with occupational radiation exposure; however, the precision of low-dose radiation exposure limits conclusions regarding risks. Although latency periods remain similar, epidemiology data from Russian workers exposed to excessive radiation at Mayak PA suggests dividing radiation doses into long-term, low doses reduces the overall cancer risk compared with single, high-dose radiation exposures. The leukemia rate in workers at this plant peaked ~2–5 years after the peak radiation exposure rates; the excess relative risk (ERR) of leukemia was ~1.4/Gy. This value is ~$^1/_3$ the risk of leukemia in Japanese atomic bomb survivors.[387,388] Epidemiological data from the Three-Country Study (the United States, Canada, the United Kingdom) and the UK National Registry of Radiation Workers provide relatively good estimates of the radiation-induced leukemia and all-cancer risks. The leukemia risk for these workers was intermediate between the linear and linear-quadratic models derived from Japanese atomic bomb survivors. The estimated risk for all cancers was smaller than the leukemia risk with the confidence interval including no risk and a doubling of the risk.

International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry (15-Country Study) collected data on estimates of radiation-induced cancer risk following protracted low ionizing radiation doses for ~600,000 workers. Within

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the 15-Country Study, the cohorts of nuclear workers from France, the United Kingdom, and the United States provided most data on early workers starting in 1943. The International Nuclear Workers Study (INWORKS) is a retrospective cohort study of 308,297 workers employed for at least 1 year and followed for a mean of 27 years in the French, English, and American nuclear industries using data from the 15-Countries Study.[389] The study included 1,791 deaths from hematological cancers. The central estimate of the ERR/Sv in the French portion of the INWORKS study for leukemia excluding CLL was 3.96 (90% CI: <0–16.82; $n = 60$; $P = 0.18$) compared with 1.93 (95% CI: <0–8.47, $n = 196$) in the 15-Country Study and 1.71 (90% CI: 0.06–4.29; $n = 198$) in the UK study.[390,391] The central estimate of 15.83 for myeloid leukemia was statistically significant (90% CI: 1.53–46.12; $n = 35$; $P = 0.01$) in the French study.

Solid Tumors

Hiroshima and Nagasaki Atomic Bomb Survivors In contrast to leukemia, the temporal pattern of radiation-related risks of solid tumors gradually increases beginning several years after the bombing with approximately proportional age-related increases in the baseline cancer rates; these results are consistent with a life-long, approximately linear elevation of the natural age-specific cancer risk.[392] Follow-up studies of the atomic bomb survivors detected an excess relative risk for most solid cancers, including brain/central nervous system, colon, stomach, esophagus, liver, bladder, lung, female breast, ovary, nonmelanoma skin, and thyroid. Bladder, lung, and female breast cancers demonstrated the highest ERR (>80%/Gy) with relatively high (50–80%/Gy) risks found for the brain/central nervous system, esophagus, colon, ovary, and thyroid. The highest excess absolute risk in descending order occurred for female breast, stomach, colon, lung, liver, bladder, and thyroid cancers; these absolute risks depend on the baseline cancer rate in the Japanese population. The risks of rectum, pancreas, uterus, prostate, and kidney parenchyma cancers in irradiated and nonirradiated survivors were similar.[393,394]

Factors affecting solid cancer risk include age at exposure, attained age, and sex. In a study of 105,401 members of the Life Span Study cohort of Japanese atomic bomb survivors followed from 1958–2005, the estimated excess relative risk of thyroid cancer at 1 Gy of radiation exposure was 1.28 (95% CI: 0.59–2.70) at age 60 years after acute exposure at age 10 years using a linear dose-response model.[395] The risk sharply declined as age-at-exposure increased with little increased risk from radiation exposure at ages over 20 years. Although the magnitude of the risk decreased with age, the risk of thyroid cancer persisted for >50 years following childhood radiation exposure. The risk was greater for females than males.

The excess relative risks (ERR) of solid cancer incidence in atomic bomb survivors from the Life Span Study exposed *in utero* (2.4/Sv, 95% CI: 0.3–6.7) and survivors exposed between birth and 6 years of age (1.4/Sv, 95% CI: 0.4–3.1)[396] are similar. For all solid tumors in the Japanese survivors exposed to whole-body radiation doses of >0.005 Gy, the attributable portion related to radiation is ~11% (853/17,448 solid cancer incidence cases).[21] This attributable portion of solid cancers increases to 48% for survivors receiving at least 1 Gy. Both the ERR and the EAR estimates for solid cancers are ~50% higher for women than men. The risks of cancer are highly age dependent with the risk of developing cancer ~2 times higher for exposure at age 10 years than at age 40 years. The excess lifetime risk per Sv for solid cancers in Japanese survivors exposed at age 30 is 0.10 (male) and 0.14 (female); the values are $\sim{}^1/_3$ for survivors exposed at age 50 years.[392] The excess risk for solid tumors appears linear up to ~3 Sv. Risk estimates currently do not indicate that *in utero* radiation exposure confers a greater risk of solid tumors in adults than childhood exposure. The estimated lowest dose range with a statistically significant elevation of the ERR for all solid cancer mortality included zero (range, 0–0.20); formal dose-threshold analysis did not suggest the presence of a threshold.[393]

Environmental Exposure Ecological studies of populations residing near nuclear facilities or exposed to nuclear fallout do not typically contain individual estimates of radiation doses or risks. A follow-up study of 3,440 persons exposed as young children primarily to ^{131}I from the Hanford nuclear facility in eastern Washington State detected no increased thyroid cancer risk.[397] The estimated median dose was 97 mGy (range 0.003–2,823 mGy) with a mean of 174 mGy. The cumulative incidence of thyroid cancer did not increase with increasing dose ($P = 0.25$). A retrospective cohort study screened 3,709 Marshall Island residents born before the Castle BRAVO hydrogen-thermonuclear test on March 1, 1954.[398] Age-specific radiation doses for the Utirik atoll and ^{137}Cs deposition levels on individual atolls provided the estimated radiation dose based on the atoll of residence. Although the results suggested the prevalence of thyroid cancer increased with quartile of estimated dose, the increase was not statistically significant (adjusted OR = 1.67, 95% CI: 0.73–3.83; $P = 0.15$) when comparing the highest (weighted Utirik

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dose = 187.2–6,766.6 mGy) and lowest (weighted Utirik dose = 0–34.1 mGy) quartiles of radiation exposure. The estimated risk coefficient of thyroid cancer following exposure to radioactive iodide in fallout on the Marshall Islands was 1.5×10^6 persons per cGy/year.[399]

In the Extended Techa River Cohort, residents in the Southern Urals exposed to radioactive waste from the Mayak PA complex, the excess relative risk per gray for mortality from solid cancers in this cohort was 0.92 (95% CI: 0.2–1.7); radiation exposure accounted for an estimated 2.5% of solid cancer-related deaths.[386] The relative risks of esophagus, lung, and stomach cancers were similar in the Techa River and Japanese atomic bomb survivor cohorts.

In cleanup workers exposed to radiation at Chernobyl, the estimated excess relative and absolute risks of thyroid cancer were 5.31 (95% CI: 0.04–10.58)/Gy and 1.15 (95% CI: 0.08–2.22) $\times 10^4$ person-years/Gy, respectively.[400] The estimated risk of excess thyroid cancers is ~40 cancers/year/Sv/100,000 persons.[401] An 8-year follow-up study of a cohort of workers at Chernobyl detected an excess absolute risk of thyroid cancer of 11.5 cases/10^5/Gy (95% CI: 0.8–22.2).[400] The estimated range of the radiation dose was 0–0.25 Gy with an uncertainty factor of 2.5–3.0. After 30 years, follow-up of 110,645 Ukrainian cleanup workers mostly with low-level radiation exposures, the standardized incidence rate was elevated for thyroid cancer (SIR = 4.18, 95% CI: 3.76–4.59) along with multiple myeloma (SIR = 1.61, 95% CI: 1.01–2.21) and female breast cancer (SIR = 1.57, 95% CI: 1.40–1.73).[402]

In a study of 309,130 residents from the most contaminated Russian territories of Bryansk, Kaluga, Oryol, and Tula oblasts affected by the Chernobyl accident during the follow-up period of 1991–2008, the excess relative risk per Gy (ERR/Gy) was statistically significant for children and adolescents ≤17 years of age at the time of the Chernobyl accident, but not for older residents.[403] The ERR/Gy was 3.22 (95% CI: 1.56–5.81). A study of ^{131}I exposure from atmospheric nuclear tests in Nevada during the 1950s analyzed thyroid cancer incidence data on 18,545 cases from 8 Surveillance, Epidemiology, and End Results (SEER) tumor registries for nearby residents from 1973–2004.[404] The estimated ERR per Gy for radiation doses received before 1 year of age was 1.8 with a 95% CI of 0.5–3.2; however, the lack of a dose-response for children exposed during ages 1–15 years suggests the presence of biases (dose estimation, case ascertainment from migration) inherent in ecological studies. Most recent epidemiological studies did not detect any substantial deviation from currently accepted risk estimates for low-dose radiation exposure, including the Japanese atomic bomb survivor cohort.[207,358]

Occupational Exposure The nominal cancer fatality rates for working populations are usually slightly lower than those for the general population because of the susceptibility of younger persons to the stochastic effects of radiation. Bias in dose estimates, confounding factors, and comparability of the populations (e.g., age at study, sex, age-at-exposure, follow-up period) complicate the precision of comparing data from workers and Japanese atomic bomb survivors.[405] Except for the Oak Ridge National Laboratory study, early studies of workers in the United States exposed to external radiation were negative; however, the confidence limits are wide; the upper limits of the combined data did not exclude risks compatible with Japanese atomic bomb survivor cohort.[406,407] The overall mortality of the Oak Ridge population was small; the median cumulative radiation dose of this cohort was only slightly above the average annual background dose (1 mSv) of external radiation in the general population. The all-cancer dose-response estimates from this cohort were an order of magnitude above current estimates; however, the number of cancer cases was small in the higher dose groups, and the increase in cancer mortality occurred primarily in those cancers related to smoking (e.g., lung cancer). Several studies of European nuclear workers suggest a positive but statistically nonsignificant relationship between cumulative radiation dose and cancer risk (all solid cancers, leukemia excluding chronic lymphocytic leukemia); these studies also report similar risk estimates. In a mortality study of 59,021 French nuclear workers with a mean cumulative radiation exposure of 22.5 mSv followed for ~25 years, the central estimate of the excess relative risk/Sv (ERR/Sv) was 0.34 (90% CI: –0.56 to 1.38; $n = 2{,}312$; $P = 0.30$) for all solid tumors.[408] In comparison, the central estimate of the ERR/Sv for all solid tumor mortality (excluding leukemia) in the 15-country European nuclear workers was 0.87 (90% CI: 0.16–1.71; $n = 4{,}770$ deaths),[409] compared with an ERR/Gy of 0.47 (90% CI: 0.18–0.79 lagged 10 years, $n = 17{,}957$ deaths) in the INWORKS study of nuclear industry workers from France, the United Kingdom, and the United States;[410] an ERR/Sv of 0.28 (90% CI: 0.02–0.56 lagged 10 years, $n = 6{,}921$ deaths) in the UK National Registry for Radiation Workers Study;[411] and an ERR/Sv of 0.14 (95% CI: −0.17 to 0.48) in 119,195 US Department of Energy nuclear workers.[412] In comparison, the excess relative rate for male Japanese survivors of the atomic bombing exposed at ages 20–60 years was 0.32/Sv (95% CI: 0.01–0.50).[390] In the cumulative dose range 0–100 mGy (mean = 17.4 mGy primarily

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from external photons), the INWORKS data on excess relative risk were similar to the Japanese data, with the excess risk persisting for several decades; however, the INWORKS data were less precise. Excluding lung cancer did not significantly alter the excess relative risk of cancer death, suggesting smoking did not confound the results. Solid cancer excess risk was restricted to radiation exposure at age 35–50 years (ERR/Gy = 0.75, 90% CI: 0.23–1.32; 10-year fixed lag), diminishing 30 years after exposure.[413] For exposure at age 50 years and older, the ERR/Gy was 0.51 (90% CI: −0.15 to 1.23).

Estimated Noncancer Risks

Although studies of Japanese survivors indicate an increased risk of some noncancer diseases, direct evidence of increased noncancer risks at low radiation doses (<0.1 Gy) is lacking.[207] Consequently, data are inadequate to determine risk in this range.

Lens

Cataracts developed in Japanese survivors receiving high radiation doses within 3–4 years after the bombing; posterior subcapsular opacities were the characteristic ocular lesion.[414] The estimated threshold for the development of these opacities was 1.5–2 Gy; cataracts that significantly obstruct vision were not present at radiation doses below 5 Gy.[366] Analysis of longitudinal data from the Adult Health Study cohort of atomic bomb survivors collected during 1958–1986 did not detect a statistically significant dose-response relationship ($P = 0.39$) between lens opacities and radiation dose.[415] However, following the cohort for an additional 12 years (1958–1998) resulted in a statistically significant positive dose-response for cataracts ($P = 0.026$); the $RR_{1\,Sv}$ was 1.06 (95% CI: 1.01–1.11).[416] The excess cataract cases/Sv/10^4 person's years was 8 with an attributable risk of 4%. Overall, the excess risk of cataracts decreased with age after exposure.

Current data suggest the threshold for cataracts is lower. Of 6,066 Japanese atomic bomb survivors, 1,028 underwent their first cataract surgery between 1986–2005.[417] The estimated threshold dose was 0.50 Gy (95% CI: 0.10–0.95 Gy) for the ERR model and 0.45 Gy (95% CI: 0.10–1.05 Gy) for the EAR model. Using the linear ERR model for a 70-year-old individual exposed to 1 Gy at age 20 years, the excess relative risk was 0.32 (95% CI: 0.17–0.52).

Thyroid Disease

A survey study of thyroid disease in 4,091 atomic bomb survivors exposed over 50 years earlier demonstrated a statistically significant ($P < 0.001$) linear dose-response relationship for the prevalence of all solid nodules, benign nodules, and cysts.[210] The incidence of thyroid diseases was identified in 44.8% of the participants ($n = 1833$), including 32.2% of the men ($n = 436$) and 51.0% of the women ($n = 1397$); the difference between exposed and unexposed controls was statistically significant ($P < 0.001$). The mean and median thyroid radiation doses were 0.449 Sv and 0.087 Sv, respectively. The authors estimated ~28% of all solid nodules, 31% of benign nodules, and 25% of cysts were attributed to radiation exposure. No statistically significant dose-response relationship was observed for positive antithyroid antibodies ($P = 0.20$), antithyroid antibody-positive hypothyroidism ($P = 0.92$), or Graves' disease ($P = 0.10$). The estimated risk coefficient of thyroid nodules following exposure to radioactive iodide in fallout on the Marshall Islands was 8.3×10^6 persons per cGy/year.[399]

Circulatory Disease

Uncertainty about lifetime risk estimates is greater for noncancer diseases than solid cancer risks. Data from the Japanese atomic bomb survivors suggest the lifetime risk of death from radiation-associated noncancer disease after childhood exposure to 1 Sv is ~$^1/_2$ the risk for solid cancer, whereas the estimated lifetime risk in individuals exposed as adults is similar for radiation-associated noncancer disease and solid cancers.[418] These data are compatible with a threshold of 0.5 Sv for radiation-induced noncancer disease. In the Life Span Study, cardiovascular disease mortality including stroke accounts for over ½ of the overall deaths. Data suggest a radiation-related dose-response for heart disease independent of smoking and other confounders. For heart disease in this cohort of 86,611 Japanese atomic bomb survivors, the estimated excess relative risk per gray was 0.14 (95% CI: 6–23%, $P < 0.001$).[419] Although a linear model best fits the data, suggesting excess risk even at lower doses, the dose-response effect over the range of 0–0.5 Gy was not statistically significant.

In the Russian cohort of 53,772 recovery operation workers (liquidators) arriving at Chernobyl within the first year after the Chernobyl accident, the mean external whole-body dose was 0.161 Gy with a range of 0.0001–1.42 Gy.[420] The average ERR/Gy for the incidence of cerebrovascular disease was 0.45 (95% CI: 0.28–0.62, $P < 0.001$) with no latent period. Data from the cohort followed from 1986–2000 indicated a statistically nonsignificant elevation of the ERR coefficient for circulatory disease incidence of 0.18 (95% CI: −0.03 to 0.39).[421] The radiation risks were not adjusted for known cardiovascular risk factors (e.g., alcohol consumption, hypercholesterolemia, obesity, smoking). Although the

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risk of cerebrovascular disease morbidity increased for doses >150 mGy, the duration of radiation exposure did not significantly affect the risk.

The 15-Country Study of nuclear industry workers did not detect statistically significant or dose-related increase in mortality from noncancerous diseases (ERR/Sv = 0.24, 95% CI: −0.23 to 0.78; $P_{trend} = 0.16$) or circulatory diseases (EER/Sv = 0.09, 95% CI: −0.43 to 0.70; $P_{trend} = 0.37$).[422] The clinical significance of radiation exposure in this range on factors influencing cardiovascular mortality including atherosclerosis, hypertension, and chronic renal disease remains unclear. Although some studies suggest a positive relationship between circulatory diseases and low-level ionizing radiation, the causal relationship between circulatory disease and cumulative radiation exposure in the workplace is not well established, in part due to the lack of an agreed mechanism for radiation-induced circulatory disease at low radiation doses.

Mental Retardation

Based on the BEIR V review of Japanese atomic bomb survivor data, the risk of mental retardation for children exposed *in utero* at 8–15 weeks of gestation was a 4% chance of occurrence per 0.1 Sv.[9] The risk associated with radiation exposure during other periods of gestation appears to be less. Although the dose-response curve for the risk of developing mental retardation is not defined precisely, the BEIR V report indicated the data do not support the concept of a threshold for this effect.

Mutations

Hereditary damage and carcinogenesis are the two primary stochastic effects of ionizing radiation exposure. The risk of radiation-induced human genetic disease following exposure to low-dose radiation is very small compared with baseline risks in the general population.[207]

Although there is no clear evidence for radiation-induced germ cell mutations (birth defects, chromosome aberrations, Mendelian disorders) in humans, the lack of sensitive, economic biomarkers and few data limit conclusions regarding the presence of these changes in humans. The extrapolation of mouse data to humans suggests at least 1 Gy of low-LET radiation is necessary to double the underlying mutation rate in humans. Heritable effects have not been conclusively documented in Japanese atomic bomb survivors; however, the low mean radiation level (<0.5 Gy) and limited sample sizes restrict the power of a study to detect statistically significant increases in genetic damage in Japanese children.[9] Stable chromosomal aberrations remain in Japanese survivors over 65 years after the bombing.[284] The shape of the dose-response curve was concave upward for doses of 1.5 Gy, but the curve plateaued somewhat at higher doses.

The BEIR V report concluded more research was necessary to estimate the amount of genetic damage produced by a given radiation level, whereas the United Nations Scientific Committee on the Effects of Ionizing Radiation (UNSCEAR) estimated the genetic risk coefficient for hereditary harm to the first two generations of a population of reproductive age to be 0–1.2%/Sv of the effective dose equivalent delivered. The estimate of the risk of hereditary disease for all generations in an average population that includes persons in the nonreproductive year was 0–2%/Sv of the effective dose equivalent. The BEIR V Committee estimated the risk of a clinically severe autosomal dominant mutation at 5–20 cases/10^6 live births/0.01 Sv/generation.[9] The risk of a clinically mild autosomal dominant aberration was slightly less; the risk of X-linked and recessive mutations was <1 case/10^6 live births/0.01 Sv/generation.

Occupational/Environmental Monitoring

The primary radiation exposure for workers occurs in the nuclear power industry and the medical field with potentially high background radiation levels in uranium miners and flight personnel.[423] Occupational radiation exposure of workers in nuclear fuel cycle activities may average an annual dose of 3–8 mSv for the reactor operation. Generally accepted radiation protection principles include: 1) justification – every new practice should produce a net positive benefit, 2) optimization – all exposures should be kept As Low As Reasonably Achievable (ALARA) after considering current economic and social factors, and 3) limitations – individual radiation exposure from controllable sources should be subject to dose limits and some limitation of risk.[424] The latter typically involves limiting the radiation risk below 1 fatal cancer/1,000 person/year during the lifetime of the exposed individual. This value represents a 5% lifetime risk of fatal cancer/Sv for an annual occupational exposure limit of 20 mSv averaged over 5 years. Exceeding the dose limit is unreasonable on any basis; dose constraints may be set at a fraction of the dose limit as a boundary to optimize radiological protection from a specific source. The concept of constraints on dose and risk limits represents a shift from dose limits to radiological protection methods to ensure dose limits are not exceeded.[425] Control areas are necessary for worker protection if routine environmental monitoring cannot predict safe dose limits; supervised areas are required if radiation

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levels exceed public dose limits. The International Commission on Radiological Protection (ICRP), the National Council on Radiation Protection and Measurements (NCRP), and the American Conference of Governmental and Industrial Hygienists (ACGIH) have similar guidelines on occupational and environmental exposure to ionizing radiation. The National Radiological Protection Board estimates the lifetime excess risk of fatal cancer after fetal radiation exposure at $\sim 10^{-5}$/mSv. The most vulnerable period for the fetus is 8–15 weeks after conception; irradiation during this period is associated with an estimated reduction of 0.03 IQ points/mSv; however, the minimal size of the change is insignificant given doses usually present in the work environment.[426]

US Occupational Safety and Health Administration (OSHA)

The current US occupational guideline for chronic exposure to ionizing radiation is 5 rem (0.05 Sv) in a 12-month period. Table 39.26 lists the US OSHA maximum permissible dose equivalents for occupational exposure.

US Nuclear Regulatory Commission (USNRC)

The USNRC established adult occupational dose limits similar to those of the ICRP and ACGIH. The total effective dose equivalent is 50 mSv (5 rem), with the committed dose equivalent to any individual organ or tissue other than the lens of the eye being 500 mSv (50 rem). The US Nuclear Regulatory Commission (USNRC) is an independent agency of the federal government that formulates regulations on radiation exposure from nuclear energy through the US Code of Federal Regulations, whereas the National Council on Radiation Protection and Measurements (NCRP) is a congressionally chartered, nongovernmental organization that provides guidelines and disseminates information on radiation exposure. The deep-dose equivalent and the shallow-dose equivalent are the whole-body and external skin dose (whole-body or extremities), respectively, from an external ionizing radiation source. The lens dose equivalent represents the equivalent radiation dose to the lens of the eye from an external ionizing radiation source. The lens dose equivalent was 150 mSv (15 rem), while the shallow-dose equivalent to the skin of the whole body or extremity was 500 mSv (50 rem). In 2017, the NCRP reduced the recommended annual lens occupational dose limit to an absorbed dose of 50 mGy.[427] Radiation doses exceeding the annual limits are subtracted from limits for planned special exposures during the current year and lifetime. The deep-dose equivalent must be applied instead of the effective dose equivalent measured by external personal monitoring, unless the dosimetry method is an approved NRC technique.

TABLE 39.26. Maximum permissible dose equivalent for occupational exposure, OSHA https://www.osha.gov/ionizing-radiation/introduction/ionizing-attachment-six. The organization website should be consulted for any updates on the specific restrictions and recommendations.

Combined Whole-Body Exposure	Value
Prospective annual limit	50 mSv (5 rem)
Retrospective annual limit	100–150 mSv (10–15 rem) any 1 year
Long-term accumulation	[(age in years) – 18] times 50 mSv (5 rem)
Skin	150 mSv (15 rem) in any 1 year
Hands	750 mSv (75 rem) in any 1 year; (250 mSv/3 months)
Forearms	300 mSv (30 rem) in any 1 year; (100 mSv/3 months)
Fertile women (with respect to fetus)	5 mSv (0.5 rem) in gestation period
Population	1.7 mSv (0.17 rem)/year

International Commission on Radiological Protection (ICRP)

The ICRP accepts a linear dose model without a threshold for stochastic effects (i.e., cancer, heritable effects) and a dose and dose-rate effectiveness factor (DDREF) of 2 for low radiation doses and dose rates. For deterministic effects (tissue reactions), absorbed doses below 100 mGy are not associated with clinically relevant functional impairment.[428] For risks to the embryo and IQ following *in utero* exposure, the threshold is ~100 mGy, whereas the threshold is ~300 mGy for the most sensitive prenatal periods (8–15 weeks postconception). The recommended exposure limits for women with declared pregnancies and the public are similar. Table 39.27 lists the ICRP annual dose limits.

The ICRP recommends that the annual dose equivalent received by pregnant women be limited to 30% of the 5 mSv limit (i.e., 1.5 mSv) for the public; the rate of accumulation should not exceed 0.5 mSv per month. The IRCP recommends a supplementary dose limit of 2 mSv in the abdomen of a pregnant woman for the duration of the pregnancy. For women with internal exposure to radionuclides, the recommended protection limit is 1/20th the annual limit on intake. The job of a pregnant woman should not involve a significant probability

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TABLE 39.27. ICRP guidelines for dose limits in planned exposure situations for adult workers. (Based on ICRP 2007).[428]

Limit	Occupational Exposure	Environmental (Public) Exposure
	Effective dose (stochastic)	
Annual	20 mSv	1 mSv
5-year average	50 mSv/year maximum not to exceed 100 mSv over 5 years	Maximum may exceed 1 mSv/year with average over 5 years not to exceed 5 mSv
	Equivalent dose (deterministic)	
Lens of eye	20 mSv per year averaged over 5 consecutive years, and 50 mSv in any single year	15 mSv/year
Skin	500 mSv/year	50 mSv/year
Hands and feet	500 mSv/year	–
Embryo/fetus		Approximately the same as public

of high, accidental radiation doses or incorporation of radionuclides.

The ICRP separates exposure situations into planned, existing, and emergency to focus attention on the control of natural and artificial radiation sources, particularly the use of dose constraints and reference levels for existing and emergency situations.[429] Emergency exposures usually result from the inability to control a planned source due to an unexpected loss. These situations require urgent and timely actions to mitigate exposure. The reference level represents the maximum residual dose or risk level to allow radiation exposure to occur; consequently, this level represents the maximum acceptable residual dose after implementation of an optimized protection strategy. For radiation protection purposes, reference levels for emergency exposure situations should be set in the band of 20–100 mSv effective dose (acute or per year), as indicated in Table 39.28.[430] In contrast, existing exposure situations do not require rapid action to ensure protection.[431]

Dose constraints limit the range of options considered during the optimization process, whereas reference levels refer to restrictions on dose or risk during existing or emergency situations that indicate the importance of optimizing protection by reducing the radiation exposure. Table 39.28 demonstrates the actions and requirements for the three bands of radiation exposure. The upper band (20–100 mSv) relates to reference levels for emergency situations, whereas the middle band refers to planned, existing, and emergency situations.

The necessity of occupational restrictions following an exposure exceeding the recommended dose limits depends on the individual situation; such an event requires a thorough examination of the design and operational aspects of the radiological protection of the involved facility.[366]

American Conference of Governmental and Industrial Hygienists (ACGIH)

The ACGIH guidelines use the effective dose in mSv (1 mSv = 0.1 rem) as the unit of radiation exposure; the effective dose is the sum of equivalent internal and external radiation doses defined by the absorbed dose for each organ multiplied by a specific weighting factor.[432] The ACGIH accepts the weighting factors defined by the ICRP.[428] Table 39.29 lists the recommended ACGIH values for occupational exposure to radiation. These guidelines exclude background radiation from cosmic, implanted, radon, and terrestrial sources. The objectives of these guidelines include: 1) preventing radiation-induced deterministic effects, 2) minimizing stochastic effects to levels comparable to fatal occupational accidents, and 3) reducing radiation doses as far below the guidelines as practicable.

TABLE 39.28. ICRP framework for reference levels and dose constraints. (Adapted from Wrixon).[429]

Effective Dose Bands (Acute or Annual)	Action for Control	Requirements	Examples
<1 mSv	Source	Periodic evaluation of exposure pathway	Public dose constraints in planned situation
1–20 mSv	Source or exposure pathway	Individual dose assessment and training in a planned situation	Reference level for household radon; dose constraints for caregivers of patients taking radiopharmaceuticals
20–100 mSv[a]	Exposure pathway	Evaluated dose reduction	Radiological emergency reference level

[a] Upper bound established for deterministic effects. The upper bound of the other two bands are the dose limits for workers and the public.

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TABLE 39.29. American Conference of Governmental and Industrial Hygienists (ACGIH) guidelines for ionizing radiation exposure. (ACGIH).[432]

Exposure Type	Annual Exposure Guideline
Effective dose	
Single year	50 mSv
5-Year average	20 mSv/year
Equivalent dose	
Skin, hands, feet	500 mSv
Cumulative effective dose	10 mSv × age (years)
Embryo/fetus equivalent dose	0.5 mSv (monthly)

US Department of Homeland Security

The US Homeland Security Department and the National Security Council-led Domestic Readiness Group provide guidance for radiation exposure limits for medical workers performing emergency services, as outlined in Table 39.30.[433] Each responder should make an informed decision regarding acceptable radiation doses from their actions to save lives based on a complete discussion of risks they may experience. Medical staff at an emergency facility is unlikely to exceed these limits unless the facility is heavily contaminated, whereas emergency workers in the field may significantly exceed these levels depending on the specific circumstances (e.g., β-radiation received by Chernobyl emergency responders).

Medical Screening

Adults exposed to excessive radiation levels (e.g., residents of Belarus, southwest Russia, northern Ukraine near the Chernobyl accident) receive routine physical examinations with emphasis on detecting thyroid abnormalities. In addition to regular cancer screening and routine blood chemistry tests, thyroid function tests, complete blood cell counts, and urinalysis also are recommended.[434] The major complications of patients developing acute radiation sickness were skin atrophy, β-burn fibrosis, and cataracts.[73]

Accidental Overdose

Routine screening tests and annual physical examinations following a single, high-dose radiation exposure are probably not necessary unless a significant radiation exposure occurred including: 1) whole-body radiation of >0.25 Sv, 2) skin dose of >6 Sv, or 3) absorbed organ dose of >0.75 Sv.[176] When specific organs are involved, baseline tests (e.g., sperm counts, slit lamp examination, mammography, digital arteriography, nuclear medicine radionuclide angiogram, technetium thyroid scans) are useful. The physical examination should be directed toward establishing baseline function in the injured organs and determining changes in function (e.g., arteriolar narrowing, cataract formation, atrophy, fibrosis).

TABLE 39.30. US Department of Homeland Security and Interagency Policy Coordination Subcommittee for Preparedness and Response to Radiological and Nuclear Threat dose limit guidelines for emergency workers. (Adapted from National Security Council led Domestic Readiness Group).[433]

Total Effective Dose Equivalent Guideline	Activity	Conditions
50 mSv (5 rem)	Annual Occupational radiation exposure limit	All reasonably achievable actions to minimize radiation dose
100 mSv (10 rem)	Infrastructure protection and restoration of necessary for public welfare in low-hazard areas (light damage zone, fallout areas)[a]	Dose of >50 mSv despite all appropriate actions/controls. Monitoring and appropriate respiratory protection provided
250 mSv (25 rem)	Lifesaving, medical response, infrastructure restoration, or protection of populations in medium-hazard areas (moderate damage zones and nondangerous fallout areas)	Dose of >50 mSv despite all appropriate actions/controls. Monitoring and appropriate respiratory protection provided
>250 mSv (>25 rem)	Life-saving and critical infrastructure missions in high-hazard zones including dangerous fallout zone to protect significant population from substantial risks of injury, illness, or death	All missions are evaluated by Incident Commander including hazards, value, chances of success, and potential exposure to lethal doses. Responder is aware doses may be ≥500 mSv with risk of cancer or acute radiation syndrome.
		Dose >50 mSv despite all appropriate actions/controls. Monitoring and appropriate respiratory protection provided

[a] Excludes dangerous fallout zone and elevated radiation areas.

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Occupational Exposure

Preemployment physical examinations should be given to employees potentially exposed to radiation levels exceeding 30% of the allowable dose limits. The basic and routine preemployment physical examinations are similar with emphasis on the route and type of radiation exposure. Careful attention should be given to documenting the existence of current or past diseases of the skin, ventilation, renal disease, and blood disorders because these types of diseases may affect the elimination or development of radiation-induced diseases.

The frequency of physical examinations depends primarily on the health of the worker and the extent and type of radiation exposure. Neither laboratory nor physical examinations are reliable methods to control radiation exposure. Routine screening for cancer among workers exposed to low levels of radiation is probably not beneficial. Routine screening (whole-body scanning, chest X-ray) of workers exposed to radionuclides is a standard practice. The use and frequency of whole body or organ radioactivity counts and the assessment of radionuclide excretion depend on the judgment of the physician about the potential exposure and the reliability of environmental monitoring.

TREATMENT

The most important determinants for initial treatment following accidental or malevolent radiation exposure involve: 1) number of victims and resources available, 2) occurrence of conventional and/or thermal injuries, 3) time since exposure (i.e., soon, minutes to 48 hours vs. late, days to weeks), and 4) presence of external and/or internal radioactive contamination.[153] Medical treatment is usually necessary only for individuals receiving a whole-body radiation dose exceeding 1 Gy. The classification of radiation injuries includes: 1) uncomplicated trauma without radiation exposure, 2) simple external irradiation without contamination or trauma, 3) combined radiation and traumatic injuries without contamination, 4) external contamination with or without wound contamination, 5) internal contamination, and 6) no radiation exposure or trauma. Immediately life-threatening injury from a radiation dose occurs extremely rarely with treatment typically limited to palliative therapy; therefore, initial treatment involves the stabilization of the patient by the basic tenets of acute trauma life support (airway management, adequacy of ventilation, control of hemorrhage, cervical spine immobilization) without regard for the radiation exposure level or extent of contamination. Patients irradiated by an external source (e.g., γ-rays, X-rays) are not radioactive; these patients do **NOT** represent a radiation hazard to medical personnel. Contamination occurs when radioactive gases, liquids, or solids are deposited on the skin, ingested, and/or inhaled. Except in Chernobyl where firefighters and medical personnel received serious irradiation from β-emitter contaminated water, emergency medical responders are not usually exposed to clinically significant radiation levels during resuscitation of irradiated victims. Treatment of radiation causalities is most effective when the whole-body radiation dose is between 2–6 Gy (200 and 600 rad), with radiation doses above 6–8 Gy often causing fatalities despite medical care.[435]

Initial Triage/Assessment

The primary responsibility of the initial medical team is the identification of injured victims and initiation of emergency medical care. Radiation sites (triage, treatment, transport) are determined by the event. Typically, these events would involve industrial accidents, power plant failures, or radiation dispersion devices ("dirty bombs"). The three general radiation sites include: 1) in/near blast zone (very limited responder time), 2) along plume (limited responder time), and 3) low-radiation dose zone for collection of causalities for transportation.[436] Triage begins with assessment of physical trauma and burns followed by radiation exposure and estimation of whole-body dose.[437] Most irradiated and/or contaminated victims require triage and decontamination rather than immediate medical care. Cardiopulmonary resuscitation of a contaminated victim is usually necessary only in the presence of life-threatening trauma or the exacerbation of an existing medical condition; the presence of contamination is rarely a serious threat to the rescuer. After the treatment of the life-threatening condition, the patient should be moved away from the area of contamination with backboards as necessary to protect the cervical spine. Intravenous lines should be inserted in uncontaminated areas of the skin only when necessary to treat hypotension or dysrhythmias. The presence of contamination does not interfere with the use of extrication equipment or medical equipment. Table 39.31 outlines the priorities during initial triage, assessment, and transport to the emergency department.

The goal of triage is the evaluation, medical stabilization, and categorization of the radiation incident victim to accomplish the greatest good for the most people. In contrast to blast injuries and thermal burns,

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TABLE 39.31. Prioritized field operation protocol. (Adapted from Ricks).[438]

1. Approach the scene with caution, looking for hazardous substances.
2. Position the command post, personnel, and vehicles at a safe distance of 200–300 ft upwind of any suspected radiation hazard.
3. Notify proper authorities and adjacent hospitals.
4. Use protective gear, survey meters, and dosimeters as soon as possible.
5. Evaluate the presence of injured victims.
6. Determine and treat life-threatening injuries immediately without delaying advanced life support to relocated victim or assess contamination. Perform routine emergency medical procedures during extrication.
7. Remove victims from the radiation hazard area with proper transfer techniques to minimize further injuries. Relocate victims with suspected radioactive contamination to a safer area within the controlled zone.
8. Identify wounds and cover them with sterile dressings.
9. Monitor victims for contamination at the control line after medical stabilization. Remove the clothing of accident victims when radiation levels above background levels indicate the presence of radioactive contamination. Wrap contaminated clothes in marked sheets or bags.
10. Move ambulance gurney to the clean side of control line after covering the gurney with a clean sheet or blanket. Place victim on the gurney; cover and secure for transport. The victim should remain on the backboard if used.
11. Rescuers should remove protective gear at the control line before leaving the controlled area. Ideally, gloved personnel who have not entered the controlled area should transport the victim.
12. Base station contact should be initiated during transport to advise the hospital of the medical condition of the victim and determine the need for additional information or treatment.
13. The hospital radiation protocol should be followed upon arrival.
14. The radiation safety officer should evaluate and clear the ambulance, equipment, and crew before returning to regular service.
15. Personnel should refrain from oral intake including smoking during initial evaluation, treatment, transport, and emergency department interactions until released by the radiation safety officer.

radiation-induced injuries are usually not immediately life-threatening; therefore, the treatment of the former injuries takes precedence over the treatment of radiation-induced injuries. The immediate priority is medical and surgical stabilization; subsequently, patients are assessed for radiation-induced injury based on the radiation type (isotope, nuclear release), presence of internal and/or external contamination, radiation dose, and expected complications. Evaluation of the latter includes location during the incident, symptoms (e.g., time to emesis, diarrhea), blood (e.g., lymphocyte counts when available), and physical examination.[438] Point of care assessment determines treatment priorities and destination of the patient. Subsequent estimates of an individual dose involve secondary assessment with high throughput screening (e.g., absolute lymphocyte count, dicentric chromosomes) as indicated. The threshold for the acute radiation syndrome is a whole-body dose of ~0.75–1 Gy with medical management and additional screening potentially necessary for estimated whole-body exposures of 1–2 Gy, particularly for long-term complications. However, treatment delays usually do not cause immediate danger to life. Victims with estimated whole-body radiation doses exceeding 2 Gy typically need prompt treatment for the biological damage associated with acute radiation syndrome.

The goal of the emergency medical responder is the administration of basic life support, removal of the victim from areas of radiation hazard, and transportation of the patient to the appropriate emergency department. The identification of a radiation hazard at the scene may be difficult because radiation is not evident to our senses like chemicals (e.g., ammonia). Three different labels are affixed to radioactive packages depending on the rate of radiation emission including: 1) white label I – almost no radiation (maximum, 0.005 mSv/hour on surface), 2) yellow label II – low radiation level (0.5 mSv/hour at 3 ft), and 3) yellow label III – higher radiation level (2 mSv/hour at 3 ft). Regulation requires vehicles transporting yellow-III packages or radioactive packages without labels to display radioactive placards. The presence of these placards alerts emergency medical responders to use the procedures for hazardous materials and notifies the dispatcher to contact the appropriate state and local agency about potential radiation hazards. A controlled zone should be established around these radiation hazards with protective gear used by emergency personnel in this zone. Contaminated victims should remain in the control zone where their contaminated clothes can be placed in safe containers, whereas uncontaminated victims should be removed from the area with proper patient transfer techniques. Emergency personnel should remove protective gear at the control line; however, ambulance personnel should wear double gloves while attending to the victim during transport. No smoking, drinking, or eating should occur during field operations.

When radioactive contamination is suspected, protective clothing (i.e., universal precautions: boots or shoe covers, mask, cap, gown, fire turnout gear, surgical or disposable gloves) should be worn if available; however, lifesaving medical care should not be delayed

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in the absence of protective gear unless there is a clear danger to the emergency medical care providers.[439] The use of self-contained breathing apparatus depends on the presence of inhalable radioactive contamination (e.g., smoke, dust, gases). Standard guidelines for protection from microbiological contamination including surgical masks (N95 masks are preferred, if available) are usually sufficient protection for most radioactive emergencies.

Previously, the most common radiation accident involved radiation exposure from sealed sources of γ-rays and X-rays utilized in industrial radiography or nondestructive testing.[438] Although these sources are frequently small, they produce high ionizing radiation levels. These sources should be shielded from any workers by dense metal, particularly within 6–10 ft of the source. An explosion in a nuclear facility may imbed highly radioactive metallic fragments in a victim; this type of accident presents a significant hazard to emergency personnel unless properly shielded. Reducing radiation exposure by emergency medical personnel includes: 1) minimizing time in the control area to the amount necessary for the proper stabilization and transportation of the patient, 2) wearing protective clothing and standing behind shielding whenever possible, 3) working at least 3 ft (i.e., arm's length) from the contamination source whenever possible, and 4) containing the contamination within a limited area. When proper precautions are observed, radionuclides on the surface of *intact* skin rarely produce hazardous exposure levels in emergency medical personnel.[440]

Triage Categories

Categories of triaged victims based on whole-body radiation exposure include: 1) mild radiation exposure with no serious injuries (<1–2 Gy), 2) immediately life-threatening radiation exposure (2–6 Gy), and 3) grave radiation exposure (>6–10 Gy) with survival less likely, particularly >10 Gy. The Radiation Emergency Assistance Center/Training Site (REAC/TS, https://orise.orau.gov/reacts/index.html) provides prehospital and hospital medical guidance and flow charts to assist clinicians with triage and prioritization of radiation accident victims, as demonstrated in Figure 39.13. Reassessment and repeat triage are necessary features of medical responses to nuclear incidents during the movement of causalities and arrival of additional resources. Table 39.32 lists the four triage categories, triage card colors, and descriptions of the triage categories. Under normal triage conditions with conventional standards of care, estimated radiation doses of 2–10 Gy indicate the need for immediate care (red card). Causalities with radiation exposure in the 2–6 Gy range are priorities to help deliver optimal cytokine treatment when few resources are available.[437] The presence of comorbid conditions and combined injuries suggests the need for more immediate care, depending on the availability of resources.

In contrast to the more common nuclear incidents (industrial accidents, nuclear power plant failures, dirty bombs), nuclear detonations create massive casualties and severely damage infrastructure. Minimization of morbidity and deaths from nuclear detonations requires implementation of the following strategies during the first 4 days: 1) organize and deliver trauma care to patients with acute injuries, 2) screen survivors to identify risks for radiation-induced injuries and determine priorities for treatment and evacuation, 3) recognize survivors with nonfatal radiation exposure and serious radiation exposure that benefit from cytokine therapy and priority evacuation, and 4) issue "shelter-in-place" orders for at least 24 hours to minimize radiation exposure in high-fallout areas. The Exposure And Symptom Triage (EAST) tool is a simple screening method that improves initial assessment and triage when sources (e.g., serial lymphocyte depletion counts) are scarce following a nuclear detonation (https://remm.hhs.gov/EAST-toolnotes.htm).

Contamination Survey

Without interfering with medical care, victims should be monitored for the presence of contamination, particularly in wounds and on the face. The initial concern is the detection of contamination rather than the amount of contamination; victims should be separated into contaminated and uncontaminated areas. Radiation levels two to three times above background radiation levels indicate contamination. Ultimately, the objectives of the survey include the measurement of the contamination level, the radiation dose rate in the treatment area, the accumulated radiation dose as measured by dosimeters (e.g., direct reading devices, thermoluminescent, quartz fiber, finger rings, film badges), and the identity of the radioactive materials. The order of scanning and decontaminating the patient begins with open wounds, then the face and facial orifices followed by intact skin. Localized contamination areas should be outlined with a permanent marker and covered with clean gauze or available wrapping until the beginning of decontamination. All persons in the control area should be identified and assessed for the presence of contamination. All contaminated persons should be decontaminated; the

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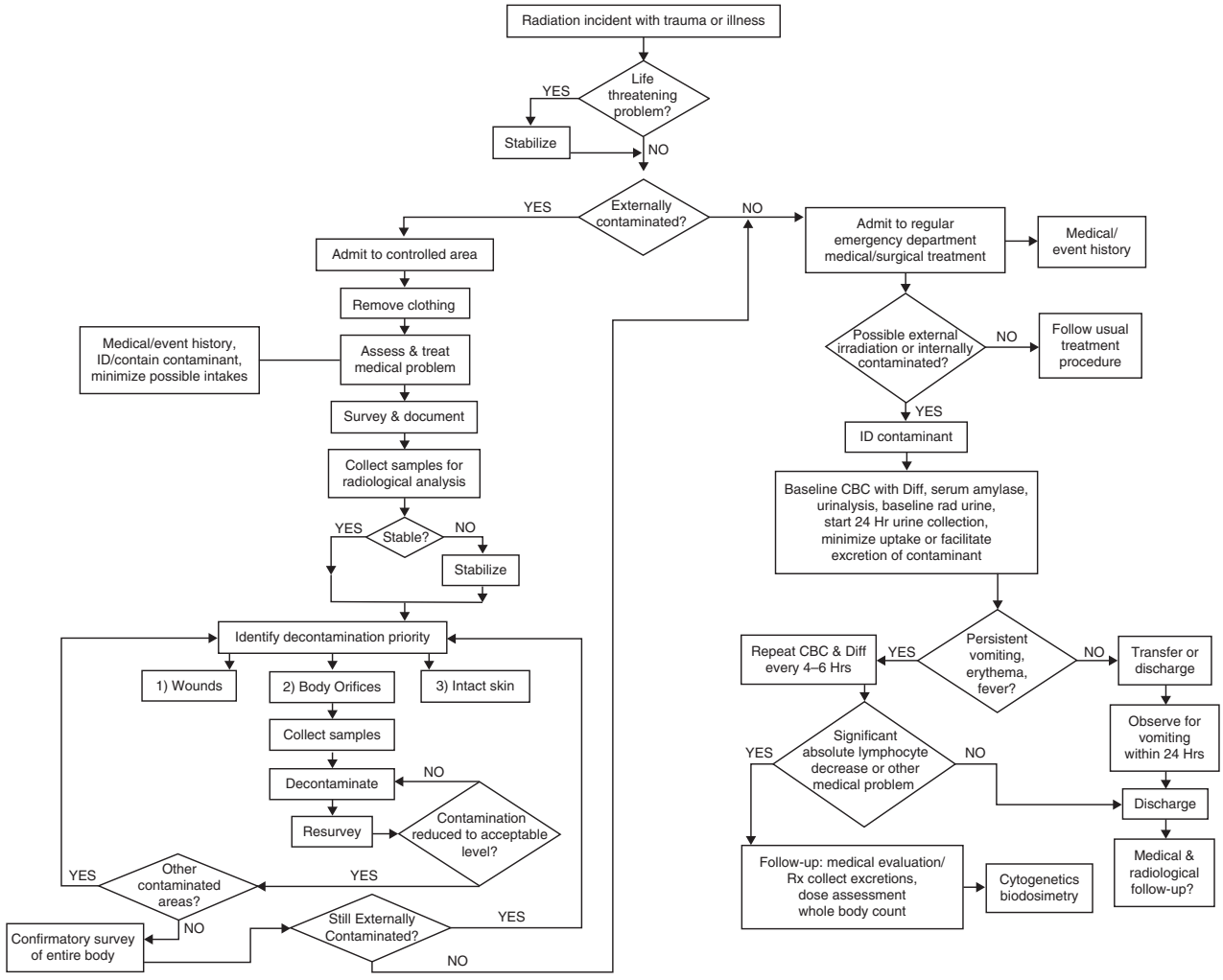


FIGURE 39.13. Radiation Emergency Assistance Center/Training Site (REAC/TS) flow diagram for prioritizing medical treatment during radiation incidents involving ionizing radiation and/or radioactive contamination.

TABLE 39.32. Triage categories for causalities from physical/burn trauma and/or radiation. (Adapted from Coleman et al.).[437]

Category (Estimated Dose)	Card Color	Description
Immediate	Red	Priority treatment group based on trauma/burn and radiation
Delayed	Yellow	Treatment is limited and safely delayed after priority group. Total body surface area burns of 10–20% indicate worsening prognosis and the need for more immediate care, especially in the elderly
Minimal A (<0.5 Gy)	Green	Minor/no physical injury or minor burns with estimated radiation dose requiring no early medical evaluation. Triage can be focused on other categories
Minimal B (0.5–2 Gy)	Green	Minor/no physical injury or minor burns with some radiation exposure. Some initial treatment (e.g., fractures) may be necessary in the initial 4-day time period. Biodosimetry and clinical reassessment (e.g., multiple initial reassessments, long-term registries) may be important in the upper ranges of this exposure range. However, treatment for acute radiation syndrome is unlikely
Expectant	Black	Symptomatic treatment only (i.e., palliative care)

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victim should be referred to the emergency department for evaluation and further decontamination regardless of the extent of obvious injuries.

Measurements of the radiation dose rate (mSv/hour) help determine the health risk to victims and responders. Typically, the dose rates to responders in the medical setting are relatively low because the amount of radioactive material is usually small. Radiation detectors may not detect very low-energy β-particles (e.g., tritium) or α-contamination, particularly when shielding (e.g., gauze, layer of blood) or distances over 3 ft separate the probe and contamination.

Initial Decontamination

Rapid decontamination of the victim decreases the amount of incorporated radionuclide while reducing long-term risks (e.g., cancer, cataracts). Radioactive contamination almost always results from radionuclides that emit high-energy α-particles, β-particles, and/or photons (γ-, X-rays). High-energy photons (γ-rays, X-rays) and neutrons penetrate the body causing internal damage; however, *direct* exposure to these radiation types does not usually produce radioactive contamination in the victim. Removal of outer clothing and shoes reduces external contamination by ~90%.[435] Subsequent decontamination of the skin and hair with soap and warm water along with gentle brushing to dislodge radioactive particles attached to skin proteins significantly reduces the remaining contamination. Contain the contamination by carefully cutting and rolling clothing away from the face and body to the bag. These bags should be sent to the laboratory for analysis in bags specially marked as radioactive material. The amount of further decontamination in the field depends on the ability of the available facilities to prevent the spread of contamination from the victim.

Special care is necessary to avoid internal contamination of the victim by spreading contamination through open wounds, nose, mouth, ears, and eyes including the use of water-proof paper rather than cloth drapes. Most contamination on intact skin functions like loose dirt; the contamination can be removed by routine washing at the appropriate facility including the emergency department. Repeated measurements of the decontaminated areas determine the effectiveness of decontamination techniques, particularly in open wounds. The presence of discomfort during the decontamination process suggests corrosive chemicals or excessive trauma from the decontamination technique rather than radioactive contamination. Medical personnel should wear protective clothing and gloves consistent with universal precautions; with appropriate precautions and adequate irrigation techniques, the radiation dose transferred to medical personnel is minimal. Decontamination of most Chernobyl workers at the accident site resulted in radiation exposures for medical personnel below 10 mGy.[118]

Transport and Hospital Notification

The patient should be transported to the emergency department as soon as the initial resuscitation and decontamination are completed. A clean stretcher covered with a sheet or blanket is placed near the control line, separating the contaminated and uncontaminated areas. Wounds should be covered with sterile dressings, and the patient should be secured to a backboard if a cervical spine injury is suspected. The patient is then placed on the clean stretcher, and the sheet securely wrapped around the patient to minimize any further spread of radioactive contamination. The extension of an arm through the sheet will allow the infusion of intravenous solutions and the measurement of vital signs; the ambulance floor should be lined with securely taped sheets or plastic. The patient should be transported by an ambulance crew that did not enter the controlled area. The emergency medical crew should change gloves and their outer clothing.

The base station should be contacted as soon as possible to prepare the radiation emergency area at the hospital. Important information to transmit from the ambulance crew to the base station includes: 1) the number and medical condition of the victims including the number of contaminated patients, 2) the extent and locations of external contamination, 3) evidence of internal contamination, 4) the identity and form of the radionuclides including all shipping papers, manifests, material safety data sheets, and labels, 5) evidence of other physical or chemical hazards, 6) the time, duration of exposure, and cause of the accident, and 7) the presence of prodromal symptoms (e.g., nausea, vomiting, weakness, fatigue, prostration, anorexia). The initial treatment of radiation-exposed patients requires no specialized facilities; after triage and stabilization, patients with high radiation doses can be transferred to specialized centers without reducing their chances of survival. Uncontaminated persons with nausea, vomiting, or diarrhea should be referred or transported to a hospital for evaluation of whole-body radiation exposure.

Emergency Department Care

Medical treatment for irradiated patients is usually necessary for victims receiving >1 Gy of whole-body

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TABLE 39.33. General objectives for treating seriously injured and contaminated victims in approximate order of importance. (Adapted from Koenig et al.).[435]

Type of Treatment
1. First aid and resuscitation
2. Medical and surgical stabilization
3. Definitive treatment of severe injuries
4. Prevention and minimization of internal contamination
5. Assessment of external contamination and subsequent decontaminationas neeeded. Decontaminated patients cause no radiation risk to medical personnel
6. Treatment of minor injuries
7. Containment of contamination to treatment area and prevention of responding personnel contamination
8. Minimization of external radiation to rescue and treatment personnel
9. Assessment of internal contamination
10. Treatment of internal contamination concurrently with other priorities, depending on urgency and time required
11. Assessment of local radiation injuries/doses
12. Patient counseling regarding expected long-term effects/risks
13. Long-term follow-up for patients with significant whole-body irradiation and/or internal contamination

radiation. Table 39.33 lists the approximate sequence of important priorities for the emergent treatment of victims exposed to serious radiation doses.

Preparation

Serious radiation incidents requiring a specialized response include nuclear reactor meltdowns, explosion of a large radiological dispersal device (dirty bomb, RDD), nuclear weapon detonations, and surreptitious placement of a radiation exposure device in a public area. Following notification of a radiation accident entailing contamination, the emergency response team should prepare the radiation emergency area (REA) for the arrival of the contaminated patient.[441] The main purpose of the REA is to limit contamination in this area by using predetermined protocols similar to strict isolation precautions. Ventilation of the REA should be stopped and the air ducts closed. All patients, uncontaminated victims, and nonessential personnel and equipment should be removed from the area. Butcher paper or brown wrapping paper secured with tape should line the REA and the ambulance path to the REA. A control line marked by rope and tape should clearly delineate the REA from noncontaminated parts of the hospital. No person or equipment should leave the REA until it is monitored for the presence of contamination. Taping saran wrap or plastic sandwich bags over handles and switches in the REA reduces the spread of contamination by hand. The treatment table should be draped with a waterproof covering (e.g., disposable surgical pack cover).

Each member of the emergency response team should be dressed in waterproof surgical clothing, double gloves with different colors, and shoe covers with all open cuffs and seams taped. Outer gloves should be changed frequently. Facial protection includes a surgical mask and eye/splash protection. A radiation dosimeter should be worn in an easily accessible place on the outside of the clothing. Documentation of the time course of clinical signs and symptoms (i.e., gastrointestinal, hematopoietic, cerebrovascular, skin) is necessary to appropriately triage the victims, select therapy, and assign a prognosis.

Arrival

Uncontaminated victims can be admitted to the normal treatment areas of the hospital. Serious medical problems in contaminated patients are a priority that should be treated before evaluation and treatment of radiation injuries. Critically ill patients should be transported immediately to the REA. Radiation-induced illness rarely causes alterations in vital signs and consciousness; therefore, patients with abnormal vital signs or mentation have concomitant injuries. If the patient is medically stable, the nuclear medicine technologist should assess the contamination level of the victim at arm's length from the patient. If the radiation level is <0.1 mGy/hour at 1 ft, personnel may work safely at arm's length from the patient. Otherwise, personnel should stay 10 ft from the contaminated patient when direct access to the patient is not necessary.[442] The treatment table or gurney should contain several layers of sheets. Pregnant healthcare workers should have the option of being exempt from the direct care of numerous contaminated patients.

The contaminated patient should be transferred to the stretcher with the decontamination tray from the ambulance and transported to the REA. Reassessment of the patency of the airway, the adequacy of ventilation, and the stability of the circulation is then necessary. A comprehensive physical examination precedes the completion of the complete survey of the victim for the location of radioactive contamination. The usual history regarding allergies, medications including recent nuclear medicine tests, occupation, accidents, past medical illness, and operations should be obtained. The patient should be specifically asked about the onset and duration of prodromal symptoms of the acute radiation

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syndrome (i.e., nausea, vomiting, diarrhea, anorexia, fatigue, weakness). Most contaminated debris reside on clothing and shoes. The clothing of the victim should be cut from the head toward the feet if not already done; the contaminated material should be placed in a bag marked nuclear waste near the ambulance. The clothes should be cut in the midline along the legs, arms, chest, and abdomen; then, the clothes should be carefully folded away from the skin to minimize the amount of radioactive material settling on the patient. An 8-ft security zone should be established around the ambulance to prevent the spread of contamination. All equipment and supplies used to treat the patient must remain in the ambulance. The ambulance personnel should change clothing; the ambulance and the personnel should be surveyed for contamination before returning to service.

If contamination is discovered after the patient has been admitted, the resuscitation and assessment of the patient should continue while the area surrounding the patient and attending staff is secured with control lines to prevent the spread of contamination. Personnel should remove contaminated clothing, shower, and dress in clean clothing before leaving the contaminated area. All people leaving the new control area should be surveyed for contamination. Contaminated clothing should be stored outside the Emergency Department in a secure area because of the potential radiation hazard. Any obvious dirt or debris should be discarded in an appropriate receptacle.

External Decontamination

Ideally, decontamination occurs in the field before transport to the emergency department, where removal of clothing can reduce ~90% of the contamination. Additional decontamination measures reduce residual contamination on the body, decrease incorporation of the radionuclides into the body, and prevent the spread of contamination to other people. The patient's questions regarding the procedures and use of protective clothing during the decontamination process should be answered by someone knowledgeable about radiation procedures. Before decontamination, moist swabs of body orifices should be collected along with moist or dry swabs of contaminated wounds. Nasal secretions can be obtained from paper tissue after instructing the patient to blow into the tissue. Long forceps should be used to collect debris and place the debris in lead containers. Orifices should be flushed gently with water or saline while using frequent suction to prevent the forcing of contamination further into the orifices. The patient must be instructed not to swallow. Table 39.34 outlines the methods for controlling contamination in the emergency department.

TABLE 39.34. Contamination control techniques in the emergency department.

1. Set up controlled area with sufficient size to treat the anticipated number of victims
2. Avoid tracking contaminants by covering floor areas
3. Restrict access to the controlled area and monitor everyone and everything leaving the controlled area
4. Observe strict isolation precautions including double bagging and protective clothing
5. Consider buffer zone or secondary control line for additional security
6. Control and label waste by using large, plastic-lined containers for suspected contaminated items (e.g., clothing, dressings, linens)
7. Control ventilation
8. Change drapes, instruments, clothes, or outer gloves if contamination occurs
9. Use waterproof materials (e.g., waterproof aperture drapes) to limit spreading contaminated liquids

The techniques for treating patients with radioactive contamination and the techniques used to control infections (i.e., universal precautions) are similar. Following removal of the clothes and shoes, most of the residual contamination occurs on the hands, head, and neck. The priorities of decontamination depend on the type of radionuclides involved. High concentrations of β-emitters, corrosive acids, or fluorides produce skin injuries unless removed immediately. The physical and chemical form of the contaminant determines the contaminant absorption and elimination rates (e.g., hydrogen fluoride is a toxic disassociation product of uranium hexafluoride, UF_6). Otherwise, contaminated wounds and body orifices should be decontaminated first, followed by the areas of greatest skin contamination. Sampling sites for radioactivity include the nose, mouth, wounds, and baseline urine. Waterproof wound dressings and drapes should be used to limit the spread of radioactive contamination. Following irritation, wounds should be dried with sterile gauze and the gauze should be retained as a sample for the evaluation of radioactive contamination.

Decontamination should begin at the periphery of the contaminated area and proceed to the areas of highest contamination. Decontamination of mobile victims involves washing their hair first while bending over rather than placing them directly under a shower. Total body showering is typically recommended only for widespread skin contamination. All noncontaminated wounds must be covered with waterproof dressings to prevent contamination. In patients receiving whole-body doses exceeding 1 Gy, wounds should be closed as soon as possible because of the

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subsequent threat of poor wound healing and infectious complications. A contaminated wound should be rinsed with saline using conventional aseptic techniques with excision reserved for contamination by long-lived radionuclides (e.g., α-emitters). Decontamination of the skin should begin with the least irritating method and progress to more aggressive techniques if needed. The skin is an important barrier to the absorption of external contamination; therefore, decontamination techniques should avoid abrading intact skin.

The goal of decontamination is the reduction of the contamination levels to <2–3 times background levels or until the contamination is <10% of the initial level. The initial priority is the decontamination of open wounds with copious saline irrigation for at least 3–5 minutes. Multiple irrigations are usually necessary to remove the contamination from the skin and wound; however, more than two to three decontamination cycles are usually not needed. After each irrigation, the fluid and surrounding area should be monitored for residual radiation with the Geiger counter. Be careful to avoid contamination of Geiger counter probe by tightly taping a surgical glove around the head of the probe. Because most radioactive contamination settles on clothing, promptly remove and double bag all clothing, shoes, and personal effects into a trash bag marked as a radiation hazard. Alternative measures for persistent radioactivity in open wounds include 3% hydrogen peroxide irrigation and debridement. Wounds with small amounts of contamination may be closed if surgically indicated.

Shaving and extensive rubbing should be avoided because such maneuvers cause abrasions and erythema. If contamination persists on the skin, other decontamination methods include the use of Lava soap, Clorox, and an equal mixture of Tide and cornmeal. Shampoo the hair several times and rinse with lemon juice or a 3% aqueous solution of citric acid. Avoid splashing water in the eyes, nose, and ears. Streams of water should be diverted away from the medial canthus to avoid forcing contaminated fluid into the lacrimal duct. If contamination remains, the hair should be removed with clippers. Contamination of the mouth requires gentle irrigation and suction of the mouth with the mouth turned sideways or down. A nasogastric tube may be inserted into the stomach, and small aliquots of irrigating fluid should be used to lavage the stomach. Large aliquots of fluid may force the contaminated fluid through the pyloric sphincter.

Decontamination measures can stop when repeat decontamination does not reduce the radiation level, the contamination level is <2–3 times background radiation levels, or when further decontamination would produce more harm than benefit.[441] Most contamination on the skin resides in the upper horny layer; this contamination will slough off within a few days.[443] Deep debridement and excision are usually necessary only when explosions force contaminated material deep into the tissues.

Following the final decontamination procedure, the patient's body should be dried and a complete survey of the body by the Geiger counter performed. The patient is then transferred to a clean stretcher by new attendants, and a final radiation check is performed. Before departure from the decontamination area and after removing all protective clothing, each member of the decontamination team requires a complete survey for radioactivity followed by a shower and new clothing. Dead radiation victims should be placed in a body bag; the bodies are stored in a mobile chilling unit rather than the hospital morgue. Contaminated bodies cannot be cremated because fire does not destroy radioactive material.

Biological Dosimetry

The prognosis and treatment of a patient exposed to radiation depend on the absorption and distribution of the radiation dose in the body. The two types of dosimetry used to determine the absorbed radiation dose are the following: 1) physical dosimetry measuring physical changes in biological tissues or closely adjacent clothing and 2) biodosimetry of radiation-induced alterations in cellular constituents or function. The former includes optically stimulated luminescence, thermoluminescence, or electron paramagnetic resonance of tooth enamel, toenails, fingers, or clothing accessories, whereas the latter involves cytogenetic analysis of radiation-induced changes at the sub-cellular level (dicentric chromosome assay, cytokinesis-blocked micronucleus assay). The most common methods to determine individual radiation doses include time to onset/severity of nausea and vomiting, reduction of absolute lymphocyte count over the first few days after exposure, and the presence of chromosomal aberrations (dicentrics, ring forms, cytokinetic block micronucleus assays) in peripheral lymphocytes.[154] A radiation casualty management software program (Biological Assessment Tool) is available from the Armed Forces Radiobiology Research Institute (https://afrri.usuhs.edu/research-assessment-of-radiation-injury) to facilitate the recording and estimation of individual radiation doses.[444] The US Department of Health and Human Services Radiation Emergency Medical Management (REMM, https://remm.hhs.gov/) provides Internet access to patient management and a radiation dose estimator based on time to onset of vomiting and lymphocyte depletion kinetics with confirmation by the dicentric chromosome assay. A rough estimation (i.e.,

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triage score) of the radiation dose in a patient without trauma using the CBC and the presence (+2) or absence (0) is Equation 39.4. A triage score of >3.7 suggests a radiation dose of >1 Gy and the potential need for further evaluation.

$$\text{Triage score} = \%\ \text{neutrophils}/\%\ \text{lymphocytes} + \text{presence or absence of vomiting} \quad \text{(Equation 39.4)}$$

Changes in the lymphocyte count and cytogenetic analysis for chromosomal aberrations are more reliable prognosticators than physical estimates of whole-body radiation doses of >100 mSv for cytogenic analysis and of >250 mSv for lymphocyte counts.[445,446] Table 39.9 outlines the clinical findings and prognosis based on the absorbed dose of whole-body irradiation. These estimated doses are approximations that may vary by up to 25%. Most radiation exposures in uncontrolled setting occur nonuniformly; consequently, recovery may occur when estimated radiation levels predict a lethal hematological or gastrointestinal syndrome. Estimations of local radiation based on these techniques are much less precise compared with homogeneous total-body irradiation.

Symptoms

The onset and severity of the acute radiation syndrome are dose-dependent with a sigmoid dose-response curve above the threshold of the specific tissue; the organ-specific threshold depends on tissue radiosensitivity with dysfunction increasing as the dose increases until function ceases due to cell death. The most radiosensitive cells are rapidly proliferating with high metabolic activity including spermatogonia, lymphocytes, erythroblasts, and other hematopoietic cells; the exception are highly differentiated, mitotically inactive peripheral lymphocytes.[447] When present, early erythema and conjunctivitis suggest the spatial distribution of the ionizing radiation exposure. The chronology of signs and symptoms should be documented carefully with the aid of photographs as they become available. Table 39.35 displays the approximate onset and severity of clinical features associated with whole-body radiation doses exceeding 1 Gy. Mild nausea and mild headaches may occur following whole-body radiation exposures of <1 Gy; however, symptoms and signs are usually subclinical. Although survival is likely following exposure to radiation doses of 1–2 Gy, these patients may require antiemetics and correction of fluid/electrolyte imbalances. Evaluation of lymphocyte, polymorphonuclear leukocyte, and platelet concentrations provides more accurate measures of absorbed radiation at doses above 2 Gy than clinical symptoms.[154] Significant bone marrow damage occurs at whole-body doses of 2.5–5 Gy with progressive marrow hypoplasia followed by aplasia at 5–6 Gy. The $LD_{50/60}$ (i.e., dose causing 50% of the population to die in 60 days) is 3.5–4 Sv without medical treatment and occasionally 7–8 Gy with aggressive and skilled medical care.[116]

Blood

Following severe radiation exposures, the lymphocyte count declines rapidly within a few days. Blood should be collected immediately for hematological analyses (CBC with differential/platelet count – 1 lavender

TABLE 39.35. Approximate onset and severity of clinical features of acute radiation syndrome associated with exposure to whole-body radiation doses over 1 Gy and early clinical features of acute radiation syndrome manifest. Because these values are based on limited data (International Atomic Energy Agency, Armed Forces Radiobiology Research Institute, National Council on Radiation Protection and Measurements), decisions on prognosis of an individual should be based on all the data available, including lymphocyte depletion, clinical examination for the presence of trauma, medical history, and details regarding the radiation exposure (e.g., source, location, shielding). Clinical features of acute radiation syndrome are not unique; therefore, other etiologies for the signs and symptoms should be considered (e.g., occult infection, sepsis). Values in parentheses represent the incidence of symptom or sign. (Adapted from IAEA).[447]

Whole-Body Exposure (Gy)	Onset Emesis (Incidence)	Onset Diarrhea (Incidence)	Onset Headache (Incidence)	Altered Consciousness (Onset/Incidence)	Temperature (Onset/Incidence)
1–2 (Mild)	≥2 hours (10–50%)	None	Slight	None	Normal
2–4 (Moderate)	1–2 hours (70–90%)	None	Mild	None	Increased (1–3 hours/10–80%)
4–6 (Severe)	<1 hour (100%)	Mild 3–8 hours (<10%)	Heavy 1–3 hours (>10%)	None	Fever (1–2 hours/80–90%)
6–8 (Very severe)	<1/2 hour (100%)	Heavy 1–3 hours (>10%)	Severe 3–4 hours (80%)	Sometimes altered	High fever (<1 hour/100%)
>8 (Grave)	<1/6 hour (100%)	Heavy <1 hour (~100%)	Severe 1–2 hours (80–90%)	Unconscious (seconds-minutes/100% at 50 Gy)	High fever (<1 hour/100%)

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top tube), biochemical (serum chemistries – 1 red top tube), and cytogenetic (chromosomal analysis, HLA typing – 2 green top tubes); the lab should be consulted for transportation requirements (e.g., temperature, time, container). Chromosomal aberrations should be evaluated as soon as possible within the first few weeks after radiation exposure. Dicentrics and rings are unstable chromosomal features that progressively disappear over a few months or longer; therefore, extrapolation of radiation doses received in the distant past (years) using these techniques is inappropriate. Analysis of the peripheral blood (i.e., lymphocytes) for chromosomal aberrations preferably should occur within 6–8 weeks of exposure and usually requires approximately 3–4 days. Collection of blood for radioisotope analyses (1 red top, 2 lavender top tubes) is necessary only in the presence of internal contamination.

The CBC with differential should be repeated every 4–6 hours within the first 48 hours when the history indicates the possibility of serious whole-body irradiation. The appearance of lymphopenia during the first two days or prodromal symptoms (nausea, vomiting) within a few hours after exposure are the best early indicators of serious radiation exposure. The significance of lymphocyte depletion must be interpreted cautiously in the presence of major trauma and correlated to other measures of irradiation (e.g., chromosomal aberrations, accident reconstruction, prodromal symptoms). After the 4th postradiation day, daily hemograms are necessary for seriously poisoned patients (>2–4 Gy), whereas daily hemograms can begin after the 18th day for mild cases of acute radiation syndrome (1–2 Gy). Figures 39.5 and 39.6 demonstrate dose-related changes in the neutrophil and lymphocyte counts, respectively, over the course of the first 180 days postexposure. In the absence of medical treatment, mortality approaches 100% within 30 days following whole-body radiation exposures above 6 Gy, whereas survival is highly unlikely following exposures of 10 Gy with the best medical care.[118] Table 39.36 correlates prognosis with absorbed dose and minimal lymphocyte count during the first 48 hours after radiation exposure.

Early collection of blood for blood type and lymphocyte typing is important in seriously irradiated patients considered for bone marrow transplantation. Potential candidates for bone marrow transplantation require immediate HLA typing because of the rapid depletion of the lymphocytes necessary for HLA typing. The time and date of collection of the blood sample should be carefully recorded. The status of fluid and electrolyte balances determines the need for other serum chemistries (e.g., electrolytes, creatinine). The onset of anemia without suppression of other blood elements soon after radiation exposure suggests a bleeding source rather than bone marrow suppression.

Combined Injuries

Although the exact effect of combined thermal and radiation injuries is not well defined, animal models and the Chernobyl experience suggest increased lethality occurs when these two types of injuries occur simultaneously. Because most burns in Japanese atomic bomb survivors were minor (i.e., <10% total body surface), the radiation dose did not correlate well to thermal burns; however, the larger size of current bombs probably would produce much greater thermal injuries.[448] Reparative surgery including burn wound excision should be performed within the first 24–36 hours postexposure to reduce infectious complications; surgery should be avoided in the next several weeks after this 2-day time period. The treatment of radiation and thermal burns is similar to conventional burn treatment started after decontamination. Partial thickness burns should be treated with topical antimicrobial agents (e.g., silver sulfadiazine) and temporary skin substitutes followed by dry dressings. Prophylactic antibiotics are reserved for traumatic cutaneous wounds, selective decontamination, and early surgery.[449]

TABLE 39.36. Approximate correlation of minimal serum lymphocyte count during the first 48 hours after acute whole-body radiation exposure with prognosis. Death precedes cytopenia when the whole-body dose exceeds 50 Gy. (Adapted from Mettler and Voelz).[118]

Minimal Lymphocyte Count/mm^3	Absorbed Dose[a] (Gy)	Injury Severity	Prognosis
1,500–3,000	0–0.4	None clinically apparent	Excellent
1,000–1,499	0.5–1.9	Clinically significant, death unlikely	Good
500–999	2.0–3.9	Severe	Fair
100–499	4.0–7.9	Very severe	Poor
<100	≥8	Grave	Death likely

[a] Approximate.

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Referrals/Relocation

Victims receiving >2 Gy of whole-body radiation exposure in Classes I–IV should be transferred to a facility capable of evaluating and treating bone marrow failure. US resources for the treatment of radiation injuries include the Radiation Emergency Assistance Center/Training Site (REAC/TS) in Oak Ridge, Tennessee (emergency telephone line: 865-576-1005; website: https://orise.orau.gov/reacts/index.html), US Department of Health and Human Services (DHHS) Radiation Emergency Medical Management (REMM) (website: https://remm.hhs.gov/), and the Chemical/Biological Hotline of the National Response Center (phone: 300-424-8802).[450] The Radiation Injury Treatment Network (RITN) is a national network of over 70 medical centers that specialize in the management of bone marrow failure and the health consequences (e.g., chelation, decontamination) associated with acute radiation syndrome (https://ritn.net/treatment/). Typically, the local population adjacent to a nuclear incident should remain indoors when the radiation dose exceeds 10 mSv (1 rem); evacuation for 1 week is recommended for population exposure exceeding 50 mSv (5 rem).[451] Temporary relocation is recommended when the estimated radiation exposure exceeds 30 mSv (3 rem) during the first month or 10 mSv (1 rem) during subsequent months. Population exposures exceeding a lifetime dose of 1 Sv (100 rem) indicate the need for permanent resettlement.

Supplemental Care

Thyroidal Blocking Agents

Following a nuclear detonation, internal contamination with radioiodine (^{131}I, ^{125}I) from fallout is a common cause of radiation exposure. ^{131}I is a fission product of uranium. Sources of radioiodine exposure include inhalation of contaminated particles or aerosols and/or the ingestion of contaminated substances (water, vegetation, meat, milk, and other dairy products from cows grazing on radioiodine-contaminated vegetation). Based on the Chernobyl experience, children are especially susceptible to radioiodine effects because of their high milk consumption and their active thyroid glands.[64] The timely ingestion of potassium iodide effectively blocks radioiodine uptake and reduces the subsequent risk of developing thyroid nodules and cancer. Local officials typically determine the need for the prophylactic use of potassium iodide (KI) following the release of this radionuclide.[452]

The efficacy of KI is time-dependent with the largest reduction of radioiodine accumulation in the thyroid resulting from KI ingestion prior to or within several hours of internal radioiodine contamination. Modeling studies of euthyroid adults suggest potassium iodide (KI) effectively reduces environmentally dispersed radioiodine accumulation in the thyroid when administered 48 hours preexposure to 8 hours postexposure. The blockage of radioiodine uptake decreases substantially a few hours postexposure depending on the amount of iodine in the diet. The protective effects of potassium chloride decrease to 80% 2 hours after ^{131}I exposure and 40% 8 hours after ^{131}I exposure in individuals with iodine sufficient diets.[453] For individuals with iodine-deficient diets, the protective effects of potassium iodide decrease to ~65% and ~15%, respectively, in those times. The ingestion of potassium iodide concurrently with radioiodine exposure blocks 97% of the internal contamination.[454,455] The protective effects of potassium chloride are minimal if ingested 96 hours prior to ^{131}I exposure or 16 hours after ^{131}I exposure.

Treatment should continue for a minimum of 3 days; KI administration >10 days postexposure is not efficacious unless radioiodine exposure continues. The decision to use potassium iodide should be individualized depending on age and time since exposure.[456] Adults >40 years of age usually do not benefit from KI unless the projected thyroid dose exceeds 5 Gy, whereas infants and children may benefit from KI use following thyroid radiation doses of >10–100 mSv. The daily adult KI dose is 130 mg, whereas the dose for children under 70 kg and 3–18 years old is 65 mg, 32 mg for children 1 month to 3 years of age, and 16 mg for infants <1 month of age. Contraindications to KI use include acute hyperthyroidism, dermatitis herpetiformis, and iodine hypersensitivity. Anaphylactoid reactions to radiocontrast material, seafood allergies, and allergic contact dermatitis from iodine-containing antibacterial preparations are not necessarily IgE antibody-mediated iodine hypersensitivity. Nausea and vomiting are the most common side effects; rash occurs occasionally.

Radioprotectors

These agents are primarily free radical scavengers; experimental evidence suggests these agents provide some protection when administered before radiation exposure. The US Food and Drug Administration (FDA) has not approved any safe, effective countermeasures for the prevention of acute radiation syndrome.[457] The FDA approved the intravenous use of amifostine [*S*-2-(3-aminopropylamino) ethylphosphorothiotic acid, WR-2721] only in radiotherapy patients because of significant potential adverse effects associated with

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prophylactic use.[458] Amifostine is a thiol compound that reduces oxidative stress by acting as a free radical scavenger when administered 15–30 minutes prior to radiation exposure; clinical uses include the prevention of renal dysfunction from cisplatin therapy and xerostomia (dry mouth) following head and neck radiotherapy.[459] Radiation induces biochemical injuries within nanoseconds; no specific therapy can reverse the subsequent sequence of events; consequently, radioprotectors are effective only when administered prior to the radiation exposure. During the US Army's Antiradiation Drug Development Program testing of the phosphorothioate class of radioprotectors including amifostine (WR-2721), the latter was the most effective based on enhanced protection for bone marrow and the gastrointestinal tract, resulting in decreased LD_{50} in animal studies.[460] However, the inability to penetrate the blood–brain barrier restricts any effect on radiation-induced central nervous system damage.[461] Although amifostine is approved by the Food and Drug Administration (FDA) for patients undergoing radiotherapy, serious side effects (e.g., nausea, vomiting, hypotension, hypocalcemia, nephrotoxicity) limit the use of this intravenous drug in emergency personnel participating in vigorous activities.

Elimination Enhancement

Chelating Agents

The primary use of chelating agents (calcium diethylenetriamine pentaacetate, Ca-DPTA, CAS: 12111-24-9; zinc diethylenetriamine pentaacetate, Zn-DTPA, CAS: 125833-02-5) is the intravenous treatment of internal contamination by transuranic elements (americium, plutonium, curium).[118] The intravenous adult loading dose of Ca-DPTA is 1 g (14 mg/kg in children <12 years) as soon as possible after exposure followed by a daily maintenance dose of 1 g (14 mg/kg in children) of Zn-DPTA over days to months, depending on the amount of internal contamination. These US FDA-approved drugs are administered to enhance the elimination of these radionuclides; data are limited regarding the efficacy of these drugs to improve survival from exposure to high ionizing radiation doses. Typically, americium, curium, and plutonium are not released during a nuclear detonation. Serum trace metals (magnesium, manganese, zinc) should be monitored during long-term therapy.

Prussian Blue

Insoluble Prussian blue (Berlin blue, ferric ferrocyanide, ferric hexacyanoferrate II, iron blue) disrupts the enterohepatic recirculation of radioactive cesium and thallium, resulting in the increased elimination of these radionuclides via ion exchange; other radionuclides do not respond to this compound.[462] This compound is a USFDA-approved treatment for internal contamination by radioactive cesium and thallium. The indication for Prussian blue is ingestion of *10 times* the annual limit of ^{137}Cs intake (3.7 MBq, 100 μCi by ingestion; 7.4 MBq, 200 μCi by inhalation), whereas the need for treatment of ^{137}Cs exposures 1–10 times the annual limit is controversial. Below the annual limit of ^{137}Cs, treatment is unnecessary.

Relative contraindications include poor gastrointestinal motility and intestinal obstruction; potential adverse effects include electrolyte imbalance, constipation, and reduced bioavailability of some orally administered drugs. The amount of cyanide released by Prussian blue is not clinically significant with no reported cases of cyanide poisoning reported in the medical literature.[463] The adult dose is 3 g by mouth three times daily while maintaining a high-fiber diet and laxatives as needed, whereas the dose for children 2–12 years of age is 1 g three times daily. Higher Prussian blue doses were used for internal contamination during the Goiania accident.[464] Food may enhance fecal elimination following administration of Prussian blue. The minimum duration of treatment is 30 days with cessation of treatment determined by the amount of radionuclide eliminated from the urine and feces. The colored dye, soluble Prussian blue, is not an effective substitution for the insoluble form of Prussian blue.

Antacids/Cathartics

Aluminum-containing antacids should be administered when internal contamination with strontium isotopes is suspected. For large radionuclide ingestions within the last few hours, the administration of cathartics is an option to decrease gastrointestinal transit time;[435] however, the effectiveness of this procedure is unproven.

Definitive Care

Radiation countermeasures include radioprotectors, radiomitigators, and radiation therapeutics. Radioprotectors (amifostine; γ-tocotrienol, a vitamin E isomer) are prophylactic agents administered prior to radiation exposure to prevent subsequent tissue injury during the early phase of deterministic effects. These agents are free radical scavengers that reduce the damage from ionizing radiation-induced oxidative stress. Radiation mitigators administered after the radiation exposure and prior to overt symptoms of acute radiation syndrome stimulate the recovery of damaged tissues. These agents include 5-androstenediol,

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truncated flagellin (CBLB502), interleukin-12, G-CSF (filgrastim, Neupogen®), PEGylated G-CSF (pegfilgrastim, Neulasta®; pegfilgrastim-cbqv, Udenyca®), GM-CSF (sargramostim, Leukine®), and angiotensin-converting enzyme inhibitors (captopril).[465] USEPA-approved radiation therapeutics ameliorate radiation-induced symptoms after presentation and accelerate tissue regeneration only prior to the onset of symptoms including G-CSF, PEGylated G-CSF, and GM-CSF.[119,466] These drugs do not improve thrombocytopenia. Romiplostim (Nplate®) is a thrombopoietin receptor agonist approved by the USEPA for the treatment of ARS in adults including pregnant and lactating women as well as children.

Supportive Measures

Supportive care (e.g., fluids, electrolytes, antimicrobials, antiemetics, antidiarrheal agents, analgesics, topical burn creams, isolation precautions, transfusions) improves survival, the effectiveness of myeloid cytokines, and the chances of spontaneous hematological recovery after exposure to radiation levels up to 5–7 Gy within 1–2 months of radiation exposure, depending on the presence of other radiation syndromes. In patients administered supportive care within 24 hours of radiation exposure, the $LD_{50/60}$ increases from ~3.5–4 Gy to ~6–7 Gy.[467,468] Following exposure to low radiation doses, vomiting usually ceases after 48–72 hours with prolonged antiemetic therapy unwarranted. Infection and hemorrhage resulting from the reduction of the granulocytes and platelets are the primary lethal complications of the hematological syndrome. The management of serious radiation exposure, bone marrow aplasia, and immune system depression is similar. Table 39.37 correlates the whole-body radiation dose with clinical features, medical treatment, and lethality based on relatively uniform radiation exposure.

Supportive care includes early evaluation of fluid and electrolyte balance, antiemetics, and reassurance to help alleviate the natural fears associated with radiation exposure. 5-Hydroxytryptamine (HT)-3 receptor antagonists (e.g., ondansetron, Zofran®; granisetron, Kytril®; dolasetron, Anzemet®; palonosetron, Aloxi®) are typically more effective for radiation-induced emesis than phenothiazine compounds (e.g., prochlorperazine, chlorpromazine); these compounds do not protect normal tissues from radiation injuries.[116] Although less data (e.g., prospective clinical trials) are available to evaluate the efficacy of dexamethasone or neurokinin (NK)-1 receptor antagonists for radiation-induced vomiting compared with 5-HT-3 receptor antagonists, some studies suggest these medications are effective antiemetics for the acute radiation syndrome-induced nausea and vomiting. Potential treatment of diarrhea includes the use of loperamide, anticholinergics, or aluminum hydroxide suspension (e.g., Amphojel®). Adult Respiratory Distress Syndrome (ARDS) is a common complication of serious burn injuries; the mixed venous pO_2 should be maintained above 35 mm Hg. A baseline electrocardiogram, electroencephalogram, urinalysis, and slit lamp examination are helpful measures to establish a baseline for the later evaluation of the potential development of radiation-induced damage to the respective areas of the body.

Mucositis

Oral mucositis is a multifactorial pathological process involving proinflammatory cytokines, oral microbes, reactive oxygen species, and second messengers that cause mucosal pain and ulceration. Antibiotic administration does not prevent radiation-induced mucositis; however, sucralfate mouthwashes improve symptoms

TABLE 39.37. Approximate correlation of whole-body radiation dose to prognosis and medical treatment. Radiation exposure is frequently nonhomogeneous; therefore, these values are estimates, and the prognosis may be better than predicted following nonuniform radiation exposure. (Adapted from IAEA).[447]

Whole-Body Dose (Gy)	Clinical Features	Lethality (Onset)	Medical Response
1–2 (Mild)	Fatigue, weakness	0	Supportive care
2–4 (Moderate)	Fever, infections, bleeding, weakness, epilation	0–50% (6–8 weeks)	Special supportive measures days 14–20 with isolation days 10–20
4–6 (Severe)	High fever, infections, bleeding, epilation	20–70% (4–8 weeks)	Special supportive measures days 7–10 with isolation from beginning of hospitalization
6–8 (Very Severe)	High fever, diarrhea, vomiting, dizziness, disorientation, hypotension	50–100% (1–2 weeks)	Special supportive measures from start of hospitalization
>8 (Grave)	High fever, diarrhea, unconsciousness	100% (1–2 weeks)	Symptomatic care

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and Biotene® reduces the risk of mucositis and improves dry mouth associated with radiation-induced mucositis.[469] Palifermin (keratinocyte growth factor-7) is the only pharmacological drug approved for the reduction of radiation-induced mucositis with therapy beginning 3 days before irradiation. This recombinant *N*-terminal truncated keratinocyte growth factor stimulates reparative proliferation of epithelial cells in a variety of tissues by interacting with the cognate receptor fibroblast growth factor recerptor-2B.[470] Episil, GelClair, Caphosol, and MuGard are topical palliative rinses approved for the control of mucositis-related symptoms; however, the efficacy of these treatments is controversial.[471] Magic mouthwash is a rinse commonly compounded from topical anesthetics (Benadryl or viscous lidocaine), a muco-adherent vehicle (milk of magnesia, Kaopectate), and other agents (steroids, antifungals, antibiotics) for pain management.[472]

Enteritis

Acute radiation enteritis results from damage to rapidly dividing intestinal epithelium (e.g., crypt stem cells) that disrupts the intestinal barrier, allowing the translocation of intestinal bacteria.[473] The subsequent interference with the Na^+/K^+ pump impairs sodium/chloride absorption, producing watery diarrhea. Chronic radiation enteritis causes progressive obliterative endarteritis causing fibrosis and bowel ischemia, manifesting as strictures, fistulae, perforations, abscesses, and hemorrhage.[474] Treatment strategies involve symptom relief, diagnosis/management of intestinal complications, and limiting fibrosis to prevent organ damage.[475]

Dietary modifications include elimination of fatty and high-residue diets, identification of lactose intolerance, and treatment of bile acid malabsorption with cholestyramine. Complications (e.g., strictures, obstruction, fistulae, perforations) of radiation enteritis typically are treated with surgery; however, surgical complications are common because of the increased risk of anastomotic leaks. The theoretical advantages of using probiotics to prevent or treat radiation enteritis include the reduction of oxidative stress, downregulation of adhesion molecules, and release of glutathione. Although some studies demonstrate reduced frequency and/or severity of medical radiation-induced enteritis in patients treated with probiotics, evidence for the efficacy of probiotics in this setting is inadequate.[476] Experimental therapies include the use of pentoxifylline and tocopherol,[477] anti-inflammatories (e.g., methylprednisolone, sulfasalazine), octreotide, hyperbaric oxygen,[478] and heparin-binding epidermal growth factor.[475]

Hematological Subsyndrome

Treatment of the hematopoietic syndrome involves the use of blood transfusions for cytopenias (anemia, neutropenia, thrombocytopenia), administration of hematopoietic cytokines or growth factors (granulocyte colony-stimulating factor, G-CSF; granulocyte-macrophage colony-stimulating factor, GM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF, or Leukine®), and transplantation of allogeneic histocompatible donor-matched bone marrow cells or stem-cell transplantation in selected cases.[479] Blood transfusions may be necessary 2–4 weeks after radiation exposure when the radiation dose is sufficiently high (>2–3 Gy) to limit the effectiveness of cytokines. Recovery from the hematological syndrome depends on prevention and/or successful treatment of hemorrhage, bone marrow failure, and infection in the immunocompromised patient until hematopoietic cell lineages (pluripotent stem cells, progenitor blood cells) replenish the bone marrow.

Transfusions

Transfusions of cellular blood elements (e.g., platelets, packed erythrocytes) are necessary for patients with severe bone marrow damage, typically after trauma or 2–4 weeks after radiation exposure. Adequate platelet replacement is particularly important in patients with thermal trauma or cutaneous radiation syndrome. The platelet count should be maintained above 20×10^3 cells/μL with platelet products, reduced white cells (leukoreduction), and irradiated with 15–25 Gy to prevent transfusion-associated graft-vs.-host disease.[445] These precautions reduce the risk of allosensitization, transmission of viral infections, and graft-vs.-host disease;[480] the presentation of the latter and radiation-induced organ toxicity is similar (fever, skin rash, desquamation, server diarrhea, pancytopenia, hyperbilirubinemia). To reduce postoperative complications, the preoperative platelet count should be $>75 \times 10^9$ cells/L. In patients without an obvious need for a bone marrow transplant, the use of random-donor blood products matched for ABO and Rh compatibility is recommended for logistical reasons. HLA-compatible platelet transfusions may be required if refractoriness develops to random-donor platelets. Red cell concentrates and fresh frozen plasma should be infused only as required to maintain perfusion; these products should also be irradiated. Prophylactic or therapeutic uses of granulocyte transfusions probably are not efficacious.[481]

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Cytokines

Radiomitigators for the hematological subsyndrome are filgrastim (G-CSF, Neupogen®), PEGylated filgrastim (PEG-CSF, Neulasta®; pegfilgrastim-cbqv, Udenyca®), and sargramostim (Leukine®). These colony-stimulating myeloid cytokines enhance neutrophil function (e.g., microbicidal activity) and recovery by improving the survival, amplification, and differentiation of granulocyte progenitors in neutropenic patients;[482] the treatment of radiation-induced and chemotherapy-induced neutropenia is similar. Whole-body radiation exposures exceeding 2 Sv suggest the need for cytokines and/or colony-stimulating factors; colony-stimulating factors should be started as soon as possible after radiation exposures of >2–3 Gy up to 6–10 Gy depending on the presence of other injuries (blunt trauma, burns, comorbidities), severities of hematotoxicity, age (>60 years, <12 years), resources (e.g., < or > 100 causalities), and likelihood of recovery.[154] The early use (1–3 days postexposure) of rhGM-CSF or G-CSF is indicated for patients absorbing large radiation doses (i.e., ~4–8 Gy) sufficient to produce prolonged neutropenia with a good prospect for eventual recovery from bone marrow depression.[445] Although most studies use human recombinant G-CSF, G-CSF is not species-specific. Colony-stimulating factors should be continued throughout the time of recovery until the neutrophil count reaches a level >1,000 cell/μL above the nadir. The subcutaneous dose is similar for radiation- and chemotherapy-induced neutropenia.

Molecular cloning and formulation of recombinant human colony-stimulating factors offer a potential tool to ameliorate the hematological damage in radiation victims. Granulocyte colony-stimulating factor (e.g., G-CSF, filgrastim, Neupogen®), recombinant human pegylated G-CSF (pegfilgrastim, Neulasta®), recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF, sargramostim, Leukine®) erythropoietin (stimulation of erythropoiesis), and interleukin-3 (IL-3) are available for experimental and clinical studies. Sargramostim, pegfilgrastim, and filgrastim are approved by the US FDA as medical countermeasures to treat patients with radiation-induced myelosuppression following a radiological/nuclear incident when administered up to 48 hours after exposure.[483] These three countermeasures are included in the US Strategic National Stockpile of medical equipment and pharmaceuticals. Although erythropoietin and IL-3 are not US FDA-approved for radiation accidents, previous use in radiation accidents suggests some efficacy.[484,485] These cytokines do not treat thrombocytopenia. Romiplostim (Nplate®) is a thrombopoietin receptor agonist approved by the USEPA for the treatment of ARS in adults including pregnant and lactating women as well as children. Knowledge of the risks and benefits is not well-defined to determine the exact role of these agents for prevention of infection and survival of radiation victims; however, filgrastim and pegfilgrastim should be considered in patients with radiation exposure of >2 Gy, significant or prolonged neutropenia (<500 cells/mm^3), or extremes of age (<12 years, >60 years), preferably within 24 hours of radiation exposure.[479] Potential adverse effects include drug-related fever, rash, gastrointestinal upset, myalgias, hypoxia, and thromboembolism, whereas rare complications associated with use of G-CSF include splenic rupture, hypersensitivity reactions (*Escherichia coli*-derived proteins), sickle cell crises, Sweet's syndrome, myelodysplasia, and myeloid malignancy.[486] The causation of these rare complications remains unclear. The typical adult dose of filgrastim is 10 μg/kg/day as a subcutaneous injection, whereas the initial adult subcutaneous dose of pegfilgrastim is 6 mg 1 week apart for 2 doses. Some data suggest loratadine may reduce the bone pain associated with the latter, but the evidence is limited. These agents are usually started as soon as possible following suspected or confirmed radiation exposure exceeding 2 Gy and continued until the absolute neutrophil count exceeds 1,000. Acute radiation syndrome countermeasures with US FDA investigational new drug (IND) status include genistein (BIO 300, radioprotector/radiomitigator), entolimod (CBLB502, radioprotector/radiomitigator), AEOL 10150 (meso-porphyrin, radiomitigator), beclomethasone 17,21-dipropionate (OrbeShield®), recombinant interleukin-12 (HemaMax, radiomitigator), myeloid progenitor cells, and ONO1210 (chlorobenzylsulfone kinase inhibitor, radiomitigator).[119,487]

The European METREPOL (Medical Treatment Protocols for radiation accident victims) recommends the use of G-CSF and keratinocyte growth factor (KGF) for 14–21 days as soon as possible after exposure; however, there is no consensus on the use of erythropoietin, thrombopoietin, thrombopoietin receptor agonists, or stem cell factors.[488] Common complications of G-CSF administration include headache, arthralgias, and fatigue, whereas life-threatening complications (stroke, myocardial infarction, splenic rupture) are rare.[489] Hematopoietic stem cell transplantation is recommended only when severe aplasia persists despite cytokine treatment. An rhGM-CSF infusion increased the granulocyte count in five patients exposed to 2.5–6 Gy of internal and external ^{137}Cs irradiation in Goiania, Brazil; however, the exact contribution of the rhGM-CSF to survival of these patients is unclear.

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The red cell and platelet counts did not increase after treatment.[490]

Toxic effects of rhGM-CSF include fluid retention, thrombophlebitis, pericarditis, capillary leak syndrome, pulmonary infiltrates, and various side effects (e.g., myalgias, arthralgias, low-grade fever, anorexia).[491] In contrast to using G-CSF that increases the granulocyte count without reducing neutrophil migration, rhGM-CSF reduces neutrophil migration into injury areas. Therefore, the latter compound is theoretically a better choice for radiation-induced injuries complicated by burn trauma. In animal models, IL-3 and rhGM-CSF act synergistically to increase granulocytes without reducing neutrophil migration.[492]

Stem Cells and Transplantation

Currently, there is no consensus on the role of hematopoietic stem cell transplantation in the treatment of ARS. Matched, related, and unrelated allogeneic stem-cell transplantations are potentially curative in patients with certain predominately hematological cancers; however, the efficacy of this procedure in radiation victims is less clear. Although stem cell transplants may prolong survival following autologous hematopoietic recovery, radiation-induced injury to other organs usually limits survival. [493] Many radiation victims recover from hematopoiesis without a bone marrow transplant because of the wide distribution and resilience of red marrow stem cells, the likelihood of nonuniform irradiation, and the ability of remaining stem cells to repopulate the whole hematopoietic system. Mesenchymal stem cells are a heterogeneous population of multipotent stromal cells found in various tissues (adipose, dermal, placental, umbilical cord), blood vessels, and the kidney; these stem cells lack hematopoietic surface proteins. Although these stem cells are relatively radioresistant, clinical data are inadequate to define their role in the treatment of radiation-induced damage.[494]

Depending on radiation exposure severity, bone marrow biopsy should be taken from different sites 24 hours after exposure and repeated as needed. Bone marrow transplantation has a limited role in the treatment of radiation victims because this procedure benefits only those patients receiving whole-body radiation doses of 6–10 Sv without comorbid conditions (i.e., irreversible damage to lungs, kidneys, gastrointestinal tract); spontaneous recovery of the bone marrow will not occur in these patients without transplantation. The presence of 500 granulocytes/μL and $>100 \times 10^3$ platelets/μL at 6 days postexposure suggests residual hematopoiesis without the need for stem-cell transplantation.

At radiation doses exceeding 8 Gy, a radiation pneumonitis occurs ~3–7 months postexposure.[495] Radiation doses of >8–12 Gy produce severe gastrointestinal toxicity, resulting in damage to mucosal epithelial cells, sepsis from enteric bacteria, and extensive diarrhea. Consequently, bone marrow transplants in patients absorbing these whole-body doses are usually not successful because of radiation pneumonitis, gastrointestinal necrosis, infectious complications from altered immunity and mucocutaneous barriers, and/or hepatorenal failure.[118,496] Following the Chernobyl accident, 6 transplants of fetal livers and 13 transplants of allogenic bone marrow grafts (7 HLA identical, 6 haploidentical donors) were performed 4–16 days postexposure.[497] The 13 patients received bone marrow transplants after absorbing estimated whole-body radiation doses of 5.6–13.4 Gy. The two survivors received haploidentical bone marrow from their sisters after receiving estimated radiation doses of 5.6 and 8.7 Gy; both patients rejected the transplant ~1 month after transplantation.[64] There were 16 survivors in the group of 43 victims receiving whole-body radiation doses of 4–6 Gy; only 1 survivor in the group received >6 Gy. The other 11 victims died of associated injuries (e.g., burns, interstitial pneumonitis, graft-vs.-host disease, acute renal failure, and adult respiratory distress syndrome).[493]

Complications of bone marrow transplantation include graft rejection, graft-vs.-host disease (GVHD), and opportunistic infection, particularly cytomegalovirus interstitial pneumonitis. The administration of G-CSF shortly after a bone marrow transplant theoretically increases the risk of GVHD. The best candidates for transplantation are young victims with relatively uniform radiation exposure in the range of 7–10 Gy and available human leukocyte antigen (HLA)-identical sibling or close family donors.[153] Few patients over 50 years of age survive bone marrow transplantation.[498] Analysis of the potential role of bone marrow transplantation is complex, depending on patient and accident characteristics. The most effective range of radiation doses for survival after bone marrow transplantation probably ranges from 8–12 Gy, depending on the uniformity of the radiation dose.[497] Below this range, the Chernobyl experience complicated by extensive β-radiation burns suggests bone marrow transplantation adversely impacts survival; above this range, radiation-induced damage to other organs is probably fatal. Animal data indicate the optimum time of transplantation is the first 3–5 days postexposure when immunosuppression peaks. Waiting more than 1 week may require chemotherapy; this treatment increases the risk of opportunistic infections.[445] The experience at Chernobyl suggests bone marrow

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transplantation is a more viable option for victims exposed to 8–12 Gy than fetal liver transplantation.

Infectious Complications

Most patients with granulocytopenia of <500 cells/μL for >5 days develop infections;[499] patients with granulocytopenia of <100 cells/μL are particularly susceptible to fatal gram-negative bacteremia. Although granulocytopenia is a major cause of increased susceptibility to infection in patients exposed to radiation, other cell and humoral agents may contribute to the increased susceptibility. In these patients, infections often occur in areas of the body where there is damage to the normal anatomic barrier that protects the body from invasion by microbes. The most common causes of infection in granulocytopenic patients are the aerobic gram-positive cocci (e.g., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* species) and the aerobic gram-rods (e.g., *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella pneumoniae*).[500] Typical prophylactic regimens include fluoroquinolones with streptococcal coverage (penicillin or penicillin congener), antiviral drugs (acyclovir or congener), and antifungal agents (e.g., fluconazole). These regimens are continued until the absolute neutrophil count exceeds 500 cells/μL or the patient develops neutropenic fever. The blunting of the normal inflammatory response in patients with aplastic bone marrow and few circulating granulocytes requires careful, repeated physical examinations and serial X-rays to identify sources of infection. Among *febrile* patients with granulocytopenia, the etiology of the fever is equally divided between bacteremia, documented infection without bacteremia, clinically identified site of infection without specific pathogen, noninfectious origin, and fever of unknown origin.[500] Subsequent antibiotic therapy is directed at the suspected pathogen based on the recommendation for treating neutropenia and fever.

Prophylaxis Most seriously injured victims at Chernobyl received whole-body radiation doses compatible with bone marrow recovery following intensive supportive measures.[2] These patients received isolation with laminar airflow, prophylactic oral antibiotics, and systemic antimicrobial therapy when fever developed. Antibiotics are not usually required during the initial 7–10 days after radiation exposure. There were no deaths from infection among Chernobyl victims except for patients with graft-vs.-host disease, extensive burns, or radiation-induced enteritis.[64] Fluoroquinolones along with penicillin or other Streptococcal coverage are typically recommended for prophylactic treatment during the neutropenic period with gram-negative coverage added and fluoroquinolones withdrawn when fever develops.[154] Although there are no guidelines specifically for irradiated patients, most physicians use the guidelines formulated for neutropenia from nonradiation causes.[501]

Table 39.38 outlines prophylactic measures for the reduction of infection risks in granulocytopenic patients. Granulocytopenic patients with neutrophil counts of <100 neutrophils/μL require aggressive supportive care and prophylactic treatment, whereas patients with neutrophil counts above this level demonstrate substantially less risk of serious infection. The presence of associated traumatic injuries worsens the prognosis for granulocytopenic patients. Important measures to reduce the load of pathogens include water treatment (e.g., acidification) as needed, diets (e.g., use of canned foods, elimination of leafy green vegetables, citrus fruits, and tomatoes) with low microbial counts, frequent handwashing, use of gloves, and laminar airflow to eliminate *Aspergillus* contamination. The reduction of food and environmental pathogens is as important as the use of gowns, masks, and booties because most acquired infections result from contact with the hands of medical personnel or environmental contamination (i.e., air, water, food).[500]

Maintaining gastric acidity by the avoidance of antacids and H_2-antagonists is a theoretical measure to reduce stomach colonization and the frequency of aspiration pneumonia from nosocomial infections. Administration of sucralfate or prostaglandin analogs helps prevent gastric hemorrhage without increasing the gastric PH. The radiation dose and the status of gastric emptying determine the decision to administer drugs or food orally. Early (within 12 hours) enteral nutrition appears superior to total parenteral nutrition to maintain gastrointestinal mucosa and structure, stimulate gut recovery and immune function, and decrease bacterial invasion of the gut mucosa.[502] However, the decision to insert thin-bore feeding tubes into the duodenum may result in mucosal ulcerations in severely granulocytopenic patients; therefore, total parenteral nutrition may be preferred over enteral nutrition in these patients.

Meticulous attention to the use of catheters and dental hygiene are important measures to reduce the spread of nosocomial infections. Surgical implantation of a subcutaneously tunneled central venous catheter with meticulous protection of the catheter site (chlorhexidine, water-tight dressings) helps reduce invasive procedures. Although total microbial suppression allows colonization of hospital-acquired bacteria, oral antibiotics reduce the aerobic bacteria and fungi

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TABLE 39.38. Reduction of infection risks in immunocompromised patients when feasible. (Adapted from Browne et al.).[445]

Goal	Action	Example
Reduce invasive procedures		Nasogastric tubes
Colonization-resistant inert surfaces		
Reduce microbial contact	Contact control	Handwashing
	Water treatment	
	Food	Low microbial diet
	Laminar air flow	↓ *Aspergillus* infections
↓ Microbes	Suppress microorganisms	
	Selective decontamination in neutropenic patients (<1,000/μL)	Oral nonabsorbable anti-bacterials that preserve anaerobes (fluoroquinolones)
	Anthelminthics if indicated	
	Monitor for resistant bacteria	
	Consider antivirals	
Physiological intervention	Maintain gastric acidity	Avoid antacids and H_2 blockers
		Sucralfate, Biotene® mouthwashes, or stress ulcer prophylaxis
		Early oral enteral nutrition as indicated
Personal hygiene	Povidone-iodine/chlorhexidine for skin disinfection	Soft toothbrushes
	Shampoo	
	Oral hygiene	Brushing, careful flossing
Host defenses	Active vaccinations for expected pathogens	Influenza, *Streptococcal* pneumonia
	Immunomodulators	

without inhibiting the anaerobic bacteria.[503] Because these drug regimens require 7–10 days to become effective, suppressive drugs should be started before the granulocyte count falls to levels of <100 neutrophils/μL. Prophylactic oral acyclovir is a standard antiviral agent for antibody-positive, granulocytopenic radiation victims. The use of cytokines improves the antibacterial activity of surviving immune cells and helps replenish lost cells.

Treatment The management of suspected infections in irradiated patients and other febrile, neutropenic patients is similar. Neutropenia alone does not require treatment, although selective decontamination of the gut is probably efficacious for severely neutropenic (<100 neutrophils/μL) patients. Knowledge of recent infection sources in the patient and hospital is an important determinant of the antibiotic regimen because most infections are hospital-acquired.[500] Iatrogenic factors (e.g., urinary catheters, exit site or tunnel infections from intravascular catheters, contamination from the administration of blood products, trauma) are potential sources of hospital-acquired infections.

Patients with neutropenia and fever (>37°C) should be treated promptly with an empirical regimen of antibiotics based on the bacterial susceptibility of nosocomial infections at the hospital and the physician's judgment. Typically, combination antibiotic therapy is administered with a broad-spectrum β-lactam-resistant penicillin or later generation cephalosporin plus an aminoglycoside. Vancomycin should be added to the antibiotic regimen if resistant gram-positive bacteria develop. Monotherapy with antibiotics (e.g., imipenem, ceftazidime) is appropriate for patients with neutrophil counts of >100 neutrophils/μL. Amphotericin B (0.5 mg/kg/day) should be added to the antibiotic regimen if the fever persists for more than 7 days after antimicrobial therapy was initiated. First-line antifungal therapeutic agents include amphotericin B, itraconazole, and voriconazole.[504,505] Antimicrobial treatment should continue at least while the patient is febrile. Radiation-induced activation of herpes simplex virus was a major complication in the Chernobyl victims exposed to high radiation doses; the viral infection responded to acyclovir.[2] Ganciclovir and high-dose γ-globulin are experimental therapies for the devastating cytomegalovirus pneumonitis.

Local injuries

Treatment of localized radiation injuries after decontamination and medical stabilization includes prophylaxis against infection (topical antibiotics), pain control (non-steroidal anti-inflammatory drugs, opioids, sedatives), anti-inflammatory creams (e.g., linoleic acid), topical steroids, topical antihistamines, careful

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debridement of devitalized tissue, protection from traumatic injury, and vasodilator therapy; more serious cases may require grafting, bilaminate skin substitute, plastic surgery, or amputation.[118] Autologous keratinocytes and allogeneic stem cell administration may follow excision of affected tissue to prevent recurrent skin necrosis.[506] Fluid losses, bleeding, and infection 2–4 weeks after exposure to large cutaneous radiation doses are the primary causes of death. Initial fluid resuscitation is an important measure in the first few days to maintain circulation. Intravenous catheters should be inserted early in nonburn areas and maintained carefully to avoid colonization by nosocomial bacteria. The temperature should be closely monitored for evidence of hypothermia and fever. The prognosis of local injuries depends on several factors including absorbed dose, type of radiation energy, and area/depth of tissue injury. Medical therapy is sufficient for injuries involving inflammation, moist desquamation, and ulceration, whereas dosimetry-guided surgical therapy is necessary for deep ulceration and necrosis.[167] Medical management of severe cases required hospitalization at specialized reconstructive surgery facilities. Newer cell and gene therapies for treating cutaneous syndrome include progenitor cells, adipose stromal cells, and stomal cells/mesenchymal stem cells.[507,508]

Erythema and Dry Desquamation

Radiation burns may progress from erythema to vesiculation, skin loss, and ultimately superficial or deep tissue necrosis that requires surgical intervention. The rule of nines applies to grading burn severity for thermal and radiation burns. The treatment of cutaneous radiation syndrome and thermal burn injuries is similar, except for the difficulty in demarcating the extent of a radiation injury. Mild, asymptomatic cutaneous erythema or dry desquamation requires no treatment other than softening the area with bland aqueous creams and avoiding tight clothing; moderate-to-severe erythema may require the addition of a low-dose, topical steroid cream. In general, inflammation and moist desquamation are treated medically, whereas deep ulcerations and necrosis require surgical treatment.[167]

Moist Desquamation

The presence of moist desquamation indicates the need to treat the burn as a wound. Contaminated burns are treated like thermal burns, except that more frequent dressing changes may be necessary in the first few days to limit the spread of contamination from the scab. Gentle rinsing of the burn wound is usually the most appropriate decontamination measure. Treatment of moist desquamation without infection or exudates involves the local application of topical antibiotic agents that do not retard epithelialization (e.g., Silvadene®, Neosporin®). Topical Bactroban® possesses limited gram-negative coverage; therefore, Bactroban® should be used with other antibiotics if a mixed infection is suspected.[509] Waterproof, occlusive dressings improve the resurfacing of the noninfectious, exudative wounds when applied in the first 6–24 hours postexposure and left in place for 24 hours including polyurethane films (Opsite®, Bioclusive®) and hydrocolloids (DuoDerm®, J & J Ulcer Dressing®).[510] Aquacel® dries the exudate by producing a gel effect. Although these materials vary in composition, they all provide a bacterial barrier. The choice of material depends on the wound's characteristics and requirements. Hydrocolloid dressings are effective for the management of radiation-induced moist skin desquamation and preventing *Pseudomonas* infections by lowering the pH,[511] whereas adhesive dressings (e.g., polyurethane films) should be used only when normal skin surrounds the wound. Vigorous cleansing and scrubbing of the burn wound should be avoided because of the potential for absorption of contamination across the damaged epithelial barrier. Contamination from insoluble radionuclides will slough with the eschar; therefore, the dressings and bed linen may become contaminated.

Deep/Full-Thickness Injury

Treatment of radiation-induced ulcers involves the administration of tetrachlorodecaoxide, hydrocolloid dressings, topical thrombocytic growth factors, and surgical intervention (i.e., aggressive debridement followed by rotation flaps or full-thickness skin graft) as needed. The timing and extent of surgical intervention depend on clinical judgment, the amount of underlying tissue damage, the presence of infection, and the persistence of pain. Determination of the extent of injury usually requires at least 24–30 hours after radiation exposure to accurately characterize the burn damage in conjunction with physical dosimetry. With the development of fixed erythema, demarcation of the burn wound appears; however, the extent of underlying damage cannot be accurately estimated from superficial changes.

Surgical intervention for life-threatening injuries in severely irradiated victims should be performed within 36–48 hours postexposure; elective procedures (closure of ostomies, reconstructive and cosmetic procedures) should be postponed for at least 45–60 days after recovery from radiation-induced immunosuppression. For a patient exposed to whole-body radiation doses of >2–4 Gy and likely to develop immunosuppression, early excision of burns and wounds, preferably with skin grafting, decreases infection risks.

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Prophylactic antibiotics should be administered before surgery.[445] Intractable pain from deep radiation-induced lesions is especially difficult to control, usually suggesting the presence of the acute phases of vasculitis.[167] Over-pressurized devices with transparent walls and invaginated gloves increase the comfort of the patient and staff.

Beta particles penetrate skin in relation to their energy at the rate of ~0.5 cm/MeV. At surgery, the extent of the excision will depend on the isodose curves and the appearance of the tissue borders. Clinical experience at Goiania suggests blood pool imaging with ^{99m}Tc RBC may help determine the extent of cutaneous damage.[512] MRI studies of thick muscular structures help delineate the depth and extent of necrotic tissue. Surgical success requires removal of all necrotic and infected tissue to the level of good vascularity along with good soft tissue coverage for all underlying structures. In contrast to thermal burns, radiation burns require long-term surgical care rather than early excision and skin grafting. These patients require lifelong follow-up to monitor progression of fibrosis-induced ischemia and emergence of cutaneous malignancies. Experimental therapies for the reduction of radiation-induced cutaneous fibrosis include topical superoxide dismutase, pentoxifylline/α-tocopherol, and proteinase inhibitors.

Hospital Protocols and Drills

Management of radiation incidents involves: 1) preparation, 2) crisis management, and 3) long-term treatment of radiation-induced complications. The preparation phase includes emergency planning, assessment and procurement of equipment, assignment of control and command, identification of organizational responsibility, and delineation of important protective actions. Training emergency personnel involves background information on radiation, risk levels, protection methods, and management priorities. Because radiation accidents are rare, written protocols and annual drills are necessary to optimize the treatment of the radiation victim. These hospital plans should assume the need to treat at least one to five contaminated victims and triage a substantial number of walk-in patients for the presence of contamination. Resources for radiation protocols containing written procedures for radiation accidents, personnel job descriptions, medical equipment lists, and decontamination methods include books[438,442] and websites (https://orise.orau.gov/reacts/index.html, https://remm.hhs.gov/). Practice drills should be as realistic as possible, with a critique to improve performance following the drill. Videotapes are instructive, especially for the orientation of new personnel in the emergency department.

The protocol should designate a Radiation Emergency Area (REA) to receive contaminated victims and prevent the spread of contamination to other hospital areas. The control procedures for this area are similar to those for patients in strict isolation with buffer zones, clean areas, and contaminated rooms. A "floating" nurse and an aide should monitor the buffer area to ensure conformity to contamination protocols.

Figure 39.14 displays a common design for the REA. Ideally, the REA should be outside the main traffic flow of the hospital; however, this area should have direct access to the outside for the transfer of contaminated patients from the ambulance to the REA. The REA is not usually a dedicated area; therefore, advance communication is necessary to prepare the room prior to the ambulance's arrival. For critically injured patients, this preparation can be performed concurrently with treatment including nonslip floor covers (e.g., Herculite®, barbecue cloth), removal of nonessential equipment, and designation of contaminated areas with tape and rope.

Resuscitation equipment and supplies should be packaged in mobile containers for easy transfer to the REA. These supplies include decontamination supplies, long pairs of forceps for removal of radioactive metallic fragments, protective clothing, dosimeters, Geiger counters, and material for designating appropriate areas and collection of specimens. Protective clothing usually consists of water-resistant gowns, caps, plastic shoe covers, and surgical gloves. This clothing protects the individual only from α-particles, functioning more as a reminder to avoid contamination than protection against β- and γ-radiation. Reducing the time spent close to the radiation source and increasing the distance between medical personnel and the radiation source are more effective means of decreasing radiation exposure than shielding with lead or other materials.[514] The presence of radioactive metallic fragments in the patient, requiring careful placement in a lead-lined container, is an exception to this rule. Security is necessary to prevent unauthorized access; the medical staff should adopt universal precautions.

The REA should contain a shower, hot and cold water, telephone, resuscitation equipment, floor drains, and easily washable walls. Installation of elaborate drainage systems or sophisticated ventilation systems is probably not necessary to limit the spread of contamination to other areas of the hospital or the public.[513] Although filtering or separating airflow from the rest of the hospital is desirable, the relatively large size of most contaminated particles limits the spread of most contamination through the ventilation system. Similarly, the use of holding tanks for the discharge of

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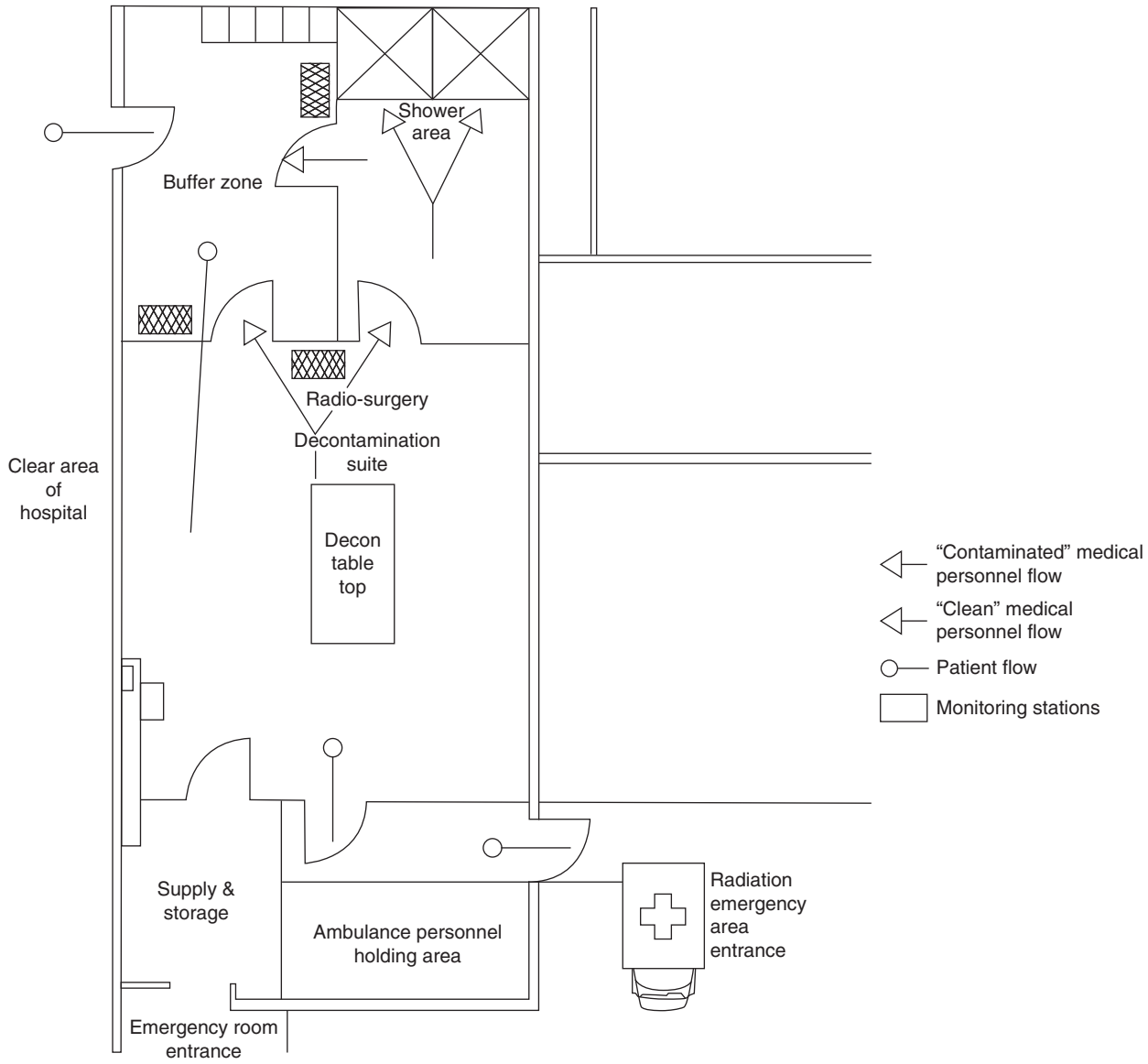


FIGURE 39.14. Common design for radiation emergency area (REA). (Adapted from AMA).[513]

contaminated water is advantageous; however, the radiation hazard to the public is minimized by the relatively small and limited discharge of radioactive waste compared with the large volume of effluent from the hospital and community. The protocols for decontamination must follow all state and federal regulations for the discharge of radioactive effluent.

Specialty referral centers are available on a 24-hour basis to receive, survey, and treat radiation accident victims. In addition, some of these centers provide information on planning, training on the current methods of treating radiation victims, and population monitoring. Examples of these centers include the US Radiation Emergency Assistance Center and Training Site (REAC/TS) located at Oak Ridge Hospital of the Methodist Church in Oak Ridge, Tennessee (emergency number: 865-576-3131), Centers for Disease Control (CDC) Radiation Studies Branch: https://emergency.cdc.gov/radiation/pdf/population-monitoring-guide.pdf, International Atomic Energy Agency Emergency Preparedness and Response Section: http://www-pub.iaea.org/MTCD/publications/PDF/EPR-MEDICAL-2005_web.pdf, and the World Health Organization (WHO) Radiation Emergency Medical Preparedness and Assistance Network (REMPAN Directory): (https://www.who.int/groups/rempan).

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Chapter 40

IONIZING MEDICAL IMAGING AND RADIOTHERAPY

Ionizing radiation contains sufficient energy to remove tightly bound electrons from their orbits and create ions including both particulates (α- and β-particles) and electromagnetic energy (γ-rays, X-rays). Health concerns regarding the use of ionizing medical radiation (i.e., conventional X-rays, CT scanning, radiotherapy, radionuclides) include primarily teratogenesis and carcinogenesis. The measure of potential radiation exposure from diagnostic medical equipment in SI units is the gray (Gy) or milligray (mGy); the radiation absorbed dose (rad) is the analogous, less commonly used, conventional unit (1 rad = 0.01 Gy). The equivalent dose is the calculated radiation dose after adjusting for different radiation types and tissue densities with the radiation weighting factor (W_R), assuming the body is homogeneous. The sievert (Sv) is the SI unit for the equivalent dose; the rem is the conventional unit. For X-ray, the γ- and β-radiation W_R is 1; therefore, 1 Gy = 1 Sv for these types of radiation. Multiplying the radiation dose equivalent by a tissue-weighting factor (W_T) to account for the radiosensitivity of different tissues and summing the doses for all the organs produces the effective radiation dose. Within the last two decades, the average effective radiation dose from medical imaging has increased substantially; medical imaging contributes almost 50% of the overall average radiation dose to the US population compared with 15% in 1980.[1]

DIAGNOSTIC RADIATION

HISTORY

Over the last 50 years, technical improvements in conventional radiography significantly reduced the radiation dose for patients and staff as image quality improved.[2] During this time, film-screen radiography transitioned from hand-dipped film processing to modern electronic image receptors (photo-simulated phosphors in computed radiography, CsI needle phosphors in indirect-conversion digital radiography flat panels, amorphous selenium photoconductors in direct-conversion digital radiography flat panels).[3] Most radiographical imaging during the 1950s involved single-phase X-ray generators that had 100% ripple in the high voltage waveforms and relatively low energy X-rays; consequently, the patient received relatively high radiation doses despite less penetrating X-rays. The first automated film processors were distributed in 1957. Three-phase equipment and then high-frequency units replaced single-phase X-ray generators, resulting in minimal high-voltage ripple and shorter X-ray exposure time.[4] Along with the implementation of quality

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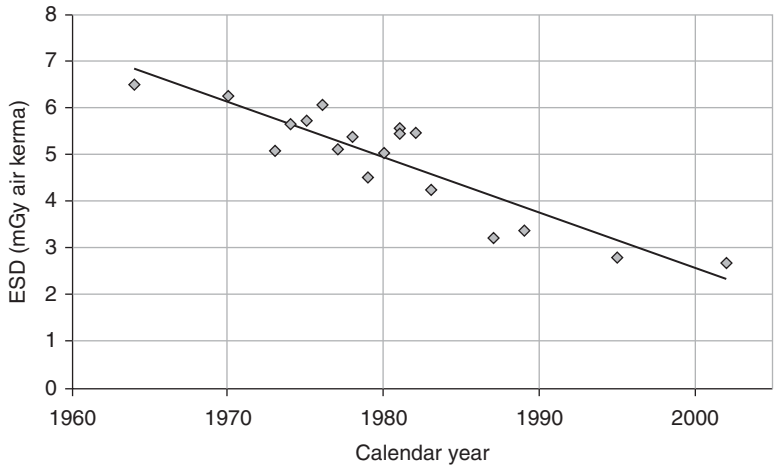


FIGURE 40.1. Estimated average surface radiation exposure (entrance surface dose, ESD) of US adults from AP abdominal X-ray as measured by the entrance radiation doses 1960–2005. (Redrawn from Huda et al.).[2]

control programs, several advancements substantially reduced the radiation dose to patients over the next 50 years, including rare earth X-ray beam filters (erbium, niobium) and fast rare earth film-screen systems. Based on historical estimates, the entrance skin radiation doses for chest X-ray examinations decreased from 68 mGy in 1902 to 0.13 mGy more recently.[5] Similarly, the radiation dose for a conventional abdominal X-ray decreased from 189 mGy in 1902 to 2.73 mGy currently. Figure 40.1 demonstrates the decrease in entrance (surface) radiation exposure from 1960–2005 for an AP abdominal X-ray in US adults; similar declines occurred for the entrance radiation dose for PA chest and AP lumbosacral spine radiographs.

In the early 1970s, the introduction of computerized tomography (CT) revolutionized diagnostic radiology by providing three-dimensional views of specific organs and body regions of interest. The use of axial and helical (spiral) CT increased rapidly with >80 million scans performed by the late 2000s.[6] Although the cancer risk is small, the CT increases the radiation dose/examination; and the overall cancer risk as CT usage dramatically increased in the 2010s and 2020s. The dose from a conventional abdominal X-ray series (three radiographs) is ~15 times smaller than the stomach receives from an abdominal CT scan.

EXPOSURE

Exposure describes the radiation intensity in the field surrounding the patient rather than the amount of interaction between the radiation and the tissue. The entrance surface dose (older term, entrance skin exposure or ESE), is a measure of the amount of radiation at the presumed skin location where the beam enters; the ESD can be calculated from the kVp and the filtration parameters of the X-ray machine.[7] Therefore, the skin dose is the maximum dose received by any portion of the body. The radiation dose equivalent (Sv) is the product of the absorbed dose (Gy) and a dimensionless weighting factor. Multiplying the organ equivalent dose by the tissue weighting factor to account for tissue radiosensitivity and summing the organ dose produces the whole-body effective radiation dose (effective dose). The value of the effective dose changes with time as various factors are adjusted, usually to reduce the radiation exposure to a level as low as reasonably achievable. Figure 40.2 displays the relationship between the absorbed dose, dose equivalent, and whole-body effective dose.

The whole-body effective radiation dose reflects radiation risk at the population level rather than the individual level; the latter depends on patient-specific factors (e.g., age, life expectancy, medical conditions,

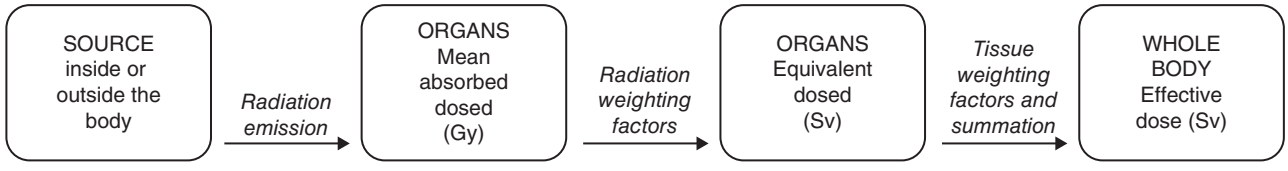


FIGURE 40.2. Relationship between absorbed, equivalent, and effective doses. (ICRP et al.).[8]

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TABLE 40.1. Estimated range of radiation doses from a variety of diagnostic X-ray procedures. (Adapted from National Research Council BEIR VII Committee).[9]

Procedure	Examination Type	Radiation Doses
Plain conventional X-rays	Chest, bones, skull, abdomen	0.02–10 mGy
Complex conventional X-rays	Gastrointestinal series, barium enema, intravenous urogram	3–10 mGy
Computed tomography (CT)	Head, abdomen-pelvis, whole-body	5–15 mGy
Spiral CT	Head, whole-body	10–20 mGy
Angiography	Coronary, aortic, peripheral, carotid, abdominal	10–200 mGy
Interventional procedures	Angioplasties with stent, percutaneous dilatations, closures, biopsy procedures	10–300 mGy

body habitus). The use of the effective radiation dose allows a comparison of typical radiation doses of various imaging technologies or procedures (e.g., barium enema vs. CT abdomen) in different hospitals or countries, assuming the patient populations are similar; thus, the effective radiation dose is a quality-control tool that can identify deviations from standard practices of a specific imaging examination. Table 40.1 lists the approximate ranges of radiation doses from several types of diagnostic X-ray procedures.

Since the 1980s, effective radiation doses from common radiographic procedures and CT examinations for adults have trended downward along with the estimated radiation dose per procedure.[10] However, the frequency of relatively high-dose diagnostic examinations has increased. These procedures include some computed tomography (chest, abdomen/pelvis), nuclear medicine (heart – ^{201}Tl chloride, tumors – PET ^{18}F-fluorodeoxyglucose, bone – ^{99m}Tc phosphate), and fluoroscopically guided (cardiac angiography, barium enema) examinations. Fetal radiation doses from maternal medical irradiation vary several 1,000-fold depending on the specific procedure.[11] High fetal radiation doses from maternal diagnostic procedures involve the use of certain radiographical imaging (AP lumbar spine, AP pelvis, AP abdomen), diagnostic (barium enema, intravenous pyelogram, AP urinary bladder), computed tomographic (pelvis, liver, lumbar spine), and nuclear medicine (^{67}Ga citrate, heart – ^{99m}Tc methoxyisobutylisonitrile, kidney – ^{99m}Tc mertiatide) examinations. Although the estimated entrance surface dose for radiographical examinations and the dose-area product for fluoroscopic procedures increase with age, the overall radiation dose is higher in pediatric patients than adult patients because the larger adult body size attenuates a relatively greater amount of the primary X-ray beam.

Radiography

An X-ray generator is a regulated high-voltage DC power supply typically with the following operating range: power (i.e., 10–200 kW); output voltage (i.e., 20–160 kV); and current (10–5,000 mA).[4] Sealed vacuum X-ray tubes produce high-speed electrons that strike a metal target and release heat and high-energy photons (X-rays). Lead containers (housing) surround the X-ray tubes to focus the X-rays through ports or windows into a useful beam. Diagnostic X-ray tubes are shielded to minimize the leakage of radiation (i.e., <1 mSv/hour at 1 m from the focus). An aperture or collimator (i.e., a device to reduce the cross-sectional area of the photon/electron beam) defines the primary field limits. A filter absorbs the low-energy photons that do not contribute to the resolution of the X-ray picture to limit patient exposure to low-energy photons in the primary beam. High frequency units replaced the single-phase X-ray generators. The advantages of the newer units include the delivery of higher and more reliable energy X-ray spectra for identical kVp settings and the reduction in the size of the high-voltage circuits.

Planar Radiographs

The complex interaction of a variety of factors determines the clarity of a radiograph including subject contrast, sharpness, resolution, radiographical mottle, fog/scatter, and radiographical contrast; these factors depend on machine parameters (voltage, amperage, grid selection, image receptors).[12] Modern electronic image receptors (e.g., photo-simulated phosphors for computed radiography, CsI needle phosphors coupled to solid-state light detectors for digital radiography) and fast rare earth film-screen systems replaced the older hand-dipping techniques.

Kerma is the sum of the initial kinetic energies of all charged particles liberated by uncharged particles (e.g., X-rays, neutrons); hence, kerma is a measure of the kinetic energy released per unit mass. The kerma-area

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product (KAP) measures the total X-ray beam intensity by multiplying the average air kerma (energy in X-ray beam per unit mass of air in small, irradiated air volume measured in Gy) by the area of the X-ray beam (cm^2) expressed as Gy-cm^2 in Equation 40.1. The KAP does not change with distance from the X-ray tube.

$$\text{Kerma-Area Product (KAP)} = \text{average air kerma (Gy)} \times \text{X-ray beam cross-sectional area } (cm^2) \quad \text{(Equation 40.1)}$$

The KAP (also known as dose-area product, DAP) provides a good estimate of the total amount of radiation delivered to the patient during a radiographical examination; the use of KAP allows the comparison of radiation exposure between various institutions and recommended values (e.g., diagnostic reference level).[13] However, KAP is not a surrogate for the effective radiation dose.[14] After accounting for X-ray beam quality, KAP (Gy-cm^2) reflects the energy incident on a patient in any area of radiological imaging; conversion of the KAP to the effective radiation dose and estimated organ doses requires adjustment for beam quality (projection, parameter settings), the patient's physical characteristics (size/age), body region, and projection of the X-ray beam.[15] Converting the KAP to conceptus dose also depends on gestational age and the closeness of the conceptus to the primary beam. Estimation of organ doses requires direct measurement in anthropomorphic phantoms or the use of Monte Carlo computational software; these values vary depending on the software and phantom design. In a study of conventional planar X-ray examinations comparing direct measurement of uterine doses in a phantom and calculated uterine doses from two software programs (WinODS,[16] PCXMC[17]), the factors for converting KAP (Gy-cm^2) to uterine radiation doses (mGy) ranged from 0.01 mGy/Gy-cm^2 (chest 2-view, fetus <3 months) to 3.8 mGy/Gy-cm^2 (L5 single frontal view, fetus 9 months).[18]

The nominal (benchmark) KAP value for radiographs is ~1 Gy-cm^2 compared with 20 Gy-cm^2 for fluoroscopy and 100–300 Gy-cm^2 for interventional radiography.[14] KAP values for common plain films range from 0.1 Gy-cm^2 (posteroanterior chest view) to 2.5 Gy-cm^2 (anteroposterior abdomen or pelvis), as displayed in Table 40.2.

Radiation exposure is typically higher for radiographs of the spine and abdomen than the chest and extremities. X-rays are not produced unless the X-ray machine is turned on; therefore, no residual X-rays remain in the room after the X-ray machine is switched off. The patient does not become radioactive after X-ray examination.

TABLE 40.2. Representative kerma-area product (KAP) values for common planar radiographs in normal-sized adults. (Data from Huda).[14]

Examination/Projection	Image Number	KAP (Gy-cm^2)
Skull – lateral	1	0.5
Skull – anteroposterior (AP)/lateral	2	1.5
Chest – posteroanterior (PA)	1	0.1
Chest – posteroanterior/lateral	2	0.3
Abdomen or pelvis – anteroposterior (AP)	1	2.5

Mammography

Mammography requires relatively high radiation exposure to achieve the resolution required for good radiographic images. In the 1960s, industrial film-based techniques delivered radiation doses up to 150 mGy/procedure. In the 1970s and early 1980s, selenium detector-based imaging (xerography) gained wide acceptance in mammography; this technique involves the use of tungsten X-ray tube operated at 40–50 kVp with an aluminum filter and a xerographic image receptor; however, by the late 1980s, screen-film imaging became the dominant technique in mammography.[19] This latter method uses a molybdenum or rhodium filter and an intensifying screen-film combination as the image receptor. The radiation dose to the glandular tissue in the breast as measured in normalized glandular dose coefficients is an important determinant of stochastic effects. Computer-based methods employing Monte Carlo techniques now are the principal tool for optimizing the X-ray spectrum for digital mammography.[2]

Fluoroscopy

The introduction of image intensifiers in the 1950s provided a much brighter screen image than older fluoroscopy screens that required a dark room for viewing and delivered large radiation doses to the patient. However, radiation levels (air kerma) remain relatively high (i.e., up to 87 mGy/minute) including scattered X-ray radiation to the staff.[12,20] Because of image quality requirements, even fluoroscopy that uses spot films with radiographical cassettes produces substantial radiation doses. Factors affecting variations in the amount of radiation exposure during fluoroscopy include screening time, number of films, the resolution of the TV or film image, and the area of imaging.[21] Technological improvements over the last 50 years have reduced radiation doses to patients and staff, including

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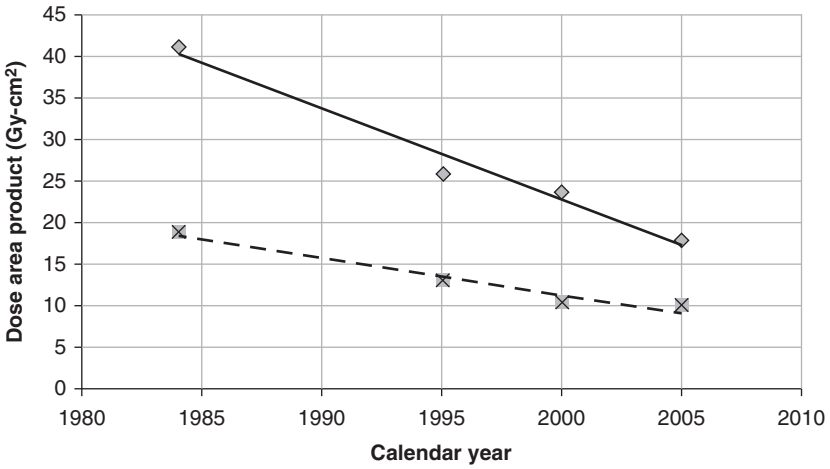


FIGURE 40.3. Mean dose area product (DAP) for UK fluoroscopy procedures (Gy-cm^2) from 1980–2005. DAP meters measure the radiation dose in air (i.e., entrance dose) over a specified area, typically Gy-cm^2; these devices are ionization chambers that cover an area larger than the X-ray beam. The upper line of diamond symbols represents barium enema examinations, whereas the lower line of "×" symbols represents barium meals. (Huda et al.).[2]

the introduction of large fields-of-view intensifiers with automatic dose control, pulsed fluoroscopy, last frame hold, and cumulative fluoroscopy times to minimize the dose area product.[22,23] Figure 40.3 demonstrates the ~50% reduction in radiation exposure from fluoroscopic examinations of the gastrointestinal tract (barium meals, barium enema) from 1980–2005 as measured by the mean dose area product (i.e., entrance dose delivered over an area, Gy-cm^2).

Using kerma-area-product (KAP) values as a measure of average X-ray beam intensity, radiation exposure during fluoroscopic examinations of the urological (cystogram, voiding cystourethrogram) and gastrointestinal (esophagram, upper GI, small bowel follow-through, barium enema) tracts is ~20 Gy-cm^2. Figure 40.4 displays KAP values for common gastrointestinal and urological studies at the Medical College of South Carolina.

Angiography

Angiography is a modified fluoroscopic procedure that requires the placement of catheters under fluoroscopic control. The amount of radiation absorbed by the patient is in the upper range of diagnostic tests because of the use of fluoroscopic placement and the utilization of large numbers of radiographs to demonstrate anatomy. The introduction of digital subtraction angiography and dose-saving features (last frame hold, shaped filters rotating and iris collimators, dose area product meters) reduced radiation exposure to patients and staff. The collimation of the X-ray beam to the specific area of interest (e.g., heart) reduces the exposure of the patient's other organs. The injection of the contrast media by pump during coronary angiography can significantly reduce the radiation exposure of the operator.

Interventional Radiology

Interventional radiology involves a wide range of procedures and potential for overexposure including embolization procedures, shunt creation, joint replacement, central venous catheter placement, hepatic/biliary and sclerotherapy interventions, and renal/visceral artery stent placement. There is large variation in radiation exposures between institutions. Pediatric interventional radiology exposure is particularly susceptible to overexposure because of the wide range of children's sizes, the complexity of the procedure, its duration, and the necessity to stand closer to the beam. In a study of 2,142 interventional radiology procedures at 12 fluoroscopic units in 7 US academic institutions, mean KAP for the 35 types of interventions was ~200 Gy-cm^2 with a range of mean values from 26 Gy-cm^2 (nephrostomy obstruction) to 560 Gy-cm^2 (arteriovenous malformation embolization spine).[24] The mean KAP value for 177 arteriovenous malformation embolizations in the head was 340 Gy-cm^2 (range, 4–1,350 Gy-cm^2). Nominal conversion factors can estimate the approximate effective radiation dose from KAP for radiographical and fluoroscopic (*but not CT*) procedures; however, using this conversion value and DAP (also known as KAP) does not substitute for the

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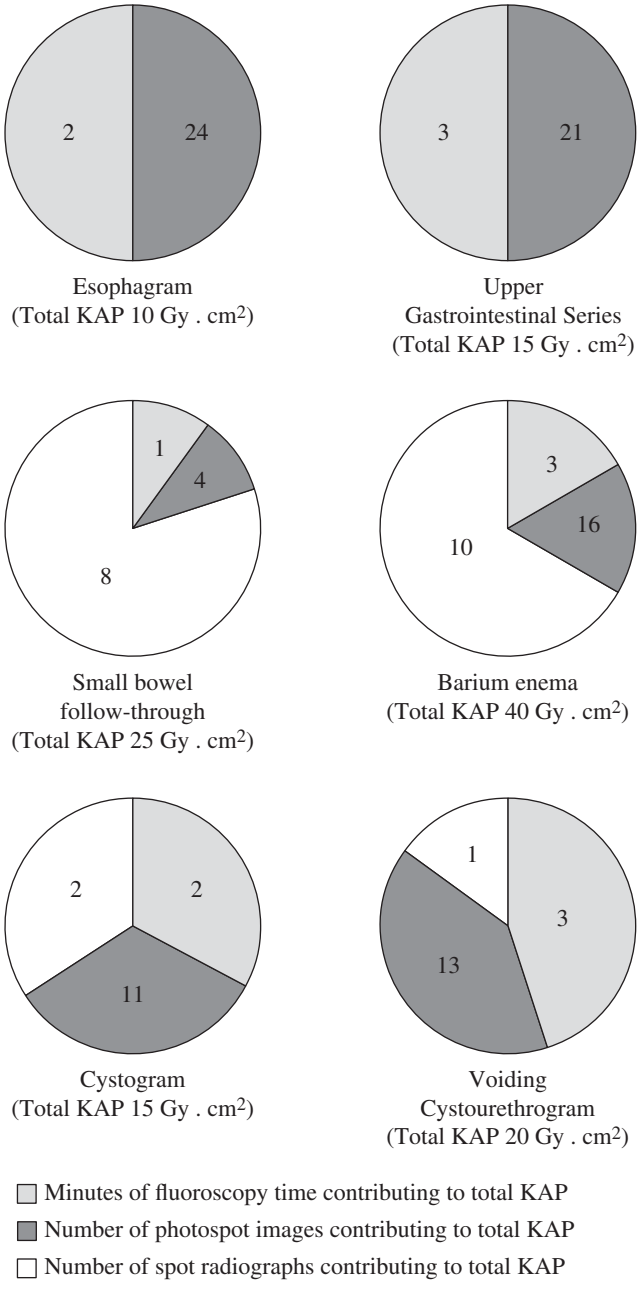


FIGURE 40.4. Percentage of total kerma-area-product (KAP) attributed to fluoroscopy time, photospot images, and spot radiographs during fluoroscopically-guided imaging of common gastrointestinal and urologic studies in normal-sized adults at the Medical College of South Carolina. The numbers within the circles represent the following: fluoroscopy time in minutes (shaded portion), total photospot images (dark portion), and total spot radiographs (clear portion). (Data from Huda).[14]

TABLE 40.3. Representative values for converting KAP to effective radiation dose for radiographic and fluoroscopic procedures on normal-sized adults. (Huda)[14]

Exposed Region – Projection	Conversion Factor (Effective Dose/KAP) (mSv/Gy-cm^2)
Head	0.03
Body – anteroposterior	0.25
Body – posteroanterior	0.15
Body – lateral	0.1

calculation of the effective dose. Table 40.3 displays representative conversion factors for normal-sized adults; these values do not apply to children or adults without normal-sized bodies.

Computed Tomography

Computed tomography (CT) links mechanically rotating detectors with the mathematical reconstruction of an image formed by a large number of small X-ray beams.[25] The scanning portion of CT incorporates an X-ray tube that includes a collimator to confine the X-ray beam to thin sections with an opposing detector that surrounds the patient. The X-ray tube irradiates a thin slice (1–10 mm) of tissue as it progresses around the patient. The distribution of energies in the polychromatic beam of X-ray photons ranges from 30–140 keV with the incident beam possessing a half-value layer up to 10–12 mm aluminum (80 keV effective energy).[26] In the 1970s, single detector CT scanners first appeared. The images were acquired in the axial plane as individual slices 8–13 mm thick; by 1975, reconstruction techniques using axial CT data allowed the construction of coronal and sagittal images. In the 1980s, 4-channel multidetector computed tomography (MDCT) scanners were introduced for commercial use. Since that time, improvements in CT scanner mechanics have resulted in faster X-ray gantry rotation and z-axis (cephalocaudal) movement, thinner collimation, and the development of electrocardiographic (ECG) gating.[27] Spatial resolution is the ability to discern two objects as separate, whereas temporal resolution is the length of time necessary to image an object. Seventh-generation 64–320 channel MDCT scanners now offer increased spatial and temporal resolution with gantry rotation times of 0.25 seconds and collimation as low as 0.24 mm. Cardiac studies account for a large majority of the collective radiation dose from nuclear medicine procedures. Electrocardiographic gating allows the acquisition of image data and image reconstruction at a specific time during the R–R

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interval. In prospective gating, the radiation source is active only during part (i.e., ~70–80%) of every other cardiac cycle; thus, the radiation dose is reduced. Using the kerma area product (KAP), typical KAP values for head CT are ~13 Gy-cm^2 and ~25 Gy-cm^2 for a body scan compared with ~1 Gy-cm^2 for head/chest radiographs, ~5 Gy-cm^2 for abdominal radiographs, and ~100 Gy-cm^2 for interventional procedures involving fluoroscopy.[28]

DOSE EFFECT

Absorbed dose is the measure of the amount of energy absorbed per unit of mass (i.e., tissue) within the radiation field measured in gray (Gy). The actual dose received by specific organs (i.e., organ dose) is the best measure of risk; calculation of this value is complex because the diagnostic beam exposes only a portion of the body; additionally, the tissues within the body attenuate the beam. The average *whole-body effective dose* measured in sievert (Sv) allows the standardization of the different risks of irradiating different organs by summing the organ dose equivalents and adjusting for tissue radiosensitivity (tissue weighting factors). Therefore, this measure permits a comparison of the estimated radiation dose between individuals. The effective dose approximates the true risk; however, substantial variation in individual doses occurs because of patient-specific factors (age, health, sex, habitus) and the difficulty estimating true radiation doses.

Adults

Figure 40.5 compares the estimated US annual per-capita effective radiation dose from various sources in 1980 (3.0 mSv) and 2006 (5.6 mSv).[29] The recent increase in medical radiation results primarily from the increased use of CT scanning, particularly in patients receiving relatively high annual radiation doses (>20 mSv).[1] In a retrospective analysis of medical records from 1996–2010 from six large integrated US health maintenance systems (1–2 million member-patients/year), the mean per capita effective dose increased from 1.2 mSv in 1996 to 2.3 mSv in 2010.[30] By 2010, 3.9% of the enrollees received annual radiation exposure exceeding 50 mSv (i.e., the US occupational limit). The utilization rates for radiography and angiography/fluoroscopy remained relatively stable during this 15-year period. Figure 40.6 displays the average contribution of various *artificial* radiation sources, including medical imaging procedures, to the overall annual US per-capita whole-body effective radiation dose during the mid-2000s; this estimate excludes natural radiation (e.g., radon, terrestrial, cosmic).

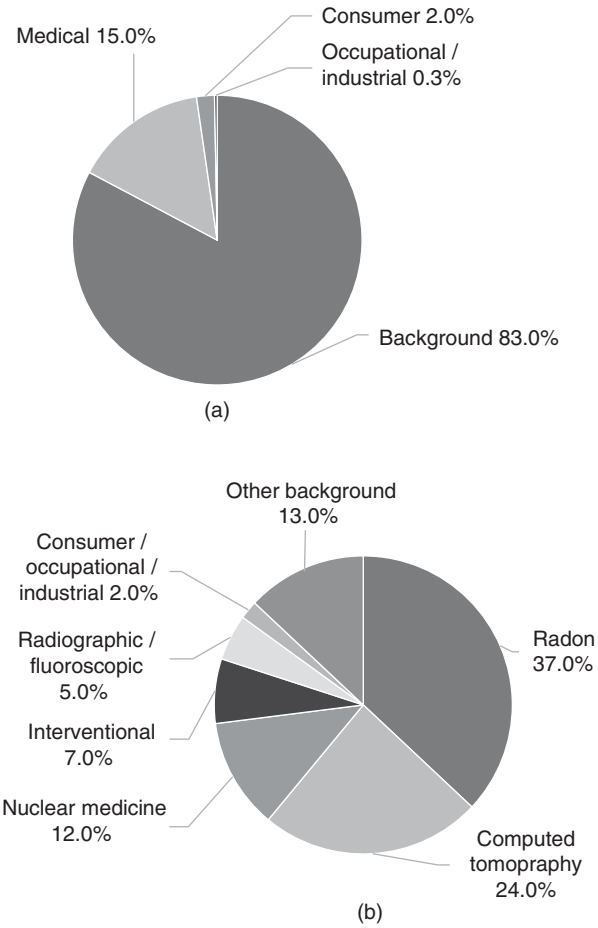


FIGURE 40.5. Annual US per-capita effective radiation dose from various sources for (a) 1980 and (b) 2006, demonstrating the increasing contribution of medical imaging to the annual effective radiation dose. (Modified from Hendee et al.).[29]

Table 40.4 displays average effective radiation doses (mSv) comparing the radiation doses of common diagnostic imaging procedures. The effective dose is a measure of the distribution of radiation in an organ when the distribution is not homogeneous (e.g., CT scans). This value multiplies the organ dose by a weighting factor specific to the anatomy of the organ scanned.

Although the radiation dose equivalent allows comparisons of different medical imaging examinations, the organ dose provides a better estimation of true risk. Organ doses are usually calculated from computer models or measured in anthropomorphic phantoms; changes in CT scanner design and operator characteristics cause variability in the results from these two methods.[31] A study of third-generation CT scanners during the early 1990s used thermoluminescent dosimeters to measure

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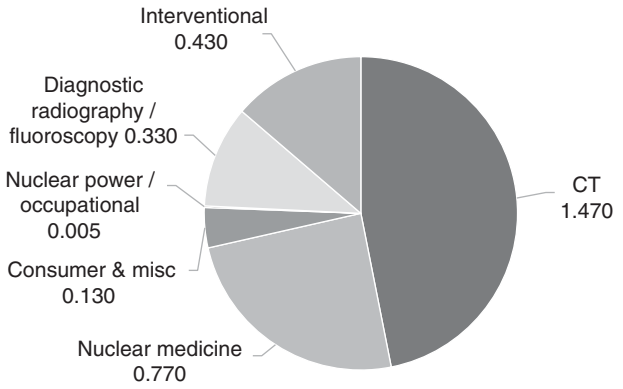


FIGURE 40.6. Annual US per-capita effective radiation dose from artificial (human) sources in 2006. Diagnostic radiography/fluoroscopy represents the portion of the effective radiation dose attributed to conventional (planar) X-rays and fluoroscopy. (Modified from Mettler et al.).[1]

TABLE 40.4. Typical effective radiation dose for common diagnostic imaging procedures using typical machine settings. The effective radiation dose allows a rough comparison between different CT and conventional radiographs, but these values are less accurate estimates of risk than the organ dose. The actual dose differs among individuals and institutions. (Adapted from Bardo et al.).[27]

Procedure	Effective Radiation Dose (mSv)
Chest X-ray	0.02
Mammogram	0.13
Brain CT	1–2
Chest CT	5–7
Coronary artery angiography (CCA)[a]	2–10
Coronary artery angiography – retrospective ECG-gating, 64 channel	10–15
Coronary artery angiography – prospective ECG-gating dose modulation (80 kV)	2–4
Coronary artery calcium electron beam CT	0.6
Coronary artery calcium CT – MDCT prospective ECG-gating	1–3
Rubidium PET stress test	4.9
Sestamibi SPECT nuclear stress test	12–23

[a] The estimated annual radiation dose of conventional CT coronary artery angiography: cardiologist, 0.1–5 mSv; nurse, 0.01–0.5 mSv.

free-in-air air kerma at the rotation axis of the CT gantry and anthropomorphic phantoms to simulate radiation exposure. The estimated mean organ doses for CT examinations of the trunk were the following: skin, 22–36 mGy; lungs, <1–18 mGy; kidneys, 7–24 mGy; and ovaries, <1–19 mGy.[32] Subsequently, newer techniques reduced the organ doses from CT scans. Table 40.5 compares the typical organ dose from several types of CT examinations using typical machine settings during the mid-2000s. The actual organ dose of an individual receiving a CT depends on multiple variables including patient size, operator characteristics, scanning parameters, and the type of scanner.

TABLE 40.5. Comparison of typical organ radiation doses for several radiological studies using common machine settings. The actual dose received by an individual depends on the scanner, operator characteristics, and study parameters. (Adapted from Brenner and Hall).[6]

Procedure	Organ	Organ Dose (mSv/mGy)[a]
Dental X-rays	Brain	0.005
Posterior-anterior Chest X-ray	Lung	0.01
Lateral chest X-ray	Lung	0.15
Screening mammography	Breast	3
Chest CT	Breast	21.4
Coronary angiography CT	Breast	51
Abdominal X-ray	Stomach	0.5
Barium enema	Colon	15
Abdominal CT (adult)	Stomach	10
Abdominal CT (adult)	Colon	4
Abdominal CT (neonate)	Stomach	20

[a] For X-ray radiation including CT scans, 1 mGy = 1 mSv. The organ dose is a more accurate measure of risk than the effective dose.

Conventional X-Rays

The radiation dose received by a patient from an X-ray machine is a complex summation of the number of projections, technical factors, anatomy, and position of the patient. Technical factors include proper collimation and filtration, orientation of the beam, leakage radiation, appropriate shielding, and machine parameters. Doses are concentration units (energy/unit mass) that do not allow the simple addition of doses following irradiation of different parts of the body.

The primary concern with radiation from medical imaging is its *potential* to increase cancer risks. Table 40.6 lists the equivalent number of chest X-rays and the equivalent length of exposure to cosmic radiation to accumulate the same effective radiation dose as absorbed during common radiographic procedures.

In children, conventional X-rays of the limbs, chest, and teeth account for ~70% of all X-ray examinations while contributing <2% of the overall population radiation dose.[33] The gonads of patients irradiated with plain X-rays receive small amounts of radiation (<10 μGy) when the X-ray beam is directed outside the abdominal area, including X-ray examinations of the chest, cervicothoracic spine, head, and upper extremities.

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TABLE 40.6. Relative comparison of typical estimated effective dose (effective dose equivalents) of various medical imaging examinations with: 1) the number of single conventional PA chest X-rays required to accumulate an equivalent radiation dose; and 2) the number of daily exposures to cosmic radiation necessary to accumulate the same radiation dose (assuming an annual cosmic radiation dose of 2.4 mSv). Some variability exists in the estimated effective radiation dose for radiographical examinations between this table, Table 40.4, and other sources in the medical literature because of differences in assumptions about the techniques. (Mazrani et al.).[33]

Examination	Typical Effective Dose (mSv)	Equivalent Chest X-rays (number)	Equivalent Length of Cosmic Radiation (days)
Skull X-ray	0.7	3.5	11
CT head	2.3	115	365
PET head scan (F-18 FDG)[a]	5	250	840
Thyroid scan[b]	1	50	183
Single PA chest X-ray	0.02	1	3
CT chest	8	400	1,314
Abdomen X-ray	1.0	50	183
Pelvis X-ray	0.7	35	122
CT abdomen or pelvis	10	500	1,643
Barium meal	3	150	488
Intravenous urogram	2.5	125	427
Kidney scan[b]	1	50	183
Hip X-ray	0.3	15	49
Lumber spine	1.3	65	213
Limb/joint X-rays[c]	<0.01	<0.5	<1.5
Bone scan[b]	4	200	657

[a] Fluorodeoxyglucose positron emission tomography (^{18}F-PET radionuclide) scan. [b] ^{99m}Technetium radionuclide study. [c] Except hip.

The estimated effective dose for lithotripsy depends on fluoroscopy time, the number of spot films, and the entrance skin doses (ESDs). The estimated effective dose in 125 patients undergoing lithotripsy using a Siemens Lithostar system was 0.75 mSv based on calculations from radiation exposure techniques (kVp, field size, number of exposures/projections) and phantom-based radiation dose measurements.[34] The estimated effective dose in the medical literature for lithotripsy varied up to 1.63 mSv in a study of 50 patients with mean fluoroscopy times of 204 seconds (range: 90–372 seconds), mean ESD for oblique projection of 76.5 mGy (range: 14–200 mGy), and mean ESD for PA projection of 44.5 mGy (range: 8–115 mGy).[35]

Computerized Tomography

CT scanning delivers substantially more radiation to the patient than conventional X-rays (e.g., PA chest, AP abdomen); the radiation exposure is usually substantially higher for single body CT scans than single head CT scans. The introduction of CT scanning has significantly impacted the per capita radiation dose from medical procedures, as displayed in Figure 40.5. Although computed tomography (CT) accounts for ~9% of all radiological examinations, the estimated portion of the total medical radiation dose for CT is ~47%.[33] By the early 2020s, CT usage increased over 30% compared with the late 2000s.

Effective Radiation Dose

The effective (radiation) dose reflects the dose and differences in the radiosensitivity of various organs and regions of the body; this value correlates to the risk of the uneven exposure delivered by a CT scan, calculated as an equivalent uniform whole-body dose.[36] Over the last several decades, the average effective radiation dose has decreased below 10 mSv with some cardiac and pediatric CT scans routinely delivering effective doses of <1 mSv.[37] The typical adult effective doses of a single head CT scan is ~1–2 mSv compared with 5–10 mSv for a single body CT scan (chest, abdomen/pelvis) and ~20 mSv (range, 12–31 mSv) for cardiac 64-detector CT angiography.[38,39] However, radiation doses for specific CT studies may vary >10-fold between institutions as a result of differences in scanner design and examination protocols.[40] The variation in dose reflected different types of CT examinations.

Newer radiation techniques account for some reductions in radiation doses from radiological procedures. In a study of the medical literature for reported and calculated effective radiation doses, the radiation from noncardiac (head, chest, abdominal) CT scans was significantly higher ($P < 0.05$) in 1991–1995 than

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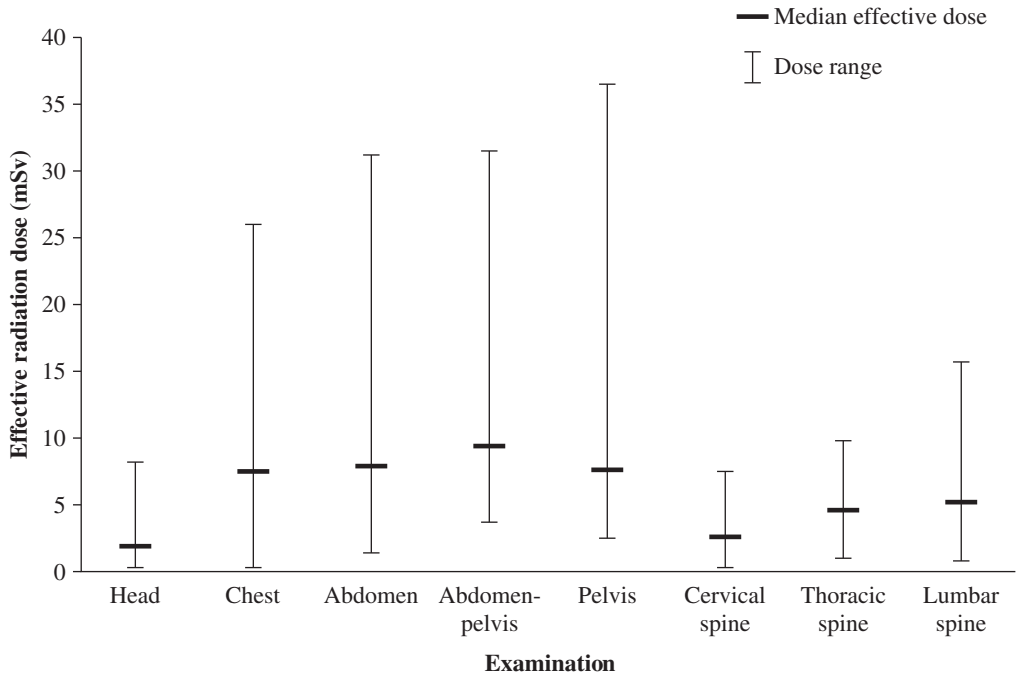


FIGURE 40.7. Reported median and range of effective radiation doses (mSv) for non-cardiac CT scans of adults in the Pantos et al. study of the medical literature, 1991–2009. (Data from Pantos et al.).[41]

in 1996–2009; the radiation doses after 1996–2009 remained statistically similar.[41] An analysis of low-dose CT radiation dose levels for 12,529 patients undergoing lung cancer screening CT scans at 72 institutions from 2016–2017 reported a median effective dose of 1 mSv (IQR: 0.7–1.4 mSv).[42] As noted in Figure 40.7, the range of effective doses received by adults during CT scanning varies widely between different institutions and commercial scanners; this variability results from differences in scanner design and examination protocols. Widespread clinical use of coronary CT angiography began in 2004 with the introduction of 64-slice multidetector scanners that delivered ~16 mSv (range, 9–21) without current modulation.[43] Since that time, new dose reduction protocols involving ECG-based tube current modulation, high-pitch spiral scanning, lower peak tube voltage, prospective or axial scanning, and iterative CT data reconstruction have reduced radiation doses from some scans to ≤1 mSv (high-pitch spiral scan).

Patient habitus affects the effective radiation dose. Obese patients typically receive greater radiation doses than patients with normal BMI from the increased dose necessary to reduce image noise and produce acceptable images. A study of 91 CT scans of the body compared the organ dose and $CTDI_{vol}$ (integrated radiation dose from acquiring a single scan divided by the total nominal scan width or beam collimation) received by patients weighing 60–100 kg when the radiation exposure was determined by the dose required to produce a constant level of image noise.[44] The organ dose to the liver varied 2-fold, whereas the $CTDI_{vol}$ varied 3-fold. Effective doses may exceed 100 mSv in extremely obese patients undergoing radiographical examination of their abdomen.[45]

CT coronary angiography is a noninvasive diagnostic modality to detect the presence of coronary atherosclerosis. The use of ECG-gating improves temporal resolution and minimizes imaging artifacts caused by cardiac motion while reducing the radiation dose by delivering the majority of the radiation dose during the passive filling of the ventricles (diastole).[46]

CT Dose Index (CTDI)

The CT dose index (CTDI, mGy) represents the average absorbed dose along the *z*-axis from a series of contiguous exposures calculated by dividing the integrated absorbed dose from one axial CT scan (i.e., one rotation of the X-ray tube) by the total beam width. The CTDI theoretically estimates the average absorbed radiation dose only in the irradiated volume independent of the scan length; however, the radiation dose in this volume varies slightly to moderately across the field of view. A weighted average of the CT dose index ($CTDI_w$) measured at the center and periphery of dose phantoms provides a convenient single number estimate of patient dose for a procedure; this value

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accounts for the nonuniform radiation dose inside the irradiated tissue. The $CTDI_w$ or a related indicator, $CTDI_{vol}$, is usually displayed on the operator's console.[47] The $CTDI_{vol}$ spreads the dose corresponding to the $CTDI_w$ over a specified length of the z-axis. This value is the best measure of the average radiation dose at a point within the scan volume for a particular scan protocol.[8] The $CTDI_w$ is a convenient indicator of scanner radiation output for a specific tube current-exposure time product (mAs) and tube voltage (kVp). The $CTDI_w$ represents the average absorbed radiation dose over the x–y directions, whereas the $CTDI_{vol}$ represents the average absorbed radiation dose over the x–y–z directions with z direction parallel to the table feed. Figure 40.8 lists the estimated median and range of the $CTDI_w$ in a study of values for noncardiac CT scans reported in the medical literature from 1991–2009.

CT dose index (CTDI) is difficult to measure in the patient. Although the CTDI is a useful quality control measure, this measurement is only indirectly correlated to organ dose (i.e., the distribution of effective radiation dose in an organ) and cancer risks. Displayed $CTDI_{vol}$ (volume CT dose index) represents the radiation **dose** over a volume in a plastic phantom rather than the actual **dose** delivered to the patient; the latter value depends on the size of the patient among other variables.[48] These values allow users to compare estimated radiation doses for each CT examination. In a study of 636 patients by the International Atomic Energy Agency, the average ($CTDI_{vol}$) was 39 mGy for head CT scan compared with 9.3 mGy for chest CT scan and 10.4 mGy for abdominal CT scan.[49] In a study of 199,656 consecutive CT examinations in 83,181 adults and 3,871 consecutive CT examinations in 2,609 children at 5 of the University of California medical centers during 2013, the average values for children were ~50% of adult head CT scans and ~25% of adult body CT scans.[50] Figure 40.9 compares the median and interquartile ranges for $CTDI_{vol}$, dose length product, and effective doses for adults during common CT scans at these institutions.

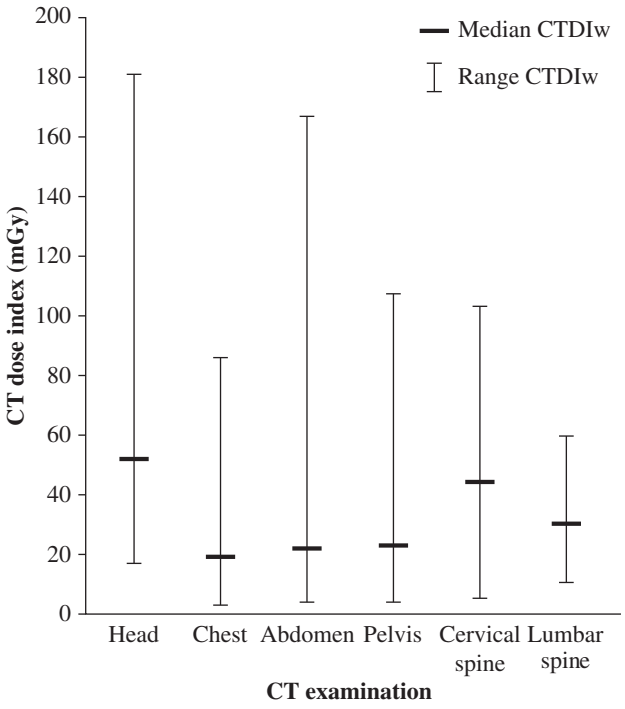


FIGURE 40.8. Reported median and range of CT dose index ($CTDI_w$, mGy) for non-cardiac CT scans of adults in the Pantos et al. study of the medical literature, 1991–2009. (Data from Pantos et al.).[41]

Size-specific dose estimates (SSDEs) are available on the American Association of Physicists in Medicine website (https://www.aapm.org/pubs/reports/rpt_204.pdf), where the report provides correction factors for the $CTDI_{vol}$ values for CT body scans for the entire range of patients (newborns to adults).[51] The SSDE is the correction factor multiplied by the $CTDI_{vol}$. This value is an estimate of the radiation dose in the soft tissues of the irradiated scan volume within ~20% when the CTDI phantom used for the displayed $CTDI_{vol}$ is known.[51]

Dose Length Product (DLP)

The displayed $CTDI_{vol}$ (volume CT dose index) on the CT scanner is an estimate of the average radiation dose in the cross-sectional area of the cylinder in a phantom rather than a direct measurement in the patient. Consequently, the $CTDI_{vol}$ does not account for size differences or other patient-specific factors. The radiation risk more closely correlates to the actual amount of radiation (energy) transferred to the patient. The dose length product (mGy-cm) is the product of the z-axis length and the $CTDI_{vol}$ (integrated radiation dose from acquiring a single scan divided by the total nominal scan width or beam collimation), as displayed in Equation 40.2. Although the DLP correlates to the total radiation dose, this parameter is not a substitute for the effective radiation dose because the DLP does not account for the radiosensitivity of the organs in the irradiated tissues as the effective radiation dose does.

$$\text{Dose length product (DLP)} = CTDI_{vol} \times \text{length of } z\text{-axis } (L) \quad \text{(Equation 40.2)}$$

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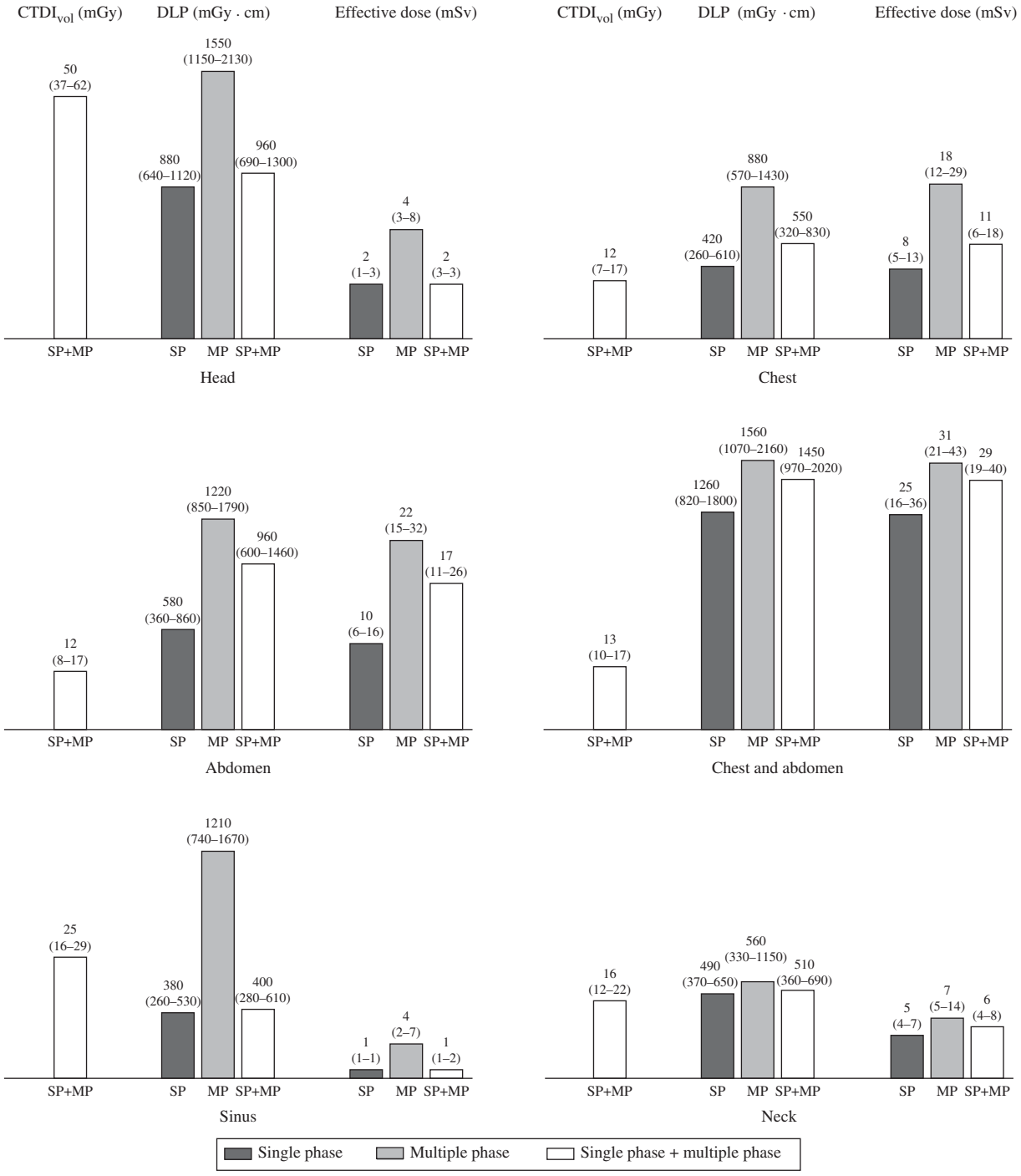


FIGURE 40.9. 2013 CT radiation doses ($CTDI_{vol}$, dose length product, effective dose) for adults at five University of California medical centers. $CTDI_{vol}$ includes adjusted estimates of the $CDTI_{vol}$ called the size-specific dose estimates (The number above the bar represents the median dose, and the numbers in parentheses are the interquartile range of doses). (Data from Smith-Bindman et al.).[50]

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TABLE 40.7. Estimated median and range of Dose Length Product (DLP) (mGy-cm) for noncardiac CT scans in a study of the medical literature from 1991–2009. (Data from Pantos et al.).[41]

CT Examination	Median DLP (mGy-cm)	Range DLP (mGy-cm)
Head	733	81–2,173
Chest	394	21–2,286
Abdomen	464	58–2,537
Pelvis	434	67–2,000
Abdomen/pelvis	472	430–1,850
Cervical spine	324	56–1,275
Thoracic spine	253	66–515
Lumbar spine	302	49–870

The effective dose can be calculated from the DPL on the CT scanner by using a conversion factor k (mSv/mGy-cm), as displayed in Equation 40.3. This conversion factor varies with several factors including X-ray tube voltage, age/size of the patient, body region, and CTDI phantom (10 cm, 16 cm, 32 cm diameter) used to calculate the DLP displayed on the scanner. Effective doses for different body regions derived from Monte Carlo calculations may differ from the values derived from the dose length product (DLP), depending on the source of the conversion factors:[52]

$$\text{Effective dose } (E) = \text{DLP} \times k \qquad \text{(Equation 40.3)}$$

where

k = conversion factor (mSv/mGy-cm).

In a study of 636 participants in the International Atomic Energy Agency Research Coordination Project, the average dose length product was 544 mGy/cm for head CT scans compared with 348 mGy-cm for chest CT scans and 549 mGy-cm for abdominal CT scans.[49] Table 40.7 lists the estimated median and range of the DLP in a study of values for noncardiac CT scans reported in the medical literature from 1991–2009. The data indicate substantial variation in the DLP between medical institutions.

Children

Pediatric CT scans account for ~10% of the total number of CT examinations. The effective and organ doses depend on the patient's size and organ mass because the smaller size of younger children increases the average organ effective dose in the irradiated region.[53] A neonate may receive a radiation dose for a single CT scan that is over double the amount received by an adult, depending on the scanner settings.[6] The effective dose also varies substantially between different studies and institutions. The calculated effective dose ranged from 0.03–69.2 mSv in a retrospective observational study of 744 pediatric CT scans performed on children <15 years at 7 large US HMO organization from 2001–2011.[54] The effective dose exceeded 20 mSv in 14–25% of abdomen/pelvis CT scans, 6–14% of spine CT scans, and 3–8% of chest CT scans. In a study of infants under 2 years of age, the average effective dose for head CT scans was 7.6 ± 3.1 mSv compared with 1.3 ± 0.1 mSv for adults. The effective doses in body CT scans can be 2-fold greater in children and 4-fold greater for newborns than adults. In a study of patients undergoing abdominal CT scans, the mean effective dose for children (≤10 years) was 6.1 ± 1.4 mSv compared with 4.4 ± 1.0 mSv for young adults (11–18 years) and 3.9 ± 1.1 mSv for adults (>18 years).[55] The median (interquartile range) of effective radiation doses in 3,871 pediatric CT scans during the large University of California study were reported for the following body regions: head, 2 mSv (1–4 mSv); chest, 3 mSv (2–5 mSv); abdomen, 4 mSv (3–7 mSv); chest/abdomen, 9 mSv (5–15 mSv); sinus, 1 mSv (1–2 mSv); and neck, 4 mSv (2–6 mSv).[50] Recently, CT usage decreased in pediatric patients in favor of ultrasound and MRI imaging.

CT scanning accounts for a relatively large portion of the average radiation dose from medical procedures compared with the number of CT examinations. Organs in the direct beam receive the highest dose of radiation.[56] In a UK survey during the early 1990s, an abdominal CT delivered more radiation than a barium enema and ~8 times the effective radiation dose from a conventional abdominal X-ray examination.[57] In this survey, the average delivered dose for head CT was 3–4 mSv (range 1–10 mSv) and 8.8 mSv for abdominal CT. New techniques reduce the effective radiation dose of relatively high-radiation procedures (e.g., multislice cardiac computed tomography angiography). In a collaborative radiation dose-reduction program, the median effective dose for cardiac computed tomography decreased from 21 mSv (IQR, 12–26 mSv) to 10 mSv (IQR, 6–16 mSv).[58] A study of CT scans on 100 consecutive pediatric neurosurgical patients ($\text{Mean}_{\text{age}} = 6.75$ years) during the late 1980s indicated the average ocular lens dose from a CT scan was 42 mGy with a cumulated dose ranging from 0–1.43 Gy ($\text{Mean}_{\text{scans}} = 7.75$, range 0–34).[59]

Conceptus

The dose to the conceptus (i.e., embryo/fetus from time of conception to birth) depends on the particular

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TABLE 40.8. Typical radiation doses to the conceptus (embryo/fetus) for selected medical procedures. The dose to the organ studied is usually substantially higher than the conceptus dose. (Adapted from McCullough[26] and Brent[60]).

Procedure	Description (Radiopharmaceutical, Activity)	Conceptus Dose (mGy)
Conventional radiography	Skull	<0.01
	Chest	<0.1
	Mammography	<0.1
	Thoracic spine	<0.01
	Lumbar spine	1–2
	Abdomen	1–3
	Pelvis	0.1–1.1
Fluoroscopy	Upper GI	7
	Barium enema	7–8
CT	Brain	<0.1
	Chest – routine	0.2
	Chest – pulmonary embolism	0.2
	Chest – coronary angiogram	0.1–1
	Chest/pelvis aortogram	34
	Abdomen – routine	4
	Abdomen/pelvis – routine	25
	Abdomen/pelvis – stone protocol[a]	10
	Pelvis	10–32
Nuclear medicine	Brain scan (^{99m}Tc-MDP)	<0.1
	Cerebral blood flow (^{99m}Tc-HMPAO, 740 MBq)	3–6.7
	Lung-ventilation (^{133}Xe, 740 MBq)	0.02–0.3
	Lung-perfusion (^{99m}Tc-MMA, 148 MBq)	0.4–0.7
	Myocardial perfusion (^{99m}Tc-sestamibi, 1,110 MBq)	5–6
	Renal scan (^{99m}Tc-MAG3, 370 MBq)	1.9–6.7
	Bone scan (^{99m}Tc-MDP, 740 MBq)	1.5–4.4
	Positron-emission tomography (PET) scan (^{18}F-FDB, 740 MBq)	13–16
Radiotherapy	Cancer therapy – 5% uptake (^{131}I, 3,700 MBq)	66–1,000
	Benign therapy – 50% uptake (^{131}I, 555 MBq)	40–150

Abbreviations: FDG = fluorodeoxyglucose; HMPAO = hexamethylpropylene amine oxime; MAA = macroaggregated albumin; MAG3 = mercaptoacetyltriglycine; MDP = methylene diphosphonate.

[a] Anatomical coverage is the same as for routine abdominopelvic CT, but the tube current is decreased and the pitch is increased because standard image quality is not necessary for the detection of high-contrast stones.

radiographical examination, technical factors (time, photon energy, intensity), number/type of projections, and maternal anatomy (abdominal thickness, uterine location/size/orientation, urinary bladder volume). Table 40.8 displays typical radiation doses to the conceptus (embryo/fetus) for selected medical procedures; the conceptus dose is typically substantially less than the maternal whole-body dose because the tissues between the maternal skin and the conceptus attenuate the radiation dose. The conceptus dose during fluoroscopy-guided interventional procedures, some CT scans, and radiotherapy frequently is much higher than during conventional radiographical examination; a qualified expert typically should evaluate the conceptus dose during these examinations.

During the first 2 months of pregnancy, the conceptus dose is equivalent to the maternal uterine dose. As the pregnancy advances, the conceptus dose becomes less uniform, requiring correction factors to convert the maternal uterine dose to the conceptus dose.[61] The *potential* effects of ionizing radiation exposure on the embryo or fetus involve deterministic and stochastic effects including growth retardation, congenital malformations, miscarriage, and cancer (primarily leukemia). The risk of these adverse effects is related to the *in utero* dose and the developmental period during the time of radiation; a threshold may exist for

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the deterministic effects. Case reports involving older therapeutic procedures suggest that large doses of fetal radiation (e.g., 888 rads during the sixth month of gestation) during the less radiosensitive second and third trimesters do not always produce fetal abnormalities.[62] The maternal tissue attenuates the energy of X-ray photons; subsequently, the fetus receives ~20% of the radiation dose absorbed by the skin on the maternal abdomen.[63] The risk of developing fetal abnormalities following *in utero* radiation doses after single diagnostic procedures (<50–100 mGy) is small compared with the other risks during pregnancy.[64] Fluoroscopic procedures deliver much higher radiation doses (i.e., 50 mGy/minute to the maternal abdomen equates to ~10 mGy/minute to the fetus) than conventional X-rays; consequently, the potential risk to the developing fetus is greater during fluoroscopy than conventional X-ray examinations. The dose absorbed by the fetus depends on the direction of the X-ray beam. The contribution of conventional X-rays (e.g., skull, neck, chest, and extremities) directed more than 10 cm from the fetal area is minimal.[65] Most diagnostic radiation procedures deliver a fetal absorbed dose of <1 mGy for imaging beyond the abdomen/pelvis and <10 mGy for direct scans or nuclear medicine imaging.[66] CT scans deliver higher fetal doses. Directing the X-ray beam directly on the embryo during abdominal CT scanning of pregnant patients results in radiation doses in the embryo of 10–35 mGy.[67]

The use of fluoroscopically or CT-guided interventional procedures in the pelvis potentially increases the risk of teratogenesis because the delivered dose may exceed the teratogenic threshold of >100 mGy, depending on the procedure.[68] All such procedures should be optimized to limit the radiation dose to the minimum amount necessary to achieve the clinical purpose of the procedure given the available technology and resources. Guidelines are available from American and European interventional radiology associations to control the radiation dose to the mother and conceptus.[68] Interventional procedures in anatomical regions remote from the conceptus (e.g., skull, chest, extremities) are typically performed safely at any time during pregnancy with proper collimation.[67] Table 40.9 lists typical and reported ranges for the conceptus radiation doses from common interventional procedures.

The most common indications for CT imaging during pregnancy are maternal trauma resulting in

TABLE 40.9. Typical and reported ranges of conceptus radiation doses from common fluoroscopic and angiographic procedures. (Adapted from Dauer et al.).[68]

Examination	Typical Estimate (mGy)	Reported Range (mGy)
Cerebral angiography (4-vessel)	0.06	
Cardiac catheter ablation		
First trimester	0.15	0.04–0.20
Second trimester	0.3	
Third trimester	0.6	
Pulmonary angiography for embolism		
First trimester	0.02	0.006–0.05
Second trimester	0.09	0.022–0.26
Third trimester	0.46	0.278–0.86
Cholecystography/cholangiography	1	0.05–16.0
Hysterosalpingography	10	2.7–92
Barium enema	10	0.28–130
Barium meal (upper GI)	1.5	0.1–5.8
Small bowel study	7	
CT aorta angiography	34	
CT low-dose nephrostomy	0.1	0.094–0.16
Uterine fibroid embolization	42	
Varicocele embolization	15.8	
Transurethral stent	44	
Ureteral stent		
Antegrade	2.5	
Retrograde	0.4	0.03–0.79
Nephrostomy	1.1	
Intravenous pyelogram		1.8–12.6
Unenhanced CT kidneys, ureters, bladder	17.7	
Endoscopic retrograde cholangiopancreatography	3.1	0.01–55.9

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a positive Focused Assessment with Sonography in Trauma (FAST) examination and suspected pulmonary embolism.[69,70] In general, fetal radiation from maternal CT of the head, neck, and extremities excluding the hips is minimal, whereas the fetal radiation dose becomes more concerning when the fetus is in the field of view.[71]

CLINICAL RESPONSE

Postcontrast Acute Kidney Injury

Postcontrast acute kidney injury (contrast-associated or contrast-induced nephropathy) is a reduction of renal function usually occurring within 48–72 hours after the administration of iodinated contrast medium during medical imaging procedures. Typically, an increase in serum creatinine of 0.3–0.5 mg/dL or 25% of baseline serum creatinine values within 2–5 days following contrast-enhanced computed tomography, coronary angiography, or percutaneous coronary procedures defines this complication. The decline in kidney function is typically reversible. The incidence ranges from ~1–20% depending on the population studied, the outcome measure of postcontrast acute kidney injury, and the type of contrast administered with the incidence in the lower range using current precautions.[72] Suggested risk factors for postcontrast acute kidney injury include diabetes, heart failure, hepatic failure, preexisting renal disease, advanced age, and multiple myeloma (hypercalcemia); however, the issue of whether contrast-associated acute kidney injury is a cause or a biomarker of adverse renal outcomes remains unclear.[73] The risk of acute renal injury in patients without these potential risk factors is not well defined; recent studies suggest these risks may have been overestimated.[74] Residual confounding and indication bias complicate the interpretation of epidemiology studies on postcontrast acute kidney injury with recent studies suggesting little evidence of reduced kidney function after intravenous contrast for CT pulmonary angiograms in emergency settings. Potential pathological mechanisms involve direct cytotoxicity to tubular epithelial cells, renal vasoconstriction/tissue hypoxia secondary to vasomotor changes, increased oxidative stress, and blood hyperviscosity.

Potential risk factors for postcontrast acute kidney injury include severe chronic kidney disease, high-osmolality contrast, repeated contrast administration within 3 days, and ST-segment elevated myocardial infarction. A meta-analysis of 28 observational, primarily retrospective studies did not detect a statistically significant difference between noncontrast and contrast-enhanced CT for the development of acute kidney injury (OR = 0.94, 95% CI: 0.83–1.07) or the necessity for postcontrast renal replacement therapy.[75] Only 1 of the 28 studies involved the use of high-osmolar contrast agents. A retrospective, propensity-matched, case-control study did not detect a statistically significant difference in the incidence of subsequent acute kidney injury between 7,201 patients undergoing contrast-enhanced CT and controls (5,499 patients undergoing unenhanced CT; 5,234 ED patients without imaging) after adjustment for patient demographics and risk factors.[76] The rate of later acute renal injury in these three groups ranged from 10.2–10.9%. The development of postcontrast acute kidney injury after contrast-enhanced radiographic studies correlates to the administration of large volumes of high osmolality contrast medium to patients with significant preexisting kidney disease. The most important mitigating factor is IV hydration (1–1.5 mL isotonic saline/kg/hour) up to 6–12 hours before and 4–12 hours up to 24 hours after the procedure. A shorter protocol (1–3 hours before and 6 hours after the procedure) may be more practical for urgent situations.[77] The volume of intravenous fluid required to prevent acute kidney injury in patients undergoing contrast-enhanced imaging is not well defined. The withdrawal of medications that reduce renal function (e.g., angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, diuretics, nonsteroidal anti-inflammatory drugs) was recommended. Evidence for the efficacy of other methods to reduce postcontrast acute kidney injury is insufficient. Isotonic sodium bicarbonate probably provides little benefit compared with isotonic saline, whereas acetylcysteine and statins are not routinely recommended for the prevention of postcontrast kidney injury.[74]

Deterministic Effects (Tissue Reactions)

Deterministic effects (near term, tissue reactions) involve the consequences of radiation-induced cell death (e.g., skin erythema/ulceration, acute radiation sickness), whereas stochastic effects involve cell damage (e.g., cancer, heritable effects). Potential deterministic effects (tissue reactions) for the developing embryo/fetus include miscarriage, stillbirth, growth retardation, microcephaly, mental retardation, neurobehavioral abnormalities, reduced intelligence (IQ), seizure disorders, and congenital malformations. For deterministic effects, the severity and incidence of the effects increase with dose, whereas the incidence of stochastic effects also increases with dose, but the

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radiation dose does not correlate to the severity or magnitude of the effect. The radiation dose from diagnostic X-ray procedures is small compared with radiation doses necessary to produce acute radiation effects; the whole-body radiation dose (i.e., 1–2 Gy) associated with the development of mild-moderate acute radiation sickness including nausea and vomiting is ~50,000–100,000 higher than a single PA chest X-ray (0.02 mSv). The main concern regarding deterministic effects from medical imaging involves skin damage from interventional procedures, particularly complex fluoroscopy-guided interventional procedures requiring long fluoroscopy times to acquire numerous images. Some studies suggest that exposure to thyroid radiation doses of 400–800 mGy during the first trimester may cause a slight reduction in birth weight.[78] Prolonged fluoroscopic imaging during procedures may cause radiation-induced skin injuries in the patient. Threshold doses for the development of skin injuries depend on several factors (i.e., age, fractionation of dose, area of skin); typical threshold entrance radiation doses include ~3 Gy for temporary epilation, ~6 Gy for erythema, and ~15–20 Gy for moist desquamation, ulceration, and dermal necrosis.[79]

Carcinogenesis

Childhood cancers represent <1% of total cancer occurrence with leukemias, brain tumors, and lymphomas representing ~70% of pediatric cancers.[80] Most epidemiology studies on *in utero*/early childhood cancer risks are case-control designed; statistical limitations of these epidemiology studies (rare diseases/low power, recall/reporting bias from questionnaire/interview data) create uncertainty over small changes in leukemia incidence following low-dose ionizing radiation exposure.[81] The detection of the leukemogenic effects following exposure to 100 mGy based on BEIR III data requires a control and an irradiated population size of 160,000.[82] The cohort size increases to 8 million following exposure to 10 mGy. Selection bias, racial differences in health experience, limited animal evidence of low-dose carcinogenic effects, and the limited low-dose data from Hiroshima and Nagasaki complicate the interpretation of data regarding the association between threshold radiation doses from diagnostic X-rays and leukemia risk.[83,84,85] Analysis of Japanese atomic bomb data indicates the lifetime risk of cancer may be considerably lower following *in utero* radiation exposure than in early childhood.[86]

Leukemia

In Utero Exposure

The association between diagnostic X-rays and childhood leukemia following *in utero* exposure is strongest for studies from the 1970s and 1980s, whereas the inclusion of later studies (i.e., with smaller radiation doses <100 mSv) reduces the risks to borderline or not statistically significant.[87,88,89] The current evidence for an association between maternal diagnostic X-rays prior to conception and a subsequent increase in the incidence of leukemia is minimal, whereas studies of *in utero* diagnostic X-ray exposure before the 1970s suggest a small increase in the leukemia incidence in these children. Case-control studies of 8,513 offspring of pregnant women receiving estimated antenatal radiation doses of 10–100 mGy during pelvimetry in the 1950s and 1960s (Oxford Survey of Childhood Cancers) indicated the relative risk of death from leukemia in these children increased by a factor up to 1.5–2.0, especially following self-reported *in utero* irradiation during the first trimester.[90,91] The risk of cancer decreased later in the study as the fetal dose from pelvic X-rays decreased; however, the risks of leukemia-related mortality in these children were relatively uniform across all tumors including both radiosensitive and radioresistant tumors. Cases were based on the recall of abdominal radiographs by the mothers during pregnancy; the actual effective radiation doses were not quantitated.[92] In a review of medical records of >32,000 twins born between 1930–1969, 31 cases of cancer including leukemia were matched with 4 twin controls based on sex, year of birth, and race. Only low birth weight was associated with an increased incidence of cancer.[93] After adjusting for low birth weight, the relative risk of cancer in the twins was marginally increased (RR = 2.4; 95% CI: 1.0–5.9). The increased leukemia incidence following *in utero* radiation occurred almost exclusively in children born to mothers with previous abortions. Other case-control studies[94] and negative studies with limited statistical power[95] suggest the actual increased childhood leukemia risk is near 1.4.[96]

The current effective radiation doses delivered by obstetric X-rays have decreased significantly compared with X-ray examinations before 1995. Acute lymphoblastic leukemia (ALL) is the most common childhood cancer in developed countries, with most cases diagnosed prior to 5 years of age. A case-control study of 389 cases of ALL and 876 frequency-matched controls conducted from 2003–2006 did not detect evidence of an increased ALL risk in fetuses receiving *in utero* radiation exposure from maternal abdominal or pelvic X-rays after adjustment for study matching

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factors and potential confounders using unconditional logistic regression.[97] The odds ratio for ALL following any diagnostic X-rays (i.e., plain X-ray, CT scan, intravenous pyelogram, barium study) during pregnancy was 0.46 (95% CI: 0.15–1.40).

Paternal Exposure

Evidence on leukemia risks of paternal diagnostic X-rays prior to conception is equivocal. A preliminary review of the Oxford Study data on childhood cancer and paternal exposure does not demonstrate *paternal* radiation exposure was a significant factor in the development of childhood cancer; the association between postnatal exposure to medical diagnostic radiation and childhood leukemia remains inconsistent.[87,98] The Children's Cancer Group study did not detect elevated risks of childhood ALL following maternal (OR = 0.9, 95% CI: 0.8–1.2) or paternal (OR = 1.1, 95% CI: 0.8–1.4) self-reported radiation exposure from lower abdominal preconception diagnostic X-rays.[10] A meta-analysis of paternal radiation exposure from abdominal X-rays prior to conception did not detect a statistically significant elevated risk of leukemia in offspring with a pooled OR of 1.17 (95% CI: 0.92–1.48).[97] The study suggested >1 paternal abdominal X-ray (OR = 1.47, 95% CI: 0.98–2.21; $n = 46$) or paternal intravenous pyelogram may increase ALL risk (OR = 3.56, 95% CI: 1.59–7.98; $n = 16$).

Postnatal Exposure

The Japanese atomic bomb survivor data indicate that young children are more sensitive to the development of radiation-induced leukemia than adults, with the risk increasing within a few years after exposure. Acute lymphoblastic leukemia is the most common type of childhood cancer in developed countries; the evidence from case-control studies for an association between childhood leukemia and postnatal exposure to medical diagnostic irradiation is equivocal and conflicting. Epidemiology studies of healthy infants receiving radiation for enlargement of the thymus and scalp radiation for *Tinea capitis* suggest an increased incidence of leukemia, whereas studies of infants irradiated for skin hemangiomas did not clearly detect a raised childhood leukemia risk, despite radiation doses near the level producing childhood leukemia in the LSS study of Japanese survivors.[99] In a case-control study (The Children's Cancer Group) of 1,842 ALL cases diagnosed under the age of 15 years, the risk of pediatric ALL was not elevated (OR = 1.2, 95% CI: 0.8–1.7) based on self-reported parental preconception, *in utero*, and postnatal X-ray exposure.[10] A cohort study of 92,957 children receiving diagnostic X-rays in a large German hospital 1976–2003 did not detect an elevated cancer risk from this radiation exposure.[100] The standardized incidence ratio (SIR) for all cancers was 0.99 (95% CI: 0.79–1.22) with multivariate Poisson regression detecting no trend in the incidence of total cancer, leukemia, or solid tumors with increasing radiation dose. The median radiation dose was relatively low (i.e., 7 μSv).

Other studies suggest a small increased risk of leukemia in children irradiated during childhood. A California case-control study of 711 cases of ALL and 116 cases of acute myeloid leukemia (AML) in children up to 18 years demonstrated an elevated risk of B cell ALL (OR = 1.40, 95% CI: 1.06–1.86) in children with reported postnatal X-rays; the risk was independent of the region of the body radiated.[87] However, the risk increased with the number of reported X-rays. The study did not detect an increased risk of T cell ALL (OR = 0.84, 95% CI: 0.59–1.19) or AML (OR = 1.05, 95% CI: 0.90–1.22) in irradiated children. Similarly, a retrospective case-control study of 412 Southern Californian children with AML did not demonstrate an association between AML risk and high-dose (≥1 mSv), low-dose (<1 mSv), or the number of postnatal diagnostic X-rays.[101]

In a population-based, cohort study of 680,000 Australian children and adolescents up to 19 years of age undergoing CT scans from 1985–2005, the incidence rate ratio (IRR) for all leukemias was 1.19 (95% CI: 1.03–1.37, $P < 0.001$) compared with unexposed children.[102] The exposed group had at least one CT scan (mean average effective radiation dose/scan = 4.5 mSv) >1 year prior to their cancer diagnosis; the mean duration of follow-up was 9.5 years. The excess rate ratio/mGy for leukemia and myelodysplasias based on a 1-year lag was 0.039 (95% CI: 0.014–0.070). The IRR for all cancers was 1.24 (95% CI: 1.20–1.29, $P < 0.001$). The relatively short follow-up for solid tumors suggests the risk may be greater for this group. Limitations of the study include the lack of clinical indications for testing and the possibility of concurrent cancer, short latency periods, uncertain dose calculations in the early part of the study, and the lack of positive results in radiosensitive tissues (e.g., breast).

The ERR values from the Australian study and the UK retrospective, record-based cohort study of 178,604 subjects under the age of 22 years were similar; the excess relative risk/mGy of leukemia with follow-up beginning at 2 years and lasting for an average of 7.3 years was 0.036/mGy (95% CI: 0.005–0.120; $P = 0.0097$).[103] The relative leukemia risk increased for patients receiving cumulative radiation doses of >30 mGy. For these patients (mean = 51.13 mGy), the relative risk of leukemia was 3.18 (95% CI: 1.46–6.94)

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compared with patients receiving <5 mGy. The data were consistent with a linear model rather than linear-quadratic or linear-exponential models for leukemia. The cumulative absolute risks are small because of the rarity of these cancers. The average follow-up was ~10 years, which is a sufficient lag time for leukemia (but not for solid tumors like the brain). The studies did not include medical conditions of the participants, raising questions about reverse causation; substantial uncertainty exists concerning the assigned radiation doses because of the lack of individual dosimetry. In a case-control study of 2,960 children with cancer and 4,858 age, sex, and region-matched controls from the United Kingdom, the odds ratio for all leukemias was marginally elevated but statistically nonsignificant (OR = 1.20, 95% CI: 0.91–2.02). The odds ratio for leukemia in cases and controls was not statistically different.[104] Most of these children received radiation doses of <1 mSv.

There are fewer epidemiological data on the radiation risk from CT scans in adults. A well-designed case-control study of adult patients with leukemia, lymphoma, and multiple myeloma in two prepaid health plans did not demonstrate a statistically significant increase in these tumors after follow-up of 15 years for 1/3 of the patients who remained in the cohort.[105] Based on data from Hiroshima and Nagasaki, excess leukemia cases following irradiation begin 2–4 years after exposure, peak at ~6–8 years, and decrease to baseline rates at 25 years.[106] Consequently, the patients were not followed for the whole latency period of these tumors; no power calculations were done to determine how much of the leukemia risk could be excluded. There was no dose-related increase in the incidence of leukemia or lymphoma, but the risk of multiple myeloma did increase among patients with frequent X-ray exposure.

Breast

Following exposure of women to radiation doses exceeding current standards, an elevated risk of breast cancer occurred in atomic bomb survivors,[107] X-ray fluoroscopy of the lung for the treatment of tuberculosis,[108] radiation treatment of malignant and benign breast disease,[109] and radiotherapy for Hodgkin's disease.[110] In a health survey of 105,385 female radiology technologists, >50% of the reported breast cancers were attributed to recognized risk factors (early age at menarche, first-degree relative with history of breast cancer, >14 alcoholic drinks/week, hyperthyroidism, and estrogens).[111] This study did not detect an elevated risk of breast cancer in technologists receiving long-term exposure to low levels of ionizing radiation including employment involving radiotherapy, radioisotopes, and fluoroscopic equipment. In a US prospective cohort of 90,957 radiology technologists responding to a 1994–1998 survey on fluoroscopically guided interventional procedures and followed to 2003–2005 for cancer incidence and 2008 for cancer mortality, breast cancer incidence was slightly increased (Hazzard Ratio = 1.16; 95% CI: 1.02–1.32) when compared with radiology technologists never using fluoroscopes.[112] Breast cancer mortality was not increased (HR = 1.07; 95% CI: 0.69–1.66) among technologists performing fluoroscopically guided interventional procedures. The Australian cohort study of patients under 19 years of age did not detect an excess risk of breast cancer in children undergoing CT scanning during their childhood (IRR = 0.99; 95% CI: 0.83–1.17).[102]

Brain

The results from case-control studies on meningioma risks and exposure to dental X-rays are conflicting, with more recent studies failing to confirm prior positive studies. In a retrospective case-control study of 200 histologically confirmed meningiomas and 400 age- and sex-matched population controls, in-person interviews determined dental X-ray history for classifying exposure into dental X-ray categories (full-mouth series, posterior bitewings, panoramic views, lateral cephalometric views) and number of examinations.[113] The odds ratio was statistically significant only for ≥6 full-mouth series (OR = 2.06, 95% CI: 1.03–4.17); however, the trend for increasing examinations did not demonstrate a dose-response relationship ($P_{\text{trend}} = 0.33$). Studies published in the 1950s estimated the radiation dose during full-mouth radiographical examination were ~1.15–2.8 Gy.[114]

Several large observational studies of children receiving CT scans report that high brain radiation doses from head CT scans (20–50 mGy) may cause a small, statistically significant excess absolute risk of brain tumors but not leukemia. The Australian cohort of patients under 19 years of age reported an excess risk of brain cancer following CT scans involving the brain and other organs.[102] The IRR for brain cancer was 2.31 (95% CI: 1.88–2.41); the excess rate ratio (ERR)/mGy was 0.021 (95% CI: 0.014–0.029). The Dutch Pediatric CT Study included 106,530 children in the solid tumor analyses and 140,612 children in the leukemia analyses.[115] The standardized cancer incidence was elevated for all sites (SIR = 1.47, 95% CI: 1.34–1.61, $n = 454$ cases), all CNS tumors (SIR = 2.05, 95% CI: 1.48–2.83, $n = 37$ cases), and hematolymphoproliferative cancers (SIR = 1.39, 95% CI: 1.13–1.70, $n = 93$ cases). The relative risk in the highest radiation exposure category

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(>120 mGy) for malignant brain tumors with a 5-year lag (RR = 1.02, 95% CI: 0.01–4.30, $n = 8$ cases, $P = 0.047$) was statistically significant. The mean follow-up period was ~8 years. These results represented 1 excess brain tumor (malignant and nonmalignant) per 10,000 pediatric CT scans projected to cause 1 of the 120 brain tumors occurring in the Dutch pediatric population annually. The authors opined that the results should be interpreted cautiously because of the small number of cases and shorter latency period for a solid tumor than current evidence suggests. The study did not detect excess leukemia risks in children receiving CT scans with a mean cumulative radiation dose of 9.5 mGy. The UK retrospective cohort study described above also demonstrated an elevated brain cancer risk following CT scans with a 5-year lag time and mean follow-up of 7.3 years.[103] The excess relative risk/mGy was 0.023 (95% CI: 0.010–0.049). The relative risk of brain cancer for patients receiving a cumulative dose of 50–74 mGy (mean = 60.42 mGy) was 2.82 (95% CI: 1.33–6.03) compared with patients receiving <5 mGy. The US prospective cohort of 90,957 radiology technologists demonstrated a ~2-fold increased risk of brain cancer mortality in technologists using fluoroscopy (HR, 2.55; 95% CI: 1.48–4.40).[112] Leukemia incidence and mortality were not increased in the radiology technologists using fluoroscopy.

Reproductive Abnormalities

Birth defects, mental retardation and other neurobehavioral effects, growth retardation, and embryonic demise are deterministic effects with thresholds and no adverse effect levels (NOAEL). These adverse effects occur spontaneously in the general population without radiation exposure above natural background; Table 40.10 demonstrates the approximate spontaneous risk of common reproductive abnormalities to the embryo at conception.

Growth retardation, gross congenital malformations, and embryo demise are classic effects of large radiation doses in mammals. Animal studies indicate estimated embryonic radiation doses in the range of 150–200 mGy during the preimplantation and presomite stages may increase the risk of embryonic loss; however, the surviving embryos do not demonstrate an increased risk of congenital malformations or growth retardation.[116] Embryonic and fetal radiation doses of <100 mSv are not clearly associated with an increased risk of deterministic effects (tissue reactions) in humans including the risk of severe mental retardation at any stage of pregnancy. Microcephaly was the most common malformation

TABLE 40.10. Spontaneous risk of adverse effects on the embryo at conception with no radiation above natural background. (Adapted from Dauer et al.).[68]

Adverse Reproductive Effect	Approximate Spontaneous Risk
Pregnancy loss before first missed menstrual period	1/3
Spontaneous abortion during known pregnancy	1/7
Genetic disease	1/10
Prematurity	1/25
Growth retardation	1/33
Major congenital malformation	1/33
Stillborn birth	1/50–1/250
Severe mental disability	1/200
Childhood leukemia risk per year	1/25,000
Infertility	1/15 couples

developing after the exposure of pregnant women at Hiroshima and Nagasaki to fetal doses of radiation of >1 Gy during the most radiosensitive period (8th–15th week postconception).[117] No radiation-induced malformation developed without the presence of growth retardation or a central nervous system abnormality. Almost all diagnostic radiological procedures of the head, neck, chest, or extremities deliver radiation doses below the NOAEL for these developmental effects.[118] Table 40.11 lists the effects of radiation during various gestational times with estimated thresholds for deterministic effects.

Small case-control studies of women exposed to diagnostic X-rays during pregnancy have not demonstrated statistically significant elevations in the risk of congenital malformation in the offspring, the risk of spontaneous abortion, or reduced fertility in the mother.[119,120] A case-control study of female veterinarians did not demonstrate an increased incidence of self-reported spontaneous abortions or low birth weight infants compared with a control group of female lawyers; however, a weak positive association occurred between the greater use of X-rays and the number of spontaneous abortions in the female veterinarians.[121] Reported birth defects were higher among the veterinarians than the lawyers (RR = 4.2, 95% CI: 1.2–15.1) after controlling for confounders. The findings were unexpected and considered hypothesis-generating by the authors, reflecting the wide confidence interval.

The determination of the risk of developing these abnormalities depends on the extrapolation with mathematical models of high-dose data from Hiroshima and Nagasaki to the radiation dose produced by diagnostic X-rays. The development of severe mental retardation

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TABLE 40.11. Radiation effects associated with various stages of gestation. (Based on Brent).[118]

Stage[a]	Effect
3rd–4th (first 2 weeks postconception)	Most sensitive time for embryonic demise. Animal studies suggest threshold of 100–200 mGy.
4th–8th (2–6 weeks postconception)	Embryo is susceptible to major malformations and growth retardation with minimal threshold for growth retardation near 200–500 mGy.
8th–15th	Most sensitive time for irreversible whole-body growth retardation, severe mental retardation, and microcephaly. The threshold for severe mental retardation is ~350–500 mGy with a potential for decreased IQ at lower radiation exposures (100–350 mGy).
16th–term	High radiation exposure can produce growth retardation and reduced brain size/intellect; however, the effects are less severe than during midgestation. The risk of major anatomical malformation is minimal. Threshold for severe mental retardation of >1,500 mGy with ↓ IQ potentially occurring at lower radiation doses. After the 25th week, the central nervous system is relatively radioresistant; major fetal malformations and functional anomalies are unlikely.

[a] Weeks after first missed menstrual period.

following the doses of radiation produced by diagnostic X-rays is unlikely, in part, because a threshold for the development of this abnormality probably exists far above standard levels of medical radiation.[71,122]

DOSIMETRY

Analytical Methods

Determination of the radiation dose delivered by CT is a complex process involving the quantification of the nonhomogeneous distribution of radiation inside the patient that results from each slice of tissue receiving radiation during direct scanning *and* indirectly from the scanning of adjacent tissue. The best measure for risk estimation is the organ dose; however, the mean absorbed radiation dose in organs or tissues of patients undergoing medical imaging cannot usually be measured directly.[8] Consequently, quantification usually requires measurements in cylindrical phantoms containing dosimeters (e.g., pencil ionization chambers with an active length of 100 mm) rather than direct measurements in the patient. The radiation dose from a CT examination depends on a variety of technical factors involving scanner design and clinical protocols including single-scan image quality, the number of scans per examination, slice scan time, scan pitch (i.e., degree of overlap between adjacent CT slices) and motion, multiple-scan geometric efficiency, axial scan range, tube voltage (kVp), X-ray beam filtration and collimation, and efficiency of the detector. [123,124] Consequently, the CT radiation dose differs between commercial CT scanners depending on the design of basic imaging parameters (i.e., scan noise, slice thickness/spacing, transverse spatial resolution as measured by pixel width).[124] The accidental loss of the aluminum filter increased the surface (entrance) dose by 24% and the center dose by 18% for head CT; the loss of the filter also enlarged the surface dose by 25% and the center dose by 16% for CT of the body.[125] The operator can adjust the radiation dose by controlling X-ray tube voltage (kVp), tube current and scan time (mAs), table pitch (table speed in longitudinal *z*-axis), detector configuration, and gantry rotation time.[126] Increasing the table pitch or gantry rotation and reducing the tube voltage decreases the radiation dose.

Hospital medical physicists and health physicists are resources for radiation dose estimation including delivered fetal and adult radiation doses. Other US resources include contacts for state radiation/control radiation experts (Conference of Radiation Control Program Directors, http://www.crcpd.org), active certified health physicists (American Board of Health Physics, https://www.aahp-abhp.org), and diplomats in medical physics specialties (American Board of Medical Physicists, http://www.abmpexam.com).

Diagnostic Reference Levels

Diagnostic reference levels for radiographs (DRLs for interventional procedures) were introduced as an advisory value to assist in the optimization of medical imaging and the radiation dose to the patient by identifying radiological practices that regularly exceed most other similar practices.[127] The UK National Patient Dose Database has collected data on radiation dose from common radiographical and fluoroscopic X-ray examinations since the mid-1980s; these data indicate a progressive decline in the entrance surface dose (ESD) to less than half the original levels.[13,128] The ESD (third quartile value) for AP lumbar spine declined from 10 mGy in the mid-1980s to 6 mGy in 2000. The current diagnostic reference level (75% upper

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limit) for this examination is 4.2 mGy. Low-radiation dose images may also be detrimental to patient care when inadequate image quality (e.g., excessive noise levels) reduces the clinical effectiveness of the imaging. Diagnostic reference levels and achievable doses are dynamic values that change with time and technological innovations. The US National Council for Radiological Protection and Measurements (NCRP) establishes DRLs using data for ionizing radiation doses provided by the Nationwide Evaluation of X-Ray Trends (NEXT) Program. The NEXT Program is a cooperative effort between the US Food and Drug Administration (FDA), state radiation control offices through the Conference of Radiation Control Program Directors, Inc., and the American College of Radiology. Table 40.12 lists the diagnostic reference levels and achievable doses recommended by the NCRP. Public Health England provides a list of recommended national diagnostic reference levels (NDRLs) for pediatric and adult diagnostic radiological examinations, CT scans, fluoroscopy, and interventional procedures.[129]

These values are established to indicate the need to review radiological practices; exceeding the DRL does necessarily imply an unacceptable practice or the need to change the practice.[8] Typically, the DRL uses quantities that are easy to measure (e.g., entrance surface dose, entrance surface air kerma, dose-area product) with the value set at the upper 75%. Achievable doses are usually set at 50%. For conventional radiography, surveyed radiographs include various projections of skull, chest, abdomen, spine, and pelvis. The pediatric DRL varies with age.

For comparison with US values, Table 40.13 lists diagnostic reference levels, tube potentials, and backscatter data from the UK Health Protection Agency for selected radiographical examinations. The absolute magnitude of DRLs in Europe varies from country to country because the values are based on local surveys of patient doses; therefore, the DRLs are not directly comparable to NCRP values based on a more uniform phantom-based approach.

Biomarkers

Determination of the incidence of chromosomal abnormalities is usually done by cytogenetic metaphase analysis of chromosomes from circulating lymphocytes. Chromosomal abnormalities do not usually occur above the normal rate of ~1% until the whole-body radiation dose exceeds 100–300 mSv; consequently, typical radiation doses from medical imaging are not associated with chromosomal abnormalities.[131] Cytogenetic analysis may be useful as a negative indicator to demonstrate the whole-body dose did not exceed a specific level or the observed adverse effects do not correlate to

TABLE 40.12. US National Council for Radiological Protection and Measurements diagnostic reference levels and achievable doses. (National Council on Radiation Protection and Measurements).[127]

Examination	Units	Diagnostic Reference Level	Achievable Dose
Adult PA chest (with grid)	mGy	0.15	0.11
Pediatric chest			
Without grid	mGy	0.06	0.04
With grid	mGy	0.12	0.07
AP abdomen	mGy	3.4	2.4
AP lumbosacral spine	mGy	4.2	2.8
Upper GI fluoroscopy			
Without oral contrast media	mGy/minute	56	40
With oral contrast media	mGy/minute	81	72
Fluorographic image			
Film – without contrast	mGy	3.9	2.5
Film – with contrast	mGy	27.5	18.7
Digital – without contrast	mGy	1.5	0.9
Digital – with contrast	mGy	9.9	5.3
Adult head CT ($CTDI_{vol}$)	mGy	75	57
Adult chest CT ($CTDI_{vol}$)	mGy	21	14
Adult abdomen/pelvis CT ($CTDI_{vol}$)	mGy	25	17
Pediatric head CT[a] ($CTDI_{vol}$)	mGy	40	31
Pediatric abdomen/pelvis CT[a] ($CTDI_{vol}$)	mGy	20	14

[a] Based on 5-year-old.

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TABLE 40.13. Diagnostic reference level (DRL), tube potentials, and backscatter data for selected radiographic examinations in the United Kingdom. (Data from Martin).[130]

Examination	DRL (mGy)	Tube Potential (kV)	Backscatter Factor
Skull PA	2	70–85	1.25
Skull lateral	1.3	70–85	1.25
Chest PA	0.15	125[a]	1.3
Chest lateral	0.6	125[a]	1.3
Thoracic spine AP	4	75–90	1.25
Thoracic spine lateral	7	75–90	1.25
Lumbar spine AP	5	75–90	1.4
Lumbar spine lateral	11	80–95	1.3
Abdomen AP	4	70–85	1.4
Pelvis AP	4	75–90	1.4

Abbreviations: AP = anteroposterior projection; PA = posteroanterior projection.
[a] 70–90 without grid.

the estimated dose based on the number of chromosomal abnormalities adjusted for patient-specific risk factors.

HEALTH SURVEILLANCE

Risk Assessment

Fetal Development

Although many studies examine the effect of radiation from medical imaging procedures, several factors limit the ability of these studies to quantify risk assessment including small sample size, poor dosimetry, and the difficulty of extrapolating results to a dissimilar population with different baseline cancer rates. Typical fetal doses from diagnostic radiographical procedures are ≪25 mGy. Diagnostic radiological and nuclear medicine procedures do not usually cause significantly increased fetal risks; however, therapeutic procedures and radiotherapy may deliver radiation doses associated with some risk.[132] The greatest risks occur during organogenesis (2nd–8th week postconception) and the rest of the first trimester. The tissue reactions of ionizing radiation (i.e., deterministic effects) include mental retardation, decreased IQ, microcephaly, neurobehavioral effects, convulsive disorders, growth retardation, congenital malformations, and embryonic and fetal death (miscarriage, stillbirth). Animal studies indicate these effects require threshold levels to develop.[60] These studies demonstrate that embryonic doses of 150–200 mGy may increase the risk of embryonic loss during preimplantation or presomite stages (i.e., up to 21 days after fertilization). Surviving embryos receiving these radiation doses have not developed growth retardation or congenital malformations.

Although infants may survive fetal radiation doses of ≥500 mGy without obvious adverse effects,[117] the probability of central nervous system damage and mental retardation becomes substantial at fetal levels over 500 mGy. Except for a Russian study, abnormal pregnancy outcomes in animals and human studies involving fetal radiation doses of <250 mGy are not well documented.[133] During blastogenesis (up to 2 weeks postconception), failure to implant occurs at radiation doses of >500 mGy; embryos that survive radiation exposure during blastogenesis have a low risk of congenital abnormalities because of the pluripotency of the stem cells. Exposure of the embryo to several thousand mGy during early organogenesis causes a significant risk of spontaneous abortion.[113] The risk of severe mental retardation following effective radiation doses of >1,000 mGy is substantial in the $8–15^{th}$ week of gestation as a result of neuronal loss during neuronal migration; however, the risk decreases ~5-fold during the $16–25^{th}$ week of gestation. The development of the central nervous system is much less sensitive to radiation effects during other parts of gestation.[134]

Delivered maternal doses may cause adverse fetal effects following radiation doses insufficient to produce acute maternal effects; a fetal dose of >100 mGy probably causes a some increase in the incidence of deterministic effects (e.g., congenital malformations, growth retardation, fetal demise) depending on the dose. There are no well-documented, radiation-induced, noncancer health effects of <50 mGy.[71,135] Growth retardation occurs at radiation doses of >1,000 mGy with a 3–4% reduction in height by age 17 years.[136] Studies of pregnant mothers irradiated during the bombing at Hiroshima indicate severe mental retardation also may occur *in utero* following radiation doses of >500 mGy during 16–25 weeks postconception.[137] The fetus is particularly sensitive during 8–15 weeks postconception with some IQ reduction above 100 mGy and severe mental retardation and microcephaly above 1,000 mGy during this gestational period.[136] Radiated infants exposed to fractionated *in utero* doses averaging 2,500 mGy developed microcephaly and mental retardation.[138] The sensitivity of the fetus to deterministic radiation effects is lower during the third trimester (>26 weeks postconception) than earlier in the pregnancy, although miscarriage and neonatal death still increase significantly at fetal doses of >1,000 mGy.

Decisions regarding the consequences of diagnostic radiation during pregnancy involve the evaluation of multiple factors listed in Table 40.14.

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TABLE 40.14. Factors in the evaluation of radiation exposure during early pregnancy. Any final decision may involve ethical considerations and input from multiple medical specialties.

Factor	Details
Gestational time	Timing of radiation exposure in relation to gestational age and development
Exposure parameters	Projections, number of views, beam quality, kVp, exposure duration, film size, distance of conceptus from beam
Radiopharmaceuticals	Activity, effective half-life, target organs, kinetics, solubility
Dose and risk	Calculation of dose and subsequent risk with input from health physicist as needed
Clinical relevance of examination	Purpose, importance of diagnostic data to outcome, optional imaging, necessity of examination during pregnancy
Fetal/maternal risk factors	Maternal age, genetic factors, maternal disease, social history, past pregnancy complications
Personal factors	Religious beliefs, maternal feelings

Teratogenesis

The most sensitive period for congenital malformation is 22 days postconception with a threshold of 200 mGy.[118] Above this value, the risk of congenital malformation increases; however, the severity remains the same (i.e., an all-or-none phenomenon). The International Commission on Radiological Protection (ICRP) considers radiation doses of >100 mSv as potentially teratogenic with a risk of central nervous system damage, cognitive impairment, and growth retardation.[136] Although conventional X-ray, ventilation-perfusion scanning, and CT pulmonary angiography in a pregnant patient expose the fetus to a relatively small amount of radiation (~4 mSv), the unshielded pregnant woman receives a substantial dose to her breasts. Models predict transgenerational effects from radiation exposure; however, no clear epidemiological evidence associates hereditary effects with radiation exposure. Analysis of data from Japanese atomic bomb survivors did not detect deleterious health effects in 75,327 singleton children born to survivors.[139] The mean gonadal radiation dose was 264 ± 463 mGy; the median follow-up period was 54.3 years (IQR: 45.4–59.3 years). Consequently, the generic risks from low-dose radiation-associated imaging procedures are very small compared with the baseline risks in the population.

Carcinogenesis

Ionizing radiation produces cancer with the risk dependent on the organ-specific dose, age during exposure, and tissue sensitivity (e.g., breast, thyroid, red bone marrow). Radiation-induced cancer does not differ pathologically from other cancer etiologies; therefore, detection of radiation-induced cancer requires epidemiological studies demonstrating increased frequency of cancer incidence and/or mortality in the exposed population. Cancer risks associated with low radiation doses occurring during medical imaging are primarily theoretical with limited epidemiological evidence cancer risks at the low radiation doses (i.e., <100 mGy) produced by radiographical examinations; these risks are usually determined by linear no-threshold models using data extrapolated from the increased cancer incidence and mortality associated with the single, high-dose radiation exposure sustained by Japanese survivors of the atomic bombs dropped in Nagasaki and Hiroshima. The Biological Effects of Ionizing Radiation (BEIR VII) Report predicts a lifetime attributable risk from a 10 mSv effective dose of 1 cancer (solid cancer, leukemia)/1,000 patients based primarily on the linear no-threshold model and Japanese atomic bomb data.[140] However, current epidemiological studies contain large statistical uncertainties that do not provide consistent estimates of radiation risk for whole-body effective doses of <100 mSv, particularly for radiation doses below 10 mSv.[141] Although radiation-induced cancer risks clearly demonstrate a dose-response relationship above 100 mSv, uncertainties substantially increase the range of risks associated with stochastic effects in the range of 100–1,000 mSv with variables including exposure rate, characteristics of the population exposed, and organs/tissues involved.[140] The linear no-threshold model assumes all radiation doses have some carcinogenic risks without any benefits (e.g., delayed detection of life-threatening diseases and/or increased rates of invasive, high-risk procedures).

The cancer risk associated with CT scans is very small, but probably not zero.[142] Epidemiology data indicate absorption of high radiation doses (i.e., >500 mGy) by the embryo or fetus produces increased cancer risks, whereas the cancer risk from radiation doses below 100 mGy depends on the linear, no-threshold model. Extrapolation of cancer risks in this range remains controversial.[143] Stochastic effects (e.g., cancer and teratogenesis including abortion during pre-implantation) may occur below 100 mGy,

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particularly the risk of childhood cancer following prenatal radiation exposure;[144] however, no current model can accurately predict the risk associated with exposure to radiation doses of <100 mSv.

Overall Cancer Risk

The overall cancer risk varies with several factors including age at exposure, organ, dose, and dose rate. Analysis of data from the Oxford Survey of Childhood Cancers case-control study of *in utero* exposure to diagnostic X-rays demonstrated an excess risk coefficient for childhood cancer before 15 years of age.[145] The excess relative risk coefficient was ~50/Gy, whereas the excess absolute risk coefficient was ~8%/Gy. The US National Research Council's committees on the Biological Effects of Ionizing Radiations (BEIR) prepared a series of reports on the health consequences of radiation exposures based on the linear no-threshold model using data from Japanese atomic bomb survivors.[9] Figures 40.10 and 40.11 list the estimated average lifetime attributable risk of cancer for males and females, respectively, following a single 100 mSv exposure based on age of radiation exposure. The model extrapolates radiation doses below 100 mSv based on a linear slope to zero (i.e., dose/100 times the value at the age of exposure). The attributable cancer risks are higher in children than adults because of their longer life expectancy and the increased radiosensitivity of pediatric tissues. The higher estimated cancer risks in women result primarily from the additional risk of breast cancer and the relatively high lung cancer risk coefficients.

Although recent analysis of the Japanese data continues to support the no-threshold concept, data in the 0–200 mSv range suggest the possibility of a linear-quadratic dose-response model that provides lower risk estimates than the linear no-threshold model at the low radiation doses involved in medical imaging.[146] This Radiation Effects Research Foundation study of 93,000 residents of Hiroshima or Nagasaki during the atomic explosions demonstrated a statistically significant increased cancer incidence for residents with single whole-body doses of >100 mSv; the mean whole-body radiation dose of the cohort was ~200 mSv. Approximately 49,000 survivors in this cohort received estimated radiation doses of ≥5 mSv with ~32,000 receiving <100 mSv and ~2,000 >1 Sv. Below 100 mSv, the cancer incidence was not statistically different than in the unexposed population. Although formal dose-threshold analysis indicated no threshold with a zero dose being the best threshold estimate, the upper 95% confidence limit of the threshold was 150 mSv. For mortality from solid cancers at age 70 years after exposure at 30 years, the sex-averaged excess relative risk was 0.42/Gy (95% CI: 0.32–0.53/Gy) based on a linear model.

Leukemia

Several case-control studies of women and their children irradiated during the 1950s–1970s primarily in the later stages of pregnancy suggest the embryo is more sensitive to radiation-induced leukemia than adults.[147,148] In the Oxford Survey of Childhood Cancers Study, *in utero* radiation exposure from diagnostic pelvimetry ranged from 5–50 mGy. An updated analysis of the Oxford study 1953–1979 demonstrated an excess mortality from childhood leukemia at levels above previous UNSCEAR estimates (i.e., 20%/Gy vs. 7–8%/Gy);[149] However, data lacked a dose-response relationship with prenatal radiation exposure; additionally, the study suggested a relationship between maternal ingestion of antipyretics or antibiotics during pregnancy and childhood cancer. Reviews of case-control studies indicated an equivalent excess absolute leukemia risk of ~3%/Gy.[150,151] The excess relative risk (ERR) coefficient (i.e., the proportional increased leukemia-related mortality risk over the background radiation dose received by the red bone marrow) increased to a maximum excess absolute risk coefficient of ~3%/Gy 7 years after radiation exposure with a minimum latent period of 2 years.[145] The author considered these risks consistent with extrapolation of the linear no-threshold model to the Japanese atomic bomb data; however, the authors stated there was considerable uncertainty with probable overestimation of the coefficients, particularly from the unusual pattern of similar relative risks for leukemia and other common types of childhood cancer in the case-control studies. This pattern was not observed in the Japanese atomic bomb survivors or cohorts of children with postnatal radiation exposure. For radiation doses of 0.1–2 Gy received during medical procedures, the estimated ERR for leukemia ranges from ~1.9–5/Gy, whereas the EAR (excessive absolute risk) ranges from ~1–2.6/10^4 PY-Gy with little information on the effect of dose rate or age at exposure.[9]

Current data indicate the risk of developing radiation-induced carcinogenesis is lower for the fetus than for an irradiated child.[118] A study of cancer deaths in New England demonstrated excess cancer deaths in children irradiated *in utero* for diagnostic purposes with an estimated relative risk of 1.52 for leukemia compared with 1.27 for other cancers.[152] Several large prospective studies have not confirmed the association between exposure to diagnostic radiation *in utero* and an increased incidence of tumors.[95,153] Although the question of whether *in utero* irradiation (primarily pelvimetry) is a causal or associative factor for the development

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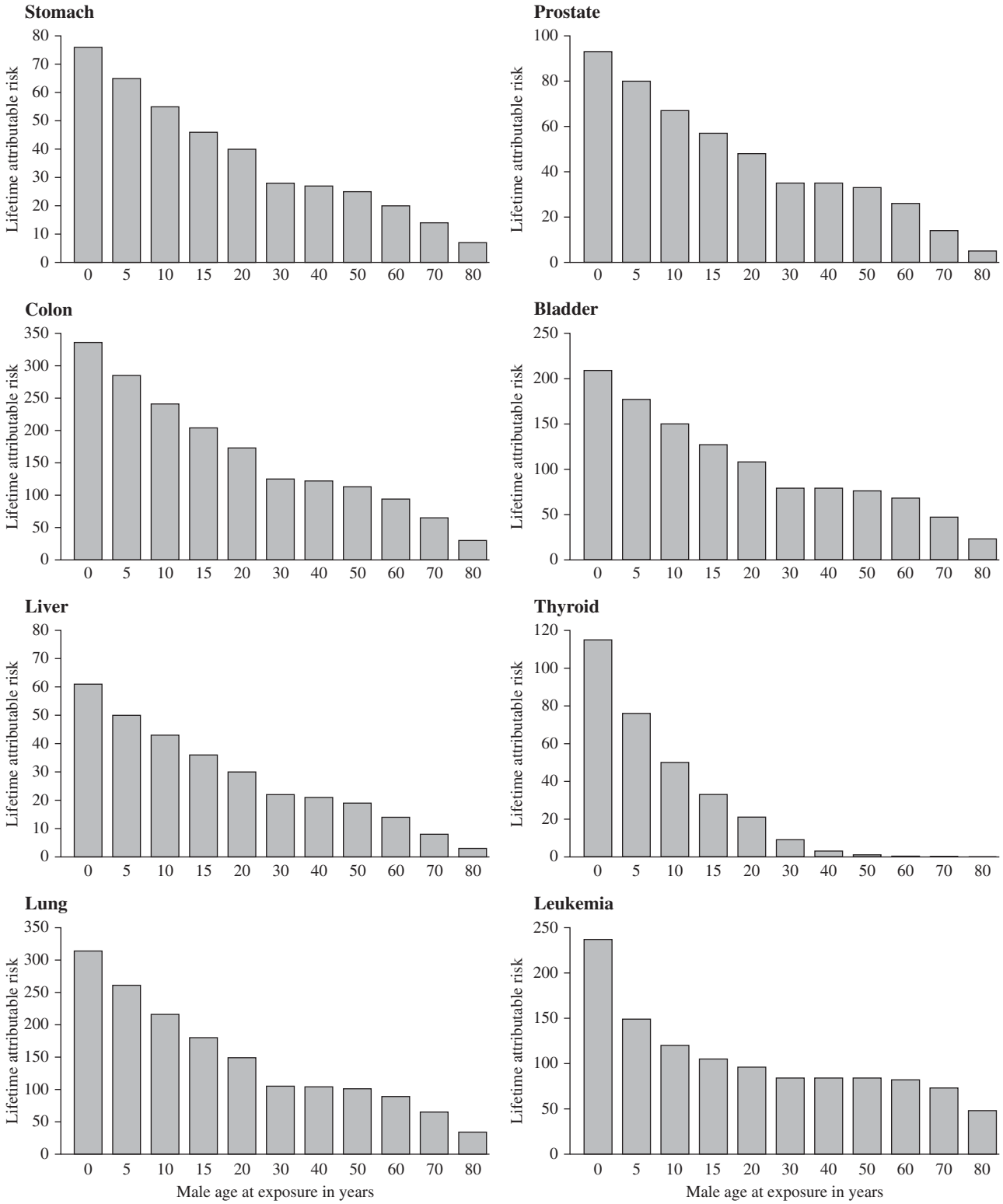


FIGURE 40.10. Lifetime attributable risk of cancer incidence per 100,000 **males** based on the linear no-threshold model assuming a single 100 mSv dose at various ages in years. This model estimates cancer incidences for radiation doses below 100 mSv by multiplying the values in the table by the percentage of lower dose to 100. (Data from BEIR VII Phase 2).[9]

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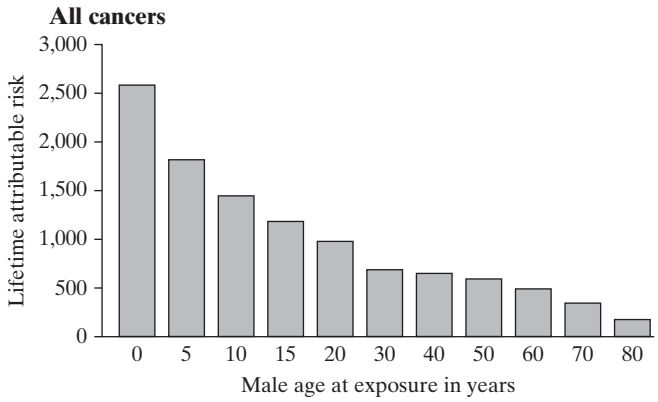


FIGURE 40.10. (*Continued*)

of leukemia remains controversial, the estimated relative risk from *in utero* exposure to 0.1–0.2 Gy in these studies consistently ranged from 1.5–2.0. *In utero* radiation doses from diagnostic radiology (i.e., <0.1 Gy) probably do not cause a substantial increase in congenital malformations, fetal demise, or *in utero* growth retardation. However, the possibility of small increases in cancer incidence or genetic hazards remains.[133,154] Although follow-up is incomplete, examination of epidemiology data from populations in Hiroshima and Nagasaki exposed to radiation *in utero* during the nuclear explosions have not detected a significant increase in childhood leukemia.[84,155,156] Japanese survivors irradiated *in utero* consist of ~800 individuals who received ≥10 mSv and an average dose of 0.25 Sv. From a public health perspective, prudence necessitates the acceptance of a causal association between *in utero* exposure to radiation and an increased risk of developing cancer; however, the potential confounding of positive studies and the inability to detect a statistically significant cancer risk in atomic bomb survivors limit conclusions regarding the nature and magnitude of the risk.

Thyroid

Although thyroid cancer is uncommon, radiation is a well-documented cause of thyroid cancer, primarily following radiation exposure in children <15 years of age. The incidence of thyroid cancer is relatively high in patients under the age of 40 years with the incidence increasing slowly with age. The linear model best describes the dose-response with little risk when exposure occurs after 20 years of age and a decreasing risk following high radiation doses used in cancer therapy.[9] The risk of thyroid cancer is 3-fold higher in women than men. Most studies of thyroid cancer involve incidence rather than mortality because the prognosis for most thyroid papillary carcinomas is good. In six case-control studies of children exposed to external radiation for benign conditions, the ERR/Gy ranges from 3/Gy in 234 children exposed for enlarged tonsils and other benign head and neck disorders[157] to 30/Gy in an Israeli study of 10,834 children exposed during the treatment of *T. capitis*.[158] The estimates for estimated excess attributable risk (EAR) in these studies vary from $0.9/10^4$ PY-Gy in the study of 14,351 Swedish children irradiated for hemangiomas[159] to $13/10^4$ PY-Gy in the *T. capitis* study.[158] In a pooled analysis of five cohort and two case-control studies, the excess relative risk per Gy (ERR/Gy) for children under 15 years of age was 7.7 (95% CI: 2.1–28.7); the excess absolute risk per 10,000 person years-Gy (EAR/10^4 PY-Gy) was 4.4 (95% CI: 1.9–10.1).[160] The attributable risk percent at 1 Gy was 88%. The studies included atomic bomb survivors, children treated for *T. capitis*, two studies of children irradiated for enlarged tonsils, infants irradiated for an enlarged thymus gland, and two case-control studies of patients with cervical cancer and childhood cancer.

Environmental Monitoring

General Population

The International Commission on Radiological Protection (ICRP) recommends an annual effective dose limit of 1 mSv exclusive of natural and medical radiation exposures.[161] The annual dose may be exceeded in any year provided the 5-year average does not exceed 1 mSv/year. The recommended annual equivalent doses for the ocular lens and the skin are 15 mSv and 50 mSv, respectively. The National Council on Radiation Protection and Measurement recommends exposure limits for the public that are ~≤10% of the occupational limit as measured by whole-body effective dose.[12]

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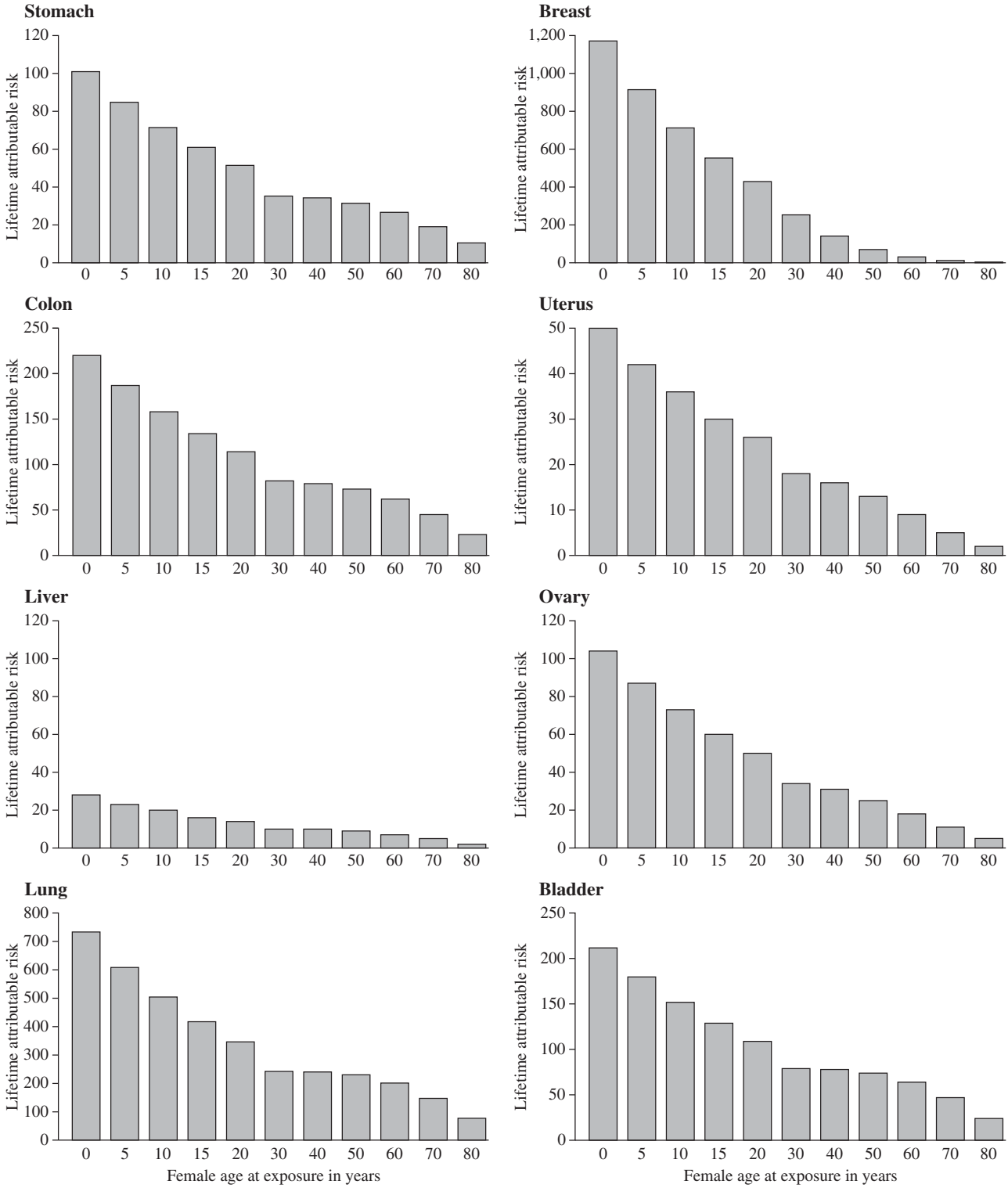


FIGURE 40.11. Lifetime attributable risk of cancer incidence per 100,000 **females** based on the linear no-threshold model assuming a single 100 mSv dose at various ages in years. This model estimates cancer incidences for radiation doses below 100 mSv by multiplying the values in the table by the percentage of lower dose to 100. (Data from BEIR VII Phase 2).[9]

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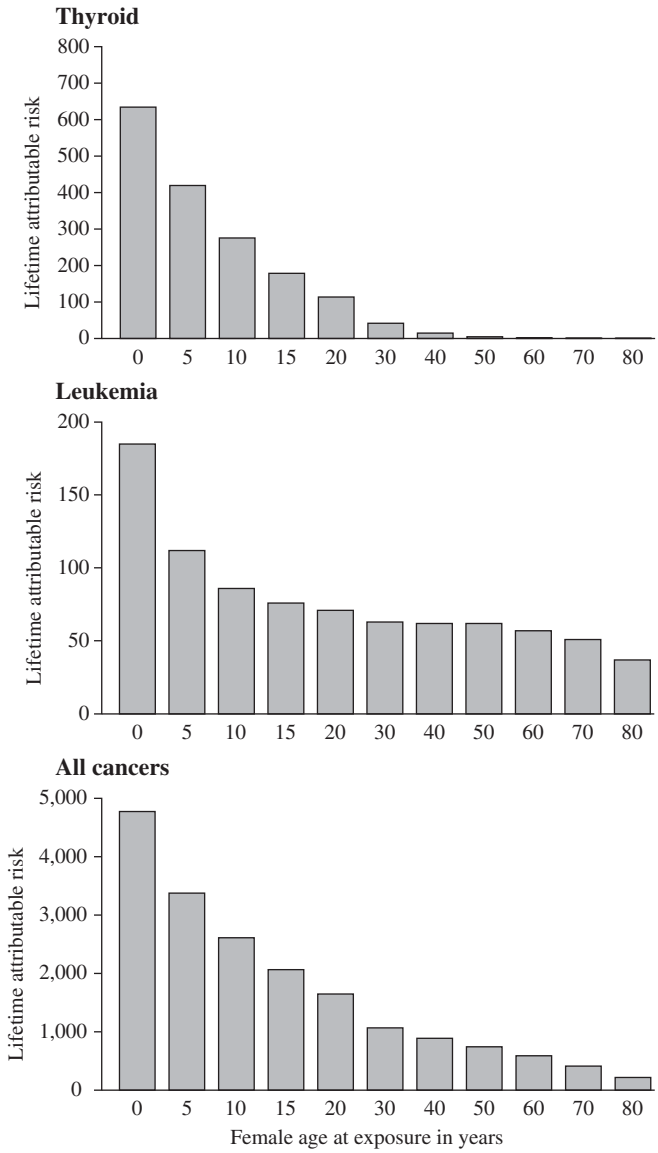


FIGURE 40.11. (*Continued*)

Patients

The decision to perform medical imaging depends on the clinical evaluation of the risks and benefits of the procedure. The radiological examination should do more good than harm, provide necessary information that usually improves the diagnosis or treatment, and produce reliable information to solve the clinical question. Examples of radiographs not routinely justified include nasal bone radiographs in children <3 years of age, cervical spine radiographs in children with torticollis in the absence of trauma, and comparison views of the opposite extremity for evaluation of a limb injury. Consideration should always be given to alternative imaging techniques that provide similar information without ionizing radiation (ultrasound, magnetic resonance imaging).

Radiological Dose Optimization

In order to deliver the lowest radiation dose necessary to achieve the required medical objective, the imaging parameters should be optimized and protective measures instituted consistent with as low as reasonably achievable (ALARA). Optimization of radiological protection includes maintaining optimum function of radiological equipment with quality control, ensuring radiological equipment and technical

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parameters provide adequate images for the patient and the intended clinical indication, and using radiographical techniques (e.g., positioning, immobilization, field size, protective shielding) to minimize image noise.[8] Beam quantity is primarily influenced by the tube current-exposure time product (mAs), whereas tube voltage (kV) and tube filtration (mm Al) mainly determine beam quality. Reducing the size of the primary field of the X-ray beam is an important method to reduce patient and operator radiation exposure.[162] The minimum distance between the X-ray tube (collimator) and the patient is usually 30 cm to prevent the delivery of high radiation doses. Personnel assisting in the use of mobile X-rays should remain at least 6 ft from the X-ray tube, the patient, and the useful beam. Leaded gloves and aprons should be worn if holding the patient requires personnel to remain within 6 ft of the safety zone during the use of the X-ray machine. Optimization of the radiation dose also requires performance tests on equipment linked to surveys of patient radiation doses with comparisons to published diagnostic reference levels.[130]

Minimizing radiation exposure for patients and healthcare professionals involves practices that reduce exposure time, increase the distance between the radiation source and the individual, and the use of appropriate barriers (e.g., lead or tungsten/tin aprons, lead-lined barriers), particularly during CT and fluoroscopy procedures.[163] Because of the higher radiation levels with fluoroscopy and angiography, the distance from the source should always be maximized and leaded gloves and aprons should be worn during the procedure. A study of gastroenterological fluoroscopy indicated radiation doses underneath the leaded apron of pregnant technicians were similar to the radiation dose received from environmental exposure; the radiation dose did not exceed current standards.[164] For CT scans, dose reduction involves adjustment of scan parameters (pitch, mAs, kVP) to patient size, weight, and age, accepting images sufficient for the radiological diagnosis, avoiding overlapping scan regions, and restricting the region scanned to region needed to answer the clinical question.

Occupational Monitoring

Workplace

Most institutions recommend the justification of all radiation doses (i.e., sufficient benefit to exposed individual or society to offset the detriment caused) and the delivery of a radiation dose as low as reasonably achievable (ALARA) to provide the needed clinical information. The annual whole-body dose limit recommended by the International Commission on Radiological Protection (ICRP) for radiation workers in planned exposure situations is an effective dose of 20 mSv averaged over 5 years with no year exceeding 50 mSv.[161] The range of reference levels for effective dose (acute or annual) during radiological emergencies is 20–100 mSv. For the hands, feet, and skin, the recommended upper limit for the annual equivalent dose in planned exposure situations is 150 mSv, whereas the equivalent dose for the eye is 20 mSv averaged over 5 years with an upper limit of 50 mSv. Occupational and public dose limits do not include natural radiation or irradiation for medical purposes. For deterministic effects (i.e., nonmalignant), annual occupational dose limits are much higher than the annual effective doses for skin and feet (150 mSv) as well as other tissues beside the lens (500 mSv). The American Conference of Governmental Industrial Hygienists (ACGIH) adopted threshold limit values (TLV) for occupational exposure to ionizing radiation (i.e., wavelengths $<\sim$100 nm), similar to guidelines by the NCRP and ICRP.[165] The recommended effective doses combine external and internal sources exclusive of background radiation (e.g., cosmic, terrestrial, internal body sources, radon) using ICRP radiation weighting factors (W_R) and tissue weighting factors (W_T). The equivalent dose represents the sum of external and internal absorbed doses adjusted for differences in the quality of radiation by multiplying the sum by W_T. Table 40.15 lists the ACGIH guidelines for occupational exposure to ionizing radiation that are under review.

Radiation to the hand is the limiting dose for purposes of preventing excessive radiation exposure to radiologists and other medical specialties involved in interventional procedures (e.g., orthopedics, cardiologists). The skin of the fingers is the limiting organ for individual monitoring of external radiation in some medical specialties (e.g., interventional radiologists/cardiologists, nuclear medicine). In these medical environments, a wide variety of radiation field characteristics and difficulties measuring the maximum skin dose with a single detector complicate accurate dosimetry of the extremity.[166] Hemodynamic procedures usually involve high dose area product (DAP) values from the intensive use of image acquisition, particularly percutaneous transluminal coronary angioplasty. Often, the hands, legs, and eye lenses remain inadequately unshielded. Without protective measures, hand doses during angiography vary from 0.12–0.71 mSv, whereas finger doses range up to 0.84 mSv during vascular radiology procedures.[167] In a literature review in the early 1970s–middle 2000s,

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TABLE 40.15. American Conference of Governmental Industrial Hygienists (ACGIH) guidelines for occupational exposure to ionizing radiation. The effective dose includes internal and external sources. The annual radiation from radon and radon daughters should be included in the calculation of the effective dose if activity concentrations in air exceed 300 Bq/m^3 after radon mitigation measures. In practice, tracking cumulative radiation doses may be difficult because of the costs and logistics. (Data from ACGIH).[165]

Exposure	Annual Guideline (mSv)
Effective dose (Stochastic effects)	
Single year[a]	50 mSv
5-Year average	20 mSv/year
Cumulative effective dose	10 mSv × age in years
Embryo/fetus effective dose	0.5 mSv/month[c]
Annual absorbed dose (Tissue reactions)	
Lens of eye	50 mSv/year
Skin, hands, feet	500 mGy/year[b]

[a] ≥18 years; for children under 18 years, the recommended limits are 1 mSv/year; [b] Annual absorbed dose of skin or extremities averaged over the most highly exposed 10 cm^2 of skin, [c] Exposure to radioiodine should be minimized or avoided in pregnant workers to avoid the risk of congenital hypothyroidism.

articles on radiation exposures to operators from diagnostic or interventional fluoroscopically guided cardiovascular procedures, the effective doses ranged from 0.00002–0.038 mSv for diagnostic catheterizations, 0.00017–0.0312 mSv for percutaneous coronary interventions, 0.00024–0.0096 mSv for ablations, and 0.00029–0.0174 mSv for pacemaker or intracardiac defibrillator implantations.[168] Measurements of radiation received by junior orthopedic staff during trauma operations indicated the radiation dose was below the 1990 ICRP guidelines (ICRP Report 60).[169,170] Considerable variation in the whole-body and organ radiation doses occurs in orthopedic staff as a result of several factors, including differences in procedures (open vs. minimally invasive), distance from the primary and secondary radiation sources, work experience (junior vs. senior surgeons), and the use of personal protective equipment (aprons, gloves, thyroid collars, eyewear). In a review of 42 articles on radiation exposure of hands, eyes, and thyroid gland in orthopedic staff, the annual cumulative dose to the hands/fingers ranged from 0.03–1.27 mSv compared with 0.06–23 mSv for the eyes/forehead and 0.07–30 mSv for the thyroid gland/neck area.[171] The average radiation dose was higher during minimally invasive procedures by the orthopedic surgeon, particularly the dominant index fingertip; all the radiation doses were below the ICRP recommendations.

Pregnancy

Once pregnancy is declared, the International Atomic Energy Agency and the International Commission on Radiological Protection recommend limiting additional fetal radiation dose to ≤1 mSv during the pregnancy.[172] This dose is the sum of the effective dose from external sources and committed effective dose from internal sources including: 1) irradiation of the embryo/fetus from mother's external exposure to radiation; 2) irradiation of the embryo/fetus from radionuclides in maternal tissues; and 3) irradiation of the newborn from radionuclides in maternal tissues. The toxicity of radionuclides depends on the radiation emitted rather than the chemical properties, except for radionuclides with extremely long half-lives. Most radiation exposures during pregnancy involve medical irradiation or air travel. In a study of diagnostic radiology workers in England, only 0.3% of the annual exposures exceeded 2 mSv with sealed-source technicians and radiotherapy theater nurses at the highest risk.[173] The exposure of medical workers to ionizing radiation is typically substantially below current recommendations; however, some areas of concern include angiography (e.g., cardiac catheterization) and C-arm fluoroscopy (hip pinning, pacemaker implants, exploration for foreign bodies).

In a postal survey of 9,208 pregnancies among 6,730 female and male radiographers, the overall risks of major congenital malformation (RR = 1.0; 95% CI: 0.9–1.2), chromosomal anomaly (RR = 1.4; 95% CI: 0.8–2.3), and cancer (RR = 1.2; 95% CI: 0.7–2.0) in offspring were not elevated based on general population rates.[174] The study suggested borderline excesses of chromosomal anomalies other than Down's syndrome in the children of female radiographers (RR = 3.9; 95% CI: 1.3–9.0; $n = 5$) and cancer in the children of male radiographers (RR = 2.7; 95% CI: 0.9–6.5, $n = 5$); however, the small numbers limit conclusions regarding causation.

TREATMENT

Preexposure

Most countries do not require dose limits for common medical imaging examinations; however, all medical radiation should be kept to the lowest level reasonably achievable (ALARA). Considerations prior to radiation exposure include reviewing the circumstances of each case, assessing the benefit of the radiographical procedure (e.g., the importance of the test to the management of the patient), determining options for alternative procedures with less or no radiation exposure, and

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discussing the risks/benefits of the radiographical procedure with the patient. The possibility of pregnancy should be considered prior to the use of X-rays. The risk of genetic damage during the first month is small; therefore, no special limitations on the use of X-rays [e.g., limitation of X-rays to the first 10 days of the menstrual cycle (10-day rule)] are necessary.[175] The risks of irradiating the ovum within several weeks prior to fertilization and the embryo within the first several weeks are similar.[176]

The sensitivity of the embryo and fetus to the effects of radiation depends, in part, on the time of gestation. During the pre-implantation period, the embryo is susceptible to the lethal effects of radiation; however, the embryo is relatively insensitive to teratogenesis and growth retardation. The embryo (i.e., the first 8 weeks of gestation) is most sensitive to the teratogenic effects of radiation as it enters the period of major organogenesis. No risk of mental retardation occurs during the first 8 weeks. The peak period of susceptibility to functional abnormalities of the central nervous system occurs in the early fetal period, primarily during weeks 8–15 of gestation. Radiosensitivity of the fetus decreases during the latter part of gestation.

A woman should not be denied a medically important diagnostic X-ray to diagnose and/or treat a medical condition only on the basis of her pregnancy.[177] The physician in consultation with the radiologist may elect to cancel or perform a complete or a modified X-ray examination based on an evaluation of the risks and benefits of the examination. Modifications to the examination include the use of leaded aprons over the abdomen and pelvis, the selection of only certain views, alternative nonionizing imaging (e.g., ultrasound), and the utilization of efficient collimators. Elective and follow-up X-ray examinations should be postponed to the postnatal period; however, the immediate medical care of the mother should take priority over potential risks to the fetus.

Postexposure

Counseling a pregnant patient about the risks of diagnostic X-rays following the radiation procedure requires a careful evaluation of the timing of radiation exposure in relation to her pregnancy, type of examination, associated maternal risk factors (age, disease, gestational history), radiation dose, and her personal beliefs. Most X-rays and nuclear medicine procedures deliver <50 mGy to the fetus; therefore, the risk of congenital malformations and growth retardation is small compared with spontaneous risks. The spontaneous abortion rate during pregnancy ranges from 30–50%,[178] whereas the average risk of major malformations is ~2.75–3% and the number of children born with any malformation ranges up to 10%. Lifetime cancer risks associated with the low, *in utero* radiation doses occurring during medical imaging are primarily theoretical based on extrapolation of Japanese atomic bomb data using a linear no-threshold model that assumes all radiation causes some risk of cancer. The actual risks are controversial with current epidemiological studies containing large statistical uncertainties that do not provide consistent estimates of small radiation risks for whole-body effective doses of <100 mSv, particularly for radiation doses below 10 mSv.[141]

Contrast-Induced Nephropathy

The two main risk factors for the development of acute contrast-induced kidney injury (CI-KI) are preexisting renal disease and the volume of contrast media. Intravascular volume depletion is also an important risk factor for acute kidney injury following contrast-enhanced radiographical studies; simple hydration with saline to treat dehydration and expand intravascular volume is an established therapy to reduce the incidence of CI-KI.[179] In a prospective study of 408 patients with ST-elevation myocardial infarction receiving isoosmolar nonionic contrast medium, the use of isotonic saline (1 mL/kg/hour) during and 24 hours after the procedure reduced the incidence of CI-KI by 48% when comparing the incidence in the saline group (11%) and the group without hydration (21%).[180] Mortality and the need for dialysis also increased in the group with CI-KI. The most important measures to prevent CI-KI include adequate hydration (with or without sodium bicarbonate) along with careful monitoring of fluid balance, serum creatinine concentrations, and urine volume during the first 72 hours after contrast-enhanced radiographical studies. The ideal isotonic saline infusion rate is unclear; however, the use of 1–1.5 mL/kg/hour 3–12 hours before the study and 6–12 hours after with the goal of a urine volume of 150 mL/hour is a reasonable protocol.[181]

In addition to the use of adequate hydration prior to contrast administration as a method to minimize the risk of contrast-induced nephropathy, several pharmacological agents (e.g., *N*-acetylcysteine, statins) have been studied as part of routine preparation. However, the role of these agents in the prevention of CI-KI remains undefined. In the PRESERVE clinical trial that was terminated early, a modified intention-to-treat analysis of 4,993 patients undergoing angiography with high risk for renal complications did not demonstrate the

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benefit of 1.26% intravenous sodium bicarbonate over intravenous sodium chloride or 5 days of oral acetylcysteine over placebo based on measured outcomes.[182] The primary end point was a composite of persistent ≥50% increase in serum creatinine from baseline at 3 months, initiation of dialysis, and death with the development of contrast-induced kidney injury as a secondary end point. Although the use of statins and sodium bicarbonate may reduce the incidence of CI-KI, the use of these preventive measures does not clearly reduce overall mortality or the need for renal replacement therapy, whereas hydration *with* forced diuresis does not reduce the incidence of CI-KI.[179]

Studies on the efficacy of *N*-acetylcysteine to prevent contrast-induced nephropathy after medical imaging are inconsistent. The addition of *N*-acetylcysteine (NAC) to preprocedural protocols may provide additional benefit to the use of IV hydration;[183] however, some studies did not demonstrate an additional benefit of adding *N*-acetylcysteine to preexamination fluid boluses in the emergency department.[184] The latter study found that the hydration of the patients undergoing contrast-enhanced CT was the most important factor in reducing contrast-induced nephropathy. The contrast-induced nephropathy rate was 3.3% in patients receiving ≥1 L normal saline prior to the examination compared with 12.9% in patients receiving <1 L saline preexamination. This difference represented a 69% risk reduction (OR = 0.41, 95% CI: 0.21–0.80). Although the use of sodium bicarbonate may reduce the risk of contrast-induced nephropathy compared with hydration alone,[185] the benefit of using sodium bicarbonate in addition to IV hydration and *N*-acetylcysteine in high-risk patients remains controversial.[186] The use of these regimens probably does not cause serious adverse effects; however, other, relatively small studies of moderate to high-risk patients have not detected statistically significant difference in the development of contrast-induced nephropathy following the use of 150 mg/kg NAC in 1000 mL of 0.9% sodium chloride (NaCl), 150 mEq of sodium bicarbonate in 1000 mL of 0.9% NaCl, or 1000 mL of IV saline infusion infused at 350 mL/hour for 3 hours.[187]

RADIOTHERAPY

HISTORY

Medical application of radium to the treatment of cancer began within a few years of the discovery of radium by Pierre and Marie Curie in 1898.[188] During the first two decades of the 20th century, radium therapy became a recognized treatment for eradicating cancer. Almost all states in the United States had hospitals with radium supplies to place radioactive material inside the body near a tumor (i.e., brachytherapy) by the early 1930s.[189] The use of brachytherapy was significantly curtailed by mid-century because the use of standard protective measures (e.g., shielding, long-handled instruments) failed to reduce risks for exposed practitioners and ancillary personnel.[190] The replacement of radium and radon by lower-energy radionuclides (^{198}Au, ^{60}Co, ^{137}Cs, ^{192}Ir, ^{182}Ta) marginally improved healthcare worker safety. The development of remote techniques to insert radionuclides into previously implanted applicators (i.e., afterloading) eliminated the radioactive source from the operating and recovery rooms, allowing implantation in a well-controlled setting following optimum dose calculation and loading.[191]

EXPOSURE

Approximately one-half of cancer patients in developed countries receive radiotherapy.[192,193] Common types of therapy equipment are cobalt teletherapy equipment and linear accelerators. The former units use γ-rays emitted from a sealed source of ^{60}Co; these units are designed to provide continuous shielding from the radionuclide unless the patient is ready for therapy. In contrast to betatrons and X-ray machines that do not emit radiation unless the power is switched on, sources using ^{60}Co or ^{137}Cs are potential radiation sources at all times. Linear accelerators produce high-energy X-rays or electron beams when energized; therefore, little radiation exposure occurs unless the unit is in operation. Electron beams are effective only for shallow tumors because of their limited penetration. When linear accelerators operate above 10 MeV, neutron activation can produce some radionuclides in the patient; however, the hazard to health personnel and the patient half-lives is minimal because of the short half-lives and low energy of these radionuclides. The development of computerized control of treatment parameters and 3-dimensional (3-D) imaging allows the delivery of radiation to complex volumes of tissue that closely resemble the tumor.[194,195] The transition from conventional radiotherapy to 3-D conformal radiation therapy (3D-CRT) produces increased radiation doses to the target volume with a reduction in the volume of normal tissues receiving high radiation doses. By contrast, a change from 3D-CRT to intensity-modulated radiation therapy (IMRT) involves

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more fields with dose-volume histograms suggesting larger volume of normal tissue receives lower radiation doses.[196] Modeling of the carcinogenic risks suggests the absolute risks of second primary malignancies associated with these two modalities are similar (2.1% and 1.7%, respectively).[197] Experimental radiotherapy applications include charged-particle radiotherapy (proton, heavy-ion) and boron neutron capture therapy. High construction costs, large size, need for specialized equipment, and availability of particle accelerators (e.g., cyclotrons, synchrotrons, linear accelerators) limit the use of these therapies for large numbers of cancer patients.[198] High-energy cyclotrons produce high-energy (14–66 MeV) neutron beams comparable with linear accelerators, but questions on efficacy, cost, and the extent of adverse reactions restrict this treatment to experimental uses (e.g., metastatic head and neck cancer, recurrent glioma).[199,200]

Brachytherapy is the branch of radiotherapy associated with the permanent or temporal placement of radioactive sources close to irradiated tissue. This technique produces the greatest risk to health personnel using medical radiation.[162] Grenz rays are ionizing radiation between UV light and X-rays (0.007–0.4 nm) on the light spectrum that possess very low energy levels in the range of 8–15 kV; these rays penetrate the first 2–3 mm of the skin with 50% of the energy absorbed in the first 0.5 mm.[201] Gustav Bucky developed the first grenz ray apparatus in 1923. This type of radiation has been used for several decades to treat benign dermatoses (e.g., hand eczema, psoriasis, allergic contact dermatitis);[202] however, basal cell and squamous cell carcinomas developed in patients receiving high skin doses (i.e., 100–293 Gy).[203,204]

CLINICAL RESPONSE

Deterministic Effects (Tissue Reactions)

The incidence and severity of deterministic effects are dose-related after the dose exceeds the threshold for the effect, typically >500 mSv.[205] Cell death and subsequent dysfunction after the exposure exceeding the threshold are characteristic of all deterministic effects except radiation-induced cataracts. The success of radiotherapy depends on the differential effect of the radiation on normal and cancerous cells. Of the 75 children of mothers exposed *in utero* to radiation doses of >1 Gy from radium therapy implanted for uterine cancer during the 1920s, 19 children developed mental retardation, microcephaly, and growth retardation. Three of these children had eye malformations (e.g., cataracts, strabismus, retinal degeneration, microphthalmia, optic atrophy).[206] Approximately 30% of cancer patients develop brain metastases with over ½ receiving whole-brain radiotherapy (WBRT). Frequently, cognitive decline occurs in patients treated with cranial radiation, particularly with WBRT).[207] Typically, the cognitive changes are late changes; however, neuropsychological testing may demonstrate abnormalities within 3–4 months post-radiation, particularly in executive function and memory.[208,209]

Carcinogenesis

Patients receiving radiotherapy develop an excess cancer incidence (i.e., 10–40% ↑RR) of second cancers in sites remote from the treatment fields, in addition to the excess incidence of sarcomas in the heavily irradiated in-field tissues.[196,210] The short life expectancy of patients receiving radiotherapy and the subsequent limited follow-up for solid tumors with latency period of >10 years complicate the determination of the incidence of second primary malignancies following radiotherapy. In a study of 104,760 1-year survivors of cervical cancer, the standardized incidence ratio (SIR) of second primarily malignancies in heavily irradiated sites (>3 Gy) remained elevated >40 years after exposure; the sites included colon, rectum/anus, urinary bladder, ovary, and female genitalia.[211] Sites irradiated with ≤3 Gy did not demonstrate a statistically significant elevation of second tumors at these sites. Current estimates suggest these tumors may occur in up to 20% of radiotherapy patients receiving fractionated radiation doses >2 Gy.[212] All second primary malignancies in these patients do not result from radiation because: 1) sporadic cancer occurs in any cohort; 2) genetic factors increase the risk of cancer in these patients; 3) exogenous factors (e.g., alcohol, tobacco, obesity) contribute to tumor induction; and 4) enhanced medical surveillance increases the detection of low-grade malignancies frequently undetected in the general population. The incidence of second primary tumors varies with several factors, including the tissue and organs, patient age at time of treatment, hereditary factors, dose, dose rate/fractionation, dose distribution, and size of the irradiated volume. The most sensitive organs to the development of secondary tumors after radiotherapy are the thyroid, breast, leukemia (excluding chronic lymphocytic leukemia), bone, central nervous system, basal cell skin carcinoma, and lung (especially in smokers).[213] Preliminary data suggest these tumors occur in a dose-response relationship, primarily after the absorption of radiation doses of >2 Gy as fractionated irradiation. Threshold doses for thyroid and breast cancers may be as low as 100 mGy

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in children and 500 mGy for lung tumors in smoking adults. The risk of brain tumors following irradiation in adults is relatively low.[214] Important follow-up studies of patients treated with radiotherapy for nonmalignant diseases include ankylosing spondylitis, arthritis, benign gynecological disease, hemangiomas, hyperthyroidism, peptic ulcer, polycythemia, postpartum mastitis, thymic hyperplasia, *T. capitis*, and tuberculosis.

Leukemia

Radiation-induced leukemia may manifest after a few years with an elevated risk persisting up to 15–25 years for acute myeloid and lymphocytic leukemia but not for chronic myeloid leukemia.[215] The latency period depends on leukemia subtype (e.g., chronic myelocytic leukemia has the shortest mean latency of ~5 years) and age at exposure (i.e., children are 2-fold more sensitive with shorter latencies than adults).[216] In an Israeli study of 10,834 children treated for *T. capitis* and followed for an average of 26 years, the relative risk for all leukemia was marginally statistically significant (RR = 2.3, 95% CI: 1.0–5.6; $n = 14$) with mortality increasing for three main subtypes at that time (acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia); no cases of chronic lymphocytic leukemia were reported.[217] The estimated radiation dose over 5 days to the upper brain was 121–139 rad (1.21–1.39 Gy) and 400 rad (4 Gy) to the bone marrow in the skull. The number of leukemia cases was too small to calculate the relative risks for the three leukemia subtypes. A smaller study of 2,224 New York children treated with scalp radiation for *T. capitis* following a median of 39 years did not detect an elevated mortality in the treated group; however, the standardized incidence ratio (SIR) was elevated for leukemia (SIR = 3.2; 95% CI: 1.5–6.1; $n = 8$).[218] A UK study of 14,106 ankylosing spondylitis patients demonstrated 3-fold increased mortality from leukemia when compared with the general UK population.[219] The risk of death from leukemia peaked 10–12.4 years after the single radiation treatment for ankylosing spondylitis. The estimated mean radiation dose for the active bone marrow in these patients was 3.83 ± 2.20 Gy with a range of 0–13.10 Gy using Monte Carlo methods.[220] Follow-up studies of women receiving radiotherapy for cervical cancer indicate an increased risk of radiosensitive leukemia subtypes.[210] In women receiving several Gy to the cervix for cervical cancer, the relative risk of leukemia increased 2-fold (RR = 2.0; 90% CI: 1.0–4.2); the radiation doses in this study did not increase the risk of chronic lymphocytic leukemia (RR = 1.03; $n = 52$).[221] The risk of leukemia after radiotherapy for cervical cancer increased with increasing mean bone marrow doses to 4 Gy while decreasing with higher doses. The risk of leukemia increased beginning 2–5 years after radiotherapy of the cervix with the peak observed/expected ratio peaking 10–15 years after radiotherapy.[215]

Thyroid

The thyroid gland in children is particularly radiosensitive with relatively high risk coefficients and convincing evidence for increased risk above ~1.1 Gy. The relative risk of thyroid cancer is highest for children <5 years of age, with the risk decreasing 2-fold between 5–10 years and 5-fold for adolescents.[216] Adults over 40 years of age have a low risk of developing thyroid cancer after radiotherapy. In a pooled analysis of five cohort studies (atomic bomb survivors, children treated for *T. capitis* and enlarged tonsils, infants irradiated for an enlarged thymus gland) and two case-control studies (cervical cancer, childhood cancer), the pooled excess relative risk per Gy (ERR/Gy) for children exposed before the age of 15 years was 7.7 (95% CI: 2.1–28.7).[160] The risk appeared linear to 100 mGy with doses mostly <10 Gy; however, little risk occurred when the radiation exposure occurred after 20 years of age. More thyroid cancer cases than expected occurred in the New York study on children irradiated for *T. capitis*, but the difference did not reach statistical significance.[218] The incidence of thyroid cancer was elevated in the study of 2,657 US infants irradiated during infancy for an enlarged thymus and followed for a mean of 37 years; 37 pathologically confirmed thyroid cancers occurred in the irradiated group vs. 5 in sibling controls.[222] After adjustment for sex and attained age, the relative risk for thyroid cancer in the irradiated group was 18.2 (90% CI: 8.5–43) compared with sibling controls. The estimated thyroid doses ranged from 0.03 to over 10 Gy with 62% receiving >0.5 Gy. The risk ratio declined with time; however, the risk remained elevated 45 years after irradiation. In a review of pooled data from 12 studies of thyroid cancer patients exposed to radiation before the age of 20 years, the relative risks increased supra-linearly through 2–4 Gy, flattened 10–30 Gy, and subsequently declined while remaining significantly elevated above 50 Gy.[223] The ERR/Gy varied from 1.4–4.5 with the upper bound similar to acute childhood Japanese exposures and previous pooled analyses of thyroid cancer studies.

Breast

Women aged 15–25 years are the most sensitive to radiation-induced breast cancer, whereas women over 40 years of age have little risk of radiation-induced

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breast cancer. Consequently, the breast cancer incidence rates after radiation exposure vary with the cohort studied. In an analysis of breast cancer rates in eight large cohorts with and without primary tumors, no single model described the breast cancer rates following radiation doses varying from protracted low-dose-rate exposures of 0.1–5 Gy (two Swedish skin hemangioma cohorts) to single or few high-dose-rate exposures of >5 Gy (US infants with thymic enlargement, Japanese atomic bomb survivors, Swedish benign breast disease patients, US acute postpartum mastitis patients) and highly fractionated high-dose-rate exposures (US tuberculosis cohorts).[224] The excess relative risk per unit dose was four times lower in the tuberculosis or thymus cohorts than in Japanese atomic bomb survivors, reflecting in part the low breast cancer background rates in Japanese women. In a study of 1,201 women irradiated during infancy for an enlarged thymus gland and their 2,469 nonirradiated sisters (controls), the adjusted rate ratio for breast cancer was 3.6 (95% CI: 1.8–7.3; $n = 22$).[225] The mean follow-up for this cohort was 36 years with the first case of breast cancer in the irradiated group occurring 28 years after irradiation. In a systematic review of three studies of the occurrence of breast cancer after radiotherapy for a primary cancer, the ERR/Gy varied from 0.13–0.27; these values were 5–16-fold lower than the risk for similar age at exposure and attained age in studies of lower doses,[224] primarily in studies without primary malignancies.[226] An important confounder in these risk estimates is ablation of the ovaries with doses exceeding 5 Gy and the subsequent suppression of hormonal stimulation of the breast along with the cell death associated with high radiation doses during radiotherapy. In a case-control study of >150,000 women irradiated for invasive cancer of the uterine cervix, the risk of breast cancer was not increased; the estimated average radiation dose was 300 mGy.[227] A confounding factor was the large number of women over 35 years of age and the decreasing susceptibility to breast cancer with increased age of exposure.

Brain

A systemic review of eight cohort studies including therapeutic radiation in children and the Life Span Study of Japanese atomic bomb survivors reported stronger association of ionizing radiation with meningiomas than gliomas; however, the strength of the association varied substantially between studies.[228] The overall summary ERR (excessive relative risk) for meningiomas was statistically insignificant (ERR = 1.81, 95% CI: -0.51 to 4.15, $n = 4$ studies, $I^2 = 44.8\%$, $P_{\text{heterogeneity}} = 0.142$). The authors did not calculate a summary ERR for gliomas. Follow-up studies of Israeli children irradiated for *T. capitis* infections during the 1950s first demonstrated an increased brain cancer risk after radiotherapy.[229] In a retrospective cohort study of 10,834 children with a mean age at irradiation of 7.1 ± 3.1 years (range, 1–15 years), the estimated median radiation dose was 1.38 Gy (95% CI: 0.98–6.0 Gy).[230] The estimated excessive relative risk per Gy (EER/Gy) after a median follow-up of 40 years was 4.63 (95% CI: 2.43–9.12, $n = 67$ exposed) for benign meningiomas and 1.98 (95% CI: 0.73–4.69, $n = 31$ exposed) for malignant brain tumors using a combination of unexposed, matched population, and sibling controls. The RR for meningiomas was 9.5 (95% CI: 3.5–25.7) and 2.6 (95% CI: 0.8–8.6) for gliomas; however, the wide confidence intervals and lack of statistical significance for gliomas suggest the estimates are imprecise.

Reproductive Abnormalities

Current medical evidence does not support an increased incidence of malformations, stillbirths, neonatal deaths, or cytogenetic markers of heritable genetic mutations in the offspring of women irradiated for cancer as children, adolescents, or young adults. In a case–cohort study of 472 Danish survivors of childhood and adolescent cancer and their 1,037 pregnancies, the risk of genetic disease in children of irradiated and nonirradiated survivors was similar (RR = 1.02; 95% CI: 0.59–1.44; $P = 0.94$).[231] The risk of congenital malformations ($n = 159$), stillbirths ($n = 7$), and neonatal deaths ($n = 9$) was not elevated in the offspring of female survivors receiving abdominopelvic radiation ($P = 0.7$) or children of mothers receiving mean uterine doses of 3.5 Gy up to a maximum of 100 Gy (RR = 2.3; 95% CI: 0.95–5.56). A retrospective cohort analysis of data from the US Childhood Cancer Survivor Study did not detect an increased risk of stillbirth and neonatal death among the offspring of 1,148 male survivors of childhood cancer.[232] The adjusted relative risk was 0.8 (95% CI: 0.4–1.6); the mean dose to the testes in 16 men was 0.53 ± 1.40 Gy. For girls irradiated before menarche, uterine and ovarian doses in the range of 1.00–2.49 Gy significantly increased the risk of stillbirth or neonatal death (RR = 4.7; 95% CI: 1.2–19.0; $n = 3$). The authors attributed the increased risk to radiation-induced uterine damage; however, the wide confidence intervals suggest imprecise estimates.

HEALTH SURVEILLANCE

A well-equipped laboratory with appropriate handling equipment and sufficient shielding is necessary

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to minimize the exposure of personnel to radiation during brachytherapy. Afterloading techniques allow the preparation of the patient and the insertion of applicators before the introduction of the radioactive source. Treatment rooms should contain alarms to indicate high radiation levels and to alert personnel to entry into the room during the operation. Radiation levels in the control room should be checked to ensure radiation in the control room remains below 25 μSv/hour.[162] Operators should stay in the control room during use of the equipment.

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Chapter 41

INTERNAL CONTAMINATION AND INDUSTRIAL, MEDICAL AND MILITARY RADIONUCLIDES

BACKGROUND

PHYSICAL PROPERTIES

Radionuclides are unstable atoms that spontaneously disintegrate while emitting ionizing radiation. Incorporation of radionuclides into the body following inhalation, ingestion, or absorption into wounds causes internal contamination. Deposition of these radionuclides exposes the tissues and organs to ionizing radiation primarily by the release of α- particles (helium nuclei), β-particles (electrons), positrons, Auger electrons, Coster–Kronig electrons (i.e., an Auger transition, when an electron from a higher subshell of the same shell replaces a vacant electron in a lower subshell), or photons (γ-rays). The same units and principles of dose-response apply to internal contamination and external radiation. The development of stochastic and deterministic effects following internal contamination depends on the absorbed dose (MeV/g) delivered to a specific organ.

Radioactivity

Radioactivity is an exposure measure related to internal dose. The actual relationship of radioactivity to dose depends on several factors including the mode of decay (α-, β-, γ-), energy of decay, physical half-life, and kinetics of the radionuclide in the body. The measure of radionuclide decay is activity; this transformation produces particles and photons capable of interacting with tissue and potentially causing DNA damage. The SI unit of activity is the *becquerel*; this unit is equivalent to 1 transformation/second. The *curie* is the traditional unit for activity; this unit is equivalent to 3.7×10^{10} transformations/second, as listed in Table 41.1.

Pure emitter radionuclides release either α- or β-particles; the subsequent decay product is a stable isotope; however, human exposure to pure emitters is rare. Because most common radionuclides emit γ-rays as well as α- and β-particles, the number of nucleus disintegrations per unit time is not necessarily equal to the number of particles emitted from the radionuclide. The amount of radioactivity released by nuclear operations varies from the mega (10^6) becquerel range for laboratory tracers to the giga-giga (10^{18}) becquerel range for nuclear reactor cores.

Dose and Dose Rate

The absorbed radiation dose in gray (Gy) represents the energy in joules deposited per kilogram of tissue. The equivalent dose in sieverts (Sv) is the absorbed dose (Gy) adjusted for the relative biological effects of each type of ionizing radiation emitted using the radiation weighting factor (Q, also known as quality factor) listed in Table 41.2. The committed equivalent dose reflects the amount of radiation over an expected lifetime of 50 years (for an adult) or 70 years (for a child) received by an organ following the intake of radioactive material. This value is multiplied by a tissue weighting factor (Table 41.3) to adjust the amount of radiation received by that tissue in relation to the total dose assuming uniform body irradiation. The committed effective dose

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TABLE 41.1. SI conversion units.

SI Unit	Traditional Units	Conversion Factors
Gray (Gy)	Rad	1 Gy = 100 rad
Sievert (Sv)	Rem	1 Sv = 100 rem
Becquerel (Bq)	Curie (Ci)	1 Bq = 2.702702702703 $\times 10^{-11}$ Ci

TABLE 41.2. Radiation weighting factors. In 2007, ICRP published a new set of radiation weighting factors (ICRP 103); however, the ICRP 60 guidelines remain the legal standards in Europe. The main difference between the two guidelines results from the use of mortality data modified for life lost by ICRP 60 guidelines, whereas ICRP 103 guidelines use incidence data rather than mortality data. The W_R for neutrons in ICRP 60 is a step function compared with a continuous function in ICRP 103 as defined by Equation 41.1. (Data from ICRP 60 and ICRP 103)

Radiation Type	Radiation Weighting Factor (W_R)
Photons, all energies	1
Electrons, myons, all energies	1
Protons and charged pions	2
α-particles, fission fragments, heavy ions	20
β-Particles	1
Neutrons	See Equation 41.1

is the sum of the products of the committed organ equivalent doses and the appropriate weighting factor.

Neutron radiation weighting factor (W_R) is a continuous function defined by Equation 41.1, which varies with the MeV (E_n).

$$W_R = 2.5+18.2e^{-[\ln(E_n)]^2/6} \quad \text{for } E_n<1 \text{ MeV}$$
$$W_R = 5.0+17.0e^{-[\ln(2E_n)]^2/6} \quad \text{for } 1 \text{ MeV} \leqslant E_n \leqslant 50 \text{ MeV}$$
$$W_R = 2.5+3.25e^{-[\ln(0.04E_n)]^2/6} \quad \text{for } E_n>50 \text{ MeV} \qquad \text{(Equation 41.1)}$$

Beta Emitters

In a medium, the average linear rate of energy loss (MeV/cm) of a heavily charged particle (e.g., α or β) is the stopping power. This value represents the retarding force acting on charged particles that results from the interaction of the particle with matter and causes loss of particle energy. There is little practical difference between stopping power and linear energy transfer (also known as restricted stopping power). Stopping power usually describes the total energy lost by the charged particle, whereas LET typically describes the energy lost by the charged particle from local absorption while traveling through the medium. Both linear energy transfer (LET, typically keV/μm in water) and stopping power are closely associated with radiation dose and biological effectiveness of the specific particle. High-energy β-particles lose ~2 MeV of energy per cm of tissue. As an approximation, 100 high-energy β-particles/cm/second = 0.1 Sv/hour. This dose rate increases for lower-energy β-particles because the rate of energy loss increases.

TABLE 41.3. Tissue weighting factors (W_T). In 2007, ICRP published a new set of tissue weighting factors; however, the ICRP 60 guidelines remain the legal standards in Europe. (Data from ICRP 60 and ICRP 103)

Tissue	Tissue Weighting Factor (W_T)	Contribution to Total W_T
Bone-marrow (red), colon, lung, stomach, breast	0.12	0.60
Remaining tissues: adrenals, extra thoracic (ET) region, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate (♂), small intestine, spleen, thymus, uterus/cervix (♀)	0.12	0.12
Gonads	0.08	0.08
Bladder, esophagus, liver, thyroid	0.04	0.16
Bone surface, brain, salivary glands, skin	0.01	0.04
	Total	1.00

Mass stopping power (MeV/cm^2/g) of the medium is the stopping power (MeV/cm) divided by the density (g/cm^2) of the medium. This value expresses the average rate of energy loss by a charged particle where the distance is measured as an aerial density (g/cm^2). In contrast to the stopping power, the mass stopping power of a gas does not depend on pressure because the density compensates for the pressure. In general, heavy atoms are less efficient than lighter atoms at slowing heavy charged particles because most of their electrons are too tightly bound in their inner shell to efficiently absorb energy.

The dose rate at a distance from a point source of radiation decreases with the square of the distance (the inverse square law) at a minimum. When the radiation traverses a medium (e.g., air or tissue) rather than a vacuum, the dose rate decreases even more with increasing distance from the source.

Gamma Rays

The exposure rate from a point source for γ-rays with energies between 0.07 and 4 MeV is approximately proportional to the rate of γ-ray emissions from the source. Their energy and exposure rate are inversely

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proportional to the square of the distance.

$$\text{Exposure Rate (mR/hour)} = (5{,}000 \times A \times E \times n)/d^2 \quad \text{(Equation 41.2)}$$

where

A = activity of source (mCi),
E = photon energy (MeV),
n = number of photons of energy E per disintegration,
d = distance (cm).

Because the relative biological effectiveness of γ-rays (and β-particles) is 1, the numerical value of the exposure rate is equivalent to the absorbed dose rate and the dose equivalent rate. The gray is related to the rad as fractions are to percentages (i.e., 1 Gy = 100 rad).

EXPOSURE

Although over 8,000 isotopes exist, only ~15 radionuclides are medically important. Sources for these isotopes include universities and medical settings (^{252}Cf, ^{14}C, ^{60}Co, ^{3}H, ^{125}I, ^{131}I, ^{32}P), industry (^{137}Cs, ^{60}Co, ^{192}Ir), and military/nuclear power uses (^{241}Am, ^{3}H, ^{239}Pu, ^{235}U). Internal contamination with radionuclides involves inadvertent radiation exposure from radioactive sources in industrial (e.g., materials testing, sterilization) and medical (e.g., theft of abandoned ^{137}Cs source in Goiania, Brazil) settings. Less commonly, these incidents occur during transportation accidents and rarely nuclear power malfunctions (e.g., Chernobyl, Fukushima) or intentional contamination (e.g., ^{210}Po poisoning of Alexander Litvinenko). Major radionuclide sources include the following isotopes: inhalation of ^{222}Rn, deposition of long- (^{40}K, uranium isotopes, thorium-232) and short-lived (^{226}Ra, ^{210}Pb, ^{210}Po) primordial isotopes, decay products of cosmic origin, and anthropogenic release of radionuclides ^{90}Sr, ^{137}Cs, ^{131}I, plutonium isotopes, ^{192}Ir, ^{241}Am, ^{106}Ru).[1] Tobacco smoke contains ^{210}Pb and ^{210}Po. Radon-222 accounts for ~50–80% of the background radiation dose. The average exposure to radionuclides from global fallout of fission products and waste from the uranium-plutonium fuel cycle (^{137}Cs, ^{134}Cs, ^{90}Sr, ^{242}Cu, ^{241}Am, ^{239}Pu, ^{241}Pu) is relatively small (<1%) compared with natural background radiation.

Natural Sources

The three main types of emission from radioactive substances are α-particles, β-particles, and γ-rays. These radiation types demonstrate different energy ranges, relative biological effectiveness, and effective distance. The body contains a background radionuclide level from the incorporation of naturally occurring and man-made radioisotopes in the air, food, and water. Life on earth evolved to coexist with this constant background radiation. The main source of radioactivity in the body is potassium-40 (^{40}K); the natural abundance of this radionuclide is 0.012%. Hence, the average 70 kg person contains 0.0169 g ^{40}K resulting in an annual absorbed dose of 0.16 mGy of β-radiation and 0.0.02 mGy of γ-radiation.[2] This dose amounts to ~0.175 mSv/year, which is relatively small compared to the total background dose of natural radiation.[1]

The other major radionuclide in the body is ^{14}C. The atmosphere constantly produces this radionuclide from the interaction of cosmic rays with nitrogen; however, the amount of radiation produced by internal doses of ^{14}C is ~18 times less than that of ^{40}K because ^{14}C emits β-particles with low energy levels. Other radionuclides include the α-emitters ^{210}Po, ^{226}Ra, and ^{90}Sr. These radionuclides deposit primarily in bones. The lung is the organ receiving the highest exposure to natural radionuclides principally in the form of α-particles from ^{222}Rn and ^{220}Rn (also known as thoron).

Cosmic Radionuclides

In contrast to the terrestrial radiation from primordial radionuclides, cosmic radionuclides form continuously from the bombardment of the atmosphere by cosmic radiation. This radiation produces radionuclides by a variety of reactions with atoms in the atmosphere including spallation and neutron activation. Spallation produces many hadrons (e.g., mostly neutrons) and atomic fragments following the interaction of light particles (e.g., proton, neutron, light nuclei) with high kinetic energy up to several GeV and a heavy nucleus. The latter reaction involves the excitation of atoms by the capture of neutrons and the subsequent emission of γ-rays, α- and β-particles, and neutrons. The most common radionuclides formed by cosmic rays are ^{14}C, ^{3}H, ^{22}Na, and ^{7}Be. The highest absorbed dose of cosmic radionuclides results from the ingestion of ^{14}C and, to a much lesser extent, ^{7}Be and tritium (H-3, 1 proton, and 2 neutrons). The very uncommon latter isotope is the only radioactive hydrogen isotope with a natural abundance of one trillionth of a percent.

Primordial Radionuclides

Terrestrial radiation results from radionuclides deposited during the formation of the earth. There are several dozen primordial radionuclides with radioactive

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half-lives equivalent to the estimated age of the earth. Primordial radionuclides are classified as: 1) **series radionuclides** (e.g., ^{238}U, ^{235}U, ^{232}Th), and 2) **nonseries radionuclides** (e.g., ^{40}K, ^{87}Rb). The former series decays by progressively forming several radionuclides to reach a stable lead isotope, whereas the latter series decays directly to a stable nuclide. The original source of these primordial radionuclides is the earth's crust or the underlying plastic mantle; transfer to the hydrosphere or the atmosphere allows absorption of these radionuclides via ingestion or inhalation. The amounts of radionuclides in the environment vary with location; unusually high radionuclide concentrations exist in old mining areas (Grand Junction, Colorado; Butte, Montana; Uravan, Colorado); major phosphate rock deposits in Florida; and the Reading Prong (geological formation extending from northeastern Pennsylvania to New Jersey and southeastern New York).

External Sources

The major sources of background radiation for the general population are radionuclides (e.g., ^{40}K, radioactive decay chain of ^{238}U and ^{232}Th) in rocks and soil near the earth's surface. ^{40}K emits β- and γ-radiation; therefore, this radionuclide can be both an internal and external source of radiation (γ-rays can penetrate from outside the body), whereas ^{87}Rb is primarily an internal radiation source (i.e., nonpenetrating β-emitter). Exposure to background radiation doses occurs outdoors from radionuclides in the soil, whereas most indoor irradiation results from inhaled radon daughters.[3] The amount of radioactivity in the soil does not vary substantially between different locations, except in a few areas (e.g., phosphate deposits from mining in Florida).

Internal Sources

^{40}K is the most important source of internal radiation, despite the relatively scarce distribution of this isotope in the earth's crust. The dissemination of ^{40}K in the food chain does not influence the amount of ^{40}K in the body because of hemostatic controls on potassium in the body. Rubidium is an alkali metal that is kinetically similar to potassium in the body; however, rubidium concentrations are much smaller than potassium. Consequently, the specific activity of ^{87}Rb is much lower than ^{40}K. Relatively large ingestions of terrestrial radionuclides occur in Eskimo and Indian populations of northwestern Canada and Alaska, where the lichen-reindeer-human food chain produces high ^{210}Pb and ^{210}Po concentrations in the diet.[3] The log-normal distribution of indoor radon concentrations creates substantial variation in the amount of inhaled radioactivity from radon daughters.

Radiopharmaceuticals

Radionuclides are the source of radioactive compounds used in radiotherapy and in diagnostic testing. The source of these radioactive compounds may be sealed (e.g., accelerators) or unsealed (e.g., radiopharmaceuticals). Table 41.4 lists the physical characteristics of radiopharmaceuticals.

Radiopharmaceuticals are present in unsealed sources in liquid, particulate, or gaseous forms that can be incorporated into the body. Only a few radionuclide-emitting α-particles are attractive diagnostic or therapeutic agents, in part because these particles are difficult to detect and measure. Radionuclides that emit β-particles are used almost exclusively in radionuclide therapy. The range of high-energy β-particles is usually greater than α-particles with sparse ionization producing low linear energy transfer (LET). The primary sources of β-emitting radionuclides are neutron activation of radioisotopes in nuclear reactors with a few radionuclides produced in charged-particle accelerators. The half-lives of radionuclides used in radiotherapy are short and average ~10 days.[5]

γ-Ray-emitting radionuclides are the most common source of radiation from radiopharmaceuticals used in medical applications; however, γ-rays increase the radiation delivered to the whole body with minimal radiation deposition in the target organ and increased exposure to medical personnel. γ-Ray-emitting radionuclides are useful for scintigraphic imaging for pharmacokinetics and dosimetry studies. Generally, γ-ray emissions from radiopharmaceuticals are relatively low energy with photons in the energy range of 75–250 keV.[6] The stable isotope tracers (deuterium or ^{2}H, ^{13}C, ^{15}N, ^{18}O) used in biomedical experimentation and diagnostic procedures do not emit ionizing radiation; therefore, they do not represent a radiation hazard.[7] Adverse effects from the administration of single doses of <250 g $^{2}H_2O$ have been limited to severe, transitory episodes of vertigo that probably result from alterations in the specific gravity of vestibular fluid.[8]

Medical Imaging

Most medical diagnostic radionuclides are single photon emitters (i.e., γ-rays with energies 80–360 keV) or positron emitters.[9] Positron emitters release positrons that react with electrons via antimatter annihilation to liberate two γ-rays of 511 keV. These two photons

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TABLE 41.4. Physical characteristics of the most common diagnostic and therapeutic radionuclides. Beta minus (β^-) decay involves the emission of an electron and the transformation of a neutron to a proton. Because the number of protons in an element determines the element, this process produces a different element. (Data from the United Nations Scientific Committee on the Effects of Atomic Radiation, UNSCEAR).[4]

Radionuclide	γ-Energy (keV)	Half-Life	Radiation Type
^{3}H	—	12.3 years	β-particles
^{11}C	511	20.3 minutes	Positron
^{14}C	—	5,730 years	β-particles
^{13}N	511	10 minutes	
^{15}O	511	2.06 minutes	
^{18}F	511	109.8 minutes	
^{32}P	—	14.3 days	β-particles
^{51}Cr	322	27.8 days	
^{57}Co	122, 136	271 days	
^{67}Ga	92, 184, 296, 388	3.2 days	
^{75}Se	121, 136, 265, 280, 401	120 days	
^{89}Sr	—	51 days	β-particles
^{90}Y	—	64 hours	β-particles
^{99m}Tc	140	6.02 hours	
^{111}In	173, 247	2.8 days	Auger electron
^{123}I	159	13 hours	
^{131}I	284, 364, 637	8.05 days	High-energy photons, many β-particles
^{133}Xe	81	5.3 days	β^- decay
^{153}Sm	70, 103	47 hours	β^- decay
^{165}Dy	95	2.3 hours	β^- decay
^{186}Re	137	91 hours	β^- decay
^{198}Au	412	2.7 days	β^- decay
^{201}Tl	135, 167	73 hours	
^{211}At	—	7.2 hours	α-particles

travel in opposite directions. Scintillation crystals in γ-cameras transform incoming γ-rays into photons of light that convert to electronic signals. This type of diagnostic study is called *scintigraphy*; in contrast to radiography and computed tomography, scintigraphy detects radiation emitted from **within** the patient. *Single photon emission computed tomography* (SPECT) involves a dedicated computer producing tomographic maps of γ-rays emitted directly from internal radionuclides. *Positron emission tomography* (PET) maps the anatomic emission source of the paired γ-photons generated by positron–electron annihilation occurring with the patient following administration of a positron-emitting radionuclide (e.g., tracer ^{18}F-fluorodeoxyglucose, FDG). In contrast to X-rays, CT, and MRI imaging techniques that provide details of normal and abnormal anatomy, SPECT and PET scans supply information on biochemical, metabolic, and functional changes in the body using 3-D color images; these techniques allow quantification of physiological parameters (blood flow, enzymatic activity, metabolism, protein density) *in vivo*. However, these methods do not usually provide the spatial resolution for adequate anatomical localization of the abnormalities; consequently, combined techniques (e.g., PET/MR, PET/CT) are necessary to provide precise anatomical lesion localization.[10] PET scans are clinical tools for probing biochemical pathways using short-lived tracers of carbon, oxygen, nitrogen, and fluoride created by cyclotrons to diagnose various diseases with local metabolic abnormalities (e.g., cancer, dementia, cardiac disease).[11,12]

SPECT scans are less expensive than PET scans; however, the latter is probably a more accurate imaging method.[13] Compared with plain radiography, SPECT scans provide a direct measure of function (e.g., cerebral

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TABLE 41.5. The United States Food and Drug Administration (USFDA) approved radiopharmaceutical for diagnostic imaging and radiotherapy.

Radiopharmaceutical	Indication
^{11}C-choline	PET imaging of prostate for cancer recurrence
^{14}C-urea	Diagnosis of *Helicobacter pylori* infection by detection of gastric urase
^{18}F-florbetaben	PET imaging of β-amyloid plaque density in brains of patients with cognitive decline
^{18}F-florbetapir	β-amyloid PET brain imaging for the presence of Alzheimer's disease
^{18}F sodium fluoride	PET bone imaging for altered bone formation
^{18}F-fludeoxyglucose (FDG)	PET imaging for evaluating cancer (abnormal glucose metabolism), cardiomyopathies, and seizures (abnormal glucose metabolism in epileptic foci)
^{18}F-flutemetamol	β-amyloid PET brain imaging for the presence of Alzheimer's disease
^{67}Gallium citrate	Evaluation of rapidly dividing cells present in bronchogenic carcinoma, Hodgkin's disease, lymphoma, and acute inflammatory lesions
^{111}Indium capromab pendetide	Imaging of prostate cancer to detect pelvic metastasis
^{111}Indium chloride, ^{111}Indium oxyquinoline	Radiolabeling for *in vivo* diagnostic imaging procedures
^{111}Indium pentetate	Radionuclide cisternography imaging
^{111}Indium pentetreotide	Scintigraphic imaging of neuroendocrine tumors with somatostatin receptors
^{123}Iodine iobenguane	Detection of pheochromocytomas and neuroblastomas; evaluation of cardiac size and failure
^{123}Iodine ioflupane	SPECT brain imaging to evaluate striatal dopamine transporter function and the presence of Parkinson's disease
^{123}Iodine sodium iodide	Thyroid morphology and function
^{125}Iodine-human serum albumin	Estimation of plasma and total blood volume
^{125}Iodine iothalamate	Estimation of glomerular filtration rate
^{131}Iodine-human serum albumin	Evaluation of cardiac output/circulation times, delineation of heart/great vessels, localization of placenta, detection of cerebral tumors
^{131}Iodine-sodium iodide	Evaluation of thyroid function/tumors, treatment of thyroid carcinomas
^{99}Molybdenum generator	Preparation of ^{99m}Tc sodium pertechnetate
^{13}Nitrogen ammonia	PET myocardial imaging for evaluation of coronary artery disease
^{223}Radium dichloride	Treatment of castration-resistant prostate cancer
^{82}Rubidium chloride	Myocardial PET imaging of suspected myocardial infarction
^{153}Samarium-lexidronam	Treatment of bone pain from metastatic osteoblastic bone tumors
^{89}Strontium chloride	Treatment of bone pain from metastatic osteoblastic bone tumors
^{99m}Technetium bicisate	SPECT imaging of suspected stroke
^{99m}Technetium disofenin	Evaluation of suspected acute cholecystitis
^{99m}Technetium exametazime	Detection of altered cerebral blood flow, localization of abdominal infection/inflammatory bowel disease
^{99m}Technetium-macroaggregated albumin	Evaluation of pulmonary perfusion
^{99m}Technetium-mebrofenin	Hepatobiliary imaging
^{99m}Technetium-medronate	Detection of abnormal bone formation
^{99m}Technetium-mertiatide	Evaluation of renal function
^{99m}Technetium-oxidronate	Detection of abnormal bone formation
^{99m}Technetium-pentetate	Brain imaging and kidney perfusion/function
^{99m}Technetium-pyrophosphate	Detection of abnormal bone formation, myocardial infarction, gastrointestinal bleeding
^{99m}Technetium-erythrocytes	Localization of gastrointestinal bleeding
^{99m}Technetium-sestamibi	Myocardial perfusion imaging agent evaluation of abnormal mammogram
^{99m}Technetium sodium pertechnetate	Cerebral radionuclide angiography, localization of placenta, imaging thyroid, salivary gland, and nasolacrimal drainage system, detection of vesicoureteral reflux
^{99m}Technetium-succimer	Evaluation of renal parenchymal abnormalities
^{99m}Technetium sulfur colloid	Imaging of reticuloendothelial cells in liver, bone marrow, and spleen; evaluation of gastrointestinal reflux/esophageal transit; and localization of lymph nodes draining tumor sites
^{99m}Technetium-tetrofosmin	Evaluation of myocardial perfusion
^{99m}Technetium-tilmanocept	Evaluation of lymph drainage from tumor sites
^{201}Thallium chloride	Evaluation of myocardial perfusion and localization of parathyroid hyperactivity
^{133}Xenon gas	Evaluation of pulmonary function and cerebral blood flow
^{90}Yttrium chloride	Radiolabeling of ^{90}Yttrium for radioimmunotherapy procedures
^{90}Yttrium-ibritumomab tiuxetan	Treatment of non-Hodgkin's lymphoma

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and coronary blood flow) with ^{123}I and ^{99m}Tc.[14] SPECT scans are sensitive for the detection of avascular necrosis of the femoral head, dementias, epilepsy, acute stroke, brain death, traumatic brain injury, Parkinson's disease, and acute cerebral infarcts.[15,16] Data on the use of SPECT scanning are too limited to use this imaging technique for the diagnosis of toxic injuries to the central nervous system and other organs.

Technetium-99 m (^{99m}Tc) is the most common radiopharmaceutical used for medical imaging.[9] Generators produce ^{99m}Tc by the decay of ^{99}Mo in an aluminum oxide column containing ^{99}Mo as sodium molybdate. Elution of this column with isotonic saline provides a source of ^{99m}Tc by yielding a stable solution of sodium pertechnetate ($Na^{99m}TcO_4^-$). Another important radiopharmaceutical is ^{123}I; this radionuclide easily combines with antibodies, peptides, and proteins for use in diagnostic nuclear medicine procedures.

Table 41.5 lists the FDA-approved radiopharmaceuticals used in radiotherapy and nuclear medicine imaging modalities. Diagnostic radiopharmaceuticals usually have short physical half-lives (hours to days) and emit low-energy γ-photons. In contrast, radioisotopes used in radiotherapy to ablate tissues and tumors deliver substantial radiation doses (i.e., β-particles from ^{131}I or ^{32}P) to selected tissue targets. Typical radiation doses from radionucleotides used in diagnostic imaging range from 3–14 mSv.[17] Radiation doses to other people near the patient are usually acceptably low. In a study of 80 adult patients receiving various diagnostic radiopharmaceuticals (^{111}In, ^{123}I, ^{99m}Tc, ^{201}Tl) in a nuclear medicine department, the maximum radiation dose rates at discharge ranged from 150 μSv/hour at 0.1 m from the patient, 30 μSv/hour at 0.5 m, and 7.3 μSv/hour at 1 m.[18] Only the bystander radiation dose from an ^{111}In leukocyte scan in an infant would have exceeded the 1-mSv level to the infant's parent, depending on the patient surface dose rate, parental habits, and the need for comforting the infant. ICRP Publication 128 provides a compendium of radiation information on major radiopharmaceuticals including effective radiation doses, absorbed organ/tissue radiation doses, biokinetic models, and biokinetic data.[19] The estimated effective doses from radiopharmaceutical administration depend on several factors, including the choice of biokinetic models, computational voxel phantoms used to simulate living tissues, and tissue radiosensitivity weighting factors.[20]

Radiotherapy

Radiopharmaceuticals used in radiotherapy typically emit most of their energy via β-particles rather than γ-photons, whereas most diagnostic radionuclides possess relatively short half-lives and emit low-energy (i.e., <300 keV) γ-rays only. The production of γ-rays increases radiation exposure of normal tissue beyond the targeted organ in the patient and health personnel involved with radiopharmaceutical administration.

Nuclear reactors produce most therapeutic radiopharmaceuticals by direct neutron activation of stable targets; however, charged-particle accelerators generate some of these isotopes. The half-lives of most therapeutic radionuclides are <10 days allowing multiple dosing. The half-life of the radiopharmaceutical must be compatible with the localization rate in the target tissue and clearance of the carrier molecule from normal tissue.[5]

TOXICOKINETICS

Absorption

Inhalation

The fate of inhaled particles (range 0.01–100 μm) depends primarily on particle size and their solubility in respiratory fluids. Particles of >100 μm usually settle on mucosal surfaces quickly before exhalation occurs, whereas particles of <0.01 μm are easily exhaled like gas molecules.[21] The upper respiratory tract is an excellent filter for particles of >7 μm in diameter; 90% of these particles are expectorated or swallowed. Inhaled particles of >3 μm impact large and medium-sized airways, whereas most particles of <0.5 μm deposit in alveoli and terminal bronchioles via random diffusion.[22] Mucociliary clearance removes most particles deposited on the bronchial mucosa and alveolar ducts within several hours; however, a significant portion of these smaller particles settles in the alveoli and alveolar ducts, where macrophages remove them or they enter the interstitial space directly. Thus, a soluble radionuclide may enter the systemic circulation directly by uptake through the alveolar membrane, or via particle transfer, to the lymphatic system. Macrophages can transfer insoluble radionuclides to peribronchial, hilar, and subpleural sites. For modeling purposes, the ICRP classifies the relative biological clearance of radionuclides into the following three categories based on the residence time for 1 μm particles: 1) D (days), half-time <10 days; 2) W (weeks), half-time 10–100 days; and 3) Y (years), half-time >100 days. The distribution of particles in the lung is not uniform, particularly for α-particles; however, this nonuniform deposition probably does not increase cancer risk compared with the uniform distribution of the same radiation amount throughout the lungs.[23,24]

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Ingestion

The physical and chemical properties of a radionuclide determine the amount of chemical passing through biological membranes. Although several factors (e.g., pH, solubility of the attached matrix) affect the transfer, radionuclides are classified as *transferable* or *nontransferable*. Transferable radionuclides are soluble in biological fluid; therefore, the gastrointestinal tract easily absorbs these radionuclides. Nontransferable radionuclides are either insoluble at all pH (e.g., certain metals or oxides produced at high temperatures) or soluble only at acidic pH (e.g., divalent mineral cations); salts of the latter (e.g., rare earth metals, plutonium, trans-plutonic elements) polymerize into hydroxides as the pH rises. The solubility of a radionuclide and its complex depends on the pH and the location in the gastrointestinal tract with the pH varying from the acid pH of the stomach to the alkaline environment in the duodenum. No material is entirely insoluble; therefore, even a highly insoluble compound (e.g., high-fired thorium oxide) may contain a small soluble fraction.[25]

Poorly absorbed (i.e., <10%) radionuclides include americium, antimony, californium, cerium, chromium, cobalt, curium, iron, manganese, mercury, plutonium, ruthenium, silver, uranium, and zirconium. For these radionuclides, the lower colon receives the highest dose of radiation because this portion of the gastrointestinal tract has the slowest motility.[26] Cesium, iodine, and tritium are almost completely absorbed from the gastrointestinal tract. Intermediate absorption occurs for radium (20%), strontium (30%), and phosphorus (80%).

Wound

Intact skin is usually an adequate barrier to the entrance of radionuclides into the body, except for tritium.[27,28] Internal contamination from wounds occurs when the radionuclide enters the blood or spreads to the regional lymph nodes. The transferability of the radionuclide depends on the physical and chemical characteristics of the wound including the pH, solubility, tissue reactivity, and contaminant particle size.[29] Prolonged exposure to relatively insoluble compounds (e.g., plutonium oxide) may result in some translocation because of the alteration of their physiochemical properties after protracted contact with the immune system.

Elimination

The process of radionuclide elimination from the body occurs through both radiological decay and biological elimination. Radioactive decays release energy from the nucleus in the form of one or more types of ionizing radiation (i.e., γ-rays, α- or β-particles, positrons, neutrons) when they reach a more stable energy state; this process varies with individual radionuclides (e.g., $^{131}I = 8$ days; $^{137}Cs \cong 30$ years). The physical half-life (λp) represents the time to reduce the radioactivity (measured in becquerels) to half of the initial level from only physical decay, whereas the biological half-life (λb) represents the time to excrete half of the absorbed radionuclide dose from the body. The effective half-life (λe) reflects both processes, as noted in Equation 41.3. The value of the effective half-life is always shorter than either the biological or the physical half-lives.

$$1/\lambda e = 1/\lambda p + 1/\lambda b \qquad \text{(Equation 41.3)}$$

where

λp = physical half-life,
λb = biological half-life,
λe = effective half-life.

Maternal-Fetal Kinetics

The radiation dose absorbed by fetal tissue depends on placental permeability to the radionuclide, fetal affinity for the radionuclide, and the type of radiation emitted from the radionuclide.[30] Inorganic iodides readily cross the placenta, whereas protein-bound iodides do not. A maternal ^{131}I dose as low as 12.2 mCi (9.2 mCi during gestational weeks 10–15) may destroy the fetal thyroid.[31] Radioactive fallout from nuclear reactor meltdowns and nuclear bomb detonations may cause elevated radioiodine concentrations in fetal thyroids.[32] Fetal uptake of radioiodine is low prior to 12 weeks of gestation; subsequently, the fetal thyroid readily absorbs radioiodine. At gestational ages of 14–22 weeks, radioiodine uptake (55–75%) exceeds adult uptake with radioiodine concentrations in the fetal thyroid 3–10-fold higher than adult thyroids.[33] Consequently, fetal hypothyroidism and cretinism may occur in pregnant women exposed to ^{131}I therapy.[34] Most inert gases probably diffuse across the placenta easily; however, ^{81m}Kr pulmonary function tests are an exception because of the very short 13-second half-life. The passage of ^{99m}Tc across the placenta depends on the associated anion; the pertechnetate oxoanion easily crosses the placenta, whereas other ^{99m}Tc radiopharmaceuticals may not cross, depending on the individual kinetics and labeled cell type. ^{90}Strontium easily crosses the placenta with the highest fetal radiation doses occurring in the red marrow.[35,36] The mouse placenta

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TABLE 41.6. Adopted ratios for the concentrations of elements in the fetus and mother (Cf/Cm) after maternal intake before and during pregnancy with corresponding placental/maternal ratios (Cp/Cm) based on the assumptions in the ICRP biokinetic models for determining fetal radiation doses. Isotopes of the same element display the same kinetics. (Adapted from Stather et al.).[42]

Element	Maternal Intake (Prior to Conception)		Maternal Intake (During Pregnancy)	
	Fetal/Maternal (Cf/Cm)	Placenta/Maternal (Cp/Cm)	Fetal/Maternal (Cf/Cm)	Placenta/Maternal (Cp/Cm)
Americium	0.01	0.1	0.1	2
Carbon, organic	1.5	1.5	1.5	1.5
Cerium	0.01	0.1	0.05	1
Cesium	1	1	1	1
H (HTO)	1.6	1	1.6	1
Plutonium	0.03	0.1	0.1 1st trimester 0.3 End 2nd trimester 1 Term	5
Ruthenium	0.01	0.1	0.2	2
Sulfur	1	2	2	2
Zinc	2	1	2	1
Zirconium	0.2	1	0.2	1

Abbreviation: HTO = tritiated water (^3H_2O).

is less permeable to cesium than strontium.[37,38] Some animal studies suggest a wide range of maternal/fetal ^{137}Cs ratios following radiopharmaceutical exposure; however, human reports suggest the ratio is close to 1.[39] The International Commission on Radiological Protection (ICRP) provides a detailed guide to maternal-fetal radiation doses following exposure to a variety of radiopharmaceuticals.[40] Table 41.6 lists the adopted fetal/maternal and placenta/maternal ratios for element concentrations used in the ICRP biokinetic models used to calculate radiation dose coefficients for the embryo and fetus following maternal intake of radionuclides. These values relate to reference levels for summing external and internal radiation exposures to compare with radiation protection guidelines rather than assessments of individual radiation exposure in epidemiology studies.[41]

DOSE

The absorbed radiation dose in the target organ largely determines the amount of tissue damage along with dose rate, radiation quality factors, fractionation, and tissue sensitivity. Therefore, determinants of radiation dose (e.g., amount, duration) transferred from the environment to the tissue include the portal of entry, the target organ where deposition occurs, the type of particles and/or photons emitted from the radionuclide, physiochemical properties affecting radionuclide absorption and distribution in the tissues, and the effective radionuclide half-life.[29] Shorter half-lives correlate to higher energy emission rates. The amount of radiation absorbed by an organ depends in part on the affinity of a radionuclide for that organ. Iodine and alkaline earth metals (strontium, barium, calcium) accumulate in the thyroid and bones, respectively, whereas alkali metals (sodium, cesium, potassium) spread throughout the body.

Cosmic and Terrestrial Radionuclides

The radiation dose from ingesting primordial radionuclides is much larger than that from cosmic radionuclides.[3] The average annual effective dose equivalent in the United Kingdom from ingesting ^{14}C is ~12 μSv compared with 3 μSv for ^{7}Be.[43] External radiation from terrestrial radionuclide-emitting α- and β-particles is small compared with the radiation from inhaling radon daughters or ingesting terrestrial radionuclides. US ground surveys of radiation dose rates from exposure to external terrestrial radionuclides in outdoor US environments indicate the annual dose ranges of 0.35–1.8 mGy.[3] The actual radiation dose received by an individual indoors depends on the location and the construction materials. Masonry buildings attenuate most γ-rays from the ground;[43] however, indoor γ-ray dose rates are usually higher because of the contribution of inhaled radon daughters.

Table 41.7 lists the estimated annual dose equivalents to soft tissues and bones from naturally occurring

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TABLE 41.7. Estimated annual soft tissue and bone dose equivalents in μSv from naturally occurring radionuclides. (Adapted from National Council on Radiation Protection and Measurements (NCRP)).[44]

Radionuclide	Soft Tissue	Osteocytes	Compact Bone	Bone Marrow
^{14}C	10	8	8	30
^{40}K	180	60	140	270
^{210}Pb–^{210}Po	140	1,400	700	140
^{226}Ra	3	170	90	15
^{228}Ra–^{228}Th	1.5	250	120	22
^{220}Rn	<0.1	—	—	—
^{222}Rn	7	—	14	14
^{230}Th	0.1	12	6	1
^{232}Th	0.1	4.2	2	0.4
^{238}U–^{234}U	4.6	6.4	3	0.4

radionuclides. α-Particles from ^{210}Po and other members of the primordial series account for most radiation received by bones, whereas ^{40}K generates most radiation received by soft tissues.[44]

Medical/Industrial Radionuclides

Skin

Radiopharmaceutical-induced dermal injury depends on the half-life and energy emitted by the radioactive isotope. α-Emitting radionuclides do not usually cause dermal injury unless the skin barrier is not intact, whereas γ-emitting radionuclides (e.g., ^{137}Cs, ^{60}Co, ^{192}Ir) may cause dermal injury from the emission of β-particles and soft X-rays.[45] High-energy, short-lived radionuclide-emitting β-particles pose a risk, particularly to the hands of nuclear medicine technologists handling these isotopes without proper shielding. These particles also dramatically affected the skin of Pacific atoll residents following the Castle Bravo thermonuclear test and first responders at Chernobyl.[29] The most severely affected patients in the latter incident received dermal radiation doses exceeding 40 Gy; the subsequent desquamation and disruption of the basal layer provided a portal of entry for fatal infections in many immunosuppressed patients.[46] Long-term dermal complications of cutaneous radiation exposure at Chernobyl include epidermal atrophy, telangiectases, altered pigmentation, fibrosis, keratosis, ulcers, and basal cell carcinomas. Fallout from nuclear detonations may provide sufficient β-radiation to cause skin burns; however, the maximum external effective distance of airborne β-particles is ~2 m, with β-radiation diminishing quickly as the distance increases by more than a few meters. Syringes and vial walls may not provide sufficient shielding for high-energy isotopes (e.g., ^{90}Y, ^{188}Re, ^{166}Ho). Computer models of β-radiation exposure (e.g., elutions from ^{99}Mo/^{99m}Tc generators) suggest the basal layer of the skin receives ~1 cGy/hour per 3.7×10^{-4} Bq/cm^2 (1 rad/hour per μCi/cm^2) from ^{99m}Tc, ^{111}In, and ^{201}Tl.[47]

Fetus

The two stages of the developing conceptus comprise the initial stage of organ formation (embryo, conception to day 56 postconception) and the subsequent growth stage (fetus, day 57 postconception to birth). Embryo and fetal radiation doses from maternal exposure to radionuclides depend on several factors including radiation type and amount, maternal and fetal radiopharmaceutical kinetics (absorption, distribution, elimination, diffusion across placenta), fetal age/growth, and amount of penetrating radiation (energetic β-particles, γ-rays, X-rays). Radiation doses to the offspring typically are similar or lower than the reference adult with a few exceptions (^{45}Ca, ^{14}C, ^{59}Fe, ^{3}H, $^{125/131}$I, $^{224/226}$Ra, $^{89/90}$Sr, ^{35}S).[42] The two major categories of fetal irradiation from maternal radionuclide exposure involve isotopes that diffuse across the placenta (e.g., strontium, iodine, gallium, xenon) and other radiopharmaceuticals (e.g., cesium, cerium, most lanthanides) limited by the placenta. The fetal/maternal concentration ratio of an element reflects the estimated ability of the element to pass the placenta; a ratio of >1 indicates the placenta easily passes the element, whereas ratios of <1 indicate the placenta acts as a barrier to the element. Table 41.6 lists placenta/maternal and fetal/maternal ratios for some common radionuclides.

The ICRP uses fetal/maternal concentration ratios to calculate the effective dose in offspring following maternal radionuclide intake before and after pregnancy for radiological protection purposes, rather than for evaluation of individual radiation exposures. The calculated value is expressed as the ratio of the effective dose of the offspring to the effective dose of the reference adult ($E_{\text{offspring}}/E_{\text{adult}}$). This value for a specific radionuclide depends on exposure time in relation to conception, fetal growth, and the physiochemical properties (e.g., gastrointestinal/pulmonary absorption, effective half-life). Tritiated water, ^{14}C, and ^{35}S easily enter the maternal circulation, distribute into body tissues, and diffuse across the placenta following ingestion. The offspring doses of these three radionuclides typically are up to twofold higher than adult doses for maternal ingestion during pregnancy, with the doses after ^{14}C dependent on the chemical form. Significant uptake of alkaline earth elements (Ba,

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TABLE 41.8. Adopted ICRP effective dose ratio of offspring to the reference adult ($E_{\text{offsprin}}g/E_{\text{adult}}$) for radionuclides following maternal ingestion at several different times in relation to conception. A number above 1 indicates the offspring dose exceeds the adult reference dose. (Adapted from Stather et al.).[42]

Radionuclide	Exposure (Gestational Week)			
	−26[a]	0[b]	25	35
^{241}Am	<0.01	0.01	0.01	0.01
^{140}Ba	<0.01	0.25	0.73	0.77
^{45}Ca	0.13	0.66	16.90	12.68
^{14}C	0.06	1.40	1.38	0.74
^{144}Ce	<0.01	<0.01	<0.01	<0.01
^{134}Cs	0.13	0.58	0.45	0.24
^{137}Cs	0.14	0.55	0.42	0.25
^{60}Co	0.12	0.68	0.50	0.41
^{55}Fe	0.24	0.29	0.70	0.76
^{59}Fe	0.03	0.78	1.50	1.33
^{3}H[c]	<0.01	1.28	1.78	1.44
^{125}I	<0.01	0.02	0.93	1.27
^{131}I	<0.01	<0.01	1.55	2.73
^{239}Pu	<0.01	0.01	0.04	0.10
^{224}Ra	<0.01	0.20	4.31	5.38
^{226}Ra	<0.01	0.05	1.79	1.29
^{106}Ru	0.02	0.11	0.04	0.05
^{89}Sr	<0.01	0.14	7.31	6.15
^{90}Sr	0.03	0.09	2.25	2.50
^{35}S	0.12	1.23	1.46	1.77
^{238}U	0.02	0.27	0.29	0.24

[a] 26 weeks before conception. [b] Conception. [c] Tritiated water.

TABLE 41.9. Adopted ICRP effective dose ratio of offspring to the reference adult ($E_{\text{offspring}}/E_{\text{adult}}$) for radionuclides following maternal inhalation of the element at several different times in relation to conception. A number above 1 (shaded area) indicates the offspring dose exceeds the adult reference dose. Absorption following inhalation is based on the absorption type (S, slow; M, moderate; F, fast; V, very fast). (Adapted from Stather et al.).[42]

Radionuclide	Exposure (Gestational Week)			
	−26[a]	0[b]	25	35
^{241}Am	<0.01	0.01	<0.01	<0.01
^{140}Ba	<0.02	0.04	0.06	0.05
^{45}Ca	0.04	0.21	0.74	0.41
^{14}C	0.01	0.04	0.03	0.01
^{144}Ce	<0.01	0.02	0.01	<0.01
^{134}Cs	0.12	0.59	0.45	0.24
^{137}Cs	0.14	0.54	0.41	0.24
^{60}Co	0.06	0.16	0.11	0.07
^{55}Fe	0.23	0.24	0.15	0.09
^{59}Fe	0.01	0.20	0.19	0.11
^{3}H[c]	<0.01	1.28	1.78	1.44
^{125}I	<0.01	0.03	0.92	1.27
^{131}I	<0.01	<0.01	1.62	2.84
^{239}Pu	<0.01	0.01	0.02	0.03
^{224}Ra	<0.01	<0.01	0.02	0.02
^{226}Ra	<0.01	0.01	0.02	0.02
^{106}Ru	0.01	0.03	0.01	<0.01
^{89}Sr	<0.01	0.05	0.44	0.34
^{90}Sr	0.04	0.10	0.31	0.26
^{35}S	<0.01	0.01	0.01	<0.01
^{238}U	<0.01	0.02	0.01	<0.01

[a] 26 weeks before conception. [b] Conception. [c] Tritiated water.

Ca, Ra, Sr) by the fetal skeleton occurs, particularly following exposure during the large fetal growth at the end of pregnancy. Although Ba, Ca, Ra, and Sr are chemically similar, the placenta limits the uptake of these radionuclides other than calcium; consequently, the effective doses of Ba, Ra, and Sr are lower than calcium. Additionally, the $E_{\text{offspring}}/E_{\text{adult}}$ ratio for ^{89}Sr is higher than ^{90}Sr because the half-life of the latter is much longer (29 years) than the former (50 days). Radioiodine uptake is much lower in the fetus than the mother until gestational week 12 when fetal thyroid function begins. Subsequently, the effective fetal dose substantially exceeds the mother's dose, particularly for the short-lived ^{131}I isotope (half-life, 9 days) compared with ^{125}I (half-life, 60 days). The poor gastrointestinal absorption and placental uptake of ^{241}Am and ^{239}Pu limit the fetal radiation dose of these predominately α-emitters to levels significantly below the adult reference value.

Tables 41.8 and 41.9 list the ratios of the effective dose to the adult reference dose following four oral and pulmonary exposure scenarios, respectively, before and during pregnancy. A value of >1 indicates the offspring dose is greater than the maternal dose, whereas a value of <1 indicates the maternal dose is greater than the offspring dose.

CLINICAL RESPONSE

Table 41.10 lists the sites of harmful tissue reactions (deterministic effects) soon after the inhalation and internal deposition of sufficient doses of a radionuclide along with cancer sites at risk following extended internal deposition of these radionuclides (stochastic effects).[48] Deterministic effects are very uncommon because of the large radiation doses required to cause these effects. Recognized serious deterministic effects associated with radionuclide exposures include the poisoning of Alexander Litvinenko (^{210}Po); bone marrow suppression, radiation burns, and deaths from the Goiania, Brazil, incident (^{137}Ce); and radiation pneumonitis and pulmonary fibrosis in early Mayak plutonium workers in the Soviet Union (primarily ^{239}Pu).

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TABLE 41.10. Following inhalation and internal deposition of radionuclides in sufficient radiation doses, organs/tissues affected by harmful tissue reactions (deterministic effects) soon after exposure or cancer (stochastic effects) from extended exposure. The absorption type represents the estimated absorption rate of the radionuclide from the respiratory tract into the blood using ICRP models.[49] (Adapted from National Council on Radiation Protection and Measurements (NCRP)).[48]

Radionuclide (Emission)	Absorption Type[a]	Tissue with Deterministic Effects	Tumor Sites with Stochastic Effects
$^{231}AmO_2$ (α)	Moderate (M)	—	Bone, lung
$^{144}CeO_2$ (γ and/or β)	Slow (S)	Lung	Lung
$^{137}CsCl$ (β and/or γ)	Fast (F)	Bone marrow	Total body
^{60}Co oxides (γ)	Slow (S)		Lung
$^{3}H_2O$ (β)	Fast (F)	—	Total body
^{131}I vapor (β)	Fast (F)	Thyroid	Thyroid
^{210}Po (α)	Moderate (M) or fast (F)	Lung, kidney, liver, bone marrow, others	Lung, kidney, blood cells, spleen
$^{238}PuO_2$ (α)	Slow (S) or moderate (M)	Lung, thoracic lymph nodes, bone liver	Lung, bone, liver
$^{239}PuO_2$ (α)	Slow (S) or moderate (M)	Lung, thoracic lymph nodes	Bone
^{226}Ra sulfate (α)	Moderate (M)		Bone
^{222}Rn and decay products	Fast (F)		Lung
$^{106}RuO_2$ (β)	Slow (S)		Lung
$^{90}SrCl_2$ (β)	Moderate (M) or fast (F)	Bone marrow	Bone marrow, bone
^{232}Th (α)	Slow (S)		Lung

[a] Absorption rate from the respiratory tract into blood based on Internal Commission on Radiation Protection (ICRP) models in ICRP Publication 66.

Tissues at risk for the development of cancer following prolonged exposure to internal deposits of radionuclides are listed in Table 41.10. Recognized stochastic effects include thyroid cancer after the Chernobyl nuclear reactor accident and ^{131}I radiotherapy, bone cancer in radium dial painters and ^{224}Ra-treated ankylosing spondylitis patients, bone and liver cancers in Thorotrast®-treated patients (^{232}Th and progeny), and lung cancer in underground uranium miners (^{222}Rn and progeny). Similar tissues are at risk following ingestion or absorption through wounds, except for insoluble forms retained in the lungs. Although wounds in contaminated areas of skin indicate possible radionuclide intakes, very heavy contamination is necessary to produce significant internal deposition including soluble radionuclides.

DOSIMETRY

Because the effectiveness of treatment depends on the type of radionuclide involved in the incident, optimal treatment necessitates a good history including initial determination of the location and time of the accident, presence of external contamination, identification of the radionuclides involved, route of exposure, and amount of radionuclide released. Helpful information includes size of released particles, solubility of the radionuclide, corrosiveness or toxicity of the radionuclide complex, and the effective half-life.

Conversion Factors

$1\,pCi = 0.037\,Bq$
$1\,pCi/L = 37\,Bq/m^3 = 2.22\,decays/minute/L$
$1\,Bq = 27\,pCi$
$1\,Bq/m^3 = 0.027\,pCi/L = 60\,decays/minute/m^3$

Analytical Methods

Although basic dosimetry calculations produce relevant clinical information sufficient to make treatment decisions, health physicists typically use complex mathematical functions to refine estimates of radiation exposures. Except for direct deposition of radionuclides into the body, the incorporation of the radionuclides is a time-dependent process that depends on the physiochemical characteristics of the individual radionuclide.[50] Estimation of absorbed radiation dose requires measurements of external radiation levels and the duration of exposure. Deriving estimates of internal radiation doses from whole-body counting methods introduces the possibility of errors resulting from nonhomogenous radionuclide distribution and inaccurate assumptions regarding radioisotope ratios (e.g.,

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americium/plutonium) following ingestion. Prompt identification of the type and amount of contamination is necessary to optimize treatment. Monitoring should begin within 24–48 hours after the radiation release to identify people with radiation doses exceeding the thresholds for serious deterministic effects.[26] Ideally, treatment for serious internal contamination should begin within 1–4 hours. Most episodes of internal contamination result from the inhalation of radioactive material, whereas a few cases of incorporation develop after the gastrointestinal absorption of the radionuclide or absorption from open wounds. Estimation of dose based on the results of bioassays is subject to several uncertainties including: 1) biological variability, 2) accuracy of the model, 3) interference from other radionuclides, 4) precision of analytical techniques, and 5) sample collection procedures.

A wide range of scenarios exist for individuals internally contaminated with radionuclides; and the type of instruments appropriate for screening persons exposed during these scenarios varies accordingly.[51] Accidental exposures in the medical, research, or industrial settings typically involve only a few individuals. Dose assessments usually occur at local facilities with bioassays and potentially whole-body counting using available instruments. Dispersal of a radionuclide with a radiological dispersion device (i.e., terrorist event) would involve tens of victims; nuclear medicine γ-cameras are makeshift whole-body counters for dose assessment and medical triage during these incidents. More rapid screening instruments are necessary following the radiological dispersal devices affecting hundreds or more patients. The use of portable survey meters near the safe zone is a first approximation used to triage individuals into ranges of effective dose (e.g., <50 mSv, 50–250 mSv, 250–500 mSv, >500 mSv) to enhance the triage process and medical treatment.

Instrumentation

Prompt initiation of appropriate triage and decontamination procedures as well as medical management requires knowledge of the presence of the radiation type, including α-particles, β-particles, or γ-radiation. Survey instruments usually measure γ-rays, α-particles, and/or β-particles rather than specific radionuclides. The best measure of internal contamination from γ-ray-releasing radionuclides is the use of detectors close to the body (i.e., whole-body or partial-body monitoring).[52] During triage situations, some handheld instruments and unshielded high-resolution detectors have sufficient sensitivity to identify accident victims requiring medical treatment. Portable instruments allow the detection of external contamination on the skin and clothing, quantification of the committed effective dose for victims of lower levels of internal contamination, identification of patients needing chelation therapy, and data collection for the estimation of individual health risks. General survey instruments with spectroscopy (e.g., handheld NaI crystal detectors with isotope identification via γ-spectroscopy picture) range in size from handheld to palm/pager size. Isotope libraries typically include Naturally Occurring Radioactive Material (NORM), nuclear industry, research, and industrial isotopes. Depending on the dose rate and energies, these detectors can often resolve isotopic mixtures. Handheld instruments are routinely used to measure ^{131}I and ^{125}I in the thyroid; they also are potentially useful for evaluating radiation exposures from ^{137}Cs, ^{60}Co, and ^{75}Se.[52] The main disadvantages of handheld detectors are their inability to quantify individual components in a radionuclide mixture released during a reactor accident and their lack of spectrometric capability.[52] The latter requires identification of radionuclide-specific action levels prior to measurements.

These relatively simple instruments accurately detect primarily radionuclide-emitting γ-rays with energies >200 keV and high emission probability. Handheld instruments (e.g., Mini Instruments type 44A) are available for the routine measurement of ^{131}I, ^{125}I, and ^{137}Cs using NaI(Tl) crystal detectors; the US Centers for Disease Control and Prevention (CDC) published tables to convert net count rates to effective radiation doses of 50, 250, and 500 mSv.[53] Calibration factors for these tables include gender, probe position, distance from probe to person, identity of radionuclide, particle size, lung solubility class, and primary route of absorption. Although radionuclides are detected by handheld devices (e.g., ^{60}Co, ^{75}Se, ^{192}Ir), determination of individual doses for highly exposed persons requires more sophisticated instruments.[52] Systems using unshielded, high-resolution detectors are not affected by the presence of naturally occurring radionuclides because NORM radionuclides do not interfere with the γ-ray spectrum.

Geiger counters measure γ-ray exposure rates and the presence of β-radiation depending on the type of probe used; both Geiger and scintillation detectors can typically detect internal contamination by γ-ray and high-energy β-particle-emitting radionuclides. The detection of α-particle or low-energy β-particle-emitting radionuclides (e.g., plutonium) requires special detectors or α-spectroscopy. Direct whole-body counters or chest counters are sensitive measures of the magnitude of internal radiation (e.g., ^{137}Cs, ^{134}Cs); however, the whole-body counters cannot detect the low levels of

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TABLE 41.11. Detection limits for various instrumentation during a specific ^{137}Cs release and the effective dose corresponding to the whole-body activity at the detection limit. (Based on Youngman).[52]

System	Detector (Diameter, cm)	Scanning Time (Minutes)	Detection Limit (Upper 95% CI, Bq)	Detectable Dose (mSv)[b]
Handheld instrument[a]	NaI(Tl) (0.25 × 3.2)	0.3	120,000	2.0000
Mobile γ-ray spectrometer	HPGe (3 × 5)	5.0	500	0.0070
Mobile γ-ray spectrometer	NaI(Tl) (5.1 × 5.1)	1.7	1,200	0.0200
Shielded, mobile instrument	HPGe (10.6 × 7.5)	10.0	200	0.0030
Shielded, mobile instrument	NaI(Tl) (7.6 × 13 × 41)	10.0	100	0.0010
Shielded, mobile instrument	NaI(Tl) (12.5 × 12.5)	10.0	450	0.0060
Shielded, mobile instrument	NaI(Tl) (5 × 5)	10.0	5,000	0.0700
Shielded, laboratory	4 HPGe (8 × 6.8)	20.0	33	0.0005
Shielded, laboratory	HPGe (10.6 × 7.5)	45.0	30	0.0004
Shielded, laboratory	5 NaI(Tl) (10 × 15)	45.0	18	0.0003

[a] Although reading is instantaneous, the count should be read for ~20 seconds to obtain the average value. [b] The scenario assumes whole-body activity at the detection limit 1 day after an adult inhales ^{137}Cs with absorption type F and activity median aerodynamic diameter of 5 μm.

external radiation emitted by internal contamination with many radionuclides. Consequently, results within the first few days can be confusing, even after the completion of decontamination measures. New field deployable γ-ray spectrometers with NaI(Tl) crystal detectors allow the rapid measurement of whole-body contamination by ^{131}I and ^{137}Cs with detection limits of ~1 kBq; this detection limit corresponds to a radiation dose of 1 mSv 1 day after exposure.[54] These monitors allow real-time spectrum analysis including thyroid (i.e., ^{131}I activity) and simple whole-body (i.e., estimate of internal contamination) measurements in the field. Portable portal monitors are available to measure β-/low γ-radiation (e.g., Ludlum 52-1-1, Ludlum Measurements, Inc. Sweetwater, TX);[55] several government agencies responsible for emergency preparedness (e.g., Canadian National Calibration Reference Centre for *In Vivo* Monitoring) evaluate instrumentation for field use.[56]

Portable hyper-pure germanium-based radionuclide identifiers (e.g., Detective™, Advanced Measurement Technology, Oak Ridge, TN) are available as easily deployable whole-body monitors that operate as standalone γ-ray spectrometry systems with the addition of appropriate software. These unshielded monitors cannot be operated in environments with significant contamination. The use of high-resolution high-purity germanium (HPGe) detectors allows the identification of individual radionuclides in mixtures; however, these very expensive systems are shielded and more difficult to transport.[57,58] Laboratory-based whole-body monitors with NaI(Tl) or HPGe detectors can identify radionuclide intakes of ≪1 mSv for radionuclide-emitting γ-rays containing energies of >100 keV.[59,60] Screening of persons exposed to radionuclides emitting few or low-energy γ-rays (e.g., ^{241}Am) requires shielded instruments with large detectors. Table 41.11 compares the detection limits, scanning time, and lower limit of detection for a specified ^{137}Cs exposure using several types of instruments for the detection of external radiation from internal contamination. The more sensitive instruments can identify radionuclide intakes occurring up to 100 days after exposure by detecting whole-body doses below 1 μSv. The relatively short half-life of ^{131}I limits screening for contamination by this radionuclide to a period of several weeks. External radiation emission from radiation sources inside the body does not occur when the ingested or inhaled radionuclide emits radiation incapable of penetrating the skin (e.g., α-particles). Urine samples are necessary to screen patients for this type of internal contamination and some radionuclides emitting few or low-energy γ-rays (^{241}Am), depending on the availability of sophisticated instrumentation. α-Spectrometry is the most common technique for determining the presence of α-emitters (e.g., actinides) in biological samples; however, inductively coupled plasma/mass spectrometry (ICP/MS) is very sensitive for measurements of long-lived radionuclides.[61] Analysis of urine samples by ICP/MS allows the detection of internal contamination by uranium, thorium, and actinides in the 1–2 μBq/L range, whereas most routine ^{239}Pu and ^{240}Pu bioassay analyses involve detection by α-spectrometry.[62] The establishment of a Radiation Monitoring Unit may be necessary to determine the extent of internal and external contamination.

Sample Collection

Sample analysis at the scene (e.g., nasal smears) may indicate the presence of inhaled radioisotopes/radio-

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TABLE 41.12. Sampling collection methods for internal contamination from radionuclides. (Ricks).[63]

Sample	Purpose	Method
Urine	Internal contamination	Four consecutive 24-hour urine specimens in urine collection container
Feces	Internal contamination	Four daily fecal specimens in refrigerated or frozen plastic containers
Vomitus	Internal contamination	Refrigerated or frozen plastic containers
Sputum	Respiratory contamination	5% propylene-glycol aerosol for deep specimen
Irrigating fluids	Radiological assessment	Save in sealed and labeled glass or plastic containers

active material assuming an absence of cross-contamination from other sources (e.g., hands). The extent and success of removing external contamination in the field is an important determinate of the significance of residual contamination in the Emergency Department. Analysis of samples or clothing collected at the scene may be necessary to establish the identity of the radionuclide responsible for the accident. The extent of external radiation, the early initiation of therapeutic measures, and the presence of associated injuries will influence the prognosis of the patient. In the presence of suspected internal contamination, samples should be collected to assess the extent of internal contamination. Table 41.12 lists the type and method of collecting these samples.

The analysis of wet nasal swabs gathered and dried in the field after a few minutes of exposure provides the most reliable method of determining the presence or absence of inhaled radioactive particles.[26] Nose blowing, insufflating water, and delayed collection (i.e., >20 minutes) reduce the accuracy of this method. Geiger counter counts of >500 dpm from both nostrils suggest significant exposure to radiation, whereas counts of <50 dpm indicate limited exposure. Elevated counts in only one nostril suggest external contamination. The amount of internal contamination with soluble radionuclides (cesium, iodine, tritium) can be estimated by the analysis of the urine for radioactivity and the use of elimination models developed by the NCRP.[64]

HEALTH SURVEILLANCE

Environmental Exposure

The Agency for Toxic Substances and Disease Registry (ATSDR) established a minimum risk level (MRL) of 4.0 mSv (400 mrem) for acute-duration (14 days or less) external exposure to ionizing radiation.[65] The derivation of this MRL was based on the development of neurological effects in children 10–11 years of age exposed at gestation weeks 8–15 during the atomic bombings of Hiroshima and Nagasaki.[66] The observed outcome in this study was an estimated reduction of 25 IQ points/Sv, resulting in a potential decrease of 0.25 IQ points at the MRL assuming an uncertainty factor of 3. The recommended MRL for chronic-duration (365 days or more) external exposure to ionizing radiation is 1.0 mSv/year (100 mrem/year) above background.

Pregnancy

Women should receive the minimum amount of medical radiation consistent with obtaining necessary clinical information, regardless of pregnancy status. During pregnancy, consideration should be given to the consequences of delaying the procedure, the fetal dose delivered, and the likelihood of additional medical procedures. Ultrasound has replaced some medical imaging techniques using radiopharmaceuticals. Significant risks of radiation-induced abnormalities occur at fetal doses of >100 mSv (10 rads). Radioiodine should be avoided during pregnancy unless it is necessary for the medical treatment of the mother and no other adequate substitute is available.

Occupational Exposure

Maximum levels for radionuclide deposition are based on dosimetry calculations using the same dose limits as those critical organs would receive for external radiation. The one exception is the radionuclides that deposit in bones because sufficient epidemiological data are available from radium exposure to allow direct calculation of allowable levels.

National Regulatory Commission

The US National Regulatory Commission (USNCR) established maximum annual radiation doses (Annual Limit on Intake, ALI). The ALI is the smaller value of the annual intake of a given radionuclide that would result in a committed effective dose equivalent to 50 mSv (5 rems, stochastic ALI) or a committed dose equivalent to 500 mSv (50 rems, nonstochastic or deterministic

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ALI) to any individual organ or tissue. The current radionuclide table for the former is available online at https://www.nrc.gov/reading-rm/doc-collections/cfr/part020/appb/. The "E" notation refers to the power of 10; a value of 6E–02 represents a value of 6×10^{-2} (i.e., 0.06), 6E+2 represents 6×10^{2} (i.e., 600), and 6E+0 represents 6×10^{0} (i.e., 6). The derivation includes multiplying the committed dose equivalent to an organ or tissue by a weighting factor, W_T.

For aerosols, the inhalation ALI and DAC assume an activity median aerodynamic diameter (AMAD) of 1 μm; the value depends on the retention classification (D, W, Y) of radioactive material in the pulmonary region of the lung. The nonstochastic ALIs were derived to avoid deterministic effects (e.g., acute tissue damage, organ dysfunction). The radiation limits for the public are 10% of the occupational limits.

Calculations of the concentrations of a radionuclide in air (Derived Air Concentration, DAC) and water involve limiting the values below the ALI in air and water, respectively. The derived air concentration values are designed to control chronic occupational exposures. These derived levels are specified for a given radionuclide depending on the physiochemical properties of the radionuclide. For radionuclides with long half-lives, the calculations are conservative because the limits assume that the body already contains the maximum permissible activity, whereas the controls begin before exposure. The ALI dose limits are designed for radiological protection; therefore, these values should not be used to calculate cancer risks.

International Commission on Radiological Protection

International Commission on Radiological Protection (ICRP) and USNRC have similar guidelines.

TREATMENT

Effective treatment requires identification of the specific isotope and an estimation of the internal radiation dose based on the calculated internal dose evaluated over 50 years (committed radiation dose) adjusted for the year of intake.[67] The presence of contamination in/around nostrils, mouth, open wounds, and/or face increases the likelihood of internal contamination. Identification of the radionuclide is critical because medical management is isotope-dependent. Of >8,000 isotopes, only ~10–15 are important isotopes in the civilian and military sectors including the Industrial 3 (^{60}Co, ^{137}Cs, ^{192}Ir), University 5 (^{14}C, ^{252}Cf, ^{125}I, ^{131}I, ^{32}P), and Military 5 (^{241}Am, ^{3}H, ^{239}Pu, ^{235}U, ^{238}U).[67] Table 41.13 lists the major categories involved with the medical management of internal contamination.

Several US government websites are available for valuable guidance on skin/wound decontamination, enhanced elimination, and chelation, including https://orise.orau.gov/reacts/ (Radiation Emergency Assistance Center/Training Center – REAC/TS, general information: 865-576-3131/after hours: 865-576-1005) and https://remm.hhs.gov/ (Radiation Emergency Medical Management, US Department of Health & Human Services). These websites provide algorithms for the diagnosis and management of internal contamination with links to the treatment of specific isotopes. Internal contamination usually occurs with external contamination except in unusual circumstances (e.g., inhalation and/or ingestion of fallout, intentional contamination of food or beverage). External contamination involves the deposition of radioactive material on the surface of the body. Treatment consists of removing the radioactive material (e.g., disrobing, cleaning the surface and any contaminated wounds); external contamination is typically easy to detect and remove. Internal

TABLE 41.13. Major categories of medical management of internal contamination along with examples of specific isotope, mechanism of action, and agent used.

Category	Isotope	Mechanism of Action	Agent
Alter absorption	Cesium, rubidium, thallium	Reduce gastrointestinal absorption	Prussian blue
Altered toxicokinetics	Uranyl ions	Inhibit binding of renal tubule surface proteins	Sodium bicarbonate
Block uptake	Radioiodine	Decrease thyroid uptake	Oral potassium iodide
Bronchoalveolar lavage	Plutonium (insoluble, inhaled contamination)	Direct removal	Lavage
Chelation	Plutonium	Binding/excretion	DTPA
Displacement	Strontium	Competitive binding of calcium	Oral aluminum hydroxide, IV calcium
Early excision	Fission-activation products	Minimize absorption	Surgery
Isotopic dilution	Tritium	Dilution/excretion	Increase fluid hydration

Abbreviation: DTPA = diethylenetriaminepentaacetate.

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contamination involves inhalation, ingestion, or dermal absorption of radionuclides that may concentrate in specific organs (e.g., thyroid, bone). Once inside the body, the kinetics of most radionuclides and their stable isotopes are similar.

Treatment is more complicated for internal than external contamination, often requiring drugs to reduce radionuclide absorption and/or enhance radionuclide elimination. Efficacy of these drugs depends on the selection of the appropriate drug for the radionuclide exposure and prompt administration (i.e., within several hours) of those drugs. Uptake of some radionuclides (e.g., ^{131}I) is rapid. One hour after the intravenous administration of ^{241}Am and ^{242}Cm to experimental animals, the blood contains 3–10% of the original dose with most of the radionuclide dose deposited in bone.[68] Frequently, few data are available on the effectiveness of these treatment modalities to reduce delayed health risks (e.g., cancer). Currently, available treatment techniques can reduce the body burden of incorporated radionuclides by factors ranging from 2–10;[26] however, treatment must begin within a few hours of exposure to optimize efficacy. The medical effects from internal contamination depend on the radiation dose, susceptibility, patient age (young children have greater susceptibility and longer expected exposure), and the general health of the patient. Consequently, the decision to initiate chelation should include a careful analysis of the estimated risks and benefits in consultation with radiation experts (Radiation Emergency Assistance Center/Training Center – REAC/TS, https://remm.hhs.gov, 24-hour phone: 865-576-3131/865-576-1005 after hours and/or Radiation Injury Treatment Network, https://ritn.net/, 612-884-8276; medical toxicologist; radiation health physicist/officer). Epidemiology studies suggest the cancer risk is not statistically evident below absorbed whole-body radiation doses of 0.1 Gy for the bone marrow and thyroid; for other organs, the estimated threshold radiation dose is 0.5 Gy.

First Aid

Associated injuries usually determine the need for first-aid measures; neither internal nor external radiation produces immediate life-threatening injuries. If radioactive contamination is suspected, gloves should be worn and the patient wrapped in a plastic sheet to prevent the spread of contamination. Serious overexposure to radiation is usually not a problem for health personnel unless a catastrophic event (e.g., Chernobyl) occurs; first aid should proceed as outlined under the treatment section on ionizing radiation incidents.

Triage

The main goal of radiological triage following an incident is the identification of patients most likely to benefit from further medical care. Governmental and institutional agencies (e.g., ICRP, NCRP) established action levels to guide patient triage following the release of radioactive radionuclides. The consensus of these agencies indicates that patients in radiation incidents receiving a committed effective dose exceeding 200 mSv should be considered for medical treatment.[52] The ICRP indicates clinically relevant functional impairment of tissues is unlikely at doses of <0.1 Gy with the threshold for deterministic effects being >1 Gy for most tissues. The IAEA uses a relative biological effectiveness (RBE)-weighted absorbed dose of 2 Gy-Eq for red bone marrow and 30 Gy-Eq for the lung, assuming the RBE for photons is 1, 7 for α-emitters in the lung, and 2 for α-emitters in the red bone marrow.[69] The IAEA recommends immediate medical evaluation, chelation if available, and accurate measurements of the organ-specific radiation doses exceeding their reference levels. The NCRP developed a Clinical Decision Guide for the maximum once-in-a-lifetime radiation exposure for stochastic risk that avoids deterministic effects. The RBE-weighted values for the red bone marrow and lungs were 0.25 Gy-Eq and 1 Gy-Eq, respectively. For most radionuclides and solubility types, Clinical Decision Guide values are lower for stochastic than deterministic (nonstochastic) risks. Nuclear detonation produces a complex environment where destruction of infrastructure, patient trauma, and limited resources create many triage issues. The Exposure and Symptom Triage (EAST) tool combines exposure maps with clinical assessments and single lymphocyte counts, if available, to identify patients with moderate radiation exposure (2–6 Gy) most likely to benefit from priority evacuation and cytokine treatment.

Decontamination

The Radiation Emergency Medical Management website (https://remm.hhs.gov/contamonly.htm#skip) provides specific guidance on decontamination measures for localized skin, open wounds, body cavity entrance sites (nose, mouth, ear), eyes, and hairy areas. The goal of skin and orifice decontamination is the reduction of the risks for acute dermal injury, internal contamination, and contamination of the environment and medical personnel.

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Skin

The goal of localized skin decontamination is the reduction of external contamination to ≤2 times the background radiation level beginning with two decontamination cycles (tepid water, mild pH-neutral soap) and, if feasible, a radiation survey after each cycle.[70] The horny layer of the skin is the most important barrier to penetration of radionuclides into the subcutaneous tissue and the systemic circulation. The lower layer of the stratum corneum can absorb and then release α-emitters within 24–48 hours after satisfactory skin decontamination.[29] Most contamination resides in the upper horny layer; this tissue desquamates in a few days. The treatment section for ionizing radiation incidents lists procedures for skin decontamination. Most radioactivity can be removed without seriously irritating the skin; therefore, excessive skin trauma from decontamination measures is unnecessary and allows systemic absorption of the radionuclide. Contaminated hair should be removed with clippers if contaminated by long-lived α-emitting radionuclides. Shaving should be avoided because of the tendency for radioactive material to enter hair follicles, where removal is difficult after the shaving process. Chemical methods of eliminating surface radioactivity seldom are necessary except for new radioactive deposits from wound seepage and extrusion of retained, radioactive foreign bodies.

In a 64-year-old worker with facial burns and multiple ^{241}Am-containing, imbedded foreign bodies following the explosion of an ion exchange column containing nitric acid and ^{241}Am, the efficacy of various decontamination measures was similar during the first 2 weeks of decontamination. Subsequently, the most comfortable decontamination measures were administered.[71] Decontamination measures in this incident included Ca-DTPA-pHisoHex or shampoo, 2-hour sweat rinse, Schubert's solution-pHisoHex or shampoo, and Clorox-rinse or shampoo. The Ca-DTPA solution was diluted 1 part Ca-DTPA to 2 parts normal saline.

Wound

All open wounds are contaminated until proven otherwise. Radionuclide absorption from a wound depends on a complex interaction between physiochemical parameters (solubility, pH, particle size, mass injected, specific gravity), biological factors (type of tissue, tissue perfusion, deposition depth, particle dispersion in the fascial planes), and the inflammatory response to the radionuclide or its complex. Wound decontamination should precede skin decontamination with techniques (sterile waterproof drapes, medium pressure irrigation with sterile saline) similar to the removal of foreign bodies. Wound radioactivity should be measured before and after decontamination measures. Embedded, radioactive particles should be lifted from the wound with forceps. If contamination levels remain high after primary irrigation, surgical debridement of the wound is an option after obtaining expert medical and health physics advice. The use of skin biopsy punches is not a routine treatment, but these instruments can be useful to remove persistently contaminated tissue around a puncture wound with expert consultation (e.g., Radiation Emergency Assistance Center/Training Center – REAC/TS, general information 865-576-3131/865-576-1005 after hours; or equivalent expertise) if important underlying structures are not damaged. Irrigation fluid should be collected and analyzed for its effectiveness in reducing radioactivity from the wound including removal of α-particles when present. Contaminated drapes, instruments, and dressings should be discarded prior to the beginning of the next irrigation.

With expert consultation, excision of the wound margins may be necessary, particularly if the wound margins are jagged or contamination is spread in the facial planes. The extent of the excision depends on clinical judgment considering the consequences of the excision and the amount of residual radiation. Long-lived α-emitters (e.g., plutonium) are the most serious long-term threats. Insoluble materials often form granulomas that can be detected and removed in 6 months. Follow-up wound counts may be necessary to evaluate the extent of wound contamination following external decontamination. Topical application of element-specific chelators should be considered, when the area of residual skin contamination is extensive and the radionuclide is soluble. Upon completion of decontamination as determined by the lack of further removal of radioactive material, the wound should be dressed with a waterproof dressing. All cases of suspected internal wound contamination should undergo analysis of urine and feces for radioactivity and/or whole-body counts to estimate residual internal contamination.[63]

Orifices and Eyes

Uptake of radioactive material may occur more rapidly through mucous membranes and body orifices than intact skin. Therefore, contaminated orifices require prompt removal of radioactive particles with special attention to prevention of contamination spreading through the nasal-lacrimal duct, ruptured

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tympanic membranes, and/or the gastrointestinal tract. Decontamination proceeds in the following order: 1) open wounds, 2) body orifices, and 3) intact skin. Ruptured globes should not be irrigated. After X-rays to exclude penetrating shrapnel in the globe, the eyes can be gently irrigated with copious amounts of saline or water if the globe is intact and examination indicates the presence of corneal contamination. The eye should be irrigated with the lids retracted and the stream directed from the medial canthus to the lateral canthus to prevent radioactive particles from entering the nasolacrimal duct.

Assessment of oral contamination involves gargling with water, expectorating, and a survey for evidence of contamination. If decontamination for oral contamination is needed, treatment includes brushing the teeth with toothpaste, 3% citric acid rinse, and 3% H_2O_2 gargles (pharyngeal contamination). Each nostril should be swabbed and surveyed for contamination including mucous from blowing their nose. Contaminated nostrils should be irrigated with saline as the head is tilted forward and nose pointed at the floor with careful attention to avoid swallowing the irrigation solution or pushing fluid down the nasal passages.

Reduced Absorption

Emetics/Stomach Lavage/Cathartics

Few data are available to guide gut decontamination following internal contamination with radionuclides. The efficacy of ipecac is unproven, and data to compare the effectiveness of the syrup of ipecac with stomach lavage following internal contamination are unavailable. Stomach lavage quickly removes material from the stomach; however, this technique potentially disrupts the pharyngeal and esophageal mucosa. There are inadequate data to document the efficacy of cathartics. This procedure has a theoretical advantage of reducing transit time in the colon, where relatively insoluble radionuclides may reside for hours. Additionally, the amount of radionuclide removed is time- and technique-dependent with clinical presentation typically after the 1–2 hours following exposure.

The option is the administration of a chelating agent before pushing the radioactive material through the stomach and into the duodenum where absorption occurs. These are radionuclide-specific and should be administered with expert advice. Aggressive treatment with traditional gastric decontamination agents (emetics, stomach lavage, cathartics) probably is not efficacious.

Binders

Aluminum-containing antacids in a single oral dose of 100 mL reduce intestinal absorption of radioactive strontium. Alkalinization of the stomach may increase the formation of less soluble hydroxides of certain metals; the acid milieu of the stomach reduces chromium absorption by converting hexavalent to less soluble trivalent chromium. Barium sulfate reduces radium and strontium absorption by forming relatively insoluble sulfates.

Magnesium sulfate is a cathartic that forms relatively insoluble sulfates with certain radionuclides (e.g., radium). Phosphorus therapy involves hydration plus phosphate binders. NCRP-suggested phosphate binders for ^{32}P include aluminum carbonate, aluminum hydroxide, potassium phosphate, dibasic potassium phosphate, sevelamer, sodium glycerophosphate, and sodium phosphate.[72] Phosphates demonstrate similar properties by reducing the gastrointestinal absorption of strontium.

Blocking and Binding Agents

The US FDA approved two agents for reducing internal contamination of radionuclides by blocking (potassium iodide) or binding (Prussian blue) the radionuclides. *Blocking agents* reduce the radionuclide uptake by saturating tissue with nonradioactive elements, whereas *isotopic dilution* refers to the reduction of radionuclide absorption by the administration of a stable compound. Blocking agents inhibit the uptake of radionuclides when administered before incorporation of the radionuclide into the tissues. Little data exist on radionuclide clearance to guide management using blocking agents, dilution, hemodialysis, or hemoperfusion.

Potassium Iodide

Potassium iodide (KI) in a single daily dose of 390 mg for 7–14 days is an effective blocking agent that prevents ~50% of radioactive iodine (^{131}I) uptake into the thyroid gland when administered within 6 hours of exposure; the effectiveness of this blocking agent rapidly diminishes by 12 hours postexposure. The occurrence of adverse effects following iodine administration (rash goiter, hypothyroidism, thyrotoxicosis, parotitis, fever, arthralgias/myalgias) requires clinical judgment regarding the radiation dose necessary to justify iodine administration. Adjunctive blocking therapy includes the use of propylthiouracil (100 mg t.i.d. for 8 days) and methimazole (10 mg t.i.d. for 2 days followed by 5 mg t.i.d. for 6 days); however, these blocking agents are less effective than KI.

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Insoluble Prussian Blue (Radiogardase®)

Prussian blue (insoluble ferric hexacyanoferrate) reduces the body burden of specific radionuclides by blocking uptake in the gastrointestinal tract followed by chelation/excretion of the radioisotope. Oral doses of 1–3 g of ferric ferrocyanide t.i.d. (Prussian blue) accelerate the removal of cesium, rubidium, and thallium from the gastrointestinal tract. The typical daily oral dose for adults and adolescents is 3 g t.i.d., whereas the daily dose for children 2–12 years of age is 1 g t.i.d. This compound has low toxicity with little absorption from the GI tract. Prussian blue is not a prophylactic agent.

Aluminum Hydroxide

The NCRP-preferred treatment for internal contamination with ^{226}Ra and ^{90}Sr is aluminum hydroxide (60–100 mL totaling 1,200 mg PO for adults and 50 mg/kg PO for children, not to exceed the adult dose), whereas barium sulfate (100–300 g PO as a single dose in 250 mL water) is a NCRP-suggested treatment. The dose should be administered within 24 hours of intake to block intestinal absorption. Additional NCRP-suggested treatments may include sodium alginate and calcium phosphate for internal radium contamination, calcium gluconate and barium sulfate for strontium inhalation, and stable strontium compounds (strontium lactate, strontium gluconate) for strontium ingestion.

Potassium Perchlorate

^{99m}Tc is a long-lived radionuclide that concentrates in the thyroid, salivary gland, lactating breast, and to a lesser extent in the alimentary tract, liver, and stomach, usually in the form of pertechnetate ($^{99}TcO_4^-$). In contrast to iodide, stable iodine (^{127}I) displaces pertechnetate in the thyroid and salivary glands; subsequently, pertechnetate does not bind organically for months in the thyroid. The NCRP recommends the use of potassium perchlorate to block the uptake of ^{99m}Tc by the thyroid gland.[72]

Diluting Agents

Dilution with water reduces tritium absorption by competing for the uptake of tritium. The administration of 3–4 L of fluid daily for 1 week with diuretics as needed reduces the biological half-life of tritium from 10 days to ~5 days.[29] The typical course of treatment is at least 3 weeks. Phosphate solutions (sodium, potassium salts, sodium glycerophosphate) function as diluting agents following excessive intake of ^{32}P. *Displacement therapy* refers to a type of dilution therapy (e.g., the use of calcium for the incorporation of ^{90}Sr) involving the competition for uptake into an organ (e.g., bone) between a stable element and a radionuclide of a different atomic number.

Enhanced Clearance

Indications for administering methods to enhance radionuclide excretion involve estimated radiation doses to critical organs exceeding values associated with adverse deterministic (nonstochastic) effects.

Chelation

Chelating agents bind metals in the extracellular fluid to form relative stable unionized ring complexes eliminated through the urine. Once radionuclide uptake into tissue occurs, the effectiveness of chelating agents decreases substantially. The primary chelator for radionuclides is diethylenetriaminepentaacetic acid (DTPA); this agent is available in the United States as the zinc and calcium salts from the US Strategic National Stockpile through the Oak Ridge Associated Universities, Radiation Emergency Assistance Center/Training Site (REAC/TS, general information 865-576-3131865-576-1005 after hours) Center, Oak Ridge Tennessee. The US FDA approved the intravenous use of DTPA for known or suspected internal contamination with three radionuclides (Am, Cm, Pu). Nebulization of DTPA is approved for adults exposed via inhalation.

Diethylenetriaminepentaacetic Acid (DTPA)

This compound effectively chelates the transuranium metals (plutonium, californium, americium, curium, berkelium), some transition metals (zirconium, niobium), and some rare earth metals (yttrium, promethium, lanthanum, scandium, cerium). The use of chelation for uranium exposure is not recommended because potentially excessive renal exposure to uranium may increase uranium-induced renal dysfunction, particularly when the systemic circulation contains >3 mg U, unless other chelatable radionuclides (e.g., plutonium) are present in sufficient concentrations to cause tissue damage.[29,73] Comprehensive support for the emotional needs of the patient undergoing chelation is an important aspect of the treatment program because treating patients with incorporated radionuclides frequently requires extended periods of isolation from their support systems. Figure 41.1 displays the chemical structure of diethylenetriaminepentaacetic acid (DTPA).

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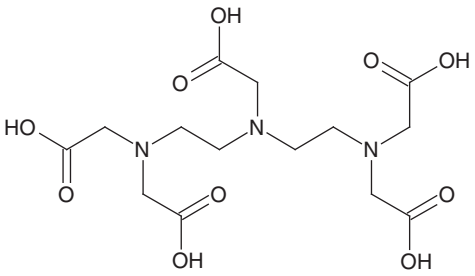


FIGURE 41.1. Chemical structure of diethylenetriaminepentaacetic acid (CAS RN: 67-43-6, DTPA).

Indications Clinical use of Ca-DTPA and Zn-DTPA primarily involves treatment of exposure to plutonium and americium at nuclear weapons or nuclear fuel processing facilities. The US distributor for DTPA is Golden State Medical Supply (https://gsms.us, 805-477-9866, Camarillo, CA). Rodent studies suggest DTPA is more effective at removing plutonium and americium than its lipophilic derivative Puchel (CAS RN: 75977-88-7)[74] or the sodium salt of N^1, N^5, N^{10}, N^{14}-tetrakis(2,3-dihydroxy-4-carboxybenzoyl)-tetra-azatetradecane (code name, 3,4,3-LICAM-C).[75] Animal studies also suggest Ca-DTPA is more effective than Zn-DTPA when administered promptly (i.e., several hours) to rats after exposure to ^{252}Cf, ^{239}Pu, and ^{241}Am.[76] Table 41.14 lists the NCRP-recommended uses of DTPA for chelation of absorbed radionuclides.

Dosage The initial recommended adult daily dose for both salts is 1 g DTPA as a single dose diluted in 250 mL normal saline and infused IV over 30 minutes. An alternative is the direct intravenous injection of 1 g of DTPA diluted in 10–20 mL of saline over 5 minutes. Extravasation of this solution may cause tissue necrosis.

TABLE 41.14. Diethylenetriaminepentaacetic acid, calcium or zinc salt (Ca-DTPA, Zn-DTPA) recommendations for chelation therapy of internal contamination by radionuclides based on National Council on Radiological guidelines.in NCRP Report 161.[72] Few clinical data are available to guide treatment decisions necessitating expert consultation (REAC/TS, medical toxicologist, RITN). The US Food and Drug Administration approved the use of DTPA for internal americium, curium, or plutonium contamination. The separate treatment recommendations in preferred and considered columns for treatment depend on the severity of exposure and medical evidence. The NCRP also considers DTPA the preferred treatment for other radionuclides of heavy metals including chromium, manganese, zinc, and zirconium.

Radionuclide	DTPA Treatment Recommendation	Other Potential Chelators
Actinium (Ac)	Considered	
Americium (Am)	Preferred	
Berkelium (Bk)	Preferred	
Californium (Cf)	Preferred	
Cerium (Ce)	Preferred	
Chromium (Cr)	Preferred	EDTA
Cobalt (Co)	Preferred	DMSA, EDTA, NAC
Curium (Cm)	Preferred	
Einsteinium	Preferred	
Europium (Eu)	Preferred	
Indium (In)	Preferred	
Iridium (Ir)	Considered	EDTA
Lanthanum (La)	Preferred	
Manganese (Mn)	Preferred	DFOA, EDTA
Neptunium (Np)	Considered	DFOA
Niobium (Nb)	Preferred	
Plutonium (Pu)	Preferred	DFOA, EDTA
Promethium (Pm)	Preferred	
Ruthenium	Preferred	EDTA
Scandium (Sc)	Preferred	
Thorium (Th)	Considered	
Yttrium (Y)	Preferred	EDTA

Abbreviations: DFOA = deferoxamine; DMSA = dimercaptosuccinic acid; DTPA = diethylenetriaminepentaacetic acid; EDTA = calcium disodium ethylenediaminetetraacetic acid; NAC = *N*-acetylcysteine.

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Administration of Ca-DTPA is recommended as soon as possible because chelation with radionuclides does not occur immediately after diffusion into tissues.[77] Ca-DTPA may be administered via nebulization in a 1 g dose over 15–20 minutes; the zinc salt produces a metallic taste. Because Zn-DTPA is less toxic than Ca-DTPA in experimental animals and depletes less Zn from the body, Ca-DTPA is usually administered during the first 24–48 hours, followed by long-term treatment with Zn-DTPA.[78] The exception is the initial treatment of pregnant women with Zn-DTPA. Animal studies suggest DTPA is more effective for water-soluble (e.g., chloride, nitrate) than water-insoluble (e.g., oxide) uranium compounds.[79] The duration of chelation by DTPA depends on the chemical form of the radionuclide. The uptake of some soluble complexes (e.g., plutonium nitrate) is rapid. DTPA effectively removes this complex from the blood; however, uptake of the relatively insoluble plutonium oxides is slow. Only small amounts of these complexes reach areas in the body where chelation can occur.

Pharmacokinetics DTPA absorption from the gastrointestinal tract is low (i.e., 3–5%); however, systemic absorption following parenteral administration is rapid.[80] The bioavailability of DTPA delivered by nebulization is ~20–30%. Following intravenous administration in the rat, the biological half-life of DTPA in the blood was 20–40 minutes; excretion occurred almost exclusively by glomerular filtration. Up to 75% of the chelate administered by inhalation appeared in the feces unabsorbed.

Adverse Reactions Generally, DTPA chelation is well tolerated;[77] the US DTPA Registry at the Radiation Emergency Assistance Center/Training Center (REAC/TS) reported no serious or long-term sequelae following parenteral administration.[80] Minor adverse reactions include nausea, diarrhea, skin rash, and pain near the injection site. Ca-DTPA binds trace minerals (e.g., zinc, manganese); in animal models, Ca-DTPA doses 100 times the recommended human dose produced hepatorenal lesions.

Other Chelating Agents

The efficacy of chelation is similar for isotopes and metallic forms of individual metals with limited clinical experience to determine the effectiveness of the therapy. Other potential chelating agents include sodium 2,3-dimercaptopropane-1-sulfonate or DMPS/unithiol (lead, mercury, polonium), penicillamine (copper, gold), and deferoxamine (iron). The decision to treat internal contamination with chelating agents involves careful consideration of the benefit of removing internal radioactive contaminants considering effectiveness and potential adverse effects compared with the risk of short- and long-term health effects from incorporation of the internal radiation dose without treatment. Table 41.15 lists the recommendations of the National Council on Radiological Protection and Measurements (NCRP) for chelating agents other than DTPA.

Bronchoalveolar Lavage

Lung lavage is a seldom-used experimental technique for removing large doses of long-acting, poorly soluble,

TABLE 41.15. NCRP treatment recommendations for chelating agents other than DTPA. Few clinical data are available to guide treatment decisions necessitating expert consultation (REAC/TS, medical toxicologist, RITN). Information on the efficacy of chelation of these isotopes is also available under individual metals.[72]

Radionuclide	NCRP Treatment Recommendation	Other Potential Chelators
Antimony (Sb)	BAL	Penicillamine
Arsenic (As)	BAL	DMSA
Bismuth (Bi)	DMSA	BAL, penicillamine
Cadmium (Cd)	DMSA	DTPA, EDTA
Copper (Cu)	Penicillamine	EDTA, trientine
Gallium (Ga)	Penicillamine	
Iron (Fe)	DFOA	Deferasirox, DTPA with DFOA
Lead (Pb)	DMSA	EDTA, EDTA with BAL
Mercury (Hg)	BAL	EDTA, penicillamine, DMSA
Palladium (Pd)	Penicillamine	DTPA
Polonium (Po)	BAL	DMSA, penicillamine

Abbreviations: BAL = dimercaprol, British anti-Lewisite; DFOA = deferoxamine; DMSA = dimercaptosuccinic acid; DTPA = diethylenetriaminepentaacetic acid; EDTA = ethylenediaminetetraacetic acid; NAC = *N*-acetylcysteine.

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inhaled α-emitting radionuclides (e.g., plutonium) deposited in the lungs; however, there are few data to determine the role of bronchoalveolar lavage and the efficacy of this procedure to reduce radiation pneumonitis and fibrosis. Lung lavage typically requires anesthesia. Animal studies using endotracheal intubation suggest 10 lung lavages with normal saline spaced 3–7 days apart remove ~25–50% of insoluble, inhaled particles.[81,82] The decision to use this procedure requires careful assessment of the risks of general anesthesia and potential benefits of bronchoalveolar lavage in consultation with radiation experts (e.g., Radiation Emergency Assistance Center/Training Center – REAC/TC, medical toxicologist, Radiation Injury Treatment Network or RITN). Consideration of this procedure usually occurs only when the estimated radiation dose from an α-emitting radionuclide is sufficient to produce radiation pneumonitis and fibrosis. Techniques to reduce gastrointestinal absorption may be necessary if the radionuclide can diffuse across the gastrointestinal mucosa after clearance from the tracheobronchial tree and secondary deglutition.

INDIVIDUAL RADIONUCLIDES

AMERICIUM

PHYSIOCHEMICAL PROPERTIES

^{241}Am is the most abundant isotope of the 13 americium isotopes resulting from the β-decay of ^{241}Pu. Table 41.16 lists the physical properties of the two most common americium isotopes (^{241}Am, ^{243}Am). The α-decay of ^{241}Am produces an X-ray with an energy of 60 keV (40% of the disintegrations). ^{243}Am is the only other americium isotope produced in significant quantities. The most important stable oxidation state in biological systems is the trivalent form.[83] These isotopes form weak complexes with components of the blood; hydrolysis and formation of americium and plutonium complexes are similar. Americium and curium oxides are more soluble than plutonium oxides; the former exists in the body exclusively in the trivalent oxidation state.

EXPOSURE

^{241}Am is one of the radionuclides released from anthropogenic sources (e.g., nuclear fission products, uranium–plutonium fuel cycle); this radionuclide is a constituent of some smoke detectors and thickness/density gauges. For the general population, the retention of this radionuclide from anthropogenic sources is usually small, including fallout from nuclear fission products and fuel components.[1] All plutonium contains some ^{241}Am from the neutron interactions of ^{241}Pu incompletely separated from ^{238}Pu or ^{239}Pu. The latter contains 15% ^{241}Am by activity.

TOXICOKINETICS

The main entry route for americium is inhalation or wound absorption. Absorption of ^{241}Am by the gastrointestinal tract is low (i.e., ~5%), whereas pulmonary absorption of most americium complexes is moderate. Urine samples from volunteers indicate the gut transfer factor (f_1 values) for americium in cockles ranges up to 2.6×10^{-4} with an arithmetic mean of 1.2×10^{-4}.[84] The toxicokinetics of americium and plutonium differ. The initial clearance is more rapid for americium than plutonium oxides, with the initial americium oxide half-life of 11–28 days; for modeling purposes, the IRCP inhalation model uses class W (weeks). In human studies, most

TABLE 41.16. Physical properties of ^{241}americium (^{241}Am) and ^{243}americium (^{243}Am) isotopes. (Adapted from Nenot).[83]

Physical Property	^{241}Americium	^{243}Americium
Radioactivity half-life (years)	458	5.66×10^{-4}
Principal decay mode	α-particles, X-rays	α-particles
Mean α-energy (MeV)	5.49	5.27
Specific activity (μCi/g)	3.25×10^{6}	1.99×10^{5}
Mass/μCi (g)	3.08×10^{-7}	5.02×10^{-6}
Relative mass[a]	0.0189	0.308

[a] Mass relative to 1 μCi of ^{239}Pu set as 1.

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americium oxides deposited in the lungs have half-lives of tens of days, with the remainder having retention half-lives of months to years.[85] Retention of ^{241}Am in the ribs complicates the analysis of long-term ^{241}Am retention in the body. The major sites of deposition are the liver and bones with long effective half-lives of 2–3 years and >20 years, respectively.[1,86] These sites account for ~50% and 30% of the ^{241}Am incorporation, respectively, with the remainder divided into other organs (e.g., kidney, spleen) based on the IRCP model. Case reports suggest that experimental kinetic data do not fit well with the ICRP multiparameter models, including the type M model for acute americium inhalation. In contrast to prediction of the model, urinary americium excretion was not detectable after the estimated intake of ~200 Bq of $^{241}AmO_2$ powder using fecal sampling and monitoring (lung, whole body).[87] A 76-year-old man died of preexisting coronary artery disease 11 years after a massive ^{241}Am cutaneous exposure requiring 4 years of chelation; the estimated ^{241}Am deposition at autopsy was 540 kBq with 90% in the bones, ~5% in the liver, and 3.5% in the muscle/fat.[88] The highest soft tissue concentrations occurred in liver (22 Bq/g), larynx (15 Bq/g), and red marrow (9.7 Bq/g).

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

In the Hanford worker contaminated with ^{241}Am, pathological findings at autopsy revealed markedly decreased bone marrow cellularity associated with dilatated blood sinusoids.[89] Damage was greatest on bone surfaces, particularly the almost acellular vertebra bodies with extensive bone marrow peritrabecular fibrosis in the ribs and clavicle. This patient underwent aggressive chelation with DTPA to reduce the liver burden and prevent liver failure. Animal studies indicate mice develop liver, bone, and hematological cancers following chronic intraperitoneal, inhalation, and injection.[1]

CLINICAL RESPONSE

An explosion in the ion exchange column containing nitric acid and essential pure ^{241}Am at the Hanford, Washington, nuclear weapons site contaminated a 64-year-old worker with >5,000 μCi of ^{241}Am; the internal ^{241}Am deposition exceeded occupational standards >1,000-fold. The cumulative absorbed radiation doses calculated after his death from preexisting cardiovascular disease 11 years postaccident were 18 Gy to the bones, 520 Gy to the bone surfaces, 8 Gy to the liver, and 1.6 Gy to the lungs.[90] Radiation-induced damage primarily involved lymphopenia and thrombocytopenia with an initial nadir of the lymphocyte count 7 days postexposure (530 lymphocytes/mm^3) and cytogenic changes in the lymphocytes;[91] Zn-DTPA chelation began 2.5 hours after exposure and continued over 2 years.[92] The IARC concluded there is sufficient evidence in experimental animals for carcinogenicity of mixed α-emitters including americium.[1]

TREATMENT

Intravenous Ca- and Zn-DTPA (diethylenetriaminepentaacetic acid, USFDA-approved since 2002) effectively chelate americium and several other transuranium ions (berkelium, curium, californium, plutonium);[93] clinical experience with these chelating agents primarily involves treatment of internal contamination with plutonium and americium. Nebulized DTPA is an option for chelating inhaled ^{231}Am depending on the level of contamination in the nares and the absence of pulmonary disease (e.g., asthma).[73] Both animal experiments and clinical experience confirm the prompt and prolonged use of DTPA as the chelating agent of choice. Therapy with DTPA should begin as soon as possible (i.e., ideally within a few hours), because even extended and intensive chelation therapy does not remove americium bone deposits.[94] Weekly chelation with DTPA over 30 months removed about half of the total-body americium burden, primarily from the lungs and liver in a man exposed over several years to ^{241}Am; however, the bone deposits were relatively unaffected.[95] Ca-DTPA is the chelating agent of choice during the first 24 hours of internal americium contamination because Ca-DTPA is more effective than Zn-DTPA during this time. After this time, both DTPA preparations are effective with the latter depleting zinc, magnesium, and manganese body stores significantly less than Ca-DTPA; clinical experience with Zn-DTPA indicates this chelator has a good safety profile during long-term therapy (e.g., 2 years).[96] In addition to trace metal depletion, other potential adverse effects include headache, lightheadedness, nausea/diarrhea, chest pain, allergic reactions, dermatitis, and local tissue reactions.

Suggested guidelines for initiating DTPA treatment for ^{241}Am nitrate and dioxide exposures include consideration for estimated internal doses of 20–200 mSv and implementation of treatment at doses exceeding 200 mSv.[93] The recommended initial Zn-DTPA dose is 1 g IV, followed by daily 1 g doses. The initial nebulized dose of Ca-DTPA is 1 g in 10 mL normal saline

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via standard nebulizer with the switch to the intravenous route dependent on the decrease in lung burden and corresponding increase in systemic absorption of ^{231}Am from the lung. The duration of treatment depends on the amount of internal contamination and the response of the patient based on monitoring radioactivity by weekly blood, urine, and fecal samples. Indication for treatment varies between organizations depending on the estimation and uncertainties of the absorbed radiation dose. Guidelines for soluble and moderately soluble chemical forms in adults include considering the initiation of chelation when the estimated committed effective dose is 20–200 mSv and definitely implementing treatment when the dose exceeds 200 mSv.[93]

CALIFORNIUM

PHYSIOCHEMICAL PROPERTIES

Californium is a member of the actinide series; the most common of the 13 isotopes (242–254) is ^{252}Cf. The latter has a unique pattern of decay with emission of a 6.12 MeV α-particle and a fission fragment; spontaneous emission of 3.8 fast neutrons results from each fission. The fragment accounts for ~50% of the total decay energy. ^{249}Cf decays by emitting α-particles and smaller amounts of γ-radiation. The decay energy/disintegration of ^{249}Cf is ~½ of ^{252}Cf.

EXPOSURE

^{252}Cf primarily is a neutron source. An encapsulated source of ^{252}Cf is substituted for radium in intracavitary and interstitial applications in radiotherapy. In industry, applications include neutron excitation in nuclear reactors, neutron activation analyses, neutron radiography, and neutron diffraction measurements.[25]

TOXICOKINETICS

Absorption of ^{252}Cf occurs primarily from the lungs and open wounds because intestinal absorption is negligible.[97] Retention, disposition, and distribution of californium and americium are similar, whereas the biological half-life of ^{252}Cf is 175 years and the effective half-life is 2.2 years. Deposition occurs quickly in the skeleton. The principal means of detecting internal contamination with ^{252}Cf is monitoring the urine for α-particles.[98] Following an initial half-life of 1 day and the initiation of chelation therapy, urinary elimination half-lives ranged from 10–12 days in two workers contaminated by inhaled californium oxide.[99]

CLINICAL RESPONSE

Although data on human carcinogenicity are few, the IARC states there is *sufficient evidence* in experimental animals for the carcinogenicity of mixed α-particle emitters including ^{249}Cf and ^{252}Cf.[1]

TREATMENT

Because of the lack of human data, treatment is based primarily on animal data. Treatment with Ca-DTPA should begin immediately to rapidly reduce deposition of ^{252}Cf in the bone; this chelator is USFDA-approved for the treatment of internal contamination by ^{252}Cf. Once deposition occurs, removal of significant amount of ^{252}Cf is difficult; however, animal experiments suggest removal continues 3 weeks after the intravenous administration of ^{252}Cf.[100]

CERIUM

PHYSIOCHEMICAL PROPERTIES

Cerium is one of the lightest (atomic number 58) members of the lanthanide group of elements that range in atomic number from 57–71. Of the 20 cerium isotopes with masses of 129–148, the 4 naturally occurring isotopes are ^{136}Ce, ^{138}Ce, ^{140}Ce, and ^{142}Ce. The most important radioisotopes are the β-emitters, ^{141}Ce, ^{143}Ce, and ^{144}Ce; these radionuclides are released abundantly in nuclear fission reactions with relatively long half-lives and could potentially cause prolonged retention in the body.

Table 41.17 lists the decay products of the important cerium isotopes. Insoluble cerium complexes include carbonates, potassium sulfates, oxalates, aluminosilicates, and oxides, whereas chlorides and citrates are relatively soluble cerium complexes. Because of the limited solubility of hydroxides, lanthanides do not exist as ions at physiological pH.

EXPOSURE

The primary sources of cerium radionuclides were relatively insoluble chemical complexes (e.g., oxides) of ^{141}Ce, ^{143}Ce, and ^{144}Ce released from nuclear explosive

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TABLE 41.17. Radioactive decay chains of cerium radioisotopes with half-lives of 17 hours–284 days. All these isotopes are considered stable except 137 (half-life 60,000 years); however, the half-life is sufficiently long to be considered stable for radiation dosimetry. (Adapted from National Council on Radiation Protection and Measurements).[101]

Isotope	Half-Life	Decay Mode	Decay Product	Decay Product Half-Life	Decay Mode	Decay Product
^{134}Ce	3 days	Electron capture	^{134}La	6.7 minutes	β^+	^{134}Ba
^{135}Ce	17 hours	Electron capture	^{135}La	19.5 hours	Electron capture	^{135}Ba
^{137}Ce	34 hours	Isomeric transition	^{137}Ce	9 hours	Electron capture	^{137}La
^{139}Ce	140 days	Electron capture	^{139}La			
^{141}Ce	32.5 days	β-particle	^{141}Pr			
^{143}Ce	33 hours	β-particle	^{143}Pr	13.6 days	β	^{143}Nd
^{144}Ce	284 days	β-particle	^{144}Pr	17.3 minutes	β	^{144}Nd

devices and nuclear power facilities. The most likely exposure sources now are nuclear fuel reprocessing plants and test reactors. The annual production of ^{144}Ce from a nuclear power facility is 5.3 kg/1,000 MW of electric power.[101] Uranium fission produces radioactive cerium isotopes; however, the relatively short half-lives compared with ^{144}Ce limit the abundance of these isotopes in radioactive waste. Industrial cerium sources include photoengraving, glass manufacturing, optical lens polishing, industrial thickness/flow gauges, radiotherapy units, and carbon arc lamp production. The low volatility and solubility of cerium compounds in aqueous solvents restrict their flow through the biological food chain.

TOXICOKINETICS

The gastrointestinal absorption of cerium compounds is low ($<10^{-3}$) in adults, whereas inhalation of ^{144}Ce/^{144}Pr from the air has intermediate solubility and is the major exposure route similar to results from experimental studies of other cerium forms (e.g., $^{144}CeCl_3$, $^{144}Ce(OH)_3$, $^{144}CeO_2$).[1] Animal studies indicate gastrointestinal absorption of soluble Ce forms is much greater for neonates than adults. The liver and bones are the primary sites of deposition following Ce absorption. The deposition fractions are ~0.45–0.50 and ~0.30–0.35, respectively, with 0.10 of the absorbed dose deposited in soft tissue and the remainder excreted in feces and urine.[101,102] The hepatic and skeletal retention times are sufficiently long that the effective biological half-life of cerium is equivalent to the physical half-life. Following an accidental exposure of a worker to ^{144}Ce during the grinding of uranium metal, the effective and physical half-lives of ^{144}Ce in the lung were similar (i.e., 280 days).[103] The effective half-lives of cerium in the liver and bones were also indistinguishable from the physical half-life, despite having biological half-lives measured in thousands of days. ^{144}Ce is a bone surface seeker that deposits on surfaces of the trabecula, periosteum, articular cartilage, and vessels of the diaphysis.

CLINICAL RESPONSE

Relatively soluble ^{144}Ce compounds transfer rapidly from the lungs and deposit in the liver and skeleton. The liver is the primary target organ for the shorter-lived cerium isotopes, whereas the bone is the critical organ for the longer-lived isotope, ^{144}Ce. Hence, health effects in the lungs are minimal with late effects (e.g., myeloproliferative diseases, hepatic fibrosis, liver and nasal cavity cancers, osteosarcomas) developing in animals after long latency periods. Relatively insoluble ^{144}Ce compounds produce effects primarily in the lungs and tracheobronchial lymph nodes, depending on the internal radiation dose. Case reports associate the development of a pneumoconiosis with long-term pulmonary exposure (i.e., >15 years) to cerium oxide;[104,105,106] these case reports involve workers (e.g., photoengravers, glass polishers) exposed to natural cerium isotopes rather than cerium radioisotopes.

The IARC lists ^{144}Ce and its decay products as an animal carcinogen based on sufficient evidence in experimental animals for the carcinogenicity of mixed β-particle emitters (i.e., ^{144}Ce). Inhaled insoluble ^{144}Ce produced lung tumors in mice, rats, Syrian hamsters, and dogs, whereas dogs developed lung, liver, bone, and hematopoietic neoplasms following chronic inhalation of soluble ^{144}Ce. There are few data on the human carcinogenicity of ^{144}Ce. Pulmonary hemangiosarcomas are rare neoplasms that occur frequently in animals exposed to insoluble forms of ^{144}Ce.[107]

TREATMENT

Animal studies suggest that chelation with DTPA should begin as soon as possible for rare earth metals,

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even though the specific protocols for DTPA do not list exposure to rare earth metals as an indication for chelation therapy. The effectiveness of DTPA therapy depends on the prompt initiation of therapy and the solubility of the cerium compound in the lung.[108] In rodent studies, the efficacy of DTPA depended on the time of administration after internal contamination, ^{144}Ce distribution in organs, and maturity of the body.[109] The treatment of ^{144}Ce contamination is usually supportive; the use of DTPA is not typically recommended for ^{144}Ce contamination.

CESIUM

PHYSIOCHEMICAL PROPERTIES

Cesium is a silvery white, soft, ductile metal with one oxidation state (+1) and a relatively low melting point (28°C/82°F); this metal is a highly water-soluble alkali metal that has 21 radioactive isotopes. Both ^{134}Cs and ^{137}Cs produce β-particles and γ-rays during disintegration. The physical half-life of ^{137}Cs is ~30 years, decaying by β-decay either to stable ^{137}Ba or a meta-stable form of barium (^{137m}Ba) that almost immediately converts to stable ^{137}Ba after emission of a γ-ray (0.662 MeV). ^{134}Cs decays primarily to stable ^{134}Ba by β-decay and emission of a γ-ray or less frequently to stable ^{134}Xe by electron capture along with emission of a single γ-ray. Cesium, rubidium, and potassium are chemically similar, blocking most K^+-selective channels. Although cesium competes with potassium for transport through potassium channels, the cesium movement through these channels is much slower than potassium.[110]

EXPOSURE

Cesium exists naturally in the earth's crust as the stable isotope ^{133}Cs, typically at concentrations of 1 ppm (in granite) to 4 ppm (in sedimentary rock).[111] Pollucite (5–32% CsO_2) is the most commercial cesium source. In industry, ^{137}Cs is used as a sealed source of γ-rays for machines that measure the thickness of materials, whereas ^{137}Cs is a tracer substance in imaging procedures and a sealed source for radiotherapy. Nuclear fission in commercial applications (e.g., nuclear power plants) and nuclear weapons testing produce the main radioactive cesium isotopes (^{134}Cs, ^{137}Cs). Routine maintenance and production of electricity at nuclear power plants produce clinically insignificant amounts of radioactive cesium isotopes.[111]

ENVIRONMENTAL FATE

Air

Prior to the accident at Chernobyl, most ^{137}Cs deposited in humans resulted from nuclear fallout from weapons testing. Following release to the atmosphere, radioactive cesium can travel thousands of miles before removal by wet and dry deposition. The persistence of radioactive cesium isotopes in the environment is long. Based on fallout from the Chernobyl nuclear reactor accident, the half-life of ^{137}Cs is 2–4 years on urban surfaces (e.g., asphalt) and 3–15 years on park lawns, sand walkways, and forested areas.[112]

Soil

Cesium demonstrates very low mobility in soil surfaces, particularly in potassium-rich clay soils that bind cesium; cesium absorption by grasses and other plants is limited.

Diet

Ingestion of contaminated food items is the greatest source of internal exposure for both naturally occurring and radioactive cesium. ^{137}Cs enters the food chain when plants absorb contaminated rain, thereby transferring this radionuclide to the food chain. Milk and meat account for about 60–80% of the total intake. Other potential sources include nuclear processing plants for persons near these facilities; however, current cesium levels are usually well below the levels present from natural radiation.[113,114] Fungi enhance the mobilization of radiocesium from natural soils, increasing the transfer of this radionuclide to the food chain.[115]

TOXICOKINETICS

Absorption

Soluble cesium compounds are almost completely absorbed by the lung and the gastrointestinal tract. In a study of 10 volunteers ingesting venison containing ^{134}Cs and ^{137}Cs, the estimated uptake of radiocesium ranged from 65–90% (mean = 78%).[116] A simulated study of ^{137}Cs absorption from radioactive fallout particles collected following a land-surface detonation and administered in a gelatin capsule to 10 volunteers suggests cesium contained within the fallout is relatively insoluble and poorly absorbed in the gastrointestinal

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tract (i.e., ~3%).[117] In this study, the gastrointestinal absorption of soluble cesium as a tracer (^{134}CsCl) by four volunteers was relatively complete (i.e., ~90%).

Distribution

Following absorption, cesium disseminates easily throughout the body as a potassium analog and no specific organ accumulates a disproportionate amount of cesium. The erythrocyte/plasma ratio is variable depending on the time after exposure. Case reports suggest this ratio varies from ~3.5 soon after exposure to 14 one month after exposure.[118]

Elimination

There is wide variability in the retention of radiocesium depending on a variety of factors including age, muscle mass, sex, and potassium content. Biokinetic modeling suggests ^{137}Cs follows a two-compartment exponential model with fast and slow components. The mean biological half-life of ^{137}Cs is ~70–110 days with about 10% rapidly eliminated with a half-life of 2 days.[117,119] Following the ingestion of venison containing ^{134}Cs and ^{137}Cs, the mean biological half-life of radiocesium was 90 ± 50 days with a range of 45–210 days.[116] In a study of two workers exposed to airborne $^{137}CsSO_4$ and followed for 285 days, the biological half-time for the two workers was 73 days and 84 days, respectively.[120] Based on a two-exponential model, the long-term biological half-time of ^{137}Cs in a worker accidentally exposed to radiocesium after the explosion of an ampule containing ^{137}cesium chloride was ~93 days.[121] The terminal half-life for <1% of ^{137}Cs is longer (i.e., ~500 days). Excretion occurs primarily through the urine.[122]

Maternal-Fetal Kinetics

^{137}Cs is excreted in breast milk based on studies of breastfeeding women living in areas contaminated with radioactive fallout from the Chernobyl nuclear accident. Analysis of whole-body measurements of radioactivity in 12 Swedish mothers and nursing infants (6–12 months old) measured radioactivity in breast milk samples and estimated that 15% of the mothers' daily ^{137}Cs intake from contaminated food was transferred to the infant.[123] The estimated absorbed doses for a newborn baby and a 1-year-old child relative to the maternal doses were ~40% and ~50%, respectively.

Clinical Response

Radiocesium

Accidents resulting from industrial, medical, and research uses of ^{137}Cs are relatively uncommon, with complications ranging from skin damage to radionecrosis of the femoral arteries requiring bilateral amputations.[45] Accidental exposure of Russian military recruits to a sealed source of ^{137}Cs caused symptoms typical of cutaneous radiation syndrome manifested by initial dermal erythema, followed by well-demarcated ulceration, hypopigmented, hairless macules, and subsequent hyperpigmentation.[124] Some of these recruits also complained of nausea, vomiting, and headache. On September 13, 1987, in Goiania, Brazil, two scavengers removed a shielded radioactive ^{137}Cs chloride source containing ~51 TBq (1,375 Ci, mass of ~100 g) from its protective housing in an abandoned clinic; they transported the unshielded source to their home for eventual sale to a junkyard. The source container was ruptured with the contents widely distributed from fascination with the blue luminosity of the ^{137}Cs. Over the next 2 weeks, extensive dissemination occurred through social contacts with contaminated individuals and the sale/transfer of contaminated material from two junkyards. The radioactivity of the source was discovered after the wife of the junk man transported the source to the Sanitary Surveillance Division after she suspected an association between the development of gastrointestinal illness in her acquaintances and exposure to the source.

The severity of the radiation illness and the number of people affected were second only to the injuries caused by the Chernobyl incident. Of the 250 people in Goiania exposed to ^{137}Cs, at least 14 displayed signs of bone marrow suppression and 8 individuals developed symptoms of the hematological phase of the acute radiation syndrome.[125] Four people died within the first month from bleeding and sepsis secondary to resistant *Klebsiella* species.[126] Internal contamination occurred in 104 patients. None of the victims displayed evidence of the gastrointestinal or CNS phase of the acute radiation syndrome.

Local radiation injuries included 7 first-degree burns (estimated dose of 5 Gy), 15 second-degree burns (estimated dose of 12–20 Gy), and 6 third-degree burns (estimated dose >25 Gy).[45] The rapid onset of erythema identified the most seriously burned patients. Significant ulceration developed without a latent period following the erythematous phase in patients with third-degree burns. Burning pain, hypoesthesias, pruritus, and paresthesias were the most common

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complaints. Most of the injured areas regenerated a thin, atrophic, fragile epithelium by 3 months. Depigmentation in dark-skinned patients and hyperpigmentation in light-skinned patients occurred following regeneration of the skin. Atrophy and sclerosis of underlying tendons, tendon sheaths, and cartilage complicated the recovery of hand injuries.

Stable Cesium

Exposure to toxic cesium concentrations is associated with cardiovascular complications. A case report suggests that chronic use of cesium may produce magnesium and potassium wasting.[127] These electrolyte changes may cause QT prolongation and serious ventricular dysrhythmias. QTc prolongation (683 msec), monomorphic ventricular tachycardia, and syncope developed in a 16-year-old girl after starting an alternative treatment regimen involving cesium chloride.[128] These abnormalities may occur in the absence of serious electrolyte depletion from the inhibition of potassium rectifier channels. A case report associated the development of QTc prolongation (QTc = 620 msec) and *Torsades de pointes* with the use of nonradioactive cesium (^{133}Cs) chloride as an unproven alternative treatment for cancer.[129] The serum potassium concentration was 2.8 mEq/L, whereas the serum magnesium and calcium concentrations were normal.

Cesium Chloride

A 16-year-old girl with metastatic hepatocellular carcinoma developed stable cesium-induced QT-interval prolongation and syncope after starting an alternative treatment regimen including cesium chloride and a diet high in potassium, magnesium, and calcium.[128] She was admitted to the cardiac care unit after an episode of monomorphic ventricular tachycardia. Her plasma cesium concentration was 2,400 µg/dL with normal serum electrolyte concentrations. During follow-up 2 months later, her cesium concentration was 1,800 µg/dL (QTc = 494 msec).

Treatment

Oral insoluble Prussian blue (insoluble ferric hexacyanoferrate[II], Radiogardase™) is the preferred agent for de-corporation of patients contaminated with radioactive cesium based on the reduction of the biological half-life during treatment.[130] In a case report on nonradioactive cesium chloride toxicity, the use of insoluble Prussian blue enhanced the gastrointestinal elimination of cesium by reducing the serum cesium half-life from 61.7days to 29.4 days during 4 weeks of therapy (total amount excreted was not reported).[129] When initiated promptly after internal contamination, administration of insoluble Prussian blue reduces absorption and disrupts the enterohepatic recirculation of cesium. The increased fecal cesium elimination decreases the total-body cesium burden by a factor of 2–3.[131] The *in vitro* binding characteristics of ^{137}Cs suggest the insoluble form of Prussian blue ($Fe_4[Fe(CN)_6]_3$) is more effective than the soluble form ($K_3Fe[Fe(CN)_6]$) because the soluble form decomposes to $[Fe(CN)_6]^{-4}$; the latter reacts with ^{134}Cs to limit excretion of this isotope in animal models.[132] In rats, 5 mg Prussian blue administered 2 minutes before ^{134}Cs decreases absorption of this tracer to 5–6% of control values.[133] Total daily doses ranging from 1–10 g of insoluble Prussian blue (ferric hexacyanoferrate[II], Radiogardase™) were administered in three equal doses during the day to patients at Goiania with internal contamination from ^{137}Cs.[134] Patients tolerated an initial daily dose up to 20 g of Prussian blue with only minor adverse effects (constipation, mild hypokalemia). In this group of patients, daily doses of >3 g of Prussian blue were efficacious in adults (pediatric dose age 2–12 years: 1 g three times daily), but the use of diuretics did not improve the elimination of ^{137}Cs from the body. Biokinetic modeling suggests Prussian blue reduces the long-term biological half-life of cesium when administered during the first year postexposure.[135]

Radiogardase™ is available through the Radiation Emergency Assistance Center in Oakridge, Tennessee (https://orise.orau.gov/reacts/resources/documents/radiogardase-package-insert.pdf). A fiber-based laxative and/or a high-fiber diet are recommended along with the administration of Prussian blue to prevent constipation and promote fecal cesium excretion. Patients should be monitored for electrolyte imbalances, particularly the serum potassium concentration. *In vitro* studies indicate that sodium polystyrene sulfonate, activated charcoal, and hemoperfusion probably would not improve the elimination of cesium from the body.[132]

COBALT

PHYSIOCHEMICAL PROPERTIES

The most important cobalt radioisotopes are ^{60}Co ($t_{½}$ = 5.27 years), ^{57}Co ($t_{½}$ = 272 days), ^{58}Co ($t_{½}$ = 70.9 days), and ^{55}Co ($t_{½}$ = 17.5 hours).[136] Decay of ^{60}Co occurs by the emission of β-particles and γ-rays, whereas ^{58}Co decays by electron capture or positron emission to ^{58}Fe.

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EXPOSURE

Radioactive contamination from nuclear reactors, fuel-reprocessing plants, nuclear waste facilities, and laboratories may contain cobalt radioisotopes from neutron activation of impurities in reactor coolant system and fuel element cladding. ^{60}Co is the neutron activation product resulting from bombardment of stable ^{59}Co with neutrons; consequently, this radioisotope is a frequent radioactive contaminant in nuclear wastewater. ^{59}Co is a pure γ-ray source for medical therapy, commercial sterilization (medical equipment, food, spices, hot cells), and industrial radiography (structural flaws, thickness gauges, leveling devices).[137,138] ^{58}Co is also a radioactive contaminant of nuclear plants; Bleomycine-^{57}Co and $^{55}CoCl_2$ are diagnostic agents in nuclear medicine for brain imaging (i.e., brain trauma, multiple sclerosis, stroke). ^{55}Co-PET has relatively high spatial resolution/absolute quantitation but limited availability due to its short half-life; ^{57}Co-SPECT has wider availability but lower spatial resolution and a relatively high radiation dose. The estimated maximum doses of $^{55}CoCl_2$ and ^{57}Co are 0.5 mCi and 0.3 mCi, respectively, assuming 2% ^{56}Co contamination.[139] ^{55}Co is commonly produced by the ^{56}Fe(p,2n)^{55}Co nuclear reaction using target material, natural iron; consequently, ^{56}Co is always a long-lived contaminant of commercial ^{55}Co.[140]

TOXICOKINETICS

Absorption

The mean gastrointestinal uptake of inorganic forms of cobalt radioisotopes in human studies ranges from ~3–40%, depending on the solubility of the radioisotope. Typically, $^{60}CoCl_2$ uptake is <5% compared with <0.1–0.5% for ^{60}CoO;[136,141] however, whole-body counting studies suggest absorption of $^{60}CoCl_2$ may increase with increasing dose. In a study of 11 male volunteers, the gastrointestinal absorption of $^{60}CoCl_2$ increased from 5% following the ingestion of <1 μg to 20% after ingestion of 1.2 mg stable cobalt.[142] The absorption of more soluble organic cobalt forms is more complete.[143]

Elimination

In a study of 19 adult volunteers, the kidneys excreted an average of 30% (range, 14–47%) of an absorbed ^{58,60}Co dose with a urine/fecal excretion ratio of 6:1.[142] The initial biological half-life for ~80% of ^{60}Co is 1 day; however, the elimination half-life for the remainder is much slower (i.e., years), as demonstrated by long-term studies of accidently inhaled insoluble forms of ^{60}Co (e.g., cobalt oxide).[141] Following the inhalation of ~0.5 μCi of ^{60}Co dust during decontamination of ductwork, the initial biological half-life in three workers was ~1.6 days during the first week postexposure, while the half-life 17–50 days postexposure increased to 42 days and ~110 days 3 months after the initial exposure.[144] Fecal excretion accounted for 80–90% of the cobalt elimination with a maximum 2–3 days postexposure. During this time, urinary cobalt excretion accounted for 10–20% of the total Co excretion with 2/3 eliminated during the first day.

In a long-term study of a worker exposed to an aerosol of ^{60}Co from a hot cell at doses well below current occupational standards, the elimination of ^{60}Co followed the ICRP inhalation class W with an initial half-life ranging from 25–78 days and a terminal half-life of 500–1,100 days (mean ~900 days).[145] The initial elimination results from cobalt clearance from the lung that may be more prolonged following inhalation of insoluble forms of ^{60}Co than predicted by the ICRP model.[136] The predicted biological half-life for long-term clearance of class Y compounds is 500 days. In a case series of four power station workers exposed to ^{60}Co (i.e., cobalt oxide) via inhalation, the average biological half-life was 664 days.[146] Long-term clearance results from the systemic clearance of cobalt from the body stores (i.e., bone) rather than soft organs (e.g., liver).[147]

CLINICAL RESPONSE

^{60}Co is a potential source of high-dose γ-radiation capable of producing severe radiation sickness including alopecia, skin necrosis, loss of limb, and death.[148,149] The mishandling of a sealed ^{60}Co source resulted in the irradiation of a worker with an estimated nonuniform, whole-body dose of 1.2–1.6 Gy.[150] Initially, minor changes in the peripheral lymphocyte count, severe skin necrosis over the left hand, and epilation of a small area over the left temporal region occurred. Secondary defects in the skin of the left hand developed after 13 months eventually requiring amputation of all of the digits except the thumb. Initial changes in the lens of the left eye appeared 18 months after the accident and progressed to significant visual impairment.

The National Toxicology Program (NTP) lists cobalt and cobalt compounds that release cobalt ions *in vivo* as reasonably anticipated to be human carcinogens based on sufficient evidence from studies in experimental animals and supporting plausible mechanisms (e.g.,

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genotoxicity, oxidative damage from generation of reactive oxygen species, stabilization of hypoxia-inducible factor resulting in enhanced cancer cell survival in oxygen-deficient environments, inhibition of DNA repair).[151] However, evidence from human studies was inadequate to adequately evaluate or quantify the risk of cancer following exposure to cobalt and cobalt compounds that release cobalt ions. The IARC listed implanted foreign bodies of metallic cobalt as possibly carcinogenic to humans (Group 2B) based on sufficient evidence in experimental animals and inadequate data in humans.[152]

DOSIMETRY

Two workers in a Canadian nuclear power plant were irradiated with individual whole-body doses of 127.4 and 92 mSv during the removal of cobalt adjuster rods.[153] Serial lymphocyte counts and cytogenetic analysis did not demonstrate significant abnormalities as interpreted by three laboratories blinded to the samples and controls. The patients developed some stress-related symptoms but no signs or symptoms related to radiation exposure. Monitoring of a radiation accident involving an unshielded ^{60}Co source indicated that exposure to an estimated whole-body radiation dose of 150 mSv produced dicentric chromosomes within 2 months after the incident.[154]

Unstable chromosomal aberrations (i.e., dicentrics, rings, micronuclei) in peripheral lymphocytes demonstrate a dose-response relationship between ionizing radiation dose and the number of these abnormalities; however, the accuracy of these estimates declines substantially several months after acute radiation exposure.[155] Stable chromosomal aberrations (e.g., translocations, inversions, deletions) persist much longer. In a Chinese study of chromosomal aberrations in peripheral blood lymphocytes from five workers 1 day to 17 years after accidental exposure to 1.9–5.1 Gy of ^{60}Co γ-ray radiation, the frequency of unstable chromosomal aberrations (dicentrics and rings) remained constant one month after exposure.[156] By 3 months postexposure, the frequency of these aberrations decreased by 20–40% in three workers with the lowest radiation doses while remaining constant in two workers with the highest radiation dose. The number of unstable chromosomal aberrations decreased by 90% from initial values by 12 years postexposure without a dose-dependent relationship. Follow-up 17 years postexposure demonstrated the persistence of high levels of stable chromosomal aberrations (i.e., translocations) in a dose-dependent relationship.

TREATMENT

Several sources suggest potential chelating agents for cobalt radioisotopes, including DTPA, DMSA (Succimer), $CaNa_2EDTA$, and *N*-acetylcysteine, based on animal experiments; however, clinical experience is inadequate to determine the efficacy of these agents. The NCRP lists DTPA as the preferred chelator.[72] Although some case reports suggest chelation substantially reduces blood cobalt concentrations,[157,158,159] results are variable and difficult to compare with the natural course of blood cobalt concentrations without treatment. The role of chelation in the treatment of symptomatic patients with elevated concentrations of stable cobalt from malfunctioning metal hip implants also remains undefined other than hip replacement.

CURIUM

PHYSICOCHEMICAL PROPERTIES

Curium is a member of the transuranic radionuclide group (i.e., ^{237}Np, ^{239}Pu, ^{241}Am) emitting primarily α-particles. Both americium and curium oxides are more soluble than plutonium oxide. Of the 12 curium isotopes, only ^{242}Cm and ^{244}Cm are produced in significant amounts. In biological solutions, the trivalent form is the most stable oxidation state.[83] The high-specific activity of curium causes spontaneous heat production in addition to the emission of energetic α-particles, neutrons, and gaseous daughter products; consequently, serious radiation injury may occur from exposure to relatively small amounts of curium.[25] Table 41.18 lists some physical properties of ^{242}curium and ^{244}curium.

EXPOSURE

The main sources of transuranic radionuclides are thermal and breeder nuclear reactors, with ^{244}Cm

TABLE 41.18. Some physical properties of ^{242}curium (^{242}Cm) and ^{244}curium (^{244}Cm).

Physical Property	^{242}Curium	^{244}Curium
Radioactivity half-life (years)	0.447	17.9
Principal decay mode	α-particles	α-particles
Mean α-energy (MeV)	6.10	5.80
Specific activity (μCi/g)	3.31×10^{9}	8.20×10^{7}
Mass/μCi (g)	3.02×10^{-10}	1.22×10^{-8}
Relative mass[a]	1.85×10^{-5}	7.48×10^{-4}

[a] Mass relative to 1 μCi of ^{239}Pu set as 1.

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accounting for >90% of the curium isotopes produced in the nuclear cycle. Curium is present in thermoelectric generators, aerospace satellites, and transuranic production processes. ^{243}Cm and ^{244}Cm possess very high-power output/unit mass (W/g) resulting in their use as compact power sources due to the very large heat release per gram. The physical half-life of the longest-lived curium radionuclide (^{247}Cm) is short compared with the earth's age; little primordial curium remains in the earth's crust, except for minute amounts in natural uranium deposits.

TOXICOKINETICS

^{244}Cm is relatively soluble; therefore, this isotope is more easily absorbed than plutonium, whereas the kinetics of ^{242}Cm, ^{244}Cm, and ^{241}Am are similar.[160] The fractional absorption rate of curium isotopes from the gastrointestinal tract (f_1 value) is low (i.e., ~0.01–0.03%) based on human volunteer studies.[161] The lungs clear curium compounds more rapidly than plutonium complexes; limited data suggest the lung clears ^{244}Cm oxide in a few days during the first week postexposure followed by ~1 month afterward.[160] In contrast to plutonium, curium distribution in the lungs is relatively uniform. Most internally deposited curium appears in the bones (i.e., 80%) and the liver (i.e., 15%) with retention in the latter being specie-dependent. Insoluble chemical forms of curium may remain in the lungs, whereas the critical target organ for soluble curium compounds is the bones, where the effective half-life of ^{244}Cm is 16.7 years. Elimination rates of transuranic radionuclides are comparatively rapid. The biological half-life of ^{244}Cm is ~10 days with excretion occurring in the urine (~10%) and feces.[162]

CLINICAL RESPONSE

Few human data on the adverse effects of curium isotopes are available. Lung and/or bone tumors are the major health risks following the absorption of ^{242}Cm and ^{244}Cm.[160] The IARC classifies ^{244}Cm as an animal carcinogen based on experimental studies; human data are unavailable because of the rarity of curium contamination.

TREATMENT

DPTA is a USFDA-approved chelator for internal contamination by curium. Animal studies suggest the weak protein binding of curium enhances DTPA chelation.[83] The prevention of curium deposition in bone and liver requires administration of DTPA chelation soon after exposure (i.e., several hours). Ca-DTPA distributes rapidly throughout extracellular fluids without diffusing across cell membranes; almost complete Ca-DTPA excretion from the body occurs within 12 hours. The urine should be monitored to determine the amount of curium and evaluate the effectiveness of chelation. Ca-DTPA is the chelator of choice during the first 24 hours after internal contamination based on animal studies; Ca-DTPA is more effective for internal contamination with curium than Zn-DTPA during this initial time.[163] After the initial 24-hour period of internal contamination, both DTPA preparations are equally effective.

GOLD

Of the 24 radioactive isotopes of gold, only ^{198}Au is commonly used in biological research, radiotherapy, and industrial calibration. ^{198}Au emits 0.97 MeV β-particles and 0.41 MeV γ-rays with a physical half-life of 2.7 days. Absorption of noncolloidal ^{198}Au is limited to ~10% of the administered dose; elimination occurs by the kidney and feces. The intravenous administration of colloidal ^{198}Au results in radionuclide deposition in reticuloendothelial cells of the spleen, liver, bone marrow, and lymph nodes with an effective half-life of 2.6 days.[164] A patient mistakenly received a dose of 200 mCi of ^{198}Au intravenously; the estimated absorbed dose to the bone marrow was 440 rads.[25] He died 70 days after administration from thrombocytopenia with subsequent intracerebral hemorrhage. There are no data on the effectiveness of chelation therapy for ^{198}Au; however, dimercaprol and penicillamine are theoretical considerations for chelation.

IRIDIUM

Iridium exists naturally as an alloy with osmium (osmiridium), primarily in the tetravalent state in multicolored complex salts. This rare member of the platinum group has good electrothermal conductivity with a density of 22.56 g/cm^3, an atomic mass of 192.217, and a melting point of 2,466°C. ^{192}Ir is a γ-ray source for industrial radiography (i.e., radiography cameras) to inspect pipes, metal vessels, and defective welds. Although relatively rare, multiple industrial exposures to ^{192}Ir have occurred from the mishandling of these cameras, resulting in radiation dermatitis.[165,166] This radionuclide emits

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β-particles and γ-rays with a physical half-life of 74 days; this isotope readily penetrates human skin. The intestinal mucosa absorbs ~1% of an orally administered dose. Inhalation of ^{192}Ir results in protracted retention (IRCP class Y) of ^{192}Ir; therefore, prolonged irradiation of pulmonary tissue occurs following inhalation. Most occupational ^{192}Ir exposures involve local skin damage rather than systemic effects, particularly to the hand.[167] Improper handling of an ^{192}Ir source resulted in permanent sequelae ranging from thin, sensitive skin[168] to local necrosis of the skin and deeper tissue layers; these changes potentially predispose the patient to frequent abscesses and brittle bones.[169]

Chronic radiodermatitis developed in a 26-year-old man several months after high-dose industrial exposure to ^{192}Ir and manifested by necrosis, sclerosis, and ulceration of the previously irradiated skin.[170] Initially, erythema, edema, vesiculation, and desquamation of the exposed skin may occur, which regress in several weeks; later, chronic radiodermatitis occurs with dark red hyperpigmentation, edema, and atrophy persisting in the necrotic areas for many years.[171] Although some sources suggest DTPA as a chelating agent for ^{192}Ir (e.g., the National Council on Radiation Protection and Measurements), insufficient animal and human data are available to determine the efficacy of DTPA following contamination with ^{192}Ir.

IODINE

PHYSIOCHEMICAL PROPERTIES

Of the 35 iodine isotopes (^{108}I–^{142}I), only ^{127}I is stable with the rest being radioactive. Approximately half of these isotopes are fission products of nuclear reactors with most of these having half-lives of <≤1 minute. Some radioactive isotopes have half-lives ranging from 1–6.7 hours (e.g., ^{132}I, ^{133}I, ^{134}I, ^{135}I), whereas six iodine isotopes have half-lives exceeding 12 hours (^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{129}I, and ^{131}I).[172] The physical half-life of ^{131}I is 8 days with the emission of β-particles and γ-rays; β-particles contribute 85% of the absorbed radiation dose. ^{131}I is one of the most important radioisotopes released during nuclear accidents because of the large quantity and high volatility of ^{131}I associated with these incidents.

EXPOSURE

Four iodine isotopes (^{123}I, ^{125}I, ^{129}I, and ^{131}I) are sufficiently long-lived to potentially cause clinically important transfer from the environment to human receptors. Iodine radioisotopes (e.g., ^{129}I, ^{131}I, ^{132}I) are important fission products of nuclear reactors and nuclear weapons testing that easily volatilize into the atmosphere. Plutonium production reactors and reprocessing facilities release substantial amounts of ^{131}I into the atmosphere. The Hanford Nuclear Facility released 19.6 PBq of ^{131}I during the early years of operation between 1944 and 1956,[173] whereas the 1986 accident at Chernobyl discharged ~1,760 PBq ^{131}I over 10 days contaminating vast areas of Ukraine, Belarus, and the Russian Federation with deposition of radionuclides beyond the 30-mi exclusion zone determined by wind direction. ^{131}I and ^{137}Cs were the most important radionuclides globally, except in the immediate area around the reactor, where expelled reactor components (carbon blocks, fuel elements) determined the radiation exposure. The estimated average effective radiation dose from external radiation for the ~116,000 individuals evacuated from the area around Chernobyl was 17 mSv (range, 0.1–380 mSv).[4] In Belarus, short-lived radionuclides (e.g., ^{131}I, ^{132}I, ^{132}Te, ^{140}Ba, ^{140}La) accounted for ~60–80% of the effective external dose, whereas the contribution by the long-lived ^{137}Cs was ~3–5%. Intake of ^{131}I and other short-lived radioiodine isotopes provided the primary internal exposure during the first days and weeks after the accident, whereas the longer-lived ^{134}Cs and ^{137}Cs subsequently were the main radionuclides. Most short-lived iodine isotopes decayed before the radioactive plume reached the main contaminated areas in the Russian Federation, 150–250 km northeast of Chernobyl. Although rainfall reduced inhalation of radionuclides released from Chernobyl, intake of ^{131}I-contaminated milk and vegetables was the primary contributor to the internal thyroid dose. Table 41.19 displays the mean and collective thyroid doses in the contaminated districts surrounding Chernobyl.

Medical iodine isotopes include ^{123}I, ^{131}I, and rarely ^{125}I (hyperthyroidism, radiotherapy). Other than ^{99m}Tc, ^{131}I is the most common medical radionuclide; medical uses of ^{131}I include the diagnosis and treatment of hyperthyroidism and thyroid cancer.

DOSE

Radioiodine is the only radionuclide absorbed by the thyroid gland; the radiation dose received by the thyroid is usually greater from internal ^{131}I than external ^{131}I exposure. Incorporation of ^{131}I into thyroid hormones exposes other tissues to radiation; however, these organs receive substantially less radiation than

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TABLE 41.19. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) estimates of the mean effective and collective thyroid dose of inhabitants in districts of the Russian Federation contaminated by the Chernobyl accident (Based on United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)).[4]

District/Region	Population	Mean Thyroid Dose (mGy)	Collective Thyroid Dose (person-Gy)
Bryansk			
8 contaminated districts	360,000	92	33,000
Whole region	1,500,000	37	55,000
Tula			
12 contaminated districts	770,000	35	27,000
Whole region	1,900,000	26	50,000
Orel (Whole region)	1,870,000	17	15,000
Kaluga (Whole region)	1,000,000	15	15,000

TABLE 41.20. Thyroid radiation doses, effective half-lives, and radiation sources for various iodine isotopes. ^{131}I delivers the highest radiation dose, whereas ^{125}I has the longest effective half-life in the thyroid. (Adapted from Agency for Toxic Substances and Disease Registry (ATSDR)).[172]

Isotope	β-Radiation Percentage	Effective Half-Life in Thyroid (Hours)	Mean Range β-Radiation in Thyroid (mm)	Total Thyroid Dose from 1 mCi (rad)
^{123}I	77	13	0.1	76
^{125}I	73	866	0.001	3,747
^{131}I	94	177	0.4	5,627
^{132}I	90	2.3	1.7	199
^{133}I	96	20	1.3	1,355
^{135}I	90	6.7	1.1	434

the thyroid gland. The estimated average ^{131}I dose administered in developed countries for thyroid malignancies ranges from 3,500–4,760 MBq compared with 220–415 MBq for hyperthyroidism.[4] The radiation dose to the thyroid gland from absorbed radioiodine depends on the radiation emission properties of the specific isotope, including emission energy, radiation type, and effective radioactive half-life, as displayed in Table 41.20.

The dose for the treatment of Graves' disease ranges up to 30 mCi (1,110 MBq) of ^{131}I. In a study of household members of patients treated with ^{131}I (mean = 4.3 MBq; range, 2.8–5.6 MBq), 65 household members received ^{131}I radiation doses ranging from 0.01–1.09 mSv with a mean of 0.24 mSv.[174] The risk from ingesting food contaminated with radioactivity following nuclear accidents is small, except for milk contaminated with radioiodine (^{131}I). In a case series of 237 children born to mothers treated for hyperthyroidism during pregnancy, 6 offspring developed hypothyroidism; 4 of these children received 12–150 mCi (440–5,550 MBq) ^{131}I after the 12th week of gestation. Thyroid function returned to low-normal activity after 23 adults (21 women, 2 men) received fractionated doses of 1.5–3.7 MBq ^{131}I (2–8 Gy) for "unquestioned toxic diffuse or recurrent goiter."[175] Following diagnostic tests for thyroid uptake with ^{131}I resulting in doses of 0.31–0.80 Gy, hypothyroidism developed in 3 of 146 patients and 5 of 151 patients receiving 0.81–19 Gy.[176]

TOXICOKINETICS

The gastrointestinal absorption of ^{131}I is almost complete within 2 hours; ICRP models classify ^{131}I absorption as Class F (complete within 24 hours). Similarly, iodine absorption from the lungs is rapid and almost complete. Distribution occurs to the salivary glands, gastrointestinal tract, kidney, and bladder in addition to the thyroid gland; however, radioiodine concentrates in the thyroid (ICRP model: 30% absorbed dose, range 5–55%) with no other organ receiving comparable radiation doses. Fractional uptake of iodine increases in the iodine-deficient individual. The retention half-life is 80 days.[1] Recycling of inorganic iodide

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occurs from metabolism of thyroxine and triiodothyronine released from the thyroid gland. The liver excretes ~20% of the organically bound iodine in the bile after glucuronidation of thyroxine. The amount of iodine remains relatively constant (i.e., adult mean ≈ 800 μg; range, 500–1,200 μg) primarily from renal excretion of inorganic iodine.[177] The fetal iodine concentration in the thyroid gradually increases during fetal life as thyroid follicles develop, with fetal iodine concentration 3–10-fold greater than maternal concentration near birth.[178] After the first trimester, the fetus accumulates radioiodine with potential complications of hypothyroidism and cognitive decline in offspring of mothers who received radioiodine during the second and third trimesters.[179]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

The histological types of thyroid cancer are follicular, medullary, papillary, and anaplastic carcinoma (undifferentiated), with papillary carcinoma being the most common histological type of thyroid cancer in atomic bomb survivors.[180] In a study of 577 Ukrainian children exposed to ^{131}I as children during the Chernobyl incident and subsequently developing thyroid cancer, 90% of the 290 cases evaluated histopathologically were papillary carcinomas.

CLINICAL RESPONSE

The International Agency for Research on Cancer lists ^{131}I and other short-lived radioisotopes of iodine as human carcinogens (Group 1), with sufficient evidence of increased thyroid cancer in children exposed to ^{131}I-contaminated fallout from reactor accidents and nuclear weapons detonations.[1] After the 1986 Chernobyl nuclear reactor explosion in the Ukraine, an increased incidence of thyroid cancer occurred among children receiving high ^{131}I exposures in Ukraine and Belarus from contaminated milk.[181] Although the incidence of thyroid cancer in adults is not usually increased following ^{131}I exposure, studies of individuals exposed to therapeutic radioiodine during childhood also suggest an increased incidence of thyroid cancer.

Some follow-up studies of patients irradiated with ^{131}I suggest an increased cancer incidence following the medical use of thyroid isotopes;[182,183] however, most studies do not demonstrate consistent, dose-related associations between adult exposure to thyroid isotopes and increased cancer rates.[184] Potential biases for the positive studies (breast, central nervous system, kidney, digestive tract, salivary gland, bone and soft tissue sarcoma, leukemia) include detection and/or surveillance bias, shared genetic or environmental risk factors, or ^{131}I treatment. A small study suggested a marginally significant excess incidence of cancers of the bladder, kidney, digestive tract, and salivary glands.[185,186] Calculation of cancer risks in 824 thyroid cancer patients given ^{131}I demonstrated significantly elevated standardized incidence rates (SIRs) for tumors of the salivary glands, genital organs, kidney, and adrenal gland; however, the lack of a detectable increase in the SIR over time did not support a causal relationship.[187] The SIR of leukemia for 46,988 Swedish patients irradiated with a mean bone marrow dose of 14 mGy ^{131}I was 1.09 (95% CI: 0.94–1.25); the study had sufficient power to detect a 25% increase in the relative risk.[188] A follow-up study of patients treated with ^{131}I for thyrotoxicosis did not detect an increased leukemia incidence; however, the average follow-up period (6.5 years) is relatively short for the development of leukemia in older patients.[189] A retrospective cohort study of patients receiving ^{131}I for diagnostic purposes did not demonstrate an elevated incidence of thyroid cancer.[190] Studies of patients receiving diagnostic or therapeutic ^{131}I typically contain primarily adults with less radiosensitivity to thyroid cancer than children.

HEALTH SURVEILLANCE

Risk Assessment

The childhood thyroid gland, red bone marrow, and premenopausal female breast are the most radiosensitive organs in the body. Based on a pooled analysis of atomic bomb survivors and children receiving radiotherapy (enlarged thymus glands, tonsils, *Tinea capitis*), the highest risk for thyroid cancer occurs 15–29 years after exposure of children <10 years of age to thyroid doses of >1 Gy with evidence of a threshold for increasing cancer risk in this age group at a thyroid dose of 0.1 Gy.[191] Currently, there is no direct evidence indicating that exposure to the medical use of ^{131}I induces thyroid cancers in humans.[1] This lack of data correlating ^{131}I treatment of adults with thyroid cancer is consistent with the studies of atomic bomb survivors that demonstrated no increased risk of thyroid cancer when exposure occurred after the age of 20 years.[192] The ^{131}I doses to organs including the red bone marrow, gastrointestinal tract, breast, and urinary tract during medical use are typically below the level associated with an increased incidence of cancer in patients exposed during adulthood.

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Environmental Monitoring

The maximum permissible thyroid dose for continuous exposure to ^{131}I is 15 rem/year. Emergency reference levels are 0.25 μCi/L as a peak level in milk and 1.5 μCi/m^2 on pasture. Exceeding these reference levels requires the diversion of contaminated milk from direct use to milk products (e.g., cheese, condensed milk) and changing the cow's forage. The US Nuclear Regulatory Commission allows the release of outpatients treated with ^{131}I when the total effective dose equivalent to any individual near the patient is <5.0 mSv.

TREATMENT

Clinically significant ^{131}I exposures typically occur after nuclear reactor incidents (e.g., Chernobyl and Fukushima) rather than nuclear bomb detonations because of the limitation of exposure from the latter by atmosphere dilution. Potassium iodide is a relatively nontoxic, USFDA-approved blocking agent that prevents ^{131}I incorporation when administered before or shortly following exposure; this agent should be given within 3–4 hours of the release of radioiodine to prevent radioiodine uptake by the thyroid gland. Blocking therapy is most effective when given before radioiodine exposure to saturate the thyroid with nonradioactive iodine; the efficacy markedly diminishes by 12 hours postexposure. Potassium iodide (KI) is available in 130 mg tablets; the shelf-life of these tablets is 5 years. The US FDA recommended dosage of KI following radioiodine exposure is listed in Table 41.21. The administration of KI should continue until the risk of exposure ceases or until other measures (evacuation, control of food sources, sheltering) eliminate the risk of radioiodine exposure. Individuals should be monitored for the development of hypothyroidism up to 2 years postexposure.[193] Potassium iodide does not prevent the uptake of ^{131}I in organs other than the thyroid or mitigate the injury of any organs to other radionuclides.

For patients receiving thyroid doses over 100 rads, thyroid function tests including the TSH level should be evaluated within 2–3 months; then, they should be followed every 6–12 months for several years.[24] Chelation with DTPA is ineffective. The role of vitamin C as a radioprotector for exposure to ^{131}I via its antioxidant properties has been suggested by animal studies;[194] however, the efficacy of vitamin C to reduce hypothyroidism or cancer is unproven.[195]

TABLE 41.21. United States Food and Drug Administration (USFDA) recommendations for potassium iodine following excessive radioiodine exposure.

Category	Age	KI Dose[a]
Adults including lactating women, adolescents over 150 lb	>18 years	130 mg
Older children and adolescents under 150 lb	3–18 years	65 mg
Young children	1 month to 3 years	32 mg
Neonates	<1 month	16 mg

[a] Potassium iodide, usually available in 130 mg tablets.

MERCURY

All but two of the five isotopes of mercury have physical half-lives of less than 1 day. The exceptions are ^{197}Hg and ^{203}Hg, which possess physical half-lives of 65 hours and 47 days, respectively. The decay of ^{197}Hg produces two X-rays, whereas the decay of ^{203}Hg emits β-particles and X-rays. Radionuclides of mercury are present in biomedical research labs and some industrial settings related to mercury isotope production. The effective half-life of ^{203}Hg in two workers inhaling this radioisotope was 16–17 days. The short half-lives of these isotopes limit the adverse effects of internal contamination. DMSA, penicillamine, and dimercaprol are chelating agents with potential usefulness; however, human data are inadequate to guide therapy.

PHOSPHORUS

^{32}P was the first radioisotope produced for biological research resulting in the introduction of $^{32}PO_4$ as a treatment for polycythemia vera in 1939.[196] Polycythemia vera is a clonal malignancy of the pluripotent hematological stem cells with an increased risk of developing leukemia.

PHYSIOCHEMICAL PROPERTIES

Phosphorus is a common, naturally occurring, reactive nonmetal that does not exist in the environment in its elemental form; ^{31}P is the natural, nonradioactive isotope, whereas ^{32}P is a synthesized radionuclide. The physical half-life of ^{32}P is 14.2 days with the emission of β-particles to decay back to ^{32}S; ^{32}P has low specific activity of 185–300 MBq (5–8 mCi). The effective half-life of ^{32}P is also 14 days. The effective mean energy of these β-particles (i.e., 0.69 MeV) corresponds to a

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maximum range in tissue of 7 mm.[25] ^{32}P does not emit photons.

EXPOSURE

The primary medical use for ^{32}P is the treatment of polycythemia vera. This isotope is also a radioactive tracer used to identify tumors prior to removal. Historical medical uses include the treatment of chronic myelocytic and lymphocytic leukemias.

DOSE

Individual treatments for polycythemia vera typically involve the use of 150–170 MBq $^{32}PO_4$. Estimates of the average skeletal dose of 300 rad/7.4×10^8 Bq are 4 nGy/Bq based on administered activities of $1.85–2.96 \times 10^8$ Bq.[1] Human exposures include intentional ingestions and inappropriate administration of four times (16.2 mCi) the prescribed dose; the latter patient developed progressive decline in red and white blood cell counts.[197] The patient remained asymptomatic during the recovery period. The ingestion of ~600 μCi resulted in a total effective dose equivalent of 48 mSv.[198] The patient remained asymptomatic.

TOXICOKINETICS

Dietary phosphorus and inorganic phosphorus compounds are generally well absorbed from the gastrointestinal tract;[199] however, the half-lives of some relatively insoluble phosphates (e.g., bismuth, iron, magnesium, tin, zinc) in the lungs after inhalation are 3 months.[1] For soluble ^{32}P compounds, the critical organ is the bone resulting in the accumulation of ~20–30% of the absorbed dose. ^{32}P distributes throughout the body; however, distribution to the skeleton exceeds soft tissue by 4–10-fold. Following intravenous injection of ^{32}P, the biological half-life of ^{32}P in the body was 39 days as measured by whole-body counting.[200] Dietary balance studies suggest that the retention half-time of phosphorus in bones is ~4 years resulting in radiation exposure primarily on bone surfaces. The kidneys excrete 5–10% of the absorbed dose within 1 day and up to 50% within 1 week.[201] Fecal elimination is low (i.e., <2%). Rodent studies suggest phosphorus easily crosses the placenta.[1]

CLINICAL RESPONSE

The IARC classifies ^{32}P as a human carcinogen (Group 1) with sufficient evidence that therapeutic ingestion or injection of ^{32}P administered as inorganic phosphate causes acute leukemia; observational follow-up studies of a series of patients with polycythemia vera treated with $^{32}PO_4$ demonstrate a clear increased incidence of acute leukemia.[1] A study of 1,222 patients treated with ^{32}P for polycythemia vera demonstrated an increased incidence of acute leukemia; however, the association of myeloproliferative disease with leukemia complicates the interpretation of the causal association between exposure to ^{32}P and an elevated risk of leukemia.[202] The study did not detect a significant difference in the incidence of nonhematological cancers. After 10–18 years of follow-up in the Polycythemia Vera Study Group trial, 2 cases of acute leukemia developed in 134 patients treated by phlebotomy (control), compared with 16 cases of acute leukemia among 156 patients treated with ^{32}P and 19 cases of acute leukemia plus 5 cases of large-cell lymphocytic lymphoma in 141 patients treated with chlorambucil.[203] Survival was comparable in the treatment and control groups because of the increased incidence of thrombosis in controls.

TREATMENT

Aluminum hydroxide antacids (600 mg tablet t.i.d. or 320 mg/5 mL t.i.d.) may reduce gastrointestinal absorption by acting as a phosphate binder; phosphate compounds act as a diluting agent. Typical treatment for internal contamination from phosphorus involves hydration plus a phosphate binder (e.g., adult dose: dibasic potassium phosphate 250 mg tabs, 1–2 tabs qid with a glass of water at meals and bedtime) listed under binders above; however, there are few data to determine the effectiveness of these agents.

NEPTUNIUM

PHYSIOCHEMICAL PROPERTIES

The physical half-lives of neptunium isotopes are highly variable ranging from <1 hour for neptunium isotopes with masses of <233 to 2,100,000 years for ^{237}Np. The half-life of ^{239}Np is 2.35 days. The form of neptunium in nature is primarily pentavalent NpO_2^+ ions; these compounds are less susceptible to hydrolysis than other actinide ions.

EXPOSURE

Neptunium exists in the environment as the long-lived, α-emitting ^{237}Np; this isotope exists in minute amounts.

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The principal sources of neptunium are: 1) fallout from nuclear explosions; 2) ^{237}Np in nuclear waste; 3) industrial processing of ^{237}Np produced in fission reactors; and 4) effluent from fission reactors.[204] Although the amount of ^{237}Np in high-level nuclear waste is small, the long half-life of ^{237}Np results in ^{237}Np being the most hazardous isotope in the waste over a period of 10,000–30,000,000 years after release.[205] Nuclear reactors using enriched uranium produce ^{237}Np levels that are somewhat >0.1% of the plutonium generated. The β-emitting isotope ^{239}Np may produce up to 75% of the β-radiation in the first 4 days following a nuclear explosion.[204] Within 48 hours of the nuclear test at Enewetak, the short-lived isotope ^{239}Np was the most prominent radionuclide in marine plankton.[206]

ENVIRONMENTAL FATE

Neptunium is more mobile and environmentally available than other transuranic elements; however, the medical significance of neptunium isotopes is limited by their short half-lives, lack of persistence in the environment (^{239}Np), and small quantity (^{237}Np). Consequently, radiation exposure from these isotopes is minimal.

TOXICOKINETICS

The mean value for the gastrointestinal absorption of ingested neptunium in a study of human volunteers was 0.02% with a range of 0.0095–0.03% consistent with animal studies suggesting GI absorption in the range of 0.1%;[161,207] however, the IRCP uses a f_1 value of 1% (i.e., medium absorption). The ICRP assigns all neptunium compounds to the inhalation class W (weeks) that includes all other actinides except the insoluble oxides and hydroxides of thorium, uranium, and plutonium. Animal studies indicate bone is the primary neptunium deposition site with most of the remaining neptunium being distributed to the liver. Early neptunium excretion probably is somewhat higher (25% reaching the blood) than plutonium (10%). The ICRP assumes 60% of the neptunium in the blood will deposit on the surface of the bone, whereas 15% of neptunium in the circulation accumulates in the liver with retention half-times of >20 years and 2–3 years, respectively. Primate studies suggest the placental transfer of ^{237}Np citrate is limited with fetal retention of ~1–2%.[208]

CLINICAL RESPONSE

Although ^{239}Np probably contributes significantly to the production of β-burns in the victims of nuclear explosions during the early phase of nuclear fallout, neptunium is not associated with other human health effects.[204] The short ^{239}Np half-life limits radiation damage to the gastrointestinal mucosa and lungs. Because of the low-specific radioactivity of ^{237}Np, chemical toxicity of ^{237}Np may contribute to the effects in animal experiments more than radiation-induced damage. The International Agency for Research on Cancer (IARC) considers ^{237}Np an animal carcinogen with sufficient evidence of carcinogenicity in animal experiments (i.e., osteosarcomas in female rats following injection of ^{237}Np nitrate,[209] squamous cell cancer, and adenocarcinomas of the lung after inhaling $^{237}NpO_2$) with little human data.[1]

TREATMENT

Because the ^{237}Np-DTPA complex is unstable *in vivo*, chelation with DTPA following exposure is ineffective.[210] Neptunium is more tightly bound to bone than plutonium; consequently, DTPA significantly removes neptunium from soft tissue stores rather than bone.[211] Animal studies suggest the combination of iron chelators (e.g., desferrioxamine or carboxylated catechoylamide 3,4,3-LICAM-C, DTPA) may be more effective than DTPA alone.[212]

PLUTONIUM

PHYSICOCHEMICAL PROPERTIES

Plutonium is primarily an artificial element formed as a by-product of uranium production; the neutron capture and β-decay of ^{238}U produce plutonium. The principal plutonium isotopes (^{238}Pu, ^{239}Pu) are produced for fuel in nuclear power reactors and components of nuclear weapons. ^{239}Pu typically refers to the combination of α-emitters, ^{239}Pu, and lesser amounts of ^{240}Pu. All plutonium contains some ^{241}Am (half-life, 432.2 years) that contributes to the overall radiation dose.

There are 15 known Pu isotopes with atomic weights ranging from 232–246. The most biologically important isotopes range from 236–243; Table 41.22 displays some physical properties of this series. These isotopes emit primarily α-particles during decay, except for the β-particles produced by ^{241}Pu. The radioactive half-lives and biological retention times of the two most common plutonium isotopes (^{238}Pu and ^{239}Pu) are very long; therefore, incorporation of these isotopes results in prolonged exposure to α-radiation.

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TABLE 41.22. Physical properties of plutonium isotopes.

Physical Property	^{236}Pu	^{237}Pu	^{238}Pu	^{239}Pu	^{240}Pu	^{241}Pu	^{242}Pu	^{243}Pu
Radioactivity half-life (years)	2.85	0.125	87.8	2.439×10^{4}	6.537×10^{3}	15.02	3.87×10^{5}	5.66×10^{-4}
Principal decay mode	α-particles	Electron capture	α-particle, X-rays	α-particle, X-rays	α-particle	β-particle	α-particle	β-particle
Mean α-energy (MeV)	5.75	—	5.46	5.15	5.15		4.89	
Specific activity (μCi/g)	5.32×10^{8}	1.21×10^{10}	1.71×10^{7}	6.13×10^{4}	2.28×10^{5}	9.90×10^{7}	3.82×10^{3}	2.60×10^{12}
Mass/μCi (g)	1.88×10^{-9}	8.28×10^{-11}	5.84×10^{-8}	1.63×10^{-5}	4.38×10^{-6}	1.01×10^{-8}	2.62×10^{-4}	3.84×10^{-13}
Relative mass[a]	1.15×10^{-4}	5.08×10^{-6}	3.58×10^{-3}	1.00	26.9	6.19×10^{4}	16.1	2.36×10^{8}

[a] Mass relative to 1 μCi of ^{239}Pu set as 1.

During decay, ^{239}Pu also emits low-energy X-rays capable of penetrating several cm of tissue; these X-rays allow detection of this isotope in the lung and wounds. Although plutonium has four valence states (3^{+}–6^{+}), almost all plutonium in biological systems appears in the IV valence. Hydrolysis of Pu (4^{+}) produces relatively insoluble polymers that degrade slowly in the body. Pu (3^{+}) and Pu (6^{+}) are more soluble than Pu (IV); therefore, the former two compounds are more easily absorbed and excreted. ^{238}Pu and some ^{239}Pu compounds (e.g., nitrates, citrates) are more soluble and easily absorbed into the circulation than ^{239}Pu oxides. However, the solubility of ^{239}Pu oxides following inhalation depends partly on formation of the aerosol with high-fired (1,000°C), completely oxidized $^{239}PuO_2$ being sparingly soluble, whereas materials formed at lower temperatures, less complete oxidation, and mixed with other metals (e.g., calcium, magnesium, potassium, sodium) are more soluble.

EXPOSURE

Thermoelectric generation systems in spacecraft, cardiac pacemakers, and other power sources use ^{238}Pu, whereas nuclear fission in nuclear reactors accounts for most of the production of ^{239}Pu and ^{240}Pu.[213] The plutonium from reactors exists primarily in the form of oxides. Plutonium dioxides formed at temperatures >700°C have much lower solubility than the oxides created by air oxidation.[214] Uranium and plutonium oxides are inhalable components of mixed oxide fuels at nuclear facilities with potential occupational exposure to inhaled radiation and increased lung cancer risk.[215,216] The United States detonated a nuclear device at the Bikini Atoll on March 1, 1954, that unexpectedly released a large amount of radioactive fallout. Based on 1991 fission tract analysis data over 40 years, mean effective dose equivalent from ^{239}Pu was 0.62 mSv for Rongelap inhabitants and 1.6 mSv for Utirik inhabitants.[217] In a 1991 study of 69 urine samples from inhabitants of Enewetak Atoll, the committed effective doses of plutonium were 0.2 mSv.[218]

TOXICOKINETICS

Absorption

Plutonium does not exist as a simple ion at physiological pH. Hydrolysis of plutonium in the gastrointestinal tract and formation of relatively insoluble polymers minimize plutonium absorption after ingestion, depending on age, nutritional factors, stomach contents, and relative solubility of the compounds.[219] Animal studies suggest gastrointestinal absorption increases with nitrate or citrate solutions (0.003–0.01%),[220] very acidic solutions, neonates (3–6%),[221] an empty stomach (0.1–0.15%),[222] and iron deficiency (4-fold increase).[223] An α-spectrometry analysis of urinary ^{238}Pu and ^{239}Pu specific activity from bioassay examinations of 1,013 Mayak workers suggested the solubility of ^{238}Pu was associated with the relative amounts of ^{238}Pu/^{239}Pu in the particles and calcination temperatures during the preparation of the dioxides.[224]

Plutonium absorption from the lungs depends on the chemical compound (i.e., solubility), valence, particle size, and the mass deposited. The insoluble forms of plutonium (oxides) remain in the reticuloendothelial system after phagocytosis by macrophages and alveolar cells for an extended time. Dermal Pu absorption from intact skin is insignificant.[219] The absorption rate of ^{239}Pu nitrate in a 0.4 N nitric acid solution through the intact palmar skin of a human volunteer was 0.0002%/hour.[225]

Distribution

Animal studies indicate the plasma protein, transferrin, binds ~90% of the absorbed dose with most incorporated Pu distributed to the skeleton and liver.[226]

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A study of former nuclear industry workers demonstrated absorbed Pu distributes primarily to bones (~50%, primarily red marrow in trabecular bone rather than yellow marrow in cortical bone) followed by the liver (~30%) and smaller amounts in striated muscle.[227,228] In contrast to the uniform distribution of radium in bones, most plutonium (i.e., 93–97%) lies on the surface of the bone rather than in the marrow.[229,230] Because ^{239}Pu dioxide is poorly soluble, the lungs and surrounding lymph nodes retain most deposited burden of ^{239}Pu;[219] however, ^{238}Pu dioxide is solubilized and transported to the skeleton and liver.[231] In postmortem studies of 85 former Mayak nuclear workers exposed to Pu aerosols, ^{238}Pu accumulation fraction in the bodies of these workers ranged from 0.13–27.5%.[232] Although early animal studies suggested systemic translocation, particularly to the skeleton, was more rapid for ^{238}Pu than ^{239}Pu, the deposition of these radionuclides in the main organs was statistically similar in this study.

Elimination

A 30-year follow-up study of workers exposed to plutonium indicates the kidney excretes more plutonium than the intestines.[233] The kidney eliminates plutonium slowly from the blood at a rate of 3–4% of plasma plutonium/day.[234] The precision of models estimating total body burden based on the urinary Pu excretion rate depends on knowledge concerning particle size, chemical properties of the specific form of plutonium, and the urinary excretion rate of the individual.[235] Based on postmortem tissue analysis, the Langham power function model as modified by Leggett and Eckerman and the two-compartment exponential model proposed by the IRCP accurately predict elimination rates within a factor of 2.[236] Plutonium retention time in bone is very long with a retention $t_{1/2}$ = 100–200 years. Over 50–90% of inhaled ^{239}Pu dioxide remains in the lung for years. In 1985, a puncture wound in the right index finger of a Hanford worker resulted in the initial deposition of 48 kBq of transuranic α-activity, primarily ^{239}Pu, ^{240}Pu, and ^{241}Am.[237] Urinary Pu excretion after cessation of chelation therapy remained relatively constant over ~22½ years at 10–20 mBq/day.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

In animals exposed via inhalation to ^{238}Pu (3.7×10^4 Bq/kg) or ^{239}Pu dioxide (3.7×10^3 Bq/kg), radiation pneumonitis develops, characterized by fibrosis, alveolar edema, and occasionally by pulmonary hyperplasia and metaplasia.[219] At all Pu doses below levels producing radiation pneumonitis, interstitial fibrosis developed from chronic pulmonary irradiation by α-particles. Depending on the animal species, chemical form, and exposure route, plutonium causes lung cancer (bronchiolar-alveolar carcinomas), liver cancers (bile duct adenomas, bile duct carcinomas, sarcomas, and rarely hepatic cell tumors), and bone tumors (primarily osteogenic sarcomas in trabecular bone). Lung tumors occur only after inhalation, but more soluble plutonium also causes liver and bone tumors in animals following inhalation. Animal studies indicating uncomplicated pulmonary emphysema does not increase lung sensitivity to carcinogenic effects of inhaled ^{239}Pu dioxide.[238]

CLINICAL RESPONSE

Lungs

Case studies of early Mayak plutonium workers in the Soviet Union reported fatal acute/chronic radiation sickness, radiation pneumonitis, and pulmonary fibrosis, primarily from exposure to ^{239}Pu.[239] In a retrospective study of 326 plutonium-exposed workers with absorbed lung doses ranging from 0–28 Sv and 194 unexposed workers, scores on interstitial abnormalities evaluated by the International Labor Organization profusion scoring system were significantly higher in the exposed group (17.5%) than the unexposed group (7.2%, $P < 0.01$) after controlling for smoking, asbestos exposure, and age, particularly for workers receiving >10 Sv.[240] The risk of pulmonary fibrosis changes was 5.3-fold higher (95% CI: 1.2–23.4) in the latter group. Animal studies using ^{238}Pu and ^{239}Pu oxides suggest the development of pulmonary fibrosis depends on cumulative dose and isotope type.[241]

Skin

Fibrous nodules appear near sites of Pu deposition within a few months to years.[242] Atrophy and dyskeratosis from α-radiation extend into basal area of the epidermis. The similarity of these epidermal lesions to precancerous skin changes suggests the possibility that cancer may develop in these lesions.[243]

Carcinogenesis

Most studies of plutonium workers in the United Kingdom and the USA did not detect elevated risks of

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cancer, primarily because of the relatively low radiation exposures with few workers accumulating plutonium body burdens exceeding 1 kBq; however, an increased incidence of lung, bone, and liver cancer occurred in Russian cohorts working at the Mayak nuclear complex in the southern Urals exposed to higher radiation doses.[1] The latter studies demonstrate statistically significant cancer risks following the accumulation of body burdens of >3 kBq with equivalent lung doses of >80 Sv assuming a RBE of 20. These three cancer sites represent the organs accumulating the highest doses of incorporated plutonium.

Although several epidemiological studies of US plutonium workers have not demonstrated a definite causal association between plutonium exposure and cancer, the IARC classifies ^{239}Pu as a Group 1 (human) carcinogen based on cancer in heavily exposed Russian Pu workers (i.e., body burden >3 kBq) to ^{239}Pu at the Mayak plutonium production plant in the Russian Federation. Generally, the cancer mortality rates were not elevated in Pu workers with estimated body burdens of 1 kBq.[244,245] Using 5-year cancer induction rates, a statistically significant elevation of the all-cause mortality rate occurred in a mortality study of 5,413 white males with at least 2 years of employment at a plutonium weapons facility; however, this elevation did not demonstrate a linear dose-response.[246] A case study of 26 Manhattan project workers reported a Pu-exposed worker with osteosarcoma of the coccyx;[247] four blood cell neoplasms (multiple myeloma, myeloid leukemia, non-Hodgkin's lymphoma, reticulum cell sarcoma) occurred in workers at Rocky Flats.[246] US plutonium workers have been examined periodically over the past 50 years to identify possible health effects from internal plutonium depositions. The effective doses for 26 white male workers employed in original plutonium research and development work at Los Alamos ranged from 0.1–7.2 Sv with a median value of 1.25 Sv.[248] Compared with 876 unexposed Los Alamos workers, the SMR for the 26 workers was not statistically elevated (SMR = 0.77; n = 8 deaths) after 50 years of follow-up; 3 of these deaths involved cancer (prostate, lung, bone).

HEALTH SURVEILLANCE

Although default values for absorption parameters in the ICRP model provide reasonable approximations of Pu absorption following inhalation,[249] accurate determination of the risk from occupational Pu exposure depends on reliable assumptions regarding the chemical form of inhaled plutonium, Pu distribution in the lungs, and absorption values for diffusion from the lungs to blood.[250] A Russian study examined the incidences of lung, liver, bone, and associated connective tissue cancers in 16,679 male and 5,687 female workers at the reactors, radiochemical manufacturing, and plutonium production facilities of the Mayak nuclear complex from 1948–1982 with follow-up through 2004.[251] Radiation exposure involved internally incorporated Pu and external γ-radiation. The study demonstrated a significant internal plutonium dose-response for evaluated lung cancer subtypes (i.e., adenocarcinoma, squamous cell, other epithelial) in *men*; the estimated excess relative risk (ERR/Gy for adenocarcinoma was 32.5; 95% CI: 16.3–71.9) compared with squamous cell lung cancer (EER/Gy = 3.1; 95% CI: 0.3–9.1). A linear-quadratic function described the dose-response for liver cancer, particularly above 2 Gy, whereas the trend for bone cancer and plutonium was nonsignificant. Analysis of smoking and lung cancer risk indicates smoking is sub-multiplicative and super-additive.[216] A study of 319 deceased US nuclear workers employed between 1943 and 1995 with histories of transuranic radionuclides intake did not demonstrate an elevated risk of overall cancer mortality; however, the risk of death from any type of cancer increased with a history of smoking (OR = 5.41; 95% CI: 1.42–20.67) and cigarette smoking rate in packs/day (OR = 2.70; 95% CI: 1.37–5.30).[252] Based on excess relative risk estimates/unit absorbed lung dose from α-radiation in plutonium workers at the Mayak nuclear facility, the relative biological effectiveness (RBE) of inhaled ^{239}Pu ranges from 10–20, with the upper limit providing a sufficient radiation weighting factor for α-particles during occupational exposures.[253]

TREATMENT

Wounds

Animal experiments indicate plutonium absorption into the systemic circulation after wound contamination is relatively slow.[254] Measurement of the amount of 17 keV X-rays emitted with the α-particles is an accurate measure of wound contamination. Treatment of skin wounds contaminated with plutonium includes decontamination, excision of the contaminated portion of the wound, and early and frequent chelation with intravenous or inhaled DTPA.[255] Solutions available to remove plutonium firmly fixed to skin include liquid soap and detergent, 4% $KMnO_4$, and 5% $NaHSO_3$. Preferably, chelation therapy should begin within several hours of the confirmation of incorporated Pu doses

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exceeding currently recommended standards. Ca-DTPA is the chelator of choice during the first 24 hours after internal contamination, whereas both DTPA preparations are probably equally effective after the initial 24 hours postexposure.[256]

Inhalation

Ca-DTPA and Zn-DTPA are effective agents for reducing the amount of plutonium in the liver and bones following systemic absorption of soluble Pu forms, particularly when administered immediately after contamination;[257] however, during the first 24 hours after internal contamination, Ca-DTPA probably enhances urinary Pu excretion more than Zn-DTPA or $CaNa_2EDTA$.[258] In animals, these chelating agents decrease the incidence of osteosarcomas after the intravenous injection of ^{239}Pu.[259] These agents are available through the Medical and Health Sciences Division of Oak Ridge Associated Universities in Oak Ridge, Tennessee (https://www.orau.gov/hsc/RadMassCasualties/assets/6_Pharmacotherapy_Handout.pdf).

After obtaining baseline blood (CBC with differential, BUN, serum creatinine) and urine samples (urinalysis and urine radioassay), 1 g Ca-DTPA is administered to adults unless Zn-DTPA is indicated for pregnant women. This dose can be diluted in 100–250 mL D5W or normal saline and administered over 1 hour. Twenty-four-hour urine and fecal samples are collected for bioassay; whole-body and chest counting are initiated to estimate the amount of contamination and efficacy of chelation. Repeat doses of 1 g CaDTPA or 1 g Zn-DTPA may be administered daily up to 5 days/week as determined by the radioassay data and exposure history. Most patients receive a single DTPA dose. Supplemental zinc therapy (220 mg zinc sulfate daily) may be necessary during long-term Ca-DTPA chelation. Ca-DTPA treatment is contraindicated in the presence of preexisting serious kidney disease or depressed myelopoietic function (e.g., leukopenia or thrombocytopenia).

The use of an aerosol of Ca-DTPA is an alternative treatment for decreasing the burden of soluble plutonium forms (^{238}Pu and ^{239}Pu nitrate or tributylphosphate) in the lungs;[83] however, there is no clear evidence that inhalation is superior to IV treatment because of the limited amount of DTPA particles reaching alveolar tissues, unless DTPA administration via inhalation is a more rapid option. Lung monitoring may be useful for the ^{238}Pu and ^{239}Pu isotopes; however, ^{241}Pu emits only nonpenetrating radiation. Suggested guidelines for initiating DTPA treatment for soluble ^{238}Pu and ^{239}Pu exposures include consideration for estimated internal doses of 20–200 mSv and implementation of treatment at doses exceeding 200 mSv.[93] Zn-DTPA is a less desirable form for aerosol administration because of its metallic taste. The removal of insoluble Pu forms is much more difficult, especially after radionuclide uptake by macrophages. Bronchopulmonary lavage is the only effective treatment for the deposition of ^{239}Pu oxides in the lungs; however, the amount (~20%) of plutonium removed from the lungs with this procedure is limited.

POLONIUM

HISTORY

Marie Curie discovered ^{210}Po when she separated this radionuclide from pitchblende in 1898;[260] in 1910, she and André-Louis Debierne isolated 0.1 mg polonium by the spark spectrum technique. She received the Nobel Prize in 1911 for the discovery of polonium and radium. The assassination of the former lieutenant colonel of the Russian Federal Security Service and Russian writer-dissident, Alexander Litvinenko, in London on November 23, 2006, focused media attention on radiation-induced toxicity from the internal polonium-210 (^{210}Po) contamination.[261] He became ill on November 1, 2006, after ingesting tea contaminated with a soluble polonium salt; autoradiography of hair samples demonstrated two regions of ^{210}Po activity suggesting an earlier poisoning attempt during October 2006 involving one-hundredth the estimated dose for November 1, 2006, with resulting renal radiation dose approaching 3 Gy from the first poisoning compared with organ doses ranging from 20 to over 100 Gy from the second poisoning.[262] British experts estimated he ingested ~0.2–8.5 μg ^{210}Po (27–1,408 MBq) from the tainted tea, assuming ^{210}Po was the only ingested radionuclide.[263] He died 23 days after drinking the tainted tea with the postmortem examination demonstrating ^{210}Po concentrations ~10^9 times normal background levels.[264]

During his medical care, hospital personnel surveyed Mr. Litvinenko with a standard Geiger–Mueller counter without detecting radioactivity; however, ^{210}Po decays primarily by the release of α-particles undetectable at the surface of the skin by a Geiger–Mueller counter following internal contamination.[265] Subsequent investigations detected widespread radioactive contamination at various local and more distant hotels, offices, and hospitals.[266] Testing involved over 700 UK residents

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with 139 individuals demonstrating evidence of internal contamination with ^{210}Po as defined by urinary ^{210}Po excretion of >30 mBq/24 hours; however, the risk of adverse effects from this contamination was not considered clinically significant with the radiation dose in only a few individuals exceeding 1 mSv.[267] The 43 healthcare providers were unaware of his radioactive contamination during his 3-week illness; these providers used standard precautions without developing significant internal contamination.

PHYSIOCHEMICAL PROPERTIES

Polonium is the first element in the periodic table with all isotopes being radioactive; there are 33 isotopes ranging in mass from 188–220; however, only isotopes 208, 209, and 210 have half-lives exceeding 1 day.[268] The most widely available Po isotope is ^{210}Polonium, a silvery-gray, soft, volatile, naturally occurring radioactive element that is part of the uranium (^{238}U) decay series. Along with ^{210}Pb, ^{210}Po is a relatively long-lived decay product of ^{222}radon. Polonium has several oxidation states (−2, 2, 4, 6), with Po^{4+} being the most stable in aqueous solutions.

^{210}Po is not a gas; therefore, release of this isotope to the air involves particulates rather than vapors. Po belongs to Group 16 (Group VIA) of the periodic table along with oxygen, sulfur, and selenium; however, the amino acids, methionine and selenomethionine do not readily incorporate Po. This radionuclide decays to ^{206}Po by α-decay accompanied by 1/100,000 decays with γ-emission, as displayed in Equation 41.4. ^{210}Po emits a pure α-particle with a relatively high kinetic energy of 5.3 MeV. The range of these α-particles in tissue is low (i.e., 40–50 μm). This radionuclide decays with a physical half-life of ~138 days and an effective biological half-life of 46 days.[1]

$$^{210}_{84}\text{Po} \rightarrow {}^{206}_{82}\text{Pb} + {}^{4}_{2}\text{He} \qquad \text{(Equation 41.4)}$$

Polonium easily forms simple, water-soluble salts (e.g., chlorides) in dilute acid solutions; this radionuclide has a high affinity for proteins. The specific activity of ^{210}Po (1.66×10^{14} Bq/g) is relatively high; 10 μg Po chloride salt is equivalent to 1 GBq.[261] One μg Po emits as many α-particles as 5 mg ^{226}Ra and 446 kg ^{238}U.[268] The linear transfer energy of ^{210}Po in water is 100 keV/μm, sufficient to penetrate ~50 μm in tissue including human cells (typically, 10–30 μm in diameter).

EXPOSURE

Production Processes

^{210}Po is a ubiquitous, naturally occurring radionuclide formed from the uranium-238 decay chain (i.e., decay of ^{210}Pb by release of ^{222}Rn), as displayed in Figure 41.2.

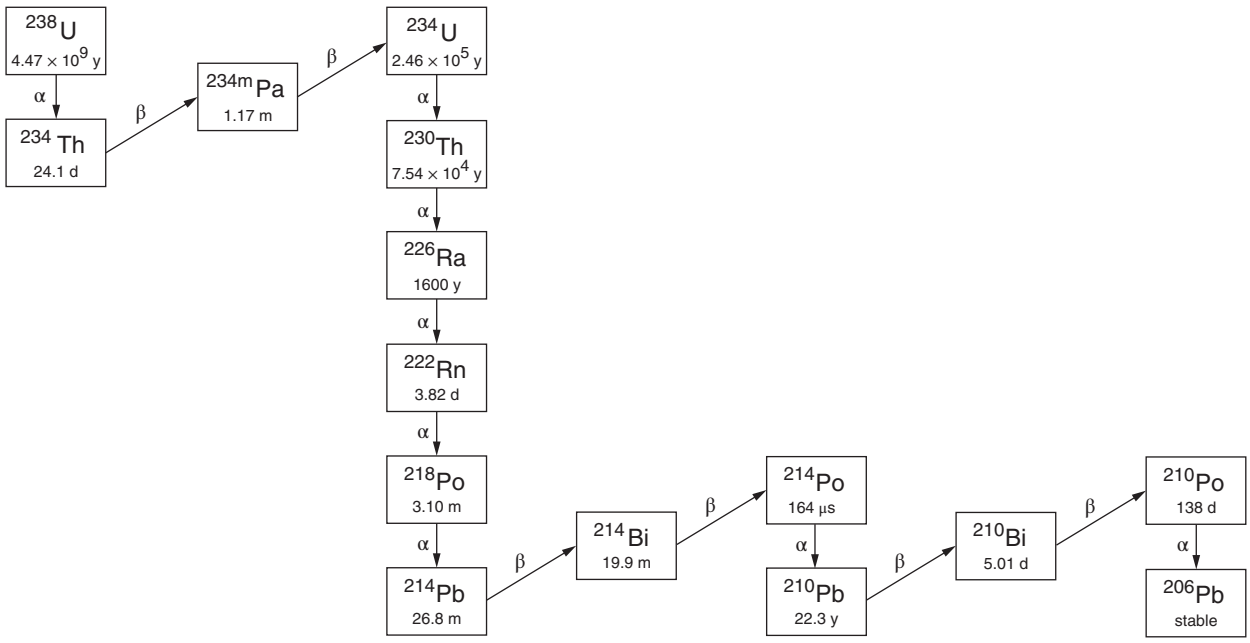


FIGURE 41.2. The ^{238}uranium (^{238}U) decay series including the formation of ^{210}polonium (^{210}Po). (Redrawn from Matthews et al.).[260]

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Neutron irradiation of ^{209}bismuth in a nuclear reactor is the main commercial process for ^{210}Po production; ^{210}bismuth decays to ^{210}Po through β-decay with a half-life of 5 days.[268] ^{210}Po is a natural soft metal with several industrial applications including static eliminator in combination with gold foil (paper rolling, spinning synthetic fibers), a lightweight heat source for thermoelectric power, and a neutron source with beryllium for early atomic weapons.

Sources

Environment

Environmental concentrations of ^{210}Po are relatively very low.[269] In aqueous environments, Po occurs primarily as a slightly soluble tetravalent compound that forms colloids and easily adheres to particulates.[268] Polonium tends to volatilize at temperatures near 50°C; alkyl derivatives of Po and the reduced form (H_2Po) are volatile. Potential sources of ^{210}Po in the atmosphere and surface waters include the deposition of ^{210}Po from the decay and volatilization of ^{226}Ra and ^{222}Rn from the ground, volcanic eruptions, fires, resuspension of soil dust, migration of sea salt, zircon processing, cement production, phosphate processing, and burning of fossil fuel.[270] ^{210}Po (and ^{210}Pb) are the final long-lived radionuclides in the decay of ^{238}U in the earth's crust. The estimated population radiation dose of ^{210}Po in surface air is ~50 μBq/m^3.[271] The typical activity concentration of ^{210}Po is 7–50 mBq/L in private wells, 1–100 mBq/L in rainwater, and 1–5 mBq/L in ocean water.[268] A study of groundwater wells in California demonstrated ^{210}Po activity in water samples ranging from 0.25–555 mBq/L with mean and median activities of 57.8 mBq/L and 3.33 mBq/L, respectively.[272] In soils, ^{210}Po associates with organic matter and adsorbs to minerals, particularly clays. The activity concentration depends on soil type, depth, and atmospheric precipitation with average activity concentrations of 20–240 Bq/kg. Contaminated soils (e.g., uranium mining residues) may contain 15,000–22,000 Bq/kg ^{210}Po.[273]

Food

The chemical form of ^{210}Po in foods is not well defined; differences in bioavailability probably account for some of the differences in dietary estimates. The estimated average median daily dietary intake of ^{210}Po for adults is 0.16 Bq corresponding to an annual effective dose of 70 μSv.[268] The main sources of ^{210}Po in the human body are food and cigarette smoke; the body burden of ^{210}Po is relatively high in smokers with high-protein diets of seafood or meat (e.g., reindeer, caribou).[274] Bioaccumulation of ^{210}Po is higher in aquatic than terrestrial environments, with activity concentrations in fish reaching 1 Bq/kg and ~40 Bq/kg in mollusks. ^{210}Po binds easily to proteins in protein-rich foods (e.g., crustaceans, shellfish) containing relatively high concentrations of ^{210}Po activity.[275] ^{210}Po accounts for a substantial portion of the α-radiation in some marine organisms (i.e., up to 75% in mussels from the Cumbrian coast).[276] The estimated annual effective dose of ^{210}Po from the ingestion of caribou meat in the Northwest Territories of Canada is ~0.3–0.4 mSv.[277]

Lifestyle

The leaves of various plants contain ^{210}Po, including tobacco. In a study of popular Italian cigarettes, the ^{210}Po activities ranged from 6.84–17.49 mBq/cigarette.[278] The long interval between tobacco harvest and cigarette production (i.e., up to 6–7 half-lives of ^{210}Po) and the volatilization of this radionuclide at temperatures of >500°C reduce some ^{210}Po in tobacco smoke, resulting in the inhalation of ~1/3 of the ^{210}Po in a cigarette.[279] Cigarette filters do not adsorb significant amounts of ^{210}Po (i.e., mean = ~14%).[278] Based on studies of the ^{210}Po content of cigarettes, the estimated annual mean effective dose for 1-ppd smoker ranges from ~35–193 μSv.[279,280] A study by the National Council on Radiation Protection and Measurements indicates ^{210}Po in smoke accounts for ~2.8 mSv of the total average exposure of the US population (~6.5 mSv). The estimated mean annual effective doses for ^{210}Po in the country with the highest prevalence of tobacco smoking (Serbia) was 724 μSv,[281] whereas the estimated mean annual committed effective dose of ^{210}Po for a Japanese smoker consuming 20 cigarettes daily was 68 ± 27 μSv.[282]

DOSE-RESPONSE

Polonium is one of the most toxic natural radioactive isotopes because of radiation-induced injury to internal organs from the high specific activity (144 GBq/mg) and the emission of high-LET α-radiation (E_α = 5.3 MeV). Although estimating a fatal ^{210}Po dose is difficult because of various uncertainties (e.g., absorption, chemical form), modeling and existing data suggest a fatal dose is 10–30 μg in the absence of medical care.[261] Estimates of the ^{210}Po dose ingested by Alexander Litvinenko reflect this uncertainty.[263]

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TOXICOKINETICS

Absorption

The risk of internal contamination results from ^{210}Po ingestion, inhalation, or contaminated wounds. Estimates of the absorption of ^{210}Po from the intestine are variable with a range of ~10–80% depending on speciation, solubility, pH, form (e.g., colloid), and complexation with other substances.[283,284] In a study of five volunteers ingesting 10 Bq ^{209}Po, the average uptake fraction by the gastrointestinal tract was 0.46 ± 0.08.[285] The ICRP initially used a low estimate (i.e., 10%) of gastrointestinal absorption of ^{210}Po,[25] but subsequently the ICRP raised this estimate to 50% based partly on an average gastrointestinal absorption of ~80% in six British volunteers ingesting naturally occurring ^{210}Po from brown crab meat.[284] The intermediate solubility (i.e., 50%) of ^{210}Po is supported by volunteer studies.[286] In a study of 14 volunteers ingesting naturally occurring ^{210}Po from caribou meat, the mean gastrointestinal absorption factor was 56% ± 4% with a range of 31–71%.[287] Dermal ^{210}Po absorption is minimal because of the inability of this radionuclide to penetrate the stratum corneum; consequently, external contamination does not produce radiation sickness when the skin remains intact.[261]

Distribution

Nonhuman primate studies on the intravenous administration of ^{210}Po indicate a rapid distribution phase that results in the disappearance of ~80–90% of the administered dose within 10–40 minutes.[288] The second elimination phase of ^{210}Po from the blood is much slower with a biological half-time of ~10–40 days. The distribution of ^{210}Po differs from other α-emitters (e.g., plutonium, uranium), which distribute primarily to the bone surfaces.[289] ^{210}Po is distributed from the blood primarily to soft tissues, with the highest concentrations occurring in the reticuloendothelial system (e.g., spleen, bone marrow, liver) and the kidney.[288] The estimated distribution of ^{210}Po in the human body in these organs is approximately as follows: liver, 30%; red bone marrow, 10%; kidney, 10%; and spleen, 5%.[290] Distribution to the skeleton is ~5% of the absorbed dose.[261] Typical concentrations of ^{210}Po in bones range from ~2–9 Bq/kg.[291] Animal studies suggest fetal transfer of ^{210}Po is relatively low.[1]

Elimination

Fecal excretion is probably the main route of ^{210}Po elimination from the body. Following the accidental inhalation of ^{210}Po oxide, fecal/urine ratios of ^{210}Po exceeded 10–20, especially during the first 20 days after exposure.[292] Although the typical estimated biological half-life for the elimination of ^{210}Po from the body ranges up to ~1–2 months, some studies of volunteers ingesting naturally occurring ^{210}Po in food suggest the retention half-life may exceed 100 days.[287] Figure 41.3 displays the urinary excretion of a 1 MBq dose of ^{210}Po with background rates for nonsmokers and smokers illustrated by solid and dotted lines, respectively.

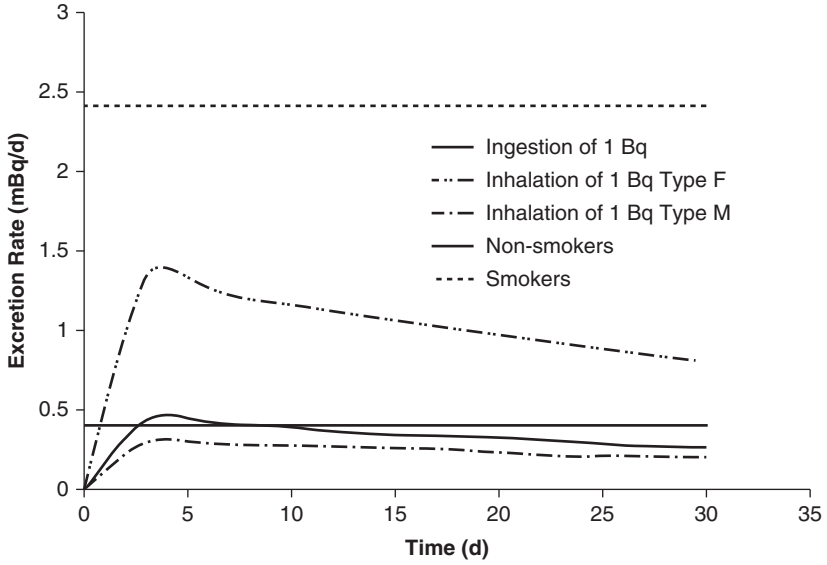


FIGURE 41.3. Daily urinary excretion of ^{210}Polonium (^{210}Po) after acute exposure to 1 Bq. (Redrawn from Anderson et al.).[293]

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Maternal-Fetal Kinetics

Little specific human data on ^{210}Po are available with limited data from animal studies. Extrapolation of animal data to humans and predicted fetal radiation doses are complicated by difference in pharmacokinetics and organ development. In baboons administered intravenous ^{210}Po during the 5th month of pregnancy, the whole-body fetal/maternal ^{210}Po ratio was 0.3 with ~1% of the Po dose retained by the fetus.[208]

CLINICAL RESPONSE

Clinical effects from ^{210}Po exposure occur only after internal contamination because this radionuclide is an α-emitter with an extremely low abundance of photon emissions. Bone marrow syndrome, gastrointestinal syndrome, and local skin damage occur rarely following contamination by ^{210}Po, exclusively after very high ^{210}Po doses. The prodromal symptoms (e.g., nausea, vomiting, diarrhea, anorexia) are common, nonspecific gastrointestinal symptoms. For acute ^{210}Po exposure, bone marrow failure is the expected short-term effect of the ingestion of 2 GBq ^{210}Po based on dose estimates, lethal dose values, and an absorption fraction of 10%.[261] The clinical features of radiation-induced bone marrow failure are similar to those of bone marrow failure from other etiologies (e.g., drugs, infections, toxins).[261]

Figure 41.4 is a schematic timeline of the clinical effects of the poisoning of Alexander Litvinenko by ^{210}Po-tainted tea.

Although there is sufficient evidence of ^{210}Po carcinogenicity in experimental animal studies, human data are inadequate including cohorts of workers in the nuclear industry.[1] In a cohort study of 4,402 Caucasian men exposed to ^{210}Po processing and Po–Be neutron sources from 1944–1974, mortality from cancer was not elevated (SMR = 1.01, 90% CI: 0.73–2.16) when compared with mortality rates for US Caucasian men.[294] Annual doses were estimated from annual cumulative doses rather than direct measurements, resulting in potential misclassification. The study detected no significant trends in mortality from all causes, all cancers, or any specific cancers.

DIAGNOSTIC TESTING

External methods for detecting radioactivity from ^{210}Po do not identify internal ^{210}Po α-radiation. Geiger–Muller detectors usually require special wand or sensor attachments to efficiently detect α-radiation. No surface detector accurately assesses total-body α-emitter burden because α-particles cannot penetrate tissues; therefore, confirmation of internal ^{210}Po requires testing of biological samples (e.g., 24-hour urine and fecal collections). Older methods of the radiochemical analysis of urine

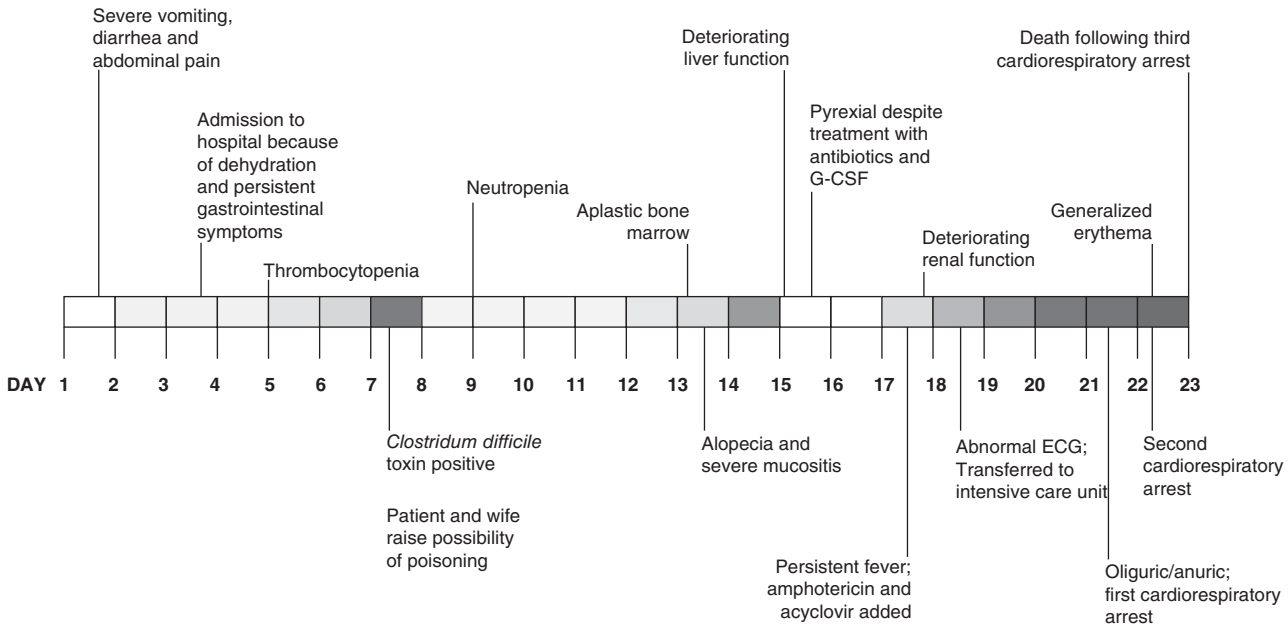


FIGURE 41.4. Schematic timeline of clinical features of ^{210}Polonium (^{210}Po) poisoning of Alexander Litvinenko. (Nathwani et al.).[264]

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sample for ^{210}Po used spontaneous deposition of this radionuclide following the direct application of raw urine to an appropriate metal disc (e.g., Ni, Cu, Ag). Subsequent studies indicated this method underestimated the amount of ^{210}Po when compared with the addition of ^{210}Po tracer to urine samples.[295] The volatility of polonium at temperatures of >100°C necessitates the use of wet-ashing techniques as part of sample preparation.[296] Following deposition of the sample on a suitable metal (e.g., silver, stainless steel), quantitation involves α-spectrometric analysis with silicon surface barrier/passivated implanted planar silicon (PIPS) detectors.

The estimated committed (50-year) effective dose equal to 250 mSv for the ingestion of ^{210}Po activity is 1.02 mBq.[293] This dose is substantially below the dose (14 mBq) associated with potential deterministic effects. A single-void urine specimen is sufficient to detect ^{210}Po activity above recommended standards during radiological emergencies.

TREATMENT

Patients with ^{210}Po contamination are not a health threat to medical responders. If polonium is present, excreta should be surveyed with α-detecting probe and handled per local radioactive waste disposal protocols. There are few human data on the use of chelating agents to enhance the excretion of ^{210}Po.[297] Animal studies suggest that dimercaprol (BAL), penicillamine, and DMSA are potential chelation agents, but the effectiveness of these agents decreases substantially following delayed administration.[298,299] Most evidence involves animal studies that administer the chelating agent soon after exposure and use higher chelating doses than typically administered in humans. Although some rodent studies demonstrate decreased blood ^{210}Po concentrations and increased survival with long-term therapy, other animal studies indicate increased retention in the kidneys and occasionally the brain and liver. The US Department of Health and Human Services (Radiation Emergency Medical Management, US Department of Health & Human Services) recommends 2.5 mg dimercaprol/kg qid × 2 days (days 1–2), then bid × 1 day (day 3) and qd (days 4–10). Newer potential chelating agents include mono-*N*-(*i*-butyl)-*meso*-2,3-dimercapto succinimide and mono-*i*-amyl-*meso*-2,3-dimercapto succinate. Although these two agents increase the total excretion of ^{210}Po, only the former compound reduces the concentration of ^{210}Po in the kidneys.[300] Neither DTPA nor EDTA was an effective chelation agent.[301]

RADIUM

HISTORY

The Curies discovered radium in 1898 while investigating uranium and pitchblende composition. Physicians in the early 20th century used radium for a variety of ailments including tuberculosis, skin lesions, cancer, arthritis, cancer, and digestive ailments, particularly before the Pure Food and Drug law was enacted in 1906. In 1902, William Hammer synthesized luminous paint by combining radium with zinc sulfide; by the time of World War I, radium paint was a constituent of watches and military instruments. Subsequently, young female radium dial painters were some of the first victims of industrial radiation poisoning.[302] In the early 1920s, ^{226}Ra and ^{228}Ra in triple-distilled water were advertised constituents of a patented radioactive medicine (i.e., Radithor) used as a metabolic stimulant and aphrodisiac. Although many patients lived years after long-term consumption of this substance, the death of Pittsburgh industrialist Eben M. Byers from an estimated dose equivalent of 350 Gy radium led to the removal of Radithor from the marketplace.[303] By the end of the 1920s, osteonecrosis of the jaw was a recognized occupational disease of radium dial workers.[304] Accumulating evidence of adverse effects from radium dial painting and subsequent lawsuits during the 1930s resulted in the passage of radium exposure standards in 1941. Luminous paints on watches and clock dials contained radium until the 1960s.

PHYSICOCHEMICAL PROPERTIES

Of the 16 known isotopes of radium, only 4 isotopes occur naturally (^{223}Ra, ^{224}Ra, ^{226}Ra, ^{228}Ra). ^{223}Ra, ^{224}Ra, and ^{226}Ra are α-emitters, whereas ^{228}Ra emits β-particles. ^{224}Ra has a short physical half-life (3.62 days); adverse health effects from exposure to this radionuclide result from its association with ^{228}Ra by the decay of ^{228}Th. Table 41.23 lists the physical properties of natural radium isotopes.

TABLE 41.23. Physical properties of natural radium isotopes.

Physical Property	^{223}Ra	^{224}Ra	^{226}Ra	^{228}Ra
Decay mode	α-particle	α-particle	α-particle	β-particle
Decay energy (MeV)	5.979	5.789	4.870	0.045
Half-life	11.4 days	3.6 days	~1,600 years	5.7 years

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TABLE 41.24. Identifying characteristics and physical properties of radium and radium compounds. (Adapted from Agency for Toxic Substances and Disease Registry).[305]

Physical Characteristic	^{226}Radium	Radium Bromide	Radium Carbonate	Radium Chloride
CAS registry number	7440-14-4	10031-23-9	7116-98-5	10025-66-8
Molecular formula	Ra	$RaBr_2$	$RaCO_3$	$RaCl_2$
Valence	0	+2	+2	+2
Molecular weight (g/mol)	226.03	385.83	286.03	296.93
Color	Silver-white	White	White	Yellow-white
Physical state	Solid	Solid	Solid	Solid
Melting/boiling points (°C)	700	728	NA	1,000
Density (20°C)	5	5.79	NA	4.91
Water solubility (20°C)	Decays	Soluble	Insoluble	Soluble
Physical Characteristic	**Radium Hydroxide**	**Radium Iodate**	**Radium Nitrate**	**Radium Sulfate**
CAS registry number	98966-86-0	NA	10213-12-4	7446-16-4
Molecular formula	$Ra(OH)_2$	$RaIO_3$	$RaNO_3$	$RaSO_4$
Valence	+2	+2	+2	+2
Molecular weight (g/mol)	260.15	575.83	350.04	382.08
Color				White
Physical state			Solid	Solid
Water solubility (20°C)	NA	Soluble	Soluble	Insoluble

The solubility of radium salts increases with increased pH. Soluble radium compounds include bromide, chloride, iodate, and nitrate salts, whereas insoluble radium compounds include carbonate and sulfate salts. Table 41.24 lists the physiochemical properties of radium.

EXPOSURE

Radium is a ubiquitous radionuclide that occurs because of the radioactive decay of uranium and thorium. Radium does not hydrolyze or oxidize; therefore, this element does not undergo biodegradation in the environment. Low concentrations of radium isotopes exist in soil, rocks, food, and water; however, groundwater in some US regions contains radium concentrations exceeding the federal standard of 5 pCi/L.[306] In a German study of 582 public drinking-water samples, the radiation dose from ^{226}Ra ranged from <0.8–350 mBq/L with a median of 5.6 mBq/L and a 95th% of 41 mBq/L.[307] For ^{228}Ra, the concentration ranged from <0.7–120 mBq/L with a median of 4.6 mBq/L and a 95th% of 26 mBq/L. Radium was the most abundant radioactive contaminant in solids collected from drinking-water distribution systems during routine fire hydrant flushing in four US states (Illinois, Minnesota, Texas, Wisconsin); the total radium concentration ranged from 3.3–592 pCi/g with a mean of 143 ± 136 pCi/g.[308] The ^{226}Ra concentrations ranged from 2.7–250 pCi/g with a mean of 74 ± 68 pCi/g, whereas the ^{228}Ra concentrations ranged from 0.4–351 pCi/g with a mean of 69 ± 75 pCi/g.

Compared with groundwater, air is not an important radium source for the general population. The leaching of uranium mine tailings and release of ore-processing effluents are important causes of well water contamination with radium.[305] On a global scale, the amount of radium released into the environment from industrial use is insignificant compared with the natural occurrence of radium.[305] Radium is a radiation source for neutrons and radon in research, industrial radiography, and cancer treatment. Potential occupational sources of ^{226}Ra and ^{228}Ra include offshore oil extraction, coal mines, fossil fuel processing, blast furnace slag, and phosphate ores.[309]

TOXICOKINETICS

Absorption

The amount of radium absorbed after inhalation depends on solubility of the salt and particle size. The ICRP model and limited experimental data suggest most radium compounds are moderately absorbable (i.e., ~10–20%). Following accidental exposure to ^{226}Ra sulfate, the average retention half-life in the lung was ~120 days.[310] In a study of elderly human volunteers, ~20% of an oral dose of $^{224}RaSO_4$ was absorbed and distributed to the skeleton.[305]

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Distribution

Depending on the solubility of the salt, inhaled radium is distributed to soft tissue and eventually to the skeleton. Soft tissue retention of ^{226}Ra peaks at 58% of the absorbed dose 18 days after a single ingestion with equilibration occurring at ~5% after 3 years.[311] Like calcium, radium deposits preferentially in areas of new bone formation, initially adsorbing into bony surfaces and red marrow followed by incorporation into the bony matrix. Hence, uptake into bone is much greater in growing than in mature bone. Chronic radium intake and bone remodeling eventually result in the uniform distribution of radium in the bone.[312] Although ^{224}Ra decays quickly with no residual radioactivity in the bone, ^{226}Ra persists in the bone because of its relatively long half-life compared with ^{224}Ra.[313]

Elimination

Most ingested radium is excreted in the feces probably involving biliary excretion. In dogs, the fecal to urinary excretion ratio of soluble radium salts following parenteral administration was 10:1.[314] Elimination of a parenteral radium dose in humans is slow with retention dropping from 2.5% of the original dose of radium at 1 year to 0.43% at 30 years.[315]

CLINICAL RESPONSE

An elevated incidence of cataracts occurred in radium dial painters and ~6% of children administered intravenous ^{224}Ra.[316] Additionally, these children frequently developed extensive resorption of the dentine, radiation-induced caries, and fractures of the teeth.[305] Although the incidence of bone marrow failure was slightly increased (10 cases vs. 7 cases expected), the statistical significance of this number of cases is unclear.[317] Ingestion of a radium-containing patent medicine, Radithor, was associated with headaches, toothaches, tooth loss, multiple areas of skeletal and soft tissue necrosis, bone marrow dyscrasia, multisystem failure, and death in the 1930s.[318] Diffuse interstitial fibrosis is a recognized complication of radiotherapy.[319] Occupational exposure to α-emitting radium in dust from fluorescent paint has been associated with the development of diffuse pulmonary fibrosis.[320]

Carcinogenesis

The IARC classifies ^{224}Ra, ^{226}Ra, and ^{228}Ra and their decay products as Group 1 (carcinogenic to humans) carcinogens.[1] Health effects following radium exposure result from the emission of α- and β-particles along with γ-radiation released during decay of radium and its daughter products including radon. The best-studied cohorts of radium-induced cancers are radium watch-dial painters (luminizers) and tuberculosis and ankylosing spondylitis patients treated with radium. Watch-dial paint contained the α-emitter ^{226}Ra and the β-emitter ^{228}Ra in zinc sulfide, whereas ^{224}Ra was the α-emitter in the intravenous German medication (Peteosthor) used to treat ankylosing spondylitis and tuberculosis from 1948–1975. In the dial industry, the ratio of ^{226}Ra/^{228}Ra in radium dial paints varied by company and time of use. Studies of US watch-dial painters demonstrated a consistently increased risk of bone sarcoma related to ingesting relatively high radium doses during the formation of finely pointed tips on the paint brush tips with their lips; the incidence of these tumors was particularly increased in women with active bone growth. The risk of bone sarcomas was not increased in British radium dial painters receiving a much smaller radium dose (i.e., estimated annual median endosteal bone surfaces and red marrow doses of 10 mGy and 1 mGy, respectively) because they did not use the pointing technique.[321] Over 900 German patients received intravenous ^{224}Ra for the treatment of tuberculosis and ankylosing spondylitis; the average absorbed radiation dose was 2 Gy to red marrow and 4 Gy to skeletal bones, with the mean bone surface dose reaching 30 Gy in the high-dose group.[322] Studies of this cohort indicated that bone sarcomas developed at radium doses of >1.03 μCi ^{224}Ra/kg.[323]

There is some evidence of an increased incidence of leukemia in the German cohort; however, a causal link between radium radionuclides and cancers other than bone sarcomas and head carcinomas is not well-established. The German studies suggested an elevated incidence of kidney, liver, breast, thyroid, and soft tissue cancers following intravenous ^{224}Ra doses.[324] The estimated mean absorbed dose from α-particle radiation was 0.56 Gy to the marrow-free skeleton of a 70-kg man with a mean bone surface dose of ~5 Gy. An increased incidence of breast cancer occurred in women receiving >12 μCi ^{224}Ra/kg intravenously before the age of 21 years.[325] All the patients in these studies were adults, in contrast to the many children and adolescents given Peteosthor in earlier studies. A follow-up study of 1,471 ankylosing spondylitis patients treated with intravenous ^{224}Ra did not confirm the elevated incidence

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of breast or liver cancer; however, the standardized incidence rates (SIR) for kidney (SIR = 1.98, n = 18, expected 9.1) and thyroid (SIR = 3.33, n = 4, expected 1.2) cancers were elevated.[326] The incidence of breast cancer and multiple myeloma was elevated in female radium watch-dial workers;[327] however, the large number of nulliparous women and exposure to γ-irradiation from ^{228}Ra paints are potential confounding effects.[328] A study of 274 Finnish residents exposed to radium in drilled wells for ~20 years did not detect an elevated hazard ratio of bladder or kidney cancer including no dose-response relationship between radium exposure and bladder or kidney cancer.[329] Overall, these studies involved small case numbers and lacked data demonstrating a dose-response relationship between radium exposure and cancer rates.

Osteosarcoma

US radium dial workers (luminizers) exposed to ^{226}Ra (α-emitter, $t_{½}$ = ~1,600 years) often along with ^{228}Ra (β-emitter, $t_{½}$ = 5.75 years) during radium dial painting developed an excessive incidence of bone sarcomas (osteogenic sarcoma, fibrosarcoma) and head carcinomas (paranasal sinuses, mastoid air cells). The bone sarcomas were widely distributed throughout the skeleton. Hazard modeling using multivariate analyses of dose-response relationships indicated both radium isotopes significantly contributed to the rate of bone sarcoma mortality; however, only ^{226}Ra was associated with mortality from paranasal sinus and mastoid air cell carcinomas.[330] ^{228}Ra decays to the noble gas ^{220}Rn (thoron) with a half-life of ~55 seconds. Examination of dose-response relationships in radium watch-dial painters indicates workers with high ^{228}Ra doses did not develop an increased incidence of carcinomas of the paranasal sinuses or mastoid processes. In a case series of 32 radium-induced cancers, the histological type of carcinomas was mostly soft tissue cancers, primarily mucoepidermoid (i.e., 8/21 mastoid; 4/11 paranasal sinuses) or epidermoid (12/21 mastoid, 3/11 paranasal sinuses).[331] The median tumor induction time from the first radium exposure to the first clinical feature of the tumor was 33 years for mastoid tumors (range, 21–50 years; n = 21) and 34 years for paranasal sinus tumors (range, 19–52 years; n = 11). Hazard modeling, histological subtypes, and association with ^{226}Ra suggest radium-induced paranasal sinus and mastoid carcinomas probably result from migration and entrapment of radon, the gaseous decay product of ^{226}Ra within these structures at relatively high doses (i.e., >12 μCi ^{226}Ra/kg).[305] These two cancers were not associated with internally deposited ^{228}Ra.

Evidence for elevated cancer rates following exposure to typical environmental radium concentrations is weak. A population-based case-control study of 238 cases of osteosarcoma from the Ontario cancer registry and 432 controls detected a weak, statistically nonsignificant association (OR = 1.31; 90% CI: 0.76–2.24) between lifetime measures of ^{226}Ra exposure in drinking water and osteosarcoma; there was no dose-response trend with increasing radium exposure.[332] The pooled analysis of 1,293 subjects from two Ontario studies for osteosarcoma was 1.44 (90% CI: 1.01–1.87) with a geometric mean absorbed dose of ~26 mrad (0.26 mGy). An ecological, population-based, case-control study of Wisconsin drinking water sources did not detect a significant association between the occurrence of osteosarcoma and median radium concentrations (OR = 0.98, 95% CI: 0.93–1.04, P = 0.56).[333] Residential ZIP codes were the basis of radium exposure estimates.

Leukemia

Analysis of the German cohort of patients receiving intravenous ^{224}Ra for ankylosing spondylitis detected an elevated risk of leukemias (observed, 21; expected, 6.8; $P < 0.001$), particularly myeloid leukemia. Although not typically associated with radiation, the incidence of chronic lymphatic leukemia was also elevated (observed 7; expected 2.4; P = 0.01). A statistically significant increased incidence of leukemia was not demonstrated in epidemiology studies of US or UK radium watch-dial workers who were administered smaller intravenous ^{224}Ra doses than the German patients.[334,335,336] The occurrence of leukemia was increased in a cohort of 899 German patients receiving high dose ^{224}Ra (mean bone surface dose, 30 Gy) with 8 leukemia cases observed and 3.8 cases expected (P = 0.04); however, the statistical significance of this value became nonsignificant when a 2-year lag period was applied (P = 0.08). Small case numbers and lack of dose-response data limit conclusions regarding causality.

Similarly, no definite causal connection was established in ecological studies of radium contamination in groundwater and an increased leukemia incidence. A study found a standardized incidence density ratio of 2.0 for the incidence of acute myeloid leukemia in counties with contaminated wells compared with the incidence of acute myeloid leukemia in counties without contaminated wells.[337] Contamination was defined by the presence of >5 μCi radium/L water in >10% of the wells. Misclassification and confounding complicate the interpretation of this study because of the lack

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of individual exposure data or data on other etiological factors for leukemia. A similar study of radium contamination in drinking water from 59 Iowa towns demonstrated a weak but statistically nonsignificant relationship between radium contamination and the incidence of leukemia.[338]

Reproductive Abnormalities

Studies in animals suggest high radiation doses cause a reduction in fertility by oocyte depletion. In a study of female workers in the radium watch-dial industry, radiation produced effects on fertility only at estimated cumulative ovarian dose equivalents >5 Sv.[339] These women were exposed to α-particles from ^{226}Ra and ^{228}Ra. At these high doses, internally deposited radium reduced fertility rather than inducing sterility.

TREATMENT

Medical management of acute radium exposure primarily involves reduction of gastrointestinal and bone absorption; recommendations are anecdotal with little experimental or clinical data to support specific recommendations. Recommendations include magnesium sulfate as an oral dose of 15 g magnesium sulfate in 100 mL of water or aluminum hydroxide in 60–100 mL water orally as a single adult dose. Barium sulfate (100 g $BaSO_4$ in 250 mL water PO) is an alternate therapy to reduce radium absorption. There are few data on the use of calcium gluconate (10 mL IV once or twice daily) to displace radium. Once absorption and deposition of radium occur in the bones, no specific antidotal therapy is effective.

RUTHENIUM

PHYSIOCHEMICAL PROPERTIES

Ruthenium (Ru) is a rare-earth, transitional metal (Group VIII with iron and osmium) that has a molecular weight of 101.7 g/mol, density of 12.45 g/cm^3, and melting point of 2,334°C. The chemistry of ruthenium is very complex with multiple oxidation states (2–4, 6–8) forming many inorganic cationic/anionic hydroxyl and halogen complexes in sulfide, chrome, and iron ores. The trivalent and tetravalent states (e.g., ruthenate) are the most stable. Most ruthenium radioisotopes are short-lived.

EXPOSURE

Occupational or environmental ruthenium exposure occurs primarily due to the longer-lived fission products from nuclear reactors and explosions, particularly ^{106}Ru (physical $t_{½}$ = 373.6 days, relatively high-energy β-emitter) and ^{103}Ru (physical $t_{½}$ = 39.3 days, β- and γ-emitter). In the nuclear fuel cycle, ruthenium usually exists as ruthenium tetroxide (RuO_4) vapor that can penetrate porous materials. Small quantities of ^{106}Ru and ^{103}Ru were detectable in the environment following the nuclear explosion at Chernobyl.[340] ^{101}Ru is a stable tracer of the isotope in blood samples. Ruthenium-based anticancer agents (e.g., NAMI-A, KP1019) are investigation drugs for the treatment of metastatic lung and neuroendocrine tumors as substitutes for platinum salts.[341]

TOXICOKINETICS

Inhaled RuO_4 vapors deposit mainly in the nasal passages and mouth; retention of a portion of these vapors as poorly soluble metallic ruthenium or ruthenium dioxide may occur for days to weeks. The reduction in radiation exposure depends on both the physical (radioactive, λp) and biological half-lives (λb) expressed as an effective half-life (λe) for the isotope in the body as displayed in Equation 41.3.

The effective half-life of accidentally inhaled air containing $^{103}RuO_4$ was ~10 days,[342] whereas the effective half-life of $^{106}RuCl_3$ administered orally and parentally to several animal species (mice, rats, monkeys, dogs) ranged from 15–50 days.[343] In a study of seven individuals monitored by external counting following accidental inhalation of airborne ^{103}Ru (possibly in the form of $^{103}RuO_4$ vapors and particulate ^{103}Ru), the biological half-time averaged ~80 days (λe = ~26 days) with a range of 64–93 days.[344] This isotope appeared in the urine and feces. Human volunteer studies with stable Ru isotopes indicate gastrointestinal absorption of sparingly soluble ruthenium radionuclides is low (i.e., <1–5%).[345,346] Limited data in humans suggest that the initial biological half-times are relatively short (several days) followed by a second component with a longer half-time (30–32 days).[347] Rodent studies suggest ^{106}Ru is poorly absorbed and rapidly eliminated, with no affinity for specific organs other than the kidney.[348]

TREATMENT

The NCRP prefers DTPA as a chelator with calcium disodium EDTA as an option;[72] however, there are inadequate clinical data to guide therapy.

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STRONTIUM

PHYSIOCHEMICAL PROPERTIES

Strontium is an alkaline earth element along with calcium, magnesium, radium, and barium that is chemically reactive and easily oxidizes; the physiochemical properties of strontium in the body are similar to calcium. Of the 16 strontium isotopes, 6 are uranium fission products; ^{90}Sr is the most important Sr radionuclide from a health perspective as a result of a physical half-life of 29.1 years. The four stable isotopes are ^{84}Sr, ^{86}Sr, ^{87}Sr, and ^{88}Sr. ^{90}Sr is a relatively high-energy, pure β-emitter that decays to short-lived yttrium-90; ^{90}Y also emits a high-energy β-particle during decay.

EXPOSURE

^{90}Sr is primarily an anthropogenic radionuclide as a constituent of fission products from nuclear reactors and nuclear weapons. The long half-life and good gastrointestinal absorption (f_1 value = 30%) of ^{90}Sr result in serious radioactive contamination from fallout after a nuclear reactor meltdown or reactor core breach (e.g., Chernobyl). Two accidents at the Mayak plutonium production plant in the Soviet Union released substantial amounts of fission products into the Techa River between 1949 and 1957. Contamination levels exceeded 0.01 Ci ^{90}Sr/km^2 over 23,000 km^2.[349] Of the 38 villages in this area, 4 remained habitable. ^{85}Sr is a tracer in medical and agricultural research. ^{99m}Tc completely replaced the use of Sr in skeletal scintigraphy.

Treatment of metastatic bone pain includes radioisotopes, bisphosphonates, hormone therapy, chemotherapy, radiotherapy, surgery, and analgesia. ^{89}Sr chloride is a β-emitter used to control pain from metastatic bone cancer; a 2011 Cochrane review demonstrated some evidence ^{89}Sr provided complete reduction in pain over 1–6 months without increased analgesic use; however, serious leukocytopenia and thrombocytopenia were frequent in the 15 clinical studies evaluated.[350] ^{90}Sr is a power source for space vehicles and navigational beacons.

TOXICOKINETICS

The lungs and gastrointestinal tract rapidly absorb most soluble ^{90}Sr (e.g., carbonate, chloride, sulfate salts) with subsequent distribution primarily to active red marrow.[85] Systemic absorption of ^{90}Sr after ingestion is ~25% compared with ~33% after inhalation with mean values ranging from 15–45%.[25,177] In a study of Sr absorption of strontium from real and simulated fallout by 10 volunteers, the estimated mean absorption rates were 3% (range, 0–9%) and 16% (range, 6–25%), respectively. The mean estimated absorption rate of $^{85}SrCl_2$ in this study was 17% (range, 8–34%).[117] Factors that increase strontium absorption in these studies include fasting and low dietary concentrations of calcium, phosphorus, and magnesium. ^{90}Sr is classified as inhalation class D (days) by the ICRP.

Strontium is a homologue of calcium resulting in an affinity of Sr for bone similar to that of radium; the skeleton contains almost all the Sr retained by the body with the initial deposition occurring on the bone surface and active red marrow followed by migration; some of the strontium deposited on the bone surface redistribute to plasma over the next few days, while other ^{90}Sr radionuclides migrate to nonexchangeable sites in bone minerals (calcium hydroxyapatite). The retention time of the latter Sr in bone is ≥20 years.[351] Human and animal data suggest the initial uptake of strontium and calcium by the skeleton is much greater in growing than in mature individuals.[352]

The body clears most ^{90}Sr (i.e., >50%) within a week after exposure, with small amounts remaining in the body after 1 year, primarily in the skeleton.[353] Biliary excretion and unabsorbed Sr in the feces account for most Sr elimination; however, the renal excretion rate of strontium is relatively greater than calcium because of the less efficient reabsorption of strontium by the renal tubules. Data from populations exposed to radioactive releases from the Mayak plutonium plant in the Southern Urals of Russia suggest elimination rates are age- and sex-dependent. In a study of 108 men and 81 women from the Techa River Valley >30 years of age and followed for 24 years, yearly Sr elimination in the men increased from 2.8–3.2% after age 55 years.[354] The Sr elimination rate in women increased after age 45 with the yearly rate increasing to 5.8% after the age of 60. Strontium passes the placental barrier; however, the transfer of strontium from the mother to the fetus is less efficient for strontium than calcium. In a study of 185 pregnant women drinking water from the Techa River contaminated by radioactive releases from the Mayak plutonium production facility from 1949–1956, ^{90}Sr in maternal skeletons during pregnancy and lactation were 1.5–2-fold greater than nonpregnant, nonlactating women with similar exposures.[355] Analysis of several stillborn fetuses from mothers of reproductive age exposed to contaminated Techa River drinking water

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demonstrated fetal/maternal ^{90}Sr ratio in bone ranged from 0.21–0.26.[356]

CLINICAL RESPONSE

The International Agency for Research on Cancer (IARC) indicates the evidence is sufficient to classify strontium as an animal carcinogen (bone, lymphoid tumors)[357] along with other pure β-emitters (^{3}H, ^{32}P, ^{90,91}Y, ^{147}Pm).[1] Currently, the IARC considers that evidence for human carcinogenicity of ^{90}Sr is limited with a positive association between ^{90}Sr exposure and leukemia.[358] Dose-related increases in mortality rates from leukemia and solid tumors occurred in Russian populations in the Techa River Valley exposed to internal contamination predominantly from ^{90}Sr (i.e., ~90%) and external radiation released from the Mayak plutonium plant as fission products.[348]

DOSIMETRY

The best biomarkers for individuals exposed to atmospheric debris from nuclear weapons testing are urinary ^{90}Sr and ^{239,240}Pu concentrations above background global fallout levels.[359]

TREATMENT

Aluminum hydroxide antacids reduce the gastrointestinal absorption of strontium when given within several hours of ingestion. Barium sulfate is a low-risk alternative oral agent that reduces ^{90}Sr absorption when administered within 24 hours of exposure. The administration of strontium (daily oral dose of 500–1,500 mg strontium lactate or daily IV dose of 600 mg strontium gluconate up to 6 days) also enhances strontium excretion when administered soon after exposure. Intravenous calcium is an alternative to strontium gluconate that may also enhance ^{90}Sr excretion when given soon after exposure. Rodent studies do not support the efficacy of chelators for Sr removal from bone. After initiating treatment 24 hours after receiving the last of 20 subcutaneous injections over the preceding 4 weeks, none of the chelators improved outcome; chelating agents tested included DPTA, Kryptofix 5® (1,11-bis(8-quinolinyloxy)-3,6,9-trioxaundecane, CAS RN: 57310-75-5), and Kryptofix 222® (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo(8.8.8)hexacosane; CAS RN: 23978-09-8; E Merck, Darmstadt, FRG).[360,361]

TECHNETIUM

PHYSIOCHEMICAL PROPERTIES

All technetium isotopes are radioactive. The metastable ^{99m}Tc decays to ^{99}Tc with a physical half-life of 6 hours by emitting a 0.14 MeV γ-ray easily detectable at a body surface. Within 24 hours, 93.7% of ^{99m}Tc decays to ^{99}Tc. Metastable means the nuclear isotope does not decay into another element. The physical half-life of ^{99}Tc is 212,000 years; therefore, this isotope has no adverse health effects from emitting radiation. Electrons emitted by ^{99m}Tc have a range of 50–70 cell diameters (<700 μm). Although the distribution of the radionuclide is not necessarily homogeneous, most energy from ^{99m}Tc decay deposits in this area.[362]

EXPOSURE

^{99m}Tc is the most common radioisotope in nuclear medicine for organ imaging, with ^{131}I being the second most common; technetium pertechnetate is the preferred compound for diagnostic procedures. Exposure to ^{99m}Tc occurs during the production of ^{99m}Tc with radionuclide generators and during injecting and imaging the patient while positioning the patient and the camera. A technetium-99m generator bombards a ^{98}Mo sample with neutrons and extracts the metastable isotope ^{99m}Tc from the radioactive decay of ^{99}Mo. This process allows the transport of short-lived ^{99m}Tc over long distances because the half-life of ^{99}Mo is ~66 hours. The internal radiation dose for personnel is typically lower than external exposures, with annual effective doses of <1 mSv;[4] the annual dose seldom exceeds 6 mSv.[363]

TOXICOKINETICS

The lungs and gastrointestinal tract absorb ^{99m}Tc rapidly and well (e.g., 70%). The biological half-life of ^{99m}Tc is ~1 day. The short physical half-life of ^{99m}Tc results in delivery of the radiation dose within hours after exposure. Animal studies suggest ^{99m}Tc selectively accumulates in the stomach, salivary glands, and thyroid gland; this radionuclide is nonbone seeking.[364] Following intravenous administration of technetium pertechnetate to volunteers, a 3-compartment model best describes whole-body Tc retention with half-times of 1.6 days (77%), 3.7 days (19%), and 22 days (4%).[365] The biological half-life of technetium pertechnetate is ~6 hours for the whole body compared with 20 days

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for the kidney and 30 days for the liver.[25] ^{99m}Tc is secreted in breast milk following injection; therefore, breastfeeding should be interrupted after ^{99m}Tc administration for 25 hours after administration of 80 MBq ^{99m}Tc-pertechnetate to prevent the infant from receiving an annual radiation dose of >1 mSv.[366,367]

CLINICAL RESPONSE

Although all types of ionizing radiation are human carcinogens, the IARC does not associate exposure to ^{99m}Tc with animal or human cancer.[1] Adverse reactions associated with the use of ^{99m}Tc are minor except rare anaphylactic reactions;[368] accidents involving ^{99m}Tc typically have not been associated with serious adverse effects.[25]

TREATMENT

Patients receiving ^{99m}Tc should be well hydrated and encouraged to urinate frequently after ^{99m}Tc administration. Potassium perchlorate displaces ^{99m}Tc from sites in the stomach, salivary gland, and thyroid gland; however, there are no human data to guide therapy. *In vitro* studies suggest DTPA chelates ^{99m}Tc in the tetravalent but not pentavalent oxidation state.[369] Data are inadequate to determine the efficacy of DTPA for chelation of ^{99m}Tc following internal contamination. The NCRP does not recommend chelation for the treatment of internal contamination by ^{99m}Tc.[72]

THORIUM

HISTORY

The Swedish chemist, Jons Jakob Berzelius, discovered thorium in 1828, naming the metal after the Norse god of thunder (Thor). The radioactivity of thorium was not demonstrated until 1898. In the early 1900s, the primary commercial use of thorium was as an incandescent constituent of gas lamp mantles. Umbrathor® was an oral, thorium-based radiological contrast agent originally introduced in Germany in the 1920s by the Heyden Chemical Company for imaging the gastrointestinal tract; this contrast agent produced excellent images and remained in aqueous solution with less risk of intestinal blockage than barium. Subsequently, Testagar and Company released a similar contrast agent, Thorotrast®, in 1931.[370] This injectable contrast agent was a colloid solution containing ~20–25% ^{232}Th dioxide stabilized by dextran. The agents were used worldwide throughout Europe, Japan, and North America until the 1950s. Thorotrast® was an excellent contrast agent for the visualization of cavities (e.g., nasal sinuses) and narrow canals (e.g., cerebral vessels); however, an iodine-based nonradioactive medium began replacing this agent in the 1940s because of the development of granuloma formation at extravasation site and the increased risk of bone marrow and liver cancer 20–30 years after use.[371] An estimated 50,000–100,000 patients received Thorotrast® worldwide,[372] typically in intravenous doses of 10–75 mL (129–962 Bq/kg or 3.5–26 nCi/kg).[373] This α-particle-emitting radionuclide remained in the body long after injection accumulating in the liver, spleen, and bone marrow.[374] Of the members of the German cohort receiving intravenous Thorotrast® and surviving the original reason for imaging, malignancies and liver cirrhosis accounted for ~40% of the deaths.[375] The effective radiation dose of Umbrathor® was substantially less than Thorotrast® because of the relatively limited gastrointestinal absorption of Umbrathor®.

PHYSIOCHEMICAL PROPERTIES

Thorium is a dense, relatively reactive, metallic element classified in the actinide series; all 12 isotopes are radionuclides that decay primarily with emission of α-particles and less commonly with β-particles and γ-rays to produce daughter radionuclides and eventually the stable elements, ^{206}Pb and ^{208}Pb. Daughter radionuclides include ^{228}Ra and thoron from ^{232}Th, whereas decay products of ^{230}Th include ^{226}Ra and ^{220}Rn. Of the 12 thorium isotopes, ^{232}Th is vastly more common in natural thorium (i.e., >99.99%) than all other Th isotopes; natural thorium contains very small amounts of ^{228}Th and ^{230}Th. ^{232}Th undergoes six α- and four β-disintegrations to form stable ^{208}Pb, as demonstrated in Figure 41.5. ^{230}Th (long-lived α-emitter) and ^{234}Th (short-lived β-emitter) are decay products of the ^{238}U series, whereas ^{227}Th and ^{231}Th are decay products of ^{235}U series. Only ^{228}Th, ^{230}Th, and ^{232}Th have sufficiently long half-lives to deposit environmentally significant amounts of radiation. Table 41.25 lists the energies and abundance of α- and β-particles emitted by thorium isotopes along with their physical half-lives.

The body retains most incorporated ^{232}Th and ^{234}Th (i.e., >90% at 3 weeks) because of their long physical and biological half-lives.[376] Water-soluble thorium complexes include chloride, fluoride sulfate, and nitrate salts, whereas carbonate, dioxide, hydroxide, oxalate, phosphate, and the salts are insoluble thorium compounds. Thorium exists in the body exclusively in the tetravalent oxidation state.

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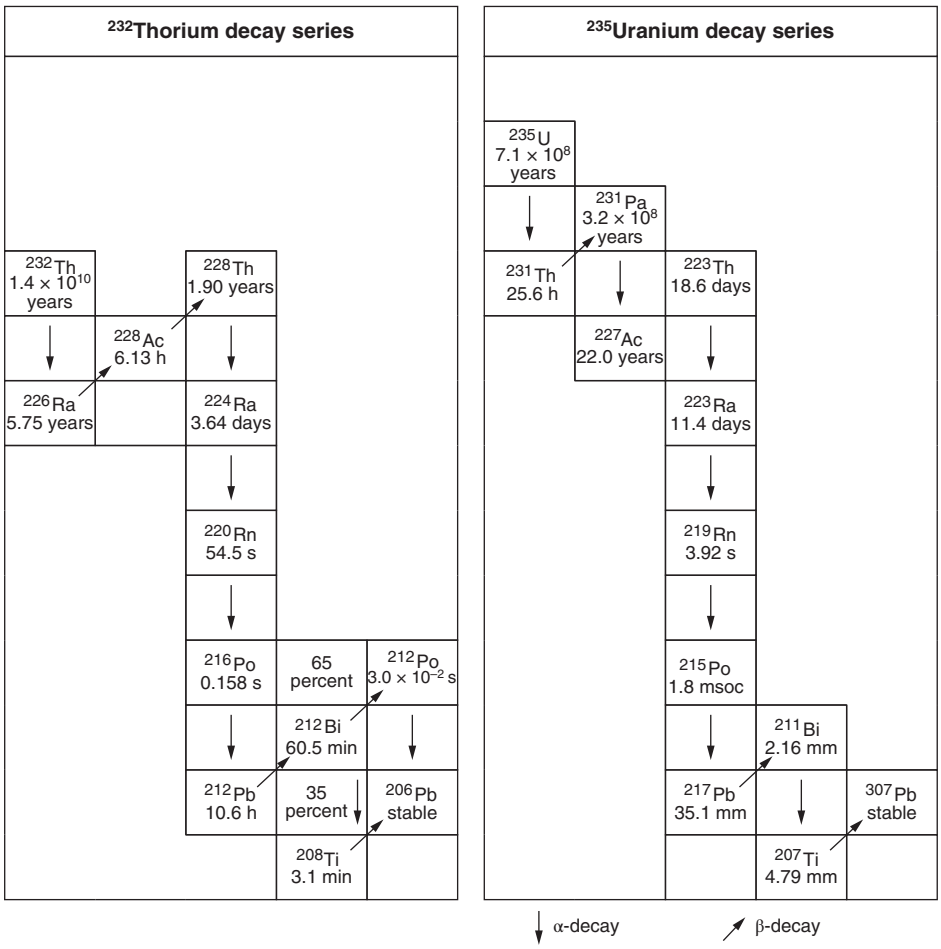


FIGURE 41.5. ^{232}Thorium and ^{235}uranium isotope decay series with subsequent decay products and half-lives. The ^{238}U decay series also produces thorium daughters as displayed in Figure 41.2.

Table 41.26 displays identifying characteristics and physical properties of thorium and thorium compounds.

EXPOSURE

In nuclear energy applications, the bombardment of ^{232}Th by neutrons and the emission of a β-particle produce the fissionable radionuclide ^{233}U that is fissile nuclear fuel for advanced heavy-water reactors. Thorium-containing ores include huttonite, monazite, thorianite, thorite, and thorogummite; these ores are more common than uranium ores. The primary commercial source of thorium is the separation of monazite as a by-product of the mining of heavy-mineral sands for titanium and zirconium. Potential occupational sources for ^{232}Th include processing of niobium or phosphate ores and production of gas mantles, high-intensity discharge lamps, and some welding rods.[309] In a study of five welding shops using thoriated electrodes during TIG welding, ^{232}Th levels in the breathing zone of the welders were generally <10 mBq/m^3.[377] The estimated annual committed effective dose from inhalation of ^{232}Th, ^{230}Th, ^{228}Th, and ^{228}Ra for a full-time TIG welder was <0.3 mSv; with conservative assumptions, the radiation dose was ≤1 mSv. A patient with a deposit of 1 μCi ^{232}Th in the reticuloendothelial system receives 0.2 Gy (20 rads) in the terminal bronchi over 10 years and 2.6 Gy (260 rads) over 10 years in the trachea.[378] After 30 years, the cumulative doses for the terminal bronchi and trachea are 0.8 Gy (80 rads) and 10 Gy (1,000 rads), respectively. The mean estimated annual radiation doses from the injection of 30 mL of Thorotrast® for specific locations in the spleen, liver, and bone are the following: 0.8 Gy (80 rads), spleen; 0.3 Gy (30 rads), liver; 0.15 Gy (15 rads), bone surface cells; 0.1 Gy (10 rads), red bone marrow; 0.048 Gy (4.8 rads), cancellous bone; 0.045 (4.5 rads), lungs; and 0.033 Gy (3.3 rads), compact bone.[379]

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TABLE 41.25. Energies and occurrence of major α- and β-particles emitted by the 12 thorium isotopes (^{223}Th to ^{234}Th). In general, the severity of biological effects following exposure to ionizing radiations is proportional to the density of the ionization produced by their passage through tissue. α-Particles deposit all their energy within a very short distance producing dense ionization, whereas β-particles produce less ionization. The ionization density of γ-rays is less than α- or β-particles.

Thorium Isotope	α-Particle Energy (MeV)	Abundance (%)	β-Particle Energy (MeV)	Half-Life
223	7.287	60	—	0.66 seconds
	7.317	40		
224	6.997	19	—	1.04 seconds
	7.170	79		
225	6.441	>15	—	8 minutes
	6.479	43		
	6.501	14		
	6.796	9		
226	6.228	23	—	31 minutes
	6.338	75		
227	5.72	14	—	18.72 days
	5.76	21		
	5.98	24		
	6.04	23		
228	5.341	26.7	—	1.91 years
	5.423	73		
229	4.814	9.3	—	7,300 years
	4.845	56.0		
	4.901	10.2		
230	4.621	23.4	—	75,400 years
	4.688	76.3		
231			0.389	25.2 hours
232	3.952	23	—	14×10^9 years
	4.010	77		
233			1.243	22.3 minutes
234			0.270	24.1 days

ENVIRONMENTAL FATE

Even though most thorium isotopes are synthetically produced, over 99% of the thorium in the earth's crust exists as the isotope ^{232}Th in combination with various minerals (e.g., silica).[380] These complexes do not dissolve in water or evaporate into air; therefore, exposure to this natural isotope from environmental sources is very small. Windblown dust and volcanic explosions are the most significant natural thorium sources, whereas major industrial thorium sources include uranium and thorium mining, tin processing, coal-fired utilities, industrial boilers, and phosphate rock processing. Medically significant thorium exposure typically requires specific areas that contain excess quantities of thorium.

Although the existence of thorium in the environment is widespread, the thorium concentrations in air, soil, water, and foods typically are very low; the USEPA does not require the monitoring of drinking water for thorium concentrations. The estimated total daily intake of ^{230}Th and ^{232}Th ranges from ~0.02 to 0.17 pCi.[219] The average population-weighted concentrations of ^{232}Th and ^{230}Th in the water supply are 0.01 pCi/L and 0.04 pCi/L, respectively. The average daily intake of ^{232}Th and ^{230}Th by New York City residents was 0.11 pCi and 0.17 pCi, respectively.[381] Thorium was the second most abundant element contributing to total radioactivity of distribution solids collected in drinking-water distribution systems during routine fire hydrant flushing in four US states (Illinois, Minnesota, Texas, Wisconsin).[308] Total thorium exposure (^{228}Th, ^{230}Th, ^{232}Th) ranged from 1.2–100 pCi/g with a mean of 40 ± 25 pCi/g. ^{228}Th was the dominant radionuclide in 90% of the solid samples.

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TABLE 41.26. Identifying characteristics and physical properties of thorium.

Physical Characteristic	Thorium	Thorium Chloride	Thorium Dicarbonate	Thorium Dioxide	Thorium Fluoride	Thorium Nitrate	Thorium Sulfate
Synonym	Metallic thorium, ^{232}Th	Thorium tetrachloride		Thorotrast®, Thoria	Tetrahydrate ($\cdot 4H_2O$)	Tetrahydrate ($\cdot 4H_2O$)	Thorium disulfate, thorium sulfate nonahydrate ($\cdot 9H_2O$)
CAS registry number	7440-29-1	10026-08-1, 54327-76-3	19024-62-5	1314-20-1	13709-59-6	110140-69-7	10381-37-0
Chemical formula	Th	$ThCl_4$	$Th(CO_3)_2$	ThO_2	ThF_4	$Th(NO_3)_4$	$Th(SO_4)_2$
Molecular weight (g/mol)	232.04	373.85	352.06	264.04	380.03	552.12	586.30
Color	Gray	White-gray		White		Colorless	White
Physical state	Solid	Crystalline solid		Powdery solid	Crystalline solid	Crystalline solid	Crystalline solid
Melting/boiling points (°C)	1,700/4,500	770/921		3,220 ± 50/4,400		500[a]	400[b]
Density (g/mL)	11.7	4.59		9.7			2.8
Water solubility (25°C)	Insoluble	Soluble	Insoluble in cold water	Insoluble	0.17 g/L	Very soluble	42 g/L

[a] Decomposes. [b] Dehydrates.

TOXICOKINETICS

Absorption

Pulmonary

The amount of thorium absorbed into the circulation by the lungs depends on the quantity of thorium reaching the alveoli (i.e., size of the particles) and the chemical properties (e.g., solubility) of the particular thorium compound. Ciliary clearance removes most inhaled thorium by expectoration and/or ingestion. Thorium dioxide usually remains in the lung for a long time. In experimental animal studies, 68–73% of ^{232}Th dioxide remained 1 day after intratracheal administration; 15–30% persisted for 21 months.[382] The ICRP model for thorium assumes the systemic circulation will absorb 5% of the thorium retained in the lung; however, pulmonary deposition of soluble thorium salts produces higher systemic absorption. In animal studies, inhalation of soluble thorium citrate and chloride salts resulted in absorption of 33% and 19% of the inhaled dose, respectively.[383]

Gastrointestinal

Although systemic Th absorption is generally higher for water-soluble than poorly soluble thorium salts, the gastrointestinal absorption of all thorium compounds is relatively low (~0.02%).[384] Animal studies indicate Th absorption of thorium from the intestine of the neonatal rat increases 40-fold more than adult rats, suggesting infants may be more susceptible to Th toxicity.[385] As a result of the low gastrointestinal absorption, inhalation accounts for ~2/3 of the systemic absorption of thorium based on epidemiology studies.[386]

Distribution

The maximum concentration of natural thorium isotopes occurs in the tracheobronchial lymph nodes with lesser amounts of thorium occurring in the lungs and bones. Based on animal data, modeling for "bone-surface-seeking" radionuclides, including thorium, suggests ^{228}Th deposits primarily on bone surfaces (~70%) with lesser amounts in the liver (4%) and soft tissues (16%).[387] Thorium deposits in the adrenals, intestines, kidneys, pancreas, and testes are

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relatively minor.[388] In an autopsy study from the US Transuranium and Uranium Registry, the maximum ^{232}Th concentrations in individuals without occupational thorium exposure ranged from 20–400 ng/g in lung and from 160–400 ng/g in lymph nodes.[389]

In contrast to the distribution of natural thorium isotopes, the intravenous administration of stabilized thorium dioxide (Thorotrast®) in a colloidal form results in the distribution of thorium into the macrophages of the reticuloendothelial system (liver, 59%; spleen, 29%; bone marrow, 9%); thus, stabilized $^{232}ThO_2$ is not classified as a bone-seeking radionuclide.[379,390] The distribution of ^{232}Th in Thorotrast® to tissues was inhomogeneous because of the uneven uptake of the ^{232}Th-transferrin complex from the serum.

Elimination

Fecal elimination following ciliary clearance accounts for up to 97% of the inhaled thorium dose (i.e., primarily unabsorbed Th) after thorium exposure from uranium ore dust inhalation during uranium processing.[391] Biliary and renal excretion account for ~10% of the systemically absorbed Th dose.[387] The biological half-lives of ^{232}Th and ^{230}Th in the lungs of residents living near the tailings of a uranium mine were 5.3 years and 1.4 years, respectively.[386] For modeling retained particles in the lungs, the ICRP considers thorium a class Y (years) compound. Animal studies suggest ^{227}Th nitrate has relatively greater pulmonary clearance than ^{232}Th dioxide with a biological half-life of ~20 days.[392] The kidney excretes very small amounts (i.e., 0.7% of the dose within the first 17 days) of insoluble thorium compounds (e.g., ^{232}Th in intravenous Thorotrast®).[393] Relatively greater excretion occurs via the kidney for soluble thorium compounds (e.g., ^{234}Th citrate).

CLINICAL RESPONSE

Occupational Exposure

The IARC classifies ^{232}Th as a Group 1 (carcinogenic to humans) carcinogen based on the increased incidence of cholangiocarcinoma following the diagnostic use of Thorotrast®.[1] Initial epidemiology studies of workers exposed to thorium did not detect significant increases in cancer mortality at estimated radiation levels of 0.001–007 Bq/m^3 over 1–33 years.[394] In the original study of the thorium-processing cohort, an increase in the incidence of respiratory disease (33 vs. 25.2), lung cancers (31 vs. 21.6), pancreatic cancer (9 vs. 4.5), and rectal cancer (6 vs. 3.2) occurred; however, high rates of smoking and coexposures (e.g., silica) confounded the results. The estimated mean committed dose from thorium exposure was 5 μSv. A follow-up study at this thorium-processing and gas mantle production plant evaluating 3,796 workers beginning employment in 1940 and followed through 1982, demonstrated a significant increase in all malignant neoplasms (SMR = 1.23; 95% CI: 1.04–1.43) and lung cancer (SMR = 1.36; 95% CI: 1.02–1.78) for male workers, but not for female workers.[395] There was no dose-response relationship between duration of employment and cancer rates; smoking data on the cohort members remained unavailable.

A definite causal relationship between occupational thorium exposure and the development of cancer has not been established.[380] A study of tungsten inert gas welding workers using thoriated rods did not demonstrate significant increases in ^{232}Th uptake; there was no increase in mortality, morbidity, or reduced renal function (retinol-binding protein, β_2-microglobulin) in these workers compared with a control group.[396]

Diagnostic Use (Thorotrast®)

Follow-up studies of patients administered intravenous Thorotrast® (colloidal $^{232}ThO_2$) from 1928–1955 demonstrate significantly increased cancer mortality, primarily hepatobiliary cancer and leukemia. These studies are not directly applicable to occupational or environmental thorium exposures because of differences in dose, distribution, and toxicokinetics. Extravasation of Thorotrast® produces pain, swelling, induration, and abscess formation. Local granulomas develop at the site of injection within 4–6 years from fibrosis, nerve paralysis, and vascular changes. Malignant tumors (soft tissue sarcomas, squamous cell carcinomas, and lymphoepithelial carcinomas) may develop at the edge of the granuloma after 10–30 years.[370,397]

Deterministic Effects

Liver cirrhosis is the most common systemic effect of intravenous administration of Thorotrast®, with latency periods averaging 25–30 years.[380] In a study of 272 war-wounded Japanese servicemen who were administered Thorotrast® and followed for 35–43 years, 13 developed cirrhosis.[398] Hematological disorders frequently appeared many years (e.g., 17 years) after injection, including leukemia, aplastic anemia, myelofibrosis, hemolytic anemia, Di Guglielmo's syndrome,

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splenic fibrosis, and fatal purpura. Severe narrowing of the coronary arteries, myocardial infarction, and internal derangement of the carotid artery developed in two patients injected with Thorotrast® 21–30 years prior to examination.[372]

Stochastic Effects (Cancer)

Carcinogenic effects of Thorotrast® result from the accumulation of α-radiation rather than chemical effects of thorium or colloid. The National Toxicology Program lists thorium dioxide as a known human carcinogen based on the increased incidence of liver tumors (primarily cholangiocarcinomas and hemangiosarcomas) in patients given Thorotrast®.[399] The International Agency for Research on Cancer (IARC) classifies ^{232}Th and its decay products as human carcinogens based on the large increases in liver cancer (e.g., hemangiosarcoma) and leukemia (excluding chronic lymphocytic leukemia) following diagnostic injection of ^{232}Th as stabilized $^{232}ThO_2$ in colloidal form (Thorotrast®).[1] All studies of patients receiving Thorotrast® intravenously demonstrated an increased incidence of tumors of the liver and leukemia with relative risks of liver cancer incidence or mortality ranging from 36–129.[400] For liver cancer, leukemia, and gallbladder cancer in the European and American cohorts of Thorotrast® patients, the risks of developing these cancers increased with α-particle dose and duration of exposure.

Liver

In the German cohort of 2,326 patients with a history of intravenous Thorotrast® administration (primarily cerebral angiography) and 1,890 hospital controls, the overall mortality of men and women increased with SMRs of 2.87 (95% CI: 2.73–3.01) and 3.87 (95% CI: 3.57–4.19), respectively, assuming a control SMR of 1.0.[375] Cause-specific mortality from cancers of the liver and hematopoietic system increased dramatically, whereas lung cancer rates were not elevated. The German study began in 1968 after a substantial portion of the exposed and control groups died; additionally, some differences existed between the control and exposed groups including the control group being on average 4 years older, having smaller cohort size, and lacking injected contrast medium as well as the existence of potential differences in underlying disease between the two groups and selection bias in the follow-up group.

In contrast to the predominance of hepatocellular carcinomas (i.e., ~90%) in unexposed patients, the portions of hepatocellular carcinomas, hemangiosarcomas, and cholangiocarcinomas are similar in Thorotrast® patients.[401,402] In these studies, the incidences of liver and gallbladder tumors were dose-related to the cumulative radiation dose from intravenous Thorotrast®, with increased risks in patients receiving larger Thorotrast® doses.[403]

The approximate mean latency periods for hemangiosarcomas and cholangiocarcinomas were 33 years and 28 years, respectively, with most liver cancers appearing >20 years after exposure.[404] Individual case reports suggest the latency period for angiosarcoma, cholangiocarcinoma, and hepatocellular carcinoma of the liver may exceed 40–50 years.[405,406] Hemangiosarcomas are very rare tumors associated with exposure to vinyl chloride monomers, arsenic, and polychlorobiphenyls (PCBs). The increased incidences of hemangiosarcomas and cholangiocarcinomas reflect the nonhomogeneous distribution of ^{232}Th in the liver, with the bile ducts and periportal tissues receiving ~15 times greater radiation from deposited α-particles than hepatic cord tissues.[407,408]

Leukemia

The diffuse distribution of Thorotrast® in the bone marrow suggests that exposure to Thorotrast® can induce bone marrow failure and leukemia;[409] in studies of Thorotrast® patients from Denmark, Germany, Japan, Portugal, Sweden, and the United States, the risk of leukemia excluding chronic lymphocytic leukemia (CLL) increased compared with national rates. The relative risk (RR) of developing all leukemias excluding CLL in the combined Thorotrast® cohorts from Denmark and Sweden was 6.1 with a 95% CI of 0.8–35.6,[403] whereas the RR for leukemia in the extended follow-up of the Portuguese Thorotrast® cohort was 10.2 (95% CI: 1.24–471, $n = 6$ with no CLL cases).[410] Although the German cohort demonstrated a dose-response relationship between injected Thorotrast® volume and the leukemia risk, the Portuguese, Swedish, and Danish cohorts did not demonstrate similar trends.

Leukemia (primarily erythroleukemia and acute myelogenous leukemia) developed in Portuguese patients exposed to Thorotrast® after a latency period of 20 years;[400] this latency period is much longer than the usual latent period (<10 years) for the development of leukemia based on studies of the Japanese atomic bomb cohort receiving external ionizing radiation. A median 40-year follow-up study of children born to parents exposed to Thorotrast® did not demonstrate an association between parental exposure to radiation and the risk of childhood leukemia or lymphoma.[411] For the 226 children of exposed fathers, the SMR for cancer was 1.3 (95% CI: 0.5–2.9) compared with 1.4 (95% CI: 0.4–3.5) for 143 children born to mothers with a history of Thorotrast® injection. There was one case

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of Hodgkin's lymphoma and no cases of leukemia or non-Hodgkin's lymphoma among the offspring.

DOSIMETRY

Conversion Factors

^{228}Th: 1 pCi = 1.2×10^{-9} μg
^{230}Th: 1 pCi = 48×10^{-9} μg
^{232}Th: 1 pCi = 9.1×10^{-9} μg
1 pCi = 10^{-12} Ci

Analytical Methods

α- and γ-Spectroscopy are traditional methods for detecting thorium in biological samples, whereas inductively coupled plasma/optical emission spectrometry (ICP/OES) is a sensitive measure of total thorium.[412] Neutron activation analysis measures ^{232}Th concentrations in the ng/L range (4×10^{-6} Bq/L),[413] whereas inductively coupled plasma/mass spectrometry (ICP/MS) is a sensitive technique for determining thorium isotopes including ^{232}Th concentrations in biological samples with a lower limit of detection in the range of ≤0.001 Bq/L.[414]

Biomarkers

The median daily intake of ^{232}Th in a study of Asian populations ranged from 0.6 mBq/L in the Philippines to 14.4 mBq/L in Bangladesh;[415] the United Nations Scientific Commission on Effects of Radiation (UNSCEAR) estimated a global intake value of 4.6 mBq for ^{232}Th. In a study of Australian mineral sand workers, the serum geometric mean thorium concentration was 480 ± 1.7 ng/L (range, 170–2,000 ng/L; $n = 25$) compared with a geometric mean of 320 ng/L for unexposed workers.[416] The geometric mean urine thorium concentration was 31 ng/L (range 3–210 ng/L; $n = 32$) in unexposed workers. Although neither serum nor urine concentrations correlated well with cumulative exposures, serum thorium concentrations were less variable than urine thorium concentrations.

Abnormalities

Plain X-ray radiographs of patients injected with Thorotrast® typically demonstrate opacification of the liver, spleen, and abdominal lymph nodes corresponding to the amount injected.[417] CT findings involve the presence of high-density deposits in the liver, spleen, and lymph nodes from deposition of ^{232}Th; splenic changes include atrophy from the fibrotic response to ^{232}Th deposition. Although multiphase contrast-enhanced CT and MR images of the liver may demonstrate early changes of ^{232}Th-induced tumors, the findings are nonspecific.[418]

Most,[419,420] but not all,[421] studies of Thorotrast® survivors demonstrate an increased frequency of stable and unstable chromosomal abnormalities when compared with age-matched controls. A statistically significant excess incidence of unstable chromosomal aberrations (dicentrics, centric ring) occurred in the pooled lymphocytes of higher body burden groups (mean = 0.56 ± 0.09 nCi) in a cohort of 47 male workers in a thorium processing plant, when compared with historical controls; the difference in 2-break chromosomal aberrations was not statistically significant.[422] The duration of employment did not correlate to the presence of chromosomal aberrations. A high incidence of chromosomal abnormalities developed in surviving Thorotrast® patients, including stable and unstable aberrations (e.g., dicentrics). In a study of eight long-term (mean = 47.4 years) Thorotrast® survivors and five controls (nonradioactive contrast medium only during the same era), the number of multicentric, centric, and acentric rings was statistically different ($P = 0.04$); the number of chromatid mutations as measured by hypoxanthine phosphoribosyltransferase (HPRT) was not different between the two groups.[423] Although dicentric chromosome aberrations occur in Thorotrast® patients, the number of chromosomal aberrations does not correlate to whole-body radioactivity.[424]

HEALTH SURVEILLANCE

The World Health Organization (WHO) guideline for individual thorium isotopes in water (^{228}Th, ^{230}Th, ^{232}Th) is 1 Bq/L.

TREATMENT

Ca-DTPA is the most effective chelating agent in animal studies; however, this chelator has only limited practical value because of the small amount of thorium removed from the body.[425] The NCRP lists DTPA as a suggested rather than preferred treatment.[72] Limitations of the effectiveness of free-DTPA result from its rapid urinary excretion (i.e., 90% in the first day) and difficulty penetrating cell membranes. In a study of rats injected with 0.6 mg thorium nitrate/kg and receiving either 11.2 mg DTPA/kg as free-DTPA or DTPA encapsulated in uncharged liposomes 6 hours later, the absorbed

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thorium dose in the liver decreased from 42–33% after DTPA and to 22% after encapsulated DTPA.[426] Liposomal encapsulation increased the DTPA concentration and duration in the liver and blood.

TRITIUM

PHYSIOCHEMICAL PROPERTIES

Tritium (CAS RN: 10028-17-8, ^{3}H) is the only radioactive isotope of hydrogen; its molecular weight is 6.032 g/mol. This radionuclide has a physical half-life of 12.3 years, decaying by emission of a low-energy β-particle. The emitted electron has a range of energies up to 18.6 keV with a mean energy of 5.7 keV; the decay process includes an electron antineutrino. The maximum track length of the emitted electron is 6 μm in water (i.e., <average diameter of a cell) and ~6 mm in air; consequently, these particles cannot penetrate the outer layer of the skin. The average aggregate relative biological effectiveness (RBE) of ^{3}H from orthovoltage X-rays in six studies using chronic γ-ray reference was 2.19 (95% CI: 2.04–2.33) compared with 1.17 (95% CI: 0.96–1.39) for three studies using chronic X-ray reference groups.[427]

EXPOSURE

Tritium exposure is common in the nuclear energy and weapons industries. Fission of a ^{235}U nucleus by a thermal neutron releases a ^{3}H nucleus (triton) once in 10^{4} fissions.[428] Heavy water (D_2O) moderated nuclear reactors also produce tritium following irradiation of deuterium (^{2}H nucleus) by neutrons. The design of some nuclear weapons requires a constant source of ^{3}H manufactured by the process of neutron capture in ^{6}Li nuclear reactor rods. Fusion nuclear reactors use ^{3}H as fuel. Other ^{3}H uses include the manufacture of radionuclide-labeled materials in medicine, industry, and research primarily to examine biologically important chemicals. Tritium is a common metabolic tracer and constituent of luminous paint (wrist watches, gunsights, emergency exit signs).

ENVIRONMENTAL FATE

Tritium is a ubiquitous component of the environment including biological systems; tritiated water is highly mobile in the environment. ^{3}H is a natural contaminant of water that is more common since discharge of tritium-contaminated waste from nuclear fuel reprocessing plants including tritiated water, tritiated hydrogen gas, and organically bound ^{3}H during the nuclear age. Although ^{3}H discharges to the environment are potentially large, the weak β energy and short half-lives limit radiation exposure for the general population. The estimated cosmogenic tritium exposure is 0.01 μSv compared with <10 μSv for the use of radio-luminous watches.[429]

DOSE-RESPONSE

The lack of ^{3}H-specific dose data, low doses, and limited power complicate the correlation of dose to the risk of adverse effects in occupational and environmental settings.[428]

TOXICOKINETICS

^{3}H penetrates the skin, lungs, and gastrointestinal tract as tritiated water or in vapor form. The body does not absorb ^{3}H in the elemental form. In a study of six workers chronically exposed to tritium, the average contribution of organically bound tritium to the total body water dose was 6.9 ± 3.1% (range, 4.7–9.9%).[430] As tritiated water, ^{3}H distributes widely and rapidly (i.e., few hours) throughout the body with a biological half-life of 12 days; however, urinary excretion of a small fraction of this radionuclide occurs at a much slower rate. A few days after the exposure of four workers during the cleanup of tritiated water, the biological half-life of tritium ranged from 7.5–9 days.[144]

CLINICAL RESPONSE

Health effects from single-dose exposure to ^{3}H have not been reported, but repeated exposure to ^{3}H has been associated with the development of aplastic anemia.[25]

DOSIMETRY

A concentration of 1 μCi/L indicates an integrated whole-body dose of 10 mrem.[25] Special survey equipment is necessary to detect the presence of the weak β-particles emitted by ^{3}H. Freshly voided samples must be collected immediately so that the amount of internal contamination can be measured.

TREATMENT

Forced diuresis guided by the analysis of daily urine samples for tritium is the recommended therapy for

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overexposure based on rodent studies; however, fluid and electrolyte balance must be monitored closely. In a study of $B6C3F_1$ female mice injected intraperitoneally with 811 MBq tritiated water, all injected mice receiving diuretics (furosemide 2 hours and 24 hours postexposure) and excess water survived, whereas 80% of controls died the first month postexposure.[431] The estimated final committed radiation dose was 60% lower in treated mice than controls.

URANIUM

HISTORY

The German apothecary Martin Heinrich Klaproth discovered uranium in 1789. Christian Gottlieb Gmelin conducted animal experiments with uranium compounds (e.g., chloride, nitrate) in 1824, 17 years prior to uranium purification. Henri Becquerel discovered uranium radioactivity in 1896 following his experiments with potassium uranyl sulfate. Before the discovery of insulin in the 1920s, some clinicians administered uranyl nitrate for the treatment of diabetes mellitus in daily doses up to 5.8 g.[432] In 1917, Wilcox reported no significant pathology following the chronic administration of 200 mg uranium nitrate daily.[433] During the 1950s, soluble uranyl nitrate was injected into comatose, terminally ill patients as a potential therapy for malignancies.[434]

PHYSICOCHEMICAL PROPERTIES

Uranium is a highly dense member of the actinide series that decays primarily by α-particle emission and lower energy γ-emissions; this element has the highest atomic mass and the second highest density of all naturally occurring elements. Uranium does not exist in the metallic form naturally because of rapid oxidation of the metallic surface to UO_2. Natural uranium exists in five oxidation states (+2 to +6) with the tetravalent (uraninite, pitchblende) and hexavalent (uranyl oxides, carbonates, phosphates, vanadates) predominating. Hexavalent uranium typically forms more systemically toxic, soluble compounds than the relatively less soluble tetravalent uranium compounds, whereas insoluble uranium compounds are potentially slightly more toxic to the lungs. Table 41.27 lists examples of uranium compounds with three relative water solubilities used in ICRP modeling.

There are 16 uranium isotopes; all of these isotopes are radioactive; however, exposure to ionizing radiation from natural uranium isotopes is very low because of the extremely long physical half-lives. Metallic uranium powder can spontaneously ignite at room temperature in the presence of oxygen, air, and water; prevention of auto-ignition requires storage in open containers under machine oil or water. At 200–400°C, uranium powder may self-ignite in atmospheres of CO_2 and N_2. Table 41.28 lists the identifying characteristics and physical properties of uranium and stable uranium compounds.

TABLE 41.27. Relative water solubility of several uranium compounds.

Water Solubility (Dissolution Rate)	Compound
Slow (S)	Uranium dioxide, uranium octaoxide
Medium (M)	Uranium tetrafluoride, uranium trioxide
Fast (F)	Uranium hexafluoride, uranyl fluoride, uranium tetrachloride, uranyl nitrate hexahydrate

The typical specific radioactivity of natural uranium is relatively low (i.e., 0.68 μCi/g) due to the very long physical half-life of natural uranium isotopes; consequently, natural uranium produces very little radioactivity/mass of uranium. As listed in Table 41.29, natural uranium consists primarily of ^{238}U. The specific activity of natural uranium increases as the relative abundance of the more rapidly decaying ^{234}U and ^{235}U increases. Enriched uranium required for nuclear reactors contains greater ^{235}U concentrations (i.e., 3–5%, low-enriched) than natural uranium, whereas enriched uranium in nuclear weapons may contain 97.3% ^{235}U (high-enriched). Depleted uranium contains less ^{234}U and ^{235}U, resulting in relatively lower radioactivity (specific activity, 0.33 μCi/g) than natural uranium. Consequently, adverse health effects following depleted uranium exposure result from chemical effects rather than radioactivity. The chemical reactions of all isotopes and isotopic mixtures of uranium are identical regardless of the specific activity (e.g., enrichment).

Figures 41.2 and 41.5 display the principal decay schemes of ^{238}U and ^{235}U, respectively. Table 41.29 lists the occurrence and radioactive properties of the three natural uranium isotopes; these isotopes are primarily α-emitters. The important uranium valences for biological systems are the primarily water-insoluble tetravalent uranium compounds and the frequently water-soluble hexavalent uranium compounds (e.g., uranyl, UO_2^{2+}). Tetravalent uranium usually oxidizes to the more soluble hexavalent form in the body with the subsequent formation of the uranyl ion. Uranium trioxide is water-insoluble; however, this compound

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TABLE 41.28. Identifying characteristics and physical properties of uranium and stable uranium compounds (tetravalent, hexavalent). (Adapted from Agency for Toxic Substances and Disease Registry (ATSDR)).[435]

Physical Characteristic	Uranium	Uranium Dioxide	Uranium Trioxide	Uranium Tetrafluoride	Uranium Hexafluoride	Uranium Tetrachloride
CAS registry number	7440-61-1	1344-57-6	1344-58-7	10049-14-6	7783-81-5	10026-10-5
Synonyms		Uranium oxide (IV)	Uranyl oxide (VI), orange oxide	Uranium fluoride (IV)	Uranium fluoride (VI)	Uranium chloride (IV), green salt
Molecular formula	U	UO_2	UO_3	UF_4	UF_6	UCl4
Molecular weight (g/mol)	238.029	270.028	286.027	314.023	352.019	379.841
Color	Silver-white	Brown	Orange-yellow	Green	White crystalline	Green
Physical state	Solid	Solid crystal	Solid crystal	Solid crystal	Solid	Octahedral crystal
Melting/boiling points (°C)	1,135/4,131	2,847/~3,700°K	Decomposes	1,036/1,417	56.2 (sublimation)	590/791
Density (g/mL, 20°C)	18.06–19.1	10.97	~7.3	6.7	5.09 (20.7°C); 3.595 (70°C)	4.72
Water solubility (25°C)	Insoluble	Insoluble	Insoluble	0.1 g/kg H_2O	Reacts with H_2O	Reacts with H_2O
Vapor pressure (mmHg)	0 (20°C)	—	—	—	115	—
Conversion factor, 1 μg = (pCi)	0.69	0.61	0.57	0.45	0.47	0.43

Physical Characteristic	Uranium Peroxide	Uranyl Acetate	Uranyl Acetate, Dihydrate	Uranyl Nitrate	Uranyl Nitrate Hexahydrate	Ammonium diuranate
CAS registry number	7440-61-1	541-09-3	6159-44-0	10102-06-4		7783-22-4
Synonyms	—	—	bis(Acetate-B) dioxouranium	—	bis(Nitrate-O) dioxouranium hexahydrate	Ammonium uranate
Molecular formula	U	$C_4H_6O_6U$	$UO_2(CH_3COO)_2 \cdot 2H_2O$	$UO_2(NO_3)_2$	$UO_2(NO_3)_2 \cdot 6H_2O$	$(NH_4)2U_2O_7$
Molecular weight (g/mol)	238.029	388.12	424.146	394.037	502.129	624.131
Color	Silver-white	Yellow	Yellow	Yellow	Yellow	Red-yellow
Physical state	Solid	Solid crystals	Solid crystals	Solid crystals	Solid crystals	Amorphous powder
Melting/boiling points (°C)	1,135/4,131	Decomposes <275°C	Decomposes 275°; dehydrates 110°	—	60/decomposes 118	—
Density (g/mL, 20°C)	18.06–19.1	2.893 (15°C)	2.893 (15°C)	—	2.81 (13°C)	—
Water solubility (25°C)	Insoluble	76.94 g/L (15°C)	77 g/L (15°C)	127 g/100 g H_2O	127 g/100 g H_2O	Insoluble
Vapor pressure (mmHg)	0 (20°C)	—	—	—	—	—
Conversion factor, 1 μg = (pCi)	0.69	0.42	0.39	0.42	0.33	0.52

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TABLE 41.29. Composition and radioactive properties of natural uranium isotopes.

Isotope	Content Natural Uranium (%)	α-Energies (MeV)	Half-Life (Years)
^{234}U	0.006	4.78 (72.5%[a])	2.45×10^5
		4.72 (27.5%[a])	
^{235}U	0.72	4.36 (11%[a])	7.04×10^8
^{238}U	99.27	4.20 (77%[a])	4.46×10^9
		4.15 (23%[a])	

[a] Abundance.

TABLE 41.30. Comparison of the uranium isotopes in natural and depleted uranium. (Miller and McClain).[440]

Isotope	Specific Activity (μCi/g)	Depleted Uranium (μCi/g)	Natural Uranium (μCi/g)
^{238}U	0.333	0.332	0.331
^{236}U[a]	63.6	0.0001	0
^{235}U	2.2	0.0044	0.051
^{234}U	6,200.0	0.093	0.310
Total		0.4295	0.692

[a] Synthetic isotope.

is highly soluble in tissue. The body converts some tetravalent compounds into more soluble hexavalent uranyl compounds. Uranium hexafluoride hydrolyzes rapidly in water. Uranium combines with bicarbonates (60%), transferrin (40%), and small amounts of citrates in the blood.[436]

Depleted uranium used in armor and munitions is ~40% less radioactive than natural U; however, depleted and natural uranium have similar chemical properties and nonradiation toxicity. Table 41.30 lists the physical characteristics of depleted and natural uranium.

EXPOSURE

Production Processes

Uranium mining and milling involve extraction of the uranium ore from underground or open-pit mines, crushing and grinding of the raw ore, chemical leaching, and precipitation of uranium as "yellowcake" from the leachate. Of the over 100 uranium ores, commercial uranium ores (e.g., autunite, pitchblende, carnotite, torbernite) usually contain >1,000 ppm uranium and typically occur in sandstone formations. Extraction of the uranium ore involves either acid or alkali leaching in the presence of the oxidizer, $NaClO_3$. Yellowcake (ammonium diuranate) is the purified precipitate of the leached liquor. Uranium hexafluoride is formed after solvent extraction, denitration, reduction, and the addition of hydrofluoric acid; the subsequent reduction of uranium hexafluoride with magnesium or calcium produces uranium metal. Niobium ores are a potential source of ^{238}U exposure.

Enrichment is the industrial process that increases the percentage of the more radioactive ^{235}U in uranium ore. Nuclear reactors except pressurized heavy-water reactors use uranium enriched from <1% ^{235}U in natural uranium to 2–3% ^{235}U; certain special reactors and nuclear bombs require uranium with ^{235}U concentrations exceeding 90%.

Uses

The primary use of uranium (uranium dioxide) is as a fuel for nuclear reactors; the primary use of depleted uranium is as a component of modern conventional weapons systems. As of 2021, nuclear reactors produced ~19.6% and ~14.8% of the electricity in the United States and the United Kingdom, respectively.[437] Types of uranium fuel used in nuclear reactors include: 1) unenriched uranium metal fuel (gas-cooled Magnox reactors), 2) unenriched UO_2 fuel (heavy water-cooled, moderated reactors), 3) low-enriched UO_2 fuel (advanced gas-cooled, graphite-moderated reactors, light water-moderated and cooled reactors), and 4) mixed UO_2–PuO_2 fuel (light-water and fast-breeder reactors). Other uses for uranium include the manufacturing of aircraft stabilizers, inertial orientation devices, gyroscopes, green or yellow glass, and luminous devices.[438] The density and hardness of depleted uranium (i.e., 70% greater than lead) are useful for specialized engineering applications including armor, armor-piercing ammunition, and weapons. Nonmilitary uses for depleted uranium include manufacture of radiation shielding material, X-ray targets, and inertial guidance systems.[439] In contrast to enriched light-water reactor fuels, depleted uranium and natural uranium contain ~0.2% and 0.71% ^{235}U, respectively; therefore, depleted uranium has ~60% of the radioactivity of natural uranium as displayed in Table 41.30.[440] Depleted uranium, a by-product of the enrichment process for nuclear reactors and weapons-grade uranium, usually contains <0.3% ^{235}U. Uranium carbide is a catalyst for ammonia production; uranium dioxide extends the life of the large incandescent lamps in the motion picture industry.

Sources

The abundance of uranium, arsenic, and molybdenum in the soil is similar.[435] Because of the presence of

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uranium in soil, air, and water, environmental exposure to uranium is common. *In vitro* studies on uranium solubility in soil indicate the predominant exposure pathway for uranium involves ingestion of soil and groundwater, whereas inhalation of uranium from dust is a relatively minor exposure pathway.[441] In addition to the incorporation of natural uranium, uranium exposure occurs during mining and processing of uranium ore, production of uranium-containing phosphate fertilizers, and contact with uranium-containing waste sites.[442]

ENVIRONMENTAL FATE

Air

The contribution of inhalation to the body burden of natural uranium is minimal, with the average amount of uranium absorbed from air containing ~0.06–0.4 ng/m^3 and ranging from ~0.00003–0.0003 Bq/day, depending on the local sources of uranium emissions.[443] Limited quantitative data on airborne uranium suggest the mean U concentrations are typically <0.1 ng/m^3.[444]

Soil

The crust of the earth contains a mean U concentration of ~2–3 ppm (~1.5–2 pCi/g) uranium composed of the following isotopes: ^{238}U (99%), ^{235}U (0.72%), and ^{234}U (minute),[445] with monazite sands, lignite, and phosphate rock containing substantial uranium concentrations. At a concentration of 2 ppm, a truckload of dirt contains a tablespoon of uranium. Because of the slow decay rate of ^{238}U, the total amount of uranium in the earth remains almost constant. The natural ratio of the two main uranium isotopes, ^{238}U and ^{235}U, in the earth's crust is 137.9:1, whereas the ^{238}U/^{235}U ratio in depleted uranium is about 490:1.

Water

Surface and groundwater typically contain similar uranium concentrations with the ^{238}U/^{234}U ratio varying between different locations.[446] In the United States, geological regions with the highest uranium water concentrations are the Rocky Mountains, Colorado Plateau, and the West Central Platform. Uranium in surface water can disperse over large distances to ponds, rivers, and oceans depending on adsorption and release of uranium from aquatic sediments. Factors determining uranium mobility include oxidation–reduction potential, pH, and sediment characteristics. The groundwater in certain mountainous areas of some countries (e.g., Canada, Finland, Norway, Sweden, United States) contains relatively high uranium concentrations.[438] Some groundwater systems in the western United States and scattered areas of the eastern United States (Connecticut, Maine, North Carolina) contain uranium concentrations exceeding 20 ng/mL.[447] In 14 community drinking-water samples from New York State, the mean uranium concentration was 548 mBq/L (range, 36–2,135 mBq/L).[448] In a German study of 582 public drinking-water samples, the radiation dose from ^{238}U ranged from <0.7–320 mBq/L, with a median of 3.2 mBq/L and a 95th% of 100 mBq/L.[307] Private wells may contain higher uranium concentrations than public water distribution systems, particularly in areas drawing water from geological formations containing metamorphic rock formations (e.g., Brookfield Gneiss, western New England).[445,449] Uranium was the element contributing the smallest total radioactivity to distribution solids contained in drinking-water distribution systems collected during routine fire hydrant flushing in four US states (Illinois, Minnesota, Texas, Wisconsin).[308] Total mean α- and β-radiation from uranium was 6.4 pCi/g compared with 143 pCi/g from radium and 40 pCi/g from thorium. In a study of drinking water from 96 bore wells in Bangalore, India, the mean uranium concentration was 92.42 μg/L (range, 0.136–2,027.5 μg/L), with 39% of the well water exceeding the WHO drinking water guideline (30 μg/L).[450] The very low assimilation efficiencies of higher trophic aquatic organisms result in a decline in uranium concentrations with each successive trophic level.[451,452]

Lifestyle

The daily US uranium intake from food averages ~1–3 μg (1 μg ≅ 5 mBq), with uranium isotopes contributing relatively small amounts to the total radiation doses.[453,454,455] In a study of New York City residents, the total estimated daily intake was 18 mBq/L for ^{234}U, 0.7 mBq/L for ^{235}U, and 16 mBq/L for ^{238}U.[381] Shellfish and root vegetables contain relatively higher uranium concentrations with lesser amounts in cereals, fish, and fresh vegetables. Uranium in drinking water usually contributes negligible amounts of α-radiation to the annual radiation dose from water and air; however, water may sometimes contain relatively high uranium concentrations in certain areas. The uranium concentration in 29 tap and bottled water samples in an Italian study ranged from 0.04–5.86 μg/L.[456] Inhalation is a relatively small source of uranium exposure (i.e., 0.0007–0.007 pCi/day; 0.001–0.01 μg/day) compared with food.[435] The contribution of natural uranium to the radiation dose

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from smoking is relatively small compared with other radionuclides (^{226}Rn, ^{228}Rn, ^{210}Pb).[444]

DOSE-RESPONSE

The uranyl ion disassociates from bicarbonate in the kidney to form ligands with phosphates potentially resulting in the disruption of cellular enzymes in the tubules. Animal studies suggest that this effect occurs at doses of 3 μg uranium/g kidney tissue, whereas other reports suggest that these effects on the kidney may occur at levels between 0.1 and 0.4 μg uranium/g kidney.[457] The disruption of cellular enzymes in the kidney produces glucosuria, proteinuria, aminoaciduria, and enzymuria.[438] Because the kidney clears uranium deposits rapidly, regeneration of the tubules typically begins within a week of exposure to the uranium.[305]

TOXICOKINETICS

Absorption

The absorption of uranium from various exposure routes is usually low, depending primarily on water solubility.

Lungs

Deposition and retention of uranium in the lungs depend on particle size and water solubility with a typical range of <1–5%. Absorption into the blood occurs within days of the deposition of the more soluble uranium compounds (uranyl nitrate hexahydrate, uranyl fluoride, uranium hexafluoride), whereas the less soluble compounds remain in the lungs for weeks (uranium tetrachloride, uranium tetrafluoride, uranium trioxide) or years (uranium dioxide, uranium oxide). The ICRP recommends that the first two groups of uranium compounds be classified as inhalation class D (days) and inhalation class W (weeks), respectively; this agency assigns an absorption factor of 5% for the ingestion of these compounds. In a study of mill workers exposed to airborne uranium, the estimated daily mean uranium absorption was 24 μg (0.34 μg U/kg for 70-kg reference man).[312] Based on fecal uranium excretion and workplace ambient air concentrations, the estimated mean pulmonary uranium absorption was 0.76% (range, 0.4–1.6%).

Gastrointestinal Tract

The gastrointestinal absorption of uranium depends on water solubility, physiochemical characteristics, nutritional status (i.e., iron content), and species; animal and human studies have not demonstrated gender differences in absorption rates. Systemic bioavailability typically ranges from 0.1–2% with a maximum of 6%.[458] A review of controlled experimental human studies and a variety of environmental studies demonstrated the average gastrointestinal uranium uptake in food and fluids averaged 1–1.5% of the total uranium intake with a range up to 5%.[459] In a study of 50 Canadians using analysis of duplicate diet samples by inductively coupled plasma/mass spectrometry to estimate daily U intake, the absorption rate averaged 0.9% with a range of 0.1–6%.[460] Another review of the literature suggested an absorption factor of 1–2% for uranium in the diet.[312] Uranium compounds in the inhalation class Y (years) are assigned an absorption factor (f_1) of 0.2%. The mean uranium absorption calculated for three volunteers living in a uranium milling community with no work experience at the mill was 0.82% (range, 0.6–1%); presumably their uranium exposure was primarily gastrointestinal from food and water.[299]

Skin

Uranium compounds can penetrate the skin, especially uranyl nitrate; this compound diffuses through the skin and accumulates in the intracellular space between the granular and horny layers.[461]

Distribution

Absorbed uranium typically exists in body fluids as uranyl ions $(UO_2)^{2+}$ complexed with anions (e.g., bicarbonate, citrate, transferrin) depending on pH. The typical body burden of uranium in the general population is ~90 μg.[435] The estimated body burden of skeletal uranium in New York City residents was ~2–4.5 μg/kg based on autopsy specimens.[453] Based on autopsy studies of workers exposed to uranium, the skeleton is the main storage depot for uranium, with the uranyl ion replacing calcium in the hydroxyapatite complex of bone crystals; lesser amounts of uranium accumulate in the kidney and small amounts in the liver. The ratio of uranium in the skeleton, liver, and kidney was 63:2.8:1 in an individual occupationally exposed to uranium.[462] In a Japanese study analyzing uranium concentrations in Tokyo residents with α-spectrometry and a fission track method, the mean distribution of the estimated 40 μg-total body uranium burden was the following: muscles, 40%; skeleton, 20%; blood, 10%; lungs, 4%; liver, 1%; and kidney, 0.3%.[463]

Animal studies suggest that ~10–20% of the absorbed uranium dose distributes to the surface of

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bones and bone marrow.[464] The kidney receives ~10% of the absorbed uranium dose. The distribution of uranium migrating from embedded depleted uranium is similar to the long-term accumulation in the kidneys, bones, and liver determined by the 1995 ICRP model for uranium.[465] However, this model provides limited information on the distribution of uranium to less frequently studied sites (e.g., lymph nodes, testicles, brain).[466]

Elimination

In a study of four volunteers on a Metabolic Research Ward, the total daily uranium intake from the diet and drinking water for ^{234}U ranged from 35–65 mBq compared with 24–46 mBq for ^{238}U.[467] Excretion of these two isotopes occurred primarily in the stool, with urinary excretion of ^{234}U and ^{238}U averaging 1.8% and 1.5%, respectively, of the daily intake. Hematological clearance of absorbed uranium is relatively rapid, with ~2/3 of the absorbed dose excreted by the kidneys within 24 hours. The ICRP model indicates the kidney excretes 80% of the absorbed uranium dose during the first day; during the first week, the kidney excretes an additional 17.6% of the absorbed uranium dose.[468] The half-life of uranium in the kidney is 1–6 days, whereas the 2-compartment ICRP model describes uranium loss from bones with half-lives of 20 and 5,000 days. The more soluble uranium compounds (uranium hexafluoride/tetrachloride, uranyl fluoride/nitrate hexahydrate) are distributed more diffusely from the alveoli to the blood (ICRP inhalation Type F, fast dissolution). In contrast, less soluble compounds (uranium tetrafluoride, uranium trioxide) remain in the lung and adjacent lymph nodes for weeks (ICRP Type M, medium dissolution), and relatively insoluble compounds (uranium dioxide, uranium oxide) may remain in the lungs for weeks to years (ICRP Type S, slow dissolution). Hence, elimination of ~2–3% of the absorbed uranium occurs over years. Uranium elimination may be delayed in some situations (e.g., uranium hexafluoride exposure) when pulmonary edema complicates the clinical course.[469] Following UF_4 powder exposure during an occupational accident, urinary uranium excretion during the first 24 hours after the accident was 156.8 μg; peak urinary excretion occurred 60 days after the accident, with normal urine uranium excretion within ~3 years of the accident.[470]

CLINICAL RESPONSE

Uranium has no known metabolic function in animals or humans. Animal studies indicate uranium toxicity from natural and depleted uranium results from chemical-induced renal tubular damage by soluble uranium compounds and respiratory tract injury (e.g., noncancerous alveolar epithelium damage of type II cells) from chronic inhalation of insoluble uranium compounds. Because of the low radioactivity of ^{238}U, the primary health hazard of this isotope results from adverse effects on the renal tubules (e.g., proteinuria, casts, polyuria, oliguria, anuria) rather than radiation-induced damage including cancer;[471,472] however, prolonged exposure to insoluble uranium compounds may produce a slightly increased ionizing radiation risk. Natural, depleted, and enriched uranium share similar chemical toxicities. Relatively insoluble enriched ^{235}U compounds (oxides, hydrides, carbides) produce theoretical risks of pulmonary fibrosis and cancer;[473] however, epidemiological studies have not detected elevated mortality rates from typical occupational and environmental uranium exposures. Evaluation of human data is often complicated by coexposures to other toxins (e.g., crystalline silica, diesel engine exhaust, hydrogen fluoride, radon).

Acute Exposure

Uranium Fluoride Compounds

Uranium hexafluoride decomposes into a severe respiratory and mucous membrane irritant, hydrofluoric acid. Exposure of two workers to a dense cloud of steam, uranium hexafluoride, uranium oxyfluoride, and hydrofluoric acid caused nausea, vomiting, dyspnea, corneal abrasions, and pulmonary edema; however, follow-up 38 years later revealed no uranium deposition and no physical sequelae including normal pulmonary function.[474] The estimated initial lung deposition of soluble natural U was ~40–50 g; the mean duration of exposure was 17 seconds. The acute effects were associated with hydrofluoric acid exposure including the death of two workers from inhaling hydrofluoric acid fumes. Following accidental occupation exposure to uranium tetrafluoride powder, a worker developed anorexia, diarrhea, abdominal pain, and hematuria during the first 6–9 days; however, he recovered without permanent sequelae.[470]

Uranium Acetate

Acute renal failure requiring 2 weeks of hemodialysis, renal tubular acidosis with glucosuria and phosphaturia, rhabdomyolysis, myocarditis, elevated hepatic transaminases with liver dysfunction (INR = 2.5, aPPT = >50), anemia, and paralytic ileus developed

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after the intentional ingestion of 15 g uranium acetate.[475] Urinary alkalinization and daily $CaNa_2EDTA$ began 16–24 hours after ingestion; chelation continued daily for 5 days without a clinically significant benefit. At 6-month follow-up, he had no evidence of cardiac, liver, or muscle toxicity; however, he was mildly anemic (hemoglobin = 11.8 g/dL) with an incomplete Fanconi syndrome requiring daily sodium bicarbonate.

Environmental Exposure

Mortality studies of populations living near uranium mining and milling operations have not demonstrated statistically significant associations between mortality and uranium exposure. Uranium is a nephrotoxic metal in large doses, primarily affecting the proximal tubules. Some, but not all, cross-sectional studies of exposure to natural uranium-containing drinking water suggest an association between uranium concentrations and elevated biomarkers of proximal renal tubular dysfunction; however, these biomarkers are not typically associated with detectable reduction in renal function (i.e., glomerular filtration) or cancer risks.[476,477] Frequently, the elevated biomarkers remain in the reference range. Consequently, the clinical relevance of the positive findings is unclear. There is little evidence that uranium exposure causes neurological or cardiovascular toxicity in humans following occupational uranium exposure.

Community-based studies in Canada, Finland, and Sweden suggest some risk of adverse effects from chronic exposure to elevated uranium concentrations in drinking water, manifested by elevated biomarkers of proximal tubule damage (e.g., urinary glucose, calcium, β_2-microglobulin, retinol binding protein).[478] In a Canadian study of residents in Nova Scotia exposed to high uranium concentrations in drinking water and food (daily range, 3–570 μg) and controls (daily range, <1–20 μg), daily uranium intake correlated with some biomarkers of proximal tubule injury (urine glucose, β_2-microglobulin), but not with enzyme activity (*N*-acetyl-*β*-D-glucosaminidase) or glomerular integrity (urine protein).[479] In a Finnish study of 325 individuals from areas with high uranium concentrations in drinking water, the median daily uranium intake was 39 μg (range, <1–4,128 μg). Urinary uranium concentrations correlated with excretion of some urinary biomarkers of proximal tubular function (fractional calcium, phosphate), but not others (β_2-microglobulin, glucose) based on analysis of spot urine samples.[480] A majority (i.e., 65%) of the β_2-microglobulin results were below the limit of detection. They did not observe a relationship between uranium exposure and urinary albumin (glomerular integrity) or creatinine clearance (glomerular filtration). Epidemiology studies typically do not demonstrate an association between chronic environmental uranium exposure and clinically apparent renal dysfunction or renal failure.[478]

Epidemiological studies of environmental uranium exposure and glomerular filtration rates are inconsistent. Follow-up studies of Gulf War veterans exposed to depleted uranium[481] and a cross-sectional study of 193 Finnish residents chronically exposed to elevated uranium concentrations in well water (median = 25 μg/L; interquartile range, 5–148 μ/L; maximum, 1,500 μ/L)[482] did not detect reduced creatinine clearance in the exposed groups as measured by overnight and 24-hour urine samples. The former study was unadjusted and underpowered due to small sample size, whereas the latter study used linear regression modeling adjusted for age, sex, body mass index, smoking, and analgesic use but not diabetes. In this latter study, biomarkers of proximal renal tubular function and renal toxicity did not correlate to well-water or urine U concentrations. An ecological study suggested an association between serum creatinine and residents living within 2 miles of a uranium processing plant, when compared with residents living over 2 miles from the facility.[483] A case report of seven family members (two adults, five children) exposed for 5 years to drinking water containing markedly elevated uranium concentrations (e.g., 1,166 μg/L) demonstrated only subclinical renal effects in one child (↑β_2-microglobulin) that resolved within 3 months.[449]

Occupational Exposure

Uranium Workers

Occupational cohort studies do not indicate an increased risk of kidney-related mortality among uranium workers; however, some occupational studies suggest chronic uranium exposure may produce proximal renal tubular damage based on elevated urinary biomarkers (e.g., calcium, glucose, low-molecular-weight proteins).[478,484] In a mortality study of 1,484 men employed in seven uranium mills in the Colorado Plateau for at least 1 year on or after 1940, deaths from all causes and all cancers, including renal cancer, were less than expected based on US mortality rates.[485] Although the study detected nonsignificant increases in mortality from lung cancer and chronic renal disease, mortality was not related to duration of employment; there was no direct measure of cumulative uranium exposure. Smoking data and individual exposure assessments were not available. In a review of eight cohort studies

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on the mortality of workers at uranium processing facilities, the standardized mortality ratio (SMR) for chronic nephritis ranged from 0.67–1.88, with wide confidence intervals and a similar distribution of the SMR around 1.[478] A cross-sectional study of uranium workers demonstrated a mild increase in the urinary clearance of β_2-microglobulin and amino acids compared with a control group without uranium exposure. However, none of the workers demonstrated elevated urinary β_2-microglobulin, amino acids, or creatinine when compared with the upper limits of normal for populations of workers.[486]

Follow-up studies of uranium millworkers suggested an inverse association between uranium exposure and serum creatinine.[486] In a cross-sectional study of 684 current and former Korean lead workers, higher log transformed urine concentrations in adjusted linear regression models were associated with lower measured creatinine clearance in models using creatinine to adjust urine concentrations; however, the association was no longer significant when using an absolute measure of creatinine (μg/4-hour urine collection).[487] This study suggests some association between urine uranium and kidney outcomes may result from statistical rather than nephrotoxic effects secondary to the use of urine creatinine in both exposure and outcome metrics.

Military Uses (Depleted Uranium)

Most studies of Gulf War veterans with embedded fragments containing depleted uranium have not detected clinically significant liver, kidney, bone, hematological, nervous, and reproductive (neuroendocrine hormone concentrations, sperm counts) abnormalities. However, some follow-up studies on military veterans suggest adverse proximal renal tubular effects (e.g., ↑ urinary β_2-microglobulin, retinol binding protein). A cross-sectional study of 29 Gulf War veterans with retained metal shrapnel fragments containing depleted uranium demonstrated increased urinary uranium concentrations 7 years after exposure.[481] No adverse renal effects were detected in this study as measured by clinical laboratory values, psychiatric evaluation, and neurocognitive assessment. An 18-year follow-up study of 80 veterans with embedded depleted uranium fragments from Gulf War I demonstrated continued uranium excretion (range, 0.006–1.88 μg uranium/g creatinine); however, there was no evidence of elevated biomarkers of renal tubular dysfunction, glomerular damage (integrity, glomerular filtration), or bone resorption.[488] Comparison of the high-urine uranium group (mean = 5.997 ± 10.773 μg/g creatinine, $n = 12$) and the low-U exposure group (mean = 0.009 ± 0.016 μg/g creatinine, $n = 25$) did not demonstrate any significant differences between the two groups in spirometry, pulmonary symptoms, serum chemistry, hematological parameters, or biomarkers of renal dysfunction.[489] In a 12-year follow-up study of 32 veterans with retained fragments of depleted uranium, uranium concentrations in 24-hour urine collections ranged from 0.001–41.8 μg/g creatinine.[490] There were no detectable abnormalities in blood chemistries, complete blood count, renal glomerular and tubular function, neuropsychological measures, or semen quality when comparing high exposure (≥10 μg/g creatinine) and low exposure (<10 μg/g creatinine) groups. A 25-year follow-up of this cohort of military veterans continued to demonstrate an absence of U-related health effects in known target organs of uranium toxicity, including normal renal function.[491] Similarly, a 20-year follow-up of exposed veterans did not demonstrate any differences in self-reported respiratory symptoms, prevalence of low-dose chest computed tomography abnormalities, or mean pulmonary function values, when comparing the low- and high-exposure groups based on 24-hour urine total U concentrations.[492]

Formation of a fine aerosol of mostly (i.e., >65%) insoluble uranium oxides occurs when a depleted uranium round strikes a target. In the Capstone Depleted Uranium (DU) Aerosol Characterization and Risk Assessment Study, all vehicle configurations and modeled exposure times with the exception of unventilated Abrams tank perforated through DU armor predicted radiation doses below the US occupational limits.[493] Risk analysis indicates leukemia and birth defect risks following exposure to depleted uranium during wartime uses are too small to observe.[494]

Carcinogenesis

The International Agency for Research on Cancer (IARC) considers the evidence for carcinogenicity of mixtures of uranium isotopes (natural, enriched, depleted) in humans limited with sufficient evidence of carcinogenicity in experimental animals.[348]

Occupational Exposure

The risk of developing cancer following exposure to natural uranium or ^{238}U is small because of the low radioactivity of these compounds and the extremely long physical half-lives. The risk of cancer is greater following internal exposure to enriched uranium, including workers involved with nuclear fuel cycles and uranium miners exposed to radon and uranium dust. Potentially, these workers are exposed to increased risk of malignancies of the lung, larynx, and lymphatic and hematopoietic

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tissues; however, the findings are inconsistent as a result of inadequate measures of radiation dose, potential concomitant exposure to chemicals, confounding by smoking, age-related effects, and ascertainment bias complicate the interpretation of epidemiological studies of workers exposed to uranium.[495]

Some studies of uranium miners demonstrated an increased incidence of oat cell and squamous cell carcinomas of the lungs,[496,497] with a lower 95% confidence limit in one study of 14.4.[498] In a population-based, case-control study of 94 incident cases of lung cancer in Navajo males identified after the closing of the local uranium mine and followed for 25 years, the relative risk of developing lung cancer in a Navajo uranium miner was 28.6 (95% CI: 13.2–61.7) compared with Navajo males without a history of working in the uranium mine.[499] The relative risk did moderate slightly over time. The prevalence of smoking among Navajo males is low and smoking did not account for the strong relationship between lung cancer and uranium mining. In a cohort mortality study of 6,409 uranium workers followed for a mean of 37 years, there was little evidence of a dose-response trend for any cancer evaluated, except intestinal cancer (excess relative risk = 1.5/100 μGy; 95% CI: 0.12–1.42/100 μGy).[500] The standardized mortality rates were elevated for lung cancer in hourly (but not salaried) male workers and lymphohematopoietic cancer in salaried men; however, there was no relationship of the SMRs to dose. Studies of uranium mill workers demonstrated a slight excess of cancers of the lymphatic and hematopoietic tissue, with a relative risk up to ~2.[501,502] A long-term mortality study of nuclear-processing plant workers exposed to low doses of internal α-radiation and external radiation demonstrated a 20% increase in the standardized mortality rate (SMR 95% CI: 1.04–1.38).[503] Other studies of uranium dust exposure and lung cancer mortality among workers employed at uranium processing plants have not demonstrated dose-related effects of uranium exposure and lung cancer.[504] Typically, the exposure to radon in these plants is much lower than uranium miners. Although separation of the effect of exposure to uranium from the effect of confounding variables (e.g., radon, smoking, silica, dusts, and diesel engine exhaust fumes) is difficult, there is insufficient evidence to support a causal relationship between cancer and exposure to natural uranium.[305] Nephrotoxicity from the chemical effects of uranium would be expected to appear before the onset of cancer.

Environmental Exposure

No clear evidence links oral environmental uranium exposure to human cancer. In a case cohort study of 61 bladder cancer and 51 kidney cancer cases, a substantially increased risk of these 2 cancers was not associated with cumulative exposure to elevated well-water uranium concentrations; however, the study had relatively low statistical power.[329] In an ecological study of county residents living near the Grants Uranium Mill operated from 1958–1990 with follow-up through 2004, there was no consistent evidence that operation of uranium mills and mines adversely affected cancer incidence or mortality of county residents.[505] Lung cancer mortality and incidence were significantly increased among men (SMR = 1.11; 95% CI: 1.02–1.21; SIR 1.40, 95% CI: 1.18–1.64) but not women (SMR = 0.97, 95% CI: 0.85–1.10; SIR 1.01, 95% CI: 0.78–1.29). The authors attributed the slight excess mortality and incidence of men with lung cancer to coexposures (i.e., radon gas and decay products, smoking) and socioeconomic factors.

Reproductive Abnormalities

Although a review suggested the possibility of an association between depleted uranium exposure and teratogenicity,[506] the data have not been evaluated in peer-reviewed journals. Few data are available to correlate uranium exposure with developmental abnormalities in humans or animals following inhalation exposures of any duration including alteration of neuroendocrine function (follicle stimulating hormone, luteinizing hormone, testosterone);[507] consequently, a causal relationship between depleted uranium and developmental toxicity (e.g., birth defects) has not been established. Animal studies indicate uranium can cross the placenta after parenteral administration.

DIAGNOSTIC TESTING

Conversion Factors

1 μg (natural uranium) = ~0.67 pCi = 24.8 mBq
1 μg/L = 4.2 nmol/L (^{238}U = 238.03 g/mol)

Analytical Methods

Uranium is a ubiquitous element commonly present in food and drinking water. Analytical techniques for quantitating uranium in medical and environmental samples include inductively coupled plasma/mass spectrometry (ICP/MS; LOD, 0.1 μg/L) and inductively coupled plasma/atomic emission spectrometry (ICP/AES; LOD, 0.2 μg/L). Although these two methods are sufficient to quantitate total uranium concentrations in biological media, determination of the

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type of uranium exposure (e.g., natural uranium, NU; enriched uranium, EU; depleted uranium, DU) requires isotopic analysis with enhanced analytical sensitivities. In natural uranium, $^{235}U/^{238}U$ is 0.00725 with little variation (i.e., ~0.1%), whereas $^{234}U/^{238}U$ is much more variable. During the enrichment process, the $^{235}U/^{238}U$ and $^{234}U/^{238}U$ increases substantially compared with natural uranium. These two ratios are substantially lower in depleted uranium than natural uranium.[508]

The most precise techniques for determining uranium isotope ratios include inductively coupled plasma/mass spectrometry (ICP/MS),[509] multicollector/inductively coupled plasma/mass spectrometry (MC/ICP/MS), and thermal ionization/mass spectroscopy (TI/MS). Typically, health physicists use magnetic sector field/inductively coupled plasma/mass spectrometry (SF/ICP/MS) because of less stringent precision requirements;[510,511] however, polyatomic interferences and low sensitivity for ultra-low isotope concentrations limit results. The use of SF/ICP/MS with a high-efficiency nebulizer (Apex PFA microflow) coupled with a membrane desolvating nebulizer system (Aridus II™) improves precision, accuracy, and LOD.[512] α-Spectrometry allows the determination of uranium in water and food;[467] however, the low specific activity of natural uranium produced highly variable recovery.[513]

Biomarkers

In the Fourth National Report on Human Exposure to Environmental Chemicals (NHANES IV), the geometric mean uranium concentration in urine samples from US residents (≥6 years) was 0.007 µg/L (95% CI: 0.006–0.008 µg/L) with an upper 95th percentile of 0.036 µg/L (95% CI: 0.029–0.044 µg/L).[514] The clearance of uranium from the body is rapid; consequently, urine uranium concentrations of >100 µg/L indicate recent or current uranium exposure. Urinary uranium concentrations of <40 µg/L suggest past or typical background uranium exposure.

Bone is a repository for absorbed uranium. In a study of seven Canadian cities, the geometric mean U concentration in ashed human bones from these cities ranged from 2.5 ± 1.4–88.7 ± 1.4 µg/kg.[515] The median of all samples in the Canadian study and a collection of ashed bone samples from the 1990s were similar (i.e., 6.0 µg/kg and 6.8 µg/kg, respectively).[516] In a 7-year follow-up study of 29 veterans with retained, depleted uranium shrapnel fragments, the urinary uranium in the veterans ranged from 0.01–30.7 µg/g creatinine compared with 0.01–0.05 µg/g creatinine in 38 unexposed veterans.[481] In a study of 579 Iraq and Afghanistan veterans monitored through the Veteran's Administration Embedded Fragment Registry, 55% of the veterans had urine uranium concentrations within the reference range, as measured by high-resolution/inductively coupled plasma/mass spectrometry at the time of analysis.[517] Most of the veterans (i.e., 79%) served in Iraq with ~20% sustaining injuries in 2004. The vast majority of veterans submitted urine specimens <10 years after injury. Elevation of dicentric and sister chromatid exchanges in the blood lymphocyte cultures from workers exposed to both soluble and insoluble uranium compounds suggests genotoxicity related to uranium exposure.[518]

HEALTH SURVEILLANCE

Risk Assessment

The intermediate-duration (15–364 days) inhalation minimum risk level (MRL) for insoluble uranium compounds is 2 µg/m^3 based on mild renal tubular changes in dogs exposed to ≥8.2 mg U/m^3 for 5 weeks,[435] whereas the intermediate-duration MRL for soluble uranium compounds is 0.1 µg/m^3 based on mild renal tubular changes (LOAEL) in rats following exposure to 0.15 mg U/m^3. The chronic-duration (>364 days) inhalation MRL for soluble uranium compounds is 0.04 µg/m^3 based on mild renal tubular atrophy in dogs exposed to 0.2 mg U/m^3 for 33 hours/week for 1 year.

The acute-duration (≤15 days) oral MRL is 2 µg U/day for soluble uranium compounds based on a benchmark dose concentration at the 95% lower confidence limit on a 5% response ($BMDL_{05}$) of 0.20 mg U/kg/day for cleft palate in mice with an uncertainty factor of 100. The intermediate-duration oral MRL for soluble uranium compounds is 0.2 µg/day based on a LOAEL value of 60 µg U/kg/day for renal effects in rats with an uncertainty factor of 300.[519] Current animal data suggest a chronic-duration MRL higher than the intermediate-duration value; assuming adequate renal repair processes at low doses, the intermediate-duration oral MRL may be protective for chronic exposures.[435]

Environmental Monitoring

Current human data do not provide a clear no-effect concentration for uranium. The relationship between uranium effects and drinking-water concentrations is complex, with a lack of reported adverse effects following uranium exposures approaching 100 µg/L in drinking water. Recommendations for the limit of natural isotopes in drinking water are based on the nephrotoxicity of natural uranium isotopes at a

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TABLE 41.31. Regulations and guidelines for exposure to uranium and uranium compounds.

Exposure Limit	Value
OSHA	
PEL–TWA (8 hour)	
Uranium, soluble compounds	50 μg/m^3
Insoluble compounds	250 μg/m^3
NIOSH	
REL–TWA (10 hour)	
Metallic/insoluble compounds	200 μg/m^3
Soluble compounds	50 μg/m^3
REL–STEL (15 minutes) – metallic/insoluble	600 μg/m^3
IDLH – metallic, insoluble, soluble compounds	10,000 μg/m^3
ACGIH	
TLV–TWA (8 hour) – soluble/insoluble	200 μg/m^3
STEL (15-minute TWA) – soluble/insoluble	600 μg/m^3
US FDA	
Bottled water allowable limit	30 μg/L
US EPA reference dose	
RfD (chronic oral exposure)	3 μg/kg/day
Maximum contaminate level (MCL)	30 μg/L
US Federal Drinking Water Guidelines	
World Health Organization (WHO)	
Provisional Drinking Water Guideline	0.015 mg/L
Tolerable daily intake (TDI)	0.6 μg/kg/day
ATSDR minimum risk level (MRL as uranium)	
Acute oral	
Soluble compounds	2 μg/kg/day
Intermediate oral	
Soluble compounds	0.2 μg/kg/day
Intermediate inhalation	
Insoluble compounds	2 μg/kg/day
Soluble compounds	0.1 μg/kg/day
Chronic inhalation	0.04 μg/kg/day

level of 100 μg/L.[312] The provisional WHO guideline for uranium in drinking water is 30 μg/L using the lower confidence limit of 637 μg/day (95% CI: 637–1,646 μg/day) from the Kurttio study[482] as the NOAEL.[520] Applying an uncertainty factor of 10 for intraspecies differences and a default daily water intake of 2 L resulted in a guideline value of 30 μg/L. The US Nuclear Regulatory Commission recommends weekly 10 mg soluble uranium limits to prevent chemical toxicity. The short-term Threshold Limit Value for uranium in air is 0.2 mg uranium/m^3 for soluble and insoluble compounds. The EPA guidelines assign an occupational ALI for ingestion of the natural uranium isotopes of 5×10^5 Bq based on a fraction uptake (f_1) of 0.05 (Table 41.31).

Biological Monitoring

Urine and blood are good biomarkers for the surveillance of individuals exposed to depleted uranium. The ACGIH BEI for uranium in urine at the end of the shift is 200 μg/L when measured within at least 60 days after uranium exposure; this value was developed to avoid kidney injury and hematopoietic abnormalities (e.g., leukemia). Interpretation of urine samples collected prior to 60 days after exposure may not reflect steady-state uranium urine concentrations because of the relatively long uranium half-life. Although 24-hour creatinine-corrected urine samples are usually more accurate than spot urine samples, the latter correlates reasonably well to the former. In a study of 22 DU-unexposed and 29 DU-exposed veterans, the mean and median uranium concentrations were similar in the two groups.[521] The creatinine-corrected spot and 24-hour urine uranium concentrations correlated well ($R^2 = 0.97$) when the two groups were combined and the urine uranium concentration was ≥0.05 μg/g creatinine. The correlation decreased ($R^2 = 0.44$) when the uranium concentration was low (<0.05 μg/g creatinine). The spot sample without adjustment for volume, concentration, or creatinine correlated relatively poorly with the adjusted 24-hour urine uranium concentration, particularly at low urinary uranium concentrations (i.e., <0.05 μg/g creatinine). The US Nuclear Regulatory Commission action level for urinary uranium is 15 μg/L.

In a study of German peacekeeping personnel and residents of the Kosovo region, the daily uranium excretion rates were similar in both study groups.[522] The geometric mean of daily uranium excretion was 13.9 ng and 12.8 ng, respectively. The intersubject variation in uranium excretion was relatively high (i.e., geometric standard deviation = 2.17 ng and 2.60 ng, respectively). Elevation of the $^{238}U/^{235}U$ ratio substantially above the natural ratio of 137.9:1 indicates past exposure to depleted uranium. Spot urine samples were analyzed for the $^{238}U/^{235}U$ ratio in the following four groups of British military personnel serving in Iraq: 1) combat ($n = 199$), 2) noncombat ($n = 96$), 3) medical ($n = 22$), and 4) "clean-up" ($n = 24$).[523] There was no statistically significant difference in the mean $^{238}U/^{235}U$ ratio between the four groups. In a study of 732 military personnel on active duty in areas without current conflicts, the adjusted uranium concentration in urine samples ranged up to 556 ng/g creatinine with a median value of 2.7 ng/g creatinine and a 95% upper percentile of 142 ng/g creatinine.[524] Isotope ratio measurements indicated a natural isotope signature without evidence of depleted uranium. Removal of workers from uranium work usually results in the rapid return of urine uranium levels to normal reference values.[525]

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In a study of 35 Gulf War I veterans exposed to depleted uranium during combat, the urine uranium concentrations ranged from 0.001–60 μg/g creatinine 16 years after exposure.[507] Although there was a trend to higher urine β_2 microglobulin and retinol-binding protein when the cohort was stratified into high and low exposure based on urine uranium, there were no statistically significant differences between these two groups. Elevated urine uranium and isotopic ratios are unlikely in military personnel without retained depleted uranium fragments.[526]

TREATMENT

Chelation

Uranium is primarily a chemical toxin because the half-lives of uranium isotopes are extremely long. Some authors recommend DTPA as a single dose within 4 hours of exposure to highly enriched uranium (~8% ^{235}U and ^{234}U) as a reasonable method to reduce the potential radiation hazard, with further therapy depending on an assessment of the absorbed uranium dose and the amount of continuing absorption from uranium deposition sites.[469] However, the administration of chelating agents is usually not recommended because of concern that the DTPA-uranium complex may cause nephrotoxicity and the lack of efficacy in human case reports, particularly when administered after the first 4 hours after exposure.[527] Additionally, DTPA chelates important essential elements (calcium, magnesium, manganese, zinc). The IND agreement for DTPA does not include approval by the US Food and Drug Administration for administration following uranium exposure; therefore, the use of DTPA in this setting requires special permission. The use of calcium DTPA and calcium disodium EDTA did not significantly increase the renal excretion of uranium or improve the clinical course following the ingestion of 15 g uranium acetate; initial chelation began 16–24 hours after ingestion.[475]

Although initial studies in mice suggested that the immediate administration of Tiron (sodium catechol sulfate or sodium 4,5-dihydroxybenzene-1,3-disulfonate, CAS RN: 149-45-1) reduced the LD_{50} of uranyl acetate,[528] subsequent rodent studies did not confirm the efficacy of Tiron or DTPA as an effective chelating agent for reducing renal toxicity following an absorbed soluble uranium dose of an order of magnitude above the permitted daily limit of 2.5 mg uranium.[529,530] In mice, administration of Tiron, DTPA, or gallic acid more than 4 hours after subcutaneous injection of uranyl acetate did not alter uranium excretion or reduce uranium tissue concentrations.[531]

Urinary Alkalinization

Urinary alkalinization following exposure to soluble uranium compounds is an effective method of preventing the dissociation of the uranium-bicarbonate complex that damages the kidney (ATN) by the release of the uranyl ion into renal tissue. The clinical endpoint is a urine pH of 8–8.5 during the first 3 days after exposure. Further administration of sodium bicarbonate depends on renal tubular function.

Supportive Care

Methods to quantify uranium exposure include 24-hour urine collections for direct counting of uranium and *in vivo* counting of the chest for the assessment of inhaled insoluble uranium. Baseline levels should be obtained for creatinine clearance and 24-hour collections for glucose and protein excretion as measures of glomerular function. Assessment of tubular function by quantitation of urinary amino acids, β_2-microglobulin, and enzymes usually requires special research techniques.

Treatment of imbedded fragments of depleted uranium includes removal of particles >1 cm unless the medical risk of removal is greater than the risk of retaining the fragment, evaluation of hepatorenal function, and monitoring urinary uranium. Rapid evaluation techniques to detect uranium fragments include using nitric acid in ultrasonic cleaner and masking agents (sodium citrate, ethylenediaminetetraacetic acid).[532]

Links for the treatment and dosing of pediatric and adult patients with internal radionuclide contamination include Advanced Hazmat Life Support (AHLS) for Radiological Incidents and Terrorism (https://www.ahls.org/ahls-courses/course-types/ahls-radiological-incidents-terrorism), DailyMed (https://dailymed.nlm.nih.gov/dailymed/), The Medical Aspects of Radiation Incidents (https://orise.orau.gov/reacts/resources/documents/medical-aspects-of-radiation-incidents.pdf), and Radiation Medical Emergency Management (https://remm.hhs.gov/).

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C

NONIONIZING RADIATION

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Chapter 42

COMPUTER SYSTEMS

MONITORS

The widespread introduction of video display terminals (e.g., desktops, laptops, tablets, smartphones) into offices and homes has raised concerns regarding the health effects of the old VDTs (video display terminals), including ocular hazards (e.g., dry eyes, visual fatigue),[1] musculoskeletal complaints, stress, facial dermatitis, and adverse pregnancy outcomes.[2] Radiation-related effects resulting from VDT emissions are highly unlikely because radiation levels are far below current standards of exposure.[3] Although chronic sequelae (cataracts, reduced visual acuity) are unlikely, VDT operators frequently report an increase in symptoms of eyestrain (pain, burning, irritation, blurring, diplopia), along with musculoskeletal complaints of stiffness and discomfort. Poorly designed workstations probably contribute significantly to the level of discomfort.[4,5] The facial rash associated with the electrostatic fields surrounding the VDT usually responds to adjustments in humidity and ventilation.[6] Public concern regarding VDT and reproduction developed in response to reports of small clusters of miscarriages and malformations among VDT operators; however, later case-control studies and the lack of teratogenic effects in animals did not support a causal association between VDT and adverse pregnancy outcomes.[7] In the early 1990s, researchers developed large-area active matrix arrays of electronic components that allowed the use of flat panel displays for laptop computers, desktop PCs, and televisions, replacing older video display terminals. Recent design improvements use a thin layer of silicon in an amorphous form rather than the crystalline form used in conventional microchips. The plasma-enhanced deposition of silane gas (SiH_4) produces an amorphous layer of silicon on glass.

EXPOSURE

Quantity

VDTs produce low radiation levels in the non-ionizing range, primarily between 50–100 Hz (ELF or extremely low-frequency range), 15–60 kHz (VLF, RF, or radiofrequency range), and 300–600 nm (ultraviolet and visible).[8] Horizontal deflection coils and the output lead of the flyback transformers (220 V AC power supplies) produce magnetic fields in the radiofrequency range, whereas vertical deflection circuitry produces magnetic fields in the ELF range. Typical electrical field strength for operators ~0.5 m from the screen is <10 V/m (RMS), while the magnetic flux densities in the ELF range are usually <0.1 μT (RMS) with a range up to 0.6 μT.[9] A study of 67 VDT operators measured the ELF magnetic field of these operators at 0.46 m during a typical 8-hour day. The 8-hour time-weighted-average geometric mean was 0.1 μT with a range of 0.03–0.36 μT.[10] Self-reported hours of VDT usage or self-reported distance between waist and VDT were poor surrogate measures of the actual magnetic field. The corresponding densities for VLF fields usually are <0.1 μT. The typical ELF magnetic flux densities in office environments that include printers, photocopiers, modems, scanners, low-voltage desk lamps, and calculators range from 0.1–0.65 μT.[11]

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TABLE 42.1. American Conference of Governmental Industrial Hygienists (ACGIH) 8-hour threshold limit values (TLV) for occupational exposure to static magnetic fields and for magnetic fields in the sub-radiofrequency ranging from 1–300 Hz.

Exposure	Ceiling (T) Static Magnetic Fields	Ceiling (mT) Sub-radiofrequency Fields (1–300 Hz)
Whole body (general workplace)[a]	2	60/*f*
Whole-body special training or controlled environment	8	60/*f*
Arms and legs	20	300/*f*
Hands and feet	20	600/*f*
Medical electronic device users	0.0005	0.1

Abbreviation: f = frequency in Hz and value in mT.
[a] For workers in a controlled workplace environment with special training (i.e., aware of transient sensory effects from rapid motion and potentially hazardous metal projectiles in static magnetic fields with flux densities exceeding 2 T).

Neon-glow tube (plasma) and light-emitting diode (LED) displays do not produce very low-frequency fields above background levels.[12]

Field Types

The physical effects of the old VDT result from 1) alternating magnetic field strengths that leak from the magnetic field bending the electron ray; and 2) the electrostatic fields generated by the positively charged, translucent film on the inside of the front glass.[13] The strongest field in terms of energy density is the electrostatic field between the charged display screen and surrounding objects. The strength of this field depends primarily on humidity, the charge surrounding objects, and the duration of exposure.[14] The ELF magnetic field is the next strongest field.

Field Forms

The complex field wave forms are periodic, but not sinusoidal; therefore, the root-mean-square (rms) is the best description of the amplitude of the field. For a series of VDT, the maximum magnetic flux density in rms values at 30 cm from the screen was 0.74 μT in the ELF range and 0.14 μT in the RF range.[15] The glass screen absorbs most of the X-rays emitted by the cathode ray tube in the VDT, so the level of exposure to X-rays is low.[16]

DOSE-EFFECT

Measurements of radiation emissions from VDT indicate the radiation dose received by VDT workers is two orders of magnitude below standards set for ultraviolet, visible, and infrared radiation and at least one order of magnitude below standards for RF and ionizing radiation. The ACGIH guidelines for static and sub-radiofrequency magnetic fields are displayed in Table 42.1.[17] The ceiling value for static magnetic fields is 2 T, whereas workers with special training may tolerate static magnetic field densities up to 8 T. Guidelines for sub-radiofrequency fields are based on frequency. Workers wearing pacemakers should not be exposed to sub-radiofrequency fields (1–300 Hz) with densities exceeding 0.1 mT unless the manufacturer confirms that the pacemaker will tolerate higher levels without electromagnetic interference.

The radiation dose from VDTs usually is well below the currently recommended levels for ELF and RF radiation. A survey of VDT indicates the dose of X-ray radiation was $<3\times10^{-9}$ R/hour with the annual effective dose equivalent to <0.002 mrem.[18] Radiation from VDTs has not been clearly associated with adverse effects. The radiofrequency radiation emitted by VDTs is similar in intensity to that emitted by most household appliances.[19]

CLINICAL RESPONSE

Skin

Many reports of dermatitis associated with VDT use originate in Northern Europe, where relative humidity in heated rooms is low and the electrostatic fields in low humidity are relatively high.[20] The rosacea-like dermatitis begins with erythema and proceeds to small papules and mild desquamation.[21] A survey of 550 VDT operators in Sweden did not detect any rashes similar to the lesions reported in Norway; however, an excess

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incidence of seborrheic dermatitis, acne, and rosacea appeared in this group of workers.[22] Adjustments in ventilation and humidity probably are more important causal factors than the use of electrostatic shields or the purchase of VDT models with low electrostatic emissions.[6] Later studies did not detect any significant difference in the prevalence of skin diseases between VDT operators and control groups without exposure, whereas the prevalence of subjective skin sensations increased in the VDT operators compared with unexposed controls.[23] Subsequent double-blind provocation testing of these "sensitive" workers did not indicate any reaction to electromagnetic fields.[24] Although work with VDT can increase the dose of radon absorbed by the skin under certain circumstances, the actual increase in radon dose is small; therefore, the contribution of VDT use to skin diseases (e.g., actinic elastosis, Civatte's poikiloderma) is negligible.[25]

Eye

The most frequent ocular complaints of VDT operators include eye fatigue, eye irritation, and blurred vision.[26,27] Symptoms of eyestrain frequently occur after extended, intense use of >4 hours/daily, particularly in poorly lit work areas and in persons over 40 years of age.[28,29] In a case series of 76 young Nepalese adults (mean = 25.8 ± 5 years) from a variety of occupations, the most common ocular complaints were tired eyes (88.2%), sore eyes (71.1%), blurred vision (64.5%), and dry/aching eyes (61.8%).[30] Headaches (85.5%) and musculoskeletal symptoms (e.g., neck pain, 67.1%) were also common. These participants used computers for a mean of 6.9 ± 2.6 hours daily. Decreased frequency of eye blinking and the subsequent increased rate of tear evaporation may contribute to dry eyes and ocular irritation.[31] The presence of glare increases eyestrain, but these effects are usually temporary and do not produce permanent sequelae.[32] The development of afterimages has been associated with the extended use of monochrome monitors.[33] Prolonged use of dark screens with green letters causes white letters on a contrasting background to appear pink (the McCullough effect). This visual aberration does not produce permanent damage; however, these aftereffects may last several weeks due to the adaptation of cortical neurons to specific combinations of form and color.[34] Antidotal case reports suggest an association between the development of cataracts and exposure to video display terminals. Subsequent studies have not confirmed this association.[35] Examination of 10 cataract cases demonstrated no clear cause-effect relationship; the ionizing radiation dose received by the VDT operators was 10,000 times below the threshold for radiation-induced cataracts.[36]

Musculoskeletal

VDT operators also frequently complain of musculoskeletal symptoms. Sharp shooting pain and stiffness of the back, neck, shoulders, and wrists are more common than discomfort of the arms, legs, and hands.[6] These effects occur most prominently in workers with conditions involving repetitive work with little variation; long, unrelenting sessions; and/or intense, visual concentration. Factors contributing to these musculoskeletal complaints include inadequately designed workstations, lack of exercise, repetitive tasks, personal traits, pace of the job, and stress. Musculoskeletal complaints are manifestations of stressors in the work atmosphere, along with illness, sleep disturbances, psychosomatic disorders, and nervous conditions.

Reproductive Abnormalities

Although data on VDT exposure and adverse outcomes other than fetal loss are limited (e.g., poor exposure data, low statistical power), current evidence does not support a strong association between VDT use and adverse pregnancy outcomes.[37,38] Several reports in the early 1980s on small clusters of miscarriages and congenital abnormalities in the offspring of VDT operators raised concern about the reproductive effects of VDT exposure; however, a dramatic decrease in the number of reported clusters of adverse pregnancy outcomes occurred after 1979–1982.[39] Several, but not most, case-control studies demonstrated slightly elevated odds ratios for spontaneous abortions among VDT operators, particularly women with more prolonged VDT use (i.e., 15–20 hour/week).[40,41] A retrospective, case-control study of clerical workers exposed to VDTs between 1975 and 1985 demonstrated an increased risk of spontaneous abortion (OR = 3.4, 95% CI 1.4–8.6) in women exposed to high levels (>0.9 μT) of extremely low-frequency magnetic fields early in pregnancy.[42] Recall bias may account for the weak effects observed in the positive studies.[43] Some of these studies used telephone interviews conducted several years after conception as a measure of exposure.[40] A retrospective case-control study of 932 infertile couples and 698 fertile couples recruited between 1991 and 1997 at university-based infertility clinics did not suggest an association between male infertility and VDT use based on self-reported

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questionnaires.[44] The odds ratio was 0.30 with a 95% CI of 0.13–0.68.

Assessment of the exposure of the VDT operators to electric and magnetic fields is difficult because the strength of these fields varies with the type of VDT and the distance from the source.[45] Most systematic epidemiological studies have not confirmed the association between VDT and adverse outcomes of pregnancy, particularly studies with more detailed magnetic field measurements.[46] In a study of 882 pregnancies in 730 directory-assistance operators exposed during their first trimester, the odds ratio for a spontaneous abortion in the exposed women was 0.93 (95% CI: 0.63–1.38) compared with general telephone operators using LED or plasma displays (no very low frequency exposure above background).[12] The study did not detect an exposure-response relationship between VDT exposure and spontaneous abortion. For women exposed to VDTs for 1–25 hours/week, the OR was 1.04 (95% CI: 0.61–1.79) compared with 1.00 (95% CI: 0.61–1.64) for VDT exposure for >25 hours/week. Measurements of abdominal exposure to ELF fields (45–60 Hz) did not demonstrate a significant difference between women using VDTs and background ELF exposure (i.e., women using non-VDT displays). A survey of adverse pregnancy outcomes among 6,212 commercial and clerical workers did not detect an increased risk of medically verified spontaneous abortions in women using VDTs.[47] A UK case-control study of 150 nulliparous women with clinically diagnosed spontaneous abortion and 297 nulliparous women attending an antepartum clinic reported no increased risk of a spontaneous abortion in women using a VDT at work (OR = 0.9, 95% confidence limit 0.6–1.4).[48] A case-control study of 508 Italian women admitted for spontaneous abortions and 1,148 hospital controls did not demonstrate an association between VDT exposure and spontaneous abortion based on the self-reporting of VDT use.[49] The odds ratio for spontaneous abortion in the exposed women was 1.0 (95% CI: 0.8–1.2). The power of most of these studies was sufficient to detect modestly elevated risks of spontaneous abortions (i.e., >1.5).

A few studies demonstrated an association between VDT exposure and fetal abnormalities, but the measures of VDT exposure were indirect. Ericson and Kallen found a borderline statistically significant increased odds ratio of 1.6 (95% CI: 1.0–2.4) for any birth defect in VDT operators that increased to 2.3 (95% CI: 1.4–3.6) for women using VDT for >20 hours/week.[41] The study identified no specific congenital defect associated with VDT exposure. Goldhaber et al. found a nonstatistically significant increase in the odds ratio of 1.4 for birth defects in women working with VDT based on self-reporting of VDT use.[40] However, most epidemiological studies demonstrate no association between VDT exposure and fetal abnormalities.

A cohort study of 2,430 telephone workers and 713 live births found no excess risk of reduced birth weight (OR = 0.9, 95% CI: 0.5–2.7) or preterm birth (OR = 0.7, 95% CI: 0.4–1.1) when comparing VDT operators with nonexposed controls.[50] An Italian case-control study of 555 neonates with small-for-gestational age at birth reported no exposure-response relationship between VDT use and small-for-gestational age at delivery.[51] Estimates of exposure were based on company records and simulated studies of electromagnetic fields near representative VDT workstations. Case-control studies of women working with VDTs from Norway[52,53] and Denmark[54] also report no association between VDT use and congenital malformations. Radiation from VDTs was not mutagenic in the standard Ames Salmonella assay.[13] Currently, the weight of evidence does not support an association between VDT use and adverse outcomes of pregnancy.

HEALTH SURVEILLANCE

Although visual or musculoskeletal problems may occur following prolonged VDT use, proper equipment, unit design, technique, and work practices minimize these issues. Guidelines are available to improve workstation design, illumination, and work regimens. (https://chemistry.osu.edu/sites/chemistry.osu.edu/files/A%20Survival%20Guide%20to%20Computer%20Workstations.pdf). Static magnetic fields and non-ionizing radiation levels associated with VDT use are far below workplace guidelines and unlikely to cause serious clinical effects.

Workstation Design

Maximum flexibility is the most important aspect of workstation design.[55] VDTs should have detachable keyboards with height-adjustable tables and chairs. In addition, the backrest of the chair should accommodate the lumbar region to provide adequate back support. The viewing distance should be adjusted to the individual with average distances from the operator to the screen ranging from 45–50 cm. The viewing angle should average 10–20° with the top edge of the screen no higher than the eye level of the operator and the bottom edge of the screen no lower than 40° below eye level.[56]

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Illumination

Lighting levels should be set at ~500–700 lux, depending on the visual needs of the surrounding area. The illumination should be increased for tasks requiring the use of hard copy and decreased for tasks requiring screen-intensive work. Sources of glare should be controlled by the placement of the VDT with respect to windows and overhead lighting, proper illumination, and the use of glare control devices on the VDT screen surface. The use of hard copy material may require a supplemental light source. Recessed direct light sources and the addition of baffles to fluorescent fixtures may be necessary to reduce glare.

Work Regimens

VDT guidelines vary between countries.[57] Periodic breaks from work may be necessary depending on the demands of the job to reduce visual fatigue and musculoskeletal complaints. As a minimum, 10- to 15-minute breaks should occur after 2 hours of continuous work and sooner for repetitive tasks with high visual demand.[58] The US Department of Labor recommends 10-minute rest breaks after 2 hours of continuous VDT use for operators under moderate visual demands, whereas a 15-minute break after 1 hour of continuous VDT work is recommended when high visual demand or intense repetitive work tasks exist.[59]

Vision Testing

A comprehensive preemployment visual examination should include both near and far central visual acuity, muscle balance and eye coordination testing, depth perception, and color discrimination.[60] The need for testing during employment depends on the severity of the visual demands and individual responses to the visual demands.

LAPTOP COMPUTERS

The electrical circuits and power supplies in laptop computers produce electromagnetic fields (EMF). The physical interaction between EMF and the human body induces electric fields and circulating electric current that potentially may produce biological effects when the current density exceeds certain threshold values. The magnetic field associated with computers is impulsive (complex) rather than a sinusoidal waveform.

The EMF decreases with the square of the distance; consequently, induced electrical currents are higher during use of the laptop computer in direct contact with the body than during use of the laptop on a desk. In a study of five popular laptop computers using the voxel phantom model of a 26-week pregnant woman, the EMF levels of the computers ranged from 1.8–6 μT compared with 0.7–29.5 μT for the power supplies.[61] Although the estimated EMF values for the laptop computers were within International Commission on Non-Ionizing Radiation Protection (ICNIRP) guidelines,[62] the estimated electric current densities in the fetus and mother from direct contact with the laptops were 2–4-fold higher than ICNIRP guidelines. This study assumed a "worst-case" scenario involving the placement of the AC power supply very close to the mother's head and the computer next to the uterus. Additionally, the spatial distribution was modeled as a uniform field in close contact with the laptop; the fields were measured in field strength mode using a weighted peak approach for a complex waveform rather than RMS amplitude for a sinusoidal waveform.[63]

WIRELESS LOCAL AREA NETWORKS (WLAN)

A WLAN uses radio technology rather than direct wiring to connect local network nodes, and includes a set of devices capable of wireless communication over a restricted geographical area (e.g., school campus, home, business, airport); the two modes of network operation include: 1) infrastructure mode – all communication passes through a controlling access point within a Basic Service Set, and 2) *ad hoc* mode – communication passes directly between individual devices. Wi-Fi is a specific type of WLAN that conforms to Institute of Electrical and Electronic Engineers (IEEE) standards, and operates in the 2.4 GHz, 5 GHz, and 6 GHz bands to connect access points to client devices. Wireless devices (i.e., wireless network adapter or client card) communicate within the Basic Service Set (access points) that may be connected to a Distribution System of multiple access points (i.e., wireless router, wireless gateway, base station) to allow access to external network infrastructures (e.g., file servers, Internet). Wi-Fi technology exists throughout the world with "hotspots" in cafes, coffee houses, homes, train stations, airports, and other heavily traveled areas. The IEEE 802.11

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standards specify band width and maximum radiated powers for WLAN devices during transmission. These devices operate primarily in the unlicensed 2.4 Gigahertz (GHz) Industrial, Scientific, and Medical Band 2,400–2,483.5 MHz (United States, 2.412–2.462 GHz unlicensed spectrum) and less commonly in the 5 GHz Unlicensed National Information Infrastructure frequency band (United States, 5.725–5.825 GHz licensed spectrum) with transmission rates up to 600 Mbps. The former bandwidth typically is 24 mHz wide; this spectrum is shared with Bluetooth wireless interfaces, cordless telephones, industrial heating, medical appliances, and microwave ovens. The maximum power in the 2.4 GHz range is 100 mW in Europe, whereas the limit for 5 GHz devices is 200 mW. These devices transmit with relatively low power for a small proportion of the time (i.e., low duty factor) to avoid monopolizing the system.

EXPOSURE

The use of Wi-Fi results in exposure to radiofrequency electromagnetic fields. The total radiofrequency exposure from a WLAN is the combination of exposure from access points and the client card with the closest source (i.e., typically the computer) accounting for the major contribution. The signals consist of intermittent bursts of radiofrequency energy, depending on duty factors. The Wi-Fi signal levels are typically far below other RF signals in the same environments. In a study involving 356 measurements of 55 US and European sites (homes, commercial spaces, education institutions, healthcare facilities), all Wi-Fi signals were very far below international exposure limits (IEEE C95.1-2005, ICNIRP).[64] Measurements were collected in public spaces as close as practical to Wi-Fi access points and ~1 m from laptops downloading and uploading large files from and to the WLAN. Using a 20 MHz bandwidth signal analyzer to measure radiofrequency power densities, the spherically integrated radiated power (IRP) for 15 laptops in the 2.45 GHz band ranged from 5–17 mW compared with 1–16 mW for 8 laptops in the 5 GHz band.[65] The IRP for 12 access points at 2.4 GHz ranged from 3–28 mW, whereas the power densities for 6 access points at 5 GHz ranged from 3–29 mW. The access points typically were wall-mounted with beams directed into the rooms, and their powers were integrated over a hemisphere. In general, the power densities were higher for access points than laptops. The maximum power densities of the laptops decreased from 22 mW/m^2 at 0.5 m to 4 mW/m^2 at 1 m, whereas the value for access points decreased from 87 mW/m^2 at 0.5 m to 18 mW/m^2 at 1 m.

DOSE-EFFECT

The low operating power of client cards and access points along with the short duty cycle of transmission limit the radiofrequency fields emanating from WLAN. The factors that determine the intensity of the radiofrequency field include the power output of the client card, antenna gain, and the duty factor (cycle) of transmission. The latter factor depends on transmission speed, signal quality, the presence of other access points or client cards using the same channel, and the capacity of the hardwired network connected to the WLAN. In a study of 55 private and public sites in the United States and Europe, all measured Wi-Fi signal levels were far below ICNIRP guidelines, and most background radiofrequency signals in these primarily suburban locations were higher than WLAN signals in the 75 MHz–3 GHz bandwidth as measured by the Narda SRM-3000 selective radiation meter (Narda Safety Test Solutions, Hauppauge, NY).[64] The median values of the power densities were ~0.001 mW/m^2 at 1 m from the laptops in the absence of uploading or downloading large files; the power density increased about 10-fold during those actions. The distance from the computer reflects field intensities in the far-field close to the computer (i.e., bystanders) rather than the near-field exposure of the computer user. The duration of monitoring was 40–120 seconds rather than the 6- or 30-minute exposure limit for ICNIRP guidelines. In a study of electric fields in 27 Belgian office locations with 7 WLAN networks, the mean dose was 0.12 ± 0.60 V/m (upper 95%, 0.90 V/m) in the 80 MHz–3 GHz range.[66] Research institutions use wireless sensor testbeds (WiLab) to evaluate wireless protocols or applications. The use of WiLab in this study resulted in an average electrical field exposure of 1.9 ± 1.41 V/m (upper 95%, 4.7 V/m), with a maximal measured electrical field value of 6.7 V/m at ≥1 m from the source.

International guidelines for limiting the thermal-related effects of exposure to radio frequency fields (e.g., International Commission of Non-Ionizing Radiation, ICNIRP) average power density exposures over time. The ICNIRP uses a 6-minute averaging period; consequently, analyzing the cumulative power density of WLAN requires applying the duty factor to the power density during transmission of the intermittent Wi-Fi bursts. In a study of 6 primary and secondary English schools, the duty factors ranged from 0.02–0.91% (mean = 0.08 ± 0.10%) for 146 laptops compared with 1.0–11.7% (mean = 4.79 ± 3.76%) for access points for 7 networks.[67] Using the data above, the maximal time-averaged exposure at 0.5 m from the laptop was 22 mW/m^2 with 1% duty factor and

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22 mW/m^2 with 12% duty factor 0.5 m from access points. These values are well below the ICNIRP reference level of 10,000 mW/m^2. Based on the torso model of a 10-year-old child and assuming a 100 mW-burst power and 20 mW maximum power, the localized SAR will scale to 0.40 mW/kg. This value is also below the ICNIRP guideline of 2 W/kg for the general public.

CLINICAL RESPONSE

There are limited data on the health effects of WLAN; however, based on estimated exposure, radiation-related health effects are unlikely.

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Chapter 43

NONIONIZING MEDICAL RADIATION

The nonionizing spectrum of electromagnetic waves ranges from extremely low-frequency electromagnetic waves to the ultraviolet portion. Energy in electromagnetic radiation varies directly with frequency and inversely with wavelength. Higher frequency is associated with greater energy and shorter wavelength. Ultraviolet waves contain the highest frequencies in the nonionizing electromagnetic spectrum; consequently, UV radiation contains the highest quantum energy. Nonionizing radiation contains enough energy to move atoms inside molecules or initiate vibrations of these atoms; however, the energy is insufficient to remove electrons. Nonionizing medical radiation (e.g., magnetic resonance imaging, ultrasound) uses low frequencies and low energy levels; some lasers use radiation from the higher frequencies in the ultraviolet range.

MAGNETIC RESONANCE IMAGING

Isidor Isaac Rabi first described the nuclear magnetic resonance (NMR) phenomenon in 1937; subsequently, he developed a molecular beam method for measuring the magnetic properties of atomic nuclei that earned him the 1944 Nobel Prize in Physics.[1] In 1946, independent observations by Felix Block and Edward Purcell first demonstrated the principle of the NMR phenomenon in liquids and solids.[2,3] They shared the Nobel Prize in Physics for their achievements in 1952. Erwin L. Hahn first used a spin-echo technique to analyze molecular diffusion in liquids; in 1966, Richard R. Ernst developed Fourier transform NMR spectroscopy.[4] He received the 1991 Nobel Prize in Chemistry. The first biomedical application of NMR occurred in 1971, when Raymond Damadian used NMR spin-echo techniques to distinguish malignant tumors from normal tissue by measuring T_1 and T_2 relaxation times in rats.[5] Paul C. Lauterbur and Peter Mansfield advanced the basis of current MR imaging machines by independently describing the use of time-varying magnetic field gradients to localize NMR signals in 1973.[6,7] They shared the 2003 Nobel Prize in Physiology and Medicine. The first magnetic resonance (MR) images of the human body were produced in 1977. In that year, Mansfield and Maudsley published MR images of the human finger with particularly good detail of the soft tissues.[8] The first whole-body MR scanner entered the commercial market in 1980; General Electric and Siemens produced the commercial scanners beginning in 1983. Subsequent advances in magnetic resonance imaging (MRI) pulse sequences, hardware (higher field strengths, improved coils), and novel techniques (magnetic resonance gating, gradient and spin-echo imaging, 2-D/3-D multislice imaging, fluid-attenuated inversion recovery, echo planar imaging, contrast-enhanced MR angiography, fat suppression, diffusion-weighted imaging, blood oxygenation-level dependence) dramatically improved the images and increased medical applications, including functional MRI and whole-body MRI.[1]

Magnetic resonance imaging (old term, nuclear magnetic resonance or NMR) depends on the absorption of nonionizing radiofrequency radiation by the magnetic moments of atomic nuclei in tissues placed

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within a strong magnetic field. The production of images requires the following types of electromagnetic fields: 1) moderately strong, uniform static magnetic fields to align protons; 2) small, alternating magnetic fields for spatial orientation; and 3) pulsed radiofrequency waves to vary the energy states of the protons and create the electrical signal necessary for imaging. Consequently, the MRI machine consists of a main magnetic system, magnetic gradient coil, radiofrequency coil assemblies, associated power supplies, filters, amplifiers, and signal analysis, along with electronic and communications equipment. Differentiation of structures by MRI results from the modulation of nuclei within the tissue by the following parameters: 1) strength of the longitudinal magnetic field, 2) phase and strength of the transverse magnetic field, 3) resonance frequency, 4) T_1 (spin–lattice) longitudinal recovery time, and 5) T_2 (spin–spin) transverse relaxation time.[9]

PHYSICAL PROPERTIES

The image from MRI reflects the composition (i.e., proton density), chemical composition, and physical characteristics (T_1 recovery time, T_2 relaxation time) of the tissue.[10] Atoms with an odd mass number of protons and neutrons in their nuclei possess the quantum property of "spin," creating a dipole that can align along the axis of the applied magnetic field.[11] The spin number defines the value of nuclear spin. Certain atoms (e.g., $^1H^+$, ^{13}C, ^{19}F, ^{23}Na, ^{31}P) possess spin numbers of ½, useful for practical applications involving magnetic resonance. The principal MR active nuclei are hydrogen nuclei consisting of a single hydrogen atom; these nuclei have a relatively large magnetic moment and are abundant in water and fat molecules in the body. The inherent spin tilts and rotates the protons into similar alignment during the application of a static magnetic field (B_0), as displayed in Figure 43.1. The application of radiofrequency waves creates an oscillating magnetic field at a vector 90° to the static field. This varying magnetic field induces a phenomenon called *resonance*, wherein the protons absorb the radiofrequency radiation. As a result, the protons move into a state of excitation and out of alignment with the static magnetic field. Removal of the superimposed, oscillating gradient magnetic field allows the protons to return to equilibrium and the nuclei release the stored energy primarily in the form of signal composed of radiofrequency waves. A minimal amount of heating also develops during this process. The intensity of the emitted radiofrequency (RF) waves is proportional to the proton density in the tissue; mapping the emitted RF waves through computer algorithms using

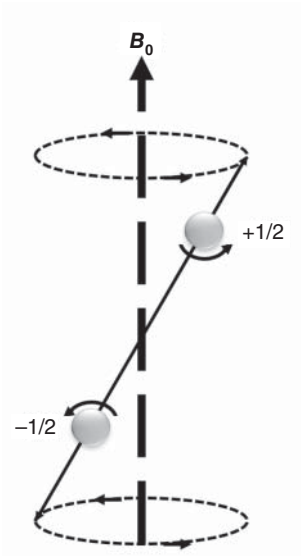


FIGURE 43.1. Precession of protons aligned with a magnetic field (B_0) applied during MR (magnetic resonance) imaging. (Tognarelli et al.).[11] Protons rotate like a spinning top about the longitudinal (vertical) axis of the magnetic field (B_0) with a precession (resonance) frequency proportional to the magnetic field strength. The magnetic vector of the spinning proton has a longitudinal component aligned with B_0 and a transverse or horizontal component related to movement about the longitudinal axis. Radiofrequency (RF) pulses of the same frequency as the resonance frequency change the energy state of protons by flipping the proton to the horizontal orientation. RF pulse strength and duration determine the flip angle. Once the RF pulse ceases, relaxation occurs with the conversion of stored energy to electrical energy, which creates a signal and subsequently a visual image.

Fourier transformation allows construction of an image of the tissue. The relationship between the emitted frequency and the field strength permits the localization of the site of the resonating nuclei.[12] The highest radiofrequency energy deposited in tissues during an MRI examination is ~6 orders of magnitude below the level required to produce ionizing radiation damage in tissue.

The T_1 (spin–lattice) recovery time represents the recapture of longitudinal magnetization parallel to the direction of the static magnetic field, whereas the T_2 (spin–spin) relaxation time characterizes the rate of signal decay after termination of the pulsed gradient radiofrequency and magnetic field. These parameters along with proton density refine the MR image of the tissue because of the diversity of the T_1/T_2 properties and the variation of proton density in different tissues. The T_1 spin–lattice or thermal recovery time represents the time for the nuclei to return to their equilibrium state in a longitudinal direction to the static magnetic field.

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This value typically is 0.3–1 second. The T_2 spin–spin or transverse relaxation time represents the time required for the excited spinning nuclei to lose their alignment with other nuclei. This value usually is shorter (i.e., 0.2 seconds) than the T_1 spin–lattice time. Although T_1 and T_2 operate in all three planes, T_1 is predominantly longitudinal to the static magnetic field, whereas T_2 is mostly a transverse, collective phenomenon.[13] Differences in T_1 between tissues enhance the RF signal and improve the resolution between different tissue types.

EXPOSURE

Uses

Magnetic flux (Φ) is the flow of energy around a magnet measured in units called Webers (Wb). The amount of magnetic flux flowing through a given area around the magnet varies. To measure the flux at a specific time, the amount of flux passing through a unit area at right angles to the magnetic field lines is recorded as the flux density (B) at that point and measured in Tesla (T; $1\,T = 1\,Wb/m^2$).

Design

Cylindrical MRI scanners use superconducting magnets immersed in a bath of liquid helium at −268.93°C that surround the patient and produce static magnetic fields with magnetic flux densities typically 1.5–3 T. By the early 2010s, closed-bore (i.e., cylindrical) scanners represented the vast majority (i.e., ~90%) of MRI scanners.[14] The use of 3 T clinical MRI scanners substantially improves the signal-to-noise ratio, resulting in better image quality and reduced scan times.[15] Less common types of MRI scanner designs include open bore, horseshoe or C-shaped arms, and dipolar electromagnetic scanners with superconducting or resistive coils. A static fringe field gradient (<25 mT/m) acts as a slow, time-varying field during movement; the ever-present fringe field exists close to the bore during scanning (e.g., during interventional procedures). Active shielding reduces stray fields outside the magnet; however, these secondary coils increase the static magnetic fields near the inside end of the cylindrical bore. Thus, the static magnetic field inside the bore is nonuniform. The maximum absolute field strength in self-shielded short bore systems above the nominal field of the magnet occurs at the entrance to the bore along the inner bore edge of the magnet end. The value typically is a few percent above the specified field strength.[16] The static field magnet always remains on, resulting in the longitudinal alignment of the patient's hydrogen atoms with the static magnetic field when placed in the bore.

In addition to the superconducting magnets, three orthogonal magnetic field gradient coils produce rapidly changing spatially varying magnetic fields as they switch on and off superimposed on the static magnetic field. These complex, trapezoidal, time-varying magnetic fields facilitate spatial encoding. Radiofrequency coils produce a radiofrequency field that excites protons in the tissues to emit signals used to form MR images. The radiofrequency waves are usually 64 MHz for 1.5 T-systems and 128 MHz for 3 T-systems. MRI systems with static fields above 4 T use frequencies in the range of 200–400 MHz.

The transverse relaxation time (T_2) is the time constant for the exponential decay of magnetization in the transverse plane (transverse relation or spin–spin relaxation). After application of the RF pulse, the component of magnetization parallel with B_0 (static magnetic field) begins decaying to the equilibrium state (magnetization vector, M_0). The longitudinal relaxation time (T_1) is the time constant for the exponential decay of magnetization in the longitudinal plane (longitudinal or spin–lattice relaxation).[17] The pulsed radiofrequency fields vary between scanners with different static field strengths; various pulse sequences also use different amplitudes and waveforms of B_1 (time-varying radiofrequency magnetic field). Conventional spin-echo and fast spin-echo sequences that prolong the repetition time are required to overcome SAR (specific absorbed power) limitations associated with 3 T MR imaging; however, the increased T_1 relaxation times reduce T_1 contrast. T_1-weighted fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging techniques improve tissue resolution compared with conventional sequences.[18] The use of T_1-weighted, time-dependent (gradient) magnetic fields (dB/dt) superimposed on the static magnetic field for spatial resolution of tissue produces position-dependent variation in the absolute magnetic field strength.

Applications

The magnetic resonance (MR) examination consists of a series of individual sequences designed to display a particular orientation or be weighted to differentiate adjacent tissue types. The advantages of MRI include lack of ionizing radiation, sensitivity to flow and iron, multiplanar capabilities, and high soft tissue contrast resolution.[19] MR imaging is particularly useful for pregnant patients, patients requiring multiple scans, and pediatric patients. MR images produce high resolution for soft tissue based on the differences in the content of

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hydrogen protons in water and fat; however, the MRI signal is poor from cortical bone because the few protons in bone move minimally in the static magnetic field.[20] T_1 signals detail soft tissue anatomy better than T_2 images, whereas the latter relaxation time produces better resolution between different tissue types. The relatively slow scan time of MRI produces biological artifacts from motion, particularly respiratory movement, gastrointestinal tract peristalsis, and movement in the cardiovascular system.[21] The T_2-weighted spin echoes produce superior images of gray matter compared with similar images produced by CT scans. Ultrasound is the initial imaging modality of choice during pregnancy. MR is a nonionizing imaging alternative to ultrasound that provides a large field of view of the placenta and fetus with excellent tissue resolution of the brain, lungs, and abdomen, including images of suspected central nervous system anomalies, neck and oropharyngeal masses, diaphragmatic hernias, and fetal infections. MRI delineates abdominal and gastrointestinal tract masses inadequately examined by ultrasound.[22] Artifacts from maternal breathing and fetal movement limit the sequences available for pregnant patients. In contrast to ultrasound, obesity, oligohydramnios, fetal/maternal bone, and fetal lying do not reduce MR image quality.

MRI is very useful for imaging the central nervous and musculoskeletal systems, particularly the posterior fossa and base of the brain because bone artifacts reduce the sensitivity of CT scans. T_2-weighted MR images are sensitive studies for the detection of arteriovenous malformations and intracranial hemorrhage with the exception of acute subarachnoid hemorrhage; however, MR images are not necessarily superior to CT images for subacute or chronic hemorrhage because of the difficulty differentiating smaller acute hemorrhages from older hemosiderin deposits with MR imaging.[23] MRI is more sensitive to focal areas of cytotoxic cerebral edema than CT scans, particularly with diffusion-weighted images;[24] therefore, MRI is more effective than CT for abscesses and parenchymal brain infections (e.g., herpes simplex).[25] MRI is the most sensitive imaging technique for the detection of multiple sclerosis; however, the changes on MR images are not unique to multiple sclerosis.[26] For suspected spinal cord compression (e.g., lumbar disc herniations), MRI is the imaging technique of choice; however, CT scans more effectively delineate facet joints. MRI is an excellent imaging modality for the detection of torn menisci in the knee joint and the early detection of avascular necrosis.[27] For thoracicoabdominal diseases and the evaluation of patients with multiple traumas, MRI offers no clear advantage over CT or ultrasound.

MRI provides spatial maps and images using water signals from the tissues, whereas proton magnetic resonance spectroscopy (MRS) detects signals from tissue metabolites.[28] The difference in the magnetic resonance properties of water between normal tissues and tumors provides images that distinguish tumors from normal tissues. T_1-weighted spin-echo images provide relatively poor image contrast of brain tissue, particularly at low-field strengths. T_1-weighted fluid-attenuated inversion recovery (FLAIR) images use special sequences to improve the contrast between edematous lesions and normal parenchyma in the brain, particularly lesions in white matter and CSF.[29] Diffusion-weighted images (DWIs) measure water diffusion in normal/abnormal brain tissue and the CSF, resulting in the differentiation of normal and abnormal tissue (e.g., tumor, abscess). The DWIs of edema are hyperintense, whereas tumor tissues are hypointense. The use of the hybrid system involving PET/MR potentially allows whole-body MR screening for cancer,[30] particularly outside the brain when combined with DWI.[31] Whole-body MR imaging for lymphoma without DWI provides nonionizing radiation in contrast to the ionizing radiation of CT imaging.[32]

Magnetic Resonance Spectroscopy

Biomedical applications of nuclear magnetic resonance involve MR imaging and magnetic resonance spectroscopy. The latter is a research and whole-body clinical tool for analyzing normal and pathological biochemical processes in tissues using high-magnetic field strengths (11–14 T). The use of MR spectroscopy after MRI provides data on metabolic functions in addition to the anatomical data from the MRI; however, the sensitivity and spatial resolution of MR spectroscopy limit its use *in vivo*.[11]

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is an MRI technique that correlates brain function and anatomy by detecting areas of increased blood flow during brain activity (brain mapping). This academic and medical research tool uses the blood oxygenation level dependent (BOLD) technique to detect changes in the cerebrovascular system based on different magnetic properties of oxygenated (diamagnetic) and deoxygenated (paramagnetic) blood.[33] The fMRI signal reflects the increased oxygenated blood concentration from vasodilation in areas of neural activity, particularly incoming synaptic activity rather than synaptic output from the region.[34] Hence, the BOLD signal is an indirect

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measure of neural activity. Measuring regional blood flow limits resolution to the distribution of venules (1 mm) with whole brain scans typically exhibiting resolution of 3 mm. Additionally, random variation of the BOLD signal increases susceptibility to signal noise more than other methodologies.

Electromagnetic Fields

MRI requires three types of magnetic fields to produce three-dimensional images including: 1) a strong, constant B_0 (static magnetic field) to generate a magnetization vector (M_0) that reflects proton density; 2) transient magnetic field gradients with pulsed energy in the extremely low frequency kHz range (100–1,000 Hz) using each of three perpendicular axes (x, y, z) to localize aligned protons and allow spatial reconstruction of tissues; and 3) radiofrequency transmitter/receiver system with time-varying radiofrequency magnetic field (B_1) in the very high-frequency range (10–400 MHz) to enhance the magnetization vector for detection of the MR signal and reconstruction of the image by the scanner.[16] In the 1970s, the first research MRI machines operated at 0.4 T. By the early 1980s, 1.5 T machines had been introduced into clinical practice. The average magnitude of exposure to multiple electromagnetic fields during an MRI included: 1) static magnetic field ranging from 0.04–1 T, 2) varying magnetic field between 0.004–20 T/second, and 3) radiofrequency magnetic fields from 1–7 MHz.[35] Permanent superconducting magnets in MRI scanners generated static magnetic fields ranging from 0.2–3 T during operation in the 2000s.[36] Research applications (e.g., laboratory MR imaging instruments) now use higher static magnetic fields (i.e., up to 9.4–10 T) for whole-body patient scanning, requiring radiofrequency signals up to 400 MHz. The magnitude of the magnetic fields near the MRI scanner ranges from 1–10 mT, whereas stray static magnetic fields in the corridors near the MRI scanner extend up to 0.5 mT.[37] The ELF magnetic fields decrease much more quickly than the static magnetic fields; the ELF fields are minimal more than several meters from the magnet.[38] RF noise may be quite high within the area between the magnetic coils. The radiofrequency specific energy absorption rate (SAR) measures the heat produced in the tissue; the typical value is <0.1 W/kg as an average whole-body exposure with a peak SAR of <1 W/kg during a typical MRI scan.[35]

Static Magnetic Field

Magnetic fields are measured by magnetic flux density (magnetic field strength) in units of tesla (T). The exposure to static magnetic fields during an MRI is substantially greater than the average static magnetic field of the earth (~0.03–0.07 mT), the magnetic fields below high direct current transmission lines (0.02 mT), or older electrically powered public transit systems (0.7 mT).[39] The magnetic fields in the passenger cabins of magnetically levitated and conventional electric trains are relatively low (0.1 mT) compared with magnetic fields (several mT) at the floor level above inductors in the passenger coaches.[40] Audio headsets typically produce static magnetic fields in the range of 10 mT, whereas telephone receivers generate field strengths of 3.5 mT. The strength of the magnetic field decreases with the cube of the distance from the source. As outlined in Figure 43.2, the force applied to ferromagnetic objects is proportional to the static magnetic field strength (B), the field gradient (dB/dt), and the mass of the object. Hence, small ferromagnetic instruments, stretchers, and wheelchairs may move toward the longitudinal axis of the magnetic field. The field also applies torque to metallic objects (e.g., surgical clips, orthopedic implants) within the patient; this force depends on the strength of the field, the mass and shape of the object, the field gradient, and anatomical considerations (e.g., anatomic location, degree of attachment, type of structures surrounding the object).[41]

Gradient Magnetic Fields

Rapidly changing, lower amplitude gradient magnetic fields are superimposed on the static magnetic field to gain spatial information. The gradient magnetic field produces different resonant frequencies of aligned protons in the tissues that allow spatial localization of bidimensional MRI slices and subsequently the

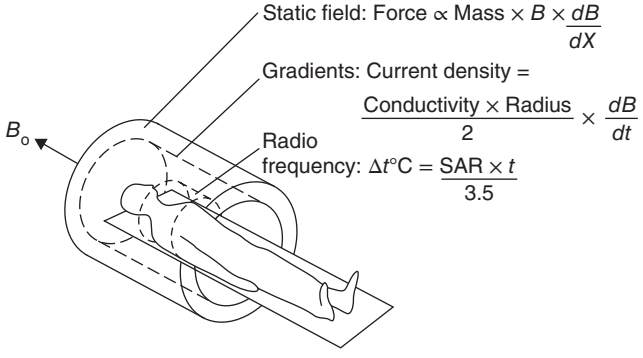


FIGURE 43.2. Three types of nonionizing radiation exposure during magnetic resonance imaging. (Budinger).[39] *Abbreviations:* B = static magnetic field strength; dB/dx = magnetic flux density; dB/dt = time-varying magnetic field gradient; SAR = specific absorbed power.

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reconstruction of three-dimensional images.[42] These gradient magnetic fields are switched on and off rapidly with varying maximum strengths depending on the particular pulse sequence and MR scanner; these imaging gradients are measured in units of milli-tesla/meter (mT/m). According to Faraday's law of induction, varying magnetic fields produce internal electrical currents in conductors (e.g., the human body) with the *potential* to stimulate nerves, muscles, and cardiac conduction. The frequencies of electric fields induced by these gradient magnetic fields (10–400 MHz) are substantially higher than the frequencies of fields created by movement in static fields (100–1,000 Hz). Modeling of the heterogeneous electric fields created by gradient magnetic fields indicates the largest electric fields occur in the periphery of the human body.[43]

Equation 43.1 describes the current density formed by time-varying gradient magnetic fields and the induced electric fields.

$$J = \rho \times r/2 \times \mathrm{dB/dt} \qquad \text{(Equation 43.1)}$$

where:

ρ = conductivity in siemens/meter,
J = current density in amperes/square meter,
r = radius of the loop in meters,
dB/dt = tesla/second.

The usual value of conductance (ρ) in the body is 0.2 siemens/meter (S/m), where the siemens is the reciprocal of an ohm. Using Equation 43.1, changes in the magnetic fields of 1 T/second induce current densities of 1 $\mu A/cm^2$ in the body. The estimated current density on the surface of the heart during a typical MRI scan is ~0.6 $\mu A/cm^2$.[44] A linear relationship exists between the rate of the varying magnetic field and the current density within a specifically shaped conducting body. Equations 43.2 and 43.3 estimate the relationship between varying magnetic field and current density in the human head and body.

$$\text{Human head: } 1\ \mathrm{T/second} \sim 0.01\ \mathrm{A/m^2} \qquad \text{(Equation 43.2)}$$

$$\text{Human body: } 1\ \mathrm{T/second} \simeq 0.015\ \mathrm{A/m^2} \qquad \text{(Equation 43.3)}$$

Radiofrequency Magnetic Fields

The radiofrequency electromagnetic radiation rotates the vector created by the static magnetic field with the time for the vector to return to equilibrium being different for each tissue. The subsequent two main imaging parameters (i.e., T_1, T_2) define image contrast created by different tissue properties. During an MRI examination, patients are typically exposed to electromagnetic radiation in the range of 8.5–340 MHz. This examination occurs in the "near-field" region; consequently, biological effects result from magnetic fields with little contribution from the electric field.[45] Exposure to RF radiation declines to insignificant levels outside the bore of the scanner. Thus, clinically significant RF exposure during MR scanning only involves the person inside the bore.

The air/surface interface reflects part of the radiofrequency (RF) radiation; the body absorbs the rest. The degree of penetration depends on the frequency of the radio waves. MRI devices operate in the range where relatively high absorption of energy occurs in the whole body (i.e., 20–300 MHz).[42] A 1 MHz wavelength penetrates 91 cm compared with 7 cm for a 100 MHz-radio wave. As a result of these properties, the skin receives the most exposure to radiofrequency radiation, whereas the subcutaneous tissue develops the greatest temperature elevation in response to currents induced by RF radiation. The primary consequence of the absorption of radiofrequency radiation is tissue heating. The specific absorption rate (SAR) is the mass normalized rate converting RF power to biological effect (local temperature elevation) defined by the total absorbed power in watts (W)/kg tissue. Thus, the SAR is the radiofrequency power absorbed per unit body mass. Equation 43.4 displays the approximate elevation in temperature/SAR.

$$\text{Change in Temp } (^\circ\mathrm{C}) = 0.29 \times (\mathrm{SAR} \times t) \qquad \text{(Equation 43.4)}$$

where:

SAR = specific absorbed power in watts (W/kg),
t = time in seconds.

All commercial MRI scanners have a display for the calculated SAR based on the patient's weight, static field strength (B_0), and scanner coil, assuming a standard RF pulse (rectangular pulse, 180° flip angle, 1 msec duration). Exceeding safety limits for SAR during an examination requires a reduction in the power deposition to the patient. Numerically simulated computer modeling of a 28-week gestation using 1.5 T and 3 T static magnetic fields indicated the mother received the highest local RF-induced heat (i.e., SAR) with the fetus receiving 40–60% of the peak SAR at 64 MHz and 50–70% at 127 MHz depending on the frequency, tissue mass used to average the local SAR, and the position of the mother relative to the magnetic coil.[46,47] The highest fetal SAR occurred in a limb; fetal movement complicates analysis of predicted maximum fetal SAR.

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DOSE EFFECT

The presence of multiple electromagnetic fields complicates the quantification of clinical effects, including exposure to static magnetic fields, varying magnetic fields, and radiofrequency radiation. Potential hazards resulting from the use of MRI scans include: 1) static magnetic forces and electric currents induced by movement in these fields, 2) current induced in patients by varying magnetic fields, and 3) heating from the absorption of radiofrequency radiation.

Static Magnetic Fields

Large turning torques may occur in metallic objects with static fields at strengths below 2 T, creating mechanical hazards depending on the ferromagnetic properties of the metallic object in the static magnetic field. Thermodynamic factors suggest that changes in the conformation of enzyme structure do not occur at body temperatures below field strengths of 10 T.[48] Magnetic torque in tissues can orient diamagnetic biofluids (e.g., collagen, fibrin) and cells (osteoblasts, Schwann cells) following the application of field strengths of 8 T.[49] No mutations (sister chromatid exchanges, gross lesions) or lethal effects were observed in human cells exposed to static magnetic fields with a strength of 1 T.[50,51] A double-blind randomized crossover study of 36 volunteers exposed to a 1.0 T static magnetic field and a 2.4 T/second time-varying magnetic field from a passively shielded 7 T MR scanner did not detect statistically significant differences on a neurocognitive battery of eight tests when compared with the sham condition.[52] Subtle differences in test scores on the Rivermead Behavioral Memory Test (long-term verbal memory), Functional Acuity Contrast Test (visual acuity), and reaction time occurred when comparing volunteers exposed to the static magnetic field and the stray, time-varying magnetic field with scores on the sham exposure with head movement. However, the test scores did not comport with any focalized neurocognitive domain.

Sensory Effects

Adverse health effects from static magnetic fields below 2 T are not well documented.[53,54,55] A survey of 11 volunteers exposed to static magnetic field levels of 4 T reported vertigo, nausea (but not vomiting), metallic taste, and transient flashing light (magnetophosphene) during the course of their exposure in the previous year.[56,57] The number of self-reported experiences was significantly different than experiences reported by volunteers exposed to 1.5 T; the occurrence of headaches, hiccups, tinnitus, and numbness was not associated with exposure to static magnetic fields in this study. In an experimental study of 21 subjects performing controlled movements in the stray field of a 7-T scanner, 12 subjects detected a metallic taste during a 1.5-second episode of head shaking in the anterior/posterior direction to the magnetic field, causing a dB/dt of 2.3 ± 0.3 T/second.[58] The sensation of a metallic taste did not correlate to the presence of dental fillings.

Magnetohydrodynamic Effects

Magnetic fields (magnetohydrodynamic effect) can retard the flow of electrically conductive fluids (e.g., blood); therefore, more pressure is necessary to push the blood through the vessels. The magnetohydrodynamic slowing of blood flow is relatively small (i.e., <5% during fields <10 T); however, theoretical models predict the reduction may exceed 10% in 15 T magnetic fields.[59] An observational study of 25 healthy volunteers exposed to a 9.4 T static magnetic field at 105.92 MHz did not detect a statistically significant change in vital signs compared with baseline values, except a slight increase in blood pressure with increasing field strength.[53] An observational study of 10 human subjects exposed for 1 hour to 8 T detected no changes in body temperature, heart rate, respiratory rate, systolic/diastolic blood pressure, or ECG comparing before and after values.[60] Positive deflections occurred on T-waves with smaller, variable oscillations in amplitude during application of an 8 T-static magnetic field. Based on animal experiments, theoretical calculations indicate blood pressures within vessels are not altered at 1.5 T; however, blood pressure increases in field strengths of 6 T and 10 T by ~10% and ~28%, respectively.[39]

Cardiac and Nerve Conduction

Magnetically induced voltage changes occur during pulsatile blood flow in the aorta, resulting in increased T-wave amplitude. Animal experiments indicate the threshold for changes in the T-wave on the electrocardiogram is 0.3 T. T-wave alterations increase with increasing field strength; however, these electrocardiographic alterations are not accompanied by physiological changes (e.g., dysrhythmias, reduction in blood pressure).[61] Theoretical models predict the leakage of induced electric fields and currents for the pulsatile aortic flow in static magnetic fields may exceed maximum values of 100 mA/m^2; however, this value is ~10% of the maximum endogenous current density

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in magnetic fields of 5 T.[59] Field strengths of 10–17 mT may close the magnetic reed switch on a demand pacemaker, converting the cardiac pacemaker to the asynchronous mode. Most patients can tolerate the change to asynchronous mode for short periods of time.

Nerve conduction is more sensitive to temperature than static magnetic fields; studies in squid-axon model suggest that field strengths of 100 T are necessary to significantly disrupt nerve conduction.[62] In a study of 25 healthy volunteers, neuropsychological testing was performed before and after exposure to an experimental protocol involving a mock (0 T) and a 9.4 T scanner. The tests included working memory (Letter Number Sequencing), information processing speed (Symbol Digit Modalities), immediate/delayed memory and learning (Hopkins Verbal Learning), sustained attention (Gordon Diagnostic System), and a 9-item Brief Fatigue Inventory. The study detected no decline in the neuropsychological tests attributable to exposure to the 9.4 T MRI machine.[53] In an observational study of 10 volunteers exposed to 8 T for 1 hour, cognitive function did not change comparing tests before and after exposure as measured by literal and sematic fluency tests, the Mini-Mental Status Examination, and grooved pegboard test.[60]

Gradient Magnetic Fields

Potentially significant biological effects from the formation of induction currents in the body include the following: 1) stimulation of visual sensation (magnetophosphene), 2) nerve stimulation, and 3) induction of ventricular fibrillation. The development of visual flashes depends on the rate of magnetic field changes and the duration of the field. The threshold for the occurrence of these flashes is 2–5 T/second. Magnetophosphenes occurred in human volunteers exposed to 1.3–1.6 T/second with a 2-msec rise time and a repetition rate of 15–30/seconds;[39] the pulse duration of field changes during an MRI is usually 0.2 seconds or less. The threshold for stimulating muscles is approximately 1 million times greater than the current densities produced by MRI scans; pulsed field of 10^4 T/second is necessary to stimulate peripheral nerves.[53]

Excitation of muscle-nerve preparations does not usually occur below magnetic field fluxes of 3 T/second regardless of the pulse duration of the field.[41] Animal experiments indicate current densities near the level (3 mA/cm^2) present in nerve action potentials are required to cause seizures.[63] The threshold for the induction of ventricular fibrillation depends on a number of factors, including amplitude, time duration, waveform, and frequency. The ventricular fibrillation threshold for the human heart is ~0.3 mA/cm^2 (3 A/m^2) at the most sensitive frequencies of 10–100 Hz; this level is ~3–4 orders of magnitude above the current densities produced by a typical MRI scan.[64] Stimulation of nerves and muscles would occur *before* the induction of ventricular fibrillation based on the large current densities in these peripherally located tissues in contrast to the deep central location of the heart.[35]

Radiofrequency Magnetic Fields

The amount of temperature elevation depends partly on the ability of the body to dissipate heat. The basal metabolic rate in humans is 1.5 W/kg; the metabolic rate increases to 15 W/kg during heavy exercise. Evaporation and radiation are the primary processes for heat dissipation from the body; therefore, environmental temperature and humidity are important factors for heat dissipation. Heating from RF radiation is not necessarily uniform; hot spots may develop, especially near surfaces with large radii (chest) and areas with sharp curvatures (axilla, groin).[39]

When compared with baseline, an observational study of six healthy volunteers exposed to a whole-body-averaged specific absorption rate (SAR) of 6.0 W/kg demonstrated statistically significant ($P < 0.05$) increases in heart rate, cutaneous blood flow, tympanic membrane temperature, and skin temperature in the chest, abdomen, upper arm, hand, and thigh.[65] However, none of these changes were physiologically significant. A 70-kg man dressed in pajamas can tolerate a SAR of 8 W/kg. During a 20-minute scan at this intensity, the core temperature rose by <1°C, while skin temperature and blood flow increased substantially.[66] No elevation in the temperature of a stomach probe occurred in a healthy, 88.5 kg, 178 cm tall patient during a 2-echo, 10-slice MRI scan at 25 MHz (0.6 T) that lasted 20 minutes.[39]

HISTOLOGY AND PATHOPHYSIOLOGY

MR Imaging

Minimal magnetic susceptibility and the absence of ferromagnetic components limit the adverse effects of MR imaging in normal human tissue.[56] The short mean free paths (i.e., ~1 Å) and collision times (10^{-12} seconds) of nerve and muscle tissues also minimize the effects of magnetic fields on currents in neuromuscular tissues. Each of the three types of magnetic fields involved with

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MR examination produces different biological effects and safety hazards. Static magnetic fields potentially affect tissues by a variety of mechanisms including: 1) motion-induced currents, 2) magnetic force, 3) effect of magnetic field on moving electrical charges (Lorentz force), 4) magnetic torque, and 5) magnetic field-dependent recombination of reactive radical electron pairs.[67] Translational attraction and torque caused by the static magnetic field create movement and/or dislodgment of ferromagnetic objects in and around the human body. Low frequency (i.e., <1 Hz) static magnetic fields close to the MRI scanner induce electrical current in workers moving near the MRI scanner.[68] The induced electrical currents from movement in these nonhomogeneous, static magnetic fields are associated with transient sensory effects. Currently, there is no evidence of cumulative tissue damage following repeated use of MR imaging.[69]

Clinically significant health effects from radiofrequency radiation primarily involve heat generated during RF exposure. Adverse, nonthermal, clinical effects (e.g., blood pressure, heart rate, oxygen saturation, body temperature) from RF radiation during MR imaging are not well described in the medical literature. The amount of heat retained by the body depends on physical factors (frequency, power, repetition time, applied pulse sequence) and biological factors (specific heat of tissue, tissue sensitivity, size of current loop, conductivity, local perfusion, ability to lose heat). Spin-echo techniques typically use larger radiofrequency pulses for the 90° and 180° manipulation of tissue magnetization, resulting in higher SAR than gradient-echo sequences, particularly fast spin-echo techniques; however, certain high-speed gradient-echo sequences (e.g., time-of-flight MR angiography) also produce relatively high SAR. Altering operating procedures (e.g., ↓ flip angles, fewer slices, increased time between high and low SAR acquisitions, reduced room temperature) decreases SAR with some reduction in image quality. The currents produced by RF radiation and the SAR are negligible in areas of the body located more than several cell widths from the exposed volume of tissue.[70] Far-field approximations do not accurately characterize the SAR in a body scanned by MRI because the wavelength of RF radiation is much greater than the distance between the RF coils and the patient.

Gadolinium-Based Contrast Agents

Gadolinium (Gd)-based contrast agents (GBCAs) are nonspecific extracellular contrast agents commonly administered to enhance MR images with >300 million doses administered since their introduction in 1988; reported acute adverse reaction rates are low (0.07–2.4%).[71] GBCAs contain the MRI-active gadolinium ion (Gd^{3+}) and a carrier molecule (chelating agent) that binds gadolinium to prevent the release of free Gd^{3+} ion. The latter free ion and Ca^{2+} are similar-sized, resulting in the potential for free Gd^{3+} to replace Ca^{2+} in Ca^{2+}-binding enzymes. Intravenous administration of Gd^{3+} during an MRI shortens T_1/T_2 relaxation times and improves tissue definition. Macrocyclic and linear GBCAs can be ionic, nonionic, nonspecific extracellular, and tissue-specific, depending on the chelating agent. As defined by the retention of Gd^{3+} ion within the complex, rodent studies indicate macrocyclic chelates are thermodynamically more stable than linear chelates; ionic linear chelates are more stable than nonionic linear chelates, with the lowest tissue retention occurring following the use of nonionic, macrocyclic agents (e.g., gadoteridol).[72] The kidneys almost exclusively excrete these contrast agents. In patients with renal dysfunction, disassociation of the gadolinium complex occurs due to the extended retention of these substances in the body. In an observational, prospective pilot study of urine samples from 13 healthy subjects receiving IV gadolinium, their urine gadolinium concentrations remained above the current reference standard for >50 days based on reference standards using healthy subjects without previous gadolinium administration.[73] Although gadolinium deposition may occur in the brain (dentate nucleus, globus pallidus) and bone tissue following use of GBCAs in patients with normal renal function, the form of the gadolinium (i.e., free vs. chelated) is unclear.[74]

CLINICAL RESPONSE

Medical Exposure

Clinically significant adverse physiological effects and cognitive dysfunction are not well-established for patients undergoing MR imaging in static magnetic fields from current MRI scanners (typically 0.15–3 T), except for movements of *in vivo* metallic foreign bodies and disruption of cardiac pacemaker activity. Limited clinical data on the health effects of high static magnetic fields (i.e., >7–8 T) from MRI scanners used in research also suggest minimal adverse effects on physiological or neurocognitive function.[75] Much higher magnetic fields (i.e., 25–50 T) have the potential to cause neuromuscular stimulation and disruption of enzymatic processes. Cutaneous reactions (edema, erythema, burns) may occur when the material in contact with the

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patient conducts excessive RF-induced heat to the skin, including analgesic patches, cardiorespiratory monitors, tattoos, wires, pulse oximeters, athletic/"tech" clothing containing metallic microfibers, or inadvertent contact with the MR bore or coil.[76,77] In the absence of contact with metal, conduction of current through a closed loop formed by body parts (e.g., trunk and hand) may cause skin injuries.

Sensory Effects

Sensory effects associated with patients in MRI machines include vertigo, nausea, headaches, metallic taste, and transient flickering lights (magnetophosphenes).[78] The transitory sensations reported in these patients are dose-related with some individual sensitivity; however, these symptoms typically disappear after exposure ceases. Anxiety and suggestibility confound the interpretation of the mild, subjective effect associated with MR imaging. In a small observational study, mild vertigo, slight nausea, and metallic taste were more often reported by volunteers undergoing MR imaging in a 4 T scanner than a 1.5 T machine.[79] Responses to symptoms questionnaires by 504 individuals undergoing imaging in a 7 T MRI scanner indicated ~10% of these subjects developed transient vertigo and a sensation of spatial disorientation (e.g., leaning).[80] Reports of nausea, metallic taste, and magnetophosphenes were much less common. A meta-analysis of studies from 1992–2007 on the effect of static magnetic fields on neurocognitive function (visual processing, reaction time, eye–hand coordination, working memory), sensory perception, and vital signs demonstrated some dizziness and vertigo, primarily with movement during static magnetic field gradient exposures, and some impairment of vision (near visual contrast sensitivity).[81] Magnetic field strengths varied from 1.5–8 T. Although the results for visual impairment were consistent in the three studies, analysis of the effect sizes for homogeneity of neurocognitive effects including the visual system indicated the results were heterogeneous. The study did not detect any effects on vital signs during exposure.

Claustrophobia

A common adverse effect associated with MRI scans is the development of anxiety when the patient enters the narrow tube and the surrounding magnet; loud noises created by the switching RF fields simultaneously occur. Frequently, the patient must stay in this enclosed area for long periods of time; claustrophobia may prevent the completion of the investigation. Anxiety correlates to the constrictive dimensions of the magnet, duration of the examination, noise level, and temperature in the immediate space of the patient.[82] A detailed discussion of the procedure before initiation of the MRI open bore machines helps alleviate anxiety.

Metallic Objects

The magnetic fields created during MRI scanning exert translational forces and torque on metallic objects (e.g., surgical clips, pacemakers, joint replacements, shrapnel) present inside the body, depending on the mass, shape, and ferromagnetic properties of the object. The induced ferromagnetism depends on the composition of the metal alloys used to manufacture the metallic object including surgical clips.[83] Intracranial surgical clips may rotate depending on the composition of the clips; however, heating of surgical clips by RF radiation and varying field gradients is minimal.[84] Experimental evidence and modeling suggest the thermal effects of RF magnetic fields on orthopedic implants (e.g., osteosynthetic plates) are small.[85] High (16–35%) nickel content, cobalt, and iron demonstrate strong ferromagnetism, whereas clips composed of titanium or tantalum possess little ferromagnetism.[86] Inadvertent placement of ferromagnetic objects (e.g., wheelchairs, oxygen tanks) may result in the creation of dangerous projectiles, depending on the ferromagnetic properties and the distance from the bore entrance. Metallic leads placed on the patient may cause burns during MRI examinations.

Acoustic Noise

Loud acoustic noises (i.e., knocking, tapping, twittering sounds) occur during the rapidly changing current pulses portion of the MRI sequence; the intensity and frequency depend on MR imaging parameters and sequences; reductions in the field of view, repetition time, slice thickness, and echo time increase the noise.[87] Although previously thought to result from gradient coil design, the noise probably results from eddy current-induced vibrations of metal structures (e.g., cryostat inner bore, radiofrequency body coil) in the MRI machine.[88] The induced acoustic noise is related to the pulse sequence and dose; however, the latter value does not increase exponentially. In a study of fast pulse sequences on 14 MRI machines with static field strengths of 0.2–3 T, noise levels varied from 82.5 ± 0.1 dBA (A-weighted decibels) for a 0.23 T-system to 118.4 ± 1.3 dBA for the 3 T-system.[89] The noise level varied along the z-direction with a maximum near the bore entrance; the noise level depended more on pulse sequence parameters (field

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of view, repetition time) than field strength. Permanent acoustic trauma does not usually occur below a threshold of 140 dB in adults; these values are substantially above the noise levels produced by current MRI machines. However, safety concerns dictate the use of ear protection despite this relatively high threshold. Observational reports suggest mild temporary hearing loss manifests as a temporary threshold shift of hearing (>15 dB at 1 frequency within a few minutes after imaging ceased) following MR imaging without ear protection.[90] All threshold changes returned to baseline within 15 minutes after MRI imaging ceased. A study of 35 patients undergoing head and neck MR imaging with 3 T-machines used pure tone audiometry in a variety of different frequencies before and after imaging lasting up to ~45 minutes.[91] No threshold changes of >10 dB occurred in the group; all patients used 3M™ earplugs for the duration of the procedure.

Pacemakers

Magnetic field strengths greater than 1 mT can close the magnetic reed switch, converting demand pacemakers to the asynchronous (nonsensing) mode.[92] The threshold power density required to inhibit a pacemaker is ~15 mW/cm^2. Some pacemakers have ferromagnetic components that respond to magnetic fields by developing torque; critical electronic components may respond to magnetic fields by exhibiting nonlinear output. Both effects may disrupt pacemaker operation. Patients with pacemakers should not undergo MRI scanning unless the pacemaker is resistant to the influence of magnetic fields.[21] The induced currents with pulse widths of <3 msec are well below the values required to cause ventricular fibrillation.[93] Some MRI-safe pacemakers and intracardiac defibrillators (ICDs) are now available in the commercial US market following US Food and Drug Administration approval.

Gadolinium

Acute adverse reactions are uncommon, primarily involving mild, immediate hypersensitivity reactions (rash, lightheadedness, pruritis), and physiological reactions (nausea, vomiting, headache, paresthesia, coldness/warmth, dizziness, injection site pain). More serious allergic reactions may occur (bronchospasm, laryngeal edema, hypotension, cardiac arrest). Rarely, these patients develop widespread progressive tissue fibrosis (nephrogenic systemic fibrosis, gadolinium-induced fibrosis) involving the skin, lungs, myocardium, and/or striated muscles.[94] Changes in practice patterns (e.g., ↓ doses, screening for significant renal disease, use of low-risk gadolinium agents) have substantially reduced the incidence of this disease.[95] Even in patients with normal renal function, some storage of gadolinium occurs in the bone and brain; however, the clinically significant consequences of this deposition remain poorly documented by well-designed clinical studies.[96,97] Although an anonymous online survey associated generalized sensory symptoms with exposure to gadolinium contrast agents,[98] lack of clinical data and potential selection bias limit interpretation of the clinical significance of these reports. The patients did not report signs of movement disorders characteristic of lesions in the globus pallidus and dentate nucleus where gadolinium deposits usually occur. Nephrogenic systemic fibrosis remains the only proven disease associated with gadolinium-based contrast agents with no conclusive evidence to support a causal relationship between gadolinium-based contrast agents and specific symptoms.[99] Chelating agents are not currently recommended for patients reporting symptoms following gadolinium-based contrast agent administration because of inadequate evidence of efficacy and potential adverse effects.[96]

Occupational Exposure

Movement in low-frequency, nonhomogeneous static magnetic fields near MRI scanners may cause transient sensory symptoms including headaches, metallic taste, dizziness, nausea, vertigo, and magnetophosphenes (brief flashing lights during rapid eye movement in the magnetic field). An observational study of 361 healthcare and research staff working with MRI scanners suggests symptoms related to switching gradient fields (e.g., paresthesia, muscle contractions, vomiting) occur rarely.[100] In 633 diaries, these workers reported 2 episodes of tingling and no episodes of vomiting or muscle contractions. Epidemiological studies have not established a causal relationship between long-term occupational exposure to these electromagnetic fields and adverse long-term health effects; however, many of these studies lack appropriate controls and adequate exposure data. The workers did report some dentalgia, metallic taste, nausea, and disorientation when working with large magnets. A health questionnaire and clinical tests did not detect differences between workers with prolonged exposure to field strengths up to 0.2 T and controls.[101] Russian surveys of workers exposed to much smaller static magnetic fields revealed a number of excess nonspecific signs and symptoms (fatigue, blurred vision, dizziness, anorexia, pruritus,

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insomnia, diaphoresis, hypertension, paraesthesia); however, these surveys were poorly controlled.[35]

Reproductive Abnormalities

No adverse effects of MRI scanning on the developing embryo have been documented; however, animal research suggests that chick embryos are very sensitive to heat; human data on pregnant women exposed to electromagnetic fields are limited. Observational studies suggest neural tube and facial defects may occur in mothers experiencing prolonged high fevers (>39°C for ≥24 hours).[102] These *theoretical* concerns led to recommendations that MRI scanning not be performed in the first trimester; however, if imaging is necessary for the protection of the mother, MRI is preferable to ionizing radiation (e.g., CT scan). An analysis of 1,421 questionnaires distributed to MRI technologists in the United States did not reveal any major reproductive hazards associated with work near an MRI; there was a slight, statistically nonsignificant increase in the miscarriage rate.[103]

DOSIMETRY

Hall-effect gauss meters can measure static fringe magnetic fields with 3-axis probes that have a resolution of 0.01 mT.[78] Low-frequency EMF (e.g., static/gradient fields) analysis involves the use of impedance or finite element methods, whereas higher-frequency radiofrequency fields require analysis by finite-difference, time-domain, or finite element methods.[67] No standardized technique accurately measures the complex, nonhomogeneous, static, and time-varying electromagnetic field in a human during MR imaging. Measurement of SAR requires a phantom containing tissue-equivalent material. A few types of personal dosimeters are available to measure static and gradient fields using a magnetic field probe calibrated to simultaneously record the magnetic flux density $B(x, y, z)$ with a 3-axis Hall sensor and 3 orthogonal coils to quantify the induced voltage from movements within the magnetic fields. Experimental data indicate a 20-T Hall probe displayed relatively small measurement errors (i.e., up to ±3%) in field strengths of 0.03–3 T with decreasing sensitivity as a result of the saturation effects in the Hall elements.[104] Relatively large error (i.e., ±15%) occurred in fields of >5 T. Although induced electric field or current density are potential measures of the electromagnetic field, the complexity of these measurements limits routine daily assessments.[16] Therefore, estimation of fields in the occupational environment usually requires the use of simulated numerical models; these methods typically require complex body models and long computational times. Commercial models are available depending on the frequency of the electromagnetic field (EMF).[105]

HEALTH SURVEILLANCE

Patients

Guidelines

Magnetic Fields

MRI scanning involves patient exposure to static magnetic fields, time-varying (switched gradient) magnetic fields, radiofrequency fields, and acoustic noise. The International Commission on Nonionizing Radiation Protection (ICNIRP) recommended guidelines on the use of MR imaging based on their review of the existing scientific evidence in 2004[106] with an update in 2009.[107] The biological effects most likely to occur from MR exposures include: 1) vertigo and nausea during movement in the static magnetic field; 2) discomfort and pain from time-varying-induced electric fields and currents causing neuromuscular stimulation; 3) heating of tissue from radiofrequency fields; and 4) acoustic noise from the expansion and compression of coil mountings in response to Lorentz forces-induced interactions between static magnetic fields and electric current flowing through the gradient magnetic coils. The ICNIRP recommends the following 3-tier approach: 1) normal operating mode in routine MR examination (≤4 T whole-body static magnetic field exposure); 2) controlled operating mode for MR examination outside the normal operating rate that may cause discomfort and/or adverse effects (≤8 T for static fields); and 3) experimental operating mode for exposures outside the controlled operating range that require special ethical approval (progressively cautious approach for static fields >8 T). For time-varying gradient magnetic fields, the ICNIRP set 80% of the median perception threshold of nerve stimulation for normal operations and 100% for controlled operations. The median perception threshold was based on nerve stimulation data defined by an empirical equation as noted in Equation 43.5.[106]

$$dB/dt = 20(1+0.36/\tau)\ \text{T/seconds} \qquad \text{(Equation 43.5)}$$

where:

τ = effective stimulus duration, (msec)
= peak-to-peak variations in B/maximum time derivative of B during time period

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The basic ICNIRP restrictions for radiofrequency exposure limit the rise in core body temperature to 0.5°C for normal operating mode (head, 38°C; torso, 39°C; extremities, 40°C) compared with 1°C rise for controlled mode (head, 38°C; torso, 39°C; extremities, 40°C) and >1°C for restricted mode (head, >38°C; torso, >39°C; extremities, >40°C).

The UK Health Protection Agency Radiation Protection Division (successor of the UK National Radiological Protection Board) reviewed the ICNIRP guidance.[93] Table 43.1 displays the recommended limits of the UK Health Protection Agency (HPA) for patients receiving an MRI scan.

Acoustic Noise

Acoustic noise is a potential risk to patients undergoing MR examination at operating static magnetic levels of >0.5 T. Recommended limits are typically based on chronic occupational noise exposures rather than the relatively short-term noise produced by MRI machines. Recommended hearing protection varies with different organizations. The ICNIRP recommends offering hearing protection to patients when noise levels exceed 80 dB(A) and using hearing protection when noise levels exceed 85 dB(A).[106] The HPA, the US FDA, and the American College of Radiology encourage ear protection for all patients undergoing MRI procedures and require ear protection when the sound pressures exceed 99 dB(A).[108] Headphones usually provide superior noise protection during these procedures. The US Food and Drug Administration (FDA) considers MRI machines nonsignificant risk devices based on a safety threshold of 8 T.[109]

Safety Issues

The use of MRI scans is relatively contraindicated in patients with electrically, magnetically, or mechanically activated implants (e.g., pacemakers, ear implants, metal-containing prosthetic heart valves, neurostimulators). Issues of concern include the risk of acoustic noise, certain ferromagnetic implants, claustrophobia, and the *possibility* of adverse effects during pregnancy. Patients usually wear site-supplied gowns with no metal fasteners and all metallic objects removed, if possible, to reduce the risk of thermal burns from material conduction by RF radiation. Electrically conductive designs, silver-impregnated clothing, and metallic threads potentially may cause thermal injuries during MRI scanning. MRI examinations in patients with large metallic implants should occur only if the results of the scan are highly important to the diagnosis or treatment of the patient; MRI examinations are contraindicated in patients with ferromagnetic aneurysm clips and certain metallic implants. Objects should be checked against lists of implants and materials tested for safety and compatibility with MR systems.

Magnetic translational and rotational forces potentially may move these implants. If discomfort in the area of the prosthesis develops during the scan, the scan should be stopped immediately. The presence of metallic foreign bodies near anatomically important areas (e.g., eye, large blood vessels, nerves) requires special attention, including consideration of alternate diagnostic modalities and the use of low-strength fields. Patients with hemostatic clips should not undergo MRI scanning within the first 2 months after surgery.[110]

TABLE 43.1. The UK Health Protection Agency proposed limits for static, time-varying (switched gradient), and radiofrequency fields during MRI procedures. In general, the speed of moving patients within the bore should be limited to reduce vertigo and nausea. Controlled operating mode signifies MRI examinations done with field strengths outside the normal limits for routine examinations because special medical circumstances justify the benefit of exceeding normal limits. Experimental operating mode represents field strengths above controlled operating mode; these procedures require the approval of an ethics committee. (Modified from Centre for Radiation, Chemical, and Environmental Hazards, Health Protection Agency).[93]

Guidance	Routine Operating Mode	Controlled Operating Mode	Experimental Operating Mode
Static field (*T*)	4	8	>8
Time-varying field[a]	80	100	120
Radiofrequency fields			
Core temperature rise (°C)	0.5	1	2
Temperature limits (°C)			
Head	38	38	39
Trunk	39	39	40
Limbs	40	40	41

[a] % of median perception threshold.

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Monitoring critically ill patients is difficult during MRI scanning. Most anesthetic equipment contains ferromagnetic parts. Nonferromagnetic transducers should be used to monitor cardiorespiratory functions. Distortion of the ECG from electromagnetic interactions with the ECG during MR scanning limits useful data. Current physiological monitoring devices, instruments, and pacemakers are more MR-compatible. The use of metallic leads to connect the body to external monitoring equipment during MR scanning may cause RF-induced skin burns. If resuscitation is necessary, the patient should be placed quickly on a nonmetallic stretcher and removed to an area beyond the 5 G line.[111] Electroconductive materials inside the bore require thermal insulation; as much as possible, the electrically conductive material should not directly contact the patient during imaging. The static fringe magnetic field near the magnets of the MR system may be strong enough to attract ferromagnetic objects; these metallic objects may become dangerous projectiles and should be removed from the examining room to eliminate the risk of traumatic injuries.

The American College of Radiology recommends a 4-zone model for MRI facilities including Zone I, entrance to the outpatient registration areas; Zone II, lockers, waiting room, and area for screening of previously unscreened MRI patients; Zone III, MRI control area accessible only to MRI personnel, and Zone IV, room housing the MR scanner.[112] Other than the patient undergoing MR imaging, the latter two zones are restricted to MRI personnel and required healthcare workers. All MRI patients undergoing nonemergent MR imaging should be screened twice for magnetically, electrically, and mechanically activated devices (pacemakers, cochlear implants, joint replacements), metal implants, shrapnel, tattoos, and permanently implanted eye shadow and body piercings by personnel trained to detect ferromagnetic material. Assessment of implants for magnetic field strength compatibility includes evaluation of device identification cards, medical records, manufacturer websites, online sources (www.MRIsafety.com), and handheld ferrous metal detection devices.[113]

Pregnancy

Although clinical data are limited on the reproductive outcomes of MRI examinations during pregnancy, MR imaging is an option for pregnant patients because the MRI uses nonionizing radiation and there is little clinical evidence of documents subsequent to reproductive abnormalities including after the administration of gadolinium contract media. The latter agents improve the contrast in MR images by lowering T_1 relaxation times to create better T_1-weighted signals during MR scanning.[114] In a retrospective, population-based cohort study of >1.4 million pregnancies in Ontario, Canada, the use of MRI during the first trimester of pregnancy (gestational weeks 2–14) was not associated with a statistically significant increased incidence of stillbirths and neonatal deaths, neoplasms, hearing loss, or congenital anomalies.[115] After adjustment using inverse probability weighting, the adjusted relative risk of stillbirths and neonatal deaths following maternal MRI was 1.68 (95% CI: 0.97–2.90), compared with an adjusted hazard ratio of 1.16 (95% CI: 0.96–1.40) for congenital anomalies. Pregnant patients may undergo MR scanning at any stage of pregnancy if risk–benefit analysis favors the MRI study based on the importance of the clinical information, the need to obtain the information during the pregnancy, and the inability to obtain the information by other, nonionizing techniques (e.g., ultrasound).

In contrast to ionizing diagnostic radiation, potential fetal risks from MR imaging are nonstochastic (teratogenic, acoustic-related fetal hearing loss) rather than teratogenic or carcinogenic. Clinical data are limited; a prospective cohort study of 26 pregnant women exposed to gadolinium derivatives during their first trimester did not demonstrate adverse effect on pregnancy and neonatal outcome.[116] In the large Canadian cohort study, the use of gadolinium-enhanced MRI was associated with a higher risk of stillbirth or neonatal deaths and rare adverse outcomes in offspring (i.e., broad set of rheumatological, inflammatory, or infiltrative skin conditions); however, the confidence limits were large. The adjusted relative risk for stillbirths/neonatal death was 3.70 (95% CI: 1.55–8.85), whereas the adjusted hazard ratio for the rare nephrogenic systemic fibrosis-like conditions was 1.00 (95% CI: 0.33–3.02). The incidence of congenital anomalies was not increased in the gadolinium group. Although currently there is no evidence that the electromagnetic fields associated with MRI scans adversely affect human development, *in vivo* studies and theoretical predictions suggest the *possibility* of adverse fetal effects because heat is a potential teratogen.[117] Therefore, MRI scans should be performed during the first trimester of pregnancy only when a clear medical indication exists and when alterative imaging procedures are not appropriate.

Animal studies indicate repeated, supra-clinical doses of gadolinium contrast agents cause skeletal and visceral abnormalities, growth retardation, and fetal loss (US FDA category C).[118] Adverse reactions to the administration of gadolinium contrast agents are uncommon; the main adverse reactions during MR examinations include nausea, urticaria, taste disturbances, anaphylactoid reactions.[119] In patients with

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renal insufficiency, nephrogenic systemic fibrosis is a serious late sequelae of gadolinium administration, and is characterized by dermal thickening, induration, subcutaneous edema, joint contractures, and limited mobility primarily in the extremities.[120] The presence of gynecological devices (e.g., intrauterine devices) is not a contraindication for women undergoing MR imaging in static fields of ≤3 T.[121]

Currently, there are no reports confirming adverse reactions in infants breastfed by mothers receiving gadolinium-based contrast agents; however, the use of these contrast agents is controversial because gadolinium is water-soluble and crosses the placenta. The European Medicines Agency suggests interrupting breastfeeding for >24 hours after receiving gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA).[122] The American College of Obstetricians and Gynecologists does not recommend interruption of breastfeeding after maternal gadolinium administration based on the small amount of gadolinium absorbed by the fetus (i.e., 0.0004% of the maternal dose) and the lack of reported adverse effects.[123] In a study of 16 radiopharmaceuticals (^{99m}Tc-DTPA, ^{99m}Tc-HMPAP-leucocytes, ^{99m}Tc-MAA, ^{99m}Tc-MAG3, ^{99m}Tc-MDP, ^{99m}Tc-MIBI, ^{99m}Tc-pertechnetate, ^{99m}Tc-*in vivo* RBC, and ^{99m}Tc-tetrofosmin; ^{14}C-GCA, ^{14}C-triolein, ^{18}F-FDG, ^{51}Cr-EDTA, ^{125}I-iodohippurate, ^{131}I-iodohippurate, ^{131}I-NaI) administered to 53 breastfeeding patients, the total fraction of administered activity excreted in breast milk varied from 0.0057% (^{99m}Tc-*in vivo* RBC) to 48% (^{131}I-NaI).[124] Based on an effective dose limit of 1 mSv for infants, cessation of breastfeeding following ^{131}I-NaI administration and interruption of breastfeeding for 12 hours after radiopharmaceutical administration were recommended for ^{125}I-iodohippurate, ^{131}I-iodohippurate, and ^{99m}Tc-pertechnetate. Interruption of breastfeeding for the remaining radiopharmaceuticals was not recommended.

Workplace

Occupational exposure during MR scanning primarily involves static magnetic fields (B_0); in addition to fringe B_0 fields within 0.5 m of the bore entrance, the possibility of exposure to switched gradient magnetic fields (dB/dt) exceeding current reference levels may occur if the worker stays close to the scanner during image acquisition.[78] Maximum dB/dt exposure occurs as the radiographer undergoes a fast translational or bending motion near the magnet bore inner edges.[125] B_0, dB/dt, and B_1 rapidly decrease with distance from the bore entrance. Guidelines for occupational exposure to electric fields frequently use values expressed as the root mean square (RMS). The RMS value of time-varying functions (e.g., dB/dt, B_1) is the square root of the mean values of the function squared [i.e., $\sqrt{(x_1)^2 + (x_2)^2 + (x_3)^2 + \cdots + (x_n)^2/n}$].

Exposure

During traditional diagnostic MR examination, the staff typically is exposed only to static magnetic fields for a short duration while positioning the patient.[126] Exposures to gradient or radiofrequency fields occur only if patient care requires the staff to remain in the MR room during scanning. The exception is interventional radiographers treating patients in the scanner room during imaging; these staff are potentially exposed to gradient fields exceeding induced current density guidelines. However, static magnetic and radiofrequency field guidelines are usually not exceeded. Wide variation in static field exposures of radiographers in clinical MR units occurs between individuals and various sessions depending on workplace activities, scanning parameters, personal characteristics (e.g., height), and field strengths. Peak and time-weighted average (TWA) exposures in a study of 324 observations of 224 workers increased by 30–76% per 1 T-increase in the static field strength near a whole-body, closed-bore scanner, varying with exposure parameters listed above.[127] In a study of 19 radiographers using a 1.5 T MRI machine over 91 days at 4 clinical units, the mean 24-hour time-averaged static field strength was 1.8 ± 1.0 mT with a range of 0.2–6.6 mT.[128] The maximum static field strength during patient setup was 554 mT. Time-varying gradient field strength potentially exceeded ICNIRP action values up to 30 cm from the bore entrance. In a study of engineers monitored with personal dosimeters during the testing and optimization of 3 MRI systems (1.5 T and 3.0 T cylindrical whole-body scanners, 1.0 T whole body open system), peak exposures ranged from 277–944 mT/second for the 1.5 T closed system with a TWA of 1.48–44.63 mT compared with 187–3,975 mT/second for the 3.0 T closed system with a TWA of 1.23–33.52 mT.[105] The 1.5 T open system had peak exposures ranging from 54–504 mT with a TWA of 1.61–36.00. Table 43.2 lists the common ranges of magnetic field properties during the operation of the MRI machine. Occupational exposure to static fringe field gradients occurs when MR workers move in the field close (i.e., 0.5 m) to the bore during scanning including MRI guided interventional procedures (e.g., biopsies), particularly in open bore machines. Usually, MRI technologists spend only approximately 10% of their work

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TABLE 43.2. Characteristic ranges of exposures to magnetic fields during MR imaging procedures. (Adapted from McRobbie).[78]

Field (Location)	Range	Frequency	Duration
Static[a]	0.2–7 T	0 Hz	Continuous
Fringe static[b]	0–25 T/m	0 Hz	Continuous. Movement within field simulates slow, time-varying field
Imaging gradients[a]	0–50 mT/m	0–>10 kHz	Intermittent multiple trapezoidal pulses lasting few msec and repeated rapidly up to 200 T/m-second. 0.1–1 msec rise time
Radiofrequency[a]	0–0.5 mT	8–300 MHz	Amplitude-modulated pulses lasting few msec with low repetition rate

[a] Inside bore, [b] Adjacent to bore.

time in the magnet room, while the rest of their time is spent in the control room or in adjacent work areas. ICNIRP reference levels are rarely exceeded outside the bore; however, movement-related exposures (e.g., monitoring general anesthesia, MRI-guided interventional procedures) may exceed ICNIRP low-frequency reference levels, particularly with motions of 1 m/second within 0.5–1 m from the magnet.[78,129]

A study of six Neonatal Intensive Care Unit (NICU) nurses using personal dosimeters demonstrated a geometric mean for the 12-hour shift-time-weighted average magnetic field exposure of 0.17 μT compared with 0.11 μT for six other neonatal nurses in the normal newborn nursery.[130] The NICU nurses had a greater portion of their shift time exposed to magnetic fields of >0.4 μT compared with nurses in the normal newborn nursery. In a study of an Italian NICU, the typical magnetic flux density (50 Hz) in the rooms of the unit was <0.2 μT, whereas higher values occurred close to medical equipment and inside the open infant warming systems.[131]

Guidelines

The limits and reference levels currently proposed by various organizations display large variations as a result of the application of different methodologies, including the values promoted by the International Commission on Nonionizing Radiation Protection (ICNIRP), the International Electrotechnical Commission (IEC), the Institute of Electrical and Electronics Engineers (IEEE), and the UK Health Protection Agency Radiation Protection Division (successor of the UK National Radiological Protection Board). The goal of the basic restrictions typically is the avoidance of short-term, acute adverse effects defined by induced electric field (E_i), using the root mean square (rms) value as the statistical measure of the magnitude of the varying electric field. Induced fields are not directly measurable in the body.

Static Magnetic Fields

In 1991, the National Radiological Protection Board (predecessor of the UK Health Protection Agency Radiation Protection Division) established a 2-tier standard based on a lower safe level and a higher level where exposure should occur only under controlled conditions by knowledgeable workers trained to recognize and minimize any health risks.[132] These recommendations were initially based on the prevention of nausea, vertigo, decreased aortic blood flow, and elevated systolic blood pressure at static magnetic field strengths above 4 T. The NRPB revised the guidelines in 2004 to recommend a whole-body, time-weighted average exposure of 0.2 T (e.g., 32 minutes for 3 T exposure, 64 minutes at 1.5 T), an instantaneous ceiling limit of 2 T for the trunk/head, and 5 T ceiling for limbs.[133] The ICNIRP recommends a 2 T ceiling, but the guidelines allow peak exposures up to 8 T in controlled situations where trained workers can avoid adverse effects by altering work practices.[134] Table 43.3 lists the ICNIRP guidelines for exposure of workers and the general public to static magnetic fields as a means to reduce adverse sensory effects from movement in the static and fringe magnetic fields. The 0.4 T limit for the general public is below the 0.5 mT limit for protection of medical devices against flying metal objects with ferromagnetic properties sufficient to produce substantial mechanical forces in static magnetic fields. Caution is also required for workers wearing implanted ferromagnetic or electronic medical devices (pacemaker/defibrillators, insulin infusion pumps, neuromuscular stimulators, operated prosthetic devices for limbs and inner ear), particularly when the static magnetic field exceeds 0.5 mT.

Static Fringe Magnetic Fields

Movement in static fringe fields induces fields within tissues that vary with speed of movement, induced electric field, and frequency. Exposure limits are designed to avoid sensory effects resulting from the induced electric fields and the subsequent induction of electric currents

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TABLE 43.3. International Commission on Nonionizing Radiation Protection (ICNIRP) guidelines for exposure to static electromagnetic fields. (Adapted from International Commission on Nonionizing Radiation Protection).[134]

Exposure Limit (Location)	Type of Exposure	Value (Magnetic Flux Density, T)
Occupational – head/trunk	Spatial peak	2 T[a]
Occupational – limbs	Spatial peak	8 T[b]
General public–any part of the body	Continuous	0.4 T

[a] Exposure up to 8 T can be justified for specific work if the environment is controlled and appropriate work practices are implemented to control movement-induced effects. [b] Inadequate information is available to recommend exposure limits >8 T.

TABLE 43.4. Exposure limits for low-frequency occupational exposure from movement in static and fringe fields as expressed in peak values. (Adapted from McRobbie).[78]

Institution	Region, Induced Fields	Frequency (Hz), Induced Fields	Induced E_i, Induced Fields (V/m)	Reference Level (Equivalent dB/dt, T/Second)
NRPB[a]	Head/trunk	<1	0.56	1.8 f (range 0–1 Hz) Peak B = 280 mT
ICNIRP	Head, CNS	1–10	0.7/f	1.8/f with range 1–8 Hz Peak B = 280 mT/f
	All head/body	1–3,000	1.1	

[a] The value is converted to induced electric field from the values published as current densities by assuming CNS conductivity is 0.1 S/m and $J = 40\,\text{mA/m}^2$; f = frequency in Hz.

in the body. Table 43.4 compares the exposure limits of the NRPB and the ICNIRP for low-frequency occupational exposure to induced electric fields resulting from movement in static magnetic fields.

Time-Varying Gradient Fields <100 kHz

The guidelines are designed to prevent the stimulation of neuromuscular units by the induction of currents in the central and peripheral nervous systems (and other excitable tissues) from time-varying magnetic fields. The basis for ICNIRP values is their analysis of data from experimental visual phosphenes studies and MRI studies on peripheral nerve stimulation thresholds.[135,136] Table 43.5 compares NRCP and ICNIRP guidelines for MRI imaging gradients. The ICNIRP value of 2.6 T/second for frequency ranges of 300–3,000 is most relevant to certain fast MRI sequences; ICNIRP peak values apply to CNS tissues in the head and any tissue in controlled situations.

Radiofrequency Fields

The basic ICNIRP (and IEEE) restrictions use whole-body SAR of 0.4 W/kg as a time-weighted average for 6 minutes; this value is 10% of the suggested limit to avoid body temperature elevations exceeding 1°C from RF magnetic field-induced heating. Most accidental burns from RF radiation result from hot spots caused by conducting material close to the person; compliance with average whole-body SAR does not necessarily guarantee the absence of hot spots. Table 43.6 displays the ICNIRP occupational exposure limits to MR imaging gradients.

Pregnancy

Pregnant healthcare practitioners may work throughout all stages of their pregnancy in and around the MR environment during archiving, injecting contrast, emergency treatment, and positioning patients prior to examination. In a survey of 280 MR-exposed technologists and nurses, the relative risk ratio for spontaneous abortions in exposed workers compared with controls (employees at other jobs) was 1.27 (95% CI: 0.92–1.77).[137] The relative risk (RR) for delivery before 39 weeks was 1.19 (95% CI: 0.76–1.88), whereas the RR was 1.01 (95% CI: 0.50–2.04) for birth weight of <2.5 kg. Adjustment for maternal age, smoking, and alcohol use did not markedly change any of these values. Although allowing pregnant workers around MRI scanners is permissible, they should not usually remain in the scanning room during data acquisition or scanning.

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TABLE 43.5. Occupational exposure limits for time-varying gradient fields as expressed in peak values. (Adapted from McRobbie).[78]

Institution	Region, Induced Fields	Frequency (Hz), Induced Fields	Induced E_i, Induced Fields (V/m)	Reference Level (Equivalent dB/dt, T/Second)
NRPB[a]	Head/trunk	4–1,000	0.28	0.22 (range 25–820 Hz).
				Peak $B = 35/f$ mT as peak spatial average over body
		1,000–100,000	$f/14{,}000$[b]	$0.00027f$ (range 820–65,000 Hz).
				Peak $B = 0.043$ mT as peak spatial average over body
ICNIRP	CNS head	25–400	$0.0028f$	0.0088 (range 25–300 Hz).
				Peak $B = 1.4$ mT as peak spatial average over body
		400–3,000	1.1	2.6 (range 300–3,000 Hz).
				Peak $B = 420/f$ mT as peak spatial average over body
	Everyone in controlled environment	1–3,000	1.1	—

Abbreviations: E_i = electric field strength measured by the arithmetic average as determined over a straight line segment of 0.5 cm length oriented in any direction within the tissue, ICNIRP = International Commission on Non-Ionizing Radiation Protection, NRPB = National Radiological Protection Board.

[a] The value is converted to induced electric field from the values published as current densities by assuming CNS conductivity is 0.1 S/m and $J = 40$ mA/m^2. [b] f = frequency in Hz.

TABLE 43.6. International Commission on Nonionizing Radiation Protection (ICNIRP) radiofrequency limits applicable for occupational exposure to MRI machines imaging gradients. The values are averaged over 6 minutes. (McRobbie).[78]

Exposure Limit	Value
Basic restriction	
SAR (10–400 MHz)	0.4 W/kg
	10 W/kg localized over 10 g head/trunk tissue
	20 W/kg localized over 10 g limb tissue
Reference levels	
Electric field strength (E)	61 V/m
Magnetic field strength (H)	0.16 A/m
Magnetic flux density (B)	0.2 μT
Power density	10 W/m^2

ULTRASOUND

Diagnostic ultrasound provides a pulsed wave instead of the continuous wave produced by therapeutic ultrasound (diathermy). Unlike diathermy, diagnostic ultrasound does not increase tissue temperature or alter local circulation through the transformation of the ultrasound waves into thermal energy. The ability of diagnostic ultrasound to provide low-cost imaging without ionizing radiation has profoundly impacted the practice of medicine. The introduction of real-time gray-scale ultrasound improved the anatomical imaging of the fetus and expanded the application of abdominal and pelvic ultrasound. Ultrasound is the initial imaging technique of choice for the kidney, liver, abdomen, pelvis, and fetus.[20] The coupling of gray-scale and Doppler in an imaging technique (duplex Doppler) allows the simultaneous imaging of anatomical detail and circulatory physiology; this technology is particularly useful for scanning shunts, valvular dysfunction, and deep vein thrombosis of the extremities.[138] Color coding of blood flow superimposed on real-time ultrasonic gray-scale images of the vessels and organs permits the imaging of flow, turbulence, and velocity in the vessels. Ultrasound does not produce tissue ionization; consequently, the use of ultrasound presents minimal to no risk to the fetus and mother.[139,140] Randomized controlled clinical trials of mothers scanned with ultrasound confirm that ultrasound carries little risk.[141,142]

PHYSICAL PROPERTIES

Ultrasound Waves

Ultrasound is the mechanical vibration produced by a source (transducer) and propagated through a medium (e.g., the body). The primary component of modern transducers is zirconate titanate (PZT); these devices

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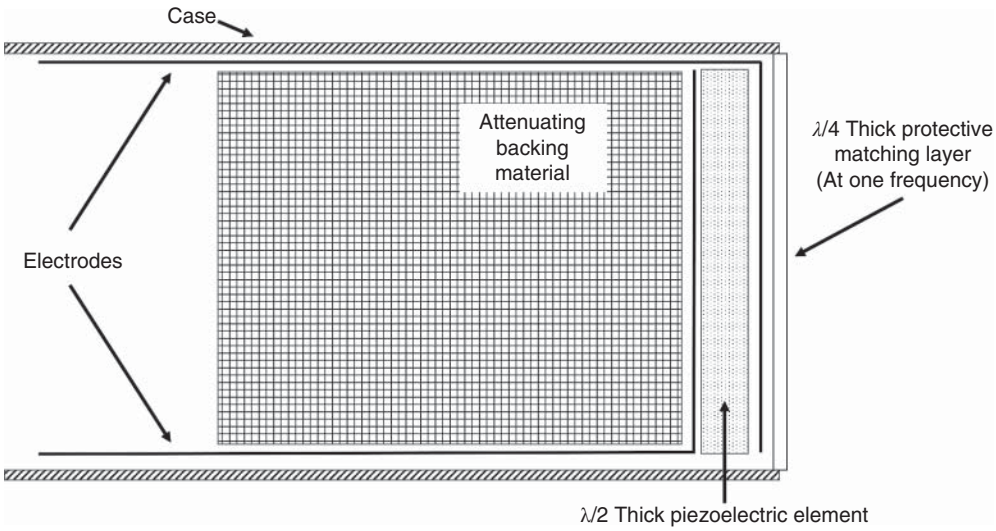


FIGURE 43.3. Ultrasound transducer construction. The transducer design incorporates a piezoelectric element thickness that resonates mechanically at the frequency (λ) of interest (i.e., $\lambda/2$). Transducers have a case for insulation from electrical interference and a wire to receive and transmit electrical inputs/outputs to the ultrasound machine. After the electrodes are attached, a case surrounds the transducer and a protective (matching) layer is attached in front of the piezoelectric crystal. Optimization of the transmission and reception of a particular frequency is maximized when the thickness of the matching layer is $\lambda/4$. The matching layer and ultrasound gel improve transmission between the patient's skin and the piezoelectric crystal by reducing the amount of reflection at this interface. The backing material shortens the spatial pulse length and improves axial resolution. Continuous-wave transducers do not require backing material. (Adapted from Chivers).[143]

convert electrical signals into ultrasonic vibrations. Figure 43.3 illustrates the design of a piezoelectric transducer. Ultrasound contains mechanical vibrations above the limit of human hearing (i.e., 0.02 MHz). Although ultrasound frequencies can be detected up to 1,000 MHz, most diagnostic ultrasound uses frequencies in the range of 2–10 MHz. In the receiving mode, ultrasound waves reflected from the body compress the surface of the crystal in the transducer; these physical alterations produce voltage changes displayed on an oscilloscope. The piezoelectric effect is the physical property describing the voltage changes resulting from the physical distortion of the crystal, as noted in Figure 43.4. The reverse piezoelectric effect occurs when the application of voltage to the crystal produces ultrasound waves. The propagation of ultrasound through the tissue depends on absorption, reflection, scattering, and refraction of the sound wave in the tissue.

Amplitude

Amplitude is the height of the sound wave; this parameter is proportional to the pressure in the tissue created by the sound wave. The voltage in the transducer reflects the amplitude of the sound wave from the piezoelectric effect within the crystal.

Intensity

Intensity (I) is the amount of energy passing per second through a specific area located perpendicular to the direction of the wave. The normal units of intensity are W/m^2 or mW/cm^2. The intensity of the ultrasound wave is a function of the square of the pressure of the wave; the intensity is a useful way to quantify the potential for damage to the tissue. Measures of intensity include temporal peak, pulsed average, and temporal average. The temporal average intensity (I_{TA}) measures many cycles, whereas the pulse average intensity (I_{PA}) averages only during the pulse, ignoring the rest of the cycle. The temporal peak intensity (I_{TP}) is the maximum instantaneous value corresponding to the peak value. The spatial average-temporal average intensity (I_{SATA}) is the intensity averaged over the time of the scan and the area of the beam. The temporal peak intensity (I_{TP}) is the maximum intensity during the pulse; the spatial peak intensity (I_{SP}) is the maximum intensity found across the beam. The symbol for the peak value over the area of the beam and the duration of the pulse is I_{SPTP}. The most common measure of the dose of ultrasound is the spatial peak-temporal average (I_{SPTA}). Figure 43.5 demonstrates the parameters used to describe the intensity of the ultrasound waves.

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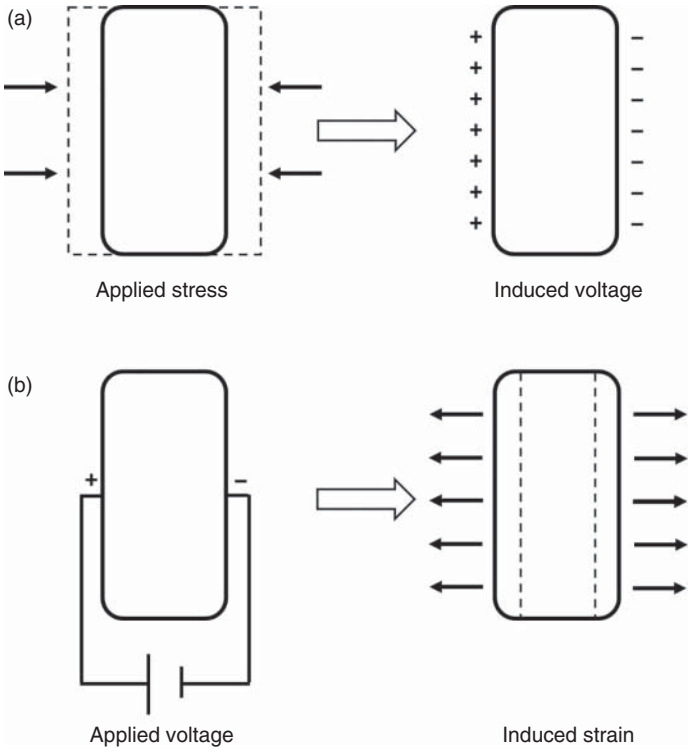


FIGURE 43.4. Schematic representation of the physical effects of applying voltage to a piezoelectric crystal. (a) piezoelectric effect resulting from applying voltage; (b) inverse piezoelectric effect when voltage ceases and crystal returns to the normal dimension. (Adapted from Lerski).[144] Mechanical stress to a piezoelectric material produces an electric field, whereas mechanical strain to a piezoelectric material causes electric displacement.

Resolution

X-ray images demonstrate better anatomical detail than ultrasound images. Axial resolution is the ability to resolve two interfaces directly in line with the ultrasound beam from the transducer. The axial or longitudinal resolution of ultrasound depends on pulse length, amplification, and frequency.[145] Axial resolution worsens as the beam penetrates the body because the tissues attenuate high-frequency portions of the pulse. The shortest resolution of a transducer is 3 wavelengths (3 λ). Higher frequencies deliver better resolution because the shortest, obtainable pulse duration is ~1 wave. Equation 43.6 describes the relationship of wavelength to velocity and frequency.

$$\text{Wavelength } (\lambda) = \text{velocity } (v)/\text{frequency } (f). \quad \text{(Equation 43.6)}$$

Consequently, a 2 MHz transducer has a wavelength of 0.77 mm; the resolution is 2.31 mm (i.e., three times the wavelength). Similarly, a 10 MHz transducer has a wavelength of 0.154 mm and a resolution of 0.462 mm. The velocity of ultrasound in most soft tissue is 1,540 m/second, whereas the velocity of ultrasound in the skull is 4,080 m/second.[145] Ultrasound waves transmit poorly in air (i.e., 330 m/second). Higher frequencies produce shorter wavelengths and greater axial resolution. Lateral resolution is the ability to detect adjacent tissues and depends on the size of the transducer aperture.[146] A larger transducer permits greater lateral resolution near the surface; however, the large transducer produces worse lateral resolution at greater depth.

EXPOSURE

Uses

Obstetrical ultrasound monitors the development and health of the fetus. During the first trimester, detection of the fetal heartbeat confirms pregnancy, whereas ultrasound during the second and third trimesters follows anatomical development. Healthy pregnant mothers typically receive two ultrasounds during the first and second trimesters of their pregnancy. The first trimester ultrasound between gestational weeks 11–14 confirms viability while screening for Down's syndrome and other serious genetic defects including severe cardiac

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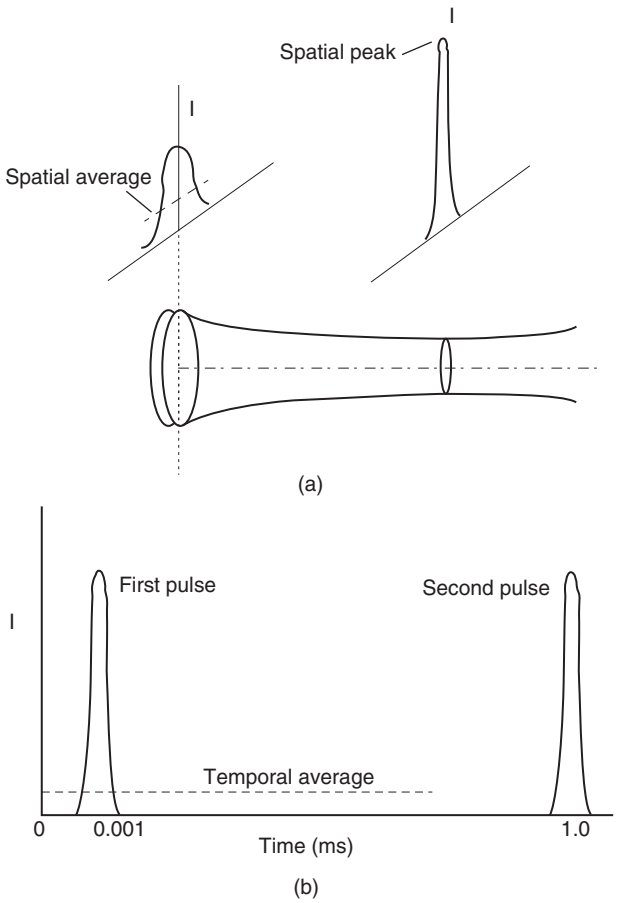


FIGURE 43.5. Parameters useful to describe the intensity of ultrasound power include the following: (a) Sound intensity across the beam near the tip of transducer at the position of focus shown. The intensity of the beam increases from the periphery to the center of the beam. The spatial peak intensity (I, mW/cm^2) is the highest intensity in the beam, typically on the axis at the focus. (a) The spatial average intensity (total power output/beam area) reflects the intensity spread evenly across the beam. (b) The intensity of the beam varies with time. The temporal peak intensity is the peak value, whereas the temporal average intensity reflects the average intensity over the whole cycle. Consequently, the latter value is much lower than the temporal peak intensity. (Adapted from Lerski).[144]

abnormalities.[147] Screening for fetal anomalies typically occurs at 18–20-week gestation, when the fetal anatomy is well visualized and the biparietal diameter provides an accurate measure of gestational age (i.e., within 9 days).[148]

Since the 1950s, physical therapy applications of ultrasound for therapeutic purposes have included treatment of musculoskeletal problems (e.g., tendinitis, bursitis) with low-power ultrasound in the 1-MHz range.[149] The use of high-pressure-amplitude shockwaves with the use of fluoroscopy and X-rays to focus the shock waves on the kidney stone began in the 1980s. Subsequently, the therapeutic use of ultrasound expanded to include cataract removal (phacoemulsification), ablation of uterine fibroids, transdermal drug delivery, acceleration of bone fracture/nonunion repair, and tissue cutting and hemostasis. Therapeutic ultrasound typically uses longer duration of heating with unfocused beams or higher intensities with focused beams. The latter is effective for ablation, whereas the former includes physical therapy applications to highly absorbing tissues (e.g., tendons, bones). Microbubble ultrasound contrast agents are routinely used in echocardiography for ventricular opacification and delineation of endocardial borders; the high compressibility of these microbubbles produces large impedance contrast with surrounding tissue and generation of nonlinear echoes that distinguish microbubbles containing fluid from tissue.

Equipment

Ultrasound utilizes a pulse-echo technique that uses energy **reflected** from the source to produce medical images, in contrast to CT scans that form images from the conversion of **transmitted** energy. For diagnostic ultrasound, the piezoelectric ceramic crystal produces very short, 1–5 cycle pulses characterized by a center frequency of the pulses ranging from 2–12 MHz. The ultrasound transducer operates as a transmitter and receiver of sound energy. Typically, the transducer emits sound energy for <1% of the duty cycle, while the transducer is either "listening" or "off" during the rest of the cycle. Most ultrasound machines produce a pulse repetition frequency of 500–3,000 pulses/second.[145] The application of 1–300 V over 1 microsecond (μsec) to the transducer emits a pulse of ultrasound waves that are quickly damped. The resultant pulse lasts 5–6 μsec with the remainder of the cycle recording echoes and processing data. Figure 43.6 displays the time sequence of a 1-millisecond (msec) pulse from the transducer of an ultrasound machine. The quiet period with no echoes prior to the next pulse accounts for the majority of the 1-msec pulse.

Modes of ultrasound include A (amplitude), B (brightness), M (motion), and D (Doppler). The latter Doppler mode includes duplex, continuous wave, pulsed wave, color, and power. Figure 43.7 displays the differences in the ultrasound signal from an artery using A-, B-, and M-modes. Pulsed mode ultrasound includes B-mode, M-mode, color flow Doppler, and pulsed wave (i.e., pulsed spectral) Doppler. Continuous wave Doppler, pulsed wave Doppler, and M-mode are nonscanning modes that involve a fixed ultrasound beam

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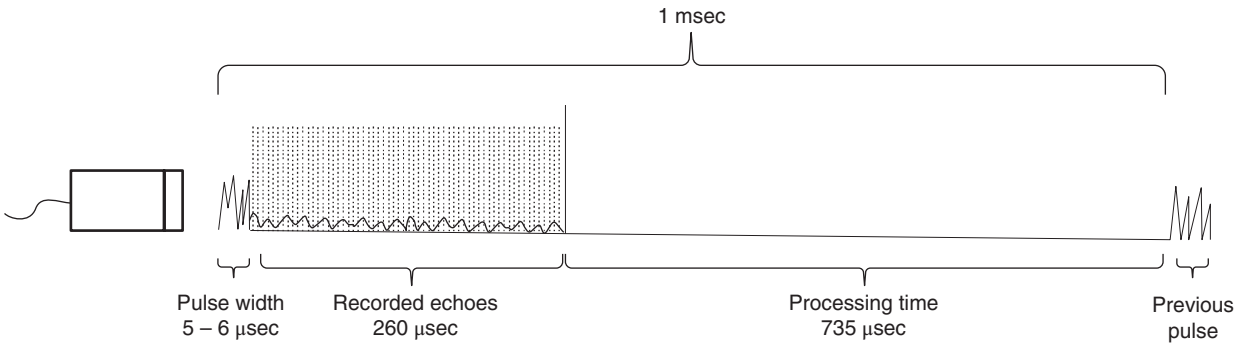


FIGURE 43.6. Pulse intensity during a 1-ms duty cycle. Processing time with no echoes returning to the transducer accounts for most of the duty cycle. (Sarti).[145]

in space unless moved manually, whereas color flow Doppler and B-mode are automatic scanning modes that use a mechanical or electronically controlled ultrasound beam.

Doppler modes potentially deliver higher energies than B- or M-modes because of the higher outputs necessary to detect frequency shifts required for Doppler images. The power of ultrasound machines increased substantially over the two decades after the FDA increased the maximum spatial-peak temporal-average intensity to 720 mW/cm^2 in 1991, particularly for fetal applications. In a study of 124 regulatory submissions to the US Food and Drug Administration for transducers indicated for diagnostic fetal imaging from 1984–2010, the ultrasound power output increased approximately by one order of magnitude, while the average center frequency decreased by 4.2–3.4 MHz. Table 43.7 displays the changes in ultrasound output parameters submitted to the US FDA from this study.[150]

A(Amplitude)-Mode

The A-mode was the first type of ultrasound used for clinical purposes (e.g., evaluation of midline shifts in the brain); the amplitude mode reflects the depth of a structure below the surface of the skin, reflected as a two-dimensional waveform with variations (e.g., peaks) at the interface of two different tissues. On the oscilloscope, the *x*-axis measures depth from the surface, whereas the *y*-axis measures the signal information. In A-mode, the transducer is placed on the surface of the skin with a coupling agent (gel, oil); no scanning motion occurs. This mode is primarily of historical interest, except for some applications in ophthalmology.

B(Brightness)-Mode

B-mode provides information on depth and position by producing a two-dimensional, cross-sectional view of the examined tissue. This mode is an essential imaging modality in diagnostic ultrasound, with the amplitude of the reflected signal converted into variations in brightness of the two-dimensional gray scale from differences in organs and other tissues. Most noncardiac applications of ultrasound are in B-mode. The transducer moves across the patient on an articulated arm, generating A-mode signals in a single plane. The distance from the transducer is proportional to the time required for the reflected signal to reach the transducer. These echo signals are converted from amplitude information to brightness-modulated lines on the oscilloscope by assigning (through the computer) gray scales to the voltage amplitudes. On the oscilloscope display, the *x*-axis is the depth from the surface, whereas the z-axis is the position of the transducer, as demonstrated in Figure 43.7. Real-time ultrasound scanners replaced static B-scanners as the primary clinical ultrasound technique.

M(Motion)-Mode

For the M-mode, the ultrasound machine operates in the B-mode with the transducer stationery. Thus, the images result from the reflection of moving surfaces within the body. One axis represents the distance from the surface, whereas the other axis represents the movement of these surfaces with time. M-mode provides accurate assessments of rapid movements as a result of excellent temporal resolution (i.e., high sampling rate).

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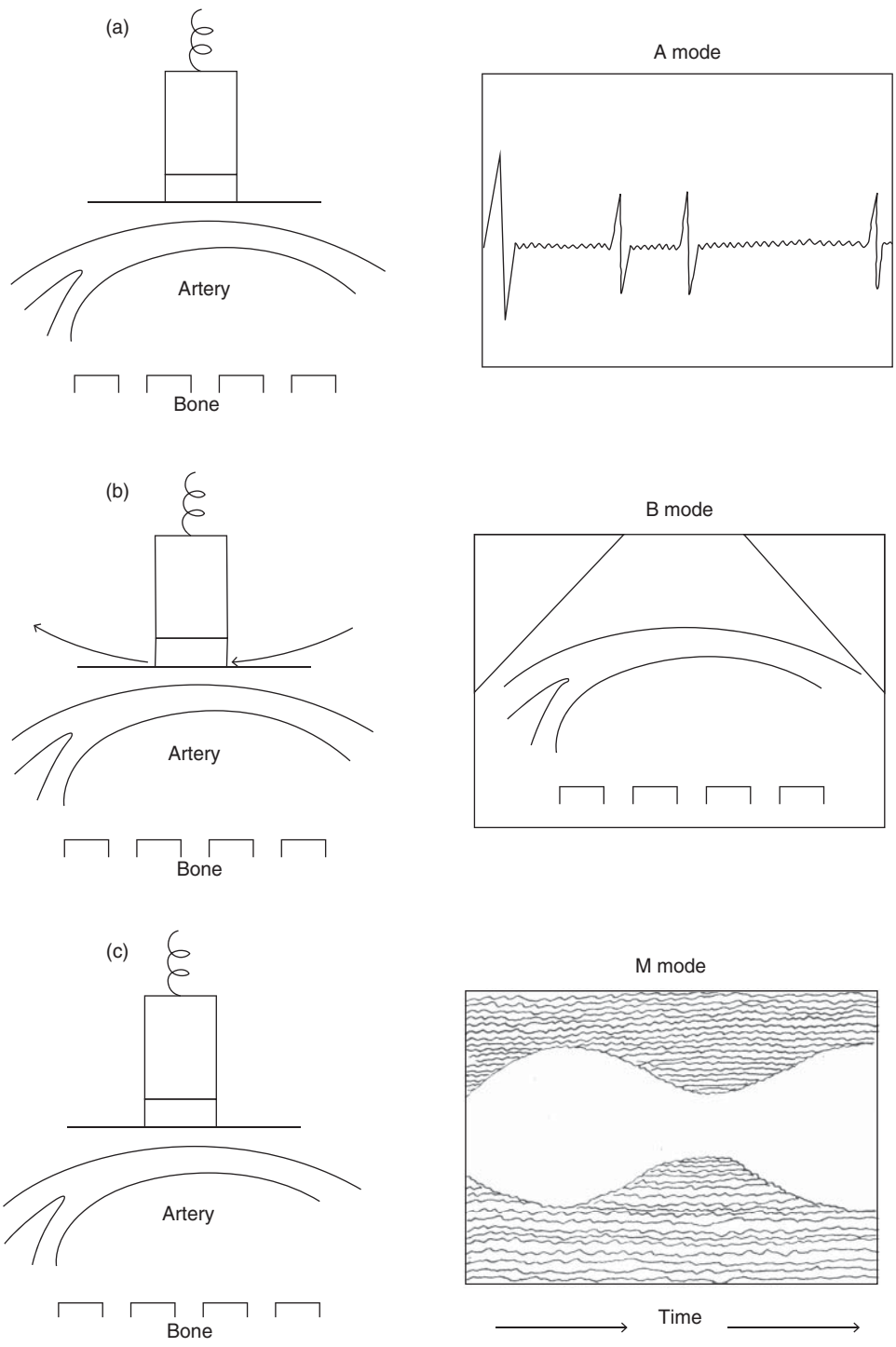


FIGURE 43.7. Differences in the image of an artery using A- (a), B- (b), and M- (c) modes during ultrasound. A-mode displays the artery as two spikes in amplitude, whereas B-mode creates a two-dimensional image through the plane of the body on the *x*–z axes as the transducer moves over the surface of the body. The x- and z-axes represent depth and amplitude, respectively. There is no y-axis in B-mode. M-mode displays a section of the artery over time and is particularly useful to image rapidly moving objects. The *y*-axis reflects pulsation of the arterial walls; the *x*-axis represents time. (Sarti).[145]

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TABLE 43.7. Changes in ultrasound output parameters for submissions to the US Food and Drug Administration (USFDA) involving transducers used for fetal applications, 1984–2010. (Adapted from Cibull et al.).[150]

Parameter	1984–1989	1992–1997	2005–2010
Mean power, (range), mW	8.4 ± 13 (0.008–73)	102 ± 115 (0.5–712)	75 ± 75 (0.3–659)
Mean center frequency (MHz)	4.2	3.7	3.4
Mean bone thermal index (TIB)	0.19	1.8	2.0

D(Doppler)-Mode

The basis of this imaging mode is the change in frequency caused by the reciprocal movement of the sound generator and the observer (i.e., Doppler shift); reflections from erythrocytes provide the ultrasound signal backscatter to analyze blood flow. The combination of Doppler technology with real-time ultrasound allows the imaging of blood flow inside vessels using B- and M-modes. Doppler duplex imaging uses both continuous-wave and pulsed-wave techniques. Continuous-wave Doppler uses two piezoelectric crystals, one sending and one receiving the signal, whereas pulsed-wave Doppler uses a single piezoelectric crystal with a definite delay before receiving the reflected signal. The former measures high-velocity signals well without identifying the Doppler signal source; the latter provides blood flow direction and precise measurements of the Doppler signal source, with limited accuracy in high-velocity states.

DOSE EFFECT

The biological effects of ultrasound result primarily from heating and acoustic cavitation. The amplitude of ultrasound waves decreases with distance from the source as a result of absorption and scattering during the propagation of the wave through tissue.[151] Absorption represents the portion of ultrasonic wave converted into heat, whereas scattering is the portion that changes direction. Temperature in the tissues rises when the rate of heat production exceeds the rate of heat removal. Consequently, the amount of temperature elevation resulting from the absorption of ultrasonic radiation depends on the intensity of the ultrasound wave, the absorptive and scattering properties of the medium, and the heat capacity and thermal conductivity of the medium.[152] Intensity is a measure of the ultrasound dose and the capability of the ultrasound waves to induce thermal changes in tissue. The spatial peak temporal average (I_{SPTA}) of typical ultrasound machines ranges from 0.01–200 mW/cm^2; the instantaneous peak (ITP) is ~5–10 W/cm^2.[152] Initial temperature rises of 0.002°C occur from a several MHz ultrasound at an intensity (I_{SPTA}) of 100 mW/cm^2. A review of the *in vivo* and the *in vitro* effects of continuous wave exposure for <10 minutes did not identify an effect at I_{SPTA} levels of <100 mW/cm^2.[153]

Low-output pulsed Doppler equipment (I_{SPTA}, 112 mW/cm^2 at the dermal surface) did not produce detectable temperature elevations (i.e., 0.05°C) in fetal subcutaneous tissue during a 10-minute span.[154] Commercial pulse-echo diagnostic machine may produce ITP in the range of 100 W/cm^2. Although the average ultrasound procedure requires 10–45 minutes, the actual scan time is 5–10 minutes. Most diagnostic instruments perform at average intensities of ~15 mW/cm^2 with peak intensities of 4–7 W/cm^2. The overall average output of ultrasound Doppler instruments is 10–100 times greater than the average output of B-scanners and real-time scanners.

The threshold for stable cavitation in the range of 1–4 MHz is an intensity of 0.2–5 W/cm^2 with continuous waves (e.g., diathermy). Alternately, the same intensity with many cycles of pulsed ultrasound is necessary to produce the phenomenon of stable cavitation.[144] Although laboratory experiments suggest cavitation can occur at a frequency of 1 MHz with a duty cycle of 0.1 and a temporal average intensity of 14 W/second,[155] currently there is no definite scientific evidence that cavitation occurs at the existing intensities of diagnostic ultrasound.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Absorption of the ultrasound energy by the tissues produces heat. Increasing frequency, pulse length, and nonlinear acoustic distortion increase heating and some nonthermal mechanisms, whereas increasing power or intensity typically increases the magnitude and risk of all ultrasound-related adverse effects. Temperature elevations and subsequent adverse effects from diagnostic ultrasound are usually clinically negligible.[156] The biological effects of therapeutic or diagnostic ultrasound do not accumulate during repeat examinations.[149]

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Cavitation is the production and movement of bubbles in a liquid medium (e.g., biological tissue). When the negative pressure created by the ultrasonic wave crossing the tissue exceeds the minimum molecular distance required to hold the fluid intact, voids in the tissue occur (i.e., cavitation bubbles). Gas diffuses out of solution (called rectified diffusion) during the rarefaction phase, enhanced by heat from the absorption of ultrasound energy.[157] Decreasing frequency with high-intensity ultrasound increases the risk of cavitation, including gas body activation.[158] Most ordinary liquids contain microbubbles of dissolved gases that expand and contract during the passage of different phases of a sound wave. Stable cavitation is the sustainable, periodic, nonlinear expansion and contraction of the gas bubble. Elevated vapor pressure within the bubble increases the bubble up to the resonant size. Cavitation-related mechanisms include microjets (high-speed, penetrating jets formed from inertial collapse near rigid surface), microstreaming (shear stresses from the transfer of momentum caused by energy absorption), shock waves, strain, and free radical formation.[151] Cavitation and gas body activation cause primarily local tissue injuries in the area of cavitation, including cell death and hemorrhage from damaged blood vessels. Cavitation typically does not occur at the power intensities used for ultrasound imaging.[159]

Microstreaming occurs when the sinusoidal sound wave alternately increases and decreases the resonant bubble size. This movement produces shear forces on the surrounding cells and organelles that may cause damage. As the intensity of the pressure wave increases, the cavity becomes unstable and collapses. At high energy levels, the bubble becomes lenticular in shape with the walls approaching the center at supersonic speeds. The very high temperatures (several thousand K) and pressures (several hundred atmospheres) of collapsing gas bubbles produce thermal dissociation of water vapor into hydroxyl radicals and hydrogen atoms.[160] The formation of a variety of short-lived free radicals *potentially* can produce cell damage and lysis;[161] however, there is no conclusive evidence that diagnostic ultrasound causes intracellular free radical formation or cellular dysfunction.

CLINICAL RESPONSE

Thermal Effects

Modern diagnostic ultrasound machines are unlikely to cause adverse thermal effects. A review of the research literature on tissue temperatures indicated an 18°C temperature elevation for 100 msec is necessary to produce tissue damage.[162]

Nonthermal Effects

Biological tissue does not typically contain gas bodies; consequently, cavitation is unlikely to occur during the use of ultrasound. When inertial cavitation or microstreaming occurs, the effect is typically localized to the small region of the gas body. The probability of a strategically placed gas body being able to cause a deleterious effect is highly unlikely.[163]

Carcinogenesis

An increase in sister chromatid exchanges (SCEs) often occurs in the presence of mutagenic agents; however, this short-term assay produces false positive and false negative results. Most studies of SCE induction after exposure to diagnostic ultrasound are negative;[164,165] however, two studies reported positive findings.[166] Subsequent studies did not confirm a clinically relevant increase in SCEs at exposure levels (e.g., 5 MHz linear transducer for 0.16–20 minutes) present during diagnostic studies.[167,168] The exact significance of SCEs remains unclear in relation to the assessment of teratogenic and carcinogenic agents. In a study of 10 patients with low back pain receiving 10 sessions of ultrasound therapy (intensity of 2 W/cm^2; frequency, 1 MHz; duration, 10 minutes; and 10 controls sham therapy), examination of peripheral blood for cytogenic damage as measured by micronucleus frequencies demonstrated no statistically significant difference comparing preexposure and postexposure values.[169]

Reproductive Abnormalities

Although the number of large prospective studies on the effects of ultrasound is limited, the results have generally been negative; there is no clear evidence that the use of diagnostic ultrasound during pregnancy causes significant health risks to the fetus or mother.[170] A study of 1,114 healthy pregnant women undergoing diagnostic ultrasound at various stages of pregnancy did not detect an elevated incidence of fetal abnormalities (i.e., 2.7%).[171] A 12-year follow-up of 425 children exposed to diagnostic ultrasound *in utero* did not demonstrate any abnormalities in hearing, vision, cognitive function, behavior, or other neurological effects.[172] A retrospective nested case-control study of physiotherapists

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exposed to ultrasound during diathermy reported a 3-fold increased incidence of spontaneous abortion, but not congenital abnormalities; however, the difference was not statistically significant after controlling for confounding variables.[173] In a study of 434 pregnant physiotherapists using shortwave diathermy and adverse pregnancy outcomes, only low birth weight reached statistical significance (OR = 2.75, 95% CI: 1.07–7.04, $P = 0.03$) after controlling for potential confounding variables.[174]

Animal studies of ultrasound indicate the presence of *in vivo* reproductive effects (e.g., fetal weight reduction, elevated postpartum fetal mortality, fetal abnormalities, hind limb paralysis, behavioral alterations, blood flow stasis); however, these changes occur at high levels (intensities >0.1–1 W/cm^2) compared with the intensity of ultrasound.[175] Figure 43.8 displays an estimation of the theoretical threshold line for potential adverse thermal effects, including teratogenesis, plotted as temperature elevation (*y*-axis) against duration (*x*-axis). Typically, temperature increases of ≥4°C for 5 minutes are necessary to produce developmental abnormalities in the animals.[156] Congenital abnormalities have not been associated with the use of diagnostic ultrasound in humans. Cavitation is unlikely to occur in the fetus because of the lack of identifiable gas bodies. A review of adverse nonthermal effects and diagnostic ultrasound did not identify any causal relationship between fetal abnormalities and the use of diagnostic ultrasound; the potential for adverse effects exists for low-intensity pulsed ultrasound effects used to accelerate bone fracture repair and induce healing of nonunions in humans.[176]

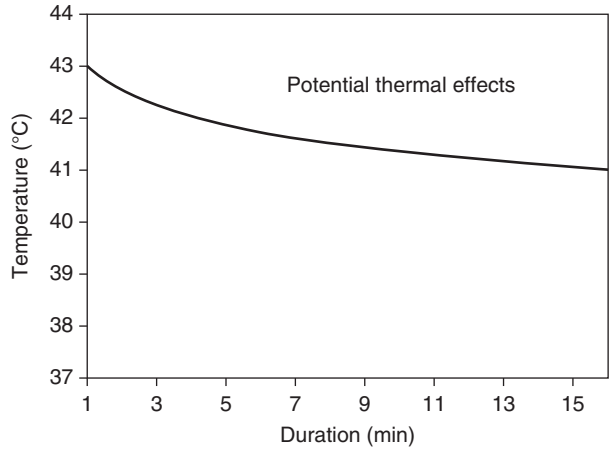


FIGURE 43.8. An estimation of the theoretical threshold line for potential adverse thermal effects including teratogenesis plotted as temperature elevation (*y*-axis) against duration (*x*-axis) based on animal studies. Although some spectral Doppler exposures may approach this line based on the thermal index display, the figure demonstrates that very long times (e.g., >4 hours for 2°C elevation above body temperature) are necessary for normal ultrasound examination duration in the fixed plane. (Adapted from Miller).[170]

DOSIMETRY

The pulsatile characteristic of ultrasound waves requires evaluation by temporal peak and temporal average exposure metrics. The energy in the pulse is typically expressed as the pulse-average intensity (power delivered/unit area, W/cm^2) at the spatial peak on the beam axis near the focus. The two primary effects of transmission of ultrasonic waves through tissues are heating from absorption of the energy by tissues and cavitation from the expansion/contraction of gases in the tissues. Heating correlates to the temporal average intensity (thermal indices), whereas cavitation correlates to temporal peak measures (mechanical indices). The screens of diagnostic ultrasound machines display these parameters as required by the Output Display Standard published by the American Institute of Ultrasound in Medicine and the National Electrical Manufacturers Association.[177]

HEALTH SURVEILLANCE

Risk

Although heating and cavitation are potential mechanisms for adverse biological effects, neither of these mechanisms has been documented under current imaging conditions for ultrasound.[162,178] Currently, there is no well-documented risk associated with the use of diagnostic ultrasound in the fetus; however, sufficiently large prospective epidemiological studies are not available to exclude subtle effects on the mother or the fetus.

Fetus

The US Food and Drug Administration 510(k) premarket approval process established an initial limit of 46 mW/cm^2 of spatial peak temporal average (SPTA) intensity for obstetrical ultrasound in 1985.[179] Following adoption of the Output Display Standard, the allowable output for obstetrical ultrasound increased to an average exposure of 720 mW/cm^2 SPTA intensity; the peak exposure was established via the Mechanical

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Index. Ultrasound machines configured for obstetric use typically produce a lower temperature than machines with nonobstetric transducers and settings including color Doppler machines.

Thermal Indices

Calculating the temperature profile from an ultrasound examination is very complex. Acoustic output from diagnostic ultrasound devices can cause temperature elevation in fetal tissue with the elevation progressively greater from D-mode to color Doppler to spectral Doppler applications.[180] Temperature elevation in the tissues depends on several factors, including the SPTA intensity, ultrasound frequency, beam width, dwell time along the beam axis, physical properties of the tissue examined, and individual patient factors. Fixed beams produce temperature elevations that reach an asymptote as heat deposition matches heat dissipation from conduction and blood flow. The temperature elevation is lower at a given intensity for focused beams than for unfocused beams because of the rapid conduction of heat from a small region. Ultrasound machines usually display the following three thermal indices: 1) regular soft tissues (TIS), 2) bone at the focus (TIB), and 3) bone at the surface (TIC). The important indices for obstetrical ultrasound are TIS for the first trimester and TIB for the second and third trimesters when bone development occurs. A TIS value in °C indicates the temperature elevation would not be expected to rise above that value.

Mechanical Index

Ultrasonic cavitation potentially causes mechanical damage and the generation of free radicals capable of altering DNA. The mechanical index provides an estimate of the peak negative (rarefactional) pressure amplitude (PRPA) of the ultrasonic beam in the tissues; this value is an important measure of the temporal peak exposure and the I_{SPPA} (spatial-peak pulse-average intensity). The occurrence of cavitation depends on the PRPA. Table 43.8 lists the upper limits for diagnostic ultrasound as formulated in spatial peak temporal average intensity and spatial-peak pulse-average intensity by the US FDA. The values represent values below which there is little risk of adverse effects. Modern ultrasound machines do not typically reach these upper limits. The minimal risk of obstetrical ultrasound implies that diagnostic ultrasound should not be withheld for safety considerations when clinically indicated. Ultrasonography and magnetic resonance imaging are not associated with significant risk to the fetus or mother; hence, these modalities are the imaging techniques of choice for the pregnant patient requiring clinical information for their health.[181]

TABLE 43.8. The US Food and Drug Administration upper limits for diagnostic ultrasound machines. The old tract 1 represents machines pre-1992 without indices displayed, whereas the current tract 3 represents modern machines with thermal and mechanical indices displayed. (United States Food and Drug Administration, USFDA).[179]

Application	$I_{SPPA.3}$[b] (mW/cm^2)	$I_{SPPA.3}$[b] (W/cm^2)	$I_{SPPA.3}$[c] (mW/cm^2)	MI[c]
Peripheral vessels	720	190	720	1.9
Cardiac	430	190	720	1.9
Fetal imaging[a]	94	190	720	1.9
Ophthalmic	17	28	50	0.23

Abbreviations: I_{SPPA} = spatial peak pulse average intensity; MI = mechanical index.
[a] Includes pediatric, intraoperative, and cephalic imaging,
[b] Old tract 1, [c] Current tract 3.

TABLE 43.9. American Conference of Industrial and Governmental Hygienists (ACGIH) 2022 threshold limit values (TLVs) for ultrasound based on mid-frequency ranges (10–100 kHz) for one-third-octave-band levels. For frequencies 10–20 kHz, some individuals may experience subjective annoyance and discomfort during exposure in the range 75–105 dB; engineering controls and/or hearing protection may be necessary to prevent subjective effects. Reducing the dB to 80 dB may be necessary for some individuals exposed to frequencies of <10 kHz. With TLV values for frequencies of 25–100 kHz, the values may increase to 30 dB if the ultrasound does not couple with the body by touching water or some other substrate, as occurs when the ultrasound source directly contacts the body. In such situations, the vibration level at the mastoid bone should be applied. Acceleration values of 15 dB above the reference of 1 g rms should be avoided by reducing the exposure or isolating the body from the coupling source.

Frequency (kHz)	Head in Air-Ceiling Value[a]	Head in Air-8-Hour TWA[a]	Head in Water-Ceiling Value[b]
10	105	88	167
12.5	105	89	167
16	105	92	167
20	105	94	167
25	110	—	172
31.5	115	—	177
40	115	—	177
50	115	—	177
63	115	—	177
80	115	—	177
100	115	—	177

[a] Measured in air in dB re: 20 μPa. [b] Measured in water in dB re: 1 μPa.

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Workplace

The basis of ACGIH threshold limit values (TLVs) for ultrasound is prevention of hearing loss and a reduction in the ability to understand normal speech. The 8-hour time-weighted average (TWA) values reflect the TLV for noise (8-hour TWA = 85 dBA). These values refer to sound pressure levels for one-third-octave bands with mid-range frequencies of 10–100 kHz. Verification of the ceiling values involves the use of sound-level meters with slow detection and one-third-octave bands. Table 43.9 lists the ceiling and 8-hour TLVs for exposure to ultrasound.

Audible, high-frequency radiation above 10 kHz may cause nausea, headache, tinnitus, pain, dizziness, and fatigue, depending on the susceptibility of the person, the intensity, and the actual spectrum of high-frequency radiation.[182] Exposure to powerful sources of ultrasound potentially may produce damage to neurovascular structures near the point of contact. No specific OSHA standards or NIOSH recommendations exist for ultrasound. Sound-insulating panels should completely cover the ultrasound equipment to prevent the leakage of sonic radiation; the equipment should be isolated from the floor by rubber seals.

LASERS

The word "laser" is an acronym for **L**ight **A**mplification by **S**timulated **E**mission of **R**adiation. Albert Einstein first conceived of the concept of a laser in 1917, when he postulated that stimulation of atoms would release energy with a specific wavelength and direction.

Figure 43.9 demonstrates a simplified version of the laser. The basic components of a laser include: 1) a lasing medium, 2) an energy source, and 3) a reflecting cavity. Ordinary light sources produce a continuum of wavelengths over the spectrum of visible light; these photons of light diverge rapidly as they leave the source. The laser beam is powerful and highly focused. In contrast to ordinary light sources, laser radiation is monochromatic (i.e., all photons have similar energy, wavelength, and frequency) *and* collimated (i.e., the beam does not diverge).

The wavelength of the laser depends on the lasing medium through which the photons pass. As seen in Figure 43.9, the wavelength emitted by the laser covers infrared and visible portions of the electromagnetic spectrum. The laser has many industrial and military uses, including communications (fiberop-

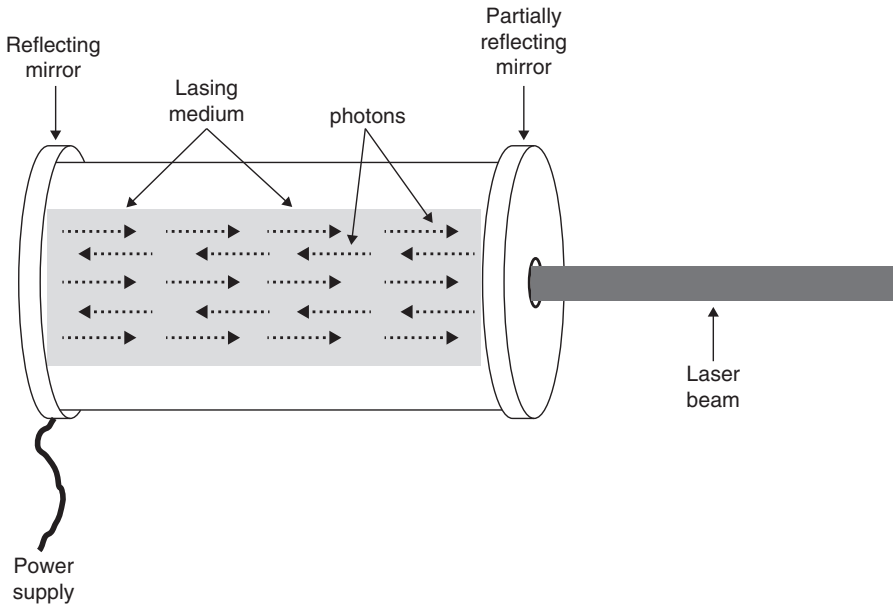


FIGURE 43.9. Simplified version of a common laser with three major parts, including a solid, liquid, or gas lasing medium, two mirrors, and a power supply. The power supply provides the energy to excite the atoms to emit photons. The energies in these photons are amplified as they are reflected by two mirrors in the central axis. Depending on the lasing medium, energy with a specific wavelength discharges as a laser beam through a partially reflecting mirror at the end of the laser.

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tic cables, supermarket scanners, laser light shows, holograms), information storage (compact disc players, laser printers), industrial (cutting, welding, soldering), and military (laser-guided missiles, range finding) applications. The US Food and Drug Administration approved the use of Nd-YAG lasers for dental surgery on the gums. The hazards associated with the use of lasers depend on the power of the laser. In general, the main hazards of the laser involve eye injuries, skin burns, and electrical injuries from the energy source.

PHYSICAL PROPERTIES

In contrast to ordinary light, light emitted from a laser possesses the following four characteristics: 1) coherence, 2) monochromaticity, 3) high intensity, and 4) collimation or little divergence.[183] Coherence implies the photons emitted by the laser are in phase with one another; hence, these electromagnetic waves possess the same amplitude, direction, frequency, and phase. Monochromatic light means all of the photons have the same energy, frequency, and wavelength or color. Although most lasers produce monochromatic light, some lasers (e.g., the helium-neon) emit light at three different wavelengths, depending on the specific design. The beam produced by a laser has high-energy density with the power measured in joules (J)/cm^2. Because the effect of a pulsed laser depends on the duration of the pulse, J/second-cm^2 or watts (W)/cm^2 are the common units of measurement for the pulsed laser. Unlike ordinary light, the beam of a laser does not spread far while traveling away from the source, with the unit of measure of divergence measured in milliradians (i.e., ~3 minutes of arc). Typically, a laser (e.g., helium-neon) diverges only by 0.5–1.5 milliradians.

EXPOSURE

Exposure to laser radiation primarily occurs in certain groups including military personnel, research workers in industrial and academic settings, patients, and healthcare personnel. Reflected laser radiation may exceed occupational guidelines for bystanders momentarily viewing a laser procedure within 1 m of the laser contact lens.[184] Diffuse reflections occur primarily with Class IV lasers, and infrared radiation may reflect unexpectedly off objects that do not reflect visible light.[185]

Uses

Medical

The principal lasers used in medical practice include the following: 1) argon, 2) neodymium-doped yttrium aluminum garnet (Nd:YAG), 3) holmium-yttrium aluminum garnet, and 4) carbon dioxide. Important medical advantages of lasers include clearer operative sites as a result of the coagulative properties of lasers, reduced trauma surrounding the wound, and improved wound healing times. Table 43.10 lists the common lasers used in certain medical procedures along with their specific wavelengths.

Dermatology

Powerful pulses of energy from CO_2 lasers heat water in tissue rapidly; these lasers can vaporize tissue with high water content near the surface of the body. In dermatology, CO_2 lasers can remove warts, ingrown toenails, and lip lesions. The blue-green emission from the argon lasers easily passes through the outer surface of the skin; however, hemoglobin absorbs this wavelength well. Consequently, this laser effectively removes hemangiomas (port-wine stains) from adult skin. The less powerful flashlamp-pumped pulsed dye (rhodamine in methanol) laser requires more treatment sessions with less scarring in children. Other types of lasers produce wavelengths that absorb melanin easily; therefore, these lasers effectively remove telangiectasias and pigmented lesions (e.g., moles, freckles, solar lentigines, dark birthmarks). Q-switching is a technique that produces shorter, higher-intensity laser pulses. Carbon and, to a lesser extent, melanin absorb the deep-red, 694-nm wavelength of the ruby laser. Hemoglobin does not absorb this wavelength well; the Q-switched ruby laser pulses (40–80 nsec, 694 nm) effectively remove tattoos without a substantial incidence of scarring or hyperpigmentation, particularly for removing black, blue, and green pigments.[187] Other lasers used for tattoo removal include Q-switched neodymium:yttrium-aluminum-garnet (532 nm – red pigments, 1,064 nm – blue/black pigments) and Q-switched alexandrite (755 nm) lasers.[188,189] The removal of multicolored tattoos requires several different wavelengths; therefore, no one laser system removes all combinations of colors and inks. Successful tattoo removal requires selecting the correct laser for the tattoo color.[190] Adverse effects include textural change, pigmentary alteration (e.g., hypopigmentation), and scarring.

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TABLE 43.10. Medical uses and types of laser systems. (Adapted from Pierce et al.).[186]

Specialty	Application	Laser Systems	Wavelength (nm)
Dermatology	Vascular lesion treatment	Argon	350–530
		KTP	532
		Pulsed dye	577, 585, 595
		Pulsed diode	800–900
	Tattoo removal	Alexandrite	755
		Nd:YAG	532, 1,064
		Ruby	694
	Skin resurfacing	Erbium	1,550
	Treatment of acne scars	Er:YAG	2,940
		CO_2	10,600
	Treatment of pigment disorders and lesions	Excimer	308
		Nd:YAG	532
		Ruby	694
	Skin tightening	Erbium	1,550
		Nd:YAG	1,440
		CO_2	10,600
Gynecology	Treatment of intraepithelial neoplasias	CO_2	10,600
Neurosurgery	Tumor removal	CO_2	10,600
		Nd:YAG	1,320
Otolaryngology	Treatment of tracheobronchial lesions, tumors, and stenosis	Nd:YAG	1,064
		CO_2	10,600
Gastrointestinal surgery	Removal of polyps and lesions	Argon	350–530
		Nd:YAG	1,064
Cardiovascular surgery	Angioplasty	Excimer	308
		Argon	350–530
Ophthalmology	Refractive eye surgeries	Excimer	308
		CO_2	10,600
		Krypton ion	400–670
		Nd:YAG	1,064
	Blepharoplasty	CO_2	10,600
	Photocoagulation of polyps, resolution of hemorrhagic pigment, epithelial detachment	Argon	350–530
	Ablation of lens capsule	Nd:YAG	l064
	Peripheral retinal coagulation	Krypton	647
		Diode	630–650
Urology	Ablation of invasive and *in situ* carcinomas	CO_2	10,600
		Nd:YAG	1,064

Abbreviations: Er:YAG = Erbium-doped yttrium aluminum garnet; KTP = potassium titanyl phosphate; Nd:YAG = neodymium-doped yttrium aluminum garnet.

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Ear, Nose, and Throat Surgery

CO_2 lasers with infrared radiation and a wavelength of 10.6 μm are routinely used in otolaryngology surgery as effective surgical cutting instruments that provide precision cuts with excellent hemostasis and little collateral damage. Water, blood, and biological material absorb infrared radiation independently of pigment. Ordinary glasses provide sufficient eye protection from corneal burns because glass and plastic readily absorb the emitted radiation. The holmium:yttrium-aluminum-garnet laser produces pulsed infrared output with a wavelength of 2.1 μm; excellent absorption in water-rich tissues favors use of this laser for nasal surgery and tonsillectomies. The neodymium (Nd):YAG laser possesses high tissue penetration (and minimal tissue absorption), making it useful for hemostasis and shrinking lower airway tumors. Oral and maxillofacial uses include coagulation of angiomas, hemostasis of nosebleeds, arthroscopic temporomandibular joint surgery, and palliation of advanced neoplasms.[191] In contrast to the CO_2 laser, this laser produces the majority of its effects below the surface of surrounding tissues. Dedicated goggles opaque to wavelengths of 1.06 μm are necessary to prevent retinal damage. The potassium titanyl phosphate (KTP) laser contains a Nd:YAG laser that emits a green light with a wavelength of 532 by passing the beam through a KTP crystal. The KTP laser is more powerful than the argon laser and produces more refined and better hemostasis than the CO_2 laser.

Ophthalmology

The ruby laser was the first laser used in ophthalmological surgery in the 1970s.[192] Laser technology offers the advantage of less pain and a lower risk of infection compared with open surgical techniques. The neodymium:yttrium aluminum garnet (Nd:YAG) laser produces an intense infrared light that can create openings in the eye for posterior capsulotomies after cataract surgery and the treatment of glaucoma. As an adjunct to retinal surgery, the Nd:YAG laser can cut deep vitreous traction bands. The blue-green pulses from the argon laser selectively heat and seal damaged blood vessels in the retina; these treatments prevent further macular deterioration in patients with macular degeneration or diabetic retinopathy. Both the argon and the krypton lasers are well suited to spot-weld tears in the retina that result from trauma. The excimer laser is a gas laser that cuts precise craters in tissue, which is useful in coronary angiography[193] and anterior corneal surgery.[194] Excimer laser technology is also a popular treatment for myopia (radical keratotomy).[195] Advances in laser technology have resulted in multiple laser platforms for refractive surgeons, including femtosecond-assisted LASIK (laser-assisted *in situ* keratomileusis) with excimer laser corneal reshaping[196] or high-frequency femtosecond laser-assisted SMILE (small incision lenticule extraction) surgery.[197]

Pulmonary

The Nd:YAG laser provides a rapid palliative treatment for obstruction of the large airways (trachea, mainstem bronchus, lobar bronchus) as a result of either benign or malignant lesions, particularly short, polypoid tumors. Benign tracheal stenosis, but not tracheomalacia, is responsive to resection by the Nd:YAG laser. Complications of the pulmonary use of the Nd-YAG laser include air embolism, hemorrhage hypoxemia, ignition of the bronchoscope or endotracheal tube, mucosal edema, and loss of the tip of the laser fiber.[198]

Industrial

Lasers are commonly used in research laboratories and industrial settings. Injuries during these processes usually occur during alignment of the laser beam or other adjustment procedures, resulting in parafoveal damage from looking directly into the laser source. Occasionally, unintentional reflections from a mirror or nearby reflective object (plastic membrane, photographic paper) cause retinal damage. Laser pointers emit a continuous narrow beam of visible light (e.g., diode laser, 670 nm; helium-neon laser, 632.8 nm) with an output power usually ranging from 1–5 mW. The retinal irradiance is similar to staring directly at the sun.[199] Although mild thermal retinal injury may occur following prolonged staring at the laser pointer (i.e., >10–20 seconds),[200,201] the blink reflex and aversion response usually prevent retinal damage.[202] Transient visual incapacitation (e.g., flash-blindness, glare, afterimages) may occur following inadvertent exposure to a laser pointer, resulting in secondary injuries, particularly in a dark-adapted person.

Military

Armed forces commonly use laser-based devices for range finding and guiding "smart" weapons. Laser-based weapons use the laser beam to damage electro-optical sensors that are vulnerable to the same visible and near-infrared radiation as the retina; these weapons have the capacity to produce visual incapacitation. Targets during these activities often involve vulnerable individuals using binoculars many kilometers from the laser source. Typically, military lasers have wavelengths in the visible or near-infrared spectrum with energies of tens of millijoules and pulses lasting nanoseconds.[203]

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Consequently, retinal burns occur following military use of these lasers with bilateral eye injuries being much more common than civilian laser injuries.[204]

Laser Design

Lasers are devices that produce and amplify light, resulting in the focusing of radiant power over very small areas with the potential to direct this energy over great distances. The power of the light created by these devices varies from a few mW in the helium–neon gas laser to thousands of watts in the CO_2 laser.[205] Lasers may operate either continuously or intermittently with pulses containing millions of watts of power. A laser has three major components including: 1) a lasing medium (liquid, gas, solid) where photons form, 2) a pumping system that provides a power source for the lasing medium, and 3) an optical cavity (e.g., lenses, mirrors, shutter) that focuses and intensifies the output of the laser.

Lasing Medium

The lasing medium provides the material where electrons are trapped in an exited (metastable) state for up to several milliseconds before decaying to lower, stable states by emitting photons. The four common families of lasers are based on the type of lasing medium. The ruby laser is an example of a **solid-state laser** that uses a solid matrix of aluminum oxide and emits a deep red beam with a wavelength of 695.3 nm. The neodymium-YAG laser uses neodymium atoms in a crystal of **Y**ttrium, **A**luminum, and **G**arnet to produce an invisible beam with a wavelength of 1,064 nm. The **gas lasers** use a gas or a mixture of gases enclosed in a glass tube, including the CO_2 laser (invisible infrared beam with a wavelength of 10,600 nm), the helium-neon laser (632.8 nm), the argon laser (488 nm), and the krypton lasers. **Semi-conductor lasers** are small, highly efficient lasers that produce red and infrared beams by using two opposing layers of semiconductor material as the lasing medium. One layer contains a surplus of electrons, whereas the other material has a deficit of electrons. **Liquid lasers** contain organic dyes as the lasing medium; they can produce a wide range of beams in the visible and near-visible portions of the electromagnetic spectrum.

Pumping System

The production of a beam requires pumping systems to raise electrons to higher energy levels (metastable state) from the ground or lower energy levels. A population inversion develops when the number of electrons in the metastable state exceeds the number of electrons in the ground state. Laser action occurs *only* when a population inversion exists. Gas lasers utilize electron collision pumping, where an electrical charge applied to the tube causes the electrons to excite electrons in the lasing medium. This method allows the formation of continuous output. Solid-state lasers use optical pumping, whereby the electrons in the lasing medium reach an excited state by absorbing photons from strobe-like devices (e.g., xenon flashtubes). Liquid lasers generally use a solid-state laser to pump the lasing material. Other lasers (e.g., hydrogen fluoride) utilize chemical pumping, whereby the formation and destruction of chemical bonds provide the energy to excite electrons in the lasing medium.

Optical Cavity

A system of parallel mirrors enhances the movement of photons through the lasing medium; reverberation of the photons between these mirrors produces a unidirectional and coherent light beam. Reflection of the beam back through the lasing medium increases the number of emitted photons until the number of excited electrons equals the number of photons lost through the mirrors. A continuous, usually low-output beam results from the pumping of the lasing medium at that time. Placing a shutter between the two reflective mirrors allows the formation of short, high-output pulses of energy from the laser. Q-switching is the technique that produces these short, powerful impulses by interrupting the optical cavity with an electro-optical switch (Pockel's cell). Reducing the loss of energy to the lasing material allows a higher population inversion. The sudden restoration of the optical cavity permits the release of a shorter (~30 nsec) but more powerful radiation burst compared with the continuous laser.

Hazard Classification

Damage to the skin and eyes from exposure to laser beams depends on the wavelength, the pulse duration, and the power of the beam. **Radiant flux** is the power received by an object measured in watts. The **irradiance** on the surface of an object is the radiant flux divided by the area of that surface. The unit of irradiance is W/cm^2; this quantity is a useful measure of the power of a *continuous* laser source. The **radiant energy** is the amount of energy emitted by a source; the unit of measure is the joule. The **radiant exposure** is the surface density of the radiant energy in a particular area, as measured in J/cm^2. For *pulsed* beams, radiant exposure is a valid measure of power.

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TABLE 43.11. Four major United States Food and Drug Administration (US FDA) laser hazard classifications with roughly equivalent International Electrotechnical Commission (IEC) laser classifications. The higher numbers imply a greater hazard. Light-emitting diodes (LEDs) differ from laser diodes; LEDs are not subject to the Federal laser product performance standard. The IEC Class 1M contains lasers usually considered incapable of producing damaging radiation levels except when viewed through certain optical instruments (eye-loupe, telescope), causing diverging or collimated beams. Similarly, IEC Class 2M normally does not cause damage with unaided viewing, whereas the use of certain optical aids produces potentially hazardous situations.

FDA Class	IEC Class	Hazard	Products
I	1, 1M	Considered nonhazardous. Hazard increases if viewed with optical aids, including magnifiers, binoculars, or telescopes (1M)	Laser printers, CD/DVD players
IIa, II	2, 2M	Low-power. Hazard increases when viewed directly for long periods of time. Hazard increases if viewed with optical aids (2M)	Bar code scanners
IIIa	3R	Medium-power. Depending on power and beam area, it can be momentarily hazardous when directly viewed or when staring directly at the beam with an unaided eye. The risk of injury increases when viewed with optical aids	Laser pointers
IIIb	3B	Medium-power. Immediate skin hazard from direct beam and immediate eye hazard when viewed directly	Laser light-show projectors, industrial and research lasers
IV	4	High-power. Immediate skin hazard and eye hazard from exposure to either the direct or reflected beam; may also present a fire hazard	Laser light-show projectors, industrial and research lasers, medical device lasers for eye surgery or skin treatments

Abbreviations: FDA = US Food and Drug Administration; IEC = International Electrotechnical Commission.

For hazard classification, the US Food and Drug Administration, International Electrotechnical Commission, and the American National Standards Institute categorize lasers into four groups, as displayed in Table 43.11. Class I lasers are exempt from regulation because the power (<0.001 mW) produced by these devices does not cause eye damage even when viewed accidentally. Class II lasers are low-output (<1 mW) devices that may require eye protection under certain circumstances. These visible lasers do not usually produce enough power to injure an individual accidentally; however, direct viewing of the beam for >0.25 seconds may cause retinal damage. Class III lasers are medium-power (<0.5 W) lasers that produce eye damage with viewing of the direct or reflected beam (Class IIIb) or require focusing (e.g., binoculars) to cause damage (Class IIIa). Class IV lasers are high-power (>0.5 W) lasers that cause damage to the eye or skin from viewing direct beams or receiving diffuse reflections.

High-power CO_2 lasers in Class IV have various industrial applications, including welding, drilling, and cutting. The power output of the infrared beam from industrial CO_2 lasers ranges from 1–10 kW, with blue light and ultraviolet radiation released from the interaction of the infrared laser with the target.[206] Ordinary glasses composed of plastic absorb the invisible radiation emitted from CO_2 lasers.

DOSE EFFECT

The eye is the primary target organ of lasers, with injuries usually involving the retina. A radiant flux exposure of 10^{-2}–10^{-1} J/cm^2 produces edema, necrosis, and hemorrhage extending into the vitreous, whereas exposure to radiation at a dose of 10^{-3} J/cm^2 causes limited coagulative necrosis.[207] In animal models, short-pulsed lasers produce retinal lesions with energies of a few μJ and retinal holes with vitreous hemorrhage at a few mJ.[208] Continuous-wave lasers produce long pulses in the millisecond range that require more total energy entering the eye, but less corneal power. A krypton laser (586.2 nm) caused a threshold retinal injury at 22.5 mW for 33 msec and 25 mW for 16 msec.[209] Doses of energy of 3–5 orders of magnitude above recommended guidelines from Q-switched lasers (wavelength 532–780 nm) produced sub- and preretinal hemorrhages.[210]

Krypton, argon, ruby, neodymium-YAG, and dye lasers have all produced retinal burns. A dye laser emitting a wavelength of 589 nm for 10 nsec burned the

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macula of a 24-year-old male, resulting in the subsequent development of a macular hole and permanent visual loss (20/100).[211] An infrared laser with a wavelength of 800 nm, an energy density of 0.003 J/cm^2, and a beam diameter of 1 cm caused a central foveal lesion and a permanent reduction in visual acuity.[212] Similar lesions resulted from the radiation from a neodymium-YAG laser with a wavelength of 1960 nm, a peak power of 100 mW, and a pulse duration of 8 nsec.[213] The beam was nonfocused with a diameter of 30 mm.

Absorption of the short-ultraviolet range (UVB, UVC) and the far-infrared region (IRB, IRC) occurs primarily in the cornea, whereas the lens absorbs most of the UVA light. Visible light and near-infrared radiation penetrate the eye, entering the retina with some absorption of IRA occurring in the vitreous humor. Optical radiation of 380–1,400 nm penetrates various ocular structures; however, the blink reflex and the aversion response limit the duration of laser exposure to 0.15–0.25 seconds. Although these actions usually prevent ocular damage from low-power laser pointers (i.e., <5 mW), prolonged exposure (>10 seconds) may cause significant photocoagulation and photodisruption of retinal injuries, particularly with blue light.[214] Natural protective mechanisms are not effective against high-energy lasers (≥500 mW);[215] these lasers may produce severe retinal damage (severe visual loss, macular holes), even after momentary exposure.[216]

Ultraviolet Region (100–400 nm)

The anterior portion of the eye receives most of the radiation from this part of the electromagnetic spectrum. The conjunctiva and the cornea absorb all UVC (100–280 nm) and almost all UVB (280–315 nm) radiation, whereas the cornea absorbs UVA (315–400 nm). Consequently, excessive UVA light may produce thermal damage to the lens; overexposure to radiation from this portion of spectrum can cause keratoconjunctivitis similar to the keratitis seen in arc welders.[217] Insignificant amounts of UVA light reach the retina.

Visible Region (380/400–780 nm)

The eye focuses visible light on the retina with excessive amounts of visible light potentially causing thermal damage to the retina. Lesions on the retina are usually small because of the spatial coherency of most lasers unless the intensity and/or duration of the exposure are high. Image magnification through binoculars or telescopes increases the hazard of a given laser radiation dose. The retinal pigment epithelium is the first layer of the retina to absorb visible light; as the intensity of the visible light increases, progressive damage occurs in the choroid and the nerve structures in the retina. Depending on the irradiance of the visible light, damage to the retina ranges from temporary erythema and edema to hemorrhage and necrosis with significant loss of visual acuity.[218]

Infrared Region (780 nm–1 mm)

The infrared portion of the electromagnetic spectrum contains three approximate band widths: 1) IRA or near-infrared (near-IR) closest to the visible spectrum (0.78–1.3 μm), 2) IRB or mid-infrared (mid-IR, 1.4–3 μm), and IRC or far-infrared closest to microwaves (far-IR, 3.1 μm–1 mm). The consequences of exposure to IRA radiation are similar to the effects of visible radiation, with the retina being the most vulnerable part of the eye. Excessive absorption of IRB (1.4–3.0 μm) and IRC (3.1 μm–1 mm) radiation as emitted by the CO_2 laser causes thermal damage to the cornea and, to a lesser extent, the lens.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Toxicity

The biological effects of laser radiation are qualitatively similar to the effects of ultraviolet, visible, and infrared radiation, but the intensity of this radiation is closer to the radiation produced by the sun, burning magnesium, or arc lights. The eye is particularly vulnerable to laser-induced injuries as a result of the ability of a laser to increase retinal irradiance 10,000-fold over the retinal irradiance produced by the cornea.[208] The amount of damage to the retina depends on the wavelength, the amount of power delivered to the retina (pulse duration, energy of the beam), and the exact location of the damage (i.e., proximity to fovea). Argon and krypton lasers produce thermal damage by increasing local temperature, coagulating proteins, and causing cell necrosis, whereas excimer lasers alter photochemical processes with low power and long pulses.[219] The major characteristics of the laser beam contributing to the amount of tissue damage are pulse duration, pulse repetition rate, wavelength, image of the laser beam on the retina, and power density. Anatomic factors include the amount of pigment in the choroid and retina, the size of the pupil at the time of exposure, and effectiveness of the blink reflex (typically

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150 msec). An 8 mm pupil (full dilation) transmits 16 times more radiation than a 2 mm pupil (maximum constriction). The duration of exposure depends on the type of laser involved in the incident. Q-switched lasers have the shortest exposure (<100 nsec); however, the high power density causes the greatest hazard for eye injury. Continuous-wave mode allows exposures ranging from milliseconds to minutes, whereas normal multiple spike mode permits exposures in the range of 0.1–2 msec.

The mechanism of injury to the retina is a complex interaction of thermal, mechanical, and displacement effects. High-intensity laser irradiation produces damage by denaturation of proteins associated with temperature elevations of 10°C and by vaporization of fluid in tissue with associated microstream explosions. The effect of the laser beam on the tissue depends on the percentage of energy absorbed by the tissue compared with the amount of energy transmitted through the tissue. Short bursts of a highly focused beam create an acoustic shock wave that propagates through the tissue as the true cutting edge of the laser.

Pathological Changes

Most serious accidents involving human injury with lasers (e.g., Nd:YAG) result from damage to the posterior portion of the eye by lasers emitting radiation in the visible and near-infrared regions. These lasers rarely produce damage to the anterior segment of the eye. The exact location of injury depends on the wavelength; the retina is particularly vulnerable to visible and infrared radiation because the eye focuses this type of radiation on the retina. The increased density of pigment in the macula along with the reduced thickness of the retina at the fovea result in increased sensitivity of the foveal areas of the retina compared with the extrafoveal areas.[220] In a consecutive case series of 14 patients presenting with sudden visual loss after exposure to high-powered, handheld blue laser devices (450 nm, 150–1,200 mW), macular damage included full-thickness macular hole, premacular subhyoid and subinternal limiting membrane hemorrhage, outer retinal disruption at the fovea, epimacular membrane, and retinoschisis-like cavity.[221] The mean visual acuity was 20/290.

Ophthalmological examination typically demonstrates retinal edema; burns or holes in or near the macula; and subretinal, subhyaloid, or vitreous hemorrhage. Intraocular pressures are typically normal. Secondary degeneration from the release of glutamate and inflammatory mediators may increase the anatomic and functional damage beyond the original lesion, resulting in an expansion of the primary injury over hours to days after the exposure.[222] Subsequently, the lesion begins receding over a few weeks to months with improvement greater for lesions more distant from the fovea.[223] Choroidal neovascularization rarely occurs after laser eye injuries; hemosiderosis bulbi and glaucoma do not usually occur.[208] Lasers emitting radiation in the far-infrared (e.g., CO_2) or ultraviolet region produce damage to the anterior segment of the eye. In experimental animals, the beams from CO_2 lasers cause corneal thickening and a central crater formation that penetrates into the anterior chamber at high power levels.[224]

Cellular vaporization and combustion release steam, cell contents, and pyrolysis by-products into the laser surgical plume; the composition of this plume depends on the irradiance, laser type, and tissue treated. This plume contains a variety of biological and chemical constituents including viable cellular matter and viruses.[225,226] Animal studies suggest the *possibility* that smoke from Nd:YAG laser-induced electrocautery on the respiratory system may produce pulmonary damage (alveolar congestion, emphysematous changes) following prolonged exposure; therefore, smoke evacuation devices are recommended during the procedure.[227] However, there are inadequate epidemiological data to determine the clinical significance of long-term exposure to surgical plumes.

CLINICAL RESPONSE

The health risks associated with the use of lasers include beam hazards (i.e., direct effects on the eyes and skin) and nonbeam hazards (i.e., laser-generated fires, electrical shock, noise, air contaminants).[186] The primary adverse health effect from the use of lasers results from ocular and, less often, dermal exposure to the laser beam. Almost all of the structures in the eye are susceptible to laser-induced injuries, depending on wavelength, duration and intensity of exposure, intraocular location of injury, pupil size, and retinal pigmentation. Most eye laser injuries involve retinal injuries following the use of short Q-switched laser pulses (nanosecond range). Pain is unusual in these cases. The typical clinical course of laser-induced retinal injuries involves sudden loss of vision with marked improvement over a few weeks, and occasionally severe, late complications include blindness in the affected eye. Temporary flash-blindness occurred in two civilian pilots following exposure to 12–15 W argon lasers used in a light show on the ground.[228]

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Because of the large voltages used with laser equipment, electrocution has occurred during use. Lasers possess the ability to ignite material including the use of CO_2 lasers near endotracheal tubes or catheters susceptible to ignition by lasers;[229] catastrophic tracheal tube fires may occur during laser surgery.[230] Surgical lasers are the second most frequent ignition source of operating room fires after electrosurgical units; however, in contrast to electrosurgical units, lasers do not require direct contact to produce a fire.[231] Filling tracheal tube cuffs and moistening surgical tape with saline provide partial protection from combustion during CO_2 laser airway surgery.[232] Green nasal cannula prongs are extremely flammable in oxygen following irradiation with a flash-lamp, pumped 585 nm tunable dye laser; however, this laser does not ignite Telfa, gauze, or polyvinyl tubes in room air.[233] Several case reports associate sudden gas embolisms with the Nd-YAG laser in women undergoing endometrial ablation, presumably as a result of the use of air or CO_2 for insufflation and/or cooling the laser tip.[234]

Eye

Immediate

Retina

The eye is the most susceptible organ to laser radiation because the eye transmits radiation in the visible and near-infrared ranges directly to the retina. Many patients sustaining damage from laser radiation did not wear protective eyewear at the time of the accident, despite the importance of eye protection. Damage to the macula can occur from direct viewing of the beam or reflection of the beam from a nearby object (e.g., target, photographic paper).[235,236,237] Injuries from lasers usually, but not always, occur when the unprotected patient is in close proximity to the laser. Ocular damage ranges from minimal retinal burns with complete recovery to extensive necrosis and macular holes with substantial reduction in central visual acuity. The ultimate outcome in terms of visual acuity depends on the location of the burn on the retina.[211] Parafoveal burns may produce paracentral scotoma with visual acuity usually maintained, whereas central foveal burns generally cause permanent loss of visual acuity, with the loss directly proportional to the proximity of the lesion to the fovea.[223,238] Examination of these patients' eyes reveals a parafoveal scotoma and a reduction in visual acuity. Exposure of the periphery to laser radiation may require contrast sensitivity, static perimetry, or dark adaptometry to detect laser-induced damage. Central scotomas usually occur in the presence of foveal lesion, with the range of the scotoma related to the degree of injury; reduction of visual acuity following accidental exposure to laser radiation does not typically occur in the absence of lesions detectable on ophthalmological examination.[207,238] The presence of submacular or vitreous hemorrhage in the absence of other retinal damage is not always associated with decreased visual acuity. Paracentral scotoma may develop in the absence of reduced visual acuity, especially when the dose of energy is several orders of magnitude above the permissible exposure limits.[239] The presence of macular holes indicates a poor prognosis. A case report documented the development of a traumatic macular hole in the central fovea of a physician assistant following the accidental activation of a 755-nm Q-switched laser during routine maintenance.[240] Poor visual acuity and the size of the macular hole remained unchanged at the last follow-up visit 7 months after the injury.

Direct exposure to the beam of a laser is usually associated with the feeling of a flash of light across the eye followed by a shadow (scotoma) of varying size and color. Immediate reduction of visual acuity occurs depending on the extent of edema, hemorrhage, or coagulation of the macula. Most injuries occur on the macula because the macula resides at the center of gaze.

Lens

Lasers producing wavelengths in the ultraviolet or far-infrared region affect primarily the anterior structure of the eye. A few case reports associate the use of the argon laser during the treatment of proliferative retinopathy with the development of cataracts.[241] Light microscopy indicates these spindle-shaped lesions occur mostly in the deep cortical area near the junction of the anterior cortex and the nucleus with extension of the cataract into the nucleus.[242] These cataracts are multiple aggregations aligned perpendicular to the lens capsule; the usual location of these cataracts is posterior to the location of senile cataracts.

Chronic

Sequelae from chronic exposure to laser radiation are not well documented in the medical literature, with ACGIH occupational standards based on the assumption that the total retinal dose from visible illumination encountered in the natural environment is not hazardous.[243,244,245] Unprotected exposure to blue-green argon lasers may produce a cumulative reduction in color contrast sensitivity as defined by a decrease in the tritan threshold (an early manifestation of blue cone photoreceptor injury); the threshold correlates to the number of years of use of the argon laser based on case reports.[246] In a study of 58 Swedish ophthalmologists

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using argon lasers, there was no significant difference ($P > 0.2$) in color vision between argon laser users and 26 age-matched controls.[247] Examination of 18 research scientists with cumulative blue-green argon laser exposure ranging from 580–7,200 hours with infrequent use of eye protection did not detect a reduction in color contrast sensitivity.[248] A case report associated the use of dermatological lasers with the development of vitreous floaters in the eyes of two dermatological laser surgery fellows.[249] These changes were not associated with a reduction in visual acuity, evidence of retinal injury, or further development of floaters. For several hours after the use of argon blue-green laser, flashbacks may produce reductions in the sensitivity for colors lying along the tritan color-confusion line.[250]

Skin

Skin injuries following exposure to the laser beam are typically minor, consisting of erythema and edema that resolve within hours to a few days; urticaria, erosions, crusting, ecchymoses, and blistering occur uncommonly.[251] Postinflammatory hyperpigmentation and, less commonly, hypopigmentation may develop after the burns heal, depending on the depth of the burn.[186] Scars and indentations occur when full-thickness burns develop. Photoepilation requires a careful balance between maximal therapeutic effect and minimum side effects; skin burns may result from the excessive use of intense pulsed-light lasers used for tattoo removal.[252]

HEALTH SURVEILLANCE

Patients

Precautions for the general population and workers regarding laser use are similar. The reproductive risks of nonionizing radiation from laser therapy for hair removal or other cosmetic procedures are minimal to none because of the limited skin penetration of the laser beam.[253]

Workplace

The four basic categories of controls useful in laser environments include engineering controls, personal protective equipment, administrative and procedural controls, and special controls. The guidelines of the US Occupational Safety and Health Administration are based upon the recommendations of the American National Standards Institute (ANSI) Z 136.1–2007 standard.[254] Accident data indicate US FDA (ANSI) Class I (1, 1M), Class II (2), Class IIa (2M), and Class IIIa (3R) lasers, as listed in Table 43.11, are not usually considered hazardous from a radiation standpoint, unless used inappropriately with optical aids; the numbers in parentheses represent ANSI and IEC classifications analogous to US FDA classifications. Table 43.12 lists the requirements of the American National Standards Institute;[255] for details on controls (engineering, procedural, administrative), training, and exceptions to these requirements, see references[254] and.[255] The ANSI Z 136.1 standard requires a Standard Operating Procedure (SOP) covering administrative and procedural controls under the guidance of a Laser Safety Officer (LSO) for Class IV lasers, whereas ANSI recommends SOPs but requires an LSO for Class IIIB lasers.

Exposure Guidelines

The skin and the eye are the primary target organs potentially damaged by radiation from lasers. The specific area of injury depends on the wavelength; thus, guidelines for exposure are based on the wavelength, duration of exposure, and measures of power

TABLE 43.12. American National Standards Institute (ANSI) requirements for specific laser classifications based on ANSI Z136.1–2014. (Based on American National Standards Institute).[255]

ANSI Class (US FDA Class)	Procedural and Administrative Controls	Training	Medical Surveillance
1 (I)	None	None	None
1M (I)	Required	Application dependent[a]	Application dependent[a]
2 (II)	None[b]	None[b]	None
2M (IIa)	Required	Application dependent[a]	Application dependent[a]
3R (IIIa)	None[b]	None[b]	None
3B (IIIb)	Required	Required	Suggested
4 (IV)	Required	Required	Suggested

[a] Certain uses of Class 1M or 2M may require hazard evaluation including training and medical surveillance similar to Class 3 and 4 lasers. [b] Except for intentional intrabeam exposure applications.

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(e.g., radiant exposure for pulsed lasers, irradiance for continuous-wave or repetitively pulsed lasers). The International Commission on Nonionizing Radiation Protection (ICNIRP) and the American Conference of Industrial and Governmental Hygienists (ACGIH) threshold limit values (TLVs) list recommended exposure limits for direct ocular exposure to laser beams based on wavelength, duration of exposure (pulse duration), correction values, and irradiance diameter (spot size) in some circumstances.[244,245] Measurement of irradiance or radiant exposure is an average over the circular areas defined by the limiting aperture. No correction is necessary for a beam size of <1 mm; however, light in the 400–1,400 nm range is hazardous to the retina. Power from the light source should be averaged over a limiting aperture of 7–8 mm (i.e., the maximum size of a dilated pupil). The only exception is a limiting aperture of 10 mm for wavelengths 0.1–1 nm. These TLVs are complicated because of the variability of penetration by different wavelengths and several correction factors for specific wavelengths, including accounting for reduced absorption of melanin, reduced photochemical sensitivity for retinal injury, and preretinal absorption of ocular media. Sources are available to explain the correction factors.[244,255] These organizations apply correction factors for wavelengths 700–1,400 nm and extended sources in the range of 400–1,400 nm that produce different effects than point sources during direct intrabeam viewing. Extended sources (e.g., laser arrays, diffuse reflecting surfaces, diodes) are distinguished from intrabeam viewing by the apparent visual angle (limiting angle subtense) between the eye of the observer and the extended source.

The exposure guidelines of ICNIRP and ACGIH for skin exposure from a laser beam are the same as the guidelines for eyes in UV (180–400 nm) and IRB/IRC (1.4–1,000 μm) wavelengths; however, for visible light and IRA (400–1,400 nm) wavelengths, correction factors are for exposure duration of >10 seconds and beam diameter. Guidelines for laser pointers primarily involve education and training for all persons involved with these products.

Safety Glasses

The primary method of preventing injury to workers is the use of shielding from high-energy beams and eye protection. Eye-protection devices designed to protect against laser radiation should be used when engineering controls are inadequate to eliminate the possibility of potentially hazardous eye exposure with class IIIb (3B) and IV (4) lasers. The filtering characteristics (optical density, OD) of the glasses should be clearly marked and must be effective for the specific wavelength in use. The plastic or glass lenses of protective eyewear may be either absorptive or reflective of laser radiation. The use of protective glasses reduces the amount of radiation received by the eye from the selective spectral absorption of colored lenses or the selective reflection of dielectric coatings on the eyewear. Some types of lasers are tunable, whereas other lasers (e.g., helium-neon) operate at three different wavelengths depending on the specific design. Eye gear should be checked for cracks, scratches (reflective design), and deterioration of the frame. In contrast to absorptive protective eyewear, scratches on reflective eyewear may allow penetration of the beam. Procedures for the operation of the laser should avoid focusing the beam on reflective surfaces; eyewear should provide protection from beams entering the eye from the side or front.

Selection of Eyewear

Optical density is the parameter that defines the amount of attenuation of the beam as it passes through the lens. The optical density is a logarithmic function defined by Equation 43.7.

$$\text{Optical Density (OD)} = \log 10\,(Io/I) \quad \text{(Equation 43.7)}$$

where:

Io = intensity of the incident beam,
I = intensity of the transmitted beam.

If the lens transmits 1% of the incident beam from the laser, then the OD is 2, whereas transmission of 1/1,000,000th of the beam through the lens correlates to an OD of 6. Typically, the intensity of the transmitted beam is the maximum laser beam radiant exposure (J/cm^2) for pulsed lasers and the maximum laser beam irradiance (W/cm^2) for continuous-wave lasers. High visible light transmittance is important because eye fatigue may occur; alterations in the ambient lighting of the work environment may be necessary. The spectral response of the eye at night should be considered if the operation of the laser occurs during periods of darkness because blue-green filters reduce night vision more than red-orange lenses.

Table 43.13 lists the factors important in selecting appropriate eyewear. Damage thresholds are important factors during the operation of high-intensity lasers. A Q-switched pulsed laser produces damage to plastic in the range of 1–100 J/cm^2 and glass in the range of 10–100 J/cm^2.

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TABLE 43.13. American National Standards Institute (ANSI) factors for selecting appropriate eyewear. (Adapted from ANSI).[255]

Wavelength of laser output
Potential for laser operation at several wavelengths
Radiant or irradiance values
Maximum permissible exposure (MPE)
Optical density of eyewear at laser output wavelength
Visible light transmission needs
Peripheral vision requirements
Total radiant flux or irradiance during the time eyewear is worn that will not damage the eyewear including transient leaching
Need for corrective glasses
Comfort and fit
Material strength and resistance to photobleaching
Capability of front surface to produce specular reflection

Medical Monitoring

ANSI guidelines suggest medical surveillance for workers using Class IIIb or Class IV lasers, whereas workers operating Class I, Class II, Class IIa, or Class IIIa lasers may need medical surveillance depending on special circumstances (e.g., use of optical aids that intensify the output of the laser, Classes 1M and 2M). Medical surveillance includes baseline Amsler grid, visual acuity, color vision, contrast sensitivity, and ocular history. Medical examinations for incidental personnel (e.g., supervisors, military personnel on maneuvers, custodians, clerks) involve only visual acuity testing. Further ophthalmological examination is necessary if abnormalities are detected on the routine eye exam. Although periodic examinations are not necessary, all personnel should be examined within 48 hours whenever a laser injury is suspected.[256] The American National Standards Institute recommends an annual skin examination for personnel exposed to UV lasers.

TREATMENT

Treatment of laser-induced injuries of the retina is symptomatic, primarily involving the use of corticosteroids with the rationale of reducing cellular inflammation associated with the retinal injury. Primate studies suggest use of methylprednisolone reduces photoreceptor damage at the periphery of the lesion and inhibits subretinal neovascularization;[257,258] however, rodent studies suggest the improvement is short term.[259] Clinical studies are limited by the rare occurrence of laser eye injuries. Surgical intervention is considered for the removal of vitreous and periretinal hemorrhages. The use of a Q-switched Nd:YAG laser may be useful in opening the anterior wall of the bubble of a subhyaloid hemorrhage.[210] Case reports on the success of retinal surgery after injury are mixed. The ultimate visual outcome depends on the location of the injury on the retina and the amount of energy delivered. Improvement in visual function may occur up to 1 year after injury.

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Chapter 44

RADIOFREQUENCY RADIATION

HISTORY

Studies on the biological effects of the radiofrequency (RF) portion of the electromagnetic radiation began in the early 1900s with investigations into biophysical mechanisms; later, in the 1920s–1930s, experimentation began on the clinical applications of hyperthermia and diathermy with these energy sources. In England during 1939, John Randall and Harry Boot invented the first cavity magnetron tube that was initially used as a microwave radar device to detect Nazi aircraft and ships during World War II. The American engineer, Percy Spencer, discovered the beneficial effects of microwaves on foods incidentally, while working near radar equipment. He subsequently built and patented the first microwave oven using the magnetron tube in 1945. Extensive research on the health and safety issues of radiofrequency electromagnetic fields began in the early 1950s followed by the development of exposure guidelines from the American National Standards Institute (ANSI) and the Institute of Electrical and Electronic Engineers (IEEE) in the 1960s. Later guidelines were formulated by the International Radiation Protection Association (IRPA) and the International Commission on Non-Ionizing Radiation Protection (ICNIRP). Recommendations were propagated for radar (1950s–1960s), radio/TV broadcasting (1960s–1970s), microwave ovens (1970s–1980s), police radar (1980s), and wireless communication equipment (1990s), including wireless fidelity (Wi-Fi), and Worldwide Interoperability for Microwave Access (WiMAX) for mobile phones, base stations, smart meters, and radiofrequency identification. In the late 2000s and early 2020s, deployment of long-term evolution (LTE) began with 4G cell technology and continued with 5G phone technology, respectively.

PHYSICAL PROPERTIES

Radiation is the transfer of energy through space with electromagnetic radiation of radio waves being nonionizing and possessing much less energy than the visible spectrum. Electromagnetic fields have always existed around the earth. In the lower portion of the electromagnetic radiation spectrum, radiofrequency electromagnetic fields (mobile telephones, base stations, induction heaters, anti-theft devices, radar, radio, and television broadcast facilities) occupy a position between static/extremely low-frequency electromagnetic fields (household electrical appliances, power lines, computers) and infrared radiation as displayed in Figure 44.1.

Electromagnetic waves constitute oscillating electric and magnetic forces that move through space at the speed of light perpendicular to each other. Moving electric charges produce these energy waves; their origin may be natural (e.g., the sun) or artificial (e.g., microwaves, radio, and television transmitters). In the radiofrequency range, tightly coupled electric and magnetic fields propagate the electromagnetic wave (radiation). Knowledge of the magnitude of electric field allows the calculation of magnetic fields and vice versa. Distance from the source affects these calculations. In the reactive near-field close to the source, the electric and magnetic fields associated with energy

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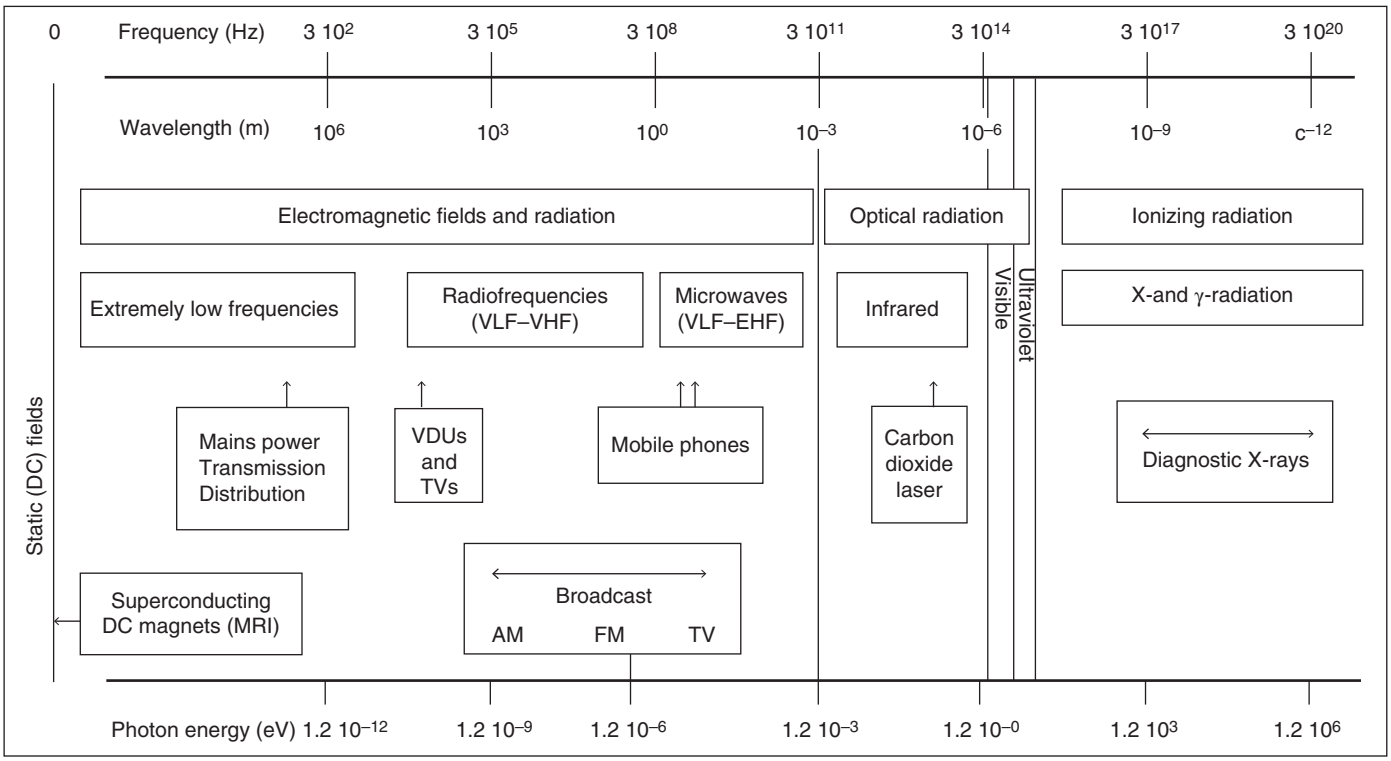


FIGURE 44.1. Electromagnetic radiation spectrum. Radiofrequency electromagnetic fields occupy a position in the nonionizing part of the electromagnetic radiation spectrum between static/extremely low-frequency fields and the infrared portion. (Redrawn from International Agency for Research on Cancer, IARC).[1] *Abbreviations:* AM = amplitude modulation; DC = direct current; EHF = extremely high frequency; eV = electron volt; FM = frequency modulation; MRI = magnetic resonance imaging; TV = television; HF = ultra-high frequency; VDU = visual display unit; VHF = very high frequency; VLF = very low frequency.

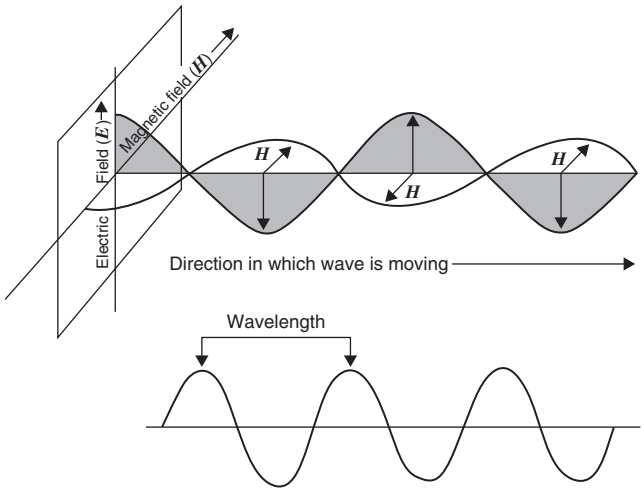


FIGURE 44.2. The electromagnetic monochromatic wave. These waves consist of electric and magnetic forces moving through space at right angles to one another in a wave-like pattern. *Abbreviations:* E = electric field; H = magnetic field.

stored in the vicinity of the source affect radiation emitted from the source, whereas the far-field represents the distance from the source sufficient to have no influence on the energy radiated away from the source. In the latter region, power density can be determined from field strengths. The reactive near-field typically extends approximately a wavelength from the source.

Figure 44.2 illustrates the propagation of an electromagnetic wave characterized by electric and magnetic fields moving at right angles to each other. Several physical parameters describe electromagnetic waves, including: 1) strength or intensity of the electric field (E) in V/m and magnetic field (H) in T (tesla); 2) frequency (f) of the oscillations in Hz; 3) wavelength (λ) in metric dimensions; 4) direction of the E-field or electric polarization (P); 5) velocity of propagation (c); and 6) the Poynting vector (S). Table 44.1 lists the quantities, units, and symbols useful for describing electromagnetic fields in the radiofrequency range.

Wavelength and frequency are inversely related with frequency increasing and wavelength decreasing from the beginning of the electromagnetic spectrum.

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TABLE 44.1. Quantities and units useful for describing radiofrequency fields.

Quantity (Symbol)	Unit (Symbol)
Conductivity (σ)	Siemens/meter (S/m)
Current (I)	Ampere (A)
Current density (J)	Ampere/square meter (A/m^2)
Electric field strength (E)	Volt/meter (V/m)
Frequency (f)	Hertz (Hz)
Impedance (Z or η)	Ohm (Ω)
Magnetic field strength (H)	Ampere/meter (A/m)
Permeability (μ)	Henry/meter (H/m)
Permittivity (ε)	Farad/meter (F/m)
Power density (S or Pd)	Watt/square meter (W/m^2)
Propagation constant (K)	Per meter (m^{-1})
Specific absorption (SA)	Joule/kilogram (J/kg)
Specific absorption rate (SAR)	Watt/kilogram (W/kg)
Wavelength (λ)	Meter (m)

In free space, the velocity (c) is proportional to the product of the frequency and wavelength as defined by Equation 44.1.

$$c = \text{frequency}\,(f) \times \text{wavelength}\,(\lambda) \quad \text{(Equation 44.1)}$$

where

c = speed of light.

Radiofrequency waves interact with the medium through which they travel; therefore, the speed of the propagation of the wave depends on the interaction of the matter in the electric field (i.e., permittivity) and the magnetic field (i.e., permeability). Propagation of radiofrequency waves through biological media is vastly different from the propagation of these waves through space. For plane waves, the Poynting vector ($\vec{s}$) represents the magnitude and direction (vector product) of the energy flux density of the electromagnetic field, as defined by Equation 44.2.

$$\vec{s} = (\vec{E}) \times (\vec{H}) \quad \text{(Equation 44.2)}$$

where

$\vec{E}$ = electric field strength,
$\vec{H}$ = magnetic field strength.

The energy of electromagnetic waves propagates as bundles of energy (photons) with the amount of energy in each photon directly proportional to its frequency. The higher frequency implies greater photon energy. Thus, photons in the X-ray portion of the electromagnetic spectrum contain much more energy than photons in the radiofrequency range of the electromagnetic spectrum. By convention, the dividing line between ionizing radiation and nonionizing radiation occurs at a photon energy of 12 eV corresponding to a wavelength of 100 nm or a frequency of 10 MHz.[2] At the upper end of the radiofrequency spectrum (300 GHz) near high-frequency microwaves, the energy/photon is 0.00125 eV, whereas the energy/photon near the lower end of the radiofrequency spectrum (100 kHz) close to AM radio is 4.1×10^{-10} eV. Consequently, photons in the radiofrequency range do not possess sufficient energy to disrupt molecular bonds. The adverse effects of the absorption of these waves result primarily from the production of heat rather than the disruption of chemical bonds. At the very low-frequency range of electric power (i.e., 60 Hz), the electromagnetic waves pass through the human body with minimal energy absorption; thus, little heating and no ionization occur in this portion of the electromagnetic spectrum.

Bandwidth

The spectrum of radiofrequency electromagnetic radiation extends from 30 kHz–300 GHz corresponding to wavelengths ranging from 10 km down to1 mm; some organizations use a lower range of 3 kHz. Radio waves have the longest wavelengths in the electromagnetic spectrum. Table 44.2 lists commercial, medical, and scientific applications of various radiofrequency bands. Microwaves represent the subset of the radiofrequency range of 300 MHz–300 GHz. This division does not imply a significant change in physical properties. Radar, satellite communications, and microwave relay stations typically operate in the 3–300 GHz range, whereas microwave ovens operate at 2.45 GHz.

The International Telecommunications Union separates the radiofrequency region into the following frequency decades: very low frequency (VLF); voice frequency (VF); low frequency (LF); medium frequency (MF); high frequency (HF); very high frequency (VHF); ultra-high frequency (UHF); super-high frequency (SHF); and extremely high frequency (EHF), as displayed in Figure 44.1.

Figure 44.3 illustrates the distribution of bandwidth in the radiofrequency range to various manufactured sources including broadcasting, communication, industrial, scientific, and medical uses. Frequency bands used for broadcasting TV and radio signals are generally similar across different countries, as displayed in Table 44.3. Analog broadcast radio uses amplitude modulation (AM) in the long, medium, and short bands. AM radio is less popular than FM radio because frequency modulation provides a better signal using band II (very high

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TABLE 44.2. Various commercial, medical, and scientific applications of radiofrequency bands. (Adapted from World Health Organization, WHO).[3]

Frequency Band	Applications
30–300 kHz	Marine and aeronautical communications, navigation, long-range communications, radiolocation, VDUs, electro-erosion treatment, induction heating and melting of metals, power inverters
300 kHz–3 MHz	Communications, navigation, marine radiophone, amateur radio, industrial RF equipment, AM broadcasting, RF-excited arc welders, sealing for packaging, production of semiconductor material, medical applications
3–30 MHz	Citizen band, amateur radio broadcasting, international communications, medical diathermy, magnetic resonance imaging, dielectric heating, wood drying and gluing, plasma heating
30–300 MHz	Police, fire, amateur FM, VHF–TV, diathermy, emergency medical radio, air traffic control, magnetic resonance imaging, dielectric heating, plastic welding, food processing, plasma heating, particle separation
300 MHz–3 GHz	Microwave point to point, amateur, taxi, police, fire, radar, citizen band, navigation, UHF–TV, microwave ovens, medical diathermy, baby monitors, food processing, material manufacture, insecticide, plasma heating, particle acceleration
3–30 GHz	Radar, satellite communications, amateur, fire, taxi, airborne weather radar, police, microwave relay, anti-intruder alarms, plasma heating, thermonuclear fusion experiments
30–300 GHz	Radar, satellite communications, microwave relay, navigation, amateur radio

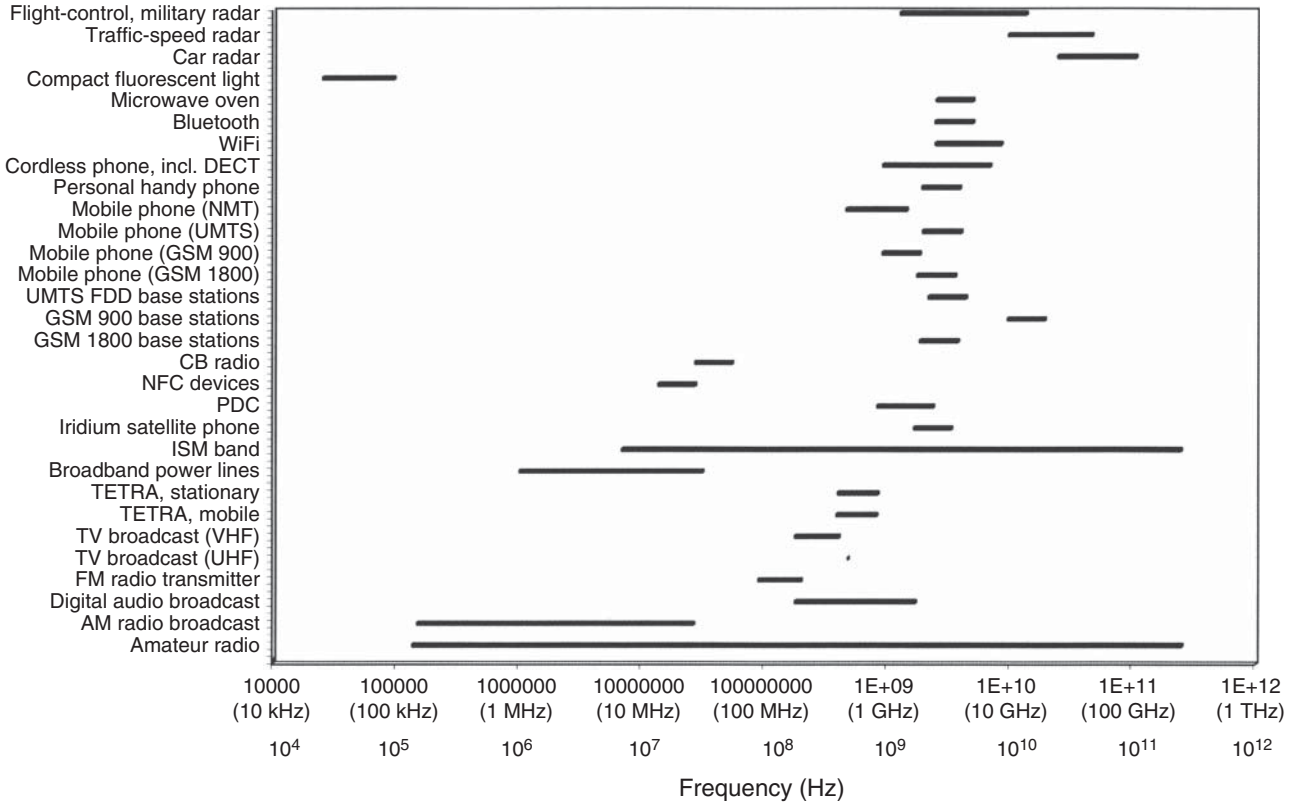


FIGURE 44.3. Distribution of bandwidths in the radiofrequency range for artificial sources. (Redrawn from International Agency for Research on Cancer Working Group on Evaluation of Carcinogenic Risks to Humans).[2] *Abbreviations*: AM = amplitude-modulated radio; CB = citizen band; DECT = digital enhanced cordless telecommunications; FDD = frequency-division duplex; FM = frequency-modulated radio; GSM = global system for mobile communications; ISM = industrial, scientific, medical use; NFC = near-field communications; NMT = Nordic mobile telephony; PDC = personal digital cellular; TETRA = terrestrial trunked radio; TV = television; UHF = ultra-high frequency; UMTS = universal mobile telecommunications system; VHF = very high frequency; Wi-Fi = standard wireless local area network (WLAN technology).

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TABLE 44.3. Distribution of frequency bands in the radiofrequency range used in various countries.

Band	Description	Source	Frequency Range (MHz)
Long wave	Amplitude modulation (LF, MF)	AM radio	0.145–0.283
Medium wave		AM radio	0.526–1.606
Short wave	High-frequency band (HF)	International radio	3.9–26.1
FM	VHF, Band II frequency modulation	FM radio	88–108
TV/DAB	VHF band III	Analog/digital TV, digital audio broadcasting	174–223
TETRA	Terrestrial trunked radio		380–400
TV	UHF, bands IV, V	Analog/digital TV	470–854
GSM/UL	Global system for mobile communications, uplink	Mobile phone to base station (European)	880–915
GSM/DL	Global system for mobile communications, downlink	Base station to mobile phone (European)	925–960
DCS/UL	Digital cellular system, uplink	Cellular phones using digital technology (TDMA, GSM, CDMA)	1,710–1,785
DCS/DL	Digital cellular system, downlink	Cellular phones using digital technology (TDMA, GSM, CDMA)	1,805–1,880
DECT	Digitally enhanced cordless telecommunication	Portable phone	1,880–1,900
UMTS/UL	Universal mobile telecommunications service, uplink	Mobile phone, frequency-division duplex base stations	1,920–1,980
UMTS/DL	Universal mobile telecommunications service, downlink	Mobile phone, frequency-division duplex base stations	2,110–2,170
Wi-Fi	Wireless fidelity	Wireless local area network (WLAN), access points	2,400–2,500

frequency, VHF) than amplitude modulation. International radio uses the short-wave band because reflection of this signal off the ionosphere allows the signal from multiple horizontal dipole antennae to travel thousands of kilometers. The original band for television was band III (VHF); however, many countries are transferring television to bands IV/V (ultra-high frequency, UHF) while assigning band III to digital audio broadcasting. Radio and TV broadcast sites typically contain a transmitter building with an RF feeder cable extending to multiple antennae that may cover an area of several square kilometers. Terrain affects the transmission of broadcast signals by creating shadow areas, particularly, UHF signals. Booster transmitters are necessary to increase the distance of the signal by propagating and rebroadcasting it in these shadow areas.

In contrast to the high-power transmitters involved with radio and TV transmissions, cellular communication requires a large number of low-power transmitters (base stations) dispersed over a much smaller service area. Each user requires two-way (duplex) communication with a dedicated communication channel for uplink (phone to base station) and downlink (base station to phone) signals. Each base station has limited capacity; therefore, higher cell phone use necessitates more base stations in the area, particularly in densely populated urban locations. Cellular networks have limited frequency channels, requiring the reuse of frequency channels that cause interference in the cells; consequently, design requirements result in minimization of the use of adjacent cells and the reduction in RF frequency exposure.[2]

Mobile phone technology involves five generations (1G–5G), with the first generation (1G) introduced in the 1980s no longer in operation and 5G now being deployed. In the 1990s, second-generation (2G) began operations that continue today. This technology involves the use of time-division multiple access (TDMA), including Global System for Mobile communication (GSM) in Europe, Personal Digital Cellular (PDC) in Japan, and Personal Communication Systems (PCS) in North America. The introduction of code-division multiple access (CDMA) in North America was a 2.5-generation system. With TDMA, the time-domain

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signal from a cellular phone appears as a continuous carrier wave that is pulse-modulated at a fixed frequency. Code division multiple access (CDMA) is a competing technology that looks more like an irregular train of 1.25-msec-side pulses of a carrier wave with widely varying amplitudes. TDMA and CDMA have their unique established carrier frequencies. The carrier frequency is always higher than the signal frequency, regardless of the type of signal (i.e., continuous or analog vs. digital).

The era of the smartphone began in the early 2000s with the introduction of third-generation (3G) systems that provided comprehensive data access. This system was compatible with 2G systems depending on the management of the network traffic. The next generation (4G) systems use orthogonal frequency-division multiplexing (OFDM) for Long-Term Evolution (LTE) systems and Worldwide Interoperability for Microwave Access (WiMax) for other systems. These technologies overlay 2G and 3G systems resulting in multiple access modes as some RF spectrums are reallocated to 3G and 4G cellular systems.

Deployment of fifth-generation (5G) systems augments current 4G technology. 5G technology transmits much greater data at higher speeds for a variety of applications than the preceding cellular technology, partly due to the use of higher frequencies in the millimeter wave range (MMW, 30–300 GHz) and greater bandwidth than older generations.[4] The MMW range typically includes radar and microwave links. This system provides the basis for the Internet of Things (IoT), where machines communicate directly with other machines. Additionally, 5G allows direct communication between personal devices and the environment (smart cities, other smart phones, autonomous vehicles, industrial Internet, home). Consequently, 5G will be a network or networks rather than a single radio access interface, necessitating higher infrastructure density from the shorter ranges of higher frequencies.[5] 5G networks operate in several frequency bands with the first phase involving lower frequencies (e.g., median $\cong$ 3.5 GHz).[6] Table 44.4 lists the applications and advantages of 5G subdivisions.

Absorption

Radio waves, including microwaves, pass through space at the speed of light until objects in their path reflect, diffract, absorb, or transmit the waves. Microwaves account for a very small portion (i.e., 0.01%) of solar radiation, depending on solar activity. Cloud cover, skin pigmentation, or altitude do not affect microwaves; however, the amount of microwave radiation is inversely related to latitude and strongly dependent on solar activity (sunspots). The relative permittivity represents a measure of a dielectric material to store energy. Greater permittivity implies greater interaction of the matter with the electric field. The velocity of microwaves decreases during transmission through biological media, depending on tissue permittivity and permeability. Tissues containing large amounts of water (brain, muscle, skin) are particularly effective at reducing the propagation of these waves; therefore, higher energy absorption (i.e., higher SAR) occurs in these tissues compared with tissues (fat, bone) containing smaller amounts of water. The human body acts like an antenna for radio waves. The amount of energy absorbed by the body from radio waves depends on several factors including the following: 1) **frequency** and energy of the wave; 2) **orientation** of the electric field relative to the long axis of the body; 3) **relative size** of the body compared with the wavelength; 4) the **shape** of the body; 5) **distance** between the body and the source; 6) local **environment** (reflection, resonance); and 7) **dielectric properties** of the tissues.[7]

Dissipation of the absorbed energy occurs through the production of electric current (conduction loss) and molecular rotation (dielectric loss). An increase in the kinetic energy of the molecules in the tissue corresponds to attenuation of radio waves and heating of the tissue. The degree and extent of temperature elevation in the tissue depend on the physical characteristics/distribution of the electromagnetic field in the body and the body's thermoregulation (e.g., conduction, convection, radiation, evaporative cooling).[8] The physical characteristics of the electromagnetic field include power density, polarization, frequency, and duration.[9]

TABLE 44.4. Anticipated 5G frequency spectrum subdivisions. (Adapted from Simkó and Mattsson).[6]

Frequency	Applications	Advantages/Disadvantages
<1 GHz	Network coverage, IoT	Overlaps with older systems, lower infrastructure costs, longer range
1–6 GHz	Network coverage, Internet of Things (IoT), improved data transfer	More available spectrum, shorter range, poorer performance than higher frequencies
>6 GHz	Very high data capacity	High-speed data transfer, short latency times, short range

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Metallic Implants

Metallic implants (e.g., disks, metallic pins/clips, needles, plates, prostheses, rings, rods) act as antennas, enhancing local electric fields when the patient receives radiofrequency waves. The degree of enhancement of the electromagnetic fields depends on the implant dimensions, orientation, shape, and location. Maximum thermal effects occur at the resonant frequency of the implant. Individuals with metallic implants located in far-fields associated with radiofrequency sources do not typically experience adverse effects because the electromagnetic fields are weak. The situation is much more complex for the general public in near-fields as a result of the more complicated interaction of the electromagnetic field with the exposure, implant, and person. Theoretically, substantial rises in SAR values can occur on a small scale near implant corners and tips; however, experimental and computational studies indicate electromagnetic field enhancement around implants is unlikely to cause excess heating of >1°C consistent with the lack of case reports documenting adverse effects.[10] Numerical modeling of worst-case scenarios of workers with a metallic implant exposed to radiofrequency electromagnetic fields suggests implants may reduce the safety limit for RF exposure by ~25% compared with workers without an implant.[11]

Dental work poses little risk from exposure to radiofrequency radiation because the teeth are relatively heat-resistant and the mouth effectively dissipates heat.[7] Current shielding of pacemakers largely prevents interference with pacemaker functions; however, strong electric fields may cause interference with some pacemakers.[12] Programmable pacemakers have security systems that usually prevent interference with radiofrequency radiation; the effect of radiofrequency exposure (duration, strength, frequency, modulations) on pacemaker function depends on the individual pacemaker. Radiofrequency radiation can produce interference with cochlear implants, simulating auditory illusions.[13]

Perception

Humans do not reliably sense the presence of radio waves, and this type of radiation is invisible to the human eye. In a study of 5,933 adults in the Netherlands using a health survey and electronic health records, the perception of radiofrequency exposure correlated poorly to estimated RF exposure based on prediction models, distance to high-voltage overhead power lines, and self-reported use of indoor electrical appliances.[14] The association between perceived RF exposure and self-reported nonspecific symptoms was stronger than the association between symptoms reported in the health records and their perceived RF exposure. Cutaneous perceptions of heat and pain are not reliable indicators of the presence of hazardous levels of RF radiation.[15] Pulse radiofrequency radiation (e.g., radar) can produce a clicking sound from the heating of the cochlear fluid.[16] Perception of microwaves results from the stimulation of the sensations of temperature and pain. Reported thresholds for heat range from 27–200 mW/cm^2 (270–2,000 W/m^2), depending on the area irradiated, frequency, and duration of exposure.[3] In an experimental study of thresholds for a warm sensation on forehead skin during *continuous* exposure to 3 GHz microwave radiation, the threshold ranged from 1 second (Pd = 58.6 mW/cm^2) to 4 seconds (Pd = 33.5 mW/cm^2).[17] Exposure to 10 GHz reduced the power densities (Pd) by ~2.7-fold. The threshold for burning pain on the inner forearm of 6 men during *continuous* exposure to 3 GHz microwave radiation ranged from 20 seconds (Pd = 3,100 mW/cm^2) to 120 seconds (1,000 mW/cm^2).[18]

EXPOSURE

RF electromagnetic fields in proximity to the body generate nonuniform electric and magnetic fields that induce currents in the tissues. The induced field strengths are approximately proportional to the time-averaged radiated power and inversely proportional to the distance from the source. These fields vary by several orders of magnitude at local hot spots.[2] The most obvious effect of the absorption of radio waves is the production of heat in the medium. The calorimetric measure of radiation intensity in SI terminology is irradiance in units of W/m^2; however, the traditional measure of radiofrequency exposure is incident power/unit area (power density), typically measured in $\mu W/cm^2$ or mW/cm^2. Power density (i.e., the energy of the RF wave) is a measure of external dose that represents the time rate of energy flow/unit area across a surface area determined by the intensity of the electric and magnetic field strengths. The power density of summer sunshine peaks at ~1,000 W/m^2 (100 mW/cm^2). Analytical instruments measure power density indirectly by quantitating induced voltages and currents.

Very complex field distributions may occur from several factors, including perturbations of electrical properties and variations in the shape, size, and orientation of objects within the field. These complex

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fields produce nonuniform fields and fluctuating depositions of energy within biological systems. At lower frequencies (<300 MHz) under near-field conditions, measurements of electric field (E) and magnetic field (M) strengths are necessary to determine power density, particularly for the quantitation of biological effects.[19] At frequencies of >300 MHz (i.e., wavelengths >1 m), far-field conditions usually exist, resulting in a constant ratio between the magnetic and electrical fields. Hence, calculation of the power density requires only measurements of the electric fields.

Far-Fields

The simplest exposure to radio waves occurs when the electromagnetic field is sufficiently removed from the receiver that the source of the field can be considered a point. At this distance, the antenna is large enough so that the radiation from each part of the antenna is in phase with the receiver and the radiation travels as plane waves. The conditions of a far-field or plane wave exist for horn antennas when the distance (d) between the transmitter and the receiver exceeds the value Equation 44.3.[20]

$$\text{Far-field pattern exists when } d = >2\,L^2/\lambda \qquad \text{(Equation 44.3)}$$

where

L = the largest dimension of the source aperture,
λ = wavelength.

Under far-field conditions, Equation 44.4 describes the power flux density; this value decreases inversely with the square of the distance from the source as measured in watts/square meter (W/m^2).

$$\text{Pd} = E \times H \qquad \text{(Equation 44.4)}$$

where

E = electric field strength (V/m),
H = magnetic field strength (A/m),
Pd = power density (W/m^2).

Under far-field conditions (>300 MHz, wavelength >1 m), the free space impedance, Z_o, in air is a constant, as described by Equation 44.5.

$$Z_o = E/H = 377\,\Omega \qquad \text{(Equation 44.5)}$$

This conversion factor allows the calculation of the power density from either the electric field strength (E) or the magnetic field strength (H), as defined in Equation 44.6.

$$\text{Pd} = E^2/377 = 377\,H^2 \qquad \text{(Equation 44.6)}$$

Hence, the electric and magnetic field strengths are equally valid measures of radiant energy flow under the conditions of plane wave exposure. The primary measurement is usually the electric field.

Near-Fields

Radiating Near-Fields

The near-field is the region close to the source antenna. As demonstrated in Figure 44.4, the near-field is divided into the reactive near-field region (i.e., closest to source) and the radiating near-field region (i.e., closest to far-field). The radiation pattern varies with distance in the radiating near-field, whereas source fields influence the field in the reactive near-field region. When the longest dimension (L) of the source antenna exceeds the wavelength (λ), the inverse square law no longer applies at distances $<2L^2/\lambda$ from the source. For horn antennas, the power density varies in an inverse linear relationship until distances are $<2L^2/\lambda$, where reflective interference complicates the calculation of the power density. Similarly, the conversion factor for power density and electromagnetic fields no longer applies. For dipole antennas where the dimension of the aperture (L) is < wavelength (λ), the near-field extends to a distance of $\lambda/2\pi$. In the near-field, most of the energy is deposited in the 20% of the total body volume closest to the antenna feed point.[21]

Reactive Near-Fields

The reactive zone is the area in the immediate vicinity of the antenna where energy is stored rather than transmitted. Objects located within this field (e.g., probes) may alter the field significantly. The electric and magnetic fields become less coupled at lower frequencies, particularly when the wavelength is large compared with the physical size of the source. From a practical perspective, near-fields at frequencies below 1 MHz represent the greatest hazard (e.g., highly localized RF-induced currents called RF hot spots).[3]

Sources

A wide variety of commercial and military applications emit radiofrequency waves, including linear beam tubes (klystrons), power grid tubes, solid-state devices, and

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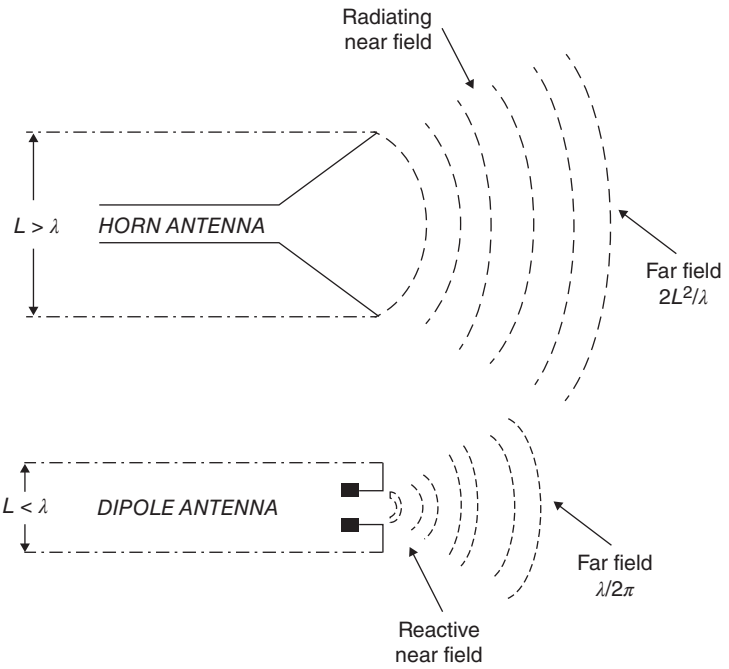


FIGURE 44.4. Schematic illustration of relative positions of the reactive near-field, radiating near-field, and the far-field with horn and dipole antennas. Within the near-fields, the strength of the radiofrequency electromagnetic fields varies rapidly with distance. The electromagnetic field of the source influences the fields in the reactive near-fields, whereas the electromagnetic fields in the radiating near-fields are related to the distance from the source. Measurement and calculation of the electromagnetic fields in the far-field are easier because the fields have the characteristics of radiation with the power density inversely related to the distance squared. The distance to the far-field depends on the longest dimension of the source antenna and wavelength rather than the distance from the source. (World Health Organization).[3] *Abbreviations:* λ = wavelength; L = longest distance to the source antenna.

crossed-field devices. These RF sources operate in one of the following three modes: 1) continuous (e.g., communications); 2) intermittent (e.g., heating); and 3) pulsed (e.g., radar, digital communication).[22] The dominant RF radiation sources for the public are transmitters held close to the body (e.g., handheld devices), whereas RF radiation sources in the near-field are the primary source of RF exposure for workers. Environmental sources near the public typically emit relatively modest field strengths; however, potential high-field strengths may occur in the industrial setting, depending on the design and operation of the equipment.[23] Electromagnetic fields vary substantially around radiofrequency sources. Consequently, spot measurements may not reflect average exposures, particularly when analyses are designed to detect maximum exposures exceeding published guidelines and workers spend substantial time away from the antennae.

Natural sources of radiofrequency radiation exposure are small compared with man-made sources (e.g., navigation, communication, industry, medicine).[24] The earth emits electromagnetic radiation (black-body radiation) at a level of ~0.003 W/m^2 (0.3 μW/cm^2) in the RF range.[3] The human body also generates electromagnetic fields internally and externally with power densities in the RF range of ~0.003 W/m^2. RF waves in the frequency range of 10 MHz–37.5 GHz can penetrate the atmosphere; however, the amount of radiation emitted by extraterrestrial sources is small compared with that from man-made sources. RF radiation sources in the home include cellular phones, microwave ovens, dimmer switches, wireless toy controllers, walkie-talkies, televisions, radios, personal computers, and electric motors that contain sparking brushes.[25] These RF sources produce variable amounts of electrical fields depending on the type and location of the antenna, phone operation, distance from base station, RF traffic conditions, output power of the antenna, directions of transmission, attenuation of interfering objects, and scatter from trees and buildings. Most appliances do not emit RF radiation, except for those that produce static on radios or televisions.

Broadcast and Telecommunications

Broadcast antennae direct the VHF/UHF signal toward the horizon in all directions; hence, field strengths

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are lower at ground level and at distances from the antennae as the waves diffuse through the air. Consequently, exposure of the public to electromagnetic fields from the transmitters is substantially less than that of workers with access to the antenna towers. The estimated median RF exposure for the US population in 1978 was ~0.02 μW/cm^2 with 98–99% of the population being <1 μW/cm^2.[26] During the early 1980s, the estimated median power density in US urban areas was 50 μW/m^2.[27] In more recent studies, the VHF-FM-UHF-cellular bands continue to contribute most of the power density with negligible contributions from the AM bands; these power densities remain substantially below recommended limits.[28] The RF field exposure of ~1% of the population exceeded 10 mW/m^2. The main source of RF exposure for the general population is broadcasting services in the UHF and VHF range.[3] Field strengths surrounding radio transmitters and transmitter towers produce relatively small RF-field exposures (<1 μW/cm^2) to the general population located in the adjacent areas. However, near-field conditions may occur near the base of these towers because of the long wavelength of RF waves used to broadcast. The electric field strengths at the base of UHF and VHF towers in the near-field are highly variable, with values ranging from 1–20 V/m for UHF television, 1–30 V/m for VHF television, and 2–200 V/m for FM radio transmitters.[29] Current studies suggest the change from analog to digital broadcasting has not significantly altered RF exposure for the general population. In a German study of 300 spot measurements around Munich and Nuremberg before and after changing from analog to digital broadcasting, the median electric field exposure for analog transmission was 11 mV/m compared with 27 mV/m for digital signals.[30] The electric field strength for FM radio signals was similar to that of analog television signals. The values of RF-field exposure were highly variable with a range of two orders of magnitude around the median.

The strength of the electromagnetic field near the antenna of portable transmitters can be high, even for low-output transmitters. Field strengths of several hundred V/m and up to 0.6 A/m at distances of >10 cm from a mobile source with a power range of up to 300 W may occur. The correlation between radiated power and field strength is typically poor; field densities decrease rapidly 50 cm from the antenna in the 10–30 MHz frequency range. For frequencies of >100 MHz and distances of >50 cm, the inverse square law applies to the power density. Data are available for the assessment of hazards from mobile transmitters based on SAR rather than field strength in the near-fields.[31]

High-level exposures occur primarily for workers near the antennas of high-power transmitters.[24] Aerial riggers working on VHF/UHF equipment in the 30–1,000 MHz region sustain intermittent electric field exposures to the whole body and extremities of 60 V/m and 140–270 V/m, respectively. In comparison, measurements of RF fields from medium frequency (MF) transmitters in urban areas indicate few residents are exposed to electric field strengths exceeding 1 V/m. In a French study of 184 urban and rural residents wearing personal dosimeters during the weekday, the electrical field strength was always <1.5 V/m as measured by the personal monitors.[32] The FM band had the highest percentage (12.3%) of measurements above the threshold of detection (0.05 V/m).

In a study of 15 cities with MF broadcast transmitters, the median electric field exposure was 0.28 V/m with 98% exposure to field strengths of >0.07 V/m.[29] Only 3% of the urban population was exposed to fields of >1 V/m. RF beam power density usually decreases with increasing distance; however, the relationship between exposure and distance from the antenna is very complex, depending on the relation to phasing in the near-source zone, scattering attenuation and reflection of interfering objects, type of building construction, and other RF sources. For exposure to electric fields 1–2 m from antennae for MF broadcast transmitter strengths of 1–50 kW, the electric field strengths ranged from 95–720 V/m and 2.5–20 V/m at 100 m from the antennae.[29]

Mobile Phones

Handheld Cell Phones

Although cell phone subscriptions increased rapidly over the last two decades, improving technology lowered the time-averaged RF power emitted from these mobile devices. Most analog phones ceased functioning around the year 2000. The power of analog mobile phones is typically higher than that of digital phones, with average time-averaged power output of up to 600 mW; however, this output translates to an average SAR in the brain below the 1998 INSI/IEEE recommended limit of 8 W/kg over 6 minutes.[33] In a study modeling analog mobile phone use with phantoms, the maximum rise in tissue temperature from peak SAR was small (<0.04°C), even during continuous (>6 minute) use of a 600 mW source.[34] The maximum SAR level in the brain ranged from 0.12–0.83 W/kg, with the highest levels closest to the phone. In comparison, the average metabolic rates for the whole body and heart muscle are 2 W/kg and 60 W/kg, respectively.[25]

The energy absorption by different tissues depends on phone design (e.g., antenna location), position of

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the phone by the head,[35] and distribution of current in the tissues; the former two factors may result in 20-fold and 10-fold differences in the exposure, respectively.[36,37] The shape of a child's head results in a closer proximity of the brain to a cell phone adjacent to the ear and higher RF exposure by a factor of ~2 compared with an adult.[38] The peak SAR over 1 g of tissue during 2G mobile telephone use in the 1990s reached 0.25–0.5 W/kg.[39] Studies of later systems indicate peak spatial SARs have not significantly changed during the replacement of analog phones with digital ones; the analog phones probably produced greater overall SAR to the brain because of the greater size and diffuse distribution of the electromagnetic fields.[2] The power absorption from the antenna of a handheld telephone occurs in the near-field; therefore, strength of the electromagnetic field is nonhomogeneous depending on radiated power, frequency, antenna design, anatomical position of the head in relation to the phone, and the duty cycle.[40] Maximum time-averaged output power of 2–4G cell phones usually ranges from 125–250 mW because lower duty factor (i.e., time during cycle switched off) substantially reduces the maximum power (0.25–2 W). In a study of 500 volunteers in 12 countries using 2G, software-modified GSM phones to measure exposure parameters, the average power was ~50% of the maximum power, with a 2–3-fold difference between countries and cell phone users.[41] The mean output power/call was 133.3 mW (900 MHz) and 64.2 mW (1,800 MHz); at 900 MHz, this value ranged from 92 mW in Israel to 171 mW in New Zealand and 47 mW in Israel to 88 mW in Finland at 1,800 MHz.

Several techniques reduce maximum operating power listed by manufacturers, including operating 3G and 4G phones at power rates far below maximum power to reduce interference, lowering duty factors during nontalking portions of a conversation, and normal use of mobile phones in positions other than worst-case scenarios calculated by manufacturers. Third-generation (3G) phone technologies reduced absorbed energy (i.e., SAR) in the brain by almost two orders of magnitude compared with GSM phones.[2] The estimated temperature rise in the brain using a 3G handheld cell phone is ≤0.1°C. Emitted power from mobile phone is minimal when not in use; some RF-field exposure occurs during the transmission of texts and emails.

In a European study of public electromagnetic field exposures estimated from 12 bands used in communication equipment and 28 exposure scenarios with selected spot measurements, the highest outdoor exposures resulted from GSM (Global System for Mobile Communications) and DCS (Digital Cellular System) downlink signals, with estimated electric field strengths

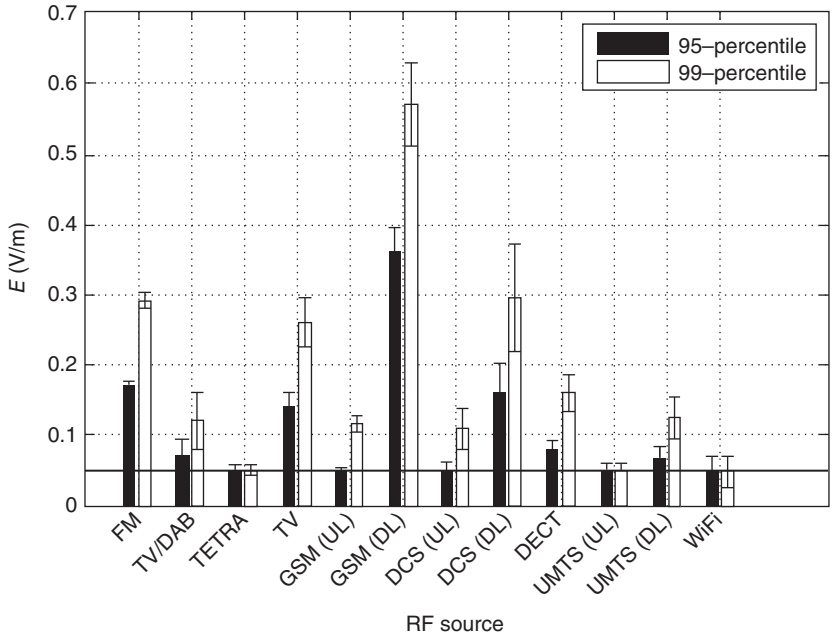


FIGURE 44.5. Upper bound personal monitor measurements (95%, 99%) of electric fields in 12 radiofrequency bands during 28 outdoor scenarios involving walking outdoors in an urban environment. Table 44.3 defines the frequencies and sources of the 12 bands. The horizontal black lines represent the sensitivity of the personal meters. (Adapted from Joseph et al.).[42]

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ranging up to 0.52 V/m.[42] Figure 44.5 illustrates the range of upper 95 and 99% electric field strengths for 12 RF bands estimated during 28 urban scenarios. GSM and DCS uplink signals from mobile phones inside moving trains or buses produced the highest total electrical field exposure. Using the upper 99% values, the estimated whole-body specific absorption rate (SAR) ranged up to 5.01 μW/kg. Data analysis from summing exposure to nine RF communication bands in this study indicated that daytime walking in the city produced the highest total electric field strengths.[43] For a 1-year-old infant in this scenario, the highest upper 95% whole-body SAR calculated from the total electric field strength was 11.5 μW/kg. The upper 95% value for electric fields produced by Wi-Fi in the 20 urban scenarios ranged from 0.36–0.58 V/m, whereas the maximum upper 95% field strength for DCS (cellular phones) was 0.33 V/m. In a French study of urban and rural residents monitored for 24 hours with a personal dosimeter, electric field strengths increased close to the antenna, with maximum field strengths developing when the beam intersected with the ground. The maximum electric field strengths of GSM and DCS waves in this study occurred 280 and 1,000 m from the antennas.[32]

Data are limited on the radiation exposure from 5G devices, primarily because the infrastructure is in a distribution phase. The 5G networks and associated IoT will substantially increase the number of wireless devices and require highly dense, multiple lower power transmitters (small cells) on utility poles and buildings for much more mobile data volume per geographic area. However, the 5G antennas require narrow antenna beams with direct alignment to receiving devices. Potentially, this infrastructure may significantly mitigate the environmental radiation exposure from very large numbers of 5G network components.[6] Although 5G networks share bandwidth with preceding 2–4G systems, 5G systems also operate in the higher frequency millimeter wave band (MMW, 30–300 GHz), previously reserved for automotive collision avoidance systems, airport scanners, and perimeter surveillance radar. MMW does not penetrate building materials, vegetation, or the outer layer of human skin. Overall, RF radiation from the 5G system is not forecast to significantly alter current RF exposures, with most radiation exposure resulting from uplink signals from personal devices.[4] However, the more superficial energy deposition, higher frequency, ultra-wideband pulsed fields, local networks and small cells for machine-to-machine communication, and use of beam forming will complicate exposure assessments.

Cordless Phones

Modern cordless phones use digital technology (Digital Enhanced Cordless Telecommunications, DECT) operating in the microwave portion of the electromagnetic spectrum (0.90 GHz, 1.88–1.90 GHz, 2.40 GHz, 5.80 GHz). This system uses TDMA technology, producing discontinuous signals of 0.4 msec each at peak power levels of 250 mW; a duty cycle of 4% reduces the time-averaged power to 10 mW. Although DECT phones do not use adaptive power control, the signal travels over short distances (i.e., few tens of meters). DECT phones emit ~5 times less RF radiation than GSM mobile phones. The handset does not emit RF waves unless the device is sending or receiving, whereas the base stations for DECT systems transmit signals in standby mode with a duty cycle of 0.8%. For a person standing in a room, the RF exposures from DECT base stations and mobile phone base stations in the neighborhood are similar.[2]

Bluetooth

The use of handsfree devices or a fixed antenna wired to the cellular telephone minimizes exposure of the brain to low-frequency radiation; studies of wired and wireless handsfree devices connected to mobile phones using GSM900, GSM1800, and UMTS1950 under maximized current coupling produce considerably lower RF exposure than handheld mobile phones.[44] These devices operate with power in the range of 1 mW. Bluetooth wireless hands-free devices emit ~100 times less RF radiation as measured by maximum peak special (psSAR) than mobile phones, reducing RF exposure to <10% of the exposure associated with holding a cell phone to the ear.[45] Wired devices may cause a local increase in RF-field exposure to the ear.

Base Stations

The height and emitted power of mobile phone base stations are highly variable. In a UK study of >30,000 base stations, radiated power ranged from 0.1–200 W, at heights of 3–60 m above ground level.[46] A group of base station antennas 15–25 m above ground emitting powers ranging from 20–100 W probably represent macrocells that provide the primary network coverage, whereas another group of base stations 2–6 m high with average power of 2 W are probably microcells relaying the signal in densely populated urban areas. As demand grew for cell phone service, base stations split the single omnidirectional signal into 3 sectors with up to 6 antennas that provided 32 signals in each sector; each signal served 1 call. Studies of maximum recorded power density from personal dosimeters in areas near cell phone base stations

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indicate RF electromagnetic field exposures are well below current public standards (e.g., ICNIRP). In an Australian study of CDMA800, GSM900, GSM1900, and 3G UMTS sites, the maximum power density was 7.8 mW/m^2, representing 0.2% of the ICNIRP public reference level.[47] Spot measurements of the >30,000 cell phone base stations in the UK study reached a maximum of 8.6% of the ICNIRP reference value with the range typically of 0.002–2% of the reference level.[46] Mobile phones held within 1 cm of the body are the dominant source of RF-field exposure compared with more powerful base stations at greater distances (i.e., >10 m). Similarly, exposure from a cell phone operated within 1 m of an individual also produces higher RF exposure than base stations in the far-field based on numerical computations using phantoms.[48] Distance from the base station is not necessarily a good proxy for RF exposure in the near-field situation because of variability in antenna design, reflections, and shielding, whereas distance more closely reflects RF exposure for TV and radio transmitters than cell phone base stations.[49]

Long-term evolution (LTE) began with 4G radio technologies. In a study of 30 locations in Stockholm, Sweden, following the deployment of LTE technology, LTE contributed 4.1% of the total average power density produced by RF sources similar to digital enhanced cordless telecommunications (DECT, 4.4%); these values are substantially less than GSM900 (35.6%), GSM1800 (26.2%), and universal mobile telecommunications system-high speed packet access (UMTS-HSPA, 26.4%).[50] The average electric field strength was 0.18 V/m with a maximum of 0.8 V/m; these values are substantially below ICNIRP reference levels of 61 V/m.

Terrestrial Trunked Radio (TETRA)

Emergency personnel and other professionals use the TETRA cellular radio system (380–470 MHz, selected bands near 900 MHz) typically in a handheld position with a push-to-talk function. The location varies from a handheld device adjacent to the mouth to a transmitter mounted on a vehicle. Typically, peak powers for the handheld device are 1–3 W, whereas mounted transmitters range from 3–10 W.[51] Spatial averaging of the SAR over 10 g produced by the handheld devices ranged from 0.24–0.53 W/kg in front of the face to 0.88–2.88 W/kg for the side of the face. Although normal use does not exceed current guidelines, the maximum SAR during continuous use over 6 minutes by the side of the head may exceed these recommendations by ~50%.[52] Other professional mobile radio systems operate in the VHF and UHF portions of the spectrum with radiating powers of 1–5 W. These systems use the push-to-talk mode, resulting in relatively low duty factors and limited transmission time.

Wireless Networks

A Wi-Fi network is a wireless local area network (WLAN); however, Wi-Fi is not the only type of WLAN. Technically, WLAN is any radio technology local network device, whereas Wi-Fi is a type of WLAN that uses a local hub (e.g., access point) to connect to the local area network and is the predominant type of WLAN today. Wi-Fi operates in several frequency bands in the ranges of 2.4–2.5 and 5–6 GHz, with some devices using multiple RF frequencies. The radiated powers usually range from a few mW to ~30 mW, with the highest powers transmitted during saturation of the network with traffic.[53] The signals from Wi-Fi are short bursts of transmitted data lasting 0.01–1 msec, depending on the need to retransmit corrupted data; hence, weak signal strength does not necessarily imply less RF exposure because of the increased duty cycle. Duty factors for laptops usually are <1% compared with <10% for access points; the latter drops to ~1% when data transfer ceases.[2] In general, Wi-Fi signal strengths are far lower than other RF signals in the same environment. In a study of American and European Wi-Fi networks in residential, commercial, healthcare, and educational sites, the maximum time-averaged power density in the 2.4 GHz band 1 m from a laptop loading and transmitting files was 7 mW/m^2 (i.e., 0.07% of ICNIRP public reference level of 10 W/m^2).[54] The highest power densities occur near the transmitting devices (i.e., access points). Local temporal peak values may reach ~100–200 mW/m^2 in these areas; however, maximum temporal peak power density spatially averaged over body dimensions is much lower (e.g., 20 mW/m^2).[55] Consequently, the RF exposure in the brain is less than mobile phones operated at the ear. Laptops typically have built-in antennas around the edges at greater distances from the head than cell phones; consequently, the estimated SARs are much less than cell phones. Using a power of 100 mW and a duty factor of 1 at 2.4 GHz, the highest localized SAR value in the head was 5.7 mW/kg based on calculations for a 10-year-old sitting voxel model.[56] In a Palestinian study of 271 measurements from 69 indoor sites (e.g., educational institutions, homes, hospitals) with radiofrequency exposure from wireless local area networks (WLAN), power density levels 1 m from WLAN systems ranged from 0.001 to ~1.9 μW/cm^2 with a mean of 0.12 μW/cm^2.[57] These values were >200-fold below

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the currently recommended ICNIRP public exposure guidelines.

Radar

Radar is an acronym for RAdio Detection And Ranging. Most radar systems generate highly directional beams with high gain at frequencies of >600 MHz, typically 1–10 GHz. High-power sources are defined by the ability to produce a main-beam density of 1 W/m^2 at 100 m; some high-power radar beams generate main-beam densities exceeding 1 kW/m^2 at that distance. Most of the radar systems are pulsed with the signal duration of a microsecond over a pulse period of a millisecond, resulting in power densities much lower than the peak power densities by a factor of 100–10,000-fold. The actual exposure depends on several variables including the duty factor, the metric of interest (e.g., average vs. peak), the time in the rotating beam, and the position of the body in relation to the beam.

Police Units

Police radar units operate by emitting a low-power microwave signal toward a specific target (e.g., speeding automobile) that reflects the signal back to the radar unit at a different frequency. Based on the Doppler principle, the difference in frequency between the emitted and reflected signals determines the speed of the target. The US Federal Communications Commission (FCC) designated the following three frequency bands for police radar units: 1) X-band, 10.525 GHz; 2) K-band, 24.150 GHz; and 3) Ka-band, 33.700–36.000 GHz. The use of police radar to detect speeding traffic began in the 1950s, with much more common use beginning in the 1970s.[58] Early traffic radar devices used X-band frequency ranges during the 1970s and early 1980s, whereas K-band radar guns were introduced in the middle of the 1970s and became popular later. During the 1990s, Ka-band radar guns were developed using higher frequencies and lower power than X-band radar units. These radar units operate in the Doppler mode that involves continuous-wave radiation rather than pulsed or intermittent radiation. Handheld radar units operate only in stationary patrol vehicles. Operation of these units occurs primarily in urban areas (e.g., intersections), where these units allow the measurement of vehicle speeds in more than one direction. The technology of mounted units allows use both in moving and stationary patrol cars; however, these units measure vehicle speeds only in one direction.

Maximum Exposure The amount of microwave radiation produced by radar units is relatively small compared with household appliances and police radios. The typical police radar unit operates at ~15–50 mW compared with 600 W for a microwave oven and 50 W for mobile police radios. The emitted power of traffic radar devices is lower than or comparable with that of garage door openers, cellular telephones, and infant monitors.[58] The *power density* refers to the intensity of microwave radiation striking a flat surface per unit time (mW/cm^2). The maximum power density external to the radar device is the aperture power density; this value occurs immediately in front of the radar antenna at the interface between the radar antenna and open space. The aperture power density does not vary with changes in power supply voltage; however, operation of the device at cold temperatures can increase the aperture power density up to 15% higher than room temperature.[59] In general, K-band radar units possess significantly lower aperture power densities than corresponding X-band units as a result of more sophisticated electronic circuits and higher frequency. In a study of the power intensity (mW/cm^2) emitted by over 5,000 radar units, the mean aperture power densities for K-band and X-band handheld radar units were 0.69 mW/cm^2 and 2.66 mW/cm^2, respectively.[59] A fixed-mounted, X-band unit produced the highest aperture power density (6.4 mW/cm^2).

External Dose The amount of external radiation received by an operator of police radar depends on the frequency (X, K, Ka), type of mount (handheld, dash-mount, rear-deck mount), distance from the unit, and temperature. The proper operation of radar devices is unlikely to produce microwave exposure levels exceeding 0.02–0.05 mW/cm^2 based on laboratory and field studies.[58] The radiation received by the operator of a handheld radar device usually is <1% of the aperture power density, except in unusual circumstances (e.g., use in the lap of the operator with reflection from nearby metal surfaces) when the external exposure may reach 5% of the aperture power density.[59] These studies indicate the operator of a rear-mounted radar device receives an external radiation dose in the range of <1–3% of the aperture power density. Passengers in vehicles receiving radar impulses are not exposed to significant amounts of microwave radiation. Directly in front of the radar gun, the radiation level decreases below 1% of the aperture power density at a distance of 12 ft from the radar gun.[59] Other studies confirm the relatively low amount of microwave radiation produced by radar guns.[60] An experimental study simulated the use of a cross-section of radar guns including handheld, rear deck-mounted, and dash-mounted

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units.[61] Measurements of power density at the estimated level of the eye and testicle of the operator demonstrated values ranging from nondetectable ($\leq$0.02 mW/cm^2) to 0.033 mW/cm^2 and nondetectable to 0.034 mW/cm^2, respectively. The highest power density (5.34 mW/cm^2) occurred immediately in front of a Ka-band, dash-mounted unit. However, none of the power density measurements at simulated sites in the body of the operator exceeded current occupational recommendations.

Air Traffic Control Units

Most moderate-range systems operate at frequencies of 2–4 GHz compared with 1–2 GHz for long-range systems. The antennae are usually mounted sufficiently high to obstruct signals from other buildings with narrow beams that sweep full circle around the sky every few seconds. The signal attenuates vertically to prevent reflection of the beam from the ground. The pulses of RF radiation are relatively high with emitted power up to a few megawatts. Air traffic control radar units produce a relatively greater hazard compared with police units because the power densities of air traffic control units are ~4-fold greater than police units. A power density of 100 W/m^2 occurs at 132 m from the source of surveillance radar compared with 33 m from the source of tracking radar.

Marine/Military Radar

The range of marine radar is shorter than that of air traffic control equipment, with the beam emitted from rotating antennae above the ship and focused at sea level. Typical operating frequencies are 2–4 and 8–12 GHz with mean power ranging from 1–25 W and peak power up to 30 kW.[62] Marine vessels contain a variety of RF sources in addition to radar X- and S-bands including radio transmitters (VHF, medium frequency/high frequency), satellite communication, and navigation. In a study of radio frequency electromagnetic fields emitted from seven transmitters on a marine ship, the measured electric fields were lowest on the upper deck (0.82–0.86 V/m) and highest on the bridge roof (2.15–3.70 V/m), with intermediate values on the bridge deck (0.47–1.15 V/m).[63] The ICNIRP guidelines for the public were exceeded only on the bridge roof, whereas all measurements were below occupational standards. Military installations use tracking radar to follow aircraft and missiles. These systems generally emit more power than navigation systems or civilian radar. These systems typically use RF in the range of 2–8 GHz with high mean power densities (e.g., >10 mW/cm^2).

Industrial Applications

Microwave Heating

Magnetron electron tubes inside domestic microwave ovens produce microwaves at a frequency of 2.45 GHz, with power output ranging from 200–2,000 W. The power output of commercial microwave ovens may reach 3,000 W. The most important source of microwave exposure during oven operations results from the leakage of microwave radiation from door seals; however, the power densities decrease rapidly with distance. Compared with current standards, RF electromagnetic field exposures are usually relatively low, with peak local SAR values of 0.256 W/kg at the emission limit of 5 mW/cm^2 at 5 cm from the source.[20] In a Palestinian study of 117 microwave ovens aged 1 month to 20 years, the leakage 1 m from the ovens ranged from 0.43–16.4 μW/cm^2 with a mean of 3.64 μW/cm^2.[64] Leakage is correlated to age and operating power, with a stronger dependence on the former.

The attenuation of microwaves within several meters and intermittent microwave exposure typically reduce RF-field exposure below current exposure limits.[65] Microwaves in the upper frequency range (i.e., 10 GHz) do not penetrate skin well, but very powerful microwaves in this range could produce heat on the skin. Microwave anti-intrusion alarm systems are typically low-power devices with power densities near 0.01 mW/cm^2 within 0.5 m of a 10 mW-microwave alarm system.[3]

Radiofrequency Heating

Induction heating involves low RF and extremely low-frequency (ELF) ranges to heat conducting materials by the formation of eddy currents in strong magnetic fields created by large coils. Applications of this type of heating include production of plasmas, mixing alloys, hardening surfaces, and melting metals. Exposure of workers occurs during activities near or within the coils. Radiofrequency sealers generate heat in materials by producing oscillating electromagnetic fields in the frequency range of 10–80 MHz. In an industrial setting, these machines heat, melt, and cure various materials including PVC plastic, rubber, and wood glue. Power ranges from <1 to tens of kW for sealers up to over 100 kW for glue dryers.[2] Although leakage from radiofrequency sealers generally ranges up to 200 V/m or 0.5 A/m, these electric and magnetic field strengths may reach 2,000 V/m and 10 A/m, respectively.[66] The high RF voltage in the sealer generates intense electric fields in workers close to the sealer, producing currents aligned longitudinally along the limbs and torso toward the lower legs.[67] The concentration of the

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current in a small cross-sectional area creates high local SAR with the maximum current occurring in the feet under grounded conditions. Direct correlation of power density to electric and magnetic fields near these sealers is limited because of nonuniform electromagnetic fields and lack of a simple mathematical equivalency between power density and electromagnetic fields in the near-field (i.e., <1–5 wavelengths from the source). Hence, direct measurement of SAR is necessary to evaluate an exposure. Because these sealers operate at frequencies near the region of human resonance, operators of RF sealers have the potential to absorb substantial amounts of radiofrequency radiation.

Smart Meters

Smart meters transmit data on electricity, gas, and potentially water consumption to central collection locations including frequency of use, time of consumption, amount used, and location. Most smart meters operate as wireless mesh networks that communicate with other neighboring meters to relay usage data to a data collection point in the region. These devices emit RF pulses at variable times throughout the day with relatively low duty cycles (i.e., <1%); consequently, RF fields typically appear around the smart meters for only a few minutes daily. Although there is no standardized approach, this technology involves wireless home area networks using radio communications (CDMA, GSM, 3G/4G/5G, LTE, Wi-Fi). The pulsed transmissions usually operate on unlicensed frequency bands (902–928 MHz, 2.4–2.48 GHz) or other nearby frequencies.[68] Smart meters eliminate the need to manually read utility meters.

Baby Monitors

These devices are radio systems that remotely monitor an infant visually and audibly with transmitter and microphone operating mostly in the microwave range (40, 466, 864, 2,450 MHz); peak operating power ranges up to 500 mW. Assuming far-field conditions with the monitor placed 1 m from the infant, the estimated maximum 10 g averaged spatial peak SAR and power flux densities are 1–2-fold below current reference levels.[69]

Whole-Body Scanners

Security screening in airports and other facilities involves ionizing (X-rays) and nonionizing (radiofrequency) radiation. These active systems direct the radiation toward the body and analyze the scattered radiation. Passive systems monitor thermal radiation emitted by the body in the RF portion of the spectrum without emitting radiation. Limited data are available from manufacturers due to security issues. Whole-body millimeter wave imaging technology used in airports and security checkpoints operates in the extremely high frequency millimeter wave range (30–300 GHz), with absorption of electromagnetic radiation confined mainly to the dermis. Manufacturers claim the active scanners are substantially less powerful than standard household devices (e.g., mobile phones, wireless handsets, Wi-Fi), with power densities below 1 mW/m^2 (<0.0001 mW/cm^2) and wavelengths of 3–10 mm in air.[2] Scanners designed to passively detect broadband microwave radiation do not expose the scanned body to electromagnetic waves.

RF Identification (RFID)

RFID technology uses radio waves to identify and track items with readers and labels; the latter contain integrated circuits and antennas to process and transmit information within several meters of the reader.[70] Various RFID applications range from access control and animal identification (≤135 kHz) and smart labels/item management in libraries (13.56–27.28 MHz) to asset tracking up to 100 m (433 MHz) and road tolling systems (5.8 GHz).[69] Passive systems for mother–newborn identity reconfirmation use RFID technology with the RF exposure depending primarily on reader-tag specifications, distance of the reader from the body, and duration of use.[71] Other healthcare industry uses for RFID include the tracking of supplies and medications in the hospital supply chain, operating room, and patient care areas.

Medical

The millimeter wave (MMW) frequency range is a subset of radio wave radiation that comprises frequencies of 30–300 GHz. In Russia, MMW therapy centers treat a broad spectrum of illnesses including cancers of the skin, ear, nose, and throat, atopic dermatitis, tuberculosis, gastroduodenal ulcers, unstable angina, and hypertension;[72] however, there are few randomized controlled clinical trials on the clinical efficacy of these therapies. The long-term benefits of radio wave therapy for analgesia remain controversial.[73] Magnetic resonance imaging (MRI) employs radiofrequency fields in conjunction with static and slowly fluctuating magnetic fields.

Physiotherapy

Physiotherapy departments use microwave diathermy (433.92 MHz, 915 MHz, 2,045 MHz) and shortwave diathermy (13.56 MHz, 27.12 MHz, 40.68 MHz) for the treatment of musculoskeletal pain with approximate powers of 200 W and 400 W, respectively. The most common shortwave diathermy devices use 27.12 MHz,

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whereas 2,045 microwave diathermy devices are uncommon now. Under normal operating conditions for microwave diathermy, operator exposure to power density levels of >10 W/m^2 occurs transiently to the part of their body <1 m from the source.[20] Treatment areas receive incident power densities in the range of 1–2 kW/m^2; however, irradiation may be nonuniform. The orientation and position of the shortwave diathermy applicator and the cables in relation to the control console produce significant variation in the RF exposure of the operator. Electric field strengths of 300 V/m extend up to 0.4 m from the cables; magnetic field strengths of 0.8 A/m exist at 0.25 m from the cables, depending on the power settings of the diathermy machine.[74] Shortwave diathermy operators are usually ~1 m from the applicator; electric fields range from 2–315 V/m around their console. A review of studies reporting RF electromagnetic field strengths (27.12 MHz) in physiotherapists' workplace indicates current ICNIRP occupational limits may be exceeded when physiotherapists stand within 2 m of an operating continuous shortwave diathermy machine, 1.5 m of an operating pulsed shortwave diathermy machine, or <1 m from a microwave diathermy device.[75]

A systematic review of management therapies for chronic spinal pain suggests some evidence for the efficacy of lumbar and cervical radiofrequency neurotomies (level II – multiple relevant moderate or low-quality randomized controlled trials), but little evidence for thoracic RF neurotomies.[76] Because of the limited penetration of this type of radiation, thermal injuries are potentially possible in the first 1–2 mm of human skin and cornea.[77]

Electrocautery

The use of electrocautery involves a handheld electrode that cuts or coagulates tissues with an operating frequency of ~500 kHz, up to 200 W of power, and ~10 A/cm^2 of current. Ablation of atrial fibrillation uses unipolar and bipolar radiofrequency energy sources for minimally invasive treatment of atrial fibrillation. The energy source operates in the range of 100–1,000 kHz, producing restive heating in a narrow band of tissue in direct contact with the electrode or between the electrodes.[78] The lesion size depends on electrode-tissue contact area, interface temperature, current, power, and duration of RF energy. Minimally invasive surgery for tumor ablation uses 9.2 GHz with ~20 W of power with coaxial lines in a slender needle.[79]

Cancer Therapy

Percutaneous radiofrequency and microwave ablation are therapeutic options for short-term amelioration of some types and stages of tumors (e.g., liver, kidney, bones, adrenal glands) when curative interventional treatments are not efficacious.[80] Tumors are more sensitive to heat than normal tissue; hyperthermia has a direct cytotoxic effect that may sensitize the tissue to other radiation.[81] Radiofrequency ablation uses electric current, whereas microwave ablation uses an electromagnetic field. Although both methods rely on thermal-induced tumor destruction, the latter has the advantages of more predictable ablation zones, larger coagulation volumes, and shorter procedural times.[82] Radiofrequency ablation devices used to treat tumors operate at 13.56 MHz with an output of 1,000 W.[83] The use of microwave-induced hyperthermia includes the treatment of chest wall metastases of breast cancer,[84] head and neck cancer,[85] ablation of functional menorrhagia,[86] and transurethral microwave thermotherapy for benign prostatic hyperplasia.[87] The latter is an alternative to transurethral resection of the prostate (TURP) and alpha-blockers for treating symptomatic benign prostatic hyperplasia in men without urinary retention or previous prostate procedures and prostate volumes of 0–100 mL.[88] However, TURP provides lower symptom scores, better urinary flow, and fewer subsequent treatments than transurethral microwave thermotherapy. Simulation studies suggest that treatment of head and neck cancer with hyperthermia by prolonged, intense radiofrequency heating (60 minutes at 434 MHz) produces peak 10 g spatial-averaged specific absorption rate in the adjacent eye exceeding current ICNIRP and IEEE guidelines up to 10-fold.[85] Although predicted SAR correlated to eye temperatures, relatively large variations (i.e., >100%) occurred in the temperature–SAR relationship. Medical review of records from 16 patients treated with hyperthermia at these RF doses did not detect any visual changes or other ocular effects, including cataracts during up to 18 months postexposure.

DOSE EFFECT

Specific Absorption Rate (SAR)

For high-frequency electromagnetic fields, the specific absorption rate (SAR) is the dose of energy transferred to the body expressed as watts/kilogram (W/kg). Absorption of energy from radiofrequency radiation depends primarily on the frequency of the source, the shape and size of the organism, the geometry of the incident, and the dielectric properties of the tissue. In biological materials, only the electric field contributes

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to energy absorption (SAR). Because of scattering, reflection, and absorption within tissues of different dielectric properties, the distribution of the energy from radiofrequency radiation is highly nonuniform throughout the body.[89] Consequently, biological effects are more closely related to the quantity of energy absorbed and the distribution of that energy in the body than to measures of exposure (e.g., incident power density). Specific absorption (SA) represents the *dose*. The specific absorption rate (SAR) is the rate at which radiofrequency radiation imparts energy to an area of mass in a biological body, as defined by Equation 44.7. Therefore, SAR is a measure of the *dose rate* of RF radiation received by the body.

$$\text{SAR} = E^2\sigma/\rho \qquad \text{(Equation 44.7)}$$

where

E = electric field strength (V/m);
ρ = electrical conductivity of medium (Siemens/m);
σ = density of medium (kg/m^3).

Frequency-Dependent SAR

Based on the absorption characteristics of the human body, the SAR varies in the following four regions of the RF portion of the electromagnetic spectrum: 1) the subresonance range (<30 MHz); 2) the resonance range (30–300 MHz); 3) the "hot-spot" range (400 MHz–3 GHz); and 4) the surface absorption range (>3 GHz). Surface absorption predominates in the human body, except for the head and neck at frequencies in the subresonance region. At incidence power densities of >100 W/m^2 (>10 mW/cm^2), energy absorption decreases with increasing frequency; the size of the hot spots decreases from several cm (915 MHz) to 1 cm (3 GHz).[3] In the surface absorption range of the RF spectrum, temperature elevations occur locally at the surface of the body. Peaks of SAR can vary up to an order of magnitude above a whole-body average; thus, a safety factor of 10 is appropriate to protect against the development of hot spots within the body due to variations in energy deposition.[90] In general, little absorption of heat occurs following exposure to radiofrequency waves at frequencies of <10 MHz; the greatest absorption of radiofrequency waves occurs near frequencies of 70 MHz.

Average SAR

The SAR is a measure of internal exposure. The whole-body average SAR represents the total energy transferred to the body per unit time divided by the total mass; this quantity depends on the biological characteristics of the body, environmental materials, and physical parameters of the RF source including frequency and polarization in the far-field situation. Table 44.5 lists the multiple factors affecting the absorption of radio waves in a body.

During exercise, heat production in the body may reach 3–5 W/kg. The whole-body SAR aids in the extrapolation of animal data to humans; however, such calculations do not account for differences in spatial distribution between animals and humans. For a worst-case scenario (i.e., extreme conditions of humidity and temperature, resonant frequency), whole-body SAR doses of 1–4 W/Kg at 70 MHz raise the core temperature in humans by ~2°C within 1 hour.[24]

Humans

The medical literature contains few reports of adverse effects on humans exposed to RF electromagnetic fields other than microwave-induced burns. Nine radio linesmen were exposed to a radiofrequency of 4.1 GHz and a power density of 4.6 mW/cm^2 for no more than 90 minutes.[91] The maximum estimated SAR for the skin was 3.8 W/kg and 1.2–1.5 W/kg for the lens. Minor changes in the posterior subcapsular region of the lens developed in the two individuals with the highest

TABLE 44.5. Factors affecting the absorption of radiofrequency radiation. (Adapted from Michaelson and Lin).[19]

Parameters	Factors
Biological	Size, geometry, dielectric properties (primarily water content), spatial relationships, relation to polarization of waves
Environmental scatter	Metallic/nonmetallic objects in electromagnetic field, shielding, internal implants, grounds, conduction plates, containers
Physical	Frequency, polarization, modulation (AM, FM, pulse), power and power density, distance from source (near-field, far-field, uniform/nonuniform field, calibration/measuring techniques, transmitting/radiation equipment, chamber dimensions/materials)

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exposure. One subject reported insomnia and irritability. Follow-up medical examinations detected no long-term sequelae.

Animals

Thermal effects result from exposure to specific absorption rates (SAR) levels of >1 W/kg, whereas nonthermal effects occur at SAR levels of <0.1 W/kg;[92] there are limited animal and human data to support the existence of permanent adverse effects from exposure to RF radiation below a few W/kg.[93,94] For a healthy adult, an SAR of 4 W/kg is associated with a 1°C rise in temperature; the ICNIRP guidelines add a 50-fold safety factor (0.08 W/kg) for public reference values. *In vitro* cell system studies do not demonstrate a consistent pattern of cell abnormalities following RF exposures below levels producing detectable heating; similarly, a variety of animal models with varying RF exposure levels and signal modulation have not demonstrated evidence of health effects below current guidelines.[69] Temperature in the tissue is the critical variable in animal experiments using frequencies of >100 kHz. At frequencies of <100 kHz, increased sensitivity to induced currents becomes important because the current produces interactions with excitable tissues (e.g., muscles, nerves).[3] RF fields can produce sufficiently high currents to cause pain and burns at frequencies of <100 kHz, whereas burns predominate at frequencies in the range of 100 kHz–100 MHz. Acute, localized delivery of microwaves at intensities of >100 mW/cm^2 over 15 minutes produced cataracts in animal models; however, the production of microwave-induced cataracts is difficult without exposing the animals to lethal radiation levels.[95]

The absorption of energy from radiofrequency waves is frequency-dependent, with resonant frequency being the portion of the spectrum producing the highest energy absorption. The resonant frequency in animals and humans varies significantly; the resonance frequency for a 70-kg man is 70 MHz compared with a resonance of 3,000 MHz for a small rodent. Hence, exposure of rodents to 2,450 MHz would cause much greater energy absorption (SAR) than human exposure to the same frequency. Consequently, extrapolation of animal data to humans must consider differences in specific absorption rates. Frequency scaling is the best means of extrapolating the effects radiofrequency radiation from animals to humans; however, such extrapolations are limited by physiological and physical differences.[8]

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Mechanism of Action

The primary effect of RF radiation in the body is the heating of tissue; the absorption of RF energy generates an oscillating current that creates motion of charged particles and strongly dipolar water molecules. Potential mechanisms for the interaction of radio waves with biological systems also include nonthermal mechanisms (e.g., membrane excitation below 1 MHz, field-induced molecular forces, induced tissue dipoles). Several reviews of thermodynamic and biophysical parameters indicate physiological effects are unlikely at RF electromagnetic field exposures that do not cause temperature increases in the tissues, with the exception of free radical formation.[96,97] However, the evidence that RF radiation affects oxidative stress or alters the concentrations of reactive oxygen species is weak.[2] Experimental studies do not provide sufficient evidence that alteration of immune function following RF radiation exposure increases cancer incidence at any site.

Adverse effects from radiofrequency radiation result primarily from the absorption of energy and the production of heat in the body. Maximum production of heat occurs at the resonant frequency ranging from 70–300 MHz. At frequencies below the resonant frequencies, the penetration of tissue is substantial; therefore, little energy absorption occurs. At radiofrequencies above resonance, penetration of the skin is limited, and thermal effects develop on the skin. Table 44.6 lists the electromagnetic properties of tissues with high water content.

A common adverse effect of microwave use is the development of burns from the differential heating between foods and their containers (e.g., jelly rolls, popcorn, baked potatoes, teas, formula bottles).[98,99] Factors favoring differential heat production in microwave-heated food include variable water content, high viscosity, and low homogeneity. The latter two factors impede convection and conduction in the food, whereas increased water content increases heat production.[100] Water molecules effectively absorb microwaves; therefore, heating occurs more rapidly in substances with higher water content. Consequently, some foods (e.g., jelly rolls) will heat nonuniformly because the jelly contains more water than the surrounding pastry portion of the roll. Microwaves pass through glass, paper, and plastic without producing heat, whereas metal objects reflect microwaves. As a result, the exterior of a formula bottle may be cool while the milk is very hot. Allowing heated food to stand for several minutes

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TABLE 44.6. Variability of electromagnetic properties of high-water-content tissues (e.g., muscle, skin) with a range of radiofrequencies. (Adapted from Michaelson and Lin).[19]

Frequency (MHz/GHz)	Relative Permittivity	Conductivity (S/m)	Penetration into Body (cm)
1 MHz	2,000	0.400	91.3
10 MHz	160	0.625	21.6
27.12 MHz	113	0.612	14.3
40.68 MHz	97.3	0.693	11.2
100 MHz	71.7	0.889	6.66
200 MHz	56.5	1.28	4.79
300 MHz	54	1.37	3.89
433 MHz	53	1.43	3.57
750 MHz	52	1.54	3.18
915 MHz	51	1.60	3.04
1.5 GHz	49	1.77	2.42
2.45 GHz	47	2.21	1.70
3.0 GHz	46	2.26	1.61
5.0 GHz	44	3.92	0.788
5.8 GHz	43.3	4.73	0.72
8.0 GHz	40	7.65	0.413
10.0 GHz	39.9	10.3	0.343

allows the heat to disperse throughout the food by conduction; the temperature of infant formula should not exceed 100°F. Microwave heating can increase the temperature of food with high fat content to 500°F. At this temperature, the transfer of the plastic polymers and, to a lesser extent, the food is possible when the food is in direct contact with the plastic; however, currently there is no evidence of toxic effects from such a transfer. Microwave-heated compresses and gel packs may heat nonuniformly and retain heat longer than other materials (e.g., cotton compresses, towels).

Pathological Changes

Microwave-induced burns produce a distinctive pattern of relative sparing of tissues with relatively low water content (e.g., subcutaneous fat, muscle, skin) compared with the features of electrical burns that cause charring and nuclear streaming.[101] Although case reports associate the development of second-degree burns with exposure to leakage from a microwave oven and the use of a transdermal patch, an *in vitro* study of transdermal delivery systems exposed to a maximum power density of 800 W/m^2 from a microwave diathermy unit demonstrated only a small increase in temperature of 2.2°C.[102]

Microwave irradiation at a frequency of 2.45 GHz produces cataracts in laboratory animals.[103] Incident power densities capable of inducing cataracts in rabbits include a single 35–40 minute exposure to 250 mW/cm^2 and 20 consecutive daily exposures of 180 mW/cm^2 lasting 1 hour.[104] Although the initial clouding of the posterior layer of the lens cortex may result from heating in the rabbit model, microwave irradiation apparently induces changes in the equatorial epithelial cells that migrate posteriorly to form an aberrant epithelial layer under the posterior capsule.[105] The scattering properties of the orbital bones and the periorbital tissue produce differences in the threshold for the development of cataracts in various species. Power densities of 500 mW/cm^2 produce facial burns in monkeys, whereas exposure to 180 mW/cm^2 causes cataracts in rabbits.[106]

CLINICAL RESPONSE

Environmental Exposure

Skin

In a retrospective cohort study using National Electronic Injury Surveillance System data from 1990–2010, US emergency departments treated an estimated 156,000 patients for microwave oven-related injuries. The most common injuries were burns to the hands and fingers from spilling microwave-heated substances on the skin. Case reports associate the ingestion of microwave-heated products with burns of the upper airway, including third-degree oropharyngeal burns from the ingestion of formula,[107] airway obstruction from the aspiration of tea,[108] and acute laryngeal burns from the ingestion of baked potatoes.[109] Serious burns occurred on the hands from holding microwave-heated liquids

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during complex partial seizures;[110] steam-induced corneal abrasion developed following the opening of a bag of microwave-heated popcorn.[111] The development of high-current radiofrequency ablation increased the risk of thermal burns on the skin surrounding the grounding pad.[112] These injuries are typically first- and second-degree burns; however, full-thickness burns may occur with delayed healing and scar formation.[113]

Eye

A study of 16 patients with head and neck cancer treated with RF ablation did not detect any serious acute ocular effects following 74 total treatment sessions.[85] A simulation study indicated RF radiation in these patients exceeded current guidelines for peak 10 g spatial-averaged SAR (10 W/kg) and peak tissue temperature increase (1°C) by a maximum of 10.4-fold and 4.6-fold, respectively.

Cochlear Implant

Cochlear implants comprise an external speech processor and an internal implant that receive heat from radio waves during mobile phone use; however, numerical modeling studies do not suggest these exposures exceed current ICNIRP guidelines of a maximum 1°C rise in temperature. Using a worst-case scenario (antenna operating at nominal full power, metallic hook behind the ear holding the speech processor, antenna adjacent to the hook and internal ball electrode), a 900 MHz half-wave dipole antenna generating continuous-wave 250 mW power produced a maximum 10 g averaged SAR of 1.31 W/kg near the hook and ball electrode.[114] The maximum temperature increase in the skin adjacent to the hook was 0.33°C. For the 1,800 MHz antenna operating at 125 mW, the maximum 10 g averaged SAR was 0.93 W/kg, and the maximum temperature increase was 0.16°C.

Electromagnetic Hypersensitivity

A few members of the population report a variety of nonspecific, multisystemic signs and symptoms that they relate to common, low-level electromagnetic radiation exposures from electronic devices and wireless communication systems. The clinical features of this phenomenon display no consistent association with a specific portion of the radiofrequency band. In some of these patients, the severity of these symptoms impairs their ability to function normally. Commonly reported signs and symptoms include headaches, difficulty concentrating, poor memory, general malaise, weakness, dizziness, fatigue, nausea, sleep disturbances, night sweats, myalgias, restless legs, paresthesias, blurred vision, tinnitus, and palpitations.[115] No specific constellation of signs and/or symptoms describes electromagnetic hypersensitivity (idiopathic environmental intolerance attributed to electromagnetic fields).[116] The geographic distribution of this perceived disorder across the world does not correlate ecologically to measured electromagnetic radiation exposures. Most of these patients also report the ability to sense electromagnetic radiation in the environment (electromagnetic sensibility).

Most mainstream medical organizations do not accept the clinical features of electromagnetic hypersensitivity as causally related to electromagnetic radiation exposure. A review of 46 blind or double-blind provocation studies involving 1,175 self-declared electromagnetic hypersensitivity patients did not detect robust evidence to support the existence of electromagnetic hypersensitivity as a biological entity.[117] The vast majority of the studies failed to find any significant effect of measured electromagnetic radiation on symptom severity. A meta-analysis of 7 studies involving 182 self-reported electromagnetic hypersensitivity patients and 332 controls (nonhypersensitive individuals) did not demonstrate a statistically significant difference between patients and controls in the ability to detect the presence or absence of electromagnetic radiation.[118] The pooled correct field detection rate better than chance for these electromagnetic hypersensitivity patients was 4.2% (95% CI: -2.1% to -10.5%). In a home-based, double-blind, provocation study of 42 volunteers (mean = 55 years, range 29–78, 76% women) with the self-described ability to detect electromagnetic radiation (electromagnetic sensibility), no participant could correctly identify sham and electromagnetic radiation exposure better than chance.[119] The scientific basis for electromagnetic hypersensitivity remains equivocal.

Occupational Exposure

Eye

In animals, cataracts develop in the eyes of rabbits (but not monkeys) following exposure for ≥30 minutes to very high, localized RF fields (e.g., 2.45 GHz), producing dose rates (≥150 W/kg) and temperatures (≥41°C) far exceeding current guidelines.[120,121] The difference in response of the two animal species to this radiation level reflects differences in head anatomy and the subsequent absorbed energy (i.e., SAR). Since 1952, over 50 case reports have associated cataracts with acute exposure to high-intensity radiofrequency radiation, mostly in the occupational setting;[122] however, the lack of adequate

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exposure data limits the interpretation of the threshold effect of the development of cataracts in humans and the causality. The results of epidemiology studies of workers exposed to radiofrequency radiation do not support a consistent association between cataracts and intermittent exposure to incident power densities within current guidelines (<10 mW/cm^2).[69,123] The lack of accurate exposure measurements and the health worker effect prevent the extrapolation of this threshold level to chronic exposure.[93] A retrospective study of military and industrial workers exposed to microwaves demonstrated an increased incidence of minor lens defects related to job specialization; however, the study did not directly assess the incidence of cataracts. The authors did not consider the lens changes as precursors to cataracts.[124] In this study, the development of lens opacities correlated most strongly to age. Several studies of military and industrial workers exposed to radiofrequency radiation have not detected any distinct morphological features of the lens that distinguish RF-exposed workers from control populations.[125,126,127]

Gastrointestinal Tract

A 42-year-old man developed diffuse inflammation of the small bowel and gangrene of the appendix within 6 hours of a 1-minute exposure to a radar beam.[128] The exact exposure was not measured; however, the history suggests he stood in front of the radar beam until the sensation of heat in his abdomen became intolerable. He died from gram-negative sepsis 10 days later. A 42-year-old male pilot stood in front of a functioning microwave radar system for approximately 5 minutes.[129] A biopsy of a persistent neck mass 1 month later was consistent with coagulation necrosis from thermal injuries. The level of this exposure was not documented.

Central Nervous System

Surveys of Soviet and Eastern European workers associated RF exposure with the development of a neurasthenic syndrome characterized by nonspecific symptoms (e.g., headache, fatigue, irritability, anorexia, depression, emotional instability, poor concentration, insomnia). The lack of exposure data and absence of adequate controls limit conclusions about the causal relationship between exposure to radiofrequency radiation and the development of a neurasthenic syndrome.[130] Most of these workers improved after being removed from the occupational setting.

During 1953–1976, occupants of the American Embassy in Moscow received clandestine RF radiation (0.5–9 GHz) with maximum power densities up to 15 μW/cm^2 for 18 hours/day; no adverse health effects were detected in the occupants.[93] The extremely low levels of radiofrequency radiation and the short follow-up period limited the power of the study to detect adverse effects.

Carcinogenesis

Although large, stable increases in cancer incidence including CNS cancers have not been detected in various countries despite rapidly increasing subscription rates,[131] the International Agency for Research on Cancer lists radiofrequency fields as possibly carcinogenic (Group 2B) based on limited evidence in experimental animals and humans, primarily the association between wireless phones and central nervous system cancer (glioma, acoustic neuromas).[2] The latter association is relatively weak, and a causal relationship is unsupported with current evidence as a result of potential selection and information bias regarding RF exposure and methodological limitations. Brain cancer rates have not increased proportionally with cell phone use.

The majority of the epidemiological evidence for determining if an association between cell phone use and CNS cancer comes from the large international, multicenter case-control (INTERPHONE) study[132,133] and a large Swedish case-control study, primarily at higher exposure levels (i.e., more than regular use).[134] Long-term rodent studies using RF radiation do not demonstrate statistically significant increases in the incidence of benign or malignant tumors in any organ site, including tumor-prone animal models. Similarly, most, but not all, studies on rodent models of initiation and promotion (i.e., through cell proliferation or enhanced transcription) did not demonstrate consistent enhancement of carcinogenesis by RF radiation exposure.[135,136] Most experimental data in animals indicate RF fields are not mutagenic. The tumor incidence was not increased in cocarcinogenesis studies, except for vascular tumors of the mesenteric lymph nodes in MX-treated Wister rats[137] and ethyl-nitrosourea-treated pregnant B6C3F1 mice.[138] The US National Toxicology Program does not list radiofrequency radiation as a possible or probable carcinogen.[139]

In most of the epidemiological studies, the surrogate for absorbed RF dose is cell phone use (subscribers, self-reported use); however, several factors affect the absorbed dose including communication system and frequency band, tumor location, duration of use, and amount of use.[140] Recall bias potentially causes exposure misclassification, particularly from the use of questionnaires, billing or network records, location or duration

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of use, research diaries, or battery use.[141] RF dosimeters have design issues that limit useful information (e.g., bulky design requiring measurements away from the ear, insensitivity to magnetic fields). Software-modified phones record exposure parameters (e.g., date, time of call, output power level, frequency band); however, the phone does not record the position of the phone or power level fluctuations. Hardware-modified phones allow the measurement of exposure parameters, power fluctuations, and cell phone location. Cost, complexity of use, and design issues limit the application of the latter to cell phone studies. Exposure misclassification may be differential when cases and controls have similar levels of difficulty recalling mobile phone use, whereas nondifferential misclassification occurs when cases and controls recall mobile phone use differently. The former may result in an underestimation of the risk in epidemiology studies, whereas differential misclassification produces unpredictable effects. Conditions of use (indoor/outdoor, moving/stationary, urban/rural), adaptive power control (except Code Division Multiple Access networks), and discontinuous transmission are minor factors in determining the total absorbed RF dose. In a study of 500 volunteers using 2G software-modified phones for a mean of one month, frequent indoor use and use in a moving vehicle did not significantly affect the average output power.[41] Output power was higher with short calls than long calls and higher in rural areas than urban areas.

Environment

Residence

Overall, ecological studies using distance as a proxy for exposure suggest an increased risk of adult and childhood leukemia with proximity to an RF source, whereas studies using better analytical design and exposure assessment demonstrated no increased risk of these diseases. A cancer cluster study of cancer incidences near the Sutton Coldfield television and FM radio transmitter in West Midlands, England, detected significant reduction in incidence of adult leukemias, skin melanoma, and bladder cancer with increasing distance from the transmitter.[142] The risk of adult leukemia within 2 km of the transmitter was 1.83 (95% CI: 1.22–2.74). A follow-up study of cancer incidences in this area did not detect a similar reduction in the risk of adult skin cancer, adult bladder cancer, childhood leukemia, or childhood brain cancer with increasing distance from the transmitters.[143] Although some decline in the incidence of adult leukemia occurred with increasing distance from the transmitters, the follow-up study did not observe an excess incidence of adult leukemia within 2 km of the transmitters (OR = 0.97, 95% CI: 0.78–1.21). In an Australian ecological study comparing cancer incidences between municipalities with and without TV towers, the rate ratio for total leukemia incidence was 1.24 (95% CI: 1.09–1.40).[144] The rate ratios for brain cancer were not increased. The calculated power density of the radiofrequency radiation in the surrounding area ranged from 8.0 $\mu W/cm^2$ near the towers to 0.2 $\mu W/cm^2$ 4 km from the towers.

Evidence from well-designed studies on a link between childhood leukemia and exposure to RF electromagnetic fields is limited. The cancer cluster study on RF radiation from the Sutton Coldfield transmitters did not detect an increased risk of childhood leukemia. In a South Korean case-control study comparing children living within 2 km of 31 AM radio transmitters and children living >20 km from the transmitters, the OR was 2.15 (95% CI: 1.00–4.67). However, the risk of leukemia was not dose-related and was marginally statistically significant. The odds ratio for leukemia in children living 2–4 km from the towers compared with referents (>20 km) was 0.95 (95% CI: 0.56–1.61), whereas the odds ratio of leukemia in the quartile with the highest exposure compared with the lowest quartile was 0.77 (95% CI: 0.54–1.10). The rate ratio for childhood leukemia in an Australian ecological study was 1.58 (95%CI: 1.07–2.34); however, other ecological studies demonstrated negative results.[143,145] A German case-control study of childhood leukemia using the German Childhood Cancer Registry data analyzed 1,959 cases and 5,848 controls for RF radiation from 16 AM and 8 FM transmitters with powers of >20 kW.[146] The RF exposure was estimated 1 year before diagnosis using a field-strength prediction program. Conditional logistic regression analysis for all subtypes of childhood leukemia did not detect an increased risk of leukemia (OR = 0.86, 95% CI: 0.67–1.11) when comparing upper and lower quantiles of RF electromagnetic field exposures. Ecological studies of environmental exposure to RF emissions from fixed transmission sources do not indicate an increased risk of brain cancer or other malignancies from these exposures.[2]

Mobile Phones

The number of mobile phone subscriptions increased dramatically in the 1990s with the deployment of the Global System of Mobile Communication (GSM, 2G); by 2016, the overall number of mobile phone subscriptions exceeded the worldwide population.[147] Epidemiological evidence for an association between radiofrequency radiation from mobile phone use and cancer is relatively limited and conflicting; however,

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the possibility of epigenetics and/or long-term (i.e., >10 years) effects remains because of poor quality and limited quantity of well-designed studies (i.e., mostly case-control) as well as poor exposure data from self-reported duration of use.[148] Changing patterns of use (e.g., increased phone use to view data on the screen vs. holding the phone near the ear to hear voices) and the adoption of more power-efficient phone technology beginning with Universal Mobile Telecommunications System (3G) dramatically reduced RF-EMF exposure in the brain. Hence, these technologies substantially reduce cumulative maximum phone emission levels and the impact of increasing duration of use.[149,150]

Multiple methodological issues (reporting bias, recall bias, selection bias/low participation rates, misclassification from imprecise, primarily self-reported exposure assessments, inadequate statistical power from rare incidence/long latency of brain tumors) limit definitive conclusions regarding cancer risks in mobile phone users. Several,[151,152,153] but not all,[154] case-control studies, biological data, animal experiments, brain tumor incidence trends, and reviews suggest that 10–15 years of mobile phone use have not significantly increased glioma risks for regular cell phone users, particularly for fast-growing tumors (e.g., malignant glioma). The relative short observation period for slow-growing tumors (e.g., meningiomas, acoustic neuromas) limits definitive conclusions regarding causal connection between these tumors and long-term cell phone use including cell phone use in childhood; current data associating cell phone use with increased meningioma risks are insufficient, whereas the data for acoustic neuromas are limited.[153,155,156] There are few data on the risk of RF radiation exposure to children under the age of 15 years.

Although hypothesis-generating studies and case series of cancer clusters suggest the *possibility* of an association between RF fields (i.e., radio and television transmitters) and several adult and childhood cancers (e.g., some central nervous system cancers, leukemia, melanoma, testicles, bladder);[157,158,159,160] generally, the relative cancer risks in these studies were low (i.e., <1.5–2), exposure data were poor, and the results were inconsistent with more robust epidemiological studies.[161] The epidemiology data for an association between RF radiation and cancer are strongest for central nervous system cancers (glioma, acoustic neuroma) and minimal for meningiomas or other CNS cancers. There is insufficient evidence of an association between mobile phone use and leukemia or lymphoma, with little evidence of an increase in malignancies other than those previously mentioned.[2]

Although exposure-response data are inconsistent, there are positive data on RF radiation and some central nervous system tumors (gliomas, acoustic neuromas rather than all brain tumors) with latency periods of 10 years or more, particularly with ipsilateral use. Multivariant analysis of a case-control study of brain cancer and cellular phone use suggests a marginally increased risk (OR = 2.62, 95% CI: 1.02–6.71) of brain cancer in the area associated with radiofrequency exposure from ipsilateral telephone use after adjusting for exposure to laboratory and diagnostic medical X-rays.[162] The contralateral use of cellular phones was not associated with an increased risk (OR = 0.97, 95% CI: 0.36–2.59) of brain cancer. Exposure to cellular phones was based on responses to questionnaires rather than direct measurement; the intensity of cell phone use was not quantified. A case-control study of 469 patients with primary brain cancer and 422 matched controls without brain cancer did not demonstrate a statistically significant difference in the use of cellular phones.[163] The exposure criteria were hours per month and years of use. There was no statistically significant correlation between histological categories and cellular phone use. In a meta-analysis of cellular phone use with a latency period of at least 10 years, the odds ratio (OR) for cell phone use and ipsilateral acoustic neuroma was 2.4 (95% CI: 1.1–5.3) and 2.0 (95% CI: 1.2–3.4) for gliomas.[164] No consistent association between cell phone use and meningiomas was detected. Higher numbers of cell phone users and longer follow-up are needed to determine causal associations, if any, between cell phone use and brain tumors.

Glioma In an international, interview-based, case-control (INTERPHONE) study of 2,708 glioma, 2,409 meningioma cases, and matched controls, there was no clear evidence of an increased risk of glioma for regular cell phone users ($OR_{glioma} = 0.81$; 95% CI: 0.70–0.94).[132] There was no dose-related increase with increasing cumulative use, with the exception of 364 high-use participants (>1,640 hours of cumulative cell phone use); the OR for this group was 1.40 (95% CI: 1.03–1.89). The authors noted that some self-reported cell phone use in this group was implausible, suggesting recall bias. The participation rate was low (64% in glioma cases; 53% in controls). A pooled analysis of Swedish mobile phone and cordless phone use from 1997–2003 included 1,148 cases of glioma and 2,438 controls.[134] The OR of glioma increased with increasing cell phone use as follows: 1–1,000 hours, OR = 1.2 (95% CI: 0.98–1.4); 1,001–2,000 hours, OR = 1.5 (95% CI: 1.1–2.1), and >2,000 hours, OR = 2.5 (95% CI: 1.8–3.5). The values

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for cordless phone use were similarly increased. Information bias remained an issue in this study. Neither of these two studies found an increase in the risk of meningiomas following RF radiation exposure.

A large Danish cohort study of 358,403 mobile phone subscription holders and 10,729 cases of central nervous system (CNS) tumors demonstrated a risk of CNS tumors near unity for both men and women.[165] There was no dose-related increase in the risk of CNS tumors with increasing lengths of mobile phone subscriptions. For the group with the longest mobile phone subscriptions (>13 years), the incidence rate ratio was 1.03 (95% CI: 0.83–1.27) in men and 0.91 (95% CI: 0.41–2.04) in women.

Acoustic Neuroma Most case-control studies of acoustic neuroma do not demonstrate an increased risk for regular mobile phone users; however, there is some evidence of an increased risk in the groups with the highest cumulative phone use. Several early case-control studies[166,167] and the Danish cohort study[165] did not support an association between RF radiation and acoustic neuromas. The results for acoustic neuroma and gliomas in the INTERPHONE study were somewhat similar for the 1,105 acoustic neuroma cases (participation rate, 82%) and 2,145 controls (participation rate, 53%).[133] The odds ratio for acoustic neuroma in regular users was not increased (OR = 0.85, 95% CI: 0.69–1.04). Although there was no consistent trend in the exposure-response relationship in the first nine deciles of RF exposure, the odds ratio was significantly increased statistically in the highest cumulative RF exposure group of ≥1,640 hours (OR = 2.79, 95% CI: 1.51–5.16) when recording exposure at 5 years. The risk estimate for acoustic neuroma was higher for ipsilateral use in long-term mobile phone users (OR = 3.74, 95% CI: 1.58–8.83; $n = 28$), but not for contralateral use in these users (OR = 0.48, 95% CI: 0.12–1.94; $n = 4$). In a pooled analysis of 2 Swedish case-control studies involving 243 acoustic neuroma cases, the odds ratio for individuals using digital mobile phones was 1.5 (95% CI: 1.1–2.1) and 1.5 (95% CI: 1.04–2.0) for cordless phone use.[168] When compared with controls (nonuse of mobile or cordless phones), the odds ratio for acoustic neuroma increased for ipsilateral use (OR = 1.7, 95% CI: 1.1–2.6), but not for contralateral use (OR = 1.3, 95% CI: 0.8–2.0). In a Japanese case-control study involving 787 cases of acoustic neuroma, regular cell phone use was not associated with an increased risk of acoustic neuroma based on self-administered postal questionnaires. The overall risk ratio was 1.08 (95% CI: 0.93–1.28) for regular mobile phone use until 1 year before diagnosis and 1.14 (95% CI: 0.96–1.40) for regular mobile phone use until 5 years before diagnosis.[169] The risk ratio increased to 2.74 (95% CI: 1.18–7.85) for mobile phone use >20 minutes daily 1 year before diagnosis and 3.08 (95% CI: 1.47–7.41) for mobile phone use >20 minutes 5 years prior to diagnosis. Potential selection and recall bias limit conclusions regarding causality in this study.

Workplace

There is no clear association between RF exposure in the occupational setting and the incidence of brain cancer. However, maximum exposures may exceed existing exposure limits for broadcasting and telecommunication transmitters, security scanners, plasma devices, radiofrequency identification, and dielectric heating. In contrast, excessive occupational exposures are rare for radar applications and microwave heating. Most cohort studies of leukemia and lymphoma following occupational exposure to RF radiation involve a small number of cases and limited exposure assessment. A study of mortality and incidence of hospitalization in a US Navy cohort of 20,000 electronic equipment repairmen did not demonstrate a statistically significant increase in the incidence of leukemia or brain cancer.[170] There was no dose-response relationship between exposure to microwave radiation based on indirect measures (length of exposure, occupational duties, and power of equipment) and mortality from malignant neoplasms including leukemia and brain cancer. A mortality study of 40,581 US Korean War navy veterans suggested an association between RF radiation and leukemia; however, limited exposure data based indirectly on job title and expert assessment along with possible confounding complicate interpretation of the data. Evaluation of the high (usually <1 mW–100 kW/cm^2) and low (<1 mW/cm^2) exposure subcohorts demonstrated a relative risk (RR) of 1.48 (95% CI: 1.01–2.17) for all leukemias and 1.87 (95% CI: 0.98–3.58) for acute nonlymphocytic leukemia.[171] The highest RR for all leukemias (RR = 2.60; 95% CI: 1.53–4.43; $n = 23$) occurred in the job with the highest estimated exposure (aviation electronics technicians). The risks were not adjusted for confounding exposures.

Brain

A statistically significant increase in the risk of brain tumors (RR = 2.9) and glioblastomas (RR = 3.4) occurred in assemblers and repairmen in the radio and television industry;[172] however, a follow-up study of a cohort with high exposure to radiofrequency radiation

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did not detect the development of malignancies in the occupational cohort with relative high exposures to radiofrequency radiation.[173] The relatively short follow-up periods and the difficulty separating cellular telephone use among categories complicate the interpretation of occupational studies on the carcinogenic effect of radiofrequency radiation. A retrospective cohort cancer incidence study among 22,197 Canadian police officers did not detect an increased standardized incidence ratio (SIR = 0.84, 95% CI: 0.48–1.36) for brain cancer.[161] A nested case-control study of US Air Force personnel did not detect an exposure-response trend between categories of RF electromagnetic field exposure intensity and the occurrence of brain tumors.[174] Exposure was based on reports of overexposure without any direct measurements of RF exposure.

Leukemia

A mortality study of amateur radio operators demonstrated a slight but nonsignificant elevation of the all-leukemia standardized mortality ratio (SMR) and significantly elevated SMR of 176 for acute myeloid leukemia (n = 15 observed, n = 8.5 expected).[175] A Norwegian study of radio/telegraph operators and radio/TV repairmen detected an elevated incidence (SIR = 2.8, 95% CI: 1.3–5.4) of leukemia based on national occupation and cancer registries.[176] There were no direct measurements of cumulative exposure to radiofrequency radiation, and job titles were surrogates for exposure. The possession of an amateur operator's license was a surrogate for exposure to radiofrequency radiation, and there was no direct measurement of exposure or examination of confounding variables. A Swedish study did not detect an increased SMR for leukemia in television/radio repairmen or assemblers.[172] No increase in the amount of chromosomal damage was found in Australian radio linesmen exposed to radiofrequency radiation at or below occupational RF exposure limits.[177] A retrospective cohort cancer incidence study among 22,197 Canadian police officers did not detect an increased standardized incidence ratio for leukemia (SIR = 0.6, 95% CI: 0.31–1.05).[161]

Reproductive Abnormalities

Humans

The association between exposure to radiofrequency radiation and teratogenesis in the absence of temperature elevation from microwave radiation remains unproven based on inconsistent epidemiology studies and methodological limitations (e.g., reporting and recall bias, misclassification). A detailed study of the incidence of congenital abnormalities at a military base did not detect an increased risk of adverse pregnancy outcomes above surrounding levels.[178] Although cross-sectional studies of paternal radiofrequency exposure on Norwegian fast patrol boats during the 90 days prior to conception suggested an increased risk of stillborn babies and congenital abnormalities,[179,180] lack of control of confounding variables, recall bias, and the absence of a clear dose-response relationship limit conclusions regarding causation. Anecdotal case reports associate the development of congenital abnormalities with the use of diathermy for the treatment of various pelvic conditions during pregnancy;[181] however, epidemiological studies have not demonstrated a consistent, statistically significant elevated risk of adverse pregnancy outcomes above baseline rate.

A nested case-control study of physical therapists detected an increased risk of miscarriage (OR = 1.28, 95% CI: 1.02–1.59) in mothers reporting the use of microwave or shortwave diathermy anytime during or 6 months prior to the first trimester as assessed by mailed questionnaires.[182] The risk of miscarriage was not associated with the reported use of shortwave diathermy equipment (OR = 1.07, 95% CI: 0.91–1.24). A case-control study of Danish physiotherapists initiated by a cluster of 4 cases of congenital malformation among 25 pregnancies among a physiotherapy staff detected a statistically nonsignificant positive association (OR = 1.7, 95% CI: 0.6–4.3) between pregnancy outcomes and radiofrequency radiation.[183] A study of all registered physiotherapists in Finland from 1973–1983 demonstrated a statistically significant increase in the risk (OR = 2.4, 95% CI: 1.0–5.3) of congenital malformations in the low exposure group, but not in the high exposure group.[184] In this study, heavy exertion was a risk factor for spontaneous abortion. In the Norwegian Mother and Child Cohort Study conducted from 1999–2009, there was no association between maternal prenatal or paternal preconceptional cell phone exposure based on reported cell phone use and studied pregnancy complications, including outcomes (total congenital malformations, perinatal mortality, low birth weight, preterm birth, preeclampsia, abruptio placentae) after adjustment for parity, maternal age, and smoking.[185] A case-control study of maternal exposure to RF radiation from macrocell base stations did not detect an association or exposure-response relationship between estimated RF exposure and the incidence of early childhood cancers up to age 4 years in the central nervous system, leukemia, non-Hodgkin's lymphomas, or all cancers combined.[186] The study did not account for cell phone use.

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Animals

Hyperthermia is a well-recognized cause of teratogenicity in animals; consequently, RF electromagnetic field-induced hyperthermia is expected to produce developmental abnormalities. Radiofrequency radiation from shortwave diathermy units in rats[187] and microwaves in Chinese hamster cells suggest radiofrequency radiation may be teratogenic and mutagenic, respectively, *when* hyperthermia results from these radiation exposure.[188] Most animal teratology studies do not demonstrate consistent detrimental effects from prenatal exposure to a variety of RF signals commonly used in mobile telecommunications,[189,190] with the exception of some subtle, transient changes (e.g., delayed ossification, serum chemistry, RBC parameters).[191,192] In general, animal experiments indicate RF radiation does not produce damage to DNA, chromosomes, or the reproductive potential of animals in the *absence* of hyperthermia.[22,193] Limited epidemiological data do not support an association between adverse outcomes of pregnancy and exposure to radiofrequency radiation.[194,195] There is no clear evidence that genetic effects occur below power densities of 100 mW/cm^2; animal studies indicate that power densities above this level are necessary to produce testicular damage.[196]

DOSIMETRY

Incident electromagnetic fields are forces external to the body that are not the result of any interaction with biological material. The incident fields couple with the human body to induce EMF and currents inside the body; the strength of the electric and magnetic fields inside the body (i.e., induced electric and magnetic fields) differs substantially from the incident electromagnetic fields. The widely divergent tissues and anatomy within the body produce large, local variations in energy absorption, resulting in differences over a thousandfold.[2] Factors determining the induced electromagnetic fields include: 1) direction, distance, and relative orientation of the source and obstacles between the field and the receiver; 2) direction and angle of wave propagation from the source; and 3) polarization, modulation, frequency, and power of the source.[197] For far-fields, the power density can be calculated from the electric field or the magnetic field strength using the simple conversion factor of space impedance. The most potentially hazardous electromagnetic fields occur close to the source in the near-field with strong field gradients (e.g., contact currents from touching towers or fences exposed to strong EM fields transmitting antennas). The characterization of power density in the near-field is much more complex because of the presence of reactive and radiation components. These components produce temporal and spatial variations in the fields depending on the physical environment and the character of the radio waves. Hence, direct measurements of each individual situation with a probe are necessary to accurately characterize the field in a near-field situation. The probe should be oriented for the maximum reading measuring only the designated field parameters (i.e., *H*-field and not the *E*-field).[24] Probe sensitivity varies with frequency; the presence of the operator of a handheld device may alter the reading from the near-field. Small errors in distance between the probe and antenna may introduce large errors in the field strength close to the source. There is no single measurement technique that is effective over the whole range of radiofrequencies; instruments that measure frequencies in the microwave range of >1 GHz are not suitable for use at lower frequencies.

Exposure Assessment

Collection of specific data on an exposure to radiofrequency radiation is necessary to calculate the specific absorption rate and correlate the radiation dose received with expected biological effects. Examination of the site of exposure is important because field enhancement may result from reflection of radiofrequency waves from the ground or nearby metal objects (e.g., metal frames on glasses, safety helmets).[198] The use of protective clothing (e.g., headgear, eyeglasses, heavy clothing) and climatic conditions may affect the thermal load produced by radiofrequency radiation.

Table 44.7 outlines the important parameters and values for the investigation of an exposure to radiofrequency radiation. Most current instruments (i.e., densitometers) measure field strength and power density in a broadband field. Broadband *E*-field instruments are available to monitor a range of 3 kHz–40 GHz; however, a single instrument will not measure the entire RF range.

Analytical Methods

Safety guidelines are based on measurements of the specific absorption rate (SAR) averaged over the whole body (i.e., whole-body-averaged SAR, wbSAR) or over a small sample of volume or tissue mass (i.e., maximum peak spatial SAR, psSAR); the psSAR does not usually correlate to specific tissues or typical exposures. For frequencies up to a few GHz, including most wireless communications, the SAR is typically averaged over 1

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TABLE 44.7. Parameters to quantify radiation exposure in the radiofrequency range. (Adapted from Hocking et al.).[91]

Parameter	Data
Radiation exposure	Frequencies transmitted, modulation characteristics (peak/average values), polarization, power transmitted including harmonics, system losses, antenna characteristics (type, size, gain, beam widths, radiation patterns), height from ground level, orientation limits, distance between source and exposure, presence of scattering objects influencing radio wave propagation, duration of exposure
Environment	Temperature, humidity, wind, work performed, protective gear worn (head gear, eyewear, clothing)
Instrumentation	Position of instrument, time and value of all measurements

or 10 g. High-frequency millimeter waves in 5G systems do not penetrate the skin; therefore, surface-dominated absorption predominates. The mass-averaged SAR depends primarily on the blood perfusion rate and the depth of radio wave penetration. For localized RF fields close to the body (<20 cm), assessment of compliance with local SAR and current density limits requires measurements and numerical simulations.[67] Noninvasive measurement of these values is extremely difficult *in vivo*, particularly in these near-field conditions; therefore, simulations of worst-case scenarios using phantoms help predict the RF exposure inside the human body. However, the standard head and body phantoms recommended for compliance testing are homogeneous rather than the heterogeneous constituents of human tissues. Numerical techniques use anatomically realistic computer (voxel) models to estimate the distribution of induced electric fields and the resulting SAR values based on methods using Maxwell's equations to analyze data from phantoms in finite-difference time-domain (FDTD) and, less often, finite-element models.[199] These models determine the compliance of commercial communication devices with safety guidelines.[36] Each voxel represents a volume of a few cm^3 with several million voxels combining to simulate a human head or body based on distributions determined anatomically from medical images (e.g., MRI, CT). These models incorporate the frequency-dependent dielectric properties of the tissues (i.e., conductivity, permittivity) into the voxels to approximate the interaction of induced electric fields within human tissues; these dielectric properties vary with water content, age, and physiological state of the tissues. Differences in the effect of RF exposure between children and adults primarily reflect differences in dielectric properties and physical size. Reflection of RF fields from bodies and secondary resonant structures necessitates the use of additional assessments for determining RF exposures in epidemiology studies.

Diode-based field probes consisting of field sensors, detectors, scatter-minimizing transmission lines, and display electronics are commonly used to assess near-field RF exposures; the primary limitation of these devices is their inherent nonlinearity over their dynamic frequency range. Other broadband *E*-field probes include true square-law detectors (thermocouple and thermistor probes) and electro-optical sensors (active, passive). The latter allows sensitive measurements of the RF domain and phase while limiting electric field interference. Thermistors provide higher resolution than thermocouple probes; however, the former requires careful calibration on multiple parameters that affect RF exposure.

Thermistor- and optical-based temperature probes allow direct measurement of SAR, whereas infrared photography (black-body equivalent radiation) is a noninvasive technique. The latter method measures only surface temperatures and has relatively less sensitivity than the former. Direct and indirect calorimetric techniques measure average wbSAR without providing data on SAR distribution. Measuring SAR in the near-field requires very complicated computer analysis of several hundred positions in a three-dimensional phantom. Analysis of RF fields under far-field conditions (e.g., radio/television broadcast antennas, mobile phone base stations, radar installations) is much simpler than in near-field situations using broadband-measurement single- and 3-axis sensor probes. Accuracy of the data from these survey meters depends on limiting sources of uncertainty including linearity, frequency response, calibration, time-domain response, and temperature response.

Protocols and instrumentation designed to test worst-case scenarios for compliance testing provide conservative estimates of maximum RF exposure. Application of this testing to personal exposure for epidemiology studies may not represent actual real-life RF exposure. Accurate analysis of personal exposure using these techniques requires evaluation of induced rather than incident RF-field exposure, analysis of the multiple sources of RF exposure operating in real-life situations, and analysis of multiple factors (e.g., geographical, usage, and temporal) applicable to the relevant exposure period of interest.

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Biomarkers

The main measure of exposure to RF of >100 kHz is the specific absorption rate (SAR) in SI units of W/kg. This measure of energy absorption and potential temperature increase in tissues is usually reported as a value averaged over time (e.g., 6 minutes) and mass (1 or 10 g). The whole-body-averaged SAR (wbSAR) is the total power from an electromagnetic field absorbed by a body divided by its mass. The maximum peak spatial SAR (psSAR) is averaged over a cubic volume containing 1 g of tissue (psSAR-1g) or 10 g of tissue (psSAR-10g). To enhance the biological meaning of these values, the psSAR often refers to power absorbed by specific tissues or organs. For radio waves of <10 MHz, current densities and electric field strengths averaged over an 8 mm^3 volume enhance measurements of internal electromagnetic field exposure.

In addition to the characteristics of the body and the incident electromagnetic field, the effect of the field on the body depends on the ratio of wavelength/body size. Consequently, the RF portion of the electromagnetic spectrum is divided into ranges based on the resonance frequency of the body (10 MHz) as follows: 1) below body resonance (30k–10 MHz); 2) body and partial-body resonances (10 MHz–2 GHz); and 3) surface-dominated absorption (2–300 GHz). At frequencies below body resonance (<10 MHz), the body is a poor conductor; the primary concern is contact currents induced by near-field sources with strong field gradients (e.g., transmitting towers). Above body-resonance frequencies (>2 GHz), absorption of RF energy occurs predominately on the surface of the body. Local anatomy of the skin, fat, and muscle alters the absorption rates with the development of local hot spots in the nonhomogeneous tissues. Thus, some difference in the intensity of RF exposure occurs in children and adults. The resulting temperature elevation depends on the thermal conductivity and perfusion of the tissues.

HEALTH SURVEILLANCE

Environmental Monitoring

The most authoritative organizations establishing safety standards and guidelines for RF exposure are the World Health Organization-associated International Commission on Nonionizing Radiation Protection (ICNIRP) and the Institute of Electrical and Electronics Engineers International Committee on Electromagnetic Safety (IEEE/ICES). Review of the BioInitiative Report: A Rationale for a Biologically based Public Exposure Standard for Electromagnetic Fields (BIR) by these organizations indicates the weight of scientific evidence does not support the 2007 BIR recommendations on safety limits for exposure to RF radiation.[200] Basic restrictions are recommendations to prevent adverse direct effects based on the interactions of RF fields within the body, primarily whole- and partial-body heating. In contrast to the Western approach, countries in Eastern Europe (Bulgaria, the Czech Republic, Hungary, Poland, Russia) use nonthermal effects from chronic exposures to low-level exposures for safety standards based on power load (intensity × duration).[201] Indirect effects result from an interaction between incident RF fields, an external object, and the human body that has the potential to cause burns.

Scientific Basis

The biological basis of current guidelines for the RF range of 10 MHz–few GHz is a threshold effect of increasing body temperature by >1°C at a whole-body specific absorption rate (wbSAR) of 4 W/kg for ~6 minutes or ~30 minutes. The most sensitive measure of this biological effect is reversible, behavioral disruption in animals (e.g., agitation, startle, vigilance task alteration, evoked body movements) following an acute exposure to a whole-body-averaged SAR of 4–8 W/kg body weight.[202,203] The deposition of energy in the tissues adds to the heat created by resting metabolism (i.e., ~1 W/kg) and vigorous exercise (5 W/kg); however, the RF-induced temperature elevations under normal circumstances are relatively small compared with the heat generated by the body and normal temperature fluctuations in the body. For RF fields of 100 kHz–10 MHz, whole-body heating remains the primary direct effect; however, the coupling of the fields to the body becomes progressively weaker as the wavelength becomes progressively longer than the body dimensions. At RF frequencies below 10 MHz, thermal effects remain important determinants of guidelines; however, restricting induced current densities in tissues also becomes important. Above 10 GHz, energy absorption from the RF fields occurs in the first few mm; hence, guidelines are based on surface heating. Pulse-modulated RF waveforms (e.g., some radar signals) may cause pulsed thermal expansion of tissues in the head, resulting in potentially stressful and harmful microwave auditory effects. Additional guidelines were added to avoid this effect. The RF radiation guidelines are designed to allow repeated exposure without causing adverse health effects, including safety factors to accommodate potentially sensitive individuals. Consequently,

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the recommended guidelines do not represent a fine line separating safe and dangerous levels of RF radiation.

Guidelines

Compliance with basic restrictions using wbSAR is not easily measured; consequently, reference levels in addition to SAR limits are formulated in values of measurable field quantities (current density, *E*- and *H*-field strengths, power density) to assess compliance with basic restrictions. Basic restrictions are reduced below the threshold for adverse effects by safety factors to accommodate uncertainty in the calculations and ensure exposures do not cause adverse effects. Recommended guidelines for occupational exposure are 10-fold below the recognized threshold for potential adverse effects (4 W/kg), whereas an extra 5-fold safety factor below the occupational recommendations is added for the public to account for potential differences in sensitivity to thermal effects from age and general health. The value of 0.08 W/kg for the public is 50-fold below the threshold (4 W/kg) and 12.5-fold below the basic metabolic rate (1 W/kg). Table 44.8 displays the guidelines for ICNIRP through 2005. In 2020, the ICNIRP replaced their 1998 radiofrequency guideline for the general public exposed to RF radiation in the range of 100 kHz to 300 GHz with more complicated basic restrictions by dividing the restrictions into average intervals of <6 minutes and ≥6 minutes (https://www.icnirp.org/cms/upload/publications/ICNIRPrfgdl2020.pdf). Additionally, the ICNIRP separated the restrictions into RF ranges of 100 kHz–6 GHz and >6 GHz–300 GHz with some exposure scenarios not requiring compliance. The IEEE updated their general public exposure criteria and associated limits for electric, magnetic, and electromagnetic fields in the frequency range 0 Hz–300 GHz. (https://ieeexplore.ieee.org/stamp/stamp.jsp?arnumber=8910342).

The 1998 ICNIRP guidelines recommended a localized SAR limit of 2 W/kg averaged over any 10-g mass of tissue in the head.[204] Exceeding these recommendations is unlikely during normal use of phones with duty cycle-weighted powers of <0.6 W for 900 MHz fields and 0.4 W for 1.8 GHz fields based on antenna to head separation of 1.4 cm and the radiation of all available power, particularly with the lower power associated with 3G and 4G mobile phones. The high-frequency millimeter waves in 5G systems do not penetrate the skin; therefore, surface-dominated absorption predominates and the risks of adverse effects are expected to be lower than in previous 3G and 4G systems.

British standards require leakage from microwave ovens of <50 W/m^2 (5 mW/cm^2) at 5 cm from the oven. At an average distance of 0.7 m from the oven, the power density emitted from a microwave oven leaking the maximum 50 W/m^2 decreases to 0.26 W/m^2 (0.026 mW/m^2). US federal regulations limit the maximum microwave leakage to 10 W/m^2 (1 mW/cm^2) at 2.5 cm from the oven when new and 50 W/m^2 (5 mW/cm^2) during the lifetime of the product. Independently operating interlocking switches are built into most microwave ovens to stop operation of the oven when the door opens. Metal

TABLE 44.8. International Commission on Non-Ionizing Radiation Protection (ICNIRP) and Institute of Electrical and Electronics Engineers (IEEE) guidelines on public (uncontrolled) exposure to radiofrequency fields based on specific absorption rates (SAR). Each organization has specific restrictions, including differences in the frequency range, averaging times, mass volumes, and definitions of extremities. This table was tabulated to compare the values of the recommendations made by different organizations at different times. Guidelines and regulations change with time. The organization website should be consulted for any updates on the specific restrictions and recommendations. Although the IEEE revised their guidelines in 2005, some countries still use the 1999 guidelines. The head-and-trunk guidelines apply to mobile phone communications.

Region	ICNIRP (1998)	IEEE (1999)	IEEE (2005)
Whole-body SAR (100 kHz–10 GHz)	0.08 W/kg	0.08 W/kg	0.08 W/kg
Localized SAR			
Head and trunk	2 W/kg	1.6 W/kg in 1-g of mass	2 W/kg in 10-g of mass
Extremities	4 W/kg	4 W/kg in 10-g of mass	4 W/kg in 10-g of mass
Current density (30 kHz–10 MHz)			
Whole body	—	157 mA/m^2 (rms)	—
Head and trunk	(f/500) mA/m^2 (rms)[a]	—	—
Power density (10 GHz–300 GHz)[b]	10 W/m^2	—	—
Whole-body induced electric field (30 kHz–10 mHz)	135 mV/m	—	—[c]

Abbreviations: f = frequency in Hz; rms = root mean square.
[a] 2 mA/m^2 for the central nervous system. [b] Spatial maximum power densities averaged over 1 cm^2 should not exceed 200 W/m^2. [c] 294.5 mV/m for the brain.

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screens on the oven doors and microwave-absorbing door seals reduce the leakage of microwaves.[205] A proper screen or a thin metal foil provides 100% screening of all microwaves. Safety measures for reducing RF electromagnetic field exposure during the use of microwave ovens include always operating the oven with the door closed, keeping a tight seal with clean surfaces around the door, and maintaining the oven in good repair. Exposure guidelines for millimeter wave whole-body scanners used in public facilities use 10 W/m^2 averaged over a time interval that decreases with increasing frequency (6 minutes at 10 GHz to 10 seconds at 300 GHz) based on avoiding mild whole-body heat stress and excessive local tissue heating.[206]

Occupational Monitoring

Occupational exposure limits for radiofrequency radiation are designed to prevent excessive thermal exposure. The body absorbs radiofrequency radiation at frequency-dependent rates with maximal absorption occurring at the resonant frequency of the body. This resonant frequency varies inversely with size. An average of 70 MHz is the resonant frequency for the average 70-kg man, whereas 3 GHz is the resonant frequency for small rodents.

Guidelines

As listed in Table 44.9, most consensus-based recommendations (IEEE, ACGIH, NCRP/Health Protection Agency, ICNIRP) use similar RF exposure guidelines based on a whole-body-averaged SAR limit of 0.4 W/kg and localized SAR limit of 8–10 W/kg for the head and trunk. These guidelines assume the primary biological effects of RF radiation are thermal and nonstochastic (i.e., biological effect depends on dose rate above a specific threshold); these guidelines are designed to prevent excessive heating of local tissue with safety factors for high levels of ambient temperature, humidity, and physical activity.[207] Consequently, these regulations average the exposure over a specific time to determine the acceptable frequency and time-dependent exposure. The threshold level for most of the reported adverse effects occurs at whole-body specific absorption rates (SAR) of >4 W/kg.[208] This SAR is equivalent to the heat generated by moderate physical activity (e.g., housecleaning, driving a truck); the body usually dissipates this heat with normal thermoregulatory mechanisms.

TABLE 44.9. International Commission on Non-Ionizing Radiation Protection (ICNIRP) and Institute of Electrical and Electronics Engineers (IEEE) guidelines on occupational (controlled) exposure to radiofrequency fields based on specific absorption rates (SAR). Each organization has specific restrictions including differences in the frequency range, averaging times, mass volumes, and definitions of extremities. This table was tabulated to compare the values of the recommendations made by different organizations at different times. The organization website should be consulted for specific restrictions and recommendations. Although the IEEE revised their guidelines in 2005 (https://ieeexplore.ieee.org/stamp/stamp.jsp?arnumber=1626482), some countries still use the 1999 guidelines. In 2020, the ICNIRP replaced their 1998 radiofrequency guideline for occupational RF radiation exposure in the range 100 kHz to 300 GHz with more complicated basic restrictions by dividing the restrictions into average intervals of <6 minutes and ≥6 minutes (https://www.icnirp.org/cms/upload/publications/ICNIRPrfgdl2020.pdf). Additionally, the ICNIRP separated the restrictions into RF ranges 100 kHz–6 GHz and >6 GHz–300 GHz with some exposure scenarios (e.g., 100 kHz–400 MHz) not requiring compliance with guidelines for other RF radiation (i.e., >400 MHz–6 GHz). The organization website should be consulted for any updates on specific restrictions and recommendations.

Region	ICNIRP (1998)	IEEE (1999)	IEEE (2005)
Whole-body SAR (100 kHz–10 GHz)	0.4 W/kg	0.4 W/kg	0.4 W/kg
Localized SAR			
Head and trunk	10 W/kg	8 W/kg in 1-g mass	10 W/kg in 10-g mass
Extremities	20 W/kg	20 W/kg in 10-g mass	20 W/kg in 10-g mass
Current density (30 kHz–10 MHz)			
Whole body	–	350 mA/m^2 (rms)	–
Head and trunk	10 mA/m^2 (rms)[a]	–	–
Power density (10 GHz–300 GHz)[b]	50 W/m^2	–	–
Whole-body induced electric field (30 kHz–10 mHz)	270 mV/m	–	–[c]

Abbreviations: f = frequency in Hz; rms = root mean square.
[a] 10 mA/m^2 for the central nervous system. [b] Spatial maximum power densities averaged over 1 cm^2 should not exceed 1,000 W/m^2. [c] See 2005 IEEE website above.

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The 1999 ANSI/IEEE revision (C95.1-1999) reaffirmed this value and a safety factor of 10.[209] The Risk Assessment Working Group found no reliable scientific data that RF exposure to a SAR of <0.4 W/kg (i.e., 4 W/kg divided by a safety factor of 10) produced adverse health effects in humans. The ICNIRP and IEEE reviewed the scientific basis for their guidelines, concluding that the lack of evidence of any adverse effects below the basic restrictions indicated an immediate revision of the guidelines was not necessary.[62,210] The biological basis of their recommendations remained the avoidance of tissue damage from excessive localized heat and disruption of workplace activities by mild whole-body heat stress. A subsequent ICNIRP workshop confirmed that RF-induced temperature elevations under normal circumstances are very small relative to the magnitude of normal temperature fluctuations with the largest impact on thermal effects following RF exposure related to factors independent of the RF-generated heat (i.e., thermoregulation).[211] The group indicated international guidelines for whole-body RF exposure were valid; however, they suggested the large uncertainty around this value indicated averaging over 30 minutes may be more appropriate than 6 minutes to prevent local hot spots. Subsequently, the ICNIRP changed their guidelines to separate the basic restrictions to reflect different basic restrictions for averaging RF exposure above and below 6 minutes.

In tabular form, Table 44.10 lists the ACGIH recommendations for RF exposure based on limiting exposure below the threshold SAR of 0.4 W/kg and frequency-dependent variations of energy absorption.[212] The basis of the recommendations of the American Conference of Governmental Industrial Hygienists is a threshold whole-body SAR of 0.4 W/kg averaged over 6 minutes plus a safety factor of 10 for radiofrequencies of >3 MHz. At frequencies of <3 MHz, a limiting value of 1 W/m^2 for plane-wave free-space power densities (S) minimizes electric field-induced reactions at the body surface and shocks from grasping large, ungrounded metallic objects. The ANSI/IEEE guidelines are similar to the ACGIH recommendations listed in Table 44.10. Figure 44.6 displays the ACGIH guidelines for radiofrequency and microwave radiation graphically, as tabulated in Table 44.10. For frequencies below 100 MHz, the recommended parameters include electric field strength, magnetic field strength, and induced currents rather than plane-wave free-space power densities.[212] The frequency range 0.1 MHz–6.0 GHz includes the resonance range for

TABLE 44.10. American Conference of Governmental Industrial Hygienists (ACGIH) recommendations for occupational exposure to radiofrequency radiation ranging from 30 kHz–300 GHz based on an SAR of 0.4 W/kg and frequency-dependent variation of energy absorption. The recommendations were established to limit tissue heating above 0.1 MHz and stimulation of nerves and muscles at RF 0.03–01 MHz. For RF 100 MHz–300 MHz, the near-field of the source defines the electric and magnetic fields. (American Conference of Governmental Industrial Hygienists).[212]

Frequency (Hz)	Power Density (S)[a] (W/m^2)	Electric Field Strength (E)[b] (V/m)	Magnetic Field Strength (H)[b] (A/m)	Maximum Current (mA)	Averaging Time for S, E, and H (Minutes)
30–100 kHz		1,842	163	Both feet: 2000[c] Either foot: 1000[c] Grasping: 1000[c]	6
100 kHz–1 MHz		1,842	16.3/f	Both feet: 200[d] Either foot: 100[d] Grasping: 100[d]	6
1–30 MHz		1842/f	16.3/f		6
30–100 MHz		61.4	16.3/f		6
100–300 MHz	10	61.4	0.163		6
300 MHz–3 GHz	f/30				6
3–30 GHz	100				33,878.2$f^{1.079}$
30–300 GHz	100				67.62$f^{0.476}$

Abbreviation: f = frequency (MHz).

[a] The power density for frequencies >30 GHz is the value over any contiguous body surface area of 0.01 m^2. [b] The electric and magnetic field strengths are spatially averaged over an area equivalent to the vertical cross-section of the human body. The maximum (peak) electric field intensity for all exposures is 100 kV/m. [c] The averaging time is 0.2 seconds for freestanding workers with no contact with metallic objects; for possible contact with metallic objects, conditions of grasping contact apply. For touch contact, the maximum RF-induced current is 50% of the maximum grasping value with a ceiling value of 500 mA. Startle reactions and burns may occur from transient discharges within the current limits. [d] The averaging time in this frequency range is 6 minutes.

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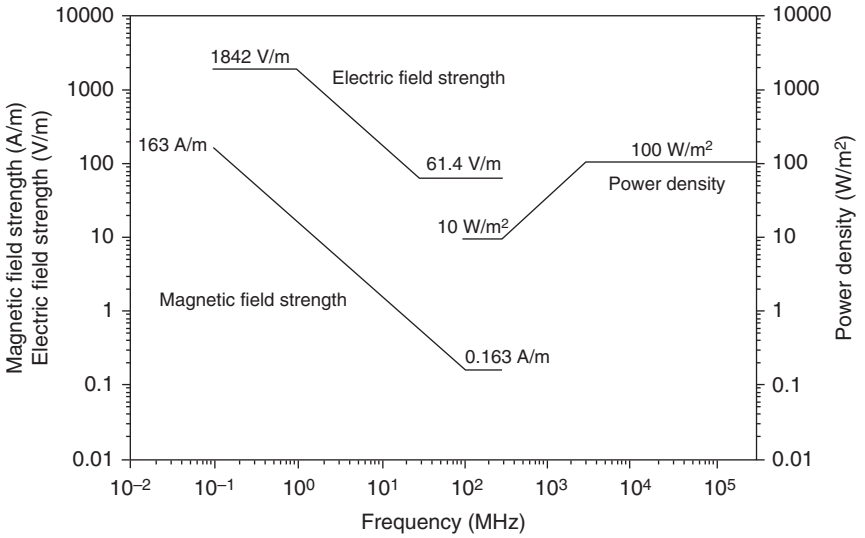


FIGURE 44.6. Graphic representation of American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs) for radiofrequency radiation including microwaves in the workplace. The electromagnetic field strengths and power density are formulated to comply with the whole-body specific absorption rate (SAR) of < 0.4 W/kg at the frequencies noted on the graph. (Redrawn from American Conference of Governmental Industrial Hygienists).[212]

humans; therefore, exposure guidelines decrease in this range compared with frequencies above 6 GHz. These recommendations for frequencies of >6 GHz are based on power density. In the frequency range <0.1 MHz, electrostimulation of biological tissue becomes more important than thermal changes. The primary parameter is internal current density rather than power density. Because of the localized nature of electromagnetic fields in the near-field (i.e., within 1 wavelength), the associated whole-body averaged SARs are below those induced by the far-field equivalent field strengths; therefore, these recommendations apply regardless of the distance from the source.[213] Measurements of field strengths should be at least 5 cm from any object.

Some low-power devices (e.g., mobile car phones, marine transmitters, citizens' band radios) generate localized fields that exceed some recommended guidelines; however, the whole-body exposure is usually below current standards, particularly with the lower power of the 3G, 4G, and 5G cell phones compared with earlier versions.[213] Some modern RF devices use ultra-wideband (UWB) radiation, including short-range wireless communication systems, security systems, car radar, and location tracking. These signals typically consist of extremely short pulses (<10 nsec) with rapid rise times (<200 psec), resulting in a very wide bandwidth characterized by a bandwidth greater than the central frequency. The ACGIH and IEEE consider the limits recommended for exposure to continuous-wave or pulsed RF and microwave radiation sufficient to protect workers from adverse effects following UWB exposure.[212]

Protective Measures

When surveys of electromagnetic fields indicate RF exposures exceed recommended limits, workplace surveillance should be conducted, particularly if RF hot spots may be present. RF hot spots are very rapid spatial variations of the RF fields that produce localized, partial-body exposure on the surfaces of nearby objects including humans. A measurement of the contact current between the person and the re-radiating object provides an alternative evaluation of the peak SAR to measurements of the RF field.

Engineering and Administrative Controls

Engineering and administrative controls are preferable to personal protection equipment as a method of reducing exposure to RF fields to acceptable limits. Engineering controls that limit exposure to the workers and the general public include design, placement, and installation of generating equipment.[3] Special techniques (e.g., grounding of metal fences and other metal objects) may be necessary to reduce exposure to excessive contact currents. Typically, leakage (stray) fields from telecommunications equipment occur at such low frequencies that electromagnetic interference is more important than RF-induced health effects. Administrative controls (e.g., limiting access, warning signs,

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restrictions on the number of workers, and the duration of exposure) supplement engineering controls.

Personal Protective Clothing

Although protective clothing (conductive suits, gloves, safety shoes) may be used for safety reasons, few commercial RF shielding suits are available; microwave suits provide protection only over a narrow range.[214] Protective clothing and eye shields are available to reduce RF exposure; however, routine use of protective equipment is not usually recommended because of the hazards of reflection and the development of secondary sources of electromagnetic fields.[19] Specific safety shoes are available to reduce high local SAR.[215] There is no convincing evidence that safety glasses are an effective measure to reduce exposure to RF fields.

Medical Surveillance

Other than a preemployment physical examination, routine surveillance of workers exposed to RF fields is not necessary unless the RF exposure exceeds current recommendations. For epidemiological purposes, assessment of the health status of workers before, during (especially after documented overexposure), and after employment ceases may help detect any early signs of adverse health effects in those workers where exposure to RF fields exceeds current limits; however, there are no unique clinical syndromes that would identify excessive RF exposure. Keeping precise records provides documentation for future studies, especially regarding the duration and degree of exposure.

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Chapter 45

STATIC AND EXTREMELY LOW FREQUENCY MAGNETIC AND ELECTRIC FIELDS

ELECTROMAGNETIC SPECTRUM

Extremely low frequency (ELF) electric and magnetic fields including static fields comprise the lowest frequencies and longest wavelengths of the electromagnetic spectrum; these frequencies are well below the upper limit of nonionizing radiation near the upper end of ultraviolet radiation region of the electromagnetic spectrum, as demonstrated in Figure 45.1.[1] Electromagnetic waves in the nonionizing portion of the spectrum lack sufficient energy to break chemical bonds and form ions, resulting in significantly different health effects than ionizing radiation. Frequency, wavelength, and energy characterize electromagnetic radiation. The energy of radiofrequency, and ELF radiation possesses relatively long wavelength, low photon energy, and low frequency compared with other electromagnetic waves in the electromagnetic spectrum. Telecommunication applications (e.g., wireless networks, mobile phones, radio/television broadcasting) dominate the uses of radiofrequency radiation, whereas the generation, distribution, and use of 50 and 60 Hz appliances dominate exposure to ELF radiation. Table 45.1 lists the physical characteristics of ELF radiation compared with radio waves and microwaves.

By convention, the primary descriptor of the nonionizing radiation region (e.g., static, ELF, radiofrequency) of the electromagnetic spectrum is wavelength (λ, meters or fractions thereof), whereas photon energy (electron volts, eV) usually characterizes γ- and X-ray radiation.[2] Table 45.2 outlines the nomenclature used to describe the frequencies covered by the portion of the nonionizing portion below infrared radiation.

HISTORY

The biological effects of ELF electromagnetic fields were studied before the time of the mystic and doctor Paracelsus (1493–1541).[3] A footnote in *Historiae Naturalis* XXXVII by the Roman naturalist Pliny the Elder (23–79 AD) attributes the discovery of a magnetic substance to the shepherd Magnes while walking in the Turkish mountain called Ida; he found a piece of mineral lodestone (magnetic Fe_3O_4) in the ground after sensing a strong attraction of the earth to the nails in his sandals.[4] The pre-Socrates Greek philosopher postulated that the attraction of a magnet to iron and amber to cloth and paper meant that these substances had a soul. Greek physicians prescribed amber for hemorrhages, and the priests of Samothrace sold magnetic rings to cure arthritis.[4] In 1289, Peter Peregrinus first described the importance of the compass for sea navigation in his *Epistola*. Many myths surrounded the use of magnets during the Middle Ages, including the ability to draw poison from a wound, cure gout, treat melancholy, enhance sexual powers, and draw gold from wells. Medieval practitioners used magnets to treat strangulated hernias and retrieve iron splinters from the eyes of workers. Paracelsus believed magnets could attract all martial humors in the human system and treat epilepsy, hemorrhage, and diarrhea. William Gilbert (1544–1603), the president of the Royal College of Physicians and personal physician of Queen Elizabeth I, created the science of terrestrial magnetism by proposing that the action of a compass resulted from interaction with the earth as a huge magnet. Interest in magnetism and electricity

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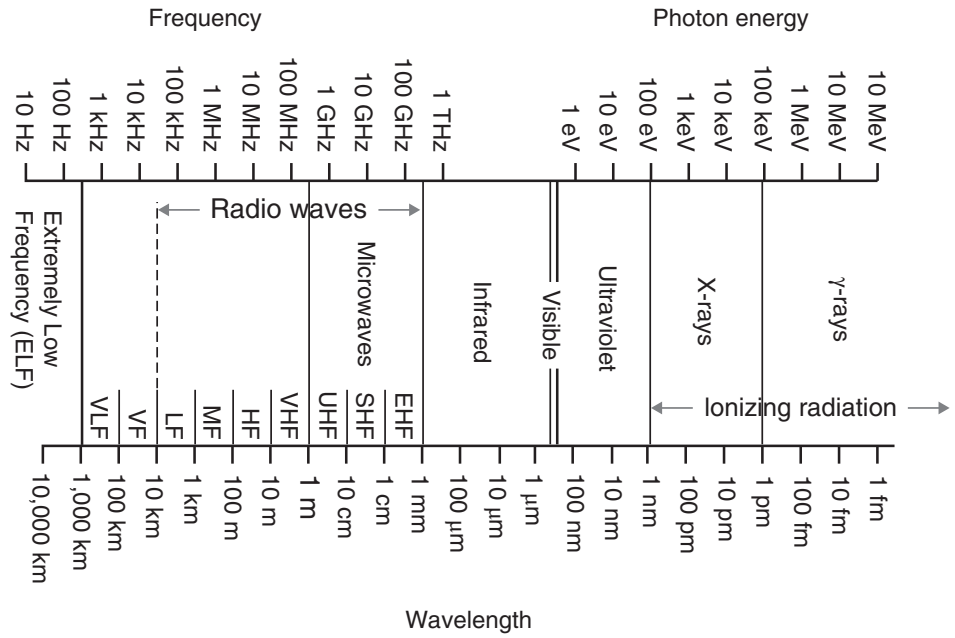


FIGURE 45.1. Electromagnetic Spectrum. Frequency increases from left to right with the symbols for frequency units and bands defined in Table 45.2. The units of frequency are multiples of the hertz (Hz) including kilohertz (kHz, 10^3), megahertz (MHz, 10^6), gigahertz (GHz, 10^9), and terahertz (THz, 10^{12}). Radiofrequency radiation includes the low frequency (LF), medium frequency (MF), high frequency (HF), very high frequency (VHF), ultra-high frequency (UHF), super-high frequency (SHF), and extremely high frequency (EHF) ranges; the latter three ranges (UHF, SHF, EHF) comprise the microwave region. The extremely low frequency (ELF) region lies below radio waves, microwaves, and the voice frequency (VF)/very low frequency (VLF) range. Beyond radio waves lie infrared, visible, and ultraviolet radiation along with X-rays and γ-rays. By convention, frequency describes the nonionizing portion of the electromagnetic spectrum (ultraviolet region and below), whereas photon energies (electron volts, eV) describe the higher frequencies including all ionizing radiation. (Adapted from International Agency for Research on Cancer, IARC).[1]

TABLE 45.1. Physical characteristics of extremely low frequency (ELF), microwaves, and radio wave radiation.

Region	Wavelength	Frequency	Photon Energy
Extremely low frequency (ELF)	1,000–10,000 km	30–300 Hz	1.2–0.12 peV
Microwave	1 m–100 km	300 MHz–3 kHz	1,200–0.12 neV
Radio wave	1 mm–1 m	300 GHz–300 MHz	1.2–0.0012 meV

flourished in the 18th century, particularly in France and Germany. Benjamin Franklin postulated that all matter contained magnetic fluid distributed throughout the body and condensed in one part of the body when magnetized. The strength of magnet depended on the force required to start the fluid in motion.

Strong, durable magnets were available throughout Europe by the middle of the 18th century. In the late 1770s and early 1780s, shortly before the French Revolution, the Viennese physician Anton Mesmer established a successful practice using magnets in dramatic clinical settings to treat medical illnesses. He obtained a supply of magnets from the Jesuit priest, court astrologer to Queen Marie Antoinette, and Professor of Astronomy at the University of Vienna, Father Maximilian Höll (1720–1792). Subsequently, Mesmer claimed his healing powers resulted from a universal force (animal magnetism) rather than the magnets themselves; his abilities included the transfer of his healing powers to his patients. Disease resulted from an obstacle to the body's natural flow of "fluidum" channeled from the stars to the body by animal magnetism. Magnets restored the normal magnetic polarity in organs that became misaligned. After a series of investigations, King Louis XVI

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TABLE 45.2. Nomenclature of bands designated in the extremely low frequency (ELF) and radio wave frequencies of the electromagnetic spectrum. (Hitchcock and Patterson).[2]

Frequency Range	Designation	Acronym
<30 Hz	Sub-extremely low frequency (static)	Sub-ELF
30–300 Hz	Extremely low frequency	ELF
300–3,000 Hz	Voice frequency	VF
3–30 kHz	Very low frequency	VLF
30–300 kHz	Low frequency	LF
300–3,000 kHz	Medium frequency	MF
3–30 MHz	High frequency	HF
30–300 MHz	Very high frequency	VHF
300–3,000 MHz	Ultra-high frequency	UHF
3–30 GHz	Super high frequency	SHF
30–300 GHz	Extremely high frequency	EHF

appointed a committee in 1784 that included Benjamin Franklin, Antoine Lavoisier, and medical faculty from the University of Paris; this group concluded Mesmer's claims of successful healing resulted from the power of suggestion in susceptible or naive patients rather than any special powers.[5] Then, the emphasis of the scientific community shifted from animal magnetism to subconscious motivation, hypnosis, and the power of suggestion. Few scientific studies on the medical effects of magnets were published during the 18th and early 19th centuries; most of these studies were unable to demonstrate any influence of magnets on biological or pathological processes.[6] However, during the late 19th and early 20th centuries, Dr. C.J. Thatcher, Dr. Rodney Maidson, and Gaylord Wilshire of Los Angeles used radio advertising and mail-order merchandizing to promote magnetic devices and garments as cures for a variety of diseases. Although evidence for the efficacy of magnetic fields in the treatment of any disease is lacking, products claiming the benefits of magnetic fields currently remain on the market and Internet.[7] During the early days of the US space program, concern about the astronauts' exposure to changing magnetic fields led to research on the effects of magnetic fields on primates.[8,9] The introduction of MRI machines into clinical practice in the 1970s resulted in substantial research and guidelines on exposure to ELF electric and magnetic fields.

PHYSICAL PROPERTIES

Radiation travels through space or other media in the form of waves or particles. Electromagnetic radiation typically encountered in the environment refers to energy propagated as sinusoidal waves carried by electric (E) and magnetic (H) fields. These fields are vector quantities that are perpendicular to each other and the direction of energy propagation, as displayed in Figure 45.2. They vary in terms of frequency, peak and mean intensity, waveform, direction of the field, and duration; the biologically important parameters of the field are not clearly identified. Electric and magnetic fields surround all conductors carrying electric current. These fields decrease in strength as the distance from the conductor increases. Electric and magnetic fields are considered separately because they do not possess a constant relationship in areas close to radiofrequency sources. Hence, **direct** measurements of both fields are necessary to characterize an exposure in the non-radiating near-field, where the ELF wavelengths are measured in many kilometers. In contrast to ionizing radiation, electromagnetic fields do not deposit energy in the body; similarly, electromagnetic fields do not transfer heat to tissue as microwave radiation does.

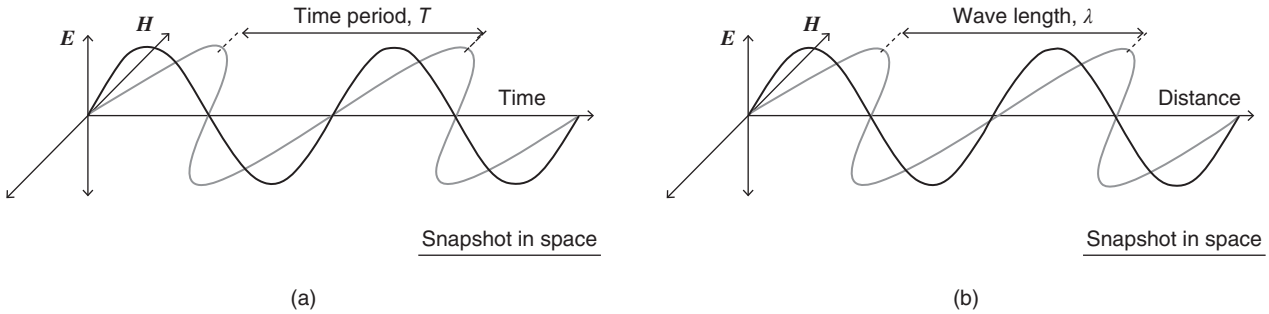


FIGURE 45.2. Schematic representation of electromagnetic waves in (a) time and (b) distance. Variation in electric and magnetic field strength depends on the source with most industrial sources of electromagnetic waves manifesting as sinusoidal waves that change over time. (Adapted from International Agency for Research on Cancer, IARC).[1]

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Magnetic Fields

Definition

Conceptually, a field is a number of lines of force (i.e., flux) that traverse a specific cross-sectional area. The field intensity is directly proportional to the number of those lines. Magnetic fields result from the *movement* of electrical charges (i.e., current), whereas electric fields occur as a result of the *separation* of charges (voltage). All circuits from major power lines to kitchen appliances produce magnetic fields. A static magnetic field forms as a result of direct current, whereas alternating currents produce time-varying magnetic fields. Neither animals nor humans distort magnetic fields; therefore, the strength and frequency of a magnetic field are similar inside and outside the body. Within the body, external magnetic fields induce the flow of currents, depending on the radius of the current path and the magnetic field's frequency and strength.[10] Time-varying magnetic fields induce eddy currents within the body that may exceed naturally occurring currents. Current densities induced by magnetic fields are greatest at the periphery of the body, where the conducting paths are longest; however, the magnitude of the induced current depends on the tissue conductivity. The latter varies substantially throughout the body.

Units

The two vector quantities describing a magnetic field are field strength (H) and magnetic flux density (B). The magnetic field strength is the force exerted on an element of current at a specific point within the field; the unit for magnetic flux density is the tesla (T). By convention, magnetic flux density (B-field) describes the magnetic fields produced by the flow of current in the conductors of transmission lines and substations. The magnetic permeability (μ) is a property of the medium that correlates the magnetic field strength to the magnetic flux density as described in Equation 45.1. For biological materials, the value of the permeability (μ) is near the value of permeability for free air (μ_o).

$$B = \mu \times H \qquad \text{(Equation 45.1)}$$

Table 45.3 lists the important quantities used to describe magnetic fields in SI units. The strength (E) of magnetic fields depends on the geometry of the circuit, the amount of current in the conductors within the circuit, and the distance from the circuit. In general, the magnetic field varies inversely with the square of the distance from the conducting elements of the circuit.

TABLE 45.3. Quantities and units important to describe the properties of electromagnetic fields.

Quantity	Symbol	Unit Name	Unit Symbol
Wavelength	λ	Meter	m
Frequency	f	Hertz	Hz
Energy	Q	Joule	J
Power	P	Watt	W
Power density	S or Pd	Watt/m^2	W/m^2
Magnetic field strength	H	Ampere/meter	A/m
Magnetic flux density	B	Tesla	T[a]
Electric field strength	E	Volt/meter	V/m
Current	I	Ampere	A
Current density	J	Ampere/m^2	A/m^2
Impedance	Z or η	Ohm	Ω
Conductivity	σ	Siemens/meter	S/m
Permittivity	ε	Farad/meter	F/m
Permeability	μ	Henry/meter	H/m
Propagation constant	K	Per meter	m^{-1}

[a] Conversion factor 1 mT = 10 gauss (G).

Electric Fields

Definition

Electric fields result from the separation of charge; these fields are much more difficult to quantify than magnetic fields because of the variability of electric fields with time. The electric field is a measure of the force a unit charge experiences at a specific point in space. Voltage measures the separation of charges, with larger voltages producing stronger electric fields. If a conductor connects two areas of separated charges, then current will flow. Because almost everything in our environment conducts charge, electric fields constantly adjust in magnitude to the movement of charge as physical objects move in the environment. Both perturbation and shielding of the electric fields contribute to the difficulty of measuring exposure to electric fields.

In general, the body attenuates external ELF electric fields by a factor of 10^5–10^7;[11] therefore, the electric field is localized primarily to the surface of the body. The strength of the electrical field at the surface of the body and the intensity of the induced current within the body depend on the following factors: 1) physical characteristics (strength, frequency, spatial direction) of the field; 2) the location of the body relative to the ground and to other conductors; 3) the shape of the body; and 4) the conduction of currents from the body to external grounds.[12] Hence, the current induced by the same electric field will be different in a human and a laboratory

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animal.[13] Changing magnetic fields create electric fields. When these electric fields are inside a conductive object (e.g., the human body), motion-induced currents (i.e., eddy currents by displacement) develop.

Units

The unit for an electric field strength is the volts/meter (V/m), as noted in Table 45.3. similar to magnetic fields, the electric field strength (E) and the electric flux density (D) are vector qualities related to each other by Equation 45.2.

$$D = \varepsilon \times E \qquad \text{(Equation 45.2)}$$

where

ε = permittivity (property of the medium)

Equation 45.3 describes the relative permittivity (ε_r) as the ratio of the permittivity (ε) to the permittivity of a vacuum (ε_o).

$$\varepsilon_r = \varepsilon/\varepsilon_o \qquad \text{(Equation 45.3)}$$

For free air, the $\varepsilon_r = 1$; however, the value of ε_r in the tissues is substantially greater. Therefore, the body greatly attenuates electric fields in contrast to the relative uniformity of internal and external magnetic fields. The permittivity or dielectric constant of tissue varies widely; consequently, structural variations in the body and the heterogeneity of living tissue complicate the prediction of induced currents.

EXPOSURE

ELF fields occur during the generation, transmission, and consumption of electricity. All humans are exposed to a wide variety of electric and magnetic fields that result from a variety of objects in the environment, including electric current flow in domestic appliances, electric power distribution systems, and specialized medical devices. In contrast to the coupled electric and magnetic (i.e., electromagnetic) fields of radiofrequency sources, ELF sources (e.g., power lines, electric appliances) have separate electric and magnetic fields that can be evaluated as if they are independent sources. These fields vary in frequency and strength with time and space in residential settings, complicating the measurements of exposure to these fields. Exposures to ELF fields are diverse; direct measurements are necessary to accurately categorize exposure to these fields. The body attenuates electric fields. Exposure to a 1 kV/m-electric field at 60 Hz produces an internal electric field ranging from 1–100 mV/m.[14] Electric fields vary from location to location; however, these fields remain relatively constant over time because electric fields depend on voltage that usually remains relatively constant. In contrast, magnetic fields depend on current that varies widely over time *and* location from the source. Figure 45.3 demonstrates the variation in intensity of 60-Hz electric and magnetic fields as a function of the distance from the source. Because of the long wavelengths of ELF fields, electric and magnetic fields are separate and independent at any practical observation point. These power-frequency fields are always in the near-field in contrast to RF radiation, which operates in the near- and far-fields, depending on the distance from the antenna.

Figure 45.4 compares the magnetic field strength (μT) of various environmental sources of ambient exposure to 60-Hz magnetic fields. Measurement of environmental exposure typically includes electric and magnetic fields. For measurement of the magnetic field, the geometric mean (log-weighted average) is a better measure of the central tendencies than the mean or median values because these values tend to clump in the lower range with a few higher values. In a study of 24-hour personal exposures to magnetic fields in the US environment, the geometric mean was 0.09 μT with 44% of the samples >0.1 μT, ~14% >0.2 μT, ~2.5% >0.5 μT, and <1% >0.75 μT.[15]

Natural Sources

Magnetic Fields

The natural magnetic field is the combination of the internal field from the earth acting as a permanent magnet and the smaller external field composed of magnetic activity in the environment from solar and atmospheric activity. The internal field results from the variable current flow in the upper layer of the earth's core; the strength of this field varies from a nadir near the equator to a maximum at the magnetic pole. Additionally, the geomagnetic field fluctuates continuously because of diurnal, lunar, and seasonal variations manifested as short-term perturbations. The vertical component of the static magnetic field is ~67 μT at the magnetic pole, whereas the horizontal component of the static field is maximal (i.e., ~33 μT) at the magnetic equator.[10] The corresponding perpendicular vectors (i.e., horizontal vector at the magnetic pole, vertical vector at the magnetic equator) of these static magnetic fields at the point of maximal strength will be zero. The natural 60 Hz magnetic field is ~10^{-6} μT, whereas the magnetic field in homes averages up to 100 μT; the magnetic field around household appliances

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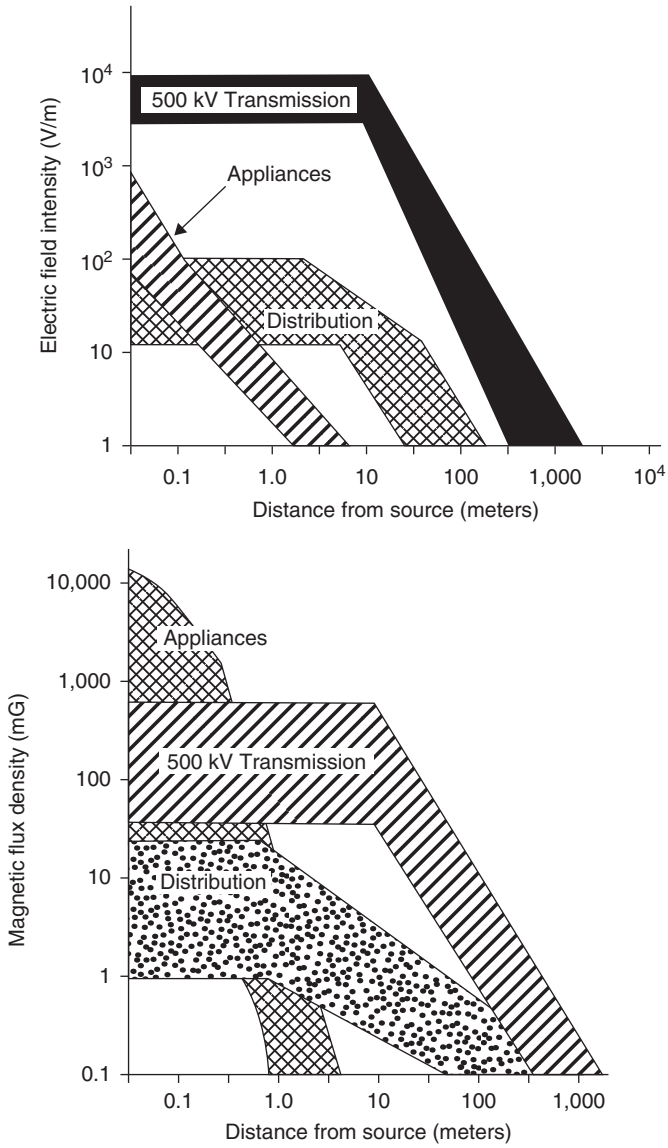


FIGURE 45.3. General comparison of ground-level variation in electric and magnetic field densities (strength) as a function of distance from common sources, including transmission lines, distribution lines, and appliances, as measured by microtesla (μT, SI units) and milligauss (mG, conventional units).

ranges up to several hundred μT close to the source.[11] In comparison to natural magnetic fields, the magnetic field below 1,100 kV transmission lines is also much stronger. At 1 m above the ground, under the centerline at the midspan of the transmission lines, the levels of the magnetic fields usually range up to 35 μT.

Electric Fields

The dominant static component and the smaller time-varying component comprise the natural electric field that is directed radially as a result of the negative charge of the earth. The field strength is highest in the temperate latitudes and lowest near the poles and equator; however, the intensity of the electric field may vary up to 500 V/m with weather, altitude, season, and time of day.[17] The strength of the static electric field near the surface of the earth is ~120 V/m as a result of the separation of charges between the atmosphere and the earth's surface.[18] Alternating low-frequency electric fields result from thunderstorms and magnetic pulsations that induce currents in the earth (telluric currents).[11]

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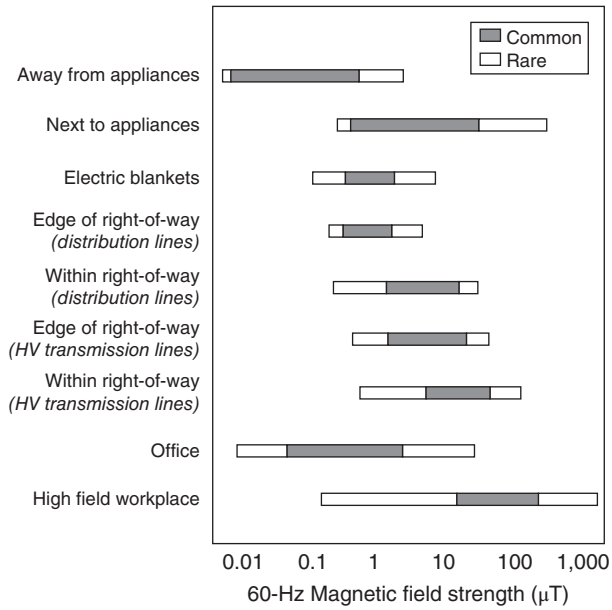


FIGURE 45.4. Approximate variability in magnetic field densities with general distances from appliances and transmission lines. (Adapted from Mader and Peralta).[16]

Residential Sources

Static and extremely low frequency (ELF) fields cover the range of the electromagnetic spectrum from 0–300 Hz, whereas low-frequency fields range from 0.3–100 kHz. The most common frequencies among ELF fields result from the transmission of electricity by sinusoidal waveforms at 50 Hz in Europe and 60 Hz in North America. Exposure to electric and magnetic fields occurs through a wide variety of human activities involving the use of electrical energy at various frequencies. At power frequencies (i.e., 50–60 Hz), electromagnetic fields from human activities are several thousand-fold greater than natural fields; the dominant sources of time-varying fields involve human activities. The major sources of magnetic and electrical fields in residential settings include multiple grounded, current-carrying plumbing and electrical circuits, appliances, and adjacent power lines (service lines, drop lines).[17] European exposure to commercial and residential magnetic fields is typically lower than exposures in North America because the higher main voltage is associated with lower currents in Europe than in North America.

Magnetic Fields

The major residential sources of ELF magnetic fields are currents flowing in conducting pipes, electrical grounds, appliances, and distribution circuits. High-voltage power lines do not typically contribute significantly to residential magnetic fields.[17] Direct measures of exposure to magnetic fields are necessary because actual measurements in residences vary over 10-fold depending on electricity consumption, wiring practices, and supply voltages. In an analysis of 27 studies reporting the intensity of residential magnetic fields in the United States and Europe measured over ≥24 hours, background field intensities followed a log-normal distribution with a US geometric mean of 0.06–0.07 μT (arithmetic mean = 0.11 μT) and a UK geometric mean of 0.036–0.039 μT (arithmetic mean = ~0.05 μT).[19]

Figure 45.5 compares the approximate ambient background level of magnetic fields in the home with sources outside the home.[20] A study of adult residents in Maine indicated the average exposure of a resident away from home was ~0.2 μT (2 mG).[21] The magnetic field at a distance of 30 cm from a home appliance ranged from ~0.03–30 μT; at 150 cm from the source, the magnetic field for the highest source was <0.5 μT.[22] In a study of 69 homemakers exposed primarily to 60-Hz fields, the time-weighted average exposure (TWA) to ELF magnetic fields was 0.113 μT with a range of 0.22–0.403 μT as measured by integrating personal magnetic-field exposure meter.[23] In a study of 301 Danish volunteers using Positron personal dosimeters with monitoring time of >7 hours, the geometric mean ± standard deviation of the magnetic field exposure in residences far from power lines was 0.04 ± 2.1 μT; the corresponding value for residences near high-power lines with a mean distance of 23 m and a range of 0–68 m was 0.29 ± 2.8 μT (maximum, 2.24 μT).[24]

Exposure to magnetic fields from appliances depends on the duration of use, the distance from the appliance, and the magnetic field strength. The magnetic flux density decreases rapidly with distance, varying inversely with the square of the cube of the distance from the appliance, beginning at a distance several times greater than the diameter of the appliance.[25] At 1 m, the value of the field approximates the background flux density. Consequently, the total chronic whole-body exposure is an order of a magnitude (i.e., ~0.02 μT) below other residential sources.[16] The domestic appliances producing the highest magnetic field contain heaters, transformers, and motors. Table 45.4 lists the magnetic flux density at 50 Hz near common UK household appliances; the magnetic field strength varied widely within groups of different appliances.[26] During the use of electric blankets, magnetic flux densities vary by an order of magnitude between the side of the body closest to and the side farthest from the electric blanket. In a study of individuals

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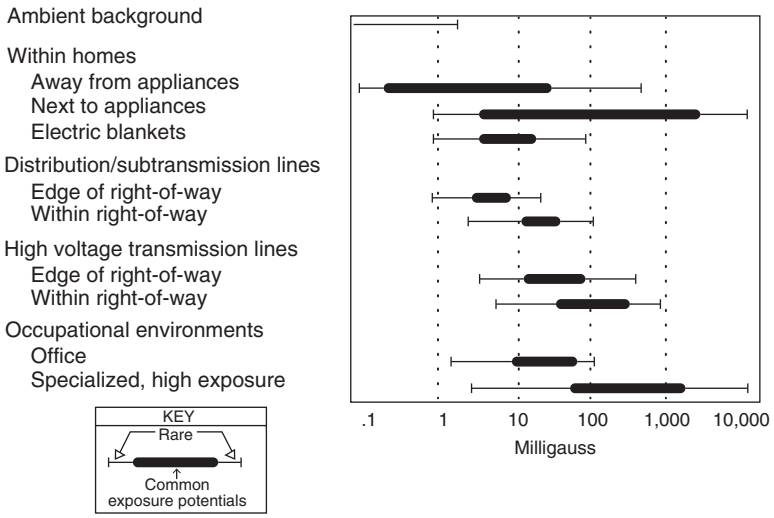


FIGURE 45.5. Estimated average 60-Hz magnetic field strengths comparing fields in the home, adjacent environment, and workplace in units of μT. The solid portion of the range connotes common occurrences of the magnetic field strength in μT, whereas the thin line connotes rare occurrences at that specific value. (Adapted from Savitz et al.).[20]

TABLE 45.4. Mean calculated magnetic field ± standard deviation at 5, 50, and 100 cm from surface of selected UK appliances (50 Hz) based on measurements at 5, 30, 60, and 100 cm from the appliance. The magnetic field strength of appliances varies between countries depending on use, supply voltage, and wiring practices. (Adapted from Preece et al.).[26]

Appliance	Measurements	5 cm (μT)	50 cm (μT)	100 cm (μT)
Alarm, burglar	10	6.20 ± 5.21	0.18 ± 0.11	0.03 ± 0.02
Clock, electric	6	5.00 ± 4.15	0.04 ± 0.00	0.01 ± 0.00
Coffee maker	2	0.57 ± 0.03	0.06 ± 0.07	0.02 ± 0.02
Computer	6	1.82 ± 1.96	0.14 ± 0.07	0.04 ± 0.02
Dishwasher	13	5.93 ± 4.99	0.80 ± 0.46	0.23 ± 0.13
Food mixer	6	69.91 ± 69.61	0.69 ± 0.69	0.11 ± 0.11
Freezer	13	0.42 ± 0.87	0.04 ± 0.02	0.01 ± 0.01
Hair dryer	39	17.44 ± 15.56	0.12 ± 0.10	0.02 ± 0.02
Iron	33	1.84 ± 1.21	0.03 ± 0.02	0.01 ± 0.00
Kettle, electric	49	2.82 ± 1.51	0.05 ± 0.06	0.01 ± 0.02
Knife, electric	5	27.03 ± 13.88	0.12 ± 0.05	0.02 ± 0.01
Light, fluorescent	3	5.87 ± 8.52	0.15 ± 0.20	0.03 ± 0.03
Oven	13	1.79 ± 0.89	0.39 ± 0.23	0.13 ± 0.09
Oven, microwave	34	27.25 ± 16.74	1.66 ± 0.63	0.37 ± 0.14
Radio	23	3.00 ± 3.26	0.06 ± 0.04	0.01 ± 0.01
Radio, clock	32	2.34 ± 1.96	0.05 ± 0.05	0.01 ± 0.01
Razor, electric	1	164.75	0.84	0.12
Refrigerator/freezer	23	0.21 ± 0.14	0.05 ± 0.03	0.02 ± 0.01
Speaker	8	0.48 ± 0.67	0.07 ± 0.13	0.02 ± 0.04
Television	73	2.69 ± 1.08	0.26 ± 0.11	0.07 ± 0.04
Toaster	29	5.06 ± 2.71	0.09 ± 0.08	0.02 ± 0.02
Vacuum cleaner	42	39.53 ± 74.58	0.78 ± 0.74	0.16 ± 0.12
Video-cassette recorder	42	0.57 ± 0.52	0.06 ± 0.05	0.02 ± 0.02
Washing machine	34	7.73 ± 7.03	0.96 ± 0.56	0.27 ± 0.14

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using electric blankets, the mean whole-body flux density was 2.2 μT with a range of 1.5–3.3 μT during use.[27]

Electric Fields

Exposures to ELF electric fields in the home result from distribution lines, electrical wiring in the building, electric heat (e.g., heated waterbeds, electric blankets), electric hot water heaters, and electrical appliances (e.g., kitchen devices, hair dryers). The electric field in the center of a typical American home ranges from ~1–20 V/m, whereas electric fields 30 cm from some appliances average ~10 V/m, with values up to several hundred V/m near domestic appliances (e.g., electric boiler) or cables.[28]

Figure 45.6 compares the average background levels of electrical fields in the home with those from sources outside the home. The shielding of external electric fields significantly limits the contribution of transmission and distribution lines to the magnitude of the electrical field within the home; however, these power lines do contribute substantially to the overall magnetic field.[29]

Transmission Sources

The most prevalent ELF fields in the environment result from the transmission of electricity through power lines. High-voltage lines frequently consist of three lines with differing time phases; consequently, the voltages and the currents reach peak values at different times. Power lines operate at voltages ranging from residential wires (120 V in the United States, 220–240 V in Europe) to high-voltage power lines (765 kV).[30] The vector of the surrounding ELF fields is the sum of the fields produced by each line; the vector moves in an ellipse rather than a sinusoidal pattern for an individual line. The magnetic fields around power lines themselves produce an electric field strength inside the body; however, the induced electric field is ~15% of the strength of the electric field produced by the power lines.[31] Under power lines, the orientation of the electrical field is perpendicular (i.e., vertical) to the surface of the earth, whereas the orientation of the magnetic field is parallel (i.e., horizontal) to the surface of the earth. Although high-voltage power lines in different countries follow similar principles, differences in power-line design produce differences in the fields surrounding power lines in different countries.

Magnetic Fields

Magnetic fields always appear when current flows through conductors (e.g., transmission lines). Besides the geometry of the conductor, the magnitude of the current determines the strength of the magnetic field

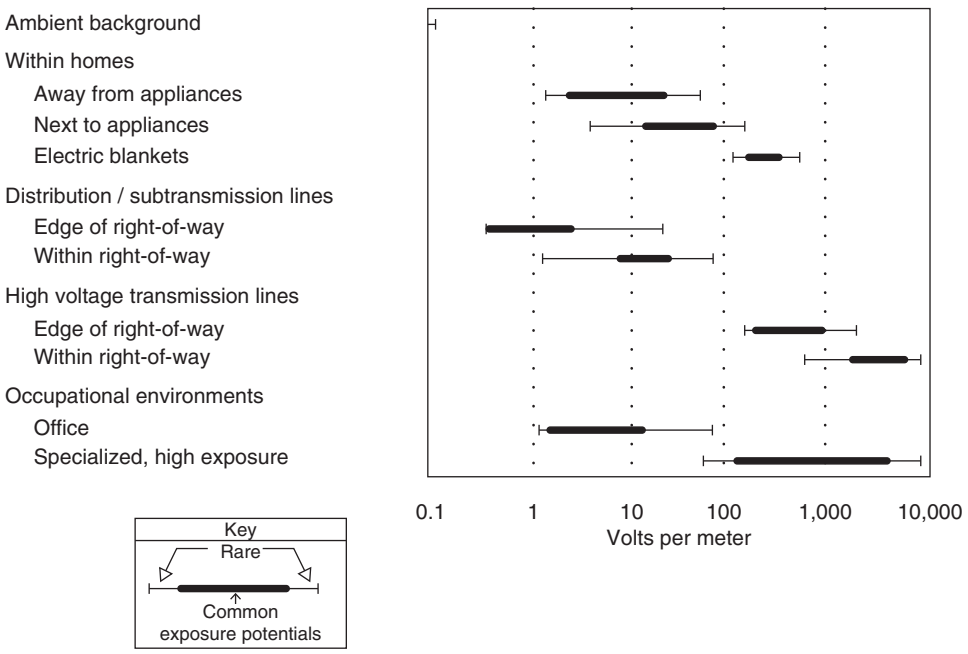


FIGURE 45.6. Approximate range of 60-Hz electric field strengths in the home, adjacent environment, and workplace in units of V/m. The solid portion of the range connotes common occurrences of the magnetic field strength in V/m, whereas the thin line connotes rare occurrences at that specific value. (Adapted from Savitz et al.).[20]

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surrounding the transmission lines. The day-to-day variation in the magnetic fields surrounding power lines is usually small; however, magnetic fields under 500 kV transmission lines can double during the ~1% of the time peak loads occur.[32,33] The strength of the magnetic field decreases with the lateral distance from the conductor. The maximum ground-level strength of the magnetic field under transmission lines ranges from ~10–50 μT, depending on the height of the power lines and the distance from the centerline. Typical magnetic flux densities directly beneath overhead power lines range up to ~10 μT for 380 kV lines and 30 μT for the less common 765 kV lines; the former value decreases to <3 μT 20 m from the centerline of the transmission wires.[34] Figure 45.7 demonstrates the values of the magnetic field for lateral distances from high-voltage transmission lines. Magnetic field strengths usually return to background values within 50–300 m from the high-voltage power lines, depending on design, current, and background factors.[17] Although this type of field can induce currents in the body, the magnitude is sufficiently small (<25%) compared with the strength of the electric field; consequently, the electric field around transmission lines is the usual exposure parameter for evaluation of health effects. Distribution lines typically run directly to residential and commercial facilities with average magnetic fields ranging from 1–2 μT for overhead and underground lines; typical maximum values for overhead and underground distribution lines are 7 μT and 4 μT, respectively.[32]

Electric Fields

The unperturbed electric field at the point of maximum field strength near the outer conductor of a high-voltage (750 kV) transmission line is ~10 kV/m. Figure 45.8 demonstrates the approximate values of the electric field near high-voltage lines. The strength of the electric field surrounding transmission lines and substations depends on a number of factors that shield the body from the electric field including trees, buildings, and other electrically grounded objects. Outdoor substations do not usually increase residential exposure to electric or magnetic fields.[35] Electric fields in buildings usually result from internal wiring and appliances rather than power lines.[35]

Electromagnetic Pulse

An electromagnetic pulse (EMP) occurs following the detonation of thermonuclear weapons above the surface of the earth. The atmosphere converts only a small portion of the energy released into the atmosphere to EMP because of the production of Compton recoil electrons. The two types of EMP are the relatively slow magnetohydrodynamic EMP that lasts ~0.01 second and the fast, high-amplitude pulse called tachy-EMP.[36] The latter type of EMP can generate currents in the kiloampere range.[37] Mechanical damage results from the induction of currents at frequencies below 100 MHz in communication equipment, computers, power lines, cables, and rails.

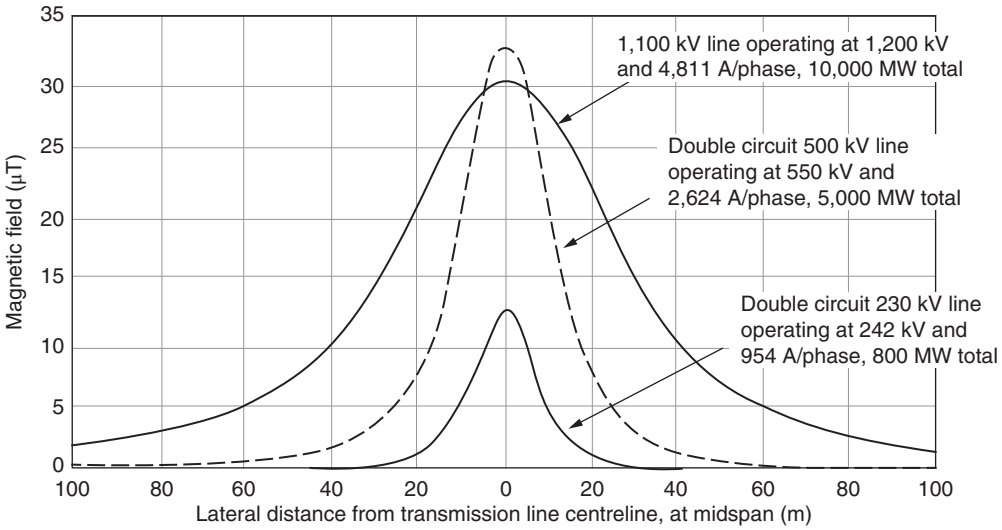


FIGURE 45.7. Calculated 60-Hz magnetic field strengths at 1 m above ground for 230 and 500 kV double circuit power lines with estimated approximate magnetic field strengths for 1,100 kV line. (Adapted from International Programme on Chemical Safety).[10]

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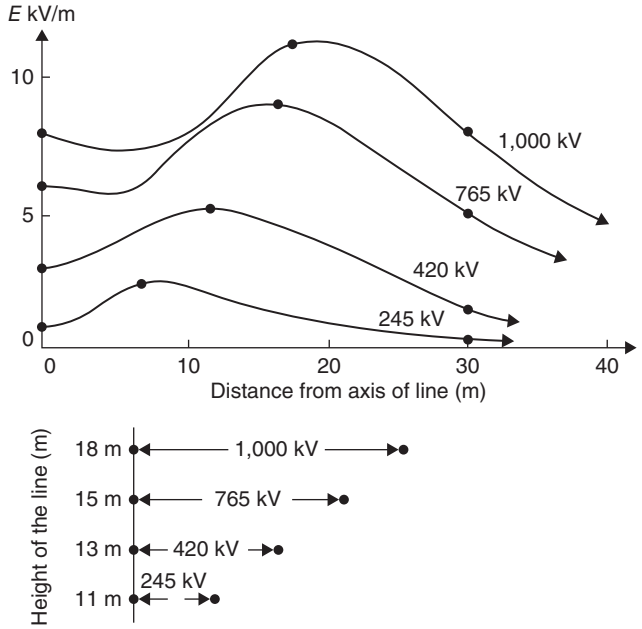


FIGURE 45.8. Calculated electric field strengths (kV/m) above ground at the end of the transmission line based on the distance (meters) from the transmission line. (Adapted from International Programme on Chemical Safety).[11]

Occupational Sources

Magnetic Fields

Exposure to magnetic fields in the occupational setting results primarily from working near industrial equipment operating with high current loads (e.g., overhead power lines, underground cables, power stations), particularly busbars close to power station generators. Magnetic field exposures may vary substantially within the same job category as a result of differences in activities and tasks. Because high-current sources are more prevalent in industry than high-voltage sources, exposures to magnetic fields are more common than exposures to electric fields in the workplace. Examples of jobs with potential chronic exposure to high-strength magnetic fields include work near utility operations (linesmen, electricians, substation operators, generation facility workers), induction furnaces, electrical transportation systems, electrical distribution vaults, cranes and hoists, railroad engines, welding machines, and small motors. In a study of 1,098 Swedish workers from a broad range of jobs, direct measurement of ELF magnetic fields with personal dosimeters calibrated at 50 Hz demonstrated a skewed curve for the workday average. The workday arithmetic mean and median were 0.28 μT and 0.14 μT, respectively.[38] The upper 95th percentile of the workday exposure was 0.66 μT, with a maximum reading of 18 μT. The study suggests occupations with potentially high exposures to magnetic fields include welders, electrical technicians/engineers, electronics engineers/technicians, train engine drivers, and glass, ceramic, and brick workers. The geometric mean of the time-weighted average exposure of six women working in industrial settings was 0.265 μT with a range of 0.054–3.436 μT as measured by an integrating personal magnetic-field exposure meter.[23] In a Canadian study of ELF magnetic fields in jobs commonly held by women, jobs estimated to exceed a weekly time-weighted-average magnetic field exposure of 0.23 μT included bakery workers, cashiers, cooks, and kitchen workers, with the highest estimated exposures in electronics workers in an assembly plant (0.70 μT) and sewing machine operators in textile factories (0.68 μT) and shoe factories (0.66 μT).[39]

Table 45.5 lists the magnetic flux densities of common industrial sources for high magnetic field exposures. The average magnetic flux density near facilities with large electrical equipment (substations, overhead power lines, power stations) is ~50 μT.[10] Magnetic flux densities in the range of 200–400 μT occur only in specialized, high-voltage occupational environments (e.g., certain types of arc welders).[40] Older video display terminals produce power frequency and higher ELF electromagnetic fields ranging from 15–35 kHz. In a study of VDT operators, the median magnetic field strength in the ELF range was 0.21 μT and 0.03 μT for the 15–35 kHz range, whereas the median electric field strength for these ranges was 20 V/m and 1.5 V/m, respectively.[41]

TABLE 45.5. Occupational sources of high exposures to magnetic fields. (Adapted from International Programme on Chemical Safety).[10]

Source	Magnetic Flux Density (μT)	Distance From Source (cm)
Welding arcs (0–50 Hz)	100–5,800	0–80
50-Hz electroslag welding	500–1,700	20–90
Induction heaters (10–50 Hz)	900–65,000	10–100
50-Hz ladle furnace	200–8,000	50–100
50-Hz furnace	<1,000	200
10-Hz induction stirrer	200–300	200
Electrolyte process (0–Hz)	7,600 (mean)	Operator position
Isotope separation (static field)	1,000–50,000	Operator position
Video display terminal	<0.28	30

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Electric Fields

Except for occupations where high-voltage sources are present, electric field exposures in most occupations are similar to those in residential settings. Occupations with high exposure to electric fields typically involve the utility industry (e.g., utility electricians, linesmen, substation operators). In a UK study of 50 Hz electric fields surrounding substations and below power transmission lines, the intensity of the electric fields ranged up to 22 kV/m and 11 kV/m, respectively.[42] Some objects (e.g., long unearthed metal fences, large vehicles) can develop substantial potential differences in large electrical fields. The human body can become the pathway for current between such objects. Steady-state short-circuit current of up to 1 mA can flow into the body from these fields, depending on the height of the person, the strength of the electric field, and the frequency. In a 10-kV/m, 60-Hz electric field, a 1.7-m-tall person carries a short circuit of ~0.16 mA.[11] A jeep wagon in a 10 kV/m field conducts 1.1 mA of current to the earth. Electric field strengths near arc welders are usually ~1 V/m and rarely exceed 50 V/m.[40]

DOSE EFFECT

Although the nonionizing radiation dose is usually measured in units of energy and the dose rate in units of power, the dose of extremely low frequency radiation has no universally accepted definition. The lack of a definition results, in part, from a scarcity of information regarding the mechanism of biological action of ELF fields. The bodies of humans and animals significantly alter the spatial distribution of low-frequency electric fields (1 Hz–100 kHz). The induced internal electric field is considerably smaller than the external electric field (e.g., five to six orders of magnitude at 60 Hz) and strongest when the feet are electrically grounded. Tissue conductivity determines the distribution of induced current within the body, whereas body shape, posture, and size determine the total current flowing in the grounded body. Extrapolation of animal data to humans is limited because electromagnetic fields vary with the size, shape, and orientation of the body. Therefore, no single animal model simulates exposure to humans.

In contrast to electric fields, human and animal bodies do not perturb magnetic fields. Tissue and air permeability in humans and animals are similar, resulting in similar internal and external magnetic fields. The application of magnetic fields to the body induces internal electric fields and currents depending on the magnetic field strength, orientation, and body size, whereas the distribution of the induced electric fields depends on tissue conductivity. The magnitude of induced current densities from ambient static magnetic, time-varying magnetic, and electric fields is at least several orders of magnitude below the endogenous currents produced by normal physiological processes. A 60-Hz magnetic field with an intensity of 0.1 μT induces a current density of 0.19 μA/m^2, whereas an electric field of 10 kV/m produces a maximum current density of ~2 μA/m^2.[13] Although many animals detect electric fields at 1–5 kV/m, there are no data demonstrating that these levels produce adverse effects. *In vitro* studies demonstrate equivocal effects at levels >1,000 times higher than the levels present in residential homes.

Magnetic Fields

Static magnetic fields up to 2 T have not been associated with significant adverse health effects in humans.[10] In an experimental study of 25 volunteers exposed to static magnetic fields up to 8 T, an average increase of 3.6 mmHg in systolic blood pressure occurred in the highest exposure group.[43,44] Otherwise, no significant changes occurred in cognitive function, heart rate, respiratory rate, diastolic blood pressures, electrocardiogram, rhythm strip, finger pulse oxygenation levels, or core body temperature as measured by the external auditory canal temperature. Static magnetic fields may produce dizziness and vertigo during motion in the field, depending partly on individual sensitivity. Mild-to-moderate dizziness developed in 8 of 10 subjects exposed to a magnetic field change (dB/dt) of 4.7 T in 1.9 seconds, whereas no subjects reported any response during exposure to 50 msec pulses of 2 T/second in amplitude.[45]

Time-varying magnetic fields and rotational motion in a uniform static field induce the flow of currents in the body, whereas linear motion within a uniform static field does not induce current. Health effects associated with these induced currents are difficult to predict within an order of magnitude; however, the induction of currents of 10 mA/m^2 has not been associated with clinically significant biological effects. In the range of 10–100 mA/m^2, short-term exposure produces minor biological changes. The human body can sense a magnetic field by detecting the presence of magnetophosphene (i.e., the sensation of flickering light that occurs following exposure to magnetic fields with an intensity >10 mT and frequencies >10 Hz). At induced current densities of >100 mA/m^2 (>50–500 mT at 50/60 Hz or 1–10 T at 3 Hz), stimulation of excitable

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tissue and the development of adverse health effects are possible.

Electric Fields

Because the body attenuates electric fields, predicting health effects from the strength or density of electromagnetic fields is much more difficult for electric than magnetic fields. Similar to magnetic fields, no single animal model adequately simulates human exposure to electric fields. Sensitivity to electric fields results from the sensation of tingling in the hair at field strengths of >10 kV/m. Workers in contact with electric fields may experience contact currents or spark discharges (microshocks). A study of the detection threshold for electric fields indicated the threshold for hairless skin on the palm was >115 kV/m, whereas the value for hairy skin on the dorsum of the hand was 30–65 kV/m.[46] The detection threshold was much lower in the fall than in the summer, when lower humidity reduced the relative permittivity of the skin.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Static Magnetic Fields

The major biological properties of static magnetic fields include 1) induction of electric currents from motions within an inhomogeneous field (motion-induced currents or eddy currents by displacement); 2) Lorentz force; 3) magnetic force; 4) magnetic torque; and 5) radical pair effect.[47] Lorentz forces operate perpendicular to the direction of the electric charge flow. The magnetically-induced potential could impede blood flow; however, static magnetic fields up to 9.4 T did not significantly affect cardiovascular function.[48] Magnetic force in a spatially inhomogeneous magnetic field moves susceptible material in the direction of the steepest field gradient (missile or projectile effect), whereas magnetic torque orients certain diamagnetic materials (e.g., fibrin, collagen) and some cells (osteoblasts, Schwann cells). *In vitro* studies suggest static magnetic fields alter the shape and orientation of osteoblasts.[49] Although strong static magnetic fields did not enhance cell proliferation, cell differentiation and matrix synthesis were upregulated. Magnetic fields cause effects by the induction of internal currents.

Some organisms use the static magnetic field of the earth for orientation and/or direction (e.g., sharks, rays, migratory birds, the waggle dance of bees, the kinetic movements of mollusks, magnetotactic bacteria).[10] *In vitro* studies on the biological effects of electromagnetic fields indicate these fields can increase the permeability of the cell membrane to calcium[50] and alter the concentrations of some enzymes (e.g., adenosine triphosphate, ornithine carboxylase).[51]

ELF Electric and Magnetic Fields

No *single* theory provides a biological basis for health effects of ELF electromagnetic fields, particularly at the low field strengths in this part of the electromagnetic spectrum. Potential mechanisms for health effects include induced electric fields in neural networks, altered reactive free radical concentrations, and the effect of these electromagnetic fields on ferromagnetic material (i.e., magnetite) within the body. ELF electric and magnetic fields couple poorly within the body; in contrast to radiofrequency and microwave exposures, the body absorbs little energy from the ELF portion of the light spectrum at ELF levels present in the environment. Therefore, the effects of ELF do not result from the heating of tissue. The cell membrane is a likely site for the biological effects of ELF fields. The dielectric constants of the cell membrane are sufficiently high that induced currents occur almost exclusively on the cell surface; consequently, the cytoplasm is shielded from the effects of the ELF field. A major difficulty in the development of a unifying theory is understanding how cells can detect weak electromagnetic fields that deposit relatively small amounts of energy compared with the much larger levels of random thermal energy in the body.

Although most physiological indices are unaffected by exposure to ELF fields, subtle biological effects may occur after short-term exposure to these fields. These physiological changes do not apparently cause serious or permanent adverse reactions. Exposure of humans to ELF electric fields may stimulate sensory receptors by hair vibration or the induction of current in the body, resulting in transient sensory effects (e.g., nausea, vertigo, magnetophosphenes).[52] The exact mechanism responsible for magnetophosphenes is unclear; however, the mechanism of action probably does not involve ELF-induced heating or deposition of energy in tissue.

There is no **direct** evidence from animal experiments linking exposure to electric and magnetic fields in the 50–60 Hz range with cancer.[32,53] Extremely low frequency fields do not break chemical bonds or ionize tissue as higher energy sources (e.g., γ-rays, X-rays) do. Electric and magnetic fields at the frequency and intensity encountered in residential and occupational settings do not typically produce chromosome breakage,

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elevated rates of sister chromatid exchanges, or disruption of DNA repair processes. Most, but not all, *in vitro* studies of the genotoxic potential of extremely low frequency electric and magnetic fields do not demonstrate increased genetic damage as assessed from DNA strand breaks, incidence of chromosomal aberrations, micronuclei, and sister chromatid exchanges, when compared with control cells.[54,55] In two eukaryotic cell systems (human blood lymphocytes, DBY747 *Saccharomyces cerevisiae*), extremely low frequency electric and magnetic fields did not induce DNA damage or affect gene expression.[56] The energy imparted by man-made electromagnetic fields is small compared with currents produced by normal neuromuscular events in the body. Because magnetic fields have not induced mutations, the hypothesized mechanism of induction of cancer is the promotion or enhancement of growth via cell membrane-associated receptors rather than initiation.[57]

Promotion at the later stages of carcinogenesis is a possible stage of cancer at which electromagnetic fields would operate; however, animal studies have not consistently demonstrated such an effect.[58]

CLINICAL RESPONSE

Environmental Exposure

Although exposure to ELF electric and magnetic fields may produce some biological effects in animals, there is no consensus that these changes are hazardous, except for the production of internal currents above the threshold for stimulation of nerve tissue.[59] The Committee on the Possible Effects of Electromagnetic Fields on Biological Systems of the US National Research Council reviewed the evidence for adverse effects from electromagnetic fields.[60] They concluded that the current body of evidence did not support an association between exposure to power-frequency electric and magnetic fields and adverse health effects (neurobehavioral, reproductive, developmental).

Electromagnetic Hypersensitivity

Some practitioners involved with idiopathic environmental intolerance attribute a constellation of nonspecific symptoms (i.e., electromagnetic hypersensitivity) to exposure to electromagnetic fields involving ELF fields (e.g., power lines, electric appliances) as well as radio frequency waves. This syndrome is not well defined and has no clear diagnostic criteria. A review of 29 studies published in the medical literature on electromagnetic hypersensitivity demonstrated no consistent pattern of objective changes in subjects with the diagnosis of electromagnetic hypersensitivity exposed to electromagnetic fields and sham controls.[61] A systematic review of 22 studies on the severity and frequency of nonspecific physical symptoms and electromagnetic field exposure detected no consistent or dose-related association between electromagnetic exposure and the occurrence of these symptoms in the general population.[62] Most studies suggested either no significant effect from higher electromagnetic exposure (fatigue-related problems OR = 1.15, 95% CI: 0.59–2.27) or negative results (headache frequency OR = 1.01, 95% CI: 0.66–1.53).

Mood and Neuropsychological Function

Most studies have not demonstrated differences in psychiatric diseases or neuropsychiatric testing between residents exposed to electromagnetic fields and controls; additionally, most experimental studies of human subjects have not detected significant changes in mood or neuropsychological function following exposure to environmental levels of electromagnetic fields. A study of 72 volunteers exposed to an average vertical electric field of 36 kV/m for 5.5 hours did not demonstrate significant changes in mood or verbal reasoning skills.[63] A case-control study of depression and personality abnormalities in residents of high-rise buildings raised concern about the possible association of suicide with exposure to electromagnetic fields from overhead high-voltage transmission lines.[64] A follow-up study indicated the suicide cases were exposed to more intense magnetic fields; however, the difference between the mean exposure of cases and controls (0.087 μT vs. 0.071 μT) was small.[65] A mortality study of 8,000 persons living within 30 m of electric transmission facilities did not support an association between suicide and exposure to electromagnetic fields.[66] Overall, the weight of the evidence does not support a causal association between electric or magnetic fields and the development of neurophysiological or psychological changes in residents near power lines.[67]

Occupational Exposure

Mood and Neuropsychological Function

Several uncontrolled studies of Russian workers in industries with high exposure to electromagnetic fields suggest these workers had an increased incidence of neurasthenic and depressive symptoms. In the 1960s, several surveys of Russian workers exposed to electric fields with intensities up to 26 kV/m demonstrated

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an excess of complaints related to the CNS and the autonomic system (e.g., dizziness, nausea, sleep disturbances, decreased libido, anorexia, headache, irritability, fatigue).[68] The lack of reference groups for comparison in these studies represents a severe limitation in the establishment of causal relationships between these neuropsychological symptoms and exposure to electric fields. Comparable, controlled studies of European and North American workers have not detected the excess of symptoms displayed in the Russian studies. A study of men with occupations associated with high exposure to electromagnetic fields did not support an association between suicide and exposure to electromagnetic fields.[69] A mortality study of 31,068 US members of the International Brotherhood of Electrical Workers suggested a small, but statistically significant increase in suicide rates of the cohort compared with the NIOSH life table (proportional mortality ratio = 115, 95% CI: 104–124, $n = 505$ cases, $P < 0.05$).[70]

A survey of 390 electrical power transmission and distribution workers found no significant correlation between exposure to electric fields and an excess of neurological symptoms.[71] Measurement of the electrical fields surrounding 28 of these workers over a period of 2 weeks indicated that these workers were exposed to electrical fields averaging 30 kV/m. A cross-sectional study of 53 workers with over 5 years of exposure to electric fields from 400 kV substations did not find any statistically significant decrements in neurasthenic symptoms, psychological tests, or EEG.[72] A study of workers exposed to a mean electric field strength of 2.8 ± 0.35 kV/m and a mean magnetic field intensity of 23.3 ± 4.2 μT did not demonstrate any acute abnormalities on neuropsychological testing (simple reaction time, color word vigilance, perceptual test – symbol digit, memory test – digit span).[73] The measurements also included an EEG, a mood scale, and a questionnaire on subjective symptoms. A study of physicists and technicians exposed to peak field strengths of 2 T with average yearly levels equivalent to 0.5 T for 3 days did not reveal any adverse sequelae.[74]

Neurological Disease

There is no clear association between occupational exposure to electromagnetic fields and the development of early dementia or amyotrophic lateral sclerosis (ALS).[75] A cohort study of Danish utility workers suggested an association between EMF exposure-based job exposure matrix and death from amyotrophic lateral sclerosis but not from dementia or multiple sclerosis.[76] This study used the Danish National Mortality Register. A retrospective case-control study of three clinical series of patients with Alzheimer's disease suggested a link between Alzheimer's disease and occupations with "probable medium to high exposure" to electromagnetic fields.[77] The analysis of electromagnetic exposure was retrospective, and the exposure analysis was based on occupation rather than direct measurement. Subsequent cohort study of electric utility workers[78] and case-control study of former electrical workers[79] did not support the association between electromagnetic exposure and Alzheimer's disease.

A large US death certificate based, case-control, hypothesis-generating study suggested an association between motor neuron disease and 60 Hz magnetic field exposure in cases younger than 65 years, but not among cases 65 years of age or older. The odds ratio for mortality from motor neuron disease was 1.63 (95% CI: 1.10–2.39) based on a job exposure matrix.[80] In a population-based US cohort study (National Longitudinal Mortality Study), there was no association between mortality from motor neuron disease including ALS and exposure to magnetic fields as measured by a population-based job-exposure matrix.[81] There was no dose-related effect; the adjusted hazard ratio (i.e., age, sex, education) for the highest exposure group (>0.2664 T) was 0.98 (95% CI: 0.39–2.50) compared with the control group (<0.155 T).

A meta-analysis of 42 peer-reviewed publications reporting occupational electric and magnetic field exposure and neurodegenerative diseases (Alzheimer disease, motor neuron diseases) did not support a causal association.[82] Although there was a modest increase in risk estimates for both diseases, misclassification of the diseases and imprecise exposure of data contributed to substantial heterogeneity and lack of a definite causal connection.

Cardiovascular Disease

Experimental studies of human subjects have not detected consistent adverse cardiovascular effects following exposure to electromagnetic fields. A cross-sectional study of 53 workers with over 5-year exposure to electric fields from 400 kV substations did not find any significant cardiovascular effects (symptoms, blood pressure, ECG).[72] A mortality study of cardiovascular disease in a cohort of 138,903 male electric utility workers from 5 US companies over the period of 1950–1988 suggested a possible association between occupational magnetic fields and arrhythmia-related heart disease.[83] Employment in exposed occupations (plant operators, linesmen, electricians) for ≥20 years was associated with a statistically nonsignificant elevation of deaths from arrhythmia-related conditions

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(RR = 1.47, 95% CI: 0.96–2.24, $n = 60$ deaths). The rate ratio for deaths from acute myocardial infarction in this group was significantly increased (RR = 1.41, 95% CI: 1.28–1.55, $n = 1{,}073$ deaths). The rate ratios were also elevated for the highest cumulative career magnetic field exposure (≥4.3 μT-years) for arrhythmia-related deaths (RR = 2.4, 95% CI: 1.48–3.89, $n = 34$ deaths) and acute myocardial infarction (RR = 1.62, 95% CI: 1.45–1.82, $n = 510$ deaths). Overall, the standardized mortality rate for these workers was below the US population for ischemic heart disease (SMR = 0.77) and heart disease (SMR = 0.74). Later studies have not confirmed this association. The Netherlands (prospective) Cohort Study of 120,852 workers aged 55–69 at baseline and followed for 10 years did not detect an association between high exposure to ELF based on a job-exposure matrix and total cardiovascular mortality (hazard ratio = 1.02; 95% CI: 0.99–1.06).[84] Additionally, there was no significant elevation of any other cause-specific subtype of cardiovascular mortality including arrhythmia-related deaths.

Carcinogenesis

The IARC lists extremely low frequency magnetic fields as possibly carcinogenic to humans (Group 2B) based on limited evidence in humans for the carcinogenicity of extremely low frequency magnetic fields in relation to childhood leukemia and inadequate evidence in experimental animals.[17] The evidence for the carcinogenicity of ELF magnetic fields as a cause of all other cancers was inadequate. Additionally, the evidence for the carcinogenicity of ELF electric fields, static electric fields, and static magnetic fields was inadequate. Although current evidence does not exclude the possibility of an association between exposure to ELF magnetic fields and an increased risk of cancer (i.e., childhood leukemia), there is no convincing evidence that industrial or environmental exposure to ELF fields in the range of 50 Hz initiates or promotes cancer.[76]

Concern over the health consequences of the possibility of an association between electromagnetic fields and cancer results primarily from the ubiquity of the exposure rather than the magnitude of risk of inducing cancer. Establishing a causal link between electromagnetic fields and the development of cancer is limited by two important elements of causation: 1) the lack of a plausible biological hypothesis confirmed in animal studies; and 2) the scarcity of data that associates direct measurements of ELF electric and magnetic fields with an increased incidence of cancer.[85] Although some epidemiological evidence suggests an association between ELF radiation and childhood leukemia, expert reviews by world health organizations did not find consistent and strong laboratory or mechanistic evidence to support the association.[17,30] Consequently, the relationship between measured electromagnetic fields and the development of cancer remains unproven, based on the lack of supporting animal data, the absence of a dose-response effect, and inconsistent measures of exposure to electric and magnetic fields.

Childhood Cancers

Early studies on children exposed to electric and magnetic fields living in proximity to ELF sources (e.g., transmission and distribution lines, electrical substations, electrical appliances) suggested an ~50% excess risk of childhood leukemia using wire-code classifications as surrogates of electromagnetic field exposure; however, these measures correlate poorly with spot measurements of residential 60 Hz magnetic fields and the small relative risk (i.e., <1.5–2.0) suggests other factors associated with wire-code classifications may be responsible for the elevated risk. In two pooled analyses of the risk for childhood leukemia published before 2000, the OR for exposures of ≥0.4 μT was <2.[86,87] A case-control study of children that used codes for residential wiring as an indirect gauge of exposure to electromagnetic fields detected a 2–3-fold increase in the incidence of childhood leukemia and childhood brain tumors.[88] However, random measurements of the actual electromagnetic fields in these homes did not demonstrate a statistically significant difference in the homes divided on the basis of wiring codes. Interpretation of these studies is complicated by study design issues including recall and selection bias, lack of control of exposure confounding variables, and random misclassification of exposure, obscuring weak associations.

More recent studies have less consistently demonstrated elevated leukemia risks with some positive and negative results.[89] The elevated odds ratio (OR) for leukemia in exposed children was often statistically nonsignificant with wide confidence intervals; however, increasing estimated magnetic field strengths (e.g., >0.4 μT) tended to increase the odds ratio. A systematic review of published studies on the influence of exposure to ELF fields and childhood leukemia concluded that these studies did not confirm or exclude an association between the two.[90]

Exposure Surrogates

No technique exists for the direct measurement of electromagnetic fields within the human body; consequently, these fields are estimated using numerical

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TABLE 45.6. Types of exposure measurements used in studies on ELF fields.

Measure of Exposure	Technique
Wire code	Distance to major electrical energy delivery devices (high-tension power lines, transformers)
Calculated magnetic fields	Theoretical calculation of magnetic field based on historical electrical loads on surrounding power lines
Spot measurements	Instantaneous measurement of magnetic field in a specific location in residence
Average measured fields	Repeated spot measurements averaged over 24 hours
Personal average measured fields	Repeated personal measurements averaged over 48 hours

simulations. High-voltage power lines produce electric fields, whereas appliances and electric motors produce magnetic fields as a result of current flow. Because almost all electrically conductive material distorts electric fields, residential exposure to ELF sources usually involves magnetic rather than electric fields.[20] Table 45.6 lists the types of measurements used to quantitate ELF exposure for epidemiological studies on the association of ELF with childhood cancer. Each type of measurement has specific limitations.[91] Measurements using wire codes and calculated fields remain fairly consistent over the period that cancer would develop; however, calculated fields do not include all sources of exposure (e.g., home appliances, ground currents), and the reliability of wire codes as a quantitative measure of magnetic fields is variable.[92,93]

Leukemia

Childhood leukemia accounts for ~1/3 of all childhood cancers with an annual incidence of ~4–5/100,000 children. The etiology of childhood leukemia is probably multifactorial with most risk factors unknown. A majority of these leukemias are acute lymphoblastic leukemia (ALL) with the rest being primarily acute myelogenous leukemia (AML). During the 1970s–1990s, when much of the data on ELF and childhood cancers were collected, the incidence of childhood leukemia was increasing by ~0.6%/year.[94] A substantial number of epidemiological studies on ELF fields and childhood leukemia have odds ratios of <1.5–2 when comparing exposures of >0.3–0.4 μT with the lowest exposure categories (<0.1 μT);[95,96] however, many of these comparisons are not statistically significant, and the issue remains regarding causation for the relatively weak association.[97] In 1979, Wertheimer and Leeper published the first case-control study of children, demonstrating a 2–3-fold increase in mortality from leukemia in children from homes with electrical wiring configurations suggestive of high-current flow.[98] This seminal study used wiring codes as a surrogate for exposure to magnetic fields based on a nonblinded visual inspection of the power lines to assess the power load and the distance of the power lines from the homes. This design flaw allows potential exposure bias to complicate the interpretation of the results. Other epidemiological studies that used wiring codes as surrogate measures of ELF demonstrated inconsistent findings with both positive[88,99] and negative[100,101] associations with childhood leukemia. The positive studies demonstrated elevated odds ratios of 1.8 for exposures >0.6 μT, but elevation of odds ratios for individual cancers has been inconsistent and lacking in a dose-response effect.[102]

Reanalysis of data from an earlier case-control study[88] using modifications of the Wertheimer–Leeper wire codes generated an elevated odds ratio for childhood leukemia (OR = 2.9, 95% CI: 1.5–5.5) and childhood brain cancer (OR = 2.5, 95% CI: 1.1–5.5).[103] Identifying and controlling potential confounders in these studies is difficult because there are few known causes of childhood leukemia and acute lymphocytic leukemia. All these studies contain potential design flaws that include selection bias (controls),[98] confounding, and the use of different types of leukemia as endpoints. In these studies, the risk of cancer mortality was more strongly correlated with wiring codes than with direct measurements of the magnetic fields;[104] the individual exposure to magnetic fields varies over a greater range than the wiring codes do.[105]

Several Nordic studies[106,107,108] and a British study[109] assessing exposure using calculated fields provided marginal support for some increased risk of childhood leukemia following exposure to ELF. Feychting et al. demonstrated statistically significant increased risk of childhood leukemia in children born to fathers with occupational exposure to ELF magnetic fields of ≥0.3 μT (RR = 2.0; 95% CI: 1.1–3.0).[110] Maternal occupational exposure to ELF magnetic fields was not associated with childhood cancers in offspring. Overall, the number of cases in these studies was small with limited data in the higher ranges of exposure.

Early studies of ELF fields and childhood cancer typically used indirect measures of ELF exposure (i.e., wire code method using distance from normal-to-high-voltage overhead power lines), adjusting for the location of the lines and wire size. Beginning in 2001, these studies used more direct measures to estimate ELF field exposures, including spot measurements in bedrooms to determine mean exposure values while

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accounting for the distance from high-voltage power lines. Studies using spot measurements of ELF generally have not demonstrated more consistent results on the risk of leukemia in children exposed to ELF magnetic fields than indirect measures.[111] The UK Childhood Cancer Study used a case-control design to compare the cancer rates of children in England with estimates of exposure to power-frequency electromagnetic fields based on historical and spot measurements.[112] The study provided no evidence that exposure to magnetic fields increased the risks for childhood leukemia; the adjusted odds ratio of acute lymphoblastic leukemia in children with mean ELF field exposure to >0.2 μT compared with children exposed to <0.1 μT was 0.92 (95% CI: 0.47–1.79) and 0.90 (95% CI: 0.49–1.63) for all leukemias. In a German case-control study of 514 cases of acute childhood leukemia using spot and 24-hour room measurements, the odds ratio (OR) of leukemia in children with ELF exposure of ≥0.4 μT compared with controls (≤0.1 μT) was 5.81 (95% CI: 0.78–43.2); the OR for ELF exposures below 0.4 μT were smaller and not statistically significant.[113] In a Japanese case-control study of 312 children (0–15 years) with ALL and 634 controls (<0.1 μT) using spot and 7-day TWA measurements of ELF exposure, the OR for children exposed to ≥0.4 μT was 4.67 (95% CI: 1.15–19.0).[114] The OR for exposures to <0.4 μT was not statistically significant.

Other Cancers

Besides childhood leukemia, the most common cancers associated with positive, but not necessarily statistically significant elevations of odds ratios for magnetic field exposure, include lymphomas, soft tissue sarcomas, and brain tumors. Current epidemiological data do not support a causal association between these tumors and childhood exposure to ELF.[115,116] Several early studies suggested an association between ELF and brain cancer in children,[88,98] but later studies using wire codes,[117,118] calculated fields,[107,119] and measured fields[117] did not support the positive observations in the earlier studies. The UK Childhood Cancer Study did not detect a significant association between ELF field exposure and childhood cancers. Comparing children with mean ELF field exposure of >0.2 μT with children exposed to <0.1 μT, the relative risk of all malignant diseases combined was 0.87 (95% CI: 0.56–1.35) and 0.46 (95% CI: 0.11–1.86) for central nervous system tumors. Postnatal exposure to electric blankets has been associated with a small increase in the incidence of childhood cancer (OR = 1.5) and in particular with acute lymphocytic leukemia, but the confidence limits in this study were wide and the odds ratios were not statistically significant.[120]

Adult Residential Exposure

Studies of adult cancers and exposure to electromagnetic fields have not demonstrated effects as consistent or as strong as studies of childhood leukemia with most studies being negative.[89,121] Although most of these studies focused on the association between exposure to magnetic fields from overhead power lines and electric substations with leukemia, only one study detected a significant association in the range of a ~2-fold increase in the risk of developing leukemia.[122] Other case-control studies of exposure to magnetic fields from electricity substations[66,123] and overhead power lines[124] do not support the association between exposure to magnetic fields and the development of cancer; however, these studies lack sufficient power to exclude a small (i.e., odd ratio <2) increase in risk of acquiring leukemia. A case-control study of the use of electric blankets in 382 *postmenopausal* women demonstrated an elevated but statistically nonsignificant increase (odds ratio = 1.31; 95% CI: 0.88–1.95) in the incidence of breast cancer for women using electric blankets continuously throughout the night, when compared with 439 age- and education-matched community controls.[125] However, the lack of a dose-response for continuous use of electric blankets during the past 10 years and breast cancer (OR = 1.25, 95% CI: 0.73–2.16) did not support the hypothesis that magnetic fields increase the incidence of breast cancer by suppressing the normal nocturnal rise in pineal melatonin. In a subsequent case-control study of 290 *premenopausal* women, the odds ratio for breast cancer in women reporting daily use of electric blankets during the winter season continuously throughout the night for the previous 10 years was 1.10 (95% CI: 0.59–2.05) when compared with controls (randomly selected residents of the same two counties matched for age).[126] This value was lower than the risk of breast cancer in women using an electric blanket at any time in the last 10 years (RR = 1.18; 95% CI: 0.83–1.68) when compared with controls.

Occupational Exposure

Over the last several decades, considerable concern has developed over the health effects of extremely low frequency electromagnetic fields, primarily with the development of leukemia and, to a lesser extent, non-Hodgkin lymphoma and brain cancer. Although a meta-analysis of occupational exposure to ELF fields suggests a small increase (i.e., 10–13%) in the risk estimates for brain cancer and leukemia, the lack of a clear pattern of ELF field exposure and outcome risk suggests

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the increased risk was probably not attributable to ELF field exposure.[127] Overall, the scientific evidence associating occupational exposures to ELF fields with adverse health effects is relatively weak and inconsistent when exposure levels are estimated by indirect means (e.g., jog titles).[102] In a comparative analysis of studies of electrical workers published before 1999, the estimated increased risk of leukemia and brain cancer following chronic exposure to magnetic fields was small.[128] The estimated relative risk of leukemia for a 10 μT-year exposure was 1.09 (95% CI: 0.98–1.21) and 1.12 (95% CI: 0.98–1.28) for brain cancer. The strongest evidence for health effects in adults is chronic lymphocytic leukemia in occupationally exposed adults; however, the overall excess risk of leukemia and in particular of acute myelogenous leukemia is small (20% and 45%, respectively) in the epidemiological studies that associate these cancers with occupations identified as exposed to electromagnetic fields.[58] The major uncertainty in these studies is the lack of a direct assessment of magnetic and electric fields and the substitution of indirect measures of electromagnetic fields that probably do not accurately reflect the strength of these fields. Mechanistic studies and animal experimentation have not confirmed the associations between ELF exposures and cancer suggested by the epidemiological studies. Nonetheless, the ubiquity of exposure to electromagnetic fields causes concern about the potential health consequences of exposure to electromagnetic fields.

The ICNIRP does not base ELF exposure guidelines on the risk of cancer following ELF exposure as a result of the lack of positive animal data and the weak epidemiological data (e.g., childhood cancer).[129,130] Recent data from studies with more sophisticated exposure data have not produced greater consistency or stronger associations between ELF and cancer, including brain tumors, salivary cancer, leukemia, acoustic neuroma, or malignant ocular melanoma. In a study of 81,842 UK electricity generation workers, there was no statistically significant increase in the incidence of brain tumors, leukemia, or leukemia subtypes, when compared with national rates.[131] A mortality study of Danish utility workers did not detect an increased risk of cancer or neurodegenerative diseases in these cohorts.[132]

Leukemia/Lymphoma

The most consistent finding of studies on the incidence and mortality of cancer in workers exposed to electromagnetic fields is a small increase in leukemia risks, particularly chronic lymphocytic leukemia and, to a much lesser extent, acute myeloid leukemia.[133] Proportional mortality studies of workers (e.g., telephone linesmen, electronic engineers) exposed to ELF fields demonstrate a small (~20%) increase in the risk of developing leukemia and, in particular, acute myelogenous leukemia.[134] A meta-analysis of 38 studies of leukemia and electromagnetic forces revealed an overall increase in risk of 18% (RR = 1.18, 95% CI: 1.12–1.24).[135] Another review of 11 studies of electrical occupations revealed a similar relative risk of 1.18 (95% CI: 1.09–1.29) for all leukemias in all electrical occupations.[134] The association with electrical workers is stronger for acute leukemias than chronic leukemias[136,137] and in particular for acute myeloid leukemia (RR = 1.46).[134] A Swedish case-control study demonstrated a positive, dose-related association between exposure to ELF and chronic lymphocytic leukemia (OR 3.0, 95% CI: 1.6–5.8 at highest exposure) based on the job held longest during the 10-year period before diagnosis. There was no association (OR = 1.0, 95% CI: 0.6–1.9) between the highest ELF exposure and acute myeloid leukemia.[138]

These studies are limited by poor exposure assessments that preclude the direct analysis of the effects of duration, latency, and magnitude of exposure to electromagnetic fields. Exposure categories were based on job titles rather than direct measurements of exposure; however, misclassification of exposure tends to underestimate rather than overestimate the associated risk. American[139] and Canadian[140] case-control studies found weak associations between exposure to ELF and the risk of leukemia, but there were no clear dose-response trends with increasing exposure and no consistency among different work sites. A cohort and nested case-control study of 36,211 electric utility workers found no consistent association between ELF exposure and mortality from leukemia, even after comparing different levels of exposure and latency periods.[141] Exposure assessment included job title analyses and direct magnetic field measurements of current job classifications.

Examination of specific occupations within the electrical industry demonstrates no consistent relationship between electromagnetic fields exposure in specific jobs and various types of cancer. Cohort studies of workers are less supportive of an association with cancer than mortality and case-control studies.[121,142] A cohort study of 83,997 UK electricity generation and transmission workers did not detect increased mortality from leukemia based on comparisons with national mortality rates.[143] Additionally, there were no significant increases in the risk of leukemia with increasing recent or lifetime exposure to magnetic fields, irrespective of leukemia subtype. Among occupations studied in Sweden, an increased incidence of chronic lymphocytic leukemia (which is not caused by

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ionizing radiation) occurred in power linesmen, who are presumably among the workers most highly exposed to magnetic fields.[144] The incidence of acute myelogenous leukemia was not elevated in these linesmen or welders exposed to high levels of magnetic fields. A review of cancer rates in welders revealed an increased incidence of lung cancer but not of leukemia.[145] A study of electrical workers in New Zealand demonstrated an increased risk of leukemia (odds ratio = 1.62) that was concentrated in the category of chronic leukemias including chronic lymphocytic leukemia,[146] whereas a large study of US Navy personnel did not confirm an increased incidence of leukemia in electrical workers.[147] Electrical workers may be exposed to other leukemogenic agents (chemicals including benzene, ionizing radiation) both inside and outside the work environment. These studies do not distinguish between different potential causes of leukemia, and the lack of a clear pattern of exposure to electromagnetic fields limits conclusions regarding the etiology of leukemia. Hence, the association between electrical occupations and leukemia does not necessarily imply a causal link.

Epidemiological data for a causal association between exposure to magnetic fields and non-Hodgkin lymphoma are weak. In an Australian study of 694 cases of non-Hodgkin lymphoma and occupational exposure to power frequency magnetic fields, the adjusted odds ratio for workers in the upper quartile of exposure (>9.85 μT-year) was 1.48 (95% CI: 1.02–2.16) when compared with the referent group (randomly selected local residents).[148] Exposure was based on a population-based job exposure matrix. The odds ratio for non-Hodgkin lymphoma was not statistically different for the other three quartiles when compared with the referent group or for the adjusted odds ratio ($OR_{adjusted}$ = 1.33, 95% CI: 0.90–1.96).

Brain

Compared with leukemia, the evidence supporting an association between exposure to electromagnetic fields and brain tumors is weaker and less consistent.[137,149] A case-control study of electrical workers suggested a small increase in the risk for brain tumors (e.g., astrocytoma);[150] however, most epidemiological studies do not demonstrate a statistically significant increased risk of brain tumors in occupations associated with relatively high ELF exposures. A mortality study of 2,173 deaths from primary brain cancer in electricians compared with other occupations demonstrated a statistically significant, increased adjusted odds ratio of 1.4 (95% CI: 1.1–1.7) with larger adjusted odds ratios for telephone workers (OR = 1.6, 95% CI: 1.1–2.4, n = 9 cases/44 controls), electric power workers (OR = 1.7, 95% CI: 1.0–2.7, n = 5 cases/30 controls), and electrical engineers/technicians (OR = 2.7, 95% CI: 2.1–3.4, n = 29 cases/95 controls).[150] A 19-year follow-up study of Swedish workers revealed an increased risk for the development of brain tumors in assemblers and repairmen in the radio and TV industries, but there was no significant increase in the risk of brain tumors for electrical engineers, linesmen, or electronic engineers.[144] A study of workers from three major utilities demonstrated a ~2-fold increase (OR = 1.95, 95% CI: 0.76–5.0) in the incidence of brain cancer in the 10% of the workers with the highest exposure to magnetic fields. The number of cases was small, the confidence interval was wide, and the results were not statistically significant.[140] A Swedish case-control study demonstrated no statistically significant, dose-related association between exposure to ELF and brain cancer (OR 1.4, 95% CI: 0.9–2.1 at the highest exposure level) based on the job held longest during the 10-year period before diagnosis.[138] A cohort and nested case-control study of 36,211 electric utility workers found no consistent association between ELF exposure and mortality from brain cancer, even after comparing different levels of exposure and latency periods.[141]

A meta-analysis suggested a small increase (10–20%) in the relative risk for a broad group of electrical occupations, but there was considerable heterogeneity among the studies.[151] The relative risk appeared higher (~30–35%) for specific occupations (e.g., electricians) that developed gliomas; however, conclusions regarding causation were limited by the lack of adequate information on exposure and the absence of a clear dose-response effect.

Breast

A case-control study of electrical workers reported a nearly 2-fold increase in the risk of developing breast cancer in men exposed to any job with exposure to electromagnetic fields based on job titles.[152] The OR was borderline increased for developing breast cancer (OR = 1.8, 95% CI: 1.0–3.7). The highest odd ratios appeared in the group of electricians, telephone linesmen, and electric power workers (OR = 6.0, 95% CI: 1.7–21), as well as a statistically nonsignificant increase in radio and communications workers (OR = 2.9, 95% CI: 0.8–10). The wide confidence intervals and marginally increased risks indicate a weak association.

The prospective Netherlands Cohort Study containing 120,852 men and women aged 55–69 years at the time of enrollment in 1986 and followed for a mean of 17.3 years did not detect an association between breast

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cancer incidence in men and exposure to ELF magnetic fields.[153]

Studies of the association between breast cancer in women and exposure to ELF fields are inconsistent. In a study of women recruited for a breast cancer study, the occupations (e.g., housewives, teachers, nurses, administration support personnel) typically associated with an increased risk of breast cancer did not have magnetic field exposures exceeding the average of the study.[23] In a population-based case-control study examining occupational exposure to electromagnetic fields and the incidence of breast cancer among 843 women with breast cancer and 773 controls, the odds ratio for lifetime cumulative exposure to ELF fields was close to null; the study demonstrated no dose-response patterns.[154] The odds ratio adjusted for age and state of residence for breast cancer in 6,213 women occupationally exposed to electromagnetic fields was 1.06 (95% CI: 0.99–1.14) for low exposure, 1.09 (95% CI: 0.96–1.23) for medium exposure, and 1.16 (95% CI: 0.90–1.50) for high exposure.[155] Randomly selected, age-matched women ($n = 7{,}390$) were the controls. An industrial hygienist estimated the amount of exposure based on the job title. A Norwegian case-control study of women with occupational exposures to magnetic fields and breast cancer compared women with the highest exposure based on exposure matrix data with unexposed women.[156] The odds ratio was 1.13 (95% CI: 0.91–1.40).

Reproductive Abnormalities

The ability of electromagnetic fields to produce reproductive damage in humans remains unproved; the majority of studies of miscarriages following exposure of the mother to video display terminals do not demonstrate an association between the electromagnetic fields produced by these machines and increased fetal loss. The reproductive effects of electromagnetic fields are not well studied. One study of women who used video display terminals for more than 20 hours per week demonstrated an 80% increase in the rate of spontaneous abortions.[157] The nonionizing radiation from flat panel screens is below levels associated with video display terminals. Other studies have not duplicated these results. A study of women exposed to electric fields through the use of electric blankets, heated waterbeds, and ceiling cable heat suggested increased fetal loss during the wintertime.[158]

Humans

Little data are available on the association between exposure to ELF magnetic fields and pregnancy outcomes. There are inadequate data to determine conclusively whether or not static or ELF electromagnetic exposure causes any adverse reproduction outcomes, in part, because of the lack of well-designed studies with adequate exposure data and control of confounding variables.[159] Some epidemiological studies suggest the possibility of an increased risk of spontaneous miscarriage associated with ELF magnetic field exposure; this association is stronger for maximum value and variability of the magnetic field than time-weighted average field levels. A nested case-control study of 177 cases of clinical miscarriage among members of the northern California Kaiser Permanente medical care system and 550 controls did not demonstrate a statistically significant association between miscarriages and ELF magnetic fields. However, examination of quartiles of exposure suggested an association between maximum ELF exposure and the rate of change of the magnetic field.[160] A prospective cohort study of 969 subjects did not detect an increased risk of miscarriage using time-weighted-average (TWA) magnetic field exposure; the study did find an increased risk of miscarriage using maximum magnetic field strength of >0.6 μT (OR = 1.8, 95% CI: 1.2–2.7).[161] The association was stronger for early miscarriages (<10 weeks of gestation). A case-control study of women who developed spontaneous miscarriages suggested a borderline increased incidence (OR = 5.1, 95% CI: 1.0–25) of early pregnancy loss after high residential exposure (>0.63 μT) to ELF magnetic fields.[162] However, the limitations of the data including the small number of heavily exposed women indicate the need for cautious interpretation of the data.

Epidemiological studies of workers and mothers using electric blankets suggest the possibility of a small increase (RR = 1–5) in the risk of birth defects and miscarriages; the small size of these studies, the lack of good exposure data, and the dearth of supportive experimental data limit the conclusions about causal relationships. An ecological study of adverse reproductive outcomes revealed significant seasonal variation in the frequency of miscarriages in women with exposure to electromagnetic fields from electric blankets[163] and ceiling cable electric heat.[158] However, the causal relationship is not convincing because of the lack of the expected delay between exposure and fetal loss. Recall bias and the failure to separate spontaneous miscarriages from induced abortions further limit the interpretation of the relationship between cause and effect.

A retrospective Swedish study of electrical substation workers revealed an increased frequency of heart defects, facial clefts, and hydroceles in the offspring of

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male workers exposed to electromagnetic fields based on job title; there was no evidence of an increased rate of fetal loss.[164] Retrospective case-control studies of male workers exposed to electromagnetic fields suggest the possibility of an association between the development of neuroblastomas in offspring and electromagnetic fields, particularly in the repair or manufacture of electrical and electronics equipment and in electronics workers. A population-based, case-control analysis of the birth certificates of 157 children succumbing to neuroblastoma reported that children of fathers employed in occupations with electromagnetic field exposures based on job title had a statistically nonsignificant increased risk of developing neuroblastoma (OR = 2.14, 95% CI: 0.95–4.82, $n = 13$ cases/12 controls) compared with 314 randomly selected population controls.[165] The occupations included electricians, electric/electronics workers, linesmen, utility employees, and welders. An Ohio case-control study of 101 incident cases of neuroblastoma demonstrated variable adjusted odds ratio of 0.5–1.9 in cases with occupational electromagnetic field exposures, depending on the definition of the jobs with potential exposure to electromagnetic fields.[166] The authors urged cautious interpretation of the data because of the imprecise odds ratio estimates and the questionable biological plausibility. A retrospective study of the Medical Birth Registry of Norway suggested the possibility of an association between *parental* exposure to 50 Hz electromagnetic fields for >24 hours/week and an increased risk of spina bifida (OR = 2.48, 95% CI: 1.18–5.25).[167] The statistical significance of the relationship between *maternal* exposure to electromagnetic fields and adverse CNS outcomes disappeared after adjustment for chemical exposure. There was no direct measurement of electromagnetic exposure; an expert panel estimated the electromagnetic field exposure from retrospective evaluation of job classification.

More recent results do not demonstrate an adverse effect of the ELF magnetic fields on reproductive function in humans. A Canadian cohort study of >700,000 live births in Montréal and Québec City during 1990–2004 did not detect an increased risk of adverse pregnancy outcomes (preterm birth, low birth weight, small for gestational age) and distance between residence and the nearest power line.[168] No increased risk of adverse pregnancy outcomes occurred in the >12,000 births classified in the highest exposure category (<50 m from the power line). The adjusted ORs in this group were 0.99–1.04 with an upper confidence limit of <1.10. Limitations of the study included the address being available only at the time of birth, no information on power line voltage, and inadequate control of confounding variables (e.g., earlier reproductive outcomes, lifestyle, smoking). A large English cohort study of 140,000 live singleton births in 2004–2008 examined the association between exposure metrics (residential proximity to power lines, cables, substations, towers) based on postal codes and pregnancy outcomes (preterm birth, low birth weight, small for gestational age).[169] Limited information was available on confounders (e.g., smoking, lifestyle). The main analysis did not reveal any significant associations. An analysis using the mean birth weight of all babies rather than the proportion of markedly reduced birth weight reported a significantly lower birth weight for residences within <50 m of the closest ELF source ($n = 89$ children). The authors did not report whether the analysis of the mean birth weight was prespecified or carried out post hoc. The validity of the exposure classification based on postal codes rather than house coordinates is unproven.

Cross-sectional studies of fertility in aluminum workers exposed to static magnetic fields up to 10 mT and alternating fields up to 0.1 mT did not detect significantly altered fertility in male workers.[170] The portion of male offspring in women exposed to static magnetic fields was significantly reduced; however, misclassification probably accounts for the difference. A case-control study of 692 potroom workers exposed to static magnetic fields ranging from 4–30 mT and 588 unexposed male workers from the same aluminum plants demonstrated a statistically significant increase in the birth rate of the exposed workers (relative birth-rate ratio = 1.1; $P < 0.001$).[171]

Animals

Animal test systems have produced inconsistent findings on the effects of electromagnetic fields on reproduction as a result of wide variations in the intensity, type of exposure (pulse, frequency), and poor control of confounding variables (background exposures, spark discharge).[172] Low-frequency magnetic fields have adverse effects on chick embryo development;[173] however, the threshold of these effects and their relevance to humans remain unclear.[174] Although adverse effects occurred in some dams and weight gain occurred in exposed offspring, multigenerational rat studies have not demonstrated a clear association between exposure to electromagnetic fields and adverse reproductive or developmental effects.[175] Under environmental conditions studied in animal testing, neither electric nor magnetic fields are conclusively teratogenic or embryotoxic.[30,174,176]

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DOSIMETRY

Static Fields

With proper techniques, methods for measuring external magnetic fields are relatively accurate using point measurements and space-integrated values for static magnetic fields. Magnetic flux density is the most common parameter used to correlate the strength of the magnetic field to health effects.[177] The most common method uses the Hall probe in personal dosimeters. The battery-operated, portable magnetic dosimeter contains thin-film Hall sensors that record the magnetic induction (B) along three orthogonal axes. During consecutive sampling intervals of ~75 msec, Hall generators in pulsed mode determine the time rate of change of the magnetic induction (dB/dt) for recorded values of B.[178] The temperature coefficient of the Hall voltage limits the accuracy of these instruments. Fluxmeters and ballistic galvanometers can directly measure variations in the magnetic flux using a search coil, providing an average magnetic field value over the volume of the coil.[179] Valid analyses of static magnetic fields require instruments that withstand strong magnetic fields without altering the external magnetic fields.

ELF Fields

External extremely low frequency electric and magnetic fields induce electric fields and currents inside the human body; in contrast to the similarity of internal and external magnetic fields, the electric fields inside the body are five to six orders of magnitude less than the external electric field.[30] The physical assessment of exposure to electric and magnetic fields requires parameters other than the field strength and frequency of a source. The two main types of instruments available to measure magnetic fields are: 1) multiturn loops with portable voltmeters; and 2) gaussmeters. Most popular commercial devices available to measure the strength of the magnetic field use the Hall probe or the shielded coil. Internal electric fields and the induced currents in humans are not easily measured; differences in body shape, posture, and size seriously limit the use of animals to model these effects in humans. Numerical simulations are necessary to estimate electric fields and currents inside the body from external electric and magnetic fields because no technique exists for direct measurements.[47] The strongest induced currents occur when the body is electrically grounded through the feet, whereas the weakest currents occur when the body is insulated by air. Tissue conductivity determines the distribution of the induced current in the body; hence, the distribution of current in the body is very heterogeneous between various tissues and organs.

Magnetic Fields

Human and animal bodies do not significantly alter external magnetic fields. The magnetic fields in these bodies are similar to the external magnetic field as a result of the similarity of magnetic permeability between the body and air. The main interaction of a magnetic field with the body is the induction of an electric field and associated current in a large variety of conductive tissues present in the human body. The induced electric field and current depend on the orientation of the external field with the highest fields typically aligned front-to-back or occasionally side-to-side depending on the individual organ. The consistently lowest induced electric fields usually occur during the orientation of the external magnetic field along the vertical axis of the body. For magnetic fields, the size of the body is the major determinant of the induction of internal currents because the body does not contain magnetic material and does not attenuate the magnetic field. Magnetic fields vary substantially in different metals and metal configurations (e.g., mesh vs. solid structures). Many epidemiological studies use the 24-hour time-average of the 60 Hz magnetic field as a measure of magnetic field strength.

Electric Fields

Because of the substantial attenuation of electric fields in the body, electric fields are not usually measured during exposure to ELF radiation. External electric fields near 1 MV/m are necessary to produce an internal electric field similar to the transmembrane potentials existing naturally.[180]

For electric fields, the induction of internal electric fields and currents depends on several factors in addition to field strength and frequency including: 1) resistance of the current flow from the body to the ground; 2) shielding of the source from the body (e.g., trees, buildings); 3) distance from the body to the source; 4) orientation of the body to the source; and 5) size and shape of the body.

HEALTH SURVEILLANCE

Risk Assessment

The International Non-Ionizing Radiation Committee of the International Radiation Protection Association

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(ICNIRP) based their 1998 recommendation of ELF electric and magnetic field exposure on a threshold current density of 100 mA/m^2 for acute changes in central nervous system function (i.e., brain and spinal cord), particularly in the frequency range of 4 Hz–1 kHz.[130] General consideration of neural physiology suggests threshold current density rises above and below this range. In the 2010 guidelines, the ICNIRP used an induced electric field strength threshold in CNS tissue of the head (brain, retina) of 50 mV/m in the range of 10–25 Hz based on the production of retinal phosphenes.[129] The phosphene threshold rises rapidly outside this range with the threshold for peripheral and CNS myelinated nerve stimulation intersecting the phosphene threshold at 400 Hz, as displayed in Table 45.7. Above this value, the latter threshold applies. For workers knowledgeable about acute effects working in a controlled environment, the induced electric field threshold increased to 800 mV/m based on a peripheral and central myelinated nerve stimulation threshold of 4 V/m reduced by a factor of 5. The threshold for the general public was 10 mV/m in the range 10–25 Hz (i.e., reduction factor of 5) and 400 mV/m for induced electric fields of >1 kHz (reduction factor of 10).

The Institute of Electrical and Electronics Engineers (IEEE) bases its guidelines on protection against painful electrostimulation in frequencies ranging from 0 Hz–5 MHZ and excessive heating in frequencies ranging from 100 kHz–300 GHz. The 2002 guidelines used an induced electric field strength threshold of 53 mV/m at 20 Hz for changes (e.g., magnetophosphenes, synaptic interactions) in brain function for 50% of healthy adults.[181] The phosphene threshold rises above 20 Hz following a frequency-proportional ratio up to 760 Hz; their recommendations are based on peripheral nerve stimulation up to 100 kHz. The recommended IEEE thresholds for workers exposed to electric and magnetic fields are 20 kV/m and 2.71 mT at 60 Hz, respectively. In comparison, the guidelines for exposure for the general public are 5 kV/m and 0.9 mT, respectively. In 2019, the IEEE updated their guidelines (IEEE Std /C95.1-2019, https://standards.ieee.org/ieee/C95.1/4940/) to separate exposures into unrestricted and restricted environments. Differences in the IEEE and ICNIRP guidelines result from differences in thresholds, safety factors, and transition frequencies.

Environmental Monitoring

Although several epidemiological studies associate chronic, low-intensity exposure (i.e., >0.3–0.4 μT) to power frequency magnetic fields with an increased risk of childhood leukemia, the ICNIRP concluded the evidence is not currently causal. Therefore, the guidelines for public exposure are based on acute effects. Table 45.8 displays the 2010 ICNIRP guidelines for public exposure to electric and magnetic fields in the sub-radiofrequency range (1 Hz–30 kHz). The 400 mT limit recommended by ICNIRP for the general public restricts acute biological effects of the static magnetic

TABLE 45.7. International Commission on Non-Ionizing Radiation Protection (ICNIRP) threshold values for induced internal electric fields for human exposure to time-varying electric and magnetic fields. All values are rms. Radiofrequency basic restrictions may apply at frequencies above 100 kHz. (ICNIRP 2010, https://www.icnirp.org/).

Exposure	Tissue	Effect	Frequency Range (Hz)	Internal Electric Field (V/m)
Workplace	CNS head	Phosphenes	1–10	0.5/f
		Phosphenes	10–25	0.05
		Phosphenes	25–400	0.002f
		Nerve stimulation	400–3,000	0.8
		Nerve stimulation	3,000–10,000,000	0.00027f
	All tissues	Nerve stimulation	1–3,000	0.8
		Nerve stimulation	3,000–10,000,000	0.00027f
Public	CNS head	Phosphenes	1–10	0.1f
		Phosphenes	10–25	0.01
		Phosphenes/nerve stimulation	25–1,000	0.0004f
		Nerve stimulation	1,000–3,000	0.4
		Nerve stimulation	3,000–10,000,000	0.000135f
	All tissues	Phosphenes/nerve stimulation	1–3,000	0.4
		Nerve stimulation	3,000–10,000,000	0.000135f

Abbreviation: f = frequency in Hz.

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TABLE 45.8. International Commission on Non-Ionizing Radiation Protection (ICNIRP) reference levels for *public* exposure to time-varying electric and magnetic fields below 30 kHz in unperturbed rms values. Some of these guidelines are modified for exposure to nonsinusoidal and multiple frequencies. (Modified from International Commission on Non-Ionizing Radiation Protection).[129]

Frequency	Electric Field Strength (kV/m)	Magnetic Field Strength (A/m)	Magnetic Flux Density (T)
0–1 Hz			0.4
1 Hz–8 Hz	5	$32{,}000/f^2$	$0.04/f^2$
8 Hz–25 Hz	5	$4{,}000/f$	$0.005/f$
25 Hz–50 Hz	5	1,600	0.0002
50 Hz–400 Hz	$250/f$	1,600	0.0002
400 Hz–3 kHz	$250/f$	$64{,}000/f$	$0.08/f$
3 kHz–30 kHz	830	21	0.00002

Abbreviation: f = frequency in Hz.

field; however, this value is substantially above the level at which mechanical forces can move external and internal ferromagnetic objects (e.g., heart valve prostheses, contraception implants, dental implants, metallic surgical clips, and stents).[177] Although many modern implants are not ferromagnetic, electromagnetic interference can occur in low-intensity static magnetic fields during the operation of some medical devices including cardiac pacemakers/defibrillators, neuromuscular stimulators (e.g., muscle, bladder), electronically operated prosthetic devices (e.g., inner ear, limbs), and infusion pumps (e.g., insulin, analgesics). The ICNIRP recommends limiting static magnetic fields for these individuals to <0.5 mT.

Occupational Monitoring

Guidelines

The ACGIH recommends limiting ELF exposure (1 Hz–30 kHz) to ceiling values inducing current densities of <10 mA/m^2 (i.e., values below the current densities normally present in the body), as displayed in Table 45.9; the ACGIH has insufficient information to promulgate TLV values for sub-radiofrequency magnetic or electric fields. These guidelines are based on current density substantially below values necessary to affect nervous system functions rather than a value near levels that cause adverse effects.[129] Although some US

TABLE 45.9. American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLV) for sub-radiofrequency magnetic fields including static magnetic and electric fields. These ceiling values are promulgated as root-mean-square (rms) values. (ACGIH 2013, https://www.acgih.org/science/tlv-bei-guidelines).[179]

Frequency (f)	Exposure	Ceiling Value
	Magnetic fields	
0 Hz (static)	Whole body – general occupational	2 T
0 Hz (static)	Whole body – special training or controlled environment	8 T
0 Hz (static)	Limbs	20 T
1–300 Hz	Whole body – general occupational	$60/f^a$ (mT)
1–300 Hz	Arms, legs	$300/f^a$ (mT)
1–300 Hz	Hands, feet	$600/f^a$ (mT)
300 Hz–30 kHz	Whole or partial body	0.2 mT
1 Hz–2.5 kHz	Point contact current limit	1.0 mA
2.5 kHz–30 kHz	Point contact current limit	$0.4f^b$ (mA)
	Electric fields	
0–220 Hz	Whole body – general occupational	25 kV/m
220 Hz–3 kHz	Whole body – general occupational	$5.525 \times 10^3/f^c$ (kV/m)
3 kHz–30 kHz	Whole body or partial body	1.842 kV/m

Abbreviations: f^a = frequency in Hz and value in mT; f^b = frequency in kHz and value in mA; f^c = frequency in Hz and value in kV/m.

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TABLE 45.10. International Commission on Non-Ionizing Radiation Protection (ICNIRP) reference levels for *occupational* exposure to time-varying electric and magnetic fields below 30 kHz in unperturbed rms values. Some of these guidelines are modified for exposure to nonsinusoidal and multiple frequencies. The guidelines for static magnetic field exposures are spatial peak exposure limits. (International Commission on Non-Ionizing Radiation Protection, https://www.icnirp.org/).[182]

Frequency	Electric Field Strength (kV/m)	Magnetic Field Strength (A/m)	Magnetic Flux Density (T)
0–0.66 Hz			2 (head, trunk)[a]
			8 (limbs)
0.66 Hz–1 Hz			2 (head, trunk)[a]
			8 (limbs)
1 Hz–8 Hz	20	$1.63 \times 10^5/f^2$	$0.2/f^2$
8 Hz–25 Hz	20	$2 \times 10^4/f$	$0.25/f$
25 Hz–300 Hz	$500/f$	800	0.001
300 Hz–3 kHz	$500/f$	$2.4 \times 10^5/f$	$0.3/f$
3 kHz–30 kHz	0.17	80	0.0001

Abbreviation: f = frequency in Hz.

[a] For special work applications with a controlled environment and appropriate work practices, static magnetic fields up to 8 T as a spatial peak exposure limit are allowed for exposure to the head and trunk. The ICNIRP recommends some restrictions on movement in static and time-varying magnetic fields to prevent sensory effects including limiting changes in the magnetic field over 3 seconds to 2 T.[182]

states set limits on exposure to ELF fields, currently there are no federal limits in the United States on exposure to fields below the radiofrequency frequency range. Workers with cardiac pacemakers or implanted ferromagnetic medical devices are particularly susceptible to electromagnetic fields; lacking specific information on implanted ferromagnetic or electronic devices, these workers should be exposed to a maximum of 0.1 mT at power frequencies (i.e., 50/60 Hz), 0.5 mT in static magnetic fields, and <1 kV/m in sub-radiofrequency electric fields. Higher ceiling values were promulgated for static magnetic ceiling TLVs for workers involved in special training and controlled workplace environments where there is no significant risk of projectile objects. These workers may experience transient sensory effects during motion in strong static magnetic fields and startle reactions associated with spark discharges or contact currents from ungrounded conductions with electric fields of >5–7 kV/m. However, these effects are not expected to cause persistent adverse effects unless they are associated with trauma.

The ICNIRP bases recommendations on time-varying electric and magnetic fields of <100 kHz on the induced electric fields in the brain for the central nervous system (retinal phosphenes) and the peripheral nervous system (direct neuromuscular stimulation); effects are monitored as peak fields averaged over a volume of tissue depending on frequency (see Table 45.7). For the 50 Hz power frequency, this restriction translates to 33 V/m/T for CNS effects and 60 V/m/T for PNS effects as measured in rms values. The reference values for exposure to electric fields up to 25 Hz include a sufficient margin to prevent stimulation from contact currents under most practical conditions. Table 45.10 displays the ICNIRP guidelines for occupational exposure to electric and magnetic fields in the sub-radiofrequency range (1 Hz–30 kHz). The objective of ICNIRP recommendations on exposure to static, time-varying magnetic fields of <1 Hz and the resulting induced internal electric fields and currents is the avoidance of peripheral nerve stimulation and sensory effects including nausea, vertigo, a metallic taste, and magnetophosphenes that may impair working ability.[182]

Protective Measures

Engineering methods to reduce electromagnetic fields exceeding guidelines are typically the first method of choice for protective measures (e.g., improving machine design, use of health protection mechanisms) along with administrative controls (e.g., limited access, audible and visible warnings). Methods to reduce exposure to high-intensity magnetic fields include: 1) distance; 2) time; 3) magnetic shielding; and 4) cancellation. Shielding is the simplest way to decrease the strength of electric fields (*E*-fields). The metal conductivity is 10^{16} times greater than air conductivity; therefore, grounded metal will terminate the electrical field by conducting the electrical charges to the ground. Most metals can shield *E*-fields when they are grounded. Isolated equipment

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requires nickel alloys, ferromagnetic materials, or other special alloys with high magnetic permeability.[183] Separation is an effective means of reducing the electric and magnetic fields when sufficient space is available. The magnetic field intensity decreases directly with distance for single wires, distance squared for parallel wires (power lines, residential electric lines), and cube of the distance for wire loops (electric stoves, motors). Because the external magnetic flux density decreases with distance from the source, the fundamental protective measure is the separation of people from the source. The use of shielding on large installations often is limited in comparison to separation. Cancellations involve the addition or rewiring of lines to produce fields with the opposite phase compared with the existing electrical field. This technique is useful where leakage of electrical fields results from inadequate grounding of equipment.[184] The use of personal protective clothing (e.g., insulated gloves) is an option when engineering and administrative controls are inadequate; however, the goal is limited exposure to values below guidelines.

Biological Monitoring

Because the basic mechanisms of adverse effects from ELF magnetic and electric fields are unknown, the most important biological index of exposure (e.g., frequency, waveform, intermittency, magnitude of magnetic field or induced electric currents, time-average fields, time above a threshold) is also unclear.

Medical Surveillance

Both static and time-varying magnetic fields may interfere with the functioning of demand pacemaker. Some demand pacemakers revert to an asynchronous mode of operation in time-varying fields with time rate changes over 40 mT/s, while static magnetic fields exceeding 1.7–4.7 mT may close the reed switch relay of other pacemakers depending on the composition of the pacemaker.[185] The displacement of metallic implants (surgical clips, prostheses, catheters) as a result of strong magnetic fields may result in internal injury. Additionally, sharp metallic objects may become missiles with high momentum in intense magnetic fields.

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Chapter 46

ULTRAVIOLET, VISIBLE AND INFRARED RADIATION

HISTORY

Ultraviolet (UV) radiation from the sun provides several benefits to human health including cutaneous production of vitamin D, stimulation hormones that regulate circadian rhythms and mood, and temporary darkening of the skin in light-skinned people. However, excessive UV radiation produces adverse health effects, including skin damage, photoaging, skin cancer, cataract formation, and immunosuppression. In the late 19th century, Unna and Dubreuilh first associated chronic sun exposure with degenerative changes in the skin of sailors and vineyard workers, including actinic keratoses and skin epitheliomas.[1,2] By the early 20th century, Hyde associated the development of skin cancer with excessive sun exposure in light-skinned races.[3] Findlay confirmed the occurrence of skin cancer following excessive sun exposure in animal experiments during the 1920s.[4] In the late 1920s, Hausser and Vahle first quantitatively documented erythema as a wavelength-dependent effect.[5] The UVB portion (280–320 nm) of the solar spectrum is the highest energy band in the UV portion of the electromagnetic spectrum; subsequent animal studies demonstrated that sunburn and photocarcinogenesis result primarily from UVB radiation.[6] Kligman first reported the accelerated aging effects of UV solar radiation in 1969.[7] He used the term "photoaging" to describe the skin changes associated with chronic sun exposure.

PHYSICAL PROPERTIES

Ultraviolet radiation lies in the electromagnetic spectrum between X-rays with shorter wavelengths (<100 nm) and visible light (400–760 nm) with longer wavelengths. The UV section (UVA, UVB, UVC) of the electromagnetic spectrum is the nonionizing radiation portion that lies in the wavelength range of 100–400 nm. Although the International Commission on Illumination defines the break between UVA and UVB as 315 nm, many scientists use 320 nm as the break point. Radiation with a wavelength of 100 nm possesses the minimum photon energy (12.4 eV) required to break the weakest macromolecular bonds; this wavelength divides ionizing and nonionizing radiation. Radiation with a wavelength below UVC (i.e., <100 nm) is considered ionizing radiation; consequently, X-rays possess ionizing properties, whereas visible light is nonionizing. The air absorbs UV radiation with wavelengths of <180 nm (i.e., 100–180 nm) within the first few centimeters; therefore, this area of the UV spectrum (i.e., vacuum UV region) has no direct biological effect on terrestrial humans.[8] The sun is the main source of UV radiation. Most artificial sources (e.g., sun lamps) of UV radiation emit a spectral continuum of UV light with characteristic peaks and troughs across the UV range of wavelengths.

Irradiance is the physical measure of UV exposure defined by the amount of energy over a demarcated surface of an object measured in watts per square meter

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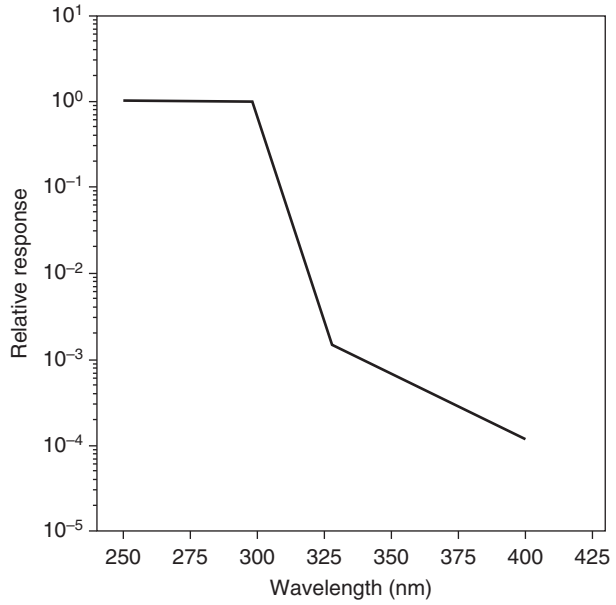


FIGURE 46.1. Action spectrum for minimal erythema at wavelength 298 nm.

(W/m^2), whereas radiant exposure is the accumulated radiant energy per unit area (J/m^2). The biological effect of a UV spectral band depends on the wavelengths displayed for minimal erythema in Figure 46.1.

Consequently, quantifying the biological effects of environmental UV radiation exposure requires conversion of physical dose into biologically meaningful dose parameters based on the response to individual wavelengths in the spectrum. The action spectrum is a graphic representation of the relative effectiveness of specific wavelengths of radiation required to produce a biological response (e.g., erythema).

Biologically weighted radiometric quantities are derived from spectral data by multiplying the spectral wavelengths by the action spectrum of relevant biological reactions (e.g., minimal erythema, DNA damage, skin cancer). Equation 46.1 determines the biologically effective solar spectral irradiance, E_{eff} (W_{eff}/m^2) by integrating the biologically effective irradiance (E_{eff}) over the spectral range. The biologically effective dose rate (i.e., effective radiant exposure), H_{eff} (J_{eff}/m^2), is the biologically effective irradiance (E_{eff}) integrated over time (e.g., 1 day for daily dose).

$$E_{\text{eff}} = \int E_{\lambda}(\lambda) \times S_{\lambda}(\lambda)\, d\lambda \qquad \text{(Equation 46.1)}$$

where

$E_{\lambda}(\lambda)$ = solar spectral irradiance ($W/m^2/nm$);
$S_{\lambda}(\lambda)$ = action spectrum (relative units);
λ = wavelength (nm).

Figure 46.1 demonstrates the action spectrum for minimal erythema at the reference wavelength of 298 nm. The relative response depends on the specific biological reaction being monitored.

EXPOSURE

Solar Radiation

Although the sun emits energy across a broad band of wavelengths, the vast majority of the energy falls in the nonionizing visible and near-infrared regions. Approximately 9% of the total energy released by the sun appears in the UV portion of the electromagnetic spectrum at the beginning of the atmosphere, whereas the visible spectrum (400–700 nm) accounts for ~40% and infrared for ~51% of the total solar energy *entering* the earth's atmosphere.[9] Both the quality (spectrum) and quantity (irradiance) of solar radiation vary with the elevation of the sun above the horizon and the solar zenith angle, as well as a variety of other factors (e.g., reflectance, atmospheric modification). The geometry of the exposure and the position of the sun in the sky are major determinates of the irradiance on the skin and eye, with geometry more important to the exposure intensity for the eye than the skin; the eyelids and eyebrow ridge provide significant protection for the eye from UV radiation.[10] Consequently, UV-induced changes in the eye occur primarily in the lower nasal part of the outer eye. Table 46.1 displays the characteristics and mitigating factors of solar radiation entering the atmosphere. The intensity of UV exposure is greatest at the equator, high altitudes, and midday in the summer (1,100–1,500).

The lens of the eye absorbs UV radiation, resulting in a sharp drop in visual acuity in the 380–420 nm range;[11] therefore, UV radiation is invisible. The epidermis also strongly absorbs UVA radiation with little UVB and UVC radiation reaching the dermis.[12]

Figure 46.2 demonstrates the average penetrance of solar radiation of <1,500 nm through human skin. The depth of penetration depends on reflection, scatter, and absorption. Luminographs of the skin using UV radiation produce greater definition of surface detail than conventional photographs as a result of reduced scattering of reflected rays; this illumination (e.g., Woods lamp or black light) allows detailed examination of forensic material (e.g., wounds, fluorescent liquids).[13] UV radiation penetrates human skin less deeply than visible light and much less deeply than infrared radiation.

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TABLE 46.1. Solar radiation entering the earth's atmosphere with mitigating factors. (Adapted from Loggie and Eddy).[9]

Mitigating Factors	Ionizing	Ultraviolet	Visible	Infrared	Microwave
Wavelength	γ-rays (<10^{-3} nm),	UVA: 320–400 nm	400–700 nm	Near: 700–7,000 nm	25 μm–1 mm
	X-rays (1 nm–1 pm), particulates	UVB: 290–320 nm		Far: >7,000 nm–25 μm	
		UVC: 100–290 nm[a]			
% Total solar energy	<10%	UVA: 6.8%	39.7%	Near: 51%	0.01%
		UVB: 1.7%		Far: <1%	
		UVC: 0.6%			
Solar activity (sunspots)	Marked	Moderate	Weak	Weak	Marked
Altitude	Strong	Strong	Weak	Strong	Weak
Latitude	Direct	Inverse	Inverse	Inverse	Inverse
Absorption atmosphere	Strong	UVA: strong	Weak	Strong	Variable[b]
		UVB: strong			
		UVC: marked			
Skin type (pigment)	None	Yes	Yes	Marginal	Weak
Cloud cover	No	Yes	Yes	Partial	Weak

[a] The portion (100–180) absorbed at the beginning of the atmosphere is called the vacuum UVC. [b] The longer wavelengths pass through the Earth's atmosphere similar to radio waves, whereas the atmosphere absorbs some of the shorter-wavelength microwaves.

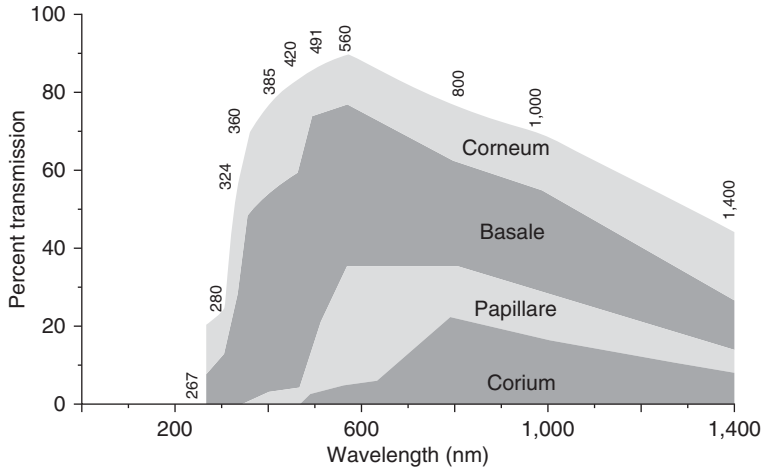


FIGURE 46.2. Estimated average penetration of radiant energy of 1,500 nm through thin human skin. The stratum basale is the deepest of the five layers comprising the avascular epidermis, whereas the stratum corneum is the most superficial epidermal layer. The papillary layer is the superficial layer of the dermis (corium) composed of loose connective tissue (collagen and elastin fibers) that projects into the stratum basale. (Adapted from West et al.).[13]

Atmospheric Modifications

As solar radiation passes through the atmosphere, molecular oxygen and ozone absorb and scatter UV radiation with ~2/3 of the radiation reaching the earth's surface; the annual variation in solar radiation at the beginning of the atmosphere is ~10%.[14] UV radiation increases by ~10–12% every 1,000 m (3,280 ft) in altitude; consequently, this type of radiation increases by ~170–290% at the cruising altitude of 35,000 ft, when compared with the earth's surface.[15] The ozone layer prevents the penetration of all UVC radiation and almost all of the UVB spectrum; thus, UV radiation exposure at the surface of the earth primarily involves the wavelengths of 290–400 nm, as demonstrated in Figure 46.3.

A number of factors affect the amount and spectral distribution of solar radiation reaching the surface of the earth (UV irradiance), as listed in Table 46.2.

Variation is much smaller for solar radiation from the source than atmospheric attenuation; consequently, the variation in the amount of UV radiation is greater at the earth's surface than at the upper edge of the

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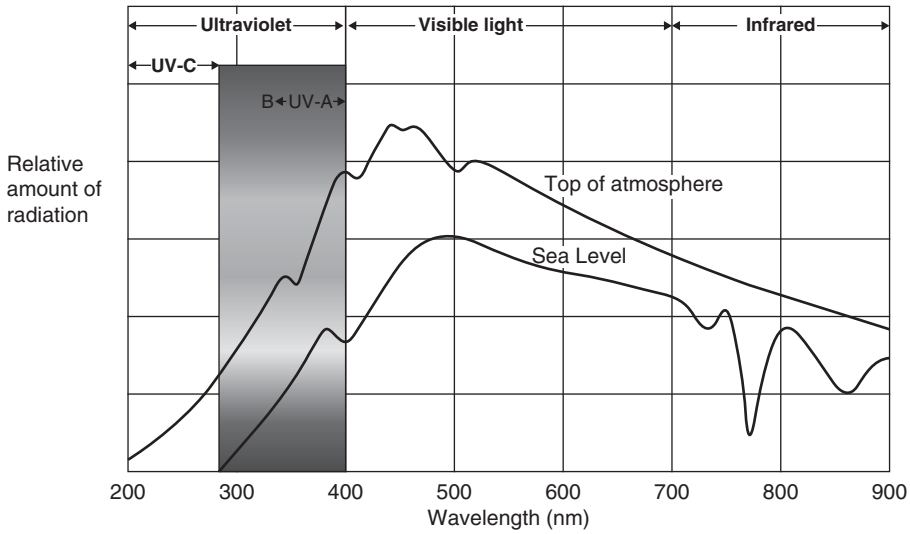


FIGURE 46.3. Amount of solar radiation penetrating the atmosphere based on a wavelength of <900 nm. The solid area represents the UV radiation spectrum (290–400 nm) reaching the terrestrial environment. (Adapted from International Programme on Chemical Safety).[8]

TABLE 46.2. Factors affecting the amount and spectral distribution of solar radiation (UV irradiance) reaching the surface of the earth (global UV). Shadowing by surrounding objects also reduces UV irradiance in the shadow. (Based on International Programme on Chemical Safety).[8]

Factor	Location	Magnitude of Effect on Solar Radiation
Altitude	Atmosphere	↑ above sea level
Clarity	Atmosphere	Mean cloudy sky = 22–38% less than clear sky[16]
Absorption or scattering	Atmosphere	↓ with ↑ airborne aerosols and pollutants
Shadowing or reflectance on the ground	Ground	Reflectance increases 16-fold at snowy to nonsnowy terrain interface[17]
Ozone concentration	Mostly stratosphere	↓ with ↓ozone thickness or vertical distribution
Solar spectrum	Atmospheric edge	Variable
Solar zenith	Atmosphere	Varies with daytime, latitude, and season (↓ 7% summer to winter)
Wavelength	Source	↓↓ 100–180 nm (vacuum UV)

atmosphere. The seasonal variation in UV radiation is much lower near the equator than in temperate zones. Approximately 20–30% of the daily UV radiation dose occurs between 11 AM and 1 PM, whereas ~75% of the dose is received between 9 AM and 3 PM.[18] The spectral irradiance decreases by $\sim^1/_3$ between the peak at 12 noon and after 3 PM.[19] Solar activity probably does not produce significant changes in the amount of damage caused by UV radiation. Sunspots are an index of solar activity that follows an 11-year cycle; however, increases in the amount of radiation across the UV portion of the spectrum are ~1% during solar flares.[20]

The stratosphere contains ~90% of the ozone in the atmosphere; the ozone layer accounts for most UV radiation absorption; thus, reduction of the ozone layer potentially increases the risk of damage from chronic UV radiation exposure, including photoaging and skin cancer.[21] The ozone layer is thinnest at the equator and thickest at the poles. Instruments on satellites orbiting the earth (e.g., TOMS and OMI/Aura) measure ozone, cloud cover, and aerosols in the atmosphere; however, information on long-term global changes in terrestrial UV radiation was limited before the launching of orbiting satellites. Radiative transfer analysis of satellite-based O_3 measurements from 1979–1992 demonstrated substantial increases in surface UVB levels in all latitudes (e.g., several less percentage points over Northern mid-latitudes) except the tropics,

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assuming other factors (e.g., cloud cover, local pollutant levels) remained constant.[22,23] These changes affect primarily the transmission of UVB to the surface of the earth. Currently, ozone column amounts are no longer decreasing, with the return to 1980 atmospheric O_3 concentrations in the mid-latitudes expected before mid-century.[24]

Irradiance is the radiant flux density falling on a surface, usually measured in W/m^2. The most sun-exposed surfaces of the skin are the forehead, nose, and upper ears; UVB exposure of these surfaces varies by up to one order of magnitude compared with less-exposed surfaces of the body (e.g., underneath the chin). The maximum summer UV irradiance is greater in the southern than the northern hemisphere because of the lower ozone concentrations in late summer and less separation between the earth and sun in early January.[25] UVB intensity can increase at a rate of 6%/km altitude, with the rate increasing somewhat more above 5 km as a result of the clearer atmosphere, assuming other factors affecting solar irradiance remain constant.[26] Scattering of UV radiation by air molecules also occurs near the earth's surface; therefore, reduced air pressure and air mass increase the amount of UV radiation at the surface of the earth near areas of high altitude and low air pressure.[27] Figure 46.4 demonstrates the seasonal and diurnal variation in UVB irradiance (307 nm) at latitude 45°S.

UVA (320–400 NM)

UVA or long UV is not visible to the human eye, but the eye will see the fluorescence of certain substances under black light. The intensity of UVA increases 2-fold from winter to summer, compared with a 10-fold increase in UVB.[1] The greater effectiveness (i.e., ~5–10-fold) of UVB radiation in producing cutaneous erythema obscures the importance of UVA as a cause of skin damage. Because the cutaneous and erythematous effects are much less potent for UVA (320–400 nm) than UVB, the cutaneous effects from UVB radiation usually occur long before sufficient amounts of UVA light can be absorbed to cause skin damage. Unlike recurrent UVB exposure, UVA exposure does not significantly induce protective factors against further UVA exposure (e.g., tanning).[28] The ability of UVA to penetrate the epidermis suggests a role for UVA in skin aging. Potentially, UVA may contribute to the development of photocarcinogenesis, immunosuppression, and drug photosensitivities.

UVB (290–320 NM)

UVB or short UV is the primary portion of the UV spectrum responsible for tanning, sunburn, and skin cancer. About 90% of the 25-OH vitamin D results from the interaction of UVB and 7-dehydrocholesterol in the skin.[29] As displayed in Figure 46.3, the clinical

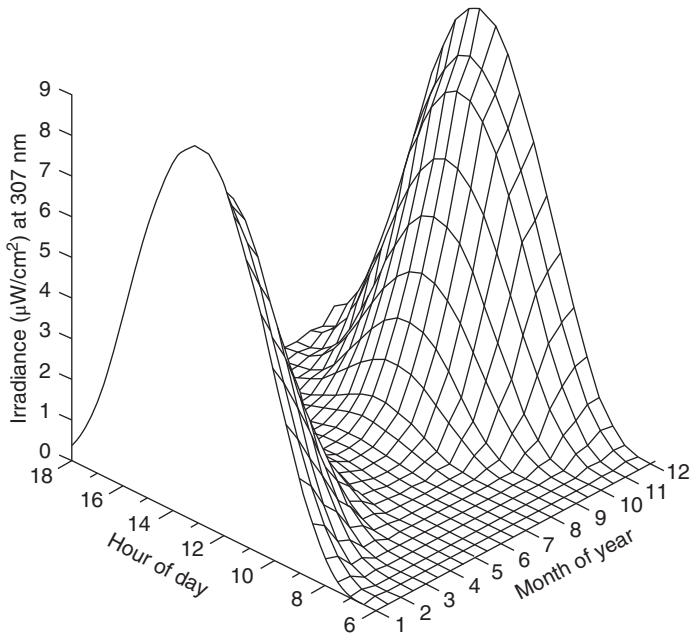


FIGURE 46.4. Seasonal and diurnal variation in UVB irradiance (307 nm) at latitude 45°S. (Redrawn from McKenzie and Elwood).[25]

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effects of UVB radiation are more important at the surface of the earth than UVA radiation. Although much more (i.e., 10–100 times more) UVA reaches the earth's surface than UVB, the latter is 1,000 times more effective at producing erythema.[30] Window glass does not transmit wavelengths of <310 nm; hence, window glass blocks UVB but not UVA radiation. Compared with UVA radiation, the atmosphere attenuates UVB to a much greater extent. Consequently, a sunbather receives relatively greater UVA doses in the summer and during noontime periods. UV radiation of <380 nm does not pass through the acrylic windows of airplanes.[31]

UVC (100–290 nm)

Atmospheric ozone absorbs almost all UVC radiation; consequently, biologically relevant UVC sources involve primarily arc welding and germicidal lamps (250–265 nm); the latter also emit a modest amount of UVB radiation. Gas welding typically does not emit significant amounts of UV radiation. Although UVC radiation has more energy than UVB or UVA, UVC radiation penetrates the skin poorly, as noted in Figure 46.2. UVC is attenuated at any altitude by four times more than UVA.[9] Vacuum UV (100–180 nm) refers to the wavelength range where a vacuum is necessary to propagate the energy because these wavelengths are easily absorbed in the presence of air. Molecules in the atmosphere absorb UV radiation of <200 nm within a few centimeters; therefore, these wavelengths occur in biologically significant amounts only in space. Vacuum UV does not contribute significantly to skin changes in humans on earth.

Artificial Sources

Broad-spectrum UV radiation has a variety of industrial and medical uses, including the diagnosis and treatment of medical illnesses (e.g., psoriasis, eczema, vitamin D deficiency, neonatal jaundice), dental restorations, food/medical instrument sterilization, commercial polymerization reactions (e.g., photo-curing protective coatings), welding, glassblowing, and tanning (sunbeds). Most of these processes involve UVA spectrum as the principal operating wavelengths; however, many of these sources also emit some UVB, UVC, and violet light. Only artificial sources emit UVC radiant energy. Prior to the mid-1970s, mercury lamps emitting UVB and UVC were the main source of UV radiation; subsequently, UVA sources replaced mercury lamps emitting 95–99% UVA radiation with typical peaks at 340, 350, and 366 nm. Artificial sources of UV radiation include incandescent (tungsten) lamps, gas-discharge lamps (mercury, xenon, hydrogen, flash tubes), electric-discharge lamps (carbon arcs, welding arcs), arc lamps, metal halide lamps, fluorescent lamps, electrodeless lamps, and some lasers (gas, dye, excimer). Xenon arc lamps encased in UV protective coatings have replaced the older carbon arc lamps used in older movie theaters; the latter emitted substantial amounts of UVB radiation.[32] In contrast to most artificial sources of UV radiation, laser units emit UV radiation at a specific wavelength (i.e., the usual range, ~300–350 nm). The exceptions to this range of wavelengths are argon excimer lasers (193 nm) and krypton excimer lasers (222 nm, 248 nm). Although exposure to artificial sources of UV radiation is common, the sun is the major source of UV exposure for most people. Exceptions include medical therapy and cosmetic tanning.

Light Sources

Artificial, low-intensity UV radiation sources include sunlamps, black-light lamps, and low-pressure mercury-vapor lamps, whereas high-pressure mercury-vapor and xenon arc lamps, welding arcs, plasma torches, and xenon-mercury arc lamps are high-intensity UV sources. An analysis of general lighting and special fluorescent lamps by the National Radiological Protection Board indicates illumination levels associated with these lamps do not emit sufficient radiation to produce an acute or chronic hazard.[33] In general, UVB and UVC emissions from fluorescent light lamps are extremely low because the soda lime glass envelope attenuates wavelengths of <320 nm. The intensity of UV emissions from older commercial UVB lamps was high; UV radiation exposure potentially exceeded permissible exposure limits within 10 minutes.

Incandescent (heated filament) lamps are usually not a retinal hazard; these sources produce peak spectral emissions in the infrared range with relatively small amounts of UV radiation. Tungsten (quartz halogen) lamps operate at higher temperatures (2,900–3,450°K) and power than incandescent lamps; these halogen lamps can emit sufficient UV radiation to cause photokeratitis and erythema. UV radiation exposure is usually higher in TV studios than theater stages because TV studios use metal halide lamps more extensively.[34] A survey of these devices indicates the permissible exposure time ranged from 2–50 minutes. Low-pressure mercury discharge (germicidal) lamps produce a monochromatic emission at the wavelength of 253.7 nm that is a potential UV hazard. High-density discharge (HID) lamps used for industrial and commercial lighting emit blue/green/white light from mercury vapor along with

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large amount of UV radiation; however, the outer glass bulb usually absorbs most of the residual UV radiation. Compact (mercury, xenon) and linear arc lamps used as search lights and solar simulators produce very high luminance that can approach the luminance of the sun; these lamps possess the greatest potential for thermal retinal and UV-induced injuries. Flash lamps and flash tubes generate integrated radiance in the range of 10^4 J/m^2 ×sr (steradian) with a pulse duration of 2–4 msec. The envelopes of most flash tubes absorb UV radiation of <300 nm; however, some flash tubes used for lasing can produce significant quantities of UVB and UVA radiation.

Sunbeds

Currently distributed sunbeds usually emit ~95% UVA radiation with <5% in the UVB spectrum; however, evaluation of UVA lamps in tanning parlors and solaria typically requires individual evaluation. Reduction in UVA and UVB emission occurs with the aging of the lamp in the range of ~20–50% after 1,000 hours of use. Pre-1980 tanning lamps usually emitted primarily UVB radiation. The European standard for the erythemal-effective irradiance for sunbeds is ≤0.3 W/m^2; some sunbeds may exceed this recommendation. In a study of 402 English artificial tanning units, the mean irradiance was 0.56 ± 0.21 W/m^2 with a range of 0.10–1.32 W/m^2.[35] Four lamp types used in tanning equipment include: 1) UVB, filtered high-intensity discharge lamps; 2) UVB, low-pressure fluorescent tubes; 3) UVA, filtered high-intensity discharge lamps; and 4) UVA, low-pressure fluorescent tubes. UVB lamps are no longer common.[8]

Occupational Exposure

Outdoor Work

Indoor workers typically receive ~300 standard erythemal doses (SED) defined as 10 mJ/cm^2 annually, primarily from recreational exposures, whereas outdoor workers at the same latitude receive ~3–5-fold greater UV exposure (i.e., >1,000 SED).[36] Workers with the greatest potential exposure to substantial amounts of solar radiation include construction workers, gardeners, agricultural employees, seafarers, water sport instructors, and lifeguards, whereas traffic police, mailmen, military personnel, and highway workers are typically less exposed depending on work activities and sun protection (e.g., hats, glasses, sunscreens, time/duration of sun exposure). A population-based survey of 889 French outdoor workers exposed to solar and artificial UV radiation demonstrated the highest UV doses in gardeners, construction workers, agricultural workers, and culture/art/social science workers as measured by median daily standard erythemal UV doses.[37] The portion of the body receiving the highest radiation dose depends on the activity and time of year. A study of 32 Italian vineyard workers demonstrated the back received 53–87% (median = 72%) of ambient sun exposure during spring compared with 36–77% (median = 50%) during the summer. The arms received 30–60% (median = 44%) during the spring compared with 19–43% (median = 29%) during summer.[38]

The springtime sun exposure exceeded the assumed threshold for sun-adapted skin in Mediterranean subjects defined as 10 SED (standard erythemal dose). In a study of 838 watermen from Chesapeake Bay, the estimated annual facial dose ranged from 30–200 MED (minimal erythema dose) based on the face receiving 5–10% of the ambient sun exposure. Assuming that the face absorbs 20% of the ambient solar radiation, the annual facial dose increases to 80–500 MED.[39] A study of Swiss outdoor workers suggests horizontal body locations receive 2.0–2.5-fold greater sun exposure than vertical locations; in this study, eating lunch outdoors daily added the equivalent of an extra day/week of occupational-related sun exposure.[40] Indoor workers with high-potential UV exposure include welders, television studio/theater staff, workers using photo curing equipment (dental, paper, graphics), and some medical/scientific workers.

Glassblowing

Most craft glassblowers use soda-lime glass, whereas scientific glassblowers usually handle borosilicate, cobalt, or quartz glass materials. During the heating and melting of glass materials, scientific glassblowers use lathes and tabletop heating systems; craft glassblowers use furnace systems. A cross-sectional survey of optical radiation associated with glassblowing suggests limited radiation in the near-UV wavelengths (315–400 nm). Potentially high irradiance occurs in the visible wavelengths (400–700 nm).[41] Glassblowing with soda-lime glass may also produce excessive irradiance in the near-infrared range (700–1,400 nm). Ocular abnormalities may develop in the cornea, lens, or retina as a result of excessive irradiance, including cataracts, keratitis, chronic dry eyes, and reduced visual acuity.

Welding

Welding arcs are the predominant and most intense artificial sources of UV radiation in the workplace.[42]

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UV radiation emitted from arc welding is complicated and highly variable, depending primarily on the metal welded and the shielding gas with several other factors modulating the UV spectrum. including electrode type, arc voltage/current, arc gap, shielding flux, fumes/smoke generated, time during the process, and joint geometry.[43] The optical radiation generated by welding includes UV, infrared, and visible radiation, depending on the specific process used.[44] Gas welding produces minimal optical radiation hazards. Oxyacetylene and oxyhydrogen flames burn at temperatures of >2000°K; these flames emit some UV radiation mostly in the UVA range. Oil, coal, and gas flames emit essentially no UV radiation. Arc welding fuses metals with the heat (~3,870°C) of an electric arc. The UV irradiances associated with arc welding are high enough to produce photokeratitis up to 20–30 m from the source.[45]

DOSE EFFECT

Biological effects of UV radiation depend on the wavelength. Because the absorption of UV radiation occurs superficially over a surface, the most common radiometric quantity used to describe the amount of exposure is the radiant energy defined as the incident energy divided by the receptor surface area and designated H_e (J/m^2). Irradiance measures the dose over a specific time, defined as the incident power divided by the receptor surface area and designated E_e (W/m^2). The proper determination of a hazard from UV radiation requires spectral emission data that sums the total irradiance over all wavelengths emitted. These data are normalized by a biological or hazard weighting factor to determine the biologically effective irradiance over the exposure period, called the biologically effective radiant exposure ($J_{effective}$/m^2).

Skin

Sunburn

Sources of UV radiation are characterized by the radiometric units of energy or dose (mJ/cm^2) and power or dose rate (mW/cm^2). The minimal erythemal dose (MED) is the UV exposure that produces barely visible erythema 8–24 hours after irradiation of the skin. This dose varies in individuals based on skin type and prior skin exposures.[46] Consequently, a standardized unit is also used, defined as standard erythemal dose (SED) equal to 10 mJ/cm^2. Table 46.3 compares the MED and SED for different skin types. The UV Index is an estimate used in public health settings to measure the sunburn risk during specific meteorological conditions; this value corresponds to 0.9 SED/hour (0.025 W/m^2). The UV Index ranges from low (<2) and moderate (3–5) to high (6–7), very high (8–10), and extreme >11. The minimal erythema dose (MED) is a unit of effective dose (dose weighted to produce a specific biological effect); this value represents the effective radiant exposure of UV radiation necessary to cause adverse effects in the skin. Unlike thermal exposure, the onset of erythema is delayed by 1–6 hours, depending on the UV dose. Blistering occurs at 6–10 MED.[47]

TABLE 46.3. Skin types and average threshold exposure necessary to produce sunburn with and without adaptation as measured in Minimal Erythema Dose (MED) and Standard Erythema Dose (SED). (Adapted from International Commission on Non-Ionizing Radiation Protection).[46]

Skin Type (Phototype)	MED Without Adaptation[a] (SED)[b]	MED with Adaptation[a] (SED)[b]
I–II (Celtic)	2	5
III–IV (Mediterranean)	5	12
V (Asian)	10	60
VI (Black)	15	80

[a] Three weeks of tanning from solar re-exposure without erythema defines adaptation. [b] The SED approximates the average MED as a result of wide variation in MED values between skin types.

The MED ranges from 15–200 mJ/cm^2, depending on several factors, including skin type (i.e., higher in dark skin),[48] the skin thickness,[49] UV intensity, wavelength, and environmental factors (e.g., wind, humidity, season, time of day).[8] The maximum sensitivity of the skin occurs in the UVB range at 295 nm.[50] For white skin, the MED averages ~20–30 mJ/cm^2 varying 4-fold between individuals with this type of skin pigment.[51] For indoor workers in mid-latitudes (40–60°N), the annual solar radiation dose to the face is ~40–160 MED compared with ~250 MED for outdoor workers;[14] outdoor workers receive ~10% (range, 7–18%) of the total available annual UV irradiance measured on a horizontal plane, whereas indoor workers and children receive 2–9-fold less (~3% with a range of 2–4%).[52]

Although up to 800–1,000 times more UVA radiation is necessary to produce the same amount of erythema as UVB radiation, UVA may contribute up to 15% of the erythematous dose at noon because UVA is much more abundant at that time of day.[53] Table 46.4 compares the ability of each type of UV radiation to produce skin changes.

The minimal erythema dose (MED) for nontanned, lightly pigmented individuals ranges from 6–30 mJ/cm^2, with skin pigmentation and conditioning changing the MED by one order of magnitude.[55]

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TABLE 46.4. Skin changes associated with subsets of UV radiation. (Adapted from Pathak).[54]

Effect	UVC (200–290 nm)	UVB (290–320 nm)	UVA (320–400 nm)
Minimal erythema dose (MED, mJ/cm^2)	10–25	20–70	20–100
Onset erythema (hours)	0.5–1.5	2–6	4–6
Peak erythema (hours)	6–8	20–24	10–12
Duration erythema (hours)	48–72	72–120	36–48
Immediate tanning	None	Low	High
Melanogenic	Low	High	Moderately high

Wind intensifies the adverse erythematous effects of UV radiation on the skin based on animal experimentation.[56] Compared with UVB intensity at sea level, the amount of UVB radiation increases by 4% with each 1,000 ft increase in elevation.[1] Clouds absorb infrared radiation better than UV radiation. The amount of UV radiation absorbed by clouds is variable, ranging from 10–80% and averaging ~40%. Reflective surfaces (e.g., snow, ice) may increase UV exposure by reflecting most of the incident UV radiation. Reflection of UV radiation from water is usually small (~5% at midday), depending on the angle of the sun in the sky, the contour of the surface of the water, and the clarity of the water.[1] Outdoor activities may provide substantial cumulative UVB exposure, particularly among athletes (e.g., golfers, mountain climbers, cyclists, marathon runners, skiers).

Snow skiers are susceptible to sunburn because of the increased amount of UV radiation from the altitude, reflectance, and wind.[57] In a study of young skiers evaluated by shoulder dosimeters, the median UVB dose for 4–5 hours of skiing was 2.1 SED with a range of 0.7–4.9 SED.[58] The median daily UV exposure for a group of hikers was 8.1 SED as measured by shoulder dosimeters, whereas tennis players received a daily median dose of 7.5 SED during training as measured by wrist dosimeters.[59]

Tanning

Melanin is the ideal sunscreen because it absorbs all UV radiation and limits the action of free radicals in the skin. Although all races possess similar numbers of melanocytes, the packaging and distribution of the melanocytes in black skin increases the MED up to 30 times compared with Caucasian skin.[1] Adaption to UV radiation results from hyperplasia of the epidermis, principally from increased production of melanin and expansion of the stratum corneum.[60] In patients with psoriasis, tolerance to UV radiation increases the MED up to 28-fold (mean = 13-fold) above pretreatment values; tolerance decreases over 6 weeks to <2 times the pretreatment MED.[61] UVA is much less effective at stimulating an increase in the horny layer of the epidermis. Most wavelengths in the UVB spectrum produce tanning and erythema.[53]

Photoaging

Skin changes associated with chronic solar radiation include solar lentigines, mottled pigmentation, dry/rough skin, wrinkles, leathery texture, and benign/malignant tumors. In a Japanese study, the estimated average annual UVB radiation dose in central Japan was 200 MED (minimal erythema dose) with a cumulative dose of 4,000 MED at age 20 years based on 1 MED equivalent to 20 mJ/cm^2.[62] The maximum daily UVB dose was 22 MED. The mean *daily* sun exposure time to maintain sun-exposed skin without solar lentigines (i.e., the most sensitive effect of sun exposure) until 80 years of age was 2.54 minutes (0.14 MED) for unprotected skin and ~2 hours for the use of SPF 50 sunscreen. The lens and cornea typically shield the retina from the acute effects of UV radiation; however, in aphakic monkeys, the threshold for acute photoretinitis is ~500 mJ/cm^2.[63]

Eye

The cornea and conjunctive strongly absorb UVB and UVC radiation. The external UV dose received by the eye depends on several factors including facial anatomy, solar elevation angle, altitude, atmospheric modification (ozone, air pollution), time of day, and ground reflectance.[64] In contrast to the large variation in individual responses of skin to UV radiation, all racial types are susceptible to cataracts and UV radiation-induced eye diseases. The threshold radiant exposure for corneal injuries ranges from <1 mJ/cm^2 at 270 nm (UVC) to 10.6 mJ/cm^2.[45] Maximum sensitivity of the eye occurs at 270 nm.[65] Two nurses were accidentally exposed for 4–6 hours to a germicidal lamp (UVC/UVB) with an estimated skin and eye effective irradiance of 194 times and 126 times, respectively, according to the ICNIRP guidelines.[66] They developed bilateral keratoconjunctivitis (conjunctival injection, blurred vision, tearing)

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and facial erythema 12–24 hours after cessation of exposure. The facial skin demonstrated chronic erythema, swelling, and telangiectasia 2 months after exposure; superficially punctuated keratopathy with lacrimal hyposecretion (dry eyes) persisted over 1 year after the initial injury.

Repeated UV exposure does not reduce the threshold for corneal injury in humans. Exposure of pilots to UV radiation during flight is highly dependent on the UVA-blocking properties of the airplane windshield and the use of sun glasses; epidemiology studies did not detect significant exposure to UVB radiation in pilots.[67] Corneal injury from UVA radiation requires >1,000 mJ/cm^2.[68] In rodent studies, thresholds for the development of transient opacities vary dramatically with wavelength (15–1,260 mJ/cm^2).[69] Additionally, animal studies suggest sensitivity to UVB-induced cataract formation decreases with increasing daily exposure.[70]

Immune System

A single dose of UVB in the range of 100 mJ/cm^2 alters Langerhans cell function and IgA receptors resulting in decreased antigen-induced contact sensitivity based on volunteer and rodent studies.[71] A single dose of UVB radiation in the range of 60–80 mJ/cm^2 almost completely eliminated Langerhans cell markers, whereas pemphigus antigens of keratinocytes were unaffected. Electron microscopy demonstrated ultrastructural changes only in Langerhans cells in the epidermis at UVB doses of 15–30 mJ/cm^2 or UVA doses of 1×40 to 2×100 mJ/cm^2. Rodent studies suggest exposure to UV radiation doses of <1 MED exacerbates a variety of infections (e.g., *Herpes simplex*,[72] *Mycobacterium lepraemurium*[73]).

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Most, but not all ecological studies of UV radiation and mortality suggest a beneficial effect of UV exposure because of vitamin D production by UVB (290–320 nm). Radiation in this spectrum converts 7-dehydrocholesterol to previtamin D that the liver and kidneys transform into the active form of vitamin D. Lack of vitamin D production in the skin increases the risk of adverse bone and skeletal effects in workers without adequate sun exposure (e.g., underground miners, long-haul flight crews, shift workers).[43] Many American indoor workers do not meet their daily minimum (600 IU) or optimum (≥1,200 IU) vitamin D_3 requirements, particularly darker skin types (III–VI) and older workers (>59 years), even with a 2–3 week summer vacation.[74]

UV radiation is nonionizing; this type of radiation affects biological molecules either by altering the electron energy levels of the atoms or by altering their rotational, transitional, or vibrational energies. These changes result in electron excitation that potentially produces the following effects: 1) degradation into heat, 2) formation of free radicals, 3) fluorescence or phosphorescence, or 4) dissociation of the molecule. DNA is a critical target for excessive UVB and UVC radiation, which cause a variety of adverse effects including chromosome changes, mutations, morphological transformations, and cell death.[8] Although damage to cell membranes and organelles may contribute to the toxic effects of UV radiation, the primary species produced by the interaction of UV radiation with cells are reactive species (free radicals). UV radiation can activate some genes and viruses including HIV, but *in vitro* studies indicate UVA radiation-induced activation differs from UVB and UVC radiation.[75]

Skin

The skin contains molecules or chromophores that scatter UV rays and absorb solar radiation (UVB, UVA, visible, infrared radiation); melanin and primarily eumelanin are the main chromophores in the skin. UV radiation doses exceeding the absorptive capacity of melanins produce an erythematous reaction (sunburn) from the release of a variety of inflammatory mediators including cytokines, chemokines, nitric oxide, histamines, and prostaglandins. UVA causes an immediate tanning response that begins soon after exposure from the release of preformed melanin; this response quickly fades. The melanotic reaction results primarily from UVB-induced stimulation of melanocyte production.[54] UVB radiation-induced delayed tanning increases melanin synthesis and the transfer of melanin via dendrites to adjacent keratinocytes. Several factors influence UV radiation-induced melanin synthesis, including inflammatory mediators, cytokines, and growth factors. Black/brown eumelanin is the primary type of melanin in dark skinned individuals, whereas yellow/red pheomelanin predominates in light-skinned, freckled individuals (skin types I–II); the latter is much less photo-protective than the former. The type of melanin in the skin accounts for differences in skin susceptibility to sun exposure. Eumelanin is a stable free radical that transforms UV energy into heat by internal conversion; pheomelanin lacks this property and produces reactive oxygen species following overexposure to the sun.[76]

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Major alterations in the histology of the epidermis involve the replacement of Langerhans cells by dyskeratotic and vacuolated keratinocytes (sunburn cells).[77] Mast cell degranulation with perivascular edema occurs acutely in the dermis along with a more protracted alteration of the endothelial cells that coincides with the period of maximum erythema. UVA radiation produces fewer sunburn cells but greater dermal infiltrate and vascular damage compared with UVB radiation[1]; consequently, UVA radiation also contributes significantly to photoaging, immunosuppression, and photocarcinogenesis.[78] The effects of UVB and UVA radiation on dermal thickness are substantially less than those on the epidermis. The effect of visible (400–700 nm) and the higher energy portion of infrared radiation (700–3,000 nm) on skin pathology is generally considered small; however, this portion of solar radiation may contribute to erythema, pigmentation, thermal damage, free radical production, and photoaging.[79] In contrast to the photochemical reactions produced by UV radiation, infrared radiation typically causes molecular vibration and increased temperature; however, infrared radiation may enhance UV radiation-induced generation of reactive oxygen species.[80]

Experimental evidence suggests the sunburn response decreases and evolves more slowly following UV exposure in the elderly.[81] An increase in the number and thickness of amorphous elastic fibers in the upper dermis is the most prominent histological change in skin chronically exposed to the sun.[7] Other chronic skin changes include thickening of the epidermis (keratinocyte proliferation), tortuous and dilated dermal vessels, the appearance of actinic keratosis and facial telangiectasias, increased number and prominence of freckles, and a hypercellular dermis manifested by an increase in mast cells and fibroblasts. The amount of mature collagen in skin chronically exposed to the sun decreases with photodamage. The mechanism of toxicity involves the UV radiation formation of reactive oxygen species, resulting in the expression of transcription factors (e.g., AP-1, TGF-β) that enhance collage breakdown and downregulate collagen synthesis.[82] The shorter UV wavelengths (UVB, UVC) damage collagen, whereas all wavelengths in the UV spectrum cause hyperplasia of elastic fiber and increased glycosaminoglycans.[83]

Eye

Ocular tissues affected by UV radiation include the eyelids, conjunctiva, cornea, crystalline lens, and retina. Ocular damage because of UV radiation occurs primarily in the cornea and lens; however, retinal injury can occur, particularly in persons without lenses to absorb UV radiation. Snow blindness and arc welders' photokeratitis are examples of acute corneal damage from UVB exposure. Retinal injuries in sun-gazers probably result from exposure to the shorter wavelengths of the visible spectrum as well as UV exposure.[84]

The cornea consists of the following five zones (exterior to interior): 1) 5-layered, ~50 μm thick, nonkeratinized squamous epithelium with apoptotic cells on the outer layer; 2) Bowman layer of randomly oriented, fine collagen fibrils ~10 μm thick; 3) the relatively thick stroma consisting of 60–70 successive layers of obliquely oriented, tight collagen fibrils (corneal lamellae) embedded in an extracellular matrix composed primarily of sulfated glycosaminoglycans; 4) a thin, PAS-positive endothelial basement membrane (Descemet membrane); and 5) a monolayer of nonmitotic, hexagonally flattened mesothelial cells (corneal endothelium). Nucleic acids and amino acids function as corneal chromophores to absorb wavelengths of >295 nm. The cornea attenuates almost all UV radiation of <290 nm, whereas the lens eliminates most UV radiation of 300–370 nm. The shorter wavelengths (UVB, 280–315 nm) contain more energy than UVA (315–400 nm); therefore, UVB light possesses greater potential to produce damage to the cornea and lens than UVA or visible light (400–700 nm). The corneal transmittance of UV radiation increases between ~280 and 320 nm, with maximum transmittance in the visible spectrum; the epithelium absorbs most of the UVA light (315–400 nm).[85] Maximum sensitivity of the cornea to UV radiation occurs at 270 nm.[86] Although some thickening of the epithelium may occur during the summer months, the cornea does not readily adapt to repeated UV exposure as the skin does.[87]

The three fundamental types of solar radiation-induced damage are: 1) thermal; 2) mechanical; and 3) photochemical.[88] Thermal and mechanical damage occur following the use of lasers. Photochemical damage results from prolonged exposure to large amounts of blue and ultraviolet radiation. Photokeratitis is the acute response to excessive UV radiation (e.g., snow blindness, welders flash) that manifests by damage to the epithelium and, in more serious injuries, to the stroma (keratocytes) and endothelium. Depending on the severity of the UV exposure, slit-lamp examination reveals debris in the tear film from cells shed from the epithelium, haze and granules (tiny bluish amorphous opacities) in the epithelium, opacities in the stroma, and keratic precipitates in the endothelium. The anterior chamber may demonstrate flare (scattering of light beam on small particles) as a result of the release of plasma proteins from local blood vessels. Corneal

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edema may develop with alteration in corneal thickness and vision. Chronic UVB radiation exposure may damage the endothelium, resulting in enlargement of the remaining (nonmitotic) cells and bulging of the endothelial membrane.[89] The amount of retinal damage (e.g., solar retinitis, arc welders' maculopathy) depends on the wavelength, power, and duration of exposure. The human lens contains a group of chromophores that absorb radiation near the UV range; these cells increase in number with age. At wavelengths >290 nm, tryptophan residues are the major chromophores; oxidative damage to the components of the lens accounts for the initiation of cataracts.[90]

Immune System

UV radiation-induced immunosuppression is a complex process involving multiple pathways, mediators, and T/B cell types.[91] Although UV radiation is a potent inflammatory agent that activates macrophages, neutrophils, and T-lymphocytes, it also causes immunosuppression by downregulating cell-mediated immunity in the mouse model.[92] Langerhans cells are mobile, dendritic, antigen-presenting cells present in all stratified epithelium. These cells originate from CD34+ (cluster of differentiation 34 positive) T cells that process exogenous antigens deposited on the skin and present these antigens to T cells; these cells may also activate mast cells in the epidermis and regulatory cells (e.g., natural killer T cells) in the draining lymph nodes. Suppression of immune responses probably results from UV radiation-induced release of soluble mediators and cytokines (IL-4, IL-10) that alter the presentation of antigen by Langerhans and other cutaneous dendritic cells. The resultant reduction in T-helper-1 cell activity increases susceptibility to infection.

Certain patients respond to solar radiation by developing photodermatological disorders. Photosensitivity disorders occur from the spectral activation of certain chemicals by UV radiation (phototoxicity) and the direct activation of the immune system (photoallergy). The presence of dense perivascular round-cell infiltrates distinguishes photoallergic reactions from phototoxic reactions. Photoimmunological diseases include polymorphous light eruptions, chronic actinic dermatitis, and cutaneous lupus erythematosus. The former displays many histological features of a delayed-type hypersensitivity reaction. Within a few hours after exposure of patients with polymorphous light eruptions to solar radiation, CD4+ T cells begin infiltrating the area of the skin exposed to UV radiation followed in the next few days by CD8+ T cells. UVA and, less commonly, UVB radiation (rarely UVC) are most commonly associated with this disease.[93] A variety of other molecules facilitate the migration of T cells to the UV radiation-exposed skin including intercellular adhesion molecule-1, vascular cell adhesion molecule 1, and adhesion molecules E-selectin (CD62).[94] These patients are more resistant to the immunosuppressive effects of UV radiation than patients without this disease. Patients with chronic actinic dermatitis are highly photosensitive; UVB radiation causes a subacute to chronic inflammatory process in sun-exposed areas; the lesion may progress to the skin without sun exposure. UVA radiation and visible light also may cause this disease. The pathophysiology of this disease is not well described.

Carcinogenesis

Skin cancers associated with solar radiation include basal cell carcinoma, squamous cell carcinoma, and melanoma. UV radiation is a complete carcinogen causing direct damage to genes that regulate growth/proliferation (e.g., *RAS*-family proto-oncogenes, *MAPK*-family,) and/or tumor suppression (e.g., *TP53*, *PTCH*-family). UVB is the most effective portion of the solar spectrum to cause DNA damage, including the formation of cyclobutane pyrimidine dimers between adjacent thymine or cytosine residues and pyrimidine (6-4) pyrimidone photoproducts among adjacent pyrimidine residues.[95,96] Animal and experimental studies suggest peak carcinogenic effects of UV radiation for squamous cell carcinoma occur at 293 and 305 nm, with smaller secondary peaks at 354 and 380 nm.[97,98] The maximal wavelengths for basal cell carcinoma and DNA damage are also primarily in the 302–306 nm range. There are insufficient data above 390 nm to determine the contribution of visible and infrared radiation; however, current evidence suggests that the effect is relatively small compared with UVB radiation below 320 nm.[64]

Chronic, excessive UV radiation exposure causes disruption of cellular control mechanisms and oxidative damage to DNA, resulting in skin inflammation, immunosuppression, photoaging, and carcinogenesis. UV radiation-induced effects enhancing the development of skin cancer include the formation of reactive oxygen species, reactive nitrogen species, and immunosuppression. The former two types of reactive oxidative species produce DNA damage (e.g., single-stranded breaks, DNA-protein crosslinks, altered DNA bases); guanine bases are particularly susceptible to oxidative conversion to 8-hydroxyguanine

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forming 7,8-dihydro-8-oxoguanine. UVA radiation is more effective than UVB in producing the latter reaction,[99] particularly the 360–380 nm portion, as a result of increased susceptibility of basal keratinocytes to UVA-induced mutations.[100]

DNA damage from UV radiation-induced immunosuppressive effects involves modification of the antigen-presenting function of cutaneous dendritic cells (i.e., Langerhans cells, dermal dendritic cells, macrophages/monocytes), generation of effector T cells, and stimulation of epidermal keratinocytes to produce immunosuppressive cytokines.[93] Immunosuppressed renal transplant patients have a 10-fold increased risk of basal cell carcinomas, whereas the risk of cutaneous squamous cell carcinomas in these patients is 65–250-fold.[101] Activation of T cells requires antigen-presenting cells (i.e., cutaneous dendritic cells including Langerhans cells). Alteration of these antigen-presenting cells by UV radiation promotes effector T cell production by stimulating interleukin 12 (IL-12). UV radiation does not affect the *number* of regulatory (suppressor) T cells. The net result is a suppressed immune response.[102] Reprogramming of regulatory T cells produced following UV radiation also suppresses skin immunity by increasing the immunosuppressive cytokine IL-10 (CD4+, CD25+, CTLA4+, FoxP3+), tumor necrosis factor, PGE2 (prostaglandin E2), and Th2 cytokine IL-4 (Natural Killer/T cell-induced interleukin-4). The latter suppresses anti-tumor immunity.[103]

A variety of other soluble mediators produced following UV radiation contribute to immunosuppression and DNA damage, including α-melanocyte-stimulating hormone, neuropeptides (e.g., calcitonin gene related peptide), serotonin, platelet activating factor, and *cis*-urocanic acid. The latter three mediators produce immunosuppression by inhibiting DNA repair processes, including direct repair, base excision repair, double-strand break repair, mismatched base repair, and nucleotide excision repair.[104] UV radiation upregulates the p53 protein that blocks cell replication prior to DNA repair process. Typically, functional cellular repair systems eliminate the UV-induced DNA damage with ~50% of the cyclobutane pyrimidine dimers repaired within the first day.[105] Severe damage activates the apoptotic pathways that eliminate the damaged cell. UV radiation also generates reactive oxygen and nitrogen species capable of inducing oxidation, including molecules listed in Table 46.5. In the skin, UVA radiation appears more efficient than UVB in inducing oxidatively generated damage to DNA bases and 2-deoxyribose moieties.[106]

TABLE 46.5. UV radiation-induced reactive oxygen and nitrogen species in skin receiving solar radiation.

Reactive Oxygen Species (ROS)	Reactive Nitrogen Species (RNS)
Hydroxyl radical (·OH)	Nitric oxide (NO)
Superoxide radical ($\cdot O_2^-$)	Nitrogen dioxide (NO_2)
Singlet oxygen ($^1O_2$, O=O)	Peroxynitrite anion ($OONO^-$)
Hydrogen peroxide (H_2O_2)	
Ozone (O_3)	

CLINICAL RESPONSE

Skin

Sunburn/Tanning

Following exposure to UV radiation, a biphasic pattern of tanning begins. Immediate pigment darkening results from the UVA-induced photooxidation of preformed melanin. This process results from the oxidation of preexisting melanin and redistribution of melanosomes from perinuclear to peripheral dendritic locations in melanocytes rather than synthesis of new melanin. Immediate pigment darkening is minimally photo-protective; this response fades within several hours with delayed pigment darkening beginning within 3 days and peaking 7–10 days after exposure. Table 46.6 outlines the six skin types based on the self-reported history of sunburn and suntan.[107]

Photosensitivity

Photosensitivity disorders occur because of the spectral activation of certain chemicals by UV radiation (phototoxicity) and the direct activation of the immune system (photoallergy). Agents that produce phototoxic reactions include drugs (sulfonamides, thiazides, nonsteroidal anti-inflammatory drugs, tetracycline), topical agents (benzocaine), and plant constituents. Psoralens (i.e., the parent compound of furocoumarin compounds) are a major group of chromophores in plant phototoxicity; exposure to citrus (limes, lemons, oranges), pine wood, perfumes, parsley, carrots, parsnips, figs,[108] or celery can cause a phototoxic reaction,[108,109] particularly when these compounds are consumed immediately prior (e.g., 1 hour) to UVA radiation exposure from commercial tanning booths.[110] The appearance of photoallergic reactions includes erythema, vesiculation, and urticaria; these lesions may resemble type IV hypersensitivity reactions, chemical burns, and atopic dermatitis.[111] Often, a transient pruritus precedes the rash.

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TABLE 46.6. Six types of skin responses to solar radiation. The Fitzpatrick classification divides these skin types by scoring genetic predisposition, reaction to sun exposure, and tanning from 0–4. (Adapted from Council on Scientific Affairs).[53]

Skin Type (Sun Sensitivity)	Sunburn History	Appearance	Tanning
I (Very sensitive)	Always burns easily	Red hair with freckles	Never
II (Moderately sensitive)	Always burns easily	Fair-skinned and fair-haired Caucasians	Minimal, light
III (Moderately insensitive)	Burns moderately	Darker Caucasians	Medium[a]
IV (Insensitive)	Burns minimally	Mediterranean type: Caucasians, some Hispanics	Dark[b]
V (Insensitive)	Rarely burn	Some Hispanics/blacks	Naturally brown[c]
VI (Insensitive)	Never burn	Darker blacks	Naturally black[d]

[a] Gradually tans light brown uniformly. [b] Always tans moderate brown. [c] Tans dark brown profusely. [d] Deeply black pigmented.

Polymorphous light eruption is the most common type of idiopathic photosensitive reaction; this condition affects 14–28% of the young adult female population in Europe. In other parts of the world, the prevalence of this disease varies from 1–21%.[112,113] Typically, this pruritic, papular, erythematous rash develops in sun-exposed areas of the skin in the late spring or early summer, beginning in patients during the second or third decade of life. This condition results from exposure to UVA radiation; therefore, sunscreens may not protect the skin of these patients.[114] Patients with chronic actinic dermatitis develop an exquisite photosensitivity beginning in sun-exposed areas; the skin lesion may become chronic and progress to skin without direct sun exposure.

Photoaging

Chronic sun exposure produces dose-dependent skin changes ranging from solar lentigines, spotty pigmentation, wrinkles, dry skin, alteration in texture (rough, leathery, furrowed, poor elasticity) of the outermost skin layers, telangiectasia, and benign/malignant skin cancer depending on skin type.[115] In light skin types, the 3–5-fold thickening of the stratum corneum within 1–7 weeks of several UVB exposures provides protection from excessive sun exposure in addition to tanning; however, the affected skin returns to normal thickness 1–2 months after sun exposure ceases.[46] In studies of Japanese subjects, the first signs of photoaging are solar lentigines that may occur as early as 20 years of age.[62] Fine wrinkles may appear after 30 years of age with seborrheic keratoses, and benign skin tumors begin appearing after 35 years of age. In contrast to deep furrows and leathery appearance of photoaging, fine lines and modest skin laxity are associated with the skin changes of chronological aging.

Eye

Keratoconjunctivitis (Welder's Flash)

Excessive short-wave UV radiation (<300 nm; maximum sensitivity, 270 nm) produces conjunctivitis, erythema of periocular skin, photophobia, lacrimation, and blepharospasm depending on the dose. The foreign body sensation, light sensitivity, and pain typically develop within 6–12 hours, with resolution within 48 hours as re-epithelialization of corneal surface occurs. Permanent ocular injury from keratoconjunctivitis is unusual.

Anterior Segment

An acute keratoconjunctivitis (photokeratitis) is a common adverse effect of arc welding.[116] Photophobia, a gritty feeling, and tearing typically develop several hours after exposure, depending on the radiation intensity. Although slight improvement in vision may occur initially as a result of the shedding of epithelial cells, vision deteriorates as stromal edema develops along with swelling (chemosis) and conjunctival injection. Symptoms usually resolve within several days because of the rapid regeneration of corneal epithelium. Pterygium, pinguecula, and chronic visual disturbances (photophobia, chronic blepharoconjunctivitis, climatic droplet keratopathy) may result from continuous, excessive exposure to solar UV radiation.[117] However, a study of 77 journeymen welders did not demonstrate an increased incidence of visual abnormalities or alteration of the anterior segment of the eye.[118] Although phototoxic compounds (e.g., psoralens) may reach the avascular cornea via tears, air, or aqueous humor, the cornea is much less sensitive to phototoxic agents than the skin.

The development of cataracts is multifactorial including age, diabetes, nutrition, obesity, cigarette smoking, genetics, alcohol, steroids, and brown irises.[119,120] UV

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radiation is a potential risk factor for the development of cataracts based on studies associating an increased incidence of cataracts with high UV radiation levels,[121,122] latitude,[123] and sunny locations;[124] however, UVB exposure alone does not account for the development of cataracts with age. A study of 2,520 65–84-year-old community-dwellers in the United States revealed a modest (13%) attributable risk for cortical opacity in patients with high UVB exposure.[125] In the cross-sectional Beaver Dam study of 2,646 women and 2,082 men, average annual ambient UVB exposure as measured by questionnaires was associated with cortical opacities in men (OR = 1.36; 95% CI: 1.02–1.79), when comparing men above and below the average sun exposure in Wisconsin.[126] The odds ratio in women for the two sun exposures was not significant (OR = 0.94, 95% CI: 0.70–1.26). Although the human cornea filters out all UVC (100–280 nm) and some UVB light (280–295 nm), the transmission characteristics change with age.[127]

Currently, there is sufficient evidence in animals to link cortical and posterior subcapsular cataracts to chronic exposure to UVB, but the evidence for causation in humans is limited.[8] Consequently, insufficient evidence is available to determine the number of cataracts attributable to UV radiation or separate the contribution of UV radiation from other causative factors in the formation of cataracts. A study of 838 watermen demonstrated a positive association between UVB radiation and the development of cortical cataracts, but there was no correlation between UVB or UVA radiation and nuclear or posterior subcapsular cataracts.[128]

Posterior Segment

The absorption of UV radiation in the anterior segment of the eye usually limits the effects of UV radiation on the retina unless the lens is absent. Retinal damage is more likely near the UVA range of ~235–441 nm.[129] Virtually no UV radiation reaches the retina in people over 25 years of age, whereas UV transmission is ~75% in people under 10 years of age.[130] Measurement of cone sensitivity in patients who had undergone bilateral cataract extraction demonstrated a 1.7 times reduction in cone sensitivity after 5 years.[131] The cross-sectional Beaver Dam study did not detect an association between posterior cataracts or nuclear sclerosis and UVB exposure in men or women.[126]

Immune System

Animal studies suggest UVB radiation alters antigen processing during the development of contact hypersensitivity in addition to initiating damage to DNA in the nucleus of replicating cutaneous cells. Both UVA and UVB radiation impair the function of Langerhans cells.[132]

Some chemicals can sensitize the skin to UV radiation, particularly the UVA portion. The photosensitization reaction is proportional to the magnitude of the UV exposure. Photosensitizers include bacteriostatic soaps, cosmetics, sunscreens, antiseptics, plants, anthraquinone dyes, antimicrobials, and furocoumarins.

Reproductive Abnormalities

There are few data to indicate UV exposure causes reproductive abnormalities. A study of pregnancy outcomes following exposure to methoxsalen photochemotherapy (PUVA) did not indicate that PUVA was a potent teratogen.[133] In a study of 504 infants born to women after PUVA treatment and 689 infants born after treatment, no increased incidence of infant mortality or congenital malformations occurred.[134]

Carcinogenesis

The International Agency for Research on Cancer (IARC) and the US National Toxicology Program list solar radiation and broad-spectrum UV radiation (UVC, UVB, UVA) as known human carcinogens (cutaneous malignant melanoma; skin squamous cell carcinoma; skin basal cell carcinoma; lip cancer; conjunctival squamous cell carcinoma; choroid and ciliary body melanoma) based on sufficient evidence in epidemiology studies and animal models. Additionally, the IARC lists the use of welding (ocular melanoma) and UV-emitting tanning devices (choroid and ciliary body melanoma, skin squamous cell carcinoma) as carcinogenic in humans.[14] Solar and artificial UV exposure are the predominant environmental risks with host pigmentation (i.e., skin type) and sun sensitivity as major modifying factors. Cutaneous malignant melanoma and basal cell cancer correlate to measures of intense, intermittent sun exposure (i.e., sunburn) rather than cumulative UV radiation doses, particularly when the intermittent exposures occurred in childhood or adolescence.[135] In contrast, squamous cell carcinoma and lip cancer more closely correlate to cumulative exposure than intense, intermittent sun exposure. Associations between sun exposure and other cancers (e.g., non-Hodgkin lymphoma, breast, prostate, colon) are weak.

A prospective study using multivariate-adjusted Cox proportional hazards models and erythemal UV radiation doses for July based on satellite measurements

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from the NASA Total Ozone Mapping Spectrometer suggested an increased risk of death among elderly non-Hispanic US whites for cancer (men), cardiovascular disease, respiratory disease, and stroke (women).[136] The hazard ratio for the highest vs. lowest quartiles for cancer deaths was 1.06 (95% CI: 1.02–1.11). Several issues limit conclusions regarding the effect of UVA and UVB on disease rates including the effect of ozone on UV radiation (UVB≫UVA), the association of nonmelanoma skin cancers (i.e., primarily basal cell carcinoma) with UVA radiation, and the use of obesity data at the beginning of the study 12–14 years earlier.

Keratinocyte Skin Cancer

In Caucasian populations, UVB radiation is a causal factor in the development of basal and squamous cell carcinomas of the skin in most epidemiological studies, as measured by recalled episodes of acute, sun-related skin damage (multiple sunburns) and clinical signs of accumulated, sun-induced skin damage (actinic keratoses, photoaging, squamous cell carcinoma).[137] Squamous cell carcinoma has a more direct relationship to cumulative (or occupational) sun exposure in cohort studies.[14,138] In a meta-analysis of squamous cell cancer, the relative risk in outdoor workers was 1.8 (95% CI: 1.4–2.2) compared with indoor workers after adjustment for squamous cell carcinoma risk factors.[139] Basal cell carcinoma is more closely associated in a dose-related response with intense, intermittent sun exposure (i.e., sunburn) and signs of photoaging (actinic keratoses),[140] particularly recreational UV radiation exposure in youth.[141] The highest incidence (1,372 cases/100,000 population in men) of nonmelanoma skin cancer occurs in Queensland, Australia.[142]

Basal cell carcinoma is the most common skin cancer in US Caucasians of 40–79 years of age with an incidence rate four times higher than squamous cell carcinoma of the skin.[143] In a population-based Australian study of 2,374 participants with 5,150 keratinocyte cancers, most basal cell carcinomas were on the head/neck (40.2%) and trunk (33.4%), whereas 33.4% of squamous cell carcinomas were on the head/neck and 34.9% on the upper limbs.[144] The squamous/basal cell carcinoma ratio on the hand was 14:1. The higher incidence of basal cell carcinomas in less-sun exposed areas suggests the association of this keratinocyte skin cancer is more complex than that of squamous cell carcinomas.

Occupational studies of light-skinned outdoor workers suggest an increased risk of basal cell carcinomas in sun-exposed areas of the skin compared with indoor workers.[145] In a meta-analysis of 19 case-control and 4 cohort studies published before 2012 on occupational UV exposure and the incidence of basal cell carcinoma, the pooled OR comparing outdoor and indoor work was 1.43 (95% CI: 1.23–1.66, $P = 0.0001$).[146] The OR for the 19 case-control studies was 1.43 with a 95% CI of 1.19–1.72 ($P = 0.0001$), whereas the OR for the four cohort studies was 1.48 with a 95% CI of 0.83–2.66 ($P = 0.19$). Sources of heterogeneity were latitude, age, sex, and recreational UV sun exposure. Basal cell carcinoma is extremely uncommon in black skin. UVB radiation is both an effective inducer and promoter of skin cancer in rodents.[147]

The oncogenicity of UVA remains unclear. Animal studies suggest that UVA radiation possesses tumor-promoting effects as well as cocarcinogenic effects with UVB radiation.[148] A study of 4,799 Swedish patients treated with UVA radiation (PUVA) and psoralen for skin disorders demonstrated a dose-dependent increase in the incidence of squamous cell cancer of the skin.[149] Although the number of squamous cell cancers was small during the average follow-up of 7 years, the relative risk for the development of squamous cell cancer at doses of UVA radiation exceeding 1,200 J/cm^2 was high. The relative risks of highly exposed men and women were 27.2 (95% CI: 11.3–53.6, $n = 225$) and 13.2 (95% CI: 0.3–73.3, $n = 180$), respectively. Epidemiology data on the risk of nonmelanoma skin cancer and sunbed use are limited; most,[150] but not all,[151] existing data suggest little increased risk of nonmelanoma cancers following sunbed use.

Melanoma

The incidence of melanoma tripled from 1950–1990 in the United States,[152] increasing annually by 2.8% since 1981 in all histological subtypes and thicknesses, with some flattening the curve in recent years. The lifetime risk of developing an invasive melanoma in the US population is 1/56 for Caucasian women and 1/38 for Caucasian men.[153] Although the prevalence of cutaneous malignant melanoma is higher in Caucasian men, the recent annual increase in CMM incidence in Caucasian women of <44 years of age was 6.1%.[154] Worldwide, the incidence of cutaneous malignant melanoma is highest in Australia, followed by the United States and parts of Europe. The relationship between UV radiation and cutaneous malignant melanoma (CMM) is more complex than that between nonmelanoma skin cancers, including a less direct relationship between incidence rates and latitude with the development of CMM in areas of the body exposed to limited sun.[155] The latter may represent alternate pathways for the development of cutaneous malignant melanoma with different environmental and genetic risk factors.[156] Melanomas of

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the head and neck are associated with actinic keratoses (i.e., sun damage), whereas melanomas on the trunk are associated with nevi rather than sun exposure.

Histological Subtypes

The most common type of melanoma is superficial spreading melanoma (~70%) followed by nodular melanoma (~20%). Lentigo maligna accounts for ~5–10% of the melanomas, and this subtype usually develops on the face of elderly patients. Acral lentigines melanoma is the rarest type of melanoma, occurring primarily in the palms, soles, nail beds, and mucous membranes. A meta-analysis of 24 observational studies of risk factors for cutaneous malignant melanoma subtypes suggests different risk factors for CMM subtypes on sun-exposed and intermittently sun-exposed body sites.[157] Lentigo maligna melanoma subtype occurs in older patients with a history of solar damage including nonmelanoma skin cancer, whereas superficial spreading melanoma and nodular melanoma histological subtypes occur more often in intermittently sun-exposed areas without sun-induced skin damage. Except for lentigo maligna, the location of melanomas does not match the areas of greatest sun exposure.

UV Exposure

In contrast to nonmelanoma skin cancer, the risk of cutaneous malignant melanoma in Caucasians increases less with long-term chronic UV exposure (e.g., outdoor occupation) than acute, intermittent, high-dose UV exposure (e.g., sunburn), particularly when UV exposure occurs during childhood.[158,159,160] In a systematic review of 23 case-control studies on the incidence of cutaneous malignant melanoma and intermittent, occupational, and total sun exposure, summary estimate of the odds ratio for intermittent sun exposure and CMM was 1.71 (95% CI: 1.54–1.90).[161] Sixteen of these studies demonstrated statistically significant associations; however, there was significant heterogeneity. Excluding three studies with outlying odds ratios, the overall OR was 1.87 (95% CI: 1.67–2.09). The overall OR for occupational sun exposure and cutaneous malignant melanoma was not increased (OR = 0.86; 95% CI: 0.77–0.96), whereas the OR for total sun exposure was marginal (OR = 1.18; 95% CI: 1.02–1.38; $n = 11$ studies) with substantial heterogeneity. Excluding three outlying odds ratios, the overall OR was 1.20 (95% CI: 1.00–1.44). Potentially, the prevalence of indoor workplaces in Western countries may limit the range of cumulative sun exposures in these studies.

Presentation

Clinical characteristics of a skin lesion suggesting melanoma include asymmetrical shape, irregular and well-defined border, multiple shades and colors, large diameter (>5 mm), and a raised lesion. In contrast to nonmelanoma skin cancer, CMM typically spares the face, hands, and forearms.[162] The EUROCARE study demonstrated summer peaks in melanoma incidence in Caucasian women (OR = 1.38, 95% CI: 1.31–1.44) and men (OR = 1.21, 95% CI: 1.14–1.29) from Western countries but not Central European countries.[163] The odds ratios for seasonal variability were higher for upper (1.44, 95% CI: 1.32–1.58) and lower limbs (1.46, 95% CI: 1.38–1.56) than head/neck (1.09, 95% CI: 0.99–1.20) or trunk (1.20, 95% CI: 1.12–1.29) regions. Although the lack of increased ascertainment on typically unexposed sites (e.g., trunk) suggests a pathological effect (e.g., late promotion effect), the confounding of greater skin exposure and increased observations of skin cancer limits conclusions regarding this association. Many melanomas appear in preexisting nevi.[164]

Risk Factors

Cutaneous malignant melanoma is a multifactorial disease with factors other than sun exposure contributing to the development of melanomas. Risk factors associated with melanoma beside solar radiation and sunbed use include Caucasian race; total acquired melanocytic (dysplastic) nevi; gender (men > women); family history of melanoma; familial atypical multiple mole melanoma (FAMMM) syndrome (cyclin-dependent kinase inhibitor 2A, cyclin-dependent kinase 4 mutations); and skin phenotype including expression of polymorphic melanocortin 1 receptor (*MC1R*) gene that determines pigment.[153] Most patients with CMM have fair skin, brown or blonde hair, blue or green eyes, and a propensity to develop sunburn following intense sun exposure.

Recent data suggest the use of sunlamps/sunbeds increases the risk of CMM (and nonmelanoma skin cancer), particularly in adolescents and frequent users of <35 years of age;[165] however, many of the studies have limited statistical power resulting from the small numbers of participants. In a meta-analysis of nine case-control and 1 cohort studies comparing "ever" and "never" use of sunlamps, the summary odds ratio was 1.25 (95% CI: 1.05–1.49) with significant heterogeneity.[166] Compared with never using sun lamps, the estimated risk of developing CMM increased with "first exposure as a young adult" (summary OR = 1.69; 95% CI: 1.32–2.18, $n = 5$ studies) and "longest duration or highest frequency of exposure" (summary OR = 1.61; 95% CI: 1.21–2.12; $n = 6$ studies). The latter studies had no significant heterogeneity. In a meta-analysis of 27 observational studies published before 2013, the summary relative risk of cutaneous malignant melanoma

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comparing "ever" use with "never" use was 1.20 (95% CI: 1.08–1.34). Restricting sun lamp use to adults and children <35 years of age increased the RR to 1.87 (95% CI: 1.41–2.48, $n = 13$ studies).[167] The dose-response was marginally significant with each use of a sunbed during the year, increasing CMM risk by 1.8% (95% CI: 0–3.8%).

Lip Cancer

Cancer of the lip is a very rare cancer that is strongly associated with tobacco use; the incidence of this cancer is declining with the reduction in smoking prevalence. Descriptive studies suggest an association between lip cancer and cumulative sun exposure. This cancer is more common in males than females. The incidence rate is also higher in light-skinned populations than in dark-skinned populations living in the same geographic area.[168] In a study of 2,341 cases of lip cancer identified in the nationwide Danish Cancer Registry, the odds ratio for lip cancer in relation to outdoor work after adjusting for covariates was 1.67 (95% CI: 1.38–2.03) as estimated by conditional logistic regression models.[169] In a Spanish case-control study of 105 males (aged 20–70 years) with squamous cell carcinoma of the lip, multiple logistic regression analysis demonstrated increased lip cancer risk associated with lifetime cumulative tobacco and alcohol consumption but not estimates of cumulative sun exposure during leisure time or holidays.[170] Although lip cancer was associated with sun exposure early in life and cumulative sun exposure during outdoor work (OR = 11.9; 95% CI: 1.3–108.9), the wide confidence limits and lack of a dose-response limit conclusions about causality.

DIAGNOSTIC TESTING

Analytical methods for quantitating UV radiation include chemical detectors (passive dosimeters) and physical detectors (broadband radiometers) with filters to select specific wavelengths. The former technique involves direct measurement of irradiance using actinometric solutions, photographic emulsions, and UV-sensitive plastic films. The latter detectors use photoelectric (detection of photons) and radiometric (detection of heat) devices to measure the solar spectrum and Equation 46.1 to calculate the biologically effective UV dose. Experimental studies suggest the erythema irradiance may vary by <20% with broadband radiometers and by <40% for passive dosimeters when compared with calculations using a spectroradiometer.[19] Photoelectric devices provide immediate feedback on current UV exposure, whereas passive film dosimeters sum the UV dose over a specific time period and require laboratory analysis. Currently, multifrequency imaging detectors on meteorological satellites measure solar UV radiation on the earth.

Extrinsic biological dosimeters are well suited for measuring exposure to UV radiation and the biological implications of environmental exposure including skiing, hiking, and sun tanning.[171] These dosimeters calculate the biological effectiveness of the different UV wavelengths in the sun exposure along with any interactions. The complexity of these dosimeters depends on the measured biological effect (e.g., photochemical changes, provitamin D_3, uracil thin layers, DNA, T7 bacteriophages, *E. coli* and *Bacillus subtilis* bacteria).[172] The values from these dosimeters represent relative biological responses at different wavelengths rather than absolute dimensions of a biological effect; consequently, the results of dosimeters measuring two different biological processes may be related but are not necessarily numerically comparable. A UVB DNA-dosimeter using mini-dots of purified and dried bacteriophage λ on UV transparent biofilm measures photo-induced DNA damage from the blockage of DNA synthesis during a polymerase chain reaction.[173] The reduction of amplified products in the UVB-exposed DNA compared with control DNA indirectly reflects DNA damage. Other dosimeters include spore dosimeters (e.g., *B. subtilis* mutant strain), mammalian cell dosimeters (e.g., quantitative polymerase chain reaction of human genomic DA fragments), and vitamin D dosimeters (e.g., photosynthesis of previtamin D).[174]

HEALTH SURVEILLANCE

Environmental Monitoring

Guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) and the International Commission on Nonionizing Radiation Protection (ICNIRP) publish similar guidelines for human exposure based on an envelope action spectrum involving cutaneous and ocular effects. The guidelines for the eye are generally considered ceiling values that apply under worst-case conditions of normal incidence; however, the skin guidelines typically are desirable goals that depend on skin type because the risk of adverse effects differs between Celtic and more heavily pigmented skin types.[46] The ACGIH recommends threshold limit values for persons exposed to broadband UV radiation (excluding lasers), provided these individuals are not photosensitive and have intact

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TABLE 46.7. International Commission on Nonionizing Radiation Protection (ICNIRP) guidelines on occupational UV exposure for monochromatic sources with spectral weighting function, $S(\lambda)$. Durations >1 second are limited to dose rate of 1 W/cm^2 to preclude thermal effects. The actual wavelength should be interpolated if it is not represented in the table. The ICNIRP updated their guidelines for laser exposures in 2013 (https://www.icnirp.org/) including spot size dependence, pulse duration dependence for short pulses, and wavelength dependence between 1,200 and 1,400 nm in retinal thermal exposure limits.

Wavelength (nm)	Exposure Limit (mJ/cm^2)[a]	Relative Spectral Effectiveness $S(\lambda)$[c]
180	250	0.012
190	160	0.019
200	100	0.030
205	59	0.051
210	40	0.075
215	32	0.095
220	25	0.120
225	20	0.150
230	16	0.190
235	13	0.240
245	8.3	0.360
250	7	0.43
254[b]	6	0.500
255	5.8	0.520
260	4.6	0.650
265	3.7	0.810
270	3.0	1.000
275	3.1	0.960
280[b]	3.4	0.880
285	3.9	0.770
290	4.7	0.640
295	5.6	0.540
297	6.5	0.460
300	10	0.300
303[b]	25	0.120
305	50	0.060
308	120	0.026
310	200	0.015
313[b]	500	0.006
315	1,000	0.003
316	1,300	0.0024
317	1,500	0.0020
318	1,900	0.0016
319	2,000	0.0012
320	2,900	0.0010
322	4,500	0.00067
323	5,600	0.00054
325	6,000	0.00050
328	6,800	0.00044
330	7,300	0.00041
333	8,100	0.00037
335	8,800	0.00034
340	11,000	0.00028
345	13,000	0.00024
350	15,000	0.00020
355	19,000	0.00016
360	23,000	0.00013
365[b]	27,000	0.00011
370	32,000	0.000093
375	39,000	0.000077
380	47,000	0.000064
385	57,000	0.000053
390	68,000	0.000044
395	83,000	0.000036
400	100,000	0.000030

[a] 1 mJ/cm^2 = 10 J/m^2. [b] Emission lines of a mercury discharge spectrum. [c] Unitless.

lenses. These exposures include carbon and welding arcs, fluorescent/incandescent/germicidal lamps, gas/vapor discharges, and solar radiation. These recommendations are designed to prevent adverse health effects (e.g., erythema, photokeratitis) in nearly all healthy, nonsensitized workers using relative spectral effectiveness calculated in Equation 46.1 with the values in Table 46.7. The use of UV radiometers with built-in spectral responses that mimic the relative spectral effectiveness values in Table 46.7 is a practical alternative to calculations.

Table 46.8 lists the ACGIH recommended duration of UV exposure based on the effective irradiance, E_{eff} (W/m^2 or mW/cm^2 for continuous exposure) by a weighting formula; recommendation for time-limited or pulsed exposures of the skin or eye use radiant energy, H_{eff} (J/m^2 or J/cm^2).[175] For daily UVA exposure of <17 minutes, the dose is limited to 1,000 mJ/cm^2, which is the maximum recommended exposure as the dose increases (and the recommended duration decreases). A variety of factors affect the risk of adverse effects (e.g., erythema), including skin type, eye color, familial melanoma history, latitude, time of day, hypersensitivity, degree of UVA exposure, sunscreens, and air pollution.

The International Commission on Nonionizing Radiation Protection (ICNIRP) guideline for maximum human biologically efficient radiant exposure of the skin is 3 mJ/cm^2 (i.e., 1.0–1.3 SED or ~0.5 MED for fair skin). For a germicidal lamp, the limit of 3 mJ/cm^2 is equivalent to 10 SED. These recommendations assume a normal 8-hour work shift and a 24-hour light/dark cycle that allows cellular repair after cessation of exposure. The ICNIRP also recommends limiting UV radiation (180–400 nm) for unprotected eyes to ≤3 mJ/cm^2 based on effective spectrally weighted factors.[176] The total (unweighted) ultraviolet radiant exposure for unprotected eyes in the spectral region

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TABLE 46.8. American Conference of Governmental Industrial Hygienists (ACGIH) recommended daily broadband UV exposure duration based on effective irradiance, E_{eff}. Guidelines and regulations change with time. The organization website (https://www.acgih.org/science/tlv-bei-guidelines/) should be consulted for any updates on specific restrictions and recommendations, particularly for guidelines on UV exposures related to a specific wavelength and for laser exposure guidelines.

Daily Duration	Effective Irradiance, E_{eff} (mW/cm^2)
8 hours	0.0001
4 hours	0.0002
2 hours	0.0004
1 hour	0.0008
30 minutes	0.0017
15 minutes	0.0033
10 minutes	0.005
5 minutes	0.01
1 minute	0.05
30 seconds	0.1
10 seconds	0.3
1 second	3.0
0.5 seconds	6.0
0.1 seconds	30.0

of 315–400 nm should not exceed 1,000 mJ/cm^2. Ocular exposure to UV radiation rarely exceeds ICNIRP guidelines, except in unusual circumstances (e.g., sunny days in snowy locations).[46]

For the most sensitive, healthy skin without protection, UV radiant exposure (180–400 nm) should not exceed 3 mJ/cm^2 effective dose spectrally weighted using the spectral weighting factors in Table 46.7. The exposure limits are less than a 5–10 minute UV exposure to skin for overhead, noonday, summer sunlight at 10°–40° latitude (2–4 times less than 1 MED). Pupillary constriction and squinting reduce outdoor UV exposure in bright, sunlit environments; however, some lamp sources (e.g., low-pressure mercury lamps) allow prolonged exposure because these UV sources emit little visible light. The American National Standards Institute (ANSI) produces technical standards for lamps and lamp systems based on the following four potential photobiological risk categories: 1) no hazard; 2) group 1, low risk; 3) group 2, moderate risk; and 4) group 3, high risk.[177]

Protection

Concern for sun exposure occurs in the tropics (30°N–30°S) all year round for individuals with white skin, whereas sun awareness is important in the temperate latitudes (40°–60°) in the 3 months before and after the summer solstice (i.e., April–September). Avoiding sun exposure around noontime in the spring–summer period and seeking shade when possible (e.g., breaks) helps reduce unnecessary UV radiation exposure, particularly for Celtic-type skin. The shadow rule (length of shadow < height) suggests the need for protective precautions to prevent excessive UV radiation exposure; this rule corresponds to a UV Index of ~4 resulting from a solar elevation angle and solar zenith angle of 45°. At this exposure level, unadapted, white-skinned individuals will develop sunburn after 2 hours of exposure. Protective measures include wide-brimmed hats, clothing (long-sleeve shirts, long trousers), umbrellas, wrap-around protective glasses, sunscreens, and shade structures; the value of clothing varies substantially depending on ambient temperature, safety requirements, culture, and occupation. Most clothing absorbs solar UV radiation relatively uniformly with protection factors ranging from >10 (summer clothing) to >10,000 (heavy denim coveralls).[46]

Engineering control measures (shade structures, trees, canopies, awnings, glass enclosures, shielding) are preferable to protective measures for some excessive UV exposures including artificial sources. In contrast to solar radiation, UV radiation from artificial sources is typically relatively uniform in quality (spectrum) and quantity (effective irradiance). The potential health risk from artificial sources depends on the distance/position of the worker in relation to the source, duration of exposure, and source spectrum/biologically effective UV radiation emissions; for the skin (but not the eye), skin type also affects the risk. Glass typically blocks UVB radiation, but the absorption of UVA radiation is variable. Most plastics (e.g., polymethylmethacrylate, polycarbonate) limit UV radiation to <370 nm, whereas some glass transmits radiation above 310 nm.

Sunscreens

Sunscreens are the most common method to reduce UV radiation exposure in recreational environments; however, clothing is usually preferable for skin protection in occupational settings. Sunscreens (i.e., SPF 15–30) are recommended for melanin-compromised (type I–II) skin when the UV Index is ≥3 and for melanin-competent skin when this value is ≥5.[46,178] Re-application may be necessary every 2 hours depending on the conditions. Sunscreens help prevent acute

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cutaneous burns as well as retard the development of skin cancer and photoaging of the skin. There are two main types of sunscreens: 1) physical (inorganic agents, primarily ZnO and TiO_2); and 2) chemical (organic). Inorganic sunscreens scatter, reflect, or absorb solar radiation depending on particle size. Reduction of particle size to the microparticle and nanoparticle range (<100 μm) significantly improves the desirability and transparency of these sunscreens without significantly increasing the systemic absorption of these compounds.[179,180] The addition of titanium dioxide nanoparticles to sunscreens increases the UVA protective factors to ~10; however, like all pigment-based sunscreens, the sunscreen is visible on the skin at the recommended dose of 2 μL/cm^2.[181]

Before 1990, most sunscreens blocked only UVB radiation; subsequently, broad-spectrum sunscreens were introduced to protect against UVB and UVA radiation. Organic sunscreens absorb UVB and/or UVA radiation, depending on the individual chemical; these sunscreens absorb energy from photons, emitting energy as heat or fluorescence. Most organic sunscreens absorb UVB radiation with a few effective in the UVA-2 range (320–340 nm); only avobenzone protects against UVA-1 (340–400 nm).[182] The main organic sunscreens include aminobenzoates (UVB), benzophenones (UVB/UVA), camphor derivatives (UVB/UVA), cinnamates (UVB), and salicylates (UVB).[183] Table 46.9 lists the approximate absorption spectrum of sunscreens available in the US market.

The SPF is the ratio of the minimum UV dose required to produce erythema in a sunscreen-protected patient to the minimum UV dose required to produce erythema in unprotected skin, as described in Equation 46.2.

$$\text{SPF} = \text{MED of sunscreen}-\text{protected skin} / \text{MED of unprotected skin} \quad \text{(Equation 46.2)}$$

where

MED = minimum erythemal dose.

The sun protection factor (SPF) refers to protection against UVB radiation and sunburn. Photosensitivity disorders (polymorphic light eruption, drug-induced photosensitivity) require protection against UVA radiation;[181] consequently, the SPF is not an indicator of UVA exposure or the ability of a sunscreen to prevent damage caused by UVA radiation (e.g., photoaging, photosensitivity reactions) unless specifically determined for a specific sunscreen. The actual effectiveness of a sunscreen also depends on the thickness of the

TABLE 46.9. Absorption spectrum of inorganic and organic sunscreens. The ranges are approximate as each type of sunscreen may not block the entire spectrum listed. (Adapted from Jou).[182]

Sunscreen Name	Sunscreen Type	UVB (290–320 nm)	UVA-2 (320–340 nm)	UVA-1 (340–400 nm)
Cinoxate	Organic	Yes	No	No
Ensulizole	Organic	Yes	No	No
Homosalate	Organic	Yes	No	No
Octinoxate	Organic	Yes	No	No
Octisalate	Organic	Yes	No	No
Octocrylene	Organic	Yes	No	No
Padimate O	Organic	Yes	No	No
PABA[a]	Organic	Yes	No	No
Trolamine	Organic	Yes	No	No
Dioxybenzone	Organic	Yes	Yes	No
Oxybenzone	Organic	Yes	Yes	No
Sulisobenzone	Organic	Yes	Yes	No
Ecamsule[b]	Organic	No	Yes	No
Meradimate[b]	Organic	No	Yes	No
Avobenzone[c]	Organic	No	No	Yes
Titanium	Inorganic	Yes	Yes	No
Zinc oxide	Inorganic	Yes	Yes	Yes

[a] Para-aminobenzoic acid. [b] Proprietary L'Oréal product. [c] Also contains octocrylene to improve photostability.

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application, duration of sun exposure, and substantivity (i.e., resistance to removal by sweat, water, and toweling). The recommended SPF for patients with type I and II (i.e., easily burned) is SPF 15–20, whereas patients tanning more easily may use a product with SPF ~10. Sunscreens above SPF >25–30 do not add protection from UVB because the solar radiation dose is not sufficient even at the equator to produce erythema during the day assuming the sunscreen is properly applied.[184] Sunscreens that contain zinc oxide or titanium dioxide pastes are more effective at blocking visible light than UV-absorbing sunscreens that contain oxybenzone or cinnamates. Measurement of UVA protection is complicated by the 1,000-fold less erythrogenic property of UVA than UVB; hence, the minimal persistent pigment darkening (PPD) at 2–24 hours is the recommended measure of UVA protection.[162] A sunscreen with a PPD of 10 provides adequate protection from UVA radiation.

Broad-spectrum sunscreens with an SPF factor ~15–20 should be applied uniformly on sun-exposed skin daily by individuals with type I or II skin; the effectiveness of the sunscreen depends on several preconditions.[53] These sunscreens should be used to reduce total UV radiation exposure rather than increase the time spent in the sun; under-applying the sunscreen reduces its efficacy. The SPF value assumes the application of the sunscreen to a thickness of 2 mg/cm^2. Generous amounts of sunscreen should be applied 15–30 minutes prior to sun exposure to allow time for the chemicals to bind to the stratum corneum.[185] Re-application of sunscreen is necessary after swimming, contact with clothes, toweling, or heavy sweating. Children should be protected with sunscreen and develop the habit of using sunscreen early.

Although potential adverse effects include allergic contact dermatitis (e.g., methoxycinnamate, oxybenzone), irritant contact dermatitis, photoallergic reactions (e.g., benzophenone-3, PABA), and phototoxic reactions, the incidence of these effects is probably relatively low.[186] UVB radiation is a potent stimulus for the activation of *Herpes simplex labialis*; sunscreens reduce the incidence of recurrent infections on sun-exposed skin;[187] however, not all *H. simplex labialis* lesions associated with UV radiation are responsive to acyclovir.[188]

Sun Protection

The use of a hat and protective clothing along with the avoidance of outdoor activities between 10 AM–2 PM reduces exposure to UV radiation. Reflective surfaces (e.g., white sand, concrete, ice, snow) substantially increase exposure to solar radiation. Additionally, the relative dose of UV radiation increases with altitude, proximity to the equator, and exposure to the midday sun. Window glass absorbs most UVB radiation; therefore, the driver's window should be kept closed during travel. Most sunglasses filter UVB radiation well, but the transmission of UVA radiation is much more variable.

Tanning is not sufficient protection from the sun because even the darkest tan on a Caucasian is only equivalent to an SPF of 4.[1] People with type I skin and those with solar keratoses or previous skin cancer should avoid the use of tanning devices. Individuals with well-tanning skin should limit their exposure to tanning machines to 30–50-minute sessions per year **or** less.[53] Current research into improving skin protection from solar radiation includes enhancement of skin pigmentation (synthetic melanins, L-tyrosine, thymidine dinucleotides), self-tanning agents (e.g., dihydroxyacetone), antioxidant enzymes, nonenzymatic antioxidants (e.g., vitamin supplementation), DNA repair enzymes (e.g., T4 endonuclease V, photolyases), and phytochemicals (e.g., plant secondary phenolic metabolites).[186]

Biological Monitoring

For research purposes, intrinsic biomarkers [e.g., cyclobutane pyrimidines, (6-4) pyrimidine-pyrimidone adducts, p53 mutations, matrix proteinases] and extrinsic biological dosimeters (i.e., measures of biological effective dose, H_{eff}, in $J_{\text{eff}}/\text{m}^2$) are available to monitor biological effects of UV radiation.[189]

Medical Surveillance

Medical surveillance is not usually recommended for workers exposed to UV radiation, in part because of the long latency periods for skin cancers and cataracts. Although the US Preventive Services Task Force found insufficient evidence to recommend skin examinations for the early detection of skin cancer in adults, high-risk individuals may benefit from these examinations. Periodic examinations may be appropriate for high-risk workers, including those exposed to other skin carcinogens (e.g., coal tar), with strong family or personal histories (e.g., multiple skin cancers, family history of melanoma), and solid-organ transplant recipients.[190] The skin and eye are the primary target organs for excessive UV radiation. Skin examination should focus on signs of excessive UV exposure, including spotty pigmentation, actinic keratoses, nevi, and evidence of photoaging (e.g., solar lentigines; wrinkles; dry, rough, leathery, furrowed, and/or poor elastic skin, telangiectasia).

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Signs of excessive ocular UV radiation include pterygiums, pingueculas, corneal opacities, and cataracts. The history should include recorded episodes of keratoconjuctivitis.

TREATMENT

Based on a mathematical model, the use of sunscreen with a sunscreen protection factor (SPF) of 15 during the first 18 years of life would reduce the incidence of basal and squamous cell carcinomas of the skin by 78%.[191] Methods to prevent sunburn include sun avoidance during peak UV radiation (e.g., 10 AM–4 PM or at least 11 AM–2 PM), wearing protective clothing (wide-brim hats, UV protective fabrics, well-shielding sunglasses with broad UV blocking properties), and the use of broad-spectrum sunscreens (UVA/UVB blocking properties). The most important aspect of treating sunburn is avoiding further sun exposure. Treatment of mild sunburn includes emollients, topical anesthetics, cool soaks with evaporative cooling (wet T-shirt and fan), topical steroids, and analgesics (aspirin, nonsteroidal anti-inflammatory).[1] Topical anesthetics with pramoxine hydrochloride produce less sensitizing effects than topical preparations with benzocaine. Emollients with small concentrations of menthol, camphor, or phenol may contribute to the soothing effect of these preparations. Aspirin or nonsteroidal anti-inflammatory medication should be taken early to blunt the effects of sunburn mediators. A short course of prednisone (60 mg daily tapered over 1 week) may reduce the clinical effects of severe sunburn. Cleansing and covering the area of blistering is similar to the treatment of partial thickness of thermal burns. Intact vesicles should not be drained. Topical tretinoin (vitamin A acid) promotes the formation of new collagen in UV-damaged and photo-aged skin.[192]

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Medical Toxicology of Occupational and Environmental Exposures

Volume 3

Carcinogens: Risk Factors, Pathophysiology, Susceptibility, and Clinical Abnormalities

DONALD G. BARCELOUX

Edited by Robert B. Palmer

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To Murali Janakiram, MD

Your friendship, wisdom, compassion, and medical expertise made the completion of this book possible.
Donald G. Barceloux, MD

To my parents, Robert L. Palmer, MD, and Linda J. (Addison) Palmer, RN; my wife, Karen E. Simone, PharmD; and my dear friend and colleague, Donald G. Barceloux, MD

You all taught me more than I could ever recount about cancer and the truly important things in life.
Rob

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FOREWORD

The multivolume *Medical Toxicology of Occupational and Environmental Exposures* covering metals, radiation, and cancer is the eagerly awaited third instalment in the seminal series of medical toxicology textbooks written by Dr. Donald Barceloux. The first two books focused on natural substances and drugs of abuse, respectively, and have quickly established themselves as reference works in their respective fields. The comprehensive coverage of topics coupled with a consistent and easy-to-follow organization of content have made them indispensable companions of physicians and researchers alike.

The newest volumes in the series, created by Dr. Barceloux and edited by Dr. Robert Palmer, is a worthy successor to the first two books. Once again, the focus is on naturally occurring and man-made toxic threats that all medical toxicologists will have heard of but few will have had first-hand experience with. This is precisely what makes this work so valuable. The first volume literally comprises an A–Z of all there is to know about the clinical toxicology of metals and metalloids, from aluminum to zirconium. Chapters on well-known toxic metals such as arsenic, lead, and mercury are almost textbooks in their own right covering their subjects in a breadth and depth rarely seen in other publications. But who would know where to look for information on the toxicokinetics of rare earths, or whether tellurium is a human teratogen?

There is an ongoing debate on whether radiation is a subject that toxicologists should concern themselves with, or whether it would best be left to physicists, radiologists, and oncologists. The second volume takes a pragmatic view: if it induces a toxic response, then it is of relevance to anyone involved in the prevention, diagnosis, and treatment of human exposures. Consequently, the chapters in the section on radiation provide a comprehensive summary on what is known about potential health effects of all forms of radiation, and what may be done to prevent them.

The final volume on cancer departs from the familiar substance-based approach of the rest of the book in that it starts from the point of view of the risk assessor, looking at the mechanism of chemical carcinogenesis and then providing an organ-centered overview. This is a useful approach since carcinogenicity is as much governed by the cascade of molecular events elicited by carcinogens as it is by human physiology, biokinetics, and organ response.

In contrast to standard textbooks on clinical toxicology, *Medical Toxicology of Occupational and Environmental Exposures* is not only aimed at those working in the treatment of the poisoned patient. As the most comprehensive source of information in its field, it will equally be an invaluable reference for occupational physicians and hygienists, those working in environmental health and indeed anyone concerned with the human health risk assessment of exposure to metals, radiation, and chemical carcinogens. It is a truly interdisciplinary work that will stand the test of time.

Professor Martin F. Wilks, MD, PhD, ERT, FRCP (Edin), FBTS, FEAPCCT

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PREFACE

This volume, *Cancer*, along with *Radiation* and *Metals and Metalloids* in the three-volume *Medical Toxicology of Occupational and Environmental Exposures* is a continuation of the *Medical Toxicology Series* that began with *Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals* and *Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants*. The *Medical Toxicology Series* provides in-depth, evidence-based coverage of the most important human toxins. Similar to the rest of the *Medical Toxicology Series*, the goal of this volume is the creation of a comprehensive and convenient reference to answer questions regarding the etiology and presentation of cancer by presenting the basic and clinical science associated with various organs.

The reader will recognize the similarities between the template in this volume and the templates in the first two books of the *Medical Toxicology* series. This organizational consistency allows easy location of the appropriate information necessary for decisions regarding the sources, effects, and regulation of occupational and environmental carcinogens. The focus on understanding the current basic science, clinical consequences, and etiology of cancer resulted in an adjustment of the standardized template by using an organ-based approach. The template in this volume emphasizes carcinogenesis (cancer pathophysiology, molecular biology, carcinogen categories), chemical carcinogenicity (chemical carcinogen classifications, risk assessment, evaluation of carcinogens, cancer surveillance), and individual tumor sites (carcinogenesis/genetics, risk factors, histology, host susceptibility, clinical features).

Medical toxicology is a field often dependent on relatively weak scientific evidence (case reports, case series, retrospective analyses), resulting in the increased risk of perpetuating equivocal statements and even folklore. This volume provides the relevant evidence necessary to understand the clinical consequences and safety measures important for the prevention of cancer in the workplace and the environment. References are documented to validate the information and provide sources for further inquiry. Although this unique volume presents a medical toxicologist's perspective on exposures to carcinogens, the coverage contains input from a variety of disciplines including other clinical specialties, public health physicians, and basic scientists.

The choice of topics in this volume reflects our desire to expand communication between medical toxicologists and related fields. Our hope remains that this interdisciplinary, evidence-based approach will increase communication between traditional clinical settings and fields aligned with medical toxicology including those in laboratories, academic settings, and regulatory agencies. We anticipate this approach will encourage more inquiry into the pathophysiology, clinical effects, biomarkers, and origins of cancer in this rapidly expanding field and will improve our efforts to decrease the incidence of cancer.

Robert B. Palmer, PhD, Editor
Donald G. Barceloux, MD, Author

March 17, 2026

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John Wiley & Sons' Staff

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Bob Esposito, former Senior Editor, made our *Medical Toxicology Series* a reality by believing in the importance of a highly detailed, structured series covering the expanding field of Medical Toxicology.

Michael Leventhal, Associate Editor, helped smooth the production process from submission to printing.

Summers Scholl, Executive Editor, whose contributions were essential to informing our medical audience of the key constituents of the *Medical Toxicology Series*.

Pomona Valley Hospital Medical Center

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UCLA Emergency Department Colleagues

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UCLA Librarians

Writing this book series was not possible without the support of the UCLA Biomedical Library, especially Juan Jaime, Access Services Manager, UCLA Science Libraries.

DONALD G. BARCELOUX, MD

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REVIEW PANEL

The critical reviews and clinical insights of the distinguished Review Panel were much appreciated as an invaluable method to validate the scientific basis of *Medical Toxicology of Occupational and Environmental Exposures: Cancer*.

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VOLUME 3

CARCINOGENS: RISK FACTORS, PATHOPHYSIOLOGY, SUSCEPTIBILITY, and CLINICAL ABNORMALITIES

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A

Carcinogenesis

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Chapter 47

CARCINOGENESIS

MOLECULAR BIOLOGY

HISTORY

Although the existence of chromosomal alterations in cells that contribute to tumor formation was hypothesized by Theodor Boveri in 1914,[1] the first chromosomal marker was not identified until 1960 when Nowell and Hungerford discovered the Philadelphia chromosome in the genomes of patients with chronic myelogenous leukemia.[2] Although hematological malignancies often have signature chromosomal abnormalities, most solid tumors display numerous clonal and nonclonal chromosomal changes. In the mid-1970s, Peter Nowell proposed a model of cancer as a sequential evolutionary process beginning with an initiating event that converts a normal cell into a potential cancer cell; then, a progressive accumulation of genetic changes endowing the cancer cells with selective growth and invasive properties to form cancer clones.[3] Before complete mapping of the human genome, oncovirus studies discovered several genes (e.g., *APC*, *KRAS*, *TP53*) with cancer-forming mutations. Avian sarcoma virus studies in the late 1970s identified the presence of the first normal cellular genes (proto-oncogenes) in the Rous sarcoma virus capable of transforming into altered versions (oncogenes) that induce sarcomas in chickens.[4] The importance of proto-oncogenes to the development of cancer became apparent in 1982 with the discovery of a point mutation as the transforming event causing the oncogenic activation of *H-RAS* in human bladder carcinoma cells. High-resolution chromosome banding techniques also revealed the other genetic alterations contributing to oncogene activation in human cancers, including gene amplification, rearrangement, and expression.[5] In 1987, the first tumor suppressor gene (retinoblastoma, *RB1*) was cloned; tumor suppressor gene inactivation resulted from a variety of genetic alterations producing gene silencing, including gene deletions, point mutations, and epigenetic alterations. Specific chromosomal locations were identified for 13 tumor suppressor genes by 1993.[6] These studies revealed over 100 oncogenes by 2002, with most of these oncogenes encoding protein tyrosine kinases that modulate signal transduction pathways involving cell division, which is important to the later development of chemotherapeutic agents.[7] During the pregenomic era (1960–2003), inefficient sequencing technologies and the enormous complexity of tumor genomes limited early attempts to identify and separate protein-encoding cancer genes (driver genes) from other genetic alterations (passenger genes) uninvolved with the cancer process. The discovery of cyclin-dependent kinases in 2001 was a very significant advance in the understanding of cell cycle regulation prior to the genomic era.[8]

The lack of a sequence-based map of the normal human genome impeded the identification of cancer genes involved with cancer and the cell cycle until the completion and publication of the Human Genome Project in 2003, which initiated the postgenomic era.[9] In 2004, the Wellcome Trust Sanger Institute established the Cancer Gene Census to catalog mutated

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human genes present in cancers at a higher frequency than predicted by chance.[10] The International Cancer Genome Consortium (http://www.icgc-argo.org) was formed in 2008 to standardize the approaches to the gene alterations identified in human cancers. Sequence-based mapping of the human genome and high-throughput Sanger sequencing allowed rapid, extensive cataloging of somatic mutations in candidate and causal cancer genes.[11] The targeting of specific biochemical pathways and large numbers of candidate genes with high-throughput resequencing resulted in the development of genotype-directed therapy initially involving primarily protein kinase-encoding genes.[12] This approach allowed specific pathway-directed therapy for genotype-defined cancer subgroups [e.g., HER2 (also known as erb-b2 receptor tyrosine kinase 2) mutation-positive breast cancer with trastuzumab]. Following the completion of the Human Genome Project, a map of non-cancerous human genomic variation (HapMap) was constructed that identified single nucleotide polymorphisms (SNPs) and underlying genomic structure. The associated development of high-density SNP genotyping arrays facilitated the classification of cancer subtypes and prediction of clinical phenotypes; however, the genetic complexity of human cancers limited systematic sequencing of tumor genomes.[11]

In 2006, a systematic analysis of coding exons involving 13,023 protein-encoding genes from 11 breast cancers and 11 colorectal cancers revealed individual tumors accumulate an average of ~90 mutant genes.[13] Considerable inter-tumor variability occurred, resulting in altered genes with a relatively small number of frequently mutated genes, many infrequently mutated genes, and a substantial subset of mutated genes uninvolved in the neoplastic process. All somatic mutations are not functionally equivalent. Hence, identification of a somatic mutation indicates the presence of a candidate gene and not necessarily a causal gene because somatic alterations can confer a selective growth advantage to a tumor cell ("driver" mutation) or produce no effect on tumor formation ("passenger" mutation). Thus, reducing the complexity of genetic diversity in human cancers required a focus on genetically induced alteration of specific biological pathways and processes rather than the altered genes.[14]

Since the postgenomic era began, multiple domestic and international multi-institutional consortia have formed to identify and rapidly distribute data on genomic and epigenomic alterations in normal and cancerous tissues, including the Encyclopedia of DNA Elements (ENCODE), Human Epigenome Project (HEP), International Cancer Genomics Consortium (ICGC), International Human Epigenome Consortium (IHEC),[15] NIH Roadmap Epigenomics Initiative (NREI), Stand Up to Cancer (SU2C), Structural Genomics Consortium (SGC), The Cancer Genome Atlas (TCGA), and Therapeutically Applicable Research to Generate Effective Treatments (TARGET).[16] Although the resequencing of cancer exons identified protein-encoding gene mutations, this method did not assess noncoding regions (i.e., introns) of the genome that contain noncoding RNA (ncRNA) and ultraconserved elements. The National Human Genome Research Institute launched a public research consortium, the Encyclopedia of DNA Elements (ENCODE), in September 2003 to identify all functional elements in the human genome sequence including ncRNA. By the mid-2000s, recognized influences of ncRNAs on the function of RNA and proteins in cell division included regulation of chromosome structure and transcription, modification and processing of RNA, translation and stability of mRNA, and transport and stability of proteins.[17] Subsequently, a subset of ncRNAs, micro-RNAs (miRNAs), was recognized as an inhibitor of abnormal gene expression; dysregulation of miRNAs contributed to the development of oncogenic and tumor suppressive properties.[18] Another of the subsets (long noncoding RNAs, Inc-RNAs) are transcripts longer than ~200 nucleotides with little or no protein-coding capacity. Transcribed ultraconserved region transcripts are a subset of lncRNAs transcribed from ultraconserved regions of the genome; studies of alterations of these transcripts in the late 2000s and 2010s associated the altered expression of these transcripts with human leukemias and carcinomas.[19,20]

In 2008, the US National Institutes of Health launched the NIH Roadmap Epigenomics Mapping Consortium (https://egg2.wustl.edu/roadmap/web_portal/) to provide a public resource of human epigenomic data with the goal of using basic biology to improve disease-oriented research. The consortium uses experimental data from next-generation sequencing technologies to map DNA methylation, histone modifications, chromatin accessibility including nucleosome positioning, and RNA transcripts in stem cells and primary *ex vivo* tissues representative of tissues and organ systems frequently involved in human disease including cancer.[21] By 2015, the Consortium reported the integrative analysis of 111 reference human epigenomes from primary human cells and tissues using a diverse set of high-throughput molecular assays including methylated DNA immunoprecipitation, methylation-sensitive restriction enzyme digestion, DNA digestion by deoxyribonuclease I, bisulfite treatment, chromatin immunoprecipitation, and RNA profiling.[22] A major advance in studying genome-wide

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DNA methylation was the separation of methylated and unmethylated DNA by sodium bisulfite conversion of unmethylated cytosines to uracil (unmethylated cytosines remained unaffected), followed by PCR amplification and analysis of PCR products.[23] Expanded knowledge of the genetic and epigenetic basis of cancer added comprehensive data to classical pathology-based tumor classification as well as to the development of personalized medicine designed to predict individual cancer risk and drug response.

DNA REPLICATION

Developing after conception, somatic cells are the cells in the body (i.e., skin, connective tissues, bone, blood, internal organs) other than undifferentiated stem cells and germline cells (i.e., sperm, ovum, gametocytes that produce sperm or ovum). Each somatic cell contains all the organism's genetic information within the deoxyribonucleic acid (DNA) sequences in the genome of the cell nucleus, whereas reproductive cells contain ½ the chromosomal material (i.e., one set of chromosomes, haploid) present in somatic cells. The genome in a human somatic cell includes ~80,000–100,000 genes arranged linearly in 2 sets of 23 chromosomes with histone proteins (i.e., diploid). These genes contain a sequence of ~3 billion base pairs. Microscopically, chromosomes are visible as dark clumps (chromatin) in the nucleus. A gene represents the whole sequence of DNA bases necessary to determine the amino acid sequence of a single polypeptide chain in a protein. The four types of nucleotide bases (adenine, guanine, thymine, cytosine) produce a unique amino acid sequence because each base triplet (i.e., codon) specifies a particular amino acid. Thus, each human cell possesses the potential to synthesize 50,000–100,000 polypeptide chains; however, the differential expression of the genes depends on genetic and epigenetic factors, with the subsequent production of proteins determining cell function. In the cell nucleus, messenger ribonucleic acid (mRNA) copies the information in a gene (i.e., the DNA) during transcription. Transcription factors bind to specific DNA sequences (enhancer, promoter sequences) and recruit RNA polymerase to an appropriate transcription site. The transcript terminates when the selected DNA strand in the exons is copied; then, during translation, the newly formed mRNA copies move to the extra-nuclear ribosomes, where protein synthesis occurs from the information contained in the mRNA.

At a grossly microscopic level, most genes contain discrete protein-coding regions (exons) separated by noncoding regions (intervening sequences, introns), as displayed in Figure 47.1. The introns represent a much greater portion of the gene than the actual

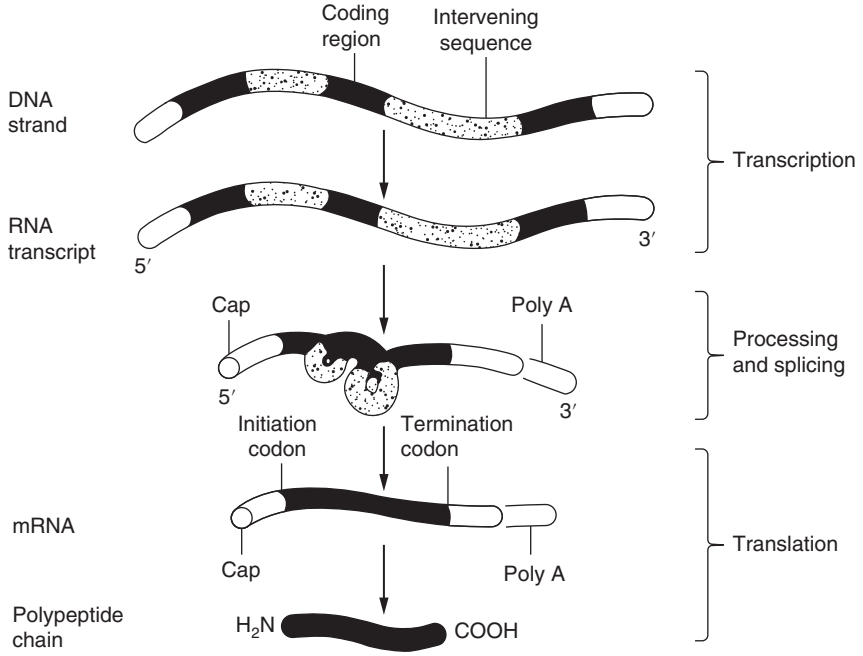


FIGURE 47.1. Schematic diagram of the genetic control of protein synthesis. Somatic cells contain activated and inactivated genes. mRNA copies the DNA information during transcription. The mature mRNA carries the protein-coding information to the cytoplasm, where protein synthesis occurs during translation in RNA-protein structures (ribosomes). (The Protein, Harrisons, p. 286).

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protein-coding sequences, with intron regions able to increase gene expression (e.g., increased steady-state concentrations of cytosolic mRNA) without functioning as a binding site for transcription factors; this intron-mediated enhancement of gene expression also increases mRNA translation efficiency and changes transcript concentrations by altering transcript stability, nuclear export, and/or transcription rates.[24] The effect of introns on gene expression is highly variable, despite similar locations on the same gene.[25]

Beginning at the promoter initiation site present ahead of the protein-coding sequence, the enzyme RNA polymerase II translates the DNA sequence of the gene into a duplicate mRNA copy. The DNA code consists of a series of three-letter combinations of nucleotides (codons), with each codon corresponding to a specific amino acid or stop signal. The promoter region upstream of the protein-coding sequence initiates transcription and influences the frequency of translation. Additionally, there are specific DNA sequences (enhancers) existing upstream and downstream of the transcribed DNA sequence. These enhancers either promote or suppress transcription. The newly transcribed mRNA contains an untranslated leader (i.e., sequence that does not code for an amino acid) in the initial 5′ portion, followed by alternating sequences of exons (coding) and introns (noncoding) regions. During the maturation process in the nucleus, the introns are deleted, the initial (5′) portion is capped or methylated, and a sequence of adenylic ribonucleotides (termed poly A tail) is added to the terminal 3′-portion of the mRNA.

Translation of mRNA by the ribosome in the cytoplasm occurs in three stages: initiation, elongation, and termination. During initiation, the small ribosomal subunit binds the beginning of the mRNA sequence, followed by the binding of methionine to the start codon by a transfer RNA (tRNA) molecule. The start codon (AUG) codes for methionine. The binding of the large ribosomal subunit forms the complete initiation complex. The elongation stage involves the linking of amino acids with peptide bonds based on the translation of each codon until every codon in the mRNA sequence is read. Termination occurs when the ribosome reaches a stop codon that tRNA does not recognize (i.e., UAA, UAG, and UGA).

CELL DIVISION

At any one time, most human cells are not cycling with most functional cells withdrawn from cell division into a reversibly quiescent (G0) state (e.g., hepatocytes, thyroid follicular cells) or permanently into a differentiated state (e.g., myocytes, neurons). Only a minority of the cells are actively proliferating, primarily stem and transit cells. Stem cells may divide without maturation, whereas mature cells approaching functional competence may not divide. In contrast, transit cells divide and mature while demonstrating intermediate properties between stem cells and mature functional cells.[26]

The goal of cell division is the generation of two genetically identical daughter cells from the precursor cell. A complex regulatory network controls DNA replication (S-phase) and the orderly segregation of cellular contents (M-phase) to preserve the fidelity of the process.[27] Changes in phosphorylation and cell cycle protein concentrations determine the progression through different cell cycle stages. Cyclin-dependent serine/threonine kinases (CDKs) initiate S- and M-phases, whereas protein phosphatases (PPs) reset the cell cycle by dephosphorylating the CDKs. The mutually exclusive activities of CDKs and PPs maintain cell regulation. The ubiquitin-proteasome system provides additional regulatory control by selective protein destruction.

Cell Cycle

Mitosis (M-phase) and interphase are the two fundamental parts of somatic cell division; the former includes various stages of nuclear and cytoplasmic division as recognized by the condensation of replicated chromosomes seen through light microscopy and outlined in Table 47.1.[28] Interphase consists of the DNA synthesis phase (S-phase), the two gap phases (G1, G2), and the reversible quiescent phase (G0) occurring in response to mitogen deprivation or high cell density. Mitosis involves cell division (cytokinesis) consisting of separation of the daughter DNA, segregation of sister chromatids, and formation of daughter nuclei. Cyclin-dependent kinases (CDKs) initiate the G1/S-phase and G2/mitosis transitions by phosphorylating various substrates. Cyclin-dependent kinase1 (CDK1) and cyclin-dependent kinase2 (CDK2) can bind several different cyclin types (A, B, D, E), whereas CDK4 and CDK6 bind only D-type cyclins. Figure 47.2 displays the essential cyclins and CDKs in the classical model of cell cycle controls.

Interphase

Most cells reside in the resting or quiescent (nonproliferative) phase (G0) with cell division interspersed at discrete intervals rather than occurring continuously. Interphase is the portion of the cell cycle other than mitosis consisting of the folllowing: 1) the nonproliferative phase (G0); 2) the phase (G1) between the end of

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TABLE 47.1. Phases of the cell cycle with key events and major regulators. Substantial redundancy of cyclin-dependent kinases (CDKs) occurs throughout the cell cycle; however, CDK1 (also known as cell division cycle protein 2, CDC2) is the only CDK essential for cell division. High cyclin B/CDK1 activity and inactivation of antagonizing protein phosphatases triggers cell entry into mitosis. Key events during mitosis include nuclear envelope breakdown, chromatin condensation, and bipolar spindle assembly. Exit from mitosis requires reactivation of protein phosphatases, inactivation of maturation-promoting factor (MPF), and degradation of cyclin B by the ubiquitin-proteasome pathway.

	G0→	G1→	S→	G2→	M
	Interphase				Mitosis
Phase	Resting State	GAP1	Synthesis	GAP2	Mitosis
Kinases		Cyclin D1–D3, CDK 4/6	Cyclin E1/E2, CDK2	Cyclin A, CDK2	Cyclin B, CDK1
Phosphatases			Phosphorylation of pRb (inhibitor) and p107/p130	Dephosphorylation by CDC25 phosphatases activates CDK 1/2	Phosphorylation byWee1protein kinase inactivates CDK1/2
Cell phases	G0/G1 transition	Middle G1→G1/S transition	G1/S transition → early S phase	G1/S transition → G2	G2/M transition → anaphase
Activity	Quiescent	↑ Responsiveness to growth factors	DNA replication	Preparation for mitosis	Nuclear envelope breakdown, chromatin condensation, spindle assembly, daughter cell formation
Substances	↑ Protein phosphatases (PP1 and PP2A), ↓MPF			↓ Protein phosphatases (PP1 and PP2A), ↑MPF (MSLN), ↓APC/C	↑ Anaphase-promoting complex/ cyclo-some (APC/C)

G0 and the initiation of DNA replication; 3) the S-phase of DNA replication with the formation of intranuclear daughter DNA; and 4) the phase (G2) between the end of DNA replication and the beginning of mitosis. Entry past the S-phase and into mitosis depends on the progression of the cell past the restriction point, spindle assembly checkpoint, replication checkpoint, and, to ensure DNA fidelity, the DNA damage response network.

G1 and the Restriction Point

Maintenance of the quiescent phase is an active process requiring transcriptional repression of DNA replication and mitosis along with the expression of antisenescence, antidifferentiation, and antiapoptotic genes.[30] Commitment to cell cycle progression or quiescence is mutually exclusive with the onset of DNA replication, an irreversible process. Passage through the restriction point at the end of mid-G1 phase commits the cell to entering the S-phase and progressing through the remaining phases of the cell cycle, whereas a state of quiescence persists when the cell does not progress past the restriction point.[31] Pocket proteins from the retinoblastoma family (RB/p105, p107, RB2/p120) block entry into the S-phase at the mid-G1 checkpoint (i.e., restriction point), as displayed in Figure 47.3.[32] The pRb protein represses gene transcription necessary for transition from G1 to S-phase by binding to the transactivation domain of E2F and forming a complex with the promoter of these genes. E2F controls the expression of genes required for DNA replication, S-phase progression, and mitosis. The retinoblastoma protein interacts with the E2F family of DNA-binding transcription factors rather than binding directly to DNA. Cell division cycle 6 (CDC6) is an essential regulator of DNA replication that assembles prereplicative complexes at replication origins during late M-phase and early G1.[33]

Multiple, redundant pathways tightly control the transition from G1 to the S-phase. External mitogens activate signal transduction activities including RAS GTPase, RAS signaling, downstream mitogen-activated protein kinases (extracellular-signal-regulated kinases, ERKs; Jun amino-terminal kinases, JNKs; stress-activated protein kinases, p38/SAPKs); and ultimately cyclin D transcription. Classically, cyclin D-CDK4,

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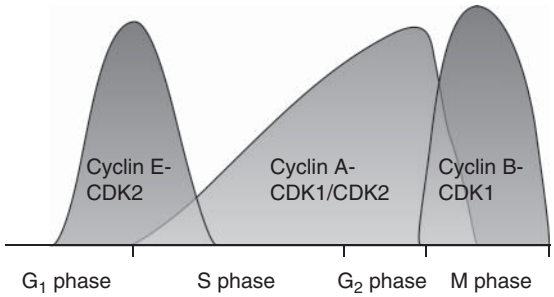


FIGURE 47.2. Classical model of relative activity of kinases and cyclins during the cell cycle. Cyclin-dependent kinases (CDKs) initiate the G1/S-phase and G2/mitosis transitions by phosphorylating various substrates, whereas anaphase-promoting complex/cyclosome (APC/C) E3 ubiquitin ligase initiates the metaphase-to-anaphase transition by ubiquitylation and proteasome-mediated degradation of B-type cyclins and other proteins. Cyclin E-CDK2 initiates DNA replication (S-phase), cyclin A-CDK1 and/or cyclin A-CDK2 control the completion of S-phase, and cyclin B-CDK1 sustains mitosis. (Adapted from Hochegger et al.).[29]

cyclin D-CDK6, and cyclin E-CDK2 drive G1 progression through the restriction point by phosphorylating and inactivating the RB protein, as displayed in Figure 47.3. RAS-driven MYC accumulation interacts with E2F transcription activity to control multiple proliferation-related genes.[34] Progressive E2F activation by cyclin D-induced RB phosphorylation in early- and mid-G1 and the positive feedback loop of progressively rising cyclin E concentrations producing RB hyperphosphorylation result in increased cyclin E transcription and entry into the S-phase; however, the gradually progressive RB phosphorylation during G1 is not easily reconciled with the binary decision to proliferate. Cyclin D-mediated RB phosphorylation may not be the only late G1 event that initiates passage through the restriction point; high CDK2 concentrations are associated with commitment to entering S-phase (threshold model).[35] This model suggests either CDK1- or CDK2-cyclin A complex controls interphase, while CDK1-cyclin B complex is essential for entry into mitosis.[29] In early and mid-G1, CDK2 activity is low, whereas it increases abruptly in later G1 and remains elevated until later in the early S-phase. The G1/S transition is a bistable switch for the steady-state distribution of two populations of cells that demonstrate different discrete CDK2 activities and interconvert in a rapid manner. The G1 restriction point is the primary passage point for quiescent cells re-entering G1, whereas the G2 decision window is more important for continuously cycling cells.[36] Actively replicating cells have the following two distinct proliferation decision points: 1) the G1 restriction point; and 2) the G2 window decision.

Synthesis Phase

Origins are sites on the chromosomal DNA where a bidirectional pair of replication forks begin. A replication licensing system coordinates the initiation of DNA replication on the chromosomes by a complex of initiator proteins (prereplication complex) that bind and unwind the DNA helix at origins prior to the formation of bidirectional replication forks.[37] During the late M- and early G1-phases, the licensing proteins assemble prereplicative complexes to prepare the chromosomes for DNA synthesis during the S-phase. These licensing proteins include the origin and recognition complex (ORC1–6), CDC6, CDT1, and the six minichromosome maintenance proteins (MCM2–7). The latter replicative helicases unwind the template DNA, whereas CDC6 and CDT1 function as clamp-loaders for the ring-shaped hetero-hexameric complex. The ORC first binds to each replication origin and then recruits CDC6 and CDT1. Down-regulation of CDC6 during the proliferation-differentiation switch in late G1 triggers loss of proliferative capacity and migration of the cell from the transit-amplifying compartment to the functionally differentiated compartment.

Figure 47.4 displays the progression of cell differentiation/maturation and expression of initiation proteins (CDC6, CDT1) and replicative helicases (MCM2–7) in the compartments of rapidly renewing tissues. Following inactivation of the replication licensing system during late G1 phase, no further MCM2–7 binding to the origins occurs during the remaining portion of the normal cell cycle (i.e., S-phase, G2, and early mitosis). A more gradual down-regulation of MCM2–7 occurs as the cell differentiates, whereas proliferating cells express high concentrations of these MCM proteins; consequently, MCM2–7 proteins are biomarkers of cell proliferation that reflect growth in diverse tumor cell populations (e.g., bladder, breast, lung, ovary, prostate).[37] The prereplication complex is functional only during late mitosis and G1 when CDK activity is low.

The S-phase-specific cyclin-dependent protein kinases (S-CDKs) and the DBF4 regulatory subunit–CDC7 kinase (DDK, Dbf4-dependent protein kinase) are essential activators for initiation of DNA replication in S-phase, with the generation of a single-stranded DNA template necessary for the recruitment of DNA synthesis machinery (replication protein A, RPA; DNA polymerase α-primase; proliferating cell nuclear antigen, PCNA).[38,39] Increased CDC7-DBF4 abundance

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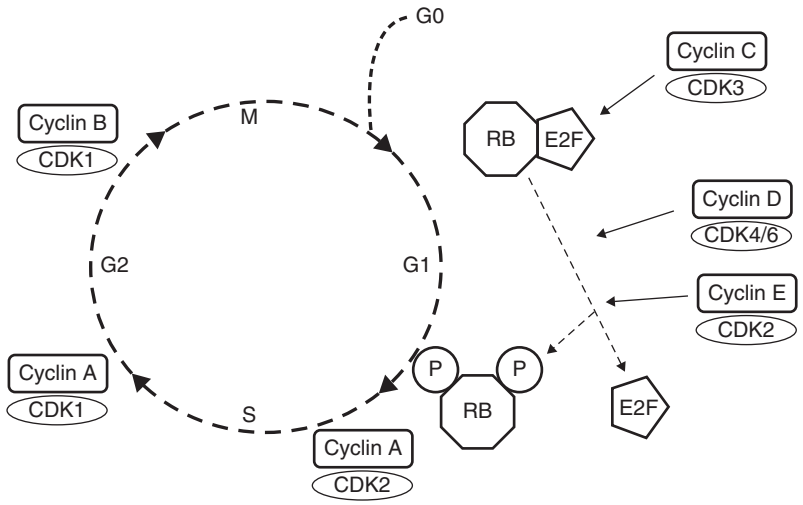


FIGURE 47.3. Retinoblastoma protein (RB) and G1 restriction point. The unphosphorylated RB protein binds to transactivation domain of E2F factors to repress gene transcription in G0 and early G1. Phosphorylation and inactivation of the RB protein (RP-P) by cyclin/cyclin-dependent kinases (cyclin D/CDK4/6, cyclin E/CDK2) release E2F factors in later G1 allowing the expression of genes necessary for S-phase progression. The mitotic cyclins A and B facilitate progression through S-phase, G2, and mitosis. (Adapted from Giacinti and Giordano).[32]

occurs in human malignancies, particularly breast cancer.[40] The binding of the regulatory protein, geminin, to CDT1 and cell cycle-dependent proteolysis of CDT1 suppress relicensing of origins after initiation of DNA synthesis.[41] High CDK activity does not displace MCM2–7 binding to origins, resulting in normal progression through the S-phase in the presence of S-phase induction by CDKs.

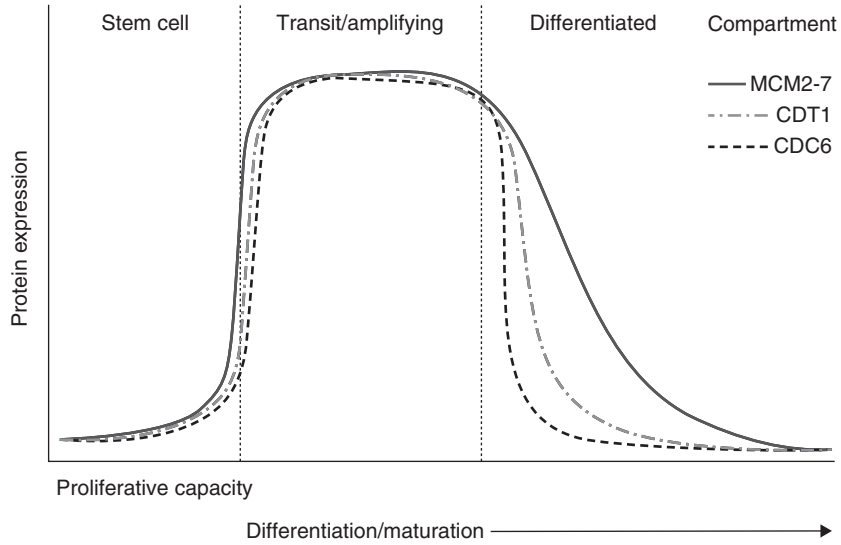


FIGURE 47.4. Progression of cell differentiation/maturation and expression of initiation proteins (CDC6, CDT1) and replicative helicases (MCM2–7) in the compartments of rapidly renewing tissues. New cells are supplied by the stem cell compartment; these cells have low expression of initiation proteins. Rapid increases in initiation proteins and MCM2–7 concentrations occur as the cells enter the transit/amplifying compartment. Gradual downregulation of MCM2–7 ensues as the cell matures and differentiates into a functional phenotype. The loss of proliferative capacity occurs with downregulation of initiation proteins (CDC6, CDT1) as the cells exit the transit/amplifying compartment. (Adapted from Williams and Stoeber).[37]

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Deregulation of the licensing system is probably an important driver of oncogenesis in some tumor types. Only licensed origins loaded with MCM2–7 can initiate a pair of replication forks with the bound MCM2–7 displaced during initiation of the origins as a fail-safe mechanism to prevent duplicate DNA replication.[42] Arrested differentiation associated with cancer results from the failure to down-regulate the replication initiation proteins.[43]

Dysplasia is associated with a failure to down-regulate the licensing system producing high MCM protein concentrations. Most premalignant lesions fail to progress through the cell cycle expressing little geminin; consequently, most neoplastic cells remain in the G1 extended or arrested state.[37] Geminin appears only in cells progressing through S, G2, and M phases. CDC6 participates in the activation and maintenance of S-phase and mitotic checkpoints; overexpression of CDC6 promotes DNA hyper-replication and senescence similar to oncogene activation along with interfering with the expression of *INK4/ARF* tumor suppressor genes.[33]

Spindle Assembly Checkpoint

The spindle assembly checkpoint controls cell cycle progression before the onset of anaphase and monitors fidelity of the spindle and proper attachment of chromosomes to spindle microtubules during prometaphase or metaphase of mitosis. Thus, spindle assembly checkpoint signaling ensures accurate chromosome segregation during mitosis. Equal segregation of sister chromatids requires the establishment of proper attachment to microtubules at opposite poles of the mitotic spindle by pairs of kinetochores. This checkpoint ensures the complete separation of chromatids into two daughter cells with a full complement of chromosomes. The chromosomal kinetochores are essential sensors for detecting spindle and/or chromosomal defects via proteins residing on the outer plate of the kinetochores at the spindle microtubule attachments (i.e., NDC80 complex and other components of the microtubule-binding interface).[44] The kinetochore is the primary location of the attachment of microtubules to mitotic chromosomes, with their scaffold proteins creating a solid link between chromatin and the mitotic spindle; kinetochores generate the spindle assembly checkpoint signal.[45,46] Structurally, kinetochores probably contain an inner plate consisting of a 15-subunit constitutive centromere-associated network (CCAN) and specialized centromeric chromatin along with a 10-subunit outer plate involved with microtubule binding through the KMN network. The major binding site for spindle assembly checkpoint proteins at the outer plate of the kinetochore is the interaction of the KMN network (KNL1, MIS12, NDC80 subunits) and microtubule binding activity.[47]

Checkpoint protein kinases include the catalytic proteins budding uninhibited by benzimidazole 1 (BUB1 or BUBR1 in humans) and monopolar spindle 1 kinase (MPS1) as well as noncatalytic proteins including mitotic-arrest deficient 1 (MAD1), mitotic-arrest deficient 2 (MAD2), and Rod-Zwilch-ZW10 complex (RZZ complex). These regulatory proteins interact to form the checkpoint effector (mitotic checkpoint complex, MCC). This complex maintains the mitotic state by protecting cyclin B and securin from ubiquitination and proteasome-induced destruction until the completion of the attachment of chromosomes to the spindle.[48] Abnormally attached kinetochores inhibit the anaphase-promoting complex/cyclosome (APC/C) cofactor, cell division cycle 20 (CDC20), following binding to MAD2 and BUBR1-BUB3 subunits of the MCC complex.[49] The subsequent inhibition of ubiquitylation and degradation of anaphase inhibitors (cyclin B, securin) prevent the initiation of anaphase until proper attachment of kinetochores to a bipolar spindle. Cyclin B is an activator of the major mitotic kinase, CDK1, whereas securin is the inhibitor of a protease that cleaves cohesin and allows sister chromatid separation. Following the correct attachment of kinetochores to microtubules, the MCC disassembles; activation of the APC/C-CDC20 complex triggers entry into anaphase, as displayed in Figure 47.5.

G_2 and the Replication Checkpoint

Actively proliferating cell populations have a decision point in G_2 (i.e., G_2 decision window) to commit to cell division or quiescence in the next cell cycle using increasing and self-reinforcing CDK activity (e.g., CDK1/CDK2) as the switch. Although the G1 restriction point and G_2 decision window require mitogen signaling through the RAS GTPase pathway,[50] the CDK- and RB-E2F-regulated networks in this decision point are similar but not identical.[36] RAS-driven MYC accumulation regulates E2F transcription during the G_2 decision window to control proliferation-related genes, particularly cyclin E transcription,[51] whereas the G1 restriction point depends primarily on the RB-E2F control pathway. Actively proliferating G_2-committed cells usually pass quickly through a subsequently shortened G1 phase.

Figure 47.6 displays the multiple molecular events in the two proliferating decision points for actively proliferating cells. The replication checkpoint prevents progression to mitosis when chromosomes remain incompletely separated. Although the signaling pathways are not identical, G2 DNA damage and replication

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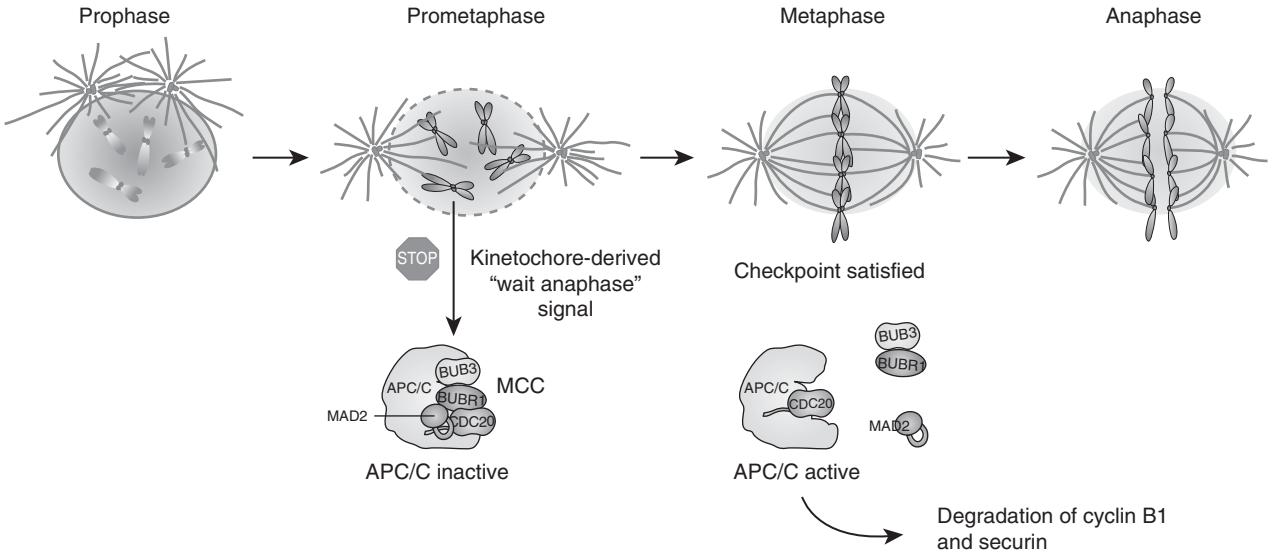


FIGURE 47.5. Spindle assembly checkpoint regulation. Nuclear envelope degradation marks the beginning of mitosis (prophase), followed by the activation of the spindle assembly checkpoint (SAC) by the presence of unattached kinetochores (prometaphase). Formation of the mitotic checkpoint complex (MCC) results from the recruitment of SAC proteins by unattached kinetochores. The mitotic checkpoint complex binds and inhibits the anaphase promoting complex (APC/C). The SAC deactivates when all the kinetochores are properly attached during metaphase; the mitotic checkpoint complex disassembles allowing the freed CDC20 to activate APC/C. The APC/C-CDC20 complex triggers entry into anaphase by degrading cyclin B1 and securin. (Adapted from Lischetti and Nilsson).[49]

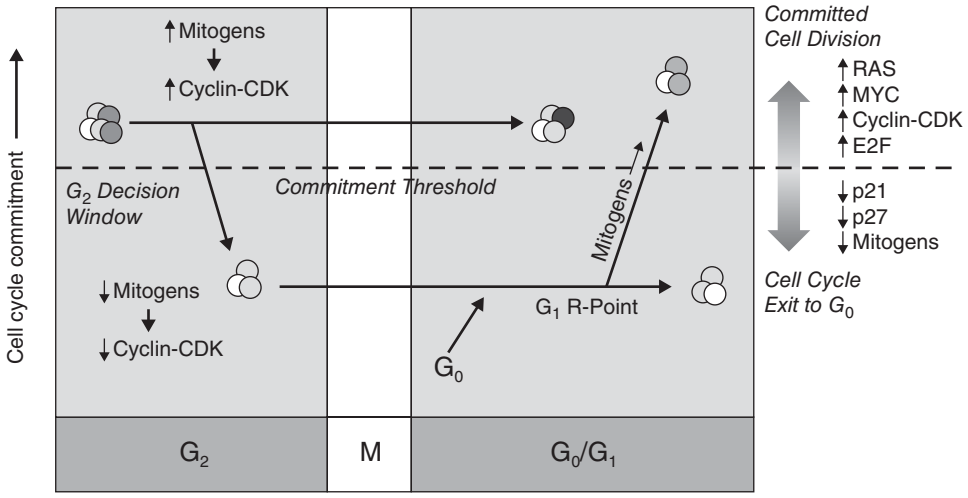


FIGURE 47.6. The G_1 restriction point and G_2 decision window proliferation decision points for actively proliferating cell populations. In G_2, cells with CDK activity above a critical threshold concentration commit the cells to completing the next cell cycle with a short G_1, whereas a subpopulation of G_2 cells with low cyclin-CDK activity and/or reduced mitogen signaling do not commit to the next cell cycle. The latter cells have a long G_0/G_1 phase with a second proliferation decision at the G_1 restriction point. Multiple molecular events noted in the figure determine the commitment to cell division and the exit to G_0. (Adapted from Matson and Cook).[36]

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checkpoints function similarly by the CHK1-induced inhibition of CDC25A and subsequent inactivation of cyclin-dependent kinase1 (CDK1).

Mitosis

Phases of mitosis include prophase, prometaphase, metaphase, anaphase, and telophase, as outlined in Table 47.2 and displayed in Figure 47.7. The process of mitosis involves nuclear division and reorganization of almost all cellular elements; during this process, chromosomes condense, the nuclear envelope breaks, mitotic spindles reform the cytoskeleton with chromosomes moving to opposite poles, and finally cell division (cytokinesis) occurs following segregation of sister chromatids and formation of daughter nuclei. The condensation of chromatin reduces the chromatin almost 1000-fold with transcription of highly dense chromatin ceasing.

A single replicated chromosome has two sister chromatids that contain identical chains of double-stranded DNA and a protein support structure (histones) held together by the centromere. The latter has a protein-binding site (kinetochore) for the eventual binding of spindle microtubules. The interruption of the nuclear envelope allows spindle microtubules to bind chromosomes at their kinetochores, beginning chromosome movement during prometaphase. Proteins at the kinetochore direct chromosomes toward the centrosome, resulting in the shuffling of chromosomes between centrosomes and the center of the spindle. Ultimately, the chromosomes align on the metaphase plate in the center of the spindle. Three mitotic engine kinases (PLK1, Aurora A, Aurora B) control most mitotic events, including centrosome maturation/separation and chromosome orientation/segregation at the spindle assembly checkpoint.[52] Histone H3 is a substrate for Aurora kinases; therefore, phosphorylated H3 (H3S10ph) is a biomarker of the M phase. Cells exit mitosis with residual CDK2 activity acquired in the G2 decision window; the amount of CDK activity determines subsequent cell cycle progression. Multiple redundant feedback loops and protein inhibitors (e.g., p21) control CDK2 activity.[53]

TABLE 47.2. Five phases of mitosis.

Mitotic Phase	Actions
Prophase	Newly replicated daughter DNA molecules formed during S-phase unwind during chromatin condensation and attach to a centromere. Centrosomes formed during interphase separate and move to opposite poles in the nucleus, where mitotic spindle formation begins during late prophase along with dissolution of the nuclear envelope.
Prometaphase	Mitotic spindle microtubules shuffle the condensed chromosomes back and forth between the spindle center and the centrosomes. Microtubules from opposite poles of the spindle bind the two sister chromatid kinetochores on opposite sides of the replicated chromosome, leading to alignment on the metaphase plate in the center of the spindle.
Metaphase	Completion of the alignment of chromosomes on the metaphase plate in the center of the spindle. Metaphase is brief compared with other phases of mitosis.
Anaphase	Breakage of the link between sister chromatids and movement of the two sister chromatids to opposite poles of the spindle.
Telophase	Reformation of the nuclei, decondensation of the chromosomes, and formation of two interphase daughter cells.

Control of Cell Division

Cell division is a highly regulated process involving multiple, redundant processes involving transcriptional, posttranscriptional, and posttranslational events. A study of cell cycle regulation by transcription factors and miRNAs identified 3,028 genes associated with the cell cycle, transcription factors regulated cell cycle-associated genes, and miRNAs targeted cell cycle-associated genes.[54] Most regulation of the cell cycle occurs during the two "gap" phases (G1, G2). Integration of information from the cell and the external environment determines if and when the cell cycle progresses to the synthesis and mitosis phases, respectively. The cyclin-dependent kinase (CDK) family of serine/threonine kinases and their regulatory units (cyclins) drive the progression of the cell cycle by altering the phosphorylation state and cell cycle protein concentrations (e.g., cyclin-dependent kinases, CDKs; maturation-promoting factor, MPF).[55] These kinases phosphorylate proteins by catalyzing the transfer of phosphates from high-energy ATP molecules to the oxygen atom of serine or threonine sidechain on the protein. Normal cell division requires the mutually exclusive regulation of mitotic kinases and antagonizing phosphatases, as displayed in Figure 47.8.

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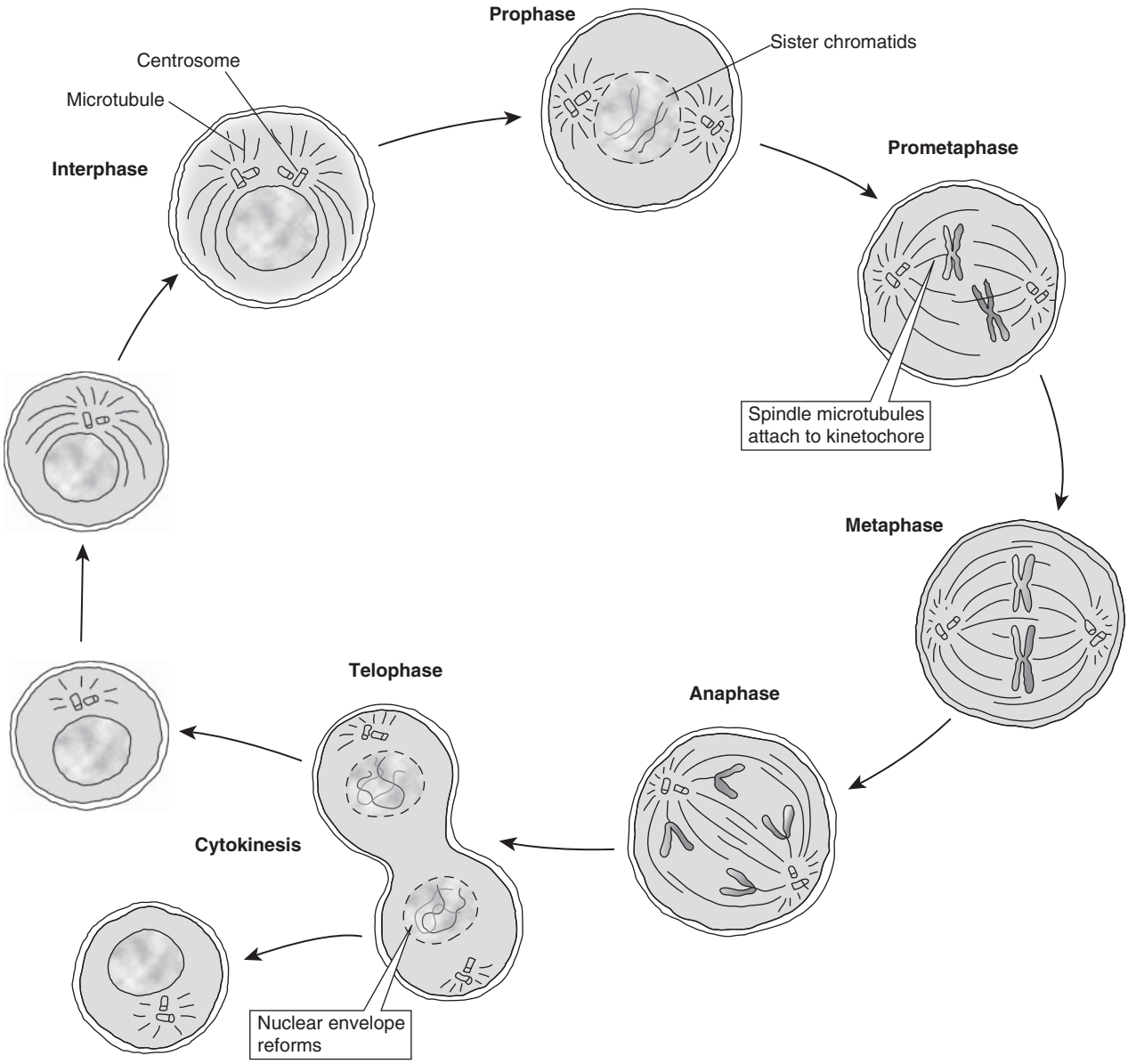


FIGURE 47.7. Stages of mitosis. Chromosomes condense and centrosomes move to opposite sides of the nucleus during prophase, starting the formation of the mitotic spindle. Dissolution of the nuclear envelope allows spindle microtubules to bind to the kinetochores on the chromosomes. Prometaphase involves chromosomes shuffling back and forth between the centrosomes and the center of the cell until alignment of the chromosomes in the center of the spindle initiates metaphase. The sister chromatids separate and move to opposite poles of the spindle during anaphase. Mitosis then ends with restoration of the nuclear envelopes, and chromosome decondensation during telophase marks the end of mitosis with cytokinesis yielding two duplicate daughter cells. Each daughter cell receives one centrosome that reproduces before the next mitosis. (Adapted from Cooper).[27]

During the G0/G1 transition, activation of immediate early genes increasingly sensitizes the cell to growth factors, while the cell progresses through G1 to the synthesis phase. D-type cyclins (D1, D2, D3) activate cyclin-dependent kinases (CDK4, CDK6) for functions from the middle G1 to G1/S transition. Cells not committed to DNA replication during G1 may differentiate and enter the resting phase (G0) or may undergo apoptosis (programmed cell death) when factors (e.g., p53) block progression. Germline cells (sperm, ovum, gametes) divide by meiosis producing four daughter cells, each with one set of chromosomes (haploid) compared with two sets of chromosomes (diploid) in each of the two daughter cells from somatic cell division

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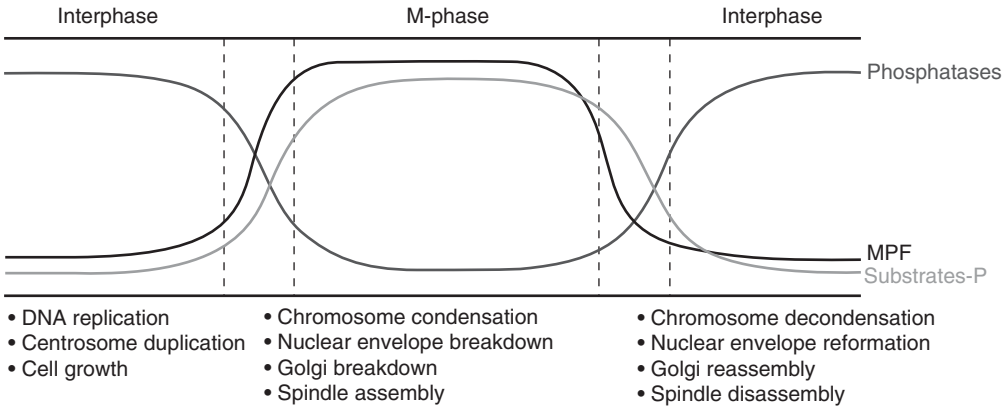


FIGURE 47.8. Phosphorylation maturation-promoting factor (MPF) and regulatory cell cycle proteins (substrates-P) during interphase (G0–G2) and mitosis. Both of these processes initiate important cell cycle events (e.g., DNA replication, chromosome decondensation). Mitotic kinases and phosphorylation are regulated as mutually exclusive processes, with dephosphorylation reversing processes enhanced by mitotic phosphoproteins. (Adapted from Heim et al.).[55]

during mitosis Table 47.2 describes the five phases of mitosis.

The cycle of cells deprived of growth factors or essential nutrients stops in mid-G1 at the restriction point.[36] Most malignant cells do not have a restriction point; this deficit helps the malignant cell evade normal growth control signals. Cells passing the restriction point progress to late G1, when the cell either enters the S-phase and divides or the G0 phase and differentiates. Progression of cell division then depends on the complicated interaction of numerous factors, including numerous cell receptors, the amount of binding of hormones and growth factors to the receptors, and the presence of specific regulatory proteins within the nucleus.[56]

Changes in the phosphorylation state of structural and regulatory components of the cell cycle by serine/threonine-directed protein kinases trigger critical mitotic events, including nuclear envelope breakdown, chromatin condensation, and bipolar spindle assembly.[57] Maturation-promoting factor (CDK1 (CDC2)/cyclin B complex, MPF) is the main regulator of mitosis; cyclin B1 is predominantly cytoplasmic during interphase, although p21 (*CDKN1A*) can induce nuclear translocation of cyclin B1 when degradation occurs.[58] MPF factor promotes entry of the cell cycle into mitosis and its own degradation by inducing anaphase-promoting complex at the beginning of mitosis. This p21-dependent process sequesters cyclin B1 in the nucleus of untransformed cells, marking the G2 restriction point for terminal cell cycle exit, whereas transformed cells exclude cyclin B1 from the nucleus and accumulate high, cytoplasmic cyclin B1 concentrations during ongoing DNA damage.[59]

MPF (G2 checkpoint) controls the expression of genes that regulate the passage of the cell from the G2 growth phase to the M phase. Activation of the *MSLN* gene produces CDK1/cyclin-B, inhibitory kinases (WEE1-like protein kinase, WEE1; membrane-associated tyrosine and threonine kinase 1, MYT1), and an activating phosphatase, CDC25.[55] Protein phosphatase 1 (PP1) contributes to the activation of CDC25 by directly dephosphorylating S287 and enhancing the activation of CDC25 by CDK1/cyclin-B.[60] Exit from mitosis depends on the inactivation of CDK1/cyclin-B, mediated primarily by the destruction of cyclin-B via the ubiquitin-proteasome pathway.[61] Control of mitosis involves multiple phosphatases. Protein phosphatase type 2A is the major CDK1 antagonizing phosphatase that dephosphorylates mitotic phosphorylations and initiates the exit from mitosis.[62]

Following passage of the metaphase checkpoint, activation of anaphase-promoting complex (a ubiquitin ligase) by MPF degrades two key regulatory proteins (PDS1, ESP1) that result in the degradation of the cohesin, SCC1; the latter protein maintains the link between sister chromatids on the metaphase plate, as displayed in Figure 47.9. Cleavage of SCC1 and the link allows sister chromatids to move to opposite poles on the spindle. All normal human somatic cells undergo a finite number of cell divisions during their lifespan; at the end of their proliferative capacity, these cells enter the programed state of replicative senescence determined by the topology of telomeres, progressive

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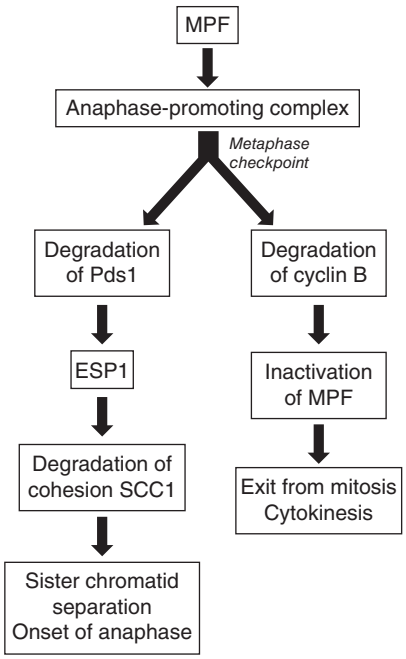


FIGURE 47.9. Anaphase and telophase regulatory controls. After passage of the metaphase checkpoint, activation of anaphase-promoting complex begins the transition from metaphase to anaphase by initiating the degradation of cohesin Scc1 and breaking the link between sister chromatids. The anaphase-promoting complex also degrades cyclin B, resulting in inactivation of MPF and the completion of mitosis (cytokinesis). (Adapted from Cooper).[27]

telomere shortening, and partly the expression of the $p16^{INK4a}$ cell cycle inhibitor.[63] Ultimately, these cells remain in permanent G1 arrest. Malignant transformation of cells overcomes replicative senescence to provide the cancer cell with unlimited proliferative capacity.

CELL SIGNALING

Cell signaling pathways inside cells involve the binding of a signaling molecule (ligand) with a receiving molecule (receptor). The ligand binds only to a specific or a few specific receptors, transmitting a signal that produces a change in shape or activity inside the cell. Kinases are enzymes that transfer phosphate groups to a protein or other targets; receptor tyrosine kinases transfer phosphate groups specifically to the amino acid tyrosine. A signaling molecule binds to the extracellular domains of two adjacent cell-surface tyrosine kinase receptors, phosphorylating each other and then transmitting the signal to intracellular molecules.

Cellular Communication

The four phases of DNA replication that produce cell division are: 1) signal generation; 2) signal recognition; 3) signal transduction; and 4) cell response (e.g., DNA replication, cell division).[64] Initiation of cell division (i.e., signal generation) results from an external signal (e.g., cytokines, growth factors, peptides/steroid hormones) that may be humoral or local. Generally, growth factors are either steroid hormones or polypeptides. Signal recognition requires the presence of receptors located on the plasma membrane, cytoplasm, or nucleus. The interaction of growth factors or hormones with the appropriate receptors results in a sequence of events (signal transduction). Events occurring during transduction that result from binding growth factor to the plasma membrane include dimerization of the receptor, activation of the phosphatidylinositol pathway, release of calcium stores, and stimulation of the serine/threonine-specific protein kinase C. Steroid hormones bind to receptors in the cytoplasm rather than plasma membranes. Gene activation results from the migration of the hormone-receptor complex to the nucleus, where the hormone-receptor complex binds to DNA. The responses to signal transduction include cell replication, protein synthesis, or programmed cell death (i.e., apoptosis). Consequently, the interaction of growth factors or hormones with their receptors is insufficient alone to initiate cell division.

Cytokines

Cytokines are critical components of signaling pathways that control cell growth and development, DNA replication and repair, differentiation, cell death, and cell migration; these proteins include inflammatory cytokines (e.g., interferons, interleukins), chemokines (e.g., macrophage inflammatory proteins, MIP-1α/1β), and growth factors (e.g., hepatocyte and epidermal growth factor).[65] Chemokines are cytokines that specifically influence cell migration. These proteins have short half-lives and interact locally with specific receptors on the cell membranes of their target cells. Plasma contains inadequate cytokine concentrations to measure in blood. Peptide and steroid hormones are not considered cytokines. In response to signal transduction, cytokines typically are released from activated cells rather than storage vesicles. Most cytokines elicit multiple biological responses in different cell types; in a specific cell type, functional overlap (i.e., cross-talk) occurs with different cytokines producing the same response in a specific cell type. Multiple factors (e.g., neighboring cells, other

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cytokines, cytokine concentrations, chemical reactions) affect the duration and type of cytokine response. Many protein products of oncogene expression are cytokine growth factors.

Kinases

Cyclin-dependent kinases (CDKs) are serine/threonine-specific, protein-directed protein kinases composed of a positive regulatory subunit (cyclins) and catalytic subunits (CDKs) with little intrinsic enzymatic activity; the kinase activity depends on the association of the CDK with a regulatory subunit. Mammal cells have several different CDKs (1, 2, 3, 4, 6) and cyclin types (A, B, D, E) performing similar functions during different phases of cell division; each cyclin type also has several variations (e.g., A1, A2) that perform the same functions. Unlike other kinases, CDK2 remains inactive without binding to cyclin; only CDK2 is essential for cell division. Although CDK concentrations are relatively constant during the cell cycle, the concentrations of various cyclins vary dramatically during the regulation of biosynthesis and degradation. Cyclin B/CDK1 phosphorylates core anaphase-promoting complex/cyclosome (APC/C) subunits, enhancing the affinity of APC/C for coactivator CDC20. Subsequently, APC/C targets cyclin-B for proteasomal destruction, resulting in the end of anaphase. Thus, APC/C helps regulate DNA replication and transcription by targeting proteins for proteasomal destruction.[55]

DNA Damage Response Network

In addition to repair of endogenous misreads by DNA polymerase (i.e., $\sim 1/10^9$ replications), proper function of organisms requires the maintenance of genome integrity, particularly against numerous endogenous and exogenous destructive agents, including reactive oxygen species, ionizing radiation, and organic/inorganic chemical substances. The DNA damage response network is the signaling pathway that senses DNA damage, halts cell cycle progression, modulates cell metabolism, and initiates DNA repair mechanisms or apoptosis depending on the severity of DNA damage.[66] This pathway ensures genome stability by regulating the transition of cell cycle phases and coordinating various DNA damage repair processes to prevent error-prone DNA replication and the loss of genetic material. The DNA damage checkpoint pathway functions as a tumor suppressor with disruption of the pathway associated with increased tumorigenesis.[67] In addition to regulating DNA damage repair, checkpoint genes are essential to cellular survival.[68] The pathogenesis of most common human cancers involves dysfunction in the DNA damage response network.[69]

Regulation of the DNA damage response involves very complex, redundant pathways expressing post-translational, protein-modifying enzymes (kinases, phosphatases, ubiquitin ligases, deubiquitinase, sumoylation, de-sumoylation, methylation, acetylation) and epigenetic regulators (mRNAs, lncRNAs).[66] Post-translational, enzyme-catalyzed alterations of proteins allow rapid conformational changes in target proteins without *de novo* synthesis, primarily by changing one or more amino acid residues on the protein. Usually, these alterations are reversible. In the presence of damaged DNA, cell cycle checkpoints sense DNA damage and delay progression of cell division until repairs are complete using signaling effector proteins (e.g., INK4 and CIP/KIP families). The INK4 family (INK4A, p16; INK4B, p15; INK4C, p18; INK4D, p19) inhibits CDK4 and CDK6, whereas the CIP/KIP family (p21, p27, p57) suppresses CDK2 activity.[70] Inactivation of tumor suppressor genes that encode INK4 and CIP/KIP family genes commonly occurs in diverse tumor types. Several checkpoints contribute to DNA fidelity, including DNA damage, replication, and spindle integrity checkpoints. These checkpoints are barriers to DNA over-replication and perpetuation of aberrant DNA; DNA damage response and oncogene-induced senescence are diminished as precancerous lesions progress to advanced cancers.[71]

DNA Damage and Cell Cycle Checkpoints

The major DNA damage checkpoints during cell division are: 1) G1 (pre-S phase); 2) intra-S phase; 3) G2 (before M-phase); and 4) mitotic (mid-mitosis), as displayed in Figure 47.10. Large DNA-bound protein kinases (phosphatidyl-inosol-3-kinase-like kinases, ATM and ATR) detect damaged DNA at these checkpoints along with activating the DNA damage signaling pathways via checkpoint mediators, Chk1 and Chk2. Activation of ATM precedes ATR activation because the latter requires processing of double-stranded breaks. The complex pathways activated by ATM include: 1) sensory proteins [e.g., Mre11-Rad50-Nbs1 (MRN) complex, RAD17 protein] that sense DNA strand breaks; 2) mediator or adaptor proteins that attract multiprotein complexes to damaged DNA and enhance phosphorylation (e.g., BRCA1, 53BP1, MDC1, H2AX variant H2A histone near the DNA break); and 3) protein components of intra-S phase checkpoint pathway (e.g., FANCD2, SMC1).[72] Additionally, ATM targets

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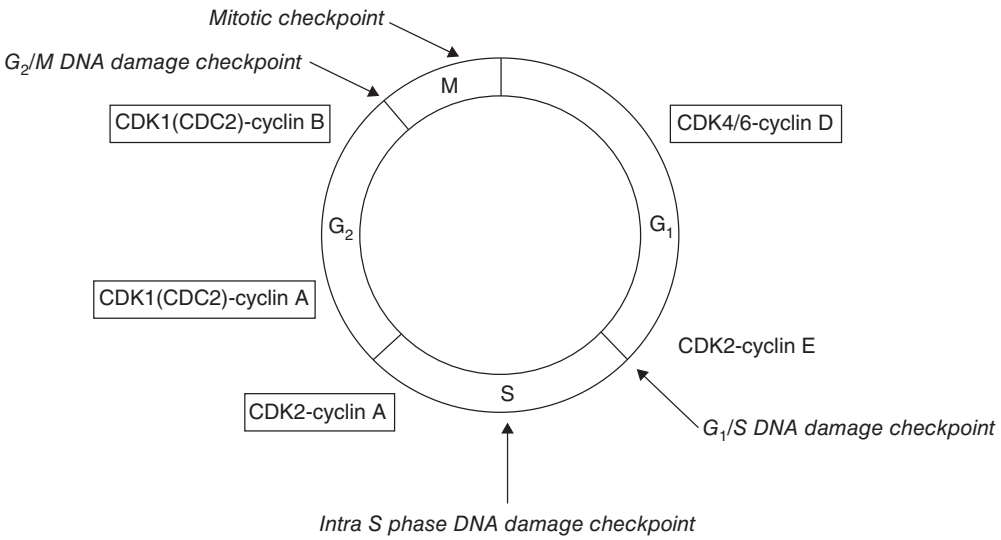


FIGURE 47.10. Cell cycle checkpoints in the DNA damage response network and the main regulatory cyclins and cyclin-dependent kinases (CDK1, CDK2). CDK1 is also known as cell division control protein 2. The DNA damage response network provides DNA repair processes and cell cycle checkpoints to ensure the fidelity of DNA replication. Regulation of cell cycle checkpoints involves ATR/ATM-Chk1/Chk2 and mitogen-activated protein kinase (MAPK) pathways as detailed in the text. Malignant tumors frequently contain mutations in cell cycle checkpoint and DNA repair genes (e.g., *BRCA1* and *BRCA2*). (Adapted from Poehlmann and Roessner).[68]

downstream substances that contribute to genomic stability, including transcription factors involved in the cell cycle and programmed cell death (e.g., E2F1, p53) and effector kinases (Chk1 and Chk2) that signal DNA damage to the CDC25 family of cell cycle regulatory phosphatases (e.g., p53, E2F1, BRCA1). These phosphatases remove critical inhibitory phosphorylations on CDK/cyclin complexes at the G1/S and G2/M checkpoints. Mutations of checkpoint components substantially increase the risk of cancer, particularly mutations in the ATM/Chk2-p53 pathway during the early stage of tumorigenesis before genomic instability and malignant conversion.[73] Mutations in the ATM pathway (e.g., *BRCA1*, *BRCA2*, *CHK2*) substantially increase the risk of breast and ovarian cancers.[74,75] Several substrates of ATM/ATR kinases (Chk1, Chk2, p53, NBS1, BRCA1, 53BP1) are tumor suppressors, whereas *CDC25A* is a proto-oncogene.[68]

An important effector at the G1 and G2 checkpoints is the transcription factor p53. High p53 concentrations ultimately reduce cyclin-dependent kinase activity via inhibition of the CIP/KIP inhibitor p21, leading to G1 and G2 arrest by depression of transcription. Although p53-dependent processes are necessary for G1 checkpoint function and long-term cell arrest, the immediate G2 and intra-S phase DNA damage checkpoints are checkpoint protein kinase Chk1/Chk2-dependent and p53-independent. A variety of DNA repair mechanisms exist, including base excision and nucleotide excision repair, mismatch repair, homologous recombination repair, and nonhomologous end joining. Until completion of DNA repair, the presence of DNA damage promotes the phosphorylation of CDK1-activating phosphatase (CDC25A) by Chk1 or Chk2, resulting in destabilization of the CDK2 complexes required for DNA synthesis.

CLASSIC PATHOLOGICAL STAGES

Normal cell replication and cancer represent opposite ends of the continuum of cell growth. In healthy tissue cells, replication replaces cells lost through normal turnover; the replication ceases following regeneration of the normal structure. Cancerous cells lack normal growth controls, invade surrounding tissues, and ultimately metastasize to distant sites. Somatic mutations are alterations of DNA that occur after conception in cells other than germ cells (i.e., not in sperm or eggs); these changes are not inherited by the children. Although most human cancers are sporadic tumors that arise from a series of somatic mutations producing genetic/epigenetic alterations and abnormal (i.e., cancerous) cell growth, every somatic mutation does not cause cancer. The acquired attributes of cancer cells (e.g., uncontrolled proliferation, resistance to exogenous growth-inhibitory signals, metastasis) result from the accumulation of multiple genetic and epigenetic alterations leading to dysregulation of protein-encoding

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genes and noncoding RNA (ncRNAs). During the formation of cancer cells, these sequential alterations result in the production of oncogenes, tumor suppressor genes, and microRNA genes that transform a single cell into a clinically detectable clone of fully invasive cells. This multifactorial, multistep process in solid tumors usually develops over 1–2 or more decades.

The tumors typically contain many infrequently mutated genes and a few frequently mutated genes, resulting in substantial genetic heterogeneity and cytogenetically different clones produced by secondary and tertiary genetic alterations of the original initiating cell.[11] This heterogeneity results in different clinical and therapeutic responses in diagnostically similar tumors due to several altered biological processes and biochemical pathways.[76] Understanding the genetic basis of individual tumors allows personalized chemotherapy.

Many human carcinogens act via multiple mechanisms that cause various pathological changes during the multistage cancer process. Before the development of a better understanding of key mechanistic data, genotoxic alterations, and epigenetic pathways, the natural history of these clones was divided into three classic stages (initiation, promotion, and progression), as displayed in Figure 47.11.[77] Chemical carcinogenesis in mammals usually involves chronic exposure to a carcinogen prior to the development of cancer, resulting in a prolonged latent period between exposure and clinical presentation. Under experimental conditions, a single high dose of a potent chemical carcinogen may cause malignant tumors after a sufficient latent period.[78]

Initiation

The progression to malignancy is a multistage process that involves loss of control over cell proliferation, alteration of the balance between cell survival and apoptosis, reduced communication with neighboring cells and the extracellular matrix, induction of tumor neovascularization (angiogenesis), and tumor migration and invasion. The first steps in the neoplastic conversion of a cell are the metabolic activation of the procarcinogen (if needed) and the covalent interaction of the ultimate carcinogen with cellular DNA and other macromolecules.[79] Tumor initiators (e.g., benzo[*a*]pyrene or other high-molecular-weight polycyclic aromatic hydrocarbons) induce heritable intracellular changes that produce dividing cells capable

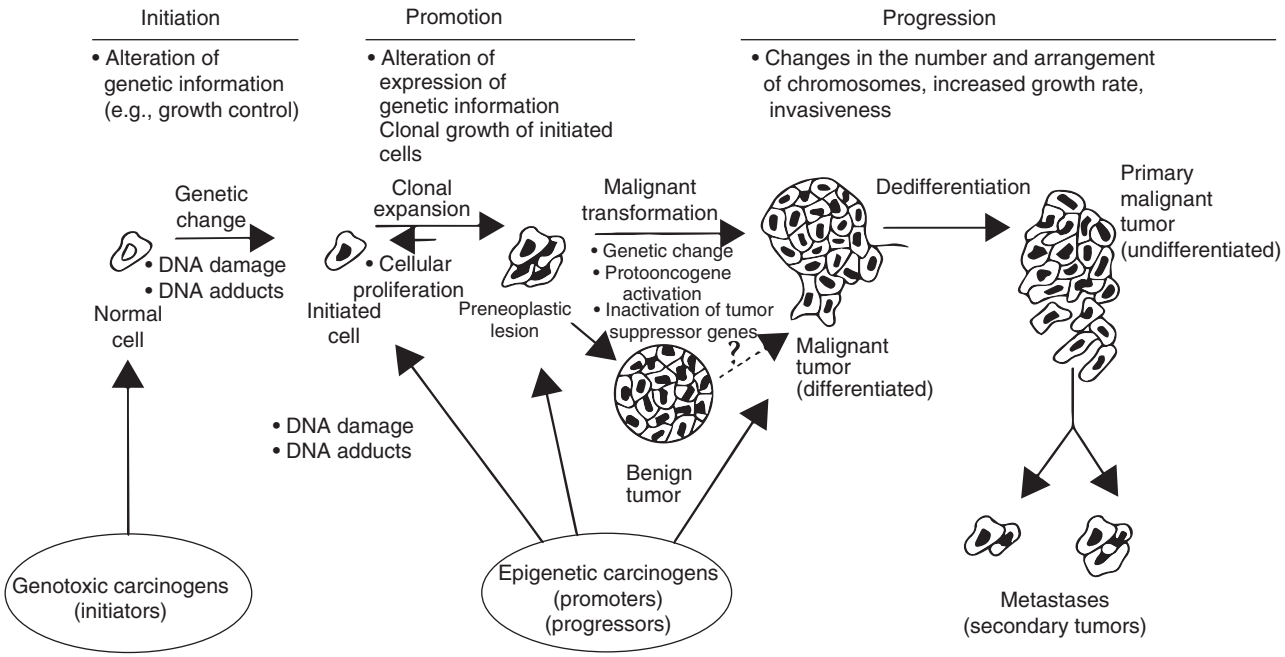


FIGURE 47.11. The three classic pathological stages of carcinogenesis, based on the multistage model developed from studies of hepatocellular carcinoma in rats. An initiator alters the genetic information of a normal cell irreversibly with subsequent prolonged exposure to a promoter, resulting in cellular proliferation, clonal expansion, and formation of preneoplastic foci. Under the influence of progressor agents, irreversible karyotypic changes occur along with increased proliferation and invasiveness that result in metastasis. Although benign and malignant tumors appear during this process, the presence of localized *in situ* malignant cells in pathologically benign tumors cannot be excluded. (Adapted from Derelanko).[77]

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TABLE 47.3. Biological characteristics of the stages of carcinogenesis. (Adapted from Pitot and Dragan).[80]

Initiation	Promotion	Progression
Irreversible	Reversible	Irreversible
Initiators are usually genotoxic	Promoters are not usually mutagenic	Progressors may not be initiators
Subtle, pathologically unobservable change in critical genes without morphological changes. Early cellular changes have not been identified	No discernible chromosomal abnormalities, but changes in gene expression	Discernible alteration in the genetic structure of cells (aneuploidy) with both benign and malignant tumors present
Spontaneous initiation occurs. Initiation requires cell division for "fixation"	Depends on continued administration of a promoting agent to expand progeny of initiated cell population	Spontaneous progression to benign and/or malignant neoplasms occurs
Lack of readily defined threshold dose with no measurable maximum response	Measurable thresholds and maximal effects depend on the total dose of initiating agent	
Efficacy of initiators sensitive to chemicals	Efficacy is sensitive to dietary and hormonal factors	Growth of altered cells sensitive to environmental factors during early progression
Single exposure may be sufficient, but usually multiple exposures	Prolonged, repeated exposure is necessary	Environmental factors influence early progression

of evolving into clones of neoplastic cells. Characteristics of initiation include irreversibility, additivity, and the absence of an easily measured threshold dose.[80] Table 47.3 compares the biological characteristics of initiation, promotion, and progression. Mutations in single cells frequently initiate carcinogenesis; these mutations can occur spontaneously in the absence of external carcinogens.[81] Although initiation may be a relatively common event, progression of an initiated cell to a neoplasm is relatively uncommon, with most initiated cells remaining dormant and failing to progress to a malignant tumor.[82] Few xenobiotics act only as initiators. Most carcinogens are complete carcinogens that act at all three cancer stages including initiation; however, many carcinogens act as initiators at low doses and complete carcinogens at high doses.[83] Initiation produces genotypic (i.e., preclinical) changes in the cell that are not visible histologically.

Initiation involves the following events: 1) absorption and distribution of the carcinogen; 2) metabolic activation of the procarcinogen, if necessary; 3) covalent interaction with the cell genome; 4) fixation of DNA damage including activation of proto-oncogenes; and 5) proliferation of the altered cells. Prime targets for initiation include proto-oncogenes and tumor suppressor genes. Under normal circumstances, these genes produce proteins that affect cell division and regulation of cell growth (e.g., genetic alterations promote cell proliferation by converting normal proto-oncogenes to oncogenes). This genetically transmissible activation occurs primarily during DNA repair processes before repair of damaged DNA sequences or after severe DNA damage occurs at multiple sites. This activation provides the cell with a growth advantage. In contrast to the deletion of genetic materials that often occurs following ionizing radiation exposure, chemical carcinogens usually produce either transversion mutations (i.e., replacement of pyrimidine with purine or purine with pyrimidine) or transitional mutations (i.e., replacement of purine with another purine or pyrimidine with another pyrimidine).[84]

Animal cancer models indicate initiation requires some cell proliferation to form heritable, preneoplastic lesions capable of responding to promoting agents.[85] Although genetic damage at various stages of oncogenesis is necessary for the development of cancer, mutations alone are not sufficient to induce cancer. Mammalian cells possess DNA repair mechanisms that remove most DNA adducts and mutations; however, further enhancement of these preneoplastic cells occurs through error-prone DNA repair mechanisms that create permanent alteration of the genome. Initiation may arise as a spontaneous event in response to naturally occurring carcinogens, radiation, or viruses; therefore, this step does not require the presence of chemical carcinogens. Nevertheless, chemical carcinogens can promote the clinical appearance of a spontaneous, initiated preneoplastic event.

Metabolic Activation

Most procarcinogens do not produce cancer on direct contact with skin; many procarcinogens require biotransformation via CYP isoenzymes to induce cancer.

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Variation in the distribution of multiple CYP isoenzymes among organs, individuals, and species explains most, but not all, differences in the response to carcinogens between animals and humans. Substantial interindividual variation in the ability to metabolize carcinogens results from a number of factors, including the presence of xenobiotic metabolizing isoenzymes with different substrates and inhibitor preferences, genetic factors (polymorphism),[86] exposure to environmental chemicals, and host factors (age, sex, health).[87] Individuals exhibiting slow acetylation have a higher risk of developing bladder cancer because these individuals inactivate the carcinogenic arylamines (e.g., 4-aminobiphenyl) more slowly compared with rapid acetylators.[88]

In animal models, oxidation by CYP1 and CYP2 enzymes activates most known procarcinogens; however, other phase I reactions (hydrolases, dehydrogenases, flavin monooxygenases) may also stimulate procarcinogens. These pathways form electrophilic (i.e., positive ions, uncharged molecules with electron-deficient regions) intermediate metabolites (ultimate carcinogens) that react with nucleophilic (electron rich) sites on the DNA in the presence of sufficient concentrations of these metabolites. Nucleophiles include some amino acids of proteins along with purine and pyrimidine bases of the nucleic acids. Phase II conjugation reactions usually inactivate chemical compounds; thus, some genes controlling phase II reactions may contribute to individual susceptibility to specific cancers.[89] The *N*-acetyltransferase 2 gene (*NAT2*) is associated with the biotransformation of aromatic amines, and the glutathione S-transferase M1 gene (*GSTM1*) is involved with detoxifying polycyclic aromatic hydrocarbons in smoke using phase II reactions. The metabolic intermediates of some chemical carcinogens (e.g., low and high molecular weight polycyclic aromatic hydrocarbons) act as promoters and cocarcinogens by activating the aryl hydrocarbon receptor complex; this pathway controls the expression of a diverse set of genes, including some CYP isoenzymes, and a broad spectrum of cellular responses (cell proliferation, cell cycle regulation, apoptosis).[90]

Mutations

The progression of neoplasia involves three broad categories of gene mutations: 1) oncogenes (e.g., *HER2*) that are growth stimulators capable of inducing the malignant transformation of cells; 2) tumor suppressor genes (e.g., *TP53*) that inhibit growth regulators; and 3) mutator genes (e.g., *HNCC*) that control the fidelity of the DNA replication process. Oncogenes are altered versions of normal genes (proto-oncogenes) that regulate cell growth and differentiation. Oncogenes produce proteins that affect every level of growth regulation.[91] The alterations of the proto-oncogenes by chemical carcinogens (e.g., point mutation, gene amplification, chromosomal translocation) confer malignant transforming potential to that gene.[92] No specific type or sequence of alterations necessarily causes cancer. Oncogenes promote cell division, whereas mutations in oncogenes result in the inappropriate stimulation of cell division. Oncogene mutations occur in a dominant fashion, resulting from alterations of a single allele altering the phenotype. These mutations are classified as gain-of-function mutations.

In contrast to oncogenes, tumor suppressor gene mutations require changes in both alleles; hence, these loss of function mutations are inherited as recessive changes that inhibit suppression of cell proliferation. Tumor suppressor genes normally block cell division either by preventing cell replication or repairing a defect in DNA replication. The inhibition of tumor suppressor genes contributes to the malignant transformation of these cells.[93] Unlike oncogene mutations, tumor suppressor gene mutations are inherited in the heterozygous state, resulting in a predisposition to human cancer.[94]

Mutator genes control the purity of the DNA replication process by eliminating endogenous mutations formed from the spontaneous deamination of 5-methylcytosine (C/T transition) and defective repair of DNA by DNA polymerase during replication. The genetic alterations include deregulation of gene expression, allelic losses, amplifications, point mutations, deletions, and translocations. Alterations of these mutator genes reduce the effectiveness of the editing process during DNA replication; consequently, the mutation rate increases. Like tumor suppressor gene mutations, these loss of function mutations contribute to the inherited predisposition to cancer.

Promotion

Initiation is the initial process that produces genetic changes to form the first clone of mutated cells; however, the development of cancer requires further epigenetic stimuli before the cellular expression of cancer appears. Early animal studies on the development of epidermal carcinogenesis in mice and later liver cancer in rats demonstrated the necessity of applying an initiating agent followed by a promoting agent.[82,95] Neither the application of benzo(a)pyrene nor croton oil to the skin of mice produced cancer; however, the application

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of benzo(a)pyrene followed by croton oil did cause cancer of the skin. Reversing the application of the chemicals (i.e., croton oil followed by benzo(a)pyrene) did not induce skin cancer. This observation indicates the action of promoting agents is reversible, whereas the effects of initiating agents are irreversible. Promotion involves alterations in gene expression rather than molecular changes in DNA; promoting agents increase cell replication only in a specific subset of the initiated cell population. Tumor promoters may be difficult to separate from mutagens because the epigenetic effects of promoters on cell and tissue homeostasis may secondarily produce mutagens.[96]

Stages

The promotion process confers a selective growth advantage to the initiated cell population and decreases the rate of cell division of uninitiated cells;[97] selective blockage of gap junctional intercellular communication limits growth control from normal adjacent cells, resulting in clonal expansion.[78] Within the multistage process of chemical carcinogenesis promotion, there is at least a two-stage process.[98] Stage I promotion is the transformation of the initiated cell; stage II is the propagation of the transformed cell into a premalignant tumor. Tumor promotion produces primarily benign foci of preneoplastic cells that must undergo one or more additional heritable changes during progression to form a malignant neoplasm.[99] The spontaneous development of a malignant lesion within the preneoplastic lesions formed during promotion is a rare event.

Course

Promotion is a slow process that represents the longest stage in cancer development.[78] During this stage, exposure to promoting agents converts dormant, initiated cells into a growing, premalignant clone by altering the expression of portions of the genes that control cell proliferation and morphology. These preneoplastic cells are more susceptible than normal cells to proteins affecting cell replication and less susceptible to apoptosis. Apoptosis (i.e., active cell death) serves at least two functions: homeostasis of cell numbers in tissues and elimination of damaged cells. Tumor promoters confer a growth advantage to the initiated cells by shifting the balance from apoptosis to cell replication.[100] This stage probably accounts for the long latent period between initiation and the clinical detection of cancer; prolonged exposure to the promoter is necessary for tumor development.

Many, if not all, initiated cells in the stage of promotion depend on the continual presence of the promoting agent to survive.[101] Consequently, promotion is the *reversible* stage of cancer development (i.e., in the early stages of promotion), involving replication of the initiated cell and alteration of gene expression. The development of nodular hyperplasia and hepatic adenomas in premenopausal women following the administration of some synthetic estrogen preparations may regress after drug cessation.[102]

Intermittent exposure and cessation of exposure reduce the carcinogenic potential of a promoting agent in experimental settings.[78,103] Epidemiology studies indicate lung cancer risk decreases exponentially with time after cessation of smoking; after 15–20 years of nonsmoking, the lung cancer risks of prior smokers and never-smokers are similar.[104] The laryngeal cancer risk also decreases in intermittent smokers compared with continuous smokers.[105]

Characteristics

Although promoting agents do not directly induce structural changes in genes, they can produce metabolic changes (e.g., free oxygen radicals) that cause chromosomal alterations, strand breaks in the deoxyribosyl DNA backbone, and base modifications.[106] Characteristics of promoting agents include the requirement of prolonged exposure, the absence of an additive effect in the early phase, a lack of mutagenicity, the insignificance of metabolic activation, the probable presence of a threshold effect, and the importance of mitogenic properties (i.e., enhanced DNA synthesis), as noted in Table 47.3.[107]

Like initiating agents, promoting agents are structurally dissimilar and represent a wide variety of compounds (drugs, synthetic chemicals, hormones, and natural products). Metabolic activation probably is not a significant part of the process of promotion. Promoting agents include phenobarbital, phorbol esters (croton oil), butylated hydroxytoluene (BHT), cigarette smoke, viral infections, hormones, bile salts, and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). These compounds often display tissue specificity.

Site of Action

Tumor promoters (e.g., the phorbol ester, phorbol 12-myristate 13-acetate) are nongenotoxic carcinogens that enhance the clonal expansion of initiated cells by preventing apoptotic loss of initiated cells. In contrast to an initiator and a progressor, phorbol ester receptors

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bind protein kinase C-α (PKCα), members of the protein kinase C (PKC) family of serine/threonine-specific protein kinases involved in phosphorylating a wide variety of cell functions and protein targets including activating protein-1 and nuclear factor kappa B depending on cell types and conditions.[108] Activation of PKCα produces lipid hydrolysis and interactions with various adapter proteins affecting cellular transformation, differentiation, proliferation, apoptosis, motility, and adhesion including the ability of preneoplastic and malignant cells to resist apoptosis-based tumor surveillance. Consequently, promotion is an epigenetic phenomenon that involves changes in the expression of the genetic information in the genome rather than alterations of DNA structure.

Modulating Factors

Environmental factors (hormones, age, diet, sex) modulate the effect of promoting agents. Although these compounds cannot initiate cells, promoting agents may produce spontaneous mutations in the environment by causing chronic inflammation and free-radical formation. Benzoyl peroxide is an example of a compound that acts as a promoter during the induction of epidermal cancer in the mouse.[109] In cell cultures, these agents modulate aspects of gene expression through discrete effects on differentiation (e.g., inhibition, stimulation, recovery, terminal phase). The mechanism of action is not known, but the inhibition of intercellular communication[110] and alteration of cell membranes are plausible effects. Protein kinase C is an enzyme formed from the receptor-mediated hydrolysis of inositol phospholipids that regulates intracellular processes by relaying information across the cell membrane to the interior of the cell.[111] Presumably, this family of enzymes plays an integral part in the response (e.g., activation of transcription, alteration of membrane functions) of the cell to external signals. Studies in cells suggest that the primary site of action of the strong promoting agent of croton oil (phorbol esters) is the cell membrane and the principal target is protein kinase C.[112]

Progression

Progression is the irreversible, genetic process in the natural history of cancer when the malignant morphological changes in the cell genome become clinically evident; consequently, a tumor progressor allows premalignant, mutated cells to irreversibly acquire the phenotype of a fully malignant cell.[113] This stage is the final step in the transition from preneoplastic foci to malignant cells. Malignant conversion frequently involves multifocal changes in the premalignant lesions. During progression, marked changes in cellular morphology and biochemistry develop, the growth rate of the premalignant cells increases, the cells become increasingly invasive, and metastasis occurs. In human hepatocellular carcinomas, progression involves the transition from an early to a more advanced tumor manifesting histologically as a nodule-in-nodule lesion (i.e., a moderately to poorly differentiated cancerous nodule growing inside a well-differentiated cancer nodule).[114]

In contrast to the subtle alterations in the cell genome during initiation (e.g., single base changes including transitions and transversions), progression produces major chromosomal abnormalities (e.g., gene amplification, karyotypic instability, loss of heterozygosity, translocations, duplications, insertions, and deletions) in the genetic structure of the nucleus.[115] At the cellular level in experimental models, malignant conversion is associated with gene amplification, upregulation of AP-1 transcriptional activity, and overexpression of cell cycle regulatory genes and secreted proteases. During the stage of progression, the cell clone continually expands and displays gradually increasing malignant properties (i.e., undifferentiated/dedifferentiated and uncontrolled growth, invasion of surrounding tissue, metastasis). Angiogenic switches and increased hypervascularity are important processes in the development of malignant tumors during progression.

CANCER PATHOPHYSIOLOGY

Abnormal cell proliferation from deregulation of the cell cycle characterizes the development of malignant lesions with loss of cell cycle checkpoint controls, promoting genetic instability. Important factors in the pathogenesis of cancer include oncogene and tumor suppressor gene mutations and dysfunction of the DNA damage response network, particularly control of cell cycle checkpoints and DNA repair systems. Oncogene proliferation results from mutation-induced activation of growth signaling networks coupled with loss of tumor suppressor protein function.[37]

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DNA DAMAGE RESPONSE NETWORK

The DNA damage response network is a complex signal transduction pathway of interacting molecules that activates DNA repair mechanisms, regulates cell cycle arrest, adjusts telomere length, and activates transcription for viable cells or apoptosis for unrepairable DNA. The major parts of this pathway are DNA damage sensors (e.g., MRN protein complex,[116] DNA-binding protein replication protein A, RPA), signal transducers (e.g., ataxia-telangiectasia mutated, ATM; ataxia-telangiectasia and RAD3-related, ATR), and downstream signal effectors that suppress kinases or phosphatases (e.g., cell division cycle 25A, CDC25A; p53). ATM and DNA-dependent protein kinase catalytic subunit (DNA-PKcs) respond primarily to double-strand DNA breaks, whereas single-stranded DNA and stalled DNA replication forks activate ATR.[117] ATM and ATR signal transducers frequently act together with the related kinase (DNA-PK) because of the common occurrence of both types of DNA damage.[118]

ATM/ATR-Chk1/2 Signaling Pathways

ATM activates the downstream protein kinase Chk2 and the tumor suppressor gene *TP53*, whereas ATR-mediated phosphorylation activates Chk1; however, a substantial amount of redundancy occurs in these two pathways.[119] Important targets of Chk1/2 are the CDC25 phosphatases that control mitotic entry (CDC25B/C) and S-phase progression (CDC25A). The ATR-Chk1 pathway is the essential direct effector of DNA damage and replication checkpoints necessary for the survival of most cell types. Although organisms survive with mutations in *ATM* (e.g., BRCA1, BRCA2), the presence of these mutations increases genomic instability and cancer risk.

The G1/S checkpoint involves Chk1- and Chk2-induced degradation of CDC25A phosphatase in response to DNA damage, resulting in the inactivation of CDK2-cyclin E complex and G1/S arrest. Activation and accumulation of p53 also occur after DNA damage catalyzed by multiple protein kinase pathways (ATM, ATR, DNA-PK, Chk1/Chk2). Upregulation of p53 enhances transcription and upregulates several genes involved with DNA damage response (e.g., *GADD45A*, $p21^{WAF1/CIP1}$). Accumulation of $p21^{WAF1}$ protein suppresses CDK2-cyclin E, producing G1 arrest. The G2M checkpoint involves Chk1-induced phosphorylation of CDC25C phosphatase; increased phosphorylation of CDK1 by WEE1/MYT1 inactivates the CDK1-cyclin B1 complex, resulting in G2/M arrest. DNA damage also activates p53 via Chk1/Chk2, resulting in the induction of $p21^{WAF1/CIP1}$, blockage of CDK1-cyclin B1 formation, and G2/M arrest.

MAPK Pathways

The DNA damage response network contains a third effector kinase complex that operates parallel to Chk1 and downstream of ATM and ATR; the p38 mitogen-activated protein kinase pathway (p38MAPK) targets the downstream effector kinase, MAPK activated protein kinase 2 (MK2).[120] In response to DNA damage, this pathway regulates G1/S and G2/M cell cycle checkpoints by multiple mechanisms, including p53 phosphorylation, stabilization of the transcriptional repressor (HBP1), and degrading CDC25A. Other members of the MAPK family (e.g., ERK, JNK) respond primarily to stress and inflammatory stimuli rather than mitogens; the JNK MAPK pathway responds to DNA damage by phosphorylation of CDC25C, resulting in G2/M arrest.[121] $p21^{WAF1}$ is a cyclin-dependent kinase inhibitor for all cyclin/CDK complexes, particularly in the G1 phase; ERK MAPK enhances $p21^{WAF1}$ accumulation and G1 arrest.[122] In response to a variety of extrinsic (ionizing radiation, osmotic stress) and intrinsic (reactive oxygen species, cytokines, DNA damage) stimuli, the p38 MAPK pathway alters transcription, protein synthesis, cytoskeletal structure, cell surface receptors, and cell survival.[123] JNK, ERK, and p38 MARK pathways participate in the activation of activating protein-1 (AP-1) transcription factor that is a component of the c-Jun proto-oncoprotein. MAPK signaling pathways regulate many aspects associated with malignant cell behavior, including proliferation, longevity, migration, and invasion with the ERK pathway deregulated in $\sim^1/_3$ of human cancers.[68]

GENE MUTATIONS

Mutations following exposure to chemical carcinogens are DNA alterations inherited by subsequent cell progeny and occurring in <1% of the general population, whereas mutations occurring at a higher frequency are polymorphisms. These DNA alterations appear as visible changes (i.e., gene translocation, inversion, amplification, rearrangement) in the chromosome or changes in the nucleotide bases of the DNA structure (e.g., insertions, deletions, point transpositions, frameshifts).[98] Single nucleotide polymorphisms (SNPs) are the most common DNA variations in the human genome (i.e., 1/300–1,000 bp).

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Malignant tumors typically contain multiple mutations that alter many cell control functions and allow the tumor to acquire malignant characteristics. On a molecular level, mediators of cell growth suppression (e.g., p53, pRb, TGF-β signaling pathway) affect multiple cancer hallmarks, including metabolism, angiogenesis, genetic instability, cell death, invasion/metastasis, inflammation, and tumor microenvironment maintenance.[124] Similarly, multiple molecular targets regulate each cancer hallmark.

The number of cells in a tissue is a balance between cell proliferation and cell death. Proto-oncogenes and tumor suppressor genes regulate the former, whereas apoptosis and anti-apoptosis genes regulate the latter. The human genome contains ~20,000 protein-coding genes; however, the number of tumor suppressor genes and oncogenes is very small (~70 and 50, respectively).[125] Other natural mechanisms limiting tumor progression include growth inhibition and senescence. Somatic mutations occur only in somatic cells from changes in cellular DNA, environmental factors, and/or DNA replication errors with the number of somatic mutations correlating strongly to the number of stem cell divisions and age; germline mutations occur in germ cells inherited from parents. Although the rate of point mutations in tumors and normal cells is similar, the rate of chromosomal changes (e.g., deletions, inversions, translocations, chromosome number) in tumors is relatively greater. Cancer genome sequencing and epidemiological data suggest DNA replication errors account for up to $\sim^2/_3$ of somatic mutations.[126]

Sequencing of common human cancers indicates tumors typically contain a few frequently mutated and many infrequently mutated genes. Driver gene mutations confer a selective growth advantage to the altered cell, whereas passenger gene mutations provide no direct or indirect growth advantages. The total number of driver genes is unknown; however, at least 140 genes can promote (i.e., drive) carcinogenesis, with typical solid tumors containing 2–8 driver gene mutations and many passenger gene mutations (i.e., ~30–60).[125] Some tumors have substantially more somatic gene mutations (i.e., ~200), particularly with exposure to potent carcinogens (e.g., cigarette smoke, UV light). Most of these mutations are single-base substitutions (e.g., C > G) resulting in missense changes; deletions or insertions of up to a few bases occur much less frequently. Driver genes usually involve mutations in 12 signaling pathways that regulate cell survival, cell fate, and/or genome maintenance, as displayed in Figure 47.12. Although metastatic cancer usually requires decades to develop,

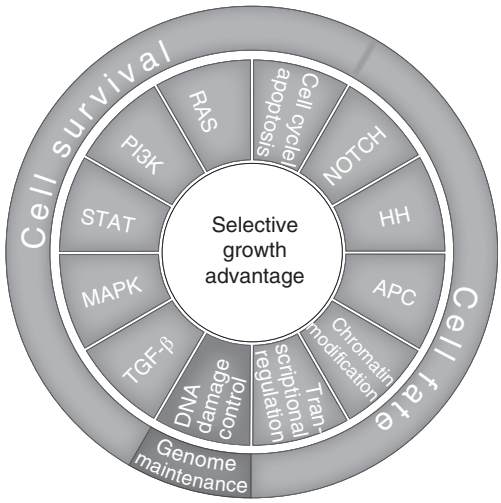


FIGURE 47.12. Cell processes and cancer cell signaling pathways are typically involved in driver gene mutations. In colon cancer, gatekeeper mutations often occur in the *APC* gene with increased clonal expansion developing after a second mutation in *K-RAS* proto-oncogene. Somatic mutations in *PIK3CA*, *SMAD4*, and *TP53* eventually confer malignant properties (e.g., invasiveness, metastasis) to the clone. (Adapted from Vogelstein et al.).[125]

almost all somatic mutations in metastatic tumors are present in the primary tumor.

Adducts

The electrophilic metabolites of known carcinogens covalently bind DNA, forming DNA-carcinogen complexes (adducts). Almost all adducts cause mutations rather than inaccurate replications.[127] Different classes of carcinogenic chemicals form adducts with different portions of the DNA molecule; however, these adducts are specific for a given chemical because the DNA-chemical adduct is the same in different animal species.[128]

An increase in adduct concentrations associated with bulk DNA usually increases the probably of mutations in critical genes. Sensitive measures (e.g., enzyme-linked immunosorbent assay, radioimmunoassay, ^{33}P-postlabeling, gas chromatography/mass spectrometry) can determine the presence of specific DNA-chemical adducts. This type of test allows monitoring of individuals exposed to chemicals capable of causing cancer; however, positive tests do not necessarily indicate the presence of mutagenesis or carcinogenesis.[129] The persistence of these adducts depends on the susceptibility of the tissue to neoplastic changes and particularly on DNA repair mechanisms.[130]

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During various cellular processes (transcription, recombination, replication, and apoptosis), these mechanisms repair DNA abnormalities including single-strand and double-strand breaks. Gene translocations, deletions, amplifications, and rearrangements occur during the repair of double-strand DNA breaks that may contribute to the initiation of a cell and subsequent tumor development.[131] Studies of the autosomal recessive disease, xeroderma pigmentosum, provide evidence for the importance of DNA repair mechanisms in carcinogenesis. Homozygotes demonstrate hypersensitivity to sunlight and marked increases in the incidence of skin cancer.[132] The fibroblasts from these patients possess defective DNA repair mechanisms for ultraviolet radiation-induced damage.

Proto-oncogenes

Proto-oncogenes are normal genes that produce proteins affecting all phases of cell signaling involved in the control of processes associated with normal cell growth, differentiation, and division.[133] These genes are essential regulators of cell proliferation, differentiation, apoptosis, and genome stability. Proto-oncogenes include genes that produce growth factors tyrosine kinases, growth factor receptors, nuclear regulatory proteins, and small membrane-associated GTPases (G proteins) that help regulate signal transduction.[134] Oncogene- and proto-oncogene-encoded proteins are structurally similar; however, the abnormal, oncogene-encoded proteins do not respond to normal regulatory limits. During carcinogenesis, mutations of proto-oncogenes (e.g., *MYC*) and tumor suppressor genes (e.g., *TP53*, RB family) alter the control of cell proliferation by altering the relationship of these regulatory proteins to growth factors.

Oncogenes

The discovery of oncogenes resulted from the isolation of a small set of cellular genes from retroviruses that produce tumors.[135] The progenitors of these oncogenes are altered versions of normal cellular genes (proto-oncogenes) acquired by retroviruses during evolution. Oncogenes produce oncoproteins that alter signal transduction pathways at the cell surface, cytosol, and nucleus. Mutations (point mutations, inversions, translocations), chromosomal rearrangement, gene fusion, and gene amplification convert proto-oncogenes to oncogenes that alter cell regulation and growth by producing oncoproteins. These oncoproteins contribute to the malignant transformation of cells by activating signaling pathways to preserve initiated cells through cell proliferation, deregulation of the cell cycle, and inhibition of apoptosis. Translocations and mutations occur during initiation and progression, whereas amplification usually occurs during progression. Over 1% of the genes in the human genome are associated with human cancers.[10,136]

Most oncogenes are positive growth signals that enhance growth factors, growth factor receptors, intracellular signaling molecules, and/or nuclear transcription factors. The six broad classes of oncogenes include: 1) transcription factors; 2) apoptosis regulators; 3) chromatin remodelers; 4) growth factors; 5) growth factor receptors (tyrosine kinases involving integral membrane proteins, receptors without protein kinase activity); and 6) signal transducers (cytoplasmic tyrosine kinases, membrane-associated G proteins, GTPase exchange factor, cytoplasmic serine/threonine kinases, cytoplasmic regulators).[76,137] The site of action for oncogenes includes the cytoplasm (e.g., growth factor, growth factor receptors, signal transducers) and nucleus (e.g., chromatin remodelers). Alterations in oncogenes affect the signal transduction process by altering cellular proteins involved in growth signal transduction pathways, including proteins in the extracellular environment (growth factors), cell membrane (growth factor receptors), cytoplasm (G proteins), and nucleus (DNA-binding proteins).[138] All tumors do not display alterations in proto-oncogene expression;[28] spontaneous translocations may create fusion (chimeric) proteins with functions similar to transcription factors produced by oncogenes.[139] The latent period between oncogene formation and progression to a malignant cell indicates that alteration of other genes in addition to a particular oncogene is necessary to produce cancer. Table 47.4 is a partial list of the six classes of oncogenes associated with specific neoplasms, protein function, and mechanism of activation.

The *RAS* oncogene family was the first oncogene family discovered; the RAS oncoprotein (p21) was the first oncogene protein identified. RAS encodes a family of membrane-bound, small GTPases including Harvey-Ras (H-RAS), neuroblastoma-Ras (N-RAS), and Kirsten-Ras (K-RAS). *RAS* oncogenes occur in ~30% of all human tumors, including lung, pancreatic, and colon cancers.[140,141] *RAS* oncogenes are downstream signal transducers of many receptor tyrosine kinases; activation of these pathways ultimately promotes cell survival and proliferation.[142] Oncogenes act on a variety of sites on cell constituents, including tyrosine kinase receptors, growth factors, serine/threonine kinases, nuclear proteins, transcription factors,[143] and

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TABLE 47.4. Mechanism of activation, protein function, and neoplasms associated with specific oncogenes. (Adapted from Croce).[76] The names for oncogenes change over time. The reader is encouraged to consult the National Library of Medicine website for genes to search for the latest abbreviations, (https://www.ncbi.nlm.nih.gov/gene/).

Oncogene	Neoplasms	Mechanism of Activation	Protein Function
		Transcription Factors	
L-MYC	Lung	Deregulated activity	Transcription factor
N-MYC	Neuroblastoma: lung cancer	Deregulated activity	Transcription factor
V-ERBA1	Erythroblastosis	Deregulated activity	T3 Transcription factor
V-ERBA2	Erythroblastosis	Deregulated activity	T3 Transcription factor
V-ETS-1	Erythroblastosis	Deregulated activity	Transcription factor
V-ETS-2	Erythroblastosis	Deregulated activity	Transcription factor
V-FOS	Osteosarcoma	Deregulated activity	AP1 Transcription factor
V-JUN	Sarcoma	Deregulated activity	AP1 Transcription factor
V-MYB	Myeloblastosis	Deregulated activity	Transcription factor
V-MYC	Myelocytomatosis	Deregulated activity	Transcription factor
V-REL	Lymphatic leukemia	Deregulated activity	Transcription factor
V-SKI	Carcinoma	Deregulated activity	Transcription factor
		Apoptosis Regulators	
BCL2	B cell lymphomas	Deregulated activity, ↑ gene amplification	Antiapoptotic protein
MDM2	Sarcomas	Protein	Complexes with p53
		Chromatin Remodelers	
ALL1 (MLL)	Acute lymphocytic leukemia, acute myelogenous leukemia	Gene fusion	Chromatin modifier
		Growth Factors	
HST	Stomach	Constitutive production	FGF family
INT2	Mammary carcinoma	Constitutive production	FGF family
KS3	Kaposi's sarcoma	Constitutive production	FGF family
V-SIS	Glioma, fibrosarcoma	Constitutive production	B chain PDGF
		Growth Factor Receptors–Tyrosine Kinases: Integral Membrane Proteins	
EGFR	Squamous cell	Gene amplification-protein-point	EGF receptor
	Non-small cell lung cancer	Mutation	
MET	MNNG-treated human osteocarcinoma cell line	DNA rearrangement/ligand-independent constitutive activation (fusion proteins)	HGF/SF receptor
HER2/NEU	Neuroblastoma, non-small cell lung cancer, breast, ovary	Constitutive activation-point mutation	Mitogen-activated protein kinase (MAPK) and phosphoinositid-3 kinase/protein kinase B signaling pathways, BCL-2 family suppression of pro-apoptotic functions of BAX and BAK
RET	Medullary thyroid carcinomas, MEN 2A-B, Hirschsprung disease	DNA rearrangement/ligand-independent, constitutive activation (fusion proteins)	Cadherin superfamily, cell-surface molecules transduce signals for cell growth and differentiation
TRK	Colon, thyroid	DNA rearrangement/ligand-independent, constitutive activation (fusion proteins)	NGF receptor
V-FMS	Sarcoma	Constitutive activation	CSF1 receptor
V-KIT	Sarcoma, GIST	Constitutive activation-point mutation	Stem cell factor
V-ROS	Sarcoma	Constitutive activation	Tyrosine kinase activity

(Continued)

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TABLE 47.4. (Continued)

Oncogene	Neoplasms	Mechanism of Activation	Protein Function
		Signal Transducers–Cytoplasmic Tyrosine Kinases	
ABL	Chronic myelogenous leukemia	DNA rearrangement (constitutive activation, fusion proteins)	Protein tyrosine kinase
SRC	Colon	Constitutive activation	Protein tyrosine kinase
V-FES	Sarcoma	Constitutive activation	Protein tyrosine kinase
V-FGR	Sarcoma	Constitutive activation	Protein tyrosine kinase
V-YES	Sarcoma	Constitutive activation	Protein tyrosine kinase
		Signal Transducers–Membrane-Associated G Proteins	
BRAF	Melanoma, thyroid, colon, ovary	Point mutation	Serine/threonine kinase
GIP	Ovary, adrenal	Point mutation	Inhibitory G protein α-subunit
GSP	Thyroid adenoma	Point mutation	Stimulatory G protein α-subunit
H-RAS	Colon, lung, pancreas	Point mutation	GTPase
K-RAS	Acute myelogenous leukemia, melanoma, thyroid, colon, lung	Point mutation	GTPase
N-RAS	Melanoma	Point mutation	GTPase
		Signal Transducers–GTPase Exchange Factor	
DBL	Diffuse B cell lymphoma	DNA rearrangement	Guanine nucleotide exchange factor for RHO subfamily of RAS-like GTP-binding proteins
VAV	Hematopoietic cells	DNA rearrangement	Guanosine nucleotide exchange factors for RHO GTPases and signaling adaptors downstream of protein tyrosine kinases involved with actin cytoskeletal rearrangements
		Signal Transducers–Cytoplasmic Serine/Threonine Kinases	
PIM-1	T cell lymphoma	Constitutive activation	Serine/threonine kinase
V-MOS	Sarcoma	Constitutive activation	Serine/threonine kinase
V-RAF	Sarcoma	Constitutive activation	Serine/threonine kinase
		Signal Transducers–Cytoplasmic Regulators	
V-CRK	—	Constitutive tyrosine phosphorylation cellular substrates	SH2/SH3 domain adaptor activity

Abbreviations: AP1 = activator protein-1; B chain PDGF = platelet-derived growth factor B chain; BAK = BCL2 antagonist/killer 1; BAX = BCL2 associated X; CSF1 = colony stimulating factor 1; EGF = epidermal growth factor; FGF = fibroblast growth factor; GIST = gastrointestinal stromal tumor; GTPase = guanosine triphosphatase; HGF/SF = hepatocyte growth factor/scatter factor; MNNG = *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine; NGF = nerve growth factor; T3 = 3,5,3′-triiodo-L-thyronine (Triiodothyronine). The prefix v refers to vial oncogenes, whereas the prefix c refers to their cellular counterpart. Oncogene names are abbreviations that reflect the history of their isolation and the types of tumors involved.

DNA, as outlined in Table 47.4. Most neoplastic transformations probably require several oncogenes and perhaps the inhibition of tumor suppressor genes or the interaction of oncogenes and promoters.[93] Cancer therapies targeting oncogenic proteins include small molecules (Gefitinib, Erlotinib) that affect intracellular processes or monoclonal antibodies (Cetuximab, Trastuzumab) that affect oncogenic proteins on the cell surface.[76]

Tumor Suppression

Most cancers demonstrate multiple genetic changes that produce enhanced proliferation (oncogenes) and loss of inhibition of cell growth (tumor suppressor genes) rather than a single mutation type.[144] The ability of cancer cells to evade cell growth-inhibitory signals is one of the hallmarks of cancer; this characteristic involves alterations in multiple cell processes, including tumor

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suppressor genes (e.g., *TP53*, *RB1*), TGF-β signaling pathway, gap junction, and contact inhibition. Point mutations in the p53 tumor suppressor gene are the most common genetic alterations detected in human cancers, with ~50–60% of tumors containing the TP53 gene mutation depending on the tumor type.[145,146] Conceptually, these genes are involved in the "checkpoint" controls of cell division that stop progression of the cell cycle when mutations occur. Loss of function of tumor suppressor genes allows the duplication of damaged DNA and increases the risk of neoplasia. The concentration of p53 proteins is frequently elevated in workers exposed to carcinogens (e.g., hexavalent chromium,[147] vinyl chloride).[148] Although ~30–40% of patients with p53 gene mutations develop antibodies against this mutation, the presence of these antibodies is not a good diagnostic marker of cancer because other methods are more sensitive.[149] The biological significance and the predictive value of high concentrations of serum p53 proteins remain unclear.

p53 Pathway

The p53 pathway maintains a normal genome by regulating cell cycle checkpoints, activating DNA damage repair, inducing apoptosis (programmed cell death), and altering angiogenesis and cellular stress response. The normal *TP53* gene produces a tetrameric nuclear transcription factor that suppresses tumor formation by detecting DNA damage and preventing cell replication until the damage is repaired. Two homologous negative proto-oncogenes (*MDM2*, *MDM4*) control p53 activity by producing proteins that degrade p53 via ubiquitination.[150] Other signaling pathways also influence p53 function including Ataxia-Telangiectasia-related (ATR)-Checkpoint kinase 1 (Chk1), Ataxia-Telangiectasia-mutated (ATM)-Checkpoint kinase 2 (Chk2), and liver kinase B1 (LKB1).[124]

The *TP53* tumor suppressor gene limits cell replication by inducing the transcription of *CDKN1A* gene, which produces an inhibitory protein that binds to the regulatory protein, cyclin and the cyclin-dependent kinase complex. The restriction of kinase activity limits cell replication and allows time for the repair of DNA. Inactivation of these genes accelerates neoplastic changes by limiting the inhibitory effect of these genes on mutated cells. This gene participates in the cell cycle checkpoint signal transduction pathway responsible for causing arrest of the cell in the G1 phase or apoptosis after the detection of DNA damage. C-to-T transitions at CpG dinucleotides account for the majority of human tumor mutations in the p53 gene, particularly in brain, colon, and blood cancers.[151] The p53 tumor suppressor gene is located on the short arm of chromosome 17; mutations of tumor suppressor genes require inherited changes in both alleles.

Retinoblastoma Protein (pRb)

First identified in a malignant retinal tumor (retinoblastoma), the nuclear RB protein is a tumor suppressor protein encoded by the retinoblastoma susceptibility gene (*RB1*); this protein is an integral part of the restriction point in mid-G1 that blocks S-phase entry (G1/S transition) and limits cell growth. The retinoblastoma family includes three "pocket proteins" (RB/p105, p107, RB2/p130) that repress gene transcription required for the G1/S transition by binding to the promoter of E2F family of transcription factors and interacting with proteins involved with nucleosome remodeling, histone acetylation/deacetylation, and methylation.[32] The pRb pathway includes cyclin D, cyclin-dependent kinases 4/6, and CDK inhibitor 2a (p16/INK4a); this pathway integrates mitogenic and antimitogenic signals including growth factor receptors, RAS, and p53 as well as affecting DNA replication, differentiation, cellular senescence, and apoptosis.[152] Many human neoplasms (e.g., osteosarcoma, retinoblastoma, small cell lung carcinoma) contain direct mutations or deletions of the *RB1* gene or alterations in the activation or expression of upstream regulators.[153]

Transforming Growth Factor-β (TGF-β)

The TGF-β inhibits cell growth by producing the downstream effector transcription factors, SMAD2 and SMAD3;[154] these proteins reduce transcription of *TGF-β* genes, including the growth inhibitors, $p15^{INK4B}$ (*CDKN2B*) and $p21^{WAF1}$ (*CDKN1A*).[155] A major upstream regulator of TGF-β is epidermal growth factor receptor (EGFR) that activates SMAD2 and SMAD3 as well as other pathways and effectors (MAPK/ERK, CDKs, glycogen synthetase kinase 3β, JNK, p38).[156] Inactivation of TGF-β-mediated growth inhibition is an important prerequisite for tumor development that allows cancer cells to resist TGF-β tumor suppression activities and utilize TGF-β as a prooncogenic factor.[157]

Gap Junctions

The large connexin family of transmembrane proteins assembles tightly packed intercellular channels (gap junctions) that allow intercellular communication for a variety of metabolites, ions (ATP, cAMP, Ca^{2+}), and small signaling molecules. Individual cells may express

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different connexins, resulting in many different subtypes of gap junctions. Thus, these channels provide communication channels between cytoplasm and the extracellular environment; these channels also dock with each other to form gap junction plaques that limit communication. Connexins are tumor suppressors in normal cells that reduce tumor cell growth and partially redifferentiate transformed cells; however, connexins promote tissue invasion and metastasis in advanced stages of some tumors.[158]

Contact Inhibition

Normal cells respond to increased cell density by undergoing G1 arrest and/or decreased cell division. Contact growth inhibition results from signal transduction events mediated by a large family of transmembrane proteins (cadherins) that alter calcium-dependent adhesive interactions between adjacent cells. Cytoplasmic proteins (e.g., β-catenin, p120) interact with the intracellular domain of cadherins. Nontransformed cells express E-cadherin to maintain intercellular contact between cells and form epithelial monolayers. This process involves CDK inhibitors (p16, p21, p27) that block cyclin D-CDK4 and cyclin E-CDK2, resulting in G1 arrest; additionally, contact growth inhibition recruits tumor suppressors (pRb, p53, p27).[159] Mutations of tumor suppressors in cancer cells allow transformed cells to evade contact inhibition and limit cell cycle progression.[160]

Nonprotein Coding RNAs

Approximately 10% of the RNA in human cells is mRNA that provides templates for protein expression, whereas the remaining 90% of RNA is nonprotein coding RNA (ncRNA). Long noncoding RNA (lncRNA) consists of transcripts of >200 nucleotides in length located in overlapping antisense transcripts of protein-coding genes or intergenic stretches. Epigenetic processes affected by lncRNAs involve chromatin remodeling, histone modification, and DNA methylation. The main functions of these lncRNAs include molecular guides for localizing mRNA to their binding sites, scaffold molecules for chromatin modification, regulation of DNA looping, alteration of RNA transcription, translation, splicing, and stability, and coactivator of transcription factors.

MicroRNA (miRNA) genes produce single RNA strands of ~21–23 nucleotides rather than oncoproteins; these RNA strands alter gene expression by degrading mRNA and blocking protein translation. Some miRNAs and lncRNAs are potential biomarkers for determining clinical typing, diagnosis, and prognosis of specific tumors (e.g., leukemia subtypes).[161,162] Deletion or downregulation of miR-15a and miR-16-1 occurs in most indolent cases of chronic lymphocytic leukemia.[163] MicroRNA genes can function as oncogenes (i.e., downregulating tumor suppressor genes) or tumor suppressor genes (downregulating oncogenes), depending on their specific tissue targets (i.e., suppressor gene or oncogene). Both genetic (deletions, amplifications) and epigenetic (demethylation, epigenetic silencing) factors affect the expression of microRNA genes. Table 47.5 displays the key cellular proteins targeted by specific miRNAs.

TABLE 47.5. Key targets of microRNA during DNA damage response. (Adapted from Liu et al.).[66]

Key Target	Function	MicroRNA Number
CDK2	Cell cycle	124a, 372, 376a, 385-5p
Cyclin D	Cell cycle	15, 16, 195
p21	Cell cycle	17, 20a/b, 93, 106a/b, 192, 215, 663
CDC25a	Cell cycle checkpoint	21, 424, 449a/b, 503
Chk1	Cell cycle checkpoint	15 family, 26a
WIP1	Cell cycle checkpoint	16
MDM2	Cell cycle checkpoint, apoptosis	192, 194, 215, 605
p53	Cell cycle checkpoint, apoptosis	125b, 504
H2AX	Sensor	24, 136
ATM	Transducer	18a, 100, 101, 181a/b, 421
BRCA1	DNA repair	146a, 146-5p, 182
BCL1	Apoptosis	15a, 16-1, 34a, 195

MiRNAs participate in most DNA damage repair processes, including sensing DNA damage, transducing DNA damage signals, repairing DNA damage, stimulating cell cycle checkpoints, and initiating apoptosis when DNA damage persists. MiRNAs regulate gene expression by degrading or inhibiting transcription of target mRNAs after attachment to complementary sequences in the mRNAs.[66] A dense network of miRNAs controls the activity and expression of p53, ensuring the rapid accumulation of p53 following DNA damage. DNA damage activates multiple transcriptional factors (e.g., C-JUN, C-MYC, E2F1, nuclear factor-kappa B, p53) that alter miRNA expression by regulating essential steps in miRNA processing and maturation. Additionally, phosphoinositide 3-kinase (pI3K)-like protein kinases (ATM, ATR, DNA-PKcs) also regulate miRNA expression following DNA damage.[164] MiRNA

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regulates gene expression by binding to the 3′ untranslated gene region, resulting in the induction of RNA degradation or blocking gene translation.[165]

CELLULAR ALTERATIONS

Conceptually, cancer is a disruption of the normal control processes that regulate cell division and differentiation. Most cancers begin as an alteration of a single cell that develops into a clone of malignant cells capable of spreading throughout the body.[166] This clone demonstrates several characteristics, including: 1) autonomy (i.e., unregulated growth independent of normal biochemical and physical control factors); 2) anaplasia (i.e., abnormal cell differentiation); and 3) metastasis (i.e., dissemination of the clone to distant sites in the body). Chemical carcinogens may exert their effect by permanently altering the DNA of the cell genome (i.e., initiation); however, DNA is not the only critical target of chemical carcinogens. Chemical carcinogens also act at other cancer stages (e.g., promotion, progression), including interactions with proteins important in the regulation of gene expression or changes in enzymatic methylation of DNA.[167,168] These epigenetic mechanisms involve inactivation of specific control points by hypermethylation of gene promoters and reactivation of suppressed genes by hypomethylation.[169] As the normal cell evolves into the malignant state, the cells acquire a succession of hallmark capabilities listed in Table 47.6.

Two enabling characteristics enhance the multistep transition from a normal cell to an invasive tumor. The most prominent characteristic in a large majority of human tumors is genome instability with the generation of random mutations.[170] Normally, DNA replication and chromosomal segregation are impressively accurate processes, with somatic cell cultures displaying overall mutation rates of $\sim 2 \times 10^{-7}$ mutation/gene/cell division and $\sim 1.4 \times 10^{-10}$ single base substitutions/nucleotide/cell division.[171] Based on the presence of ~70,000 genes/cell, each cell accumulates an estimated one mutant gene during the life span of an individual; however, cancer cells often increase spontaneous mutation rates by increased sensitivity to mutagenic agents and/or impairment of genome maintenance systems that detect and repair mutations. Almost all human tumor cells contain immune cells with infiltrates ranging from a few cell type-specific antibodies to gross inflammation.[172] Tumor-associated inflammation is the other enabling characteristic that enhances tumorigenesis and progression by supplying bioactive molecules to the tumor microenvironment. Uncontrolled release of prostaglandins, cytokines, chemokines, and reactive oxygen species enhances genomic instability, alterations in vasculature, and disruption of local immune processes.

Emerging hallmarks include: 1) reprogramming energy metabolism to glycolysis that normal cells use primarily under anaerobic conditions; and 2) the evasion of immune destruction by unclear mechanisms.[170] Immune cells within the tumor microenvironment produce conflicting effects including tumor-inhibiting and tumor promoting actions.[173] Tumors arise from a small population of cells (cancer stem cells or tumor initiating cells) that produce histopathologically diverse neoplastic lesions with various degrees of differentiation, vascularity, inflammation, proliferation, and invasiveness. Based on animal studies, the stroma and parenchyma of these tumors contain distinct cell types that enable tumor progression and the seeding of new tumors by cancer stem cells.[174] Hallmark-targeting cancer drugs direct their activity at specific molecular targets involved in enabling particular capabilities; however, the common occurrence of relapses following the use of these drugs suggests these hallmark capabilities are regulated by partially redundant signaling pathways.

Cell Proliferation

Telomeres

The telomere is a nucleoprotein complex located at the ends of linear eukaryotic chromosomes; in contrast to most plasmids and viruses with circular genomes, the linear chromosomes of eucaryotes require mechanisms to protect and replicate DNA ends. These short, dysfunctional repetitive nucleotide sequences help maintain chromosomal stability by forming a specialized complex (shelterin) that protects telomeres from the DNA damage response. This complex conceals chromosomal ends from DNA repair mechanisms and represses ATM/ATR signaling pathways.[175] Cells count the number of cell divisions based on telomere length with each cell division shortening the telomere as a result of incomplete replication of linear DNA molecules by conventional DNA polymerases. These heterochromatic DNA-protein structures (shelterin) reduce the loss of nuclear material, stabilizing chromosomes, and avoiding fusion between adjacent chromosomes during cell replication.[176]

Telomeres progressively shorten throughout the life of an individual.[177] Telomerase is the enzyme responsible for maintaining proper telomere length by compensating for telomere attrition by adding TTAGGG repeats in regenerating cells (e.g., pluripotent stem cells).[178] Telomeres shorten with every cell

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TABLE 47.6. Hallmark characteristics of cancer. The hallmarks of cancer are acquired functional capabilities that allow cancer cells to survive, proliferate, and metastasize via genetic and epigenetic changes during the multistep process of carcinogenesis. Two emerging hallmarks that enhance carcinogenesis are reprogramming energy metabolism and evading immune destruction. Enabling hallmarks include genome instability and inflammation along with the formation of a tumor microenvironment to enhance the growth of the tumor. (Adapted from Hanahan and Weinberg).[170]

Characteristic	Primary Target	Example
	Classic Hallmarks	
Sustaining proliferative signaling	Growth factors binding cell-surface receptors containing intracellular tyrosine kinase domains	RAS oncoprotein-induced disruption of negative-feedback mechanisms attenuating proliferative signaling (membrane-associated G protein signal transducers) or activation of epidermal growth factor receptor (EGFR) signaling pathway by epidermal growth factor and/or transforming growth factor-α resulting in tumor proliferation.
Evading growth suppressors	Control nodes in complementary pathways to regulate cell proliferation and activate senescence/apoptotic programs	RB (retinoblastoma-associated) and TP53 (tumor protein p53) oncoproteins inhibit tumor suppressor genes and reduce tumor senescence/apoptosis in lung tumors.
Resisting cell death	Intrinsic and extrinsic apoptotic pathways	BCL-2 family of regulatory proteins inhibits apoptosis by binding to proapoptotic triggering proteins (BAX, BAK).
Enabling replicative immortality	Telomeres protect the ends of chromosomes from progressive shortening from successive cell generations	Enhanced telomerase activity reduces telomere erosion and increases resistance to senescence and apoptosis. Telomerase reverse transcriptase and DNA methyltransferases control telomere length, producing successive generations.
Inducing angiogenesis	Neovascularization generated by angiogenesis supplies nutrients and oxygen along with eliminating CO_2 and waste	Production of aberrant vessels with erratic blood flow by activation of stimulatory angiogenic regulators (vascular endothelial growth factor-A) and downregulation of inhibitors (thrombospondin-1).
Activating invasion and metastasis	Alteration of shape and attachment of other cells and extracellular matrix via epithelial-to-mesenchymal transition	Downregulation of cell-to-cell adhesion molecules (E-cadherin) and alteration of the developmental regulatory program (epithelial-mesenchymal transition) by pleiotropically acting transcription factors (SLUG, SNAIL, TWIST, ZEB1/2).
	Emerging Hallmarks	
Reprograming energy metabolism	Cytosolic aerobic glycolysis via reprogrammed metabolic pathways in cancer cells	Upregulated glucose transporters and multiple glycolytic pathway enzymes along with hypoxia-inducible 1-α factors (HIF1α, HIF2α).
Evading immune destruction	Immune cells lose their ability to eradicate cancer cells in tumor microclimates via alteration of programmed death-ligand 1, then help support tumor survival	Unclear exact mechanism, possibly involving altered function of cytotoxic T cells, T_h1 helper T cells, and natural killer cells.
	Enabling Characteristics	
Genome instability (↑ genome alteration during cell division from changes in DNA damage checkpoints, DNA repair machinery, and mitotic checkpoints)	Chromosomal and telomere abnormalities cause ↑mutations and carcinogenic changes to genome	A succession of clonal expansions triggered by chance acquisitions of mutant genotypes by alteration of genome maintenance and repair. Some epigenetic mechanisms (DNA methylation, histone modifications) also contribute to progression.
Inflammation	Immune cell infiltration of tumors	Supply of bioactive molecules to tumor environment (growth factors, extracellular matrix-modifying enzymes) that limit cell death, facilitate angiogenesis, and activate epithelial-mesenchymal transition.

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division, particularly in aging patients with chronic diseases. In mice, the percentage of shortened telomeres is associated with shorter lifespans rather than the monthly rate of telomere shortening.[179] Shortened telomeres induce the DNA damage response that causes cell cycle arrest and replicative senescence when DNA repair is not possible. Insufficient telomerase and loss of telomeric DNA expose vulnerable chromosomal ends to subsequent amplification/deletion of chromosomal segments.[180]

Telomere shortening induces chromosomal instability and enhances tumor development in the absence of functional tumor suppressor genes. Short telomeres block stem cell proliferation and tissue regeneration; hence, telomere shorting is a potential physiological marker of aging.[181] Telomere syndromes include aplastic anemia, liver and pulmonary fibrosis, dyskeratosis congenita (nail dysplasia, skin pigmentation, and oral leukoplakia with very high risk of bone marrow failure), and Hoyeraal-Hreidarsson syndrome (multisystemic genetic disorder with very short telomeres).[182] In nonmalignant cells, the maximum number of cell divisions is ~60–70.[183] Cells enter a state of senescence when cell division stops. Normal DNA damage-sensing systems recognize erosion of telomeres, resulting in the activation of mechanisms to limit further somatic cell division. Germline cells (sperm, ova, gametes) undergo meiosis to produce haploid daughters with a single set of chromosomes. The Mendelian randomized study of genome-wide association reports associated increased telomere length in germline genetic variants with increased risk of some cancers (glioma, low-malignant-potential ovarian cancer, lung adenocarcinoma, neuroblastoma, bladder cancer, melanoma, testicular cancer, kidney cancer, endometrial cancer) and a lower risk of some nonmalignant diseases (cardiovascular diseases, abdominal aortic aneurysm, celiac disease, interstitial lung disease).[184]

Angiogenesis

The development of new blood vessels in tumors (angiogenesis) is a prerequisite for the growth, maintenance, and progression of malignant tumors. Tumor angiogenesis is a complex process involving the interaction of tumor cells, endothelial cells, phagocytes, and inflammatory cytokines. Mechanisms for tumor angiogenesis include endothelial sprouting (i.e., formation of new vessels from preexisting blood vessels) and intussusceptive vascular growth (i.e., splitting of preexisting blood vessel into two new blood vessels by formation of transvascular pillars). The sprouting process involves endothelial cell migration, proliferation, and tube formation, whereas the splitting process involves the formation and insertion of interstitial tissues into the lumen or walls of preexisting vessels. There is a large, diverse range of angiogenesis mediators, including stimulators and inhibitors of angiogenesis. Positive regulators of these two mechanisms of angiogenesis include PDGF/VEGF growth factor family. and its receptors FLK-1 (KDR) and FLT-1 for the sprouting process; factors mediating the splitting process include the angiopoietin/tie-2 and ephrin-B/EpH-B signaling pathways.[185] In some malignant tumors (e.g., glioblastomas, breast and ovarian cancer, hepatocellular carcinomas), cancer stem cells can form nonendothelium-lined blood vessels (vasculogenic mimicry).[186] This process involves several families of growth (angiogenic) factors, including vascular endothelial (VE)-cadherin, vascular endothelial growth factor receptor (VEGFR1), phosphatidyl inositol 3-kinase (PI3K), matrix metalloproteinases (MMPs), erythropoietin-producing hepatocellular receptor A2 (EPHA2), and hypoxia inducible factor-1α (HIF1α). Some of these angiogenic factors are direct-acting, binding primarily to activated epithelial cells (e.g., VE-cadherin, VEGFR1). Others are indirect-acting and express pro-angiogenic growth factors or recruit endothelial cells to the tumor, including transforming growth factor beta (TGF-β), cytokines (IL-6, IL-8, Stromal-derived factor-1, G-CSF), and sex hormones (androgens, estrogens).[187] Tumor angiogenesis produces qualitatively different blood vessels. Overexpression of pro-angiogenic factors allows for higher density along with greater permeability from the cytoplasmic projections penetrating the lumen and creating small, intercellular gaps in the vessel walls.

The body also contains a variety of endogenous angiogenesis inhibitors including the large glycoprotein thrombospondin-1 (TSP-1a), which is upregulated by p53; loss of p53 downregulates TSP-1 expression.[188] The development of angiogenesis and malignant tumors requires the downregulation of neovascularization inhibitors present in most normal cells. VEGF-induced angiogenesis upregulates the NOTCH/DLL4 signaling pathway that is essential as a stimulator of embryonic, wound, and *in utero* angiogenesis; however, in adults, activation of this pathway inhibits tumor angiogenesis by producing abnormal, poorly functioning blood vessels that inhibit tumor growth. Consequently, delta-like four Notch ligands (DLL4) produce a negative feedback system to prevent functional tumor angiogenesis.[189] The first successful randomized phase 3 clinical trial of an antiangiogenic agent involved the use of bevacizumab, a monoclonal antibody to VEGF, in metastatic colon cancer; however, the success of the drug depended on

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the coadministration of radiation or chemotherapeutic agents to alter other pathways.[190]

Apoptosis and Necroptosis

Apoptosis (programmed cell death) and necroptosis (RIPK3/RIPK1-mediated necrosis) are the phenotypic expression of energy-dependent events that cause cell death by two different pathways. The cascade of apoptotic events results from the presence of certain stimuli that produce morphological changes (DNA fragmentation, nuclear condensation, cell shrinkage) characteristic of cell death.[191] In normal adult tissue, apoptosis is an active physiological process that maintains homeostasis by eliminating damaged DNA or pathogens in defective cells (e.g., over-expressed oncogenes, infected cells) resulting from spontaneous/induced mutations from invasion by a pathogen. Apoptosis packages dying cells into fragments easily eliminated by phagocytes without disturbing normal cell function.[192] This biological process differs from necrosis because apoptosis does not produce a secondary inflammatory response and potentially the formation of additional mutations; apoptosis requires activation and inactivation of certain regulatory genes, primarily a family of cysteine-dependent, aspartate-directed proteases (caspases). The two apoptosis pathways are: 1) intrinsic or mitochondrial pathway (caspase-9 mediated); and 2) extrinsic or death receptor pathway (caspase-8- or caspase-10-mediated); both pathways utilize caspases as downstream effectors.[193]

Multiple upstream signal pathways (e.g., DNA damage, oncogenic stress) activate initiator caspases (caspases-2/-8/-9/-10) that cleave effector caspases (caspase-3/-6/-7); subsequently, the latter caspases mediate the proteolytic destruction of cells via cell death cascades.[194] Proapoptotic and antiapoptotic members of the BCL-2 family of apoptotic regulator proteins (e.g., BAX, BAK) control the disruption of mitochondrial membranes, activation of caspase-9, and intrinsic cell death.[195] Proapoptotic and antiapoptotic genes influence cell death; therefore, mutations of these genes also affect tumor growth. Some oncogenes proteins (C-MYC, p53, pRb) affect both cell proliferation and apoptosis. In mice, antiapoptotic BCL-2 proteins enhance the expression of the *MYC* oncogene;[196] overexpression of BCL-2 family proteins occurs in breast, colorectal, gastric, hepatocellular, lung, and pancreatic cancers.[193]

A protein family of death receptors activates the extrinsic apoptosis pathway (caspase-10 in humans, caspase-8 in rodents), primarily by members of the tumor necrosis factor receptor (TNFR) superfamily, including CD95, DR4, DR5, and TNFR. The role of caspase-8 in cancer varies with tumor type; frequent deletions of caspase-8 occur in small cell lung carcinomas, hepatocellular carcinomas, medulloblastomas, and gliomas, whereas decreased incidence of esophageal, colorectal, cervical, and breast cancer occurs with reduced caspase-8 expression. This variable response may be related to the variable effect (i.e., stimulation or inhibition) of caspase-8 on necroptosis, the programmed form of necrotic cell death.[193] The proinflammatory effects of necroptosis differ from the lack of inflammation in apoptosis.

Invasion and Metastasis

The invasion-metastasis cascade is a late, multistep process in malignant tumorigenesis involving: 1) invasion of local tissue parenchyma reflecting diminished cell adhesion and increased motility; 2) intravasation into neighboring microvesicles followed by survival during hematogenous dissemination via lymphatics and blood; 3) cell arrest and extravasation into distant host tissues; and 4) survival in the distant microenvironment and formation of macroscopic metastases (colonization) that successfully adapt to the new microenvironment.[197] The traditional model of progressive metastasis suggests cancer cells gradually acquire metastatic functions through progressive mutations that ultimately form macrometastatic-colonization genes with macrometastatic-colonization functions. Consequently, altered expression of these genes would be absent or rare in the primary tumor and present in the metastatic tumor. An alternative model suggests metastasis is a preprogramed event from the initiation of cells in the primary tumor that execute metastasis initiation functions. Thus, both primary and metastatic tumors share similar predetermined mutated genes and initiated cells. Some experimental evidence suggests an integrated model indicating the presence of mutated genes with dual metastasis-progression functions;[198,199] however, the exact role of each model in the development of metastatic tumors remains unclear.

Tumor-derived VEGF-A, TGF-β, and TNF-α induce premetastatic changes in distant host tissues that recruit CD11b* myeloid cells in a VEGFR1-dependent process enhanced by extracellular matrix-remodeling metalloproteinase (MMP9).[200,201] This process creates a premetastatic niche for the subsequent deposition of disseminated cancer cells. The success of the metastatic cells depends on the remodeling of the extracellular microenvironment, accessing local growth factors, resisting the host immune response, acquiring a blood supply, and forming a supportive microenvironment.

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TABLE 47.7. Metastatic cancer sites from some common primary malignant tumors. Susceptibility of tissues to metastasis depends on the tissue type and tumor characteristics. Estrogen-positive breast cancer commonly spreads to bone, whereas estrogen-negative breast tumors prefer visceral organs. The metastatic bone lesion from breast carcinomas and myeloma typically are osteolytic compared with the dense, osteoblastic lesions associated with prostate cancer. Although neuroblastomas occasionally regress, most metastatic lesions are progressive. (Adapted from Minn and Massague).[197]

Tissue Type	Metastatic Sites
Breast	Commonly to bone, liver, lung, and pleura; less frequently to brain and bone
Colon	Spread through portal system, favoring peritoneal cavity and liver with dissemination to lungs
Glioma	Metastasis outside the central nervous system is unusual
Lung	Small cell lung cancer typically spreads widely to adrenals, bones, brain, lungs, and pancreas, whereas nonsmall cell lung cancer spreads to adrenals, bones, brain, liver, and lungs
Myeloma	Primarily osteolytic bone lesions with occasional spread to other organs
Neuroblastoma	These pediatric tumors of adrenal nervous tissues usually metastasize to bones, liver, and lungs
Ovarian	Primarily local spread in peritoneal cavity
Pancreas	This aggressive tumor metastasizes to surrounding organs, particularly liver and lungs
Prostate	Almost exclusively to local bones (spine, pelvis)

The metastatic process is inherently inefficient.[202] Most extravasated tumor cells (i.e., >99%) disappear after failing to complete this process.[203] In mouse studies, only a small subset of injected B16F1 melanoma cells (i.e., ~0.02%) survive hematological spread, implant in distant tissues, and form fatal macroscopic tumors.[204] Some primary tumors can suppress distant metastases by secreting antiangiogenic factors (e.g., angiostatin, endostatin).[205] Additionally, systemic signals released by aggressive tumors can promote a supportive microenvironment in distant indolent tumor cells by enhancing the formation of growth factors (e.g., epidermal growth factor, EGF, insulin-like growth factor-1, IGF-1).[206] Pathological characteristics increasing the risk of metastasis by malignant tumors include large tumor size (i.e., increased cancer cell population), poorly differentiated tumor tissue, invasion beyond the normal tissue boundaries, and lymphatic spread. Table 47.7 lists the frequent metastatic sites of common primary malignant tumors.

Immune System

Many types of cancer activate inflammatory signaling pathways (e.g., proinflammatory signaling CXC-chemokine CXCR1/2 and their ligand CXCL8) through a complex network of inflammatory mediators. Subsequently, chronic inflammation contributes to all stages of tumorigenesis by generating genotoxic stress, producing mutations and oncogene activation, disrupting cell cycle controls and DNA repair, inducing cell initiation and proliferation, enhancing angiogenesis, remodeling tissues, and promoting tissue invasion.[207,208] Although the immune system initially protects against tumor formation, selection pressure from multiple generations of tumor cells favors the development of less immunogenic tumor cells until the tumor cells escape detection by the immune system.[209] This process (i.e., immunoediting) is a dynamic process with the three phases of elimination, equilibrium, and escape.[210] At first, tumor cell alterations and tissue necrosis activate the immune system with bone marrow-derived cells (dendritic cells, eosinophils, lymphocytes, macrophages, natural killer cells) invading the tumor during the elimination phase. The cells release various proinflammatory cytokines (IL-1β, IL-8, TNF-α), reactive oxygen species, proteases, and activated fibroblasts. Subsequently, adaptive immunity maintains an equilibrium phase while the continuous eradiation of tumor cells and the emergence of increasing resistant tumor cell variants interact to select tumor cells with reduced immunogenicity. Table 47.8 lists the normal functions of major cytokines and alterations in their function in tumor microenvironments.

The immunosuppressive environment of tumors contains immunomodulating factors (e.g., cyclooxygenase-2, COX-2; macrophage growth factor or colony stimulating factor-1, CSF-1; IL-6; IL-10; TGF-β).[212] Many immune cell types and cytokines (e.g., tissue necrosis factor family) display tumor suppressive and tumor-promoting properties.[213] During premalignant phases, TGF-β suppresses tumor proliferation in the local microenvironment; however, as tumor cells evade the immune system, TGF-β promotes the progression, invasion, and metastasis of tumor cells. The tumor cells enter the escape phase when most intrinsic and extrinsic tumor suppressor mechanisms fail as tumor cells acquire resistance to cytotoxic functions of immune cells. A complex immunosuppressive network develops in the tumor microenvironment that protects tumor cells against the host-protective antitumor response by altering the expression of inflammatory mediators, including chemokines, cytokines (e.g., interleukin 10,

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TABLE 47.8. Major cytokine function in the tumor microenvironment. Although cytokines and chemokines preserve normal cellular homeostasis by helping regulate cell growth and differentiation, chronic inflammation alters critical signaling pathways (e.g., NF-κB, STAT3 or signal transducers and activators of transcription-3), inhibits immune surveillance of preneoplastic cells, inhibits apoptosis, and promotes angiogenesis and tumor invasion. (Adapted from Fernandes et al.).[211]

Cytokine	Abbreviation	Cancer Function
Interleukin-1β	IL-1β	Suppresses p53 expression allowing stromal fibroblast proliferation.
Interleukin-6	IL-6	Stimulation of cell proliferation, angiogenesis, and survival of malignant cells while inhibiting apoptosis of cancer cells.
Interleukin-10	IL-10	Enhances interferon-γ, TNF-α, IL-6, and IL-12 production inhibiting tumor development; however, in tumor microenvironment, IL-10 promotes tumorigenesis by inhibiting T-helper cell 1 (Th1)-induced interferon-γ production.
Interleukin-12	IL-12	Protective function against cancer by stimulating cytotoxic activity of interferon-γ, TNF-α, Th1 response, and antiangiogenic activity. Tumor microenvironment inhibits IL-12 protective function by altering IL-12/IL-23 (Th17 promoter).
Interleukin-17	IL-17	Induces proinflammatory mediators (IL-1β, IL-6, TNF-α). The tumor microenvironment alters IL-17 expression and increases Th17 cell production.
Interleukin-18	IL-18	Acts with IL-12 to induce Th1 immune response and inhibit tumorigenesis. Overexpression of IL-18 occurs in several tumors (e.g., skin squamous cell carcinoma).
Tumor necrosis factor-α	TNF-α	The NF-κB pathway regulates numerous cytokines and adhesion molecules involved in the regulation of immune responses. Alteration of this pathway in tumors expresses NF-κB-dependent anti-apoptosis proteins, promotes angiogenesis, suppresses cytotoxic T cells and activated macrophages, enhances cancer cell migration/invasion, stimulates nitric oxide production and genetic stress.
Transforming growth factor-β	TGF-β	An anti-inflammatory/immunosuppressive cytokine that stimulates regulatory T cells. Attenuation of TGF-β inhibits tumor suppression, promotes tumor progression, and enhances tissue invasion/metastasis.

IL-10), growth and transcription factors (e.g., transforming growth factor-β, TGF-β); vascular endothelial growth factor, VEGF), soluble phosphatidylserines, free radicals, prostaglandin E2, and enzymes (e.g., cyclooxygenase, matrix metalloproteinase).[211]

Immunological tolerance that separates "self" from foreign material depends on immune checkpoint pathways, subsets of regulatory immune cells, and suppression of cytokines. The checkpoints are natural inhibitory feedback loops that avoid inflammation of normal tissues by reducing inflammation; tumor tissues protect themselves by aberrantly expressing ligands that interact with inhibitory immune receptors (e.g., cytotoxic T cell antigen 4, CTLA-4; programmed death 1, PD-1) and ligands (programmed death-1 ligand, PD-L1) that usually protects normal host tissues. CTLA-4 modulates the early activation of T cell immunity, whereas PD-1 modulates activated killer T cells present in the tumor.[214] The development of drugs to interrupt immune checkpoints (e.g., anti-CTLA-4, anti-PD-1, anti-PD-L1) and enhance antitumor immunity results in durable cancer regressions in a significant number of solid tumors that contain high mutational burdens (microsatellite instability).[215]

Additionally, tumors develop mechanisms to coopt immune cell functions and perpetuate tumor growth, including recruiting bone marrow-derived cells and myeloid-derived suppressor cells to enhance tumor invasion. The zinc-dependent proteolytic enzymes (matrix metalloproteinases, MMPs) regulate the destruction of various components in the extracellular matrix and basement membranes. In the tumor microenvironment, MMPs degrade matrix proteins and signaling molecules, promote angiogenesis, facilitate recruitment of stem cells, and reduce cell adhesion. MiRNAs help regulate the development of inflammatory cell subpopulations (e.g., Th1, Th17) and enhance immune cell function by controlling cytokine concentrations. Modulation of toll-like receptors (TLRs), cytokines, and signaling pathways in the tumor microenvironment promotes initiation and progression of tumors, particularly those associated with infectious agents.[216]

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Tumor Microenvironment

Solid tumors contain a heterogeneous population of neoplastic cells and tumor-associated stroma containing mesenchymal and inflammatory cells (e.g., extra-cellular matrix, endothelial cells, fibroblasts, leukocytes, pericytes) recruited from the host; together, this mass is called the tumor microenvironment.[217] The interplay in the tumor microenvironment between cancer and stromal cells is a crucial determinant of cancer growth along with tumor homeostasis and growth progression.[218] Tumor cells secrete chemokines that recruit various peripheral blood cells from the host circulation and tissues (e.g., bone marrow, spleen) to the tumor, including the tumor-derived cytokine granulocyte-colony stimulating factor (G-CSF). Alterations in certain hematopoietic progenitor cells (e.g., CD11b*/Gr1+ myeloid cells) involved in the regulation of myeloid cell mobilization and angiogenesis facilitate tumor-associated angiogenesis and protect the tumor against the inhibiting effects of anti-VEGF (vascular endothelial growth factor).[219] A variety of tumor-derived factors act systemically to promote angiogenesis, proliferation, invasion, and metastasis, including osteopontin (OPN), placental growth factor (PLGF), vascular endothelial growth factor-A (VEGF-A), angiotensin-II (ANG-II), GDF15 (growth/differentiation factor 15 or macrophage inhibitory cytokine-1), and IGF-II (insulin-like factor-II).[218] The tumor microenvironment also communicates with distant host tissues by secreting membrane-bound particles (microvesicles, exosomes, microparticles) that contain proteins, mRNAs, miRNAs, and lipids.[220]

CARCINOGEN CATEGORIES

Exogenous chemical carcinogenesis is an extremely complex, multifactorial process involving promotion, mutations, and genetic/epigenetic interactions of polymorphisms in multiple, cancer-susceptible genes and chemical carcinogen-induced cocarcinogenesis. These polymorphisms include beneficial and harmful polymorphic allelic variants (e.g., genes controlling phase I and phase II metabolic enzymes, the cell cycle, and DNA repair proteins).[221] Additionally, chemical carcinogens may produce mutagenesis indirectly by epigenetic alterations and free-radical production.

The ability of the cell to adapt to the presence of carcinogens depends on a complex interaction between individual host variations, gene mutations, and epigenetic factors. Reduction of cancer risks results from processes (detoxification, excretion, binding to noncritical sites) that decrease the carcinogen concentration at the cell genome and mechanisms (DNA repair, terminal differentiation) that inhibit the effect of the carcinogen. Numerous environmental and host factors affect cancer development by altering the action of carcinogens and cocarcinogens. Genetic factors alone are insufficient to explain the effect of chemical carcinogens on the many processes that influence cancer development, as reflected by differences in cancer incidence between genetically identical monozygotic twins;[222] hence the two broad categories of processes (genotoxic, epigenetic) affecting tumorigenesis.[223] Although some carcinogens act via both types of mechanisms, most chemical carcinogens affect cancer development predominately by a single type of mechanism. Genetic contributions associated with benzene-induced acute myelogenous leukemia include polymorphisms in microsomal epoxide hydrolase, glutathione-*S*-transferase subfamily *GSTT1* and *CYP2E1* genes involved with benzene metabolism along with alteration of genes involved with DNA repair (multifunctional DNA repair enzyme, APEX nuclease; excision repair cross-complementation group 1, ERCC1), whereas epigenetic contributions include DNA methylation and microRNA deregulation.[223] Although some epigenetic agents are genotoxic, all nongenotoxic agents are not epigenetic carcinogens (e.g., dioxin acts via a receptor-mediated, nongenotoxic, nonepigenetic mechanism). Genetic changes typically are irreversible, whereas epigenetic modifications are usually reversible.[224]

CLASSIC CARCINOGEN STAGES

Based on animal experiments, a chemical carcinogen initiates heritable, preneoplastic changes in a susceptible cell, followed by promotion of the initiated clone and progression to a visible, malignant tumor. Complete carcinogens (e.g., cigarette smoke) enhance cancer development at all three classical stages, whereas incomplete carcinogens (e.g., asbestos) act only at one stage (i.e., promotion). At low doses, some complete carcinogens may mimic the actions of incomplete carcinogens by affecting only the initiation stage. Most chemical carcinogens require metabolic activation from procarcinogens (e.g., nitrosamines, vinyl chloride, ethylene dibromide) to the intermediate form (proximate

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carcinogens) and subsequently to the biologically active form (ultimate carcinogens). CYP450 enzymes (e.g., CYP1A1) oxidize the carbon atoms in the "bay region" of benzo(a)pyrene to the dihydrodiol epoxide (proximate carcinogen) and then to the electrophilic reactant, (+)-anti-benzo[*a*]pyrene-7,8-dihydro-9,10-epoxide (ultimate carcinogen).[225] The final product irreversibly interacts with the cell genome.

Approximately 75% of chemical carcinogens (e.g., benzene, benzo[*a*]pyrene, and other high molecular weight polycyclic aromatic hydrocarbons) are procarcinogens that require metabolic activation to electrophilic (electron-deficient) metabolites primarily by phase I enzymes (e.g., CYP1/CYP2 enzyme families). About 25% of chemical carcinogens are direct (ultimate) carcinogens (e.g., 2,3,7,8-tetrachlorodibenzo-*p*-dioxin).[226] Ultimate carcinogens covalently bind to cellular macromolecules (DNA, RNA, proteins, sulfhydryl groups). Most known human carcinogens alter DNA structure (i.e., genotoxic), whereas ~½ known animal carcinogens demonstrate epigenetic properties without demonstrating mutagenic properties. Some chemicals (e.g., nitrates, nitrites) require more than one enzymatic step to produce a carcinogen; these procarcinogens are converted to an intermediate metabolite (proximate carcinogen) before final conversion to the direct (ultimate) carcinogen. DNA bases, phosphate groups, and three-dimensional DNA structure represent molecular targets for these carcinogenic metabolites, as reflected by the presence of heritable cellular changes, chromosomal abnormalities, aberrant gene expression, and activated oncogenes in cancer cells.[79] Several factors affect the induction of enzymes required for the metabolic detoxification or activation of procarcinogens, including environmental exposures, diet, and hormone concentrations; these factors add to the complexity of assessing the outcome of exposure to chemical carcinogens.

Direct-acting carcinogens [e.g., nitrogen mustard, ethylene imine, bis(chloromethyl)ether] do not require metabolic activation; hence, the procarcinogen, proximate carcinogen, and ultimate carcinogen in this class of carcinogens are structurally similar. During initiation, cocarcinogens enhance DNA damage caused by the administration of genotoxic carcinogens. Cocarcinogens are not carcinogenic agents; however, these agents activate and/or enhance the carcinogenic potential of genotoxic carcinogens. The effects of cocarcinogens include increased proliferation of initiated cells with DNA damage, enhanced metabolic activation or reduced detoxification of the carcinogen, increased delivery (i.e., absorption, transport) of the carcinogen to the cell genome, and reduced cellular repair processes.[227] Mechanisms of action include depletion of endogenous detoxifying proteins (e.g., glutathione), inhibition of phase I and/or phase II metabolic enzymes, inhibition of DNA repair mechanisms, and induction of CYP enzymes that convert procarcinogens to carcinogens.

GENOTOXIC CARCINOGENS

Genotoxic carcinogens produce heritable changes in DNA sequences and other cellular macromolecules; therefore, these carcinogens demonstrate mutagenic activity.[228] Genotoxic carcinogens include a variety of structurally diverse compounds [e.g., halogenated compounds (benzyl chloride), nitrogen mustards, dimethyl sulfate, lactones, alkylene epoxides, ethylene imine, polycyclic aromatic hydrocarbons, aromatic amines, quinolines, azo compounds including dyes (e.g., direct blue 6), dialkylhydrazines, *N*-nitroso compounds, carbamates (urethane), natural compounds (aflatoxins, daunomycin), and metals (hexavalent chromium, nickel)]. These exogenous chemical carcinogens induce bulky, stable DNA adducts that covalently bind to macromolecules, alter cell cycle control signaling pathways, and impair various repair systems in the body. Many of these chemicals require aryl hydrocarbon receptor activation and CYP enzyme induction to develop chemical carcinogenesis.[221]

In the mid-1970s, the International Agency for Research on Cancer (IARC) began including short-term mutagenicity tests in IARC Monographs on the carcinogenic risk of chemicals to humans based on the observation that most carcinogens were also mutagens, despite not all mutagens being carcinogens.[229] With the exception of asbestos and conjugated estrogens, most initially recognized human carcinogens were genotoxic (i.e., react with DNA) as defined by these short-term mutagenicity tests (Salmonella mutagenicity assay, Ames test) or the rodent bone marrow cytogenetics assay.[230] Most of these human carcinogens displayed a common tumor site in animal studies and epidemiology studies. Genotoxic carcinogens with similar affinity for a specific tissue or organ produce cumulative effects on carcinogenesis when administered together. Occasionally, genotoxic chemicals are effective after a single dose in animal studies of cancer.[95] The strength of the correlation between carcinogenicity and short-term mutagenicity tests diminished over subsequent years with identification of putative epigenetic carcinogens; however, these tests helped identify potential human carcinogens and understand carcinogenic mechanisms.[231]

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EPIGENETICS EFFECTS

Epigenetic effects describe heritable changes in gene expression without altering the DNA sequences involved in several biological (e.g., embryonic development, X-chromosome inactivation) and pathological (autoimmune diseases, cancer) processes.[232] Epigenetic mechanisms provide an interface between the genome and environment, with aberrant epigenomic changes contributing to carcinogenesis by affecting initiation, promotion, invasion, and metastasis.[233] These changes usually occur during an early stage of carcinogenesis typically preceding genetic alterations. Unlike the virtually identical composition of the genome in an organism's cells, different tissues and cell types have distinct epigenomes that undergo substantial changes in response to cellular development and maturation.[234] The plasticity produced by epigenome modifications is essential to adaptation of the cell to the environment, which occurs normally at different times in different cell types, particularly during cell differentiation, embryogenesis, and aging. Over many cell cycles, epigenetic mechanisms maintain heritable changes in gene expression and chromatin organization that are transmitted to future cell generations. Deregulation of epigenetic mechanisms disrupts key cellular processes that may cause oncogenic transformation and malignant tumor growth. DNA methylation, histone modifications (covalent alteration in core histones), nucleosome positioning (physical changes), and noncoding RNA (posttranslational gene regulation) refer to heritable, epigenetic changes in gene expression without mutation in DNA sequences. These changes may occur independently or concomitantly with genotoxic alterations, as displayed in Figure 47.13. Consequently, both epigenetic and genetic mechanisms determine the response, susceptibility, and adaptation to environmental carcinogens (e.g., tobacco smoke, radon, UV light, arsenic).

Almost all functions associated with DNA involve nongenotoxic modifications of chromatin and DNA proteins, including chromosome stability, transcriptional control, DNA replication, and DNA repair. The complex interaction between chromatin modification and DNA encodes information (i.e., epigenetic) in addition to the information provided by the genetic code; this information can also be preserved during cell replication and potentially inherited by subsequent cell generations.[236]

Epigenetic modifications are typically more abundant in malignant cells than DNA changes;[237] however, previous studies of these changes have shown that they are much less common for epigenetic than genotoxic carcinogens. Some of these epigenetic alterations are

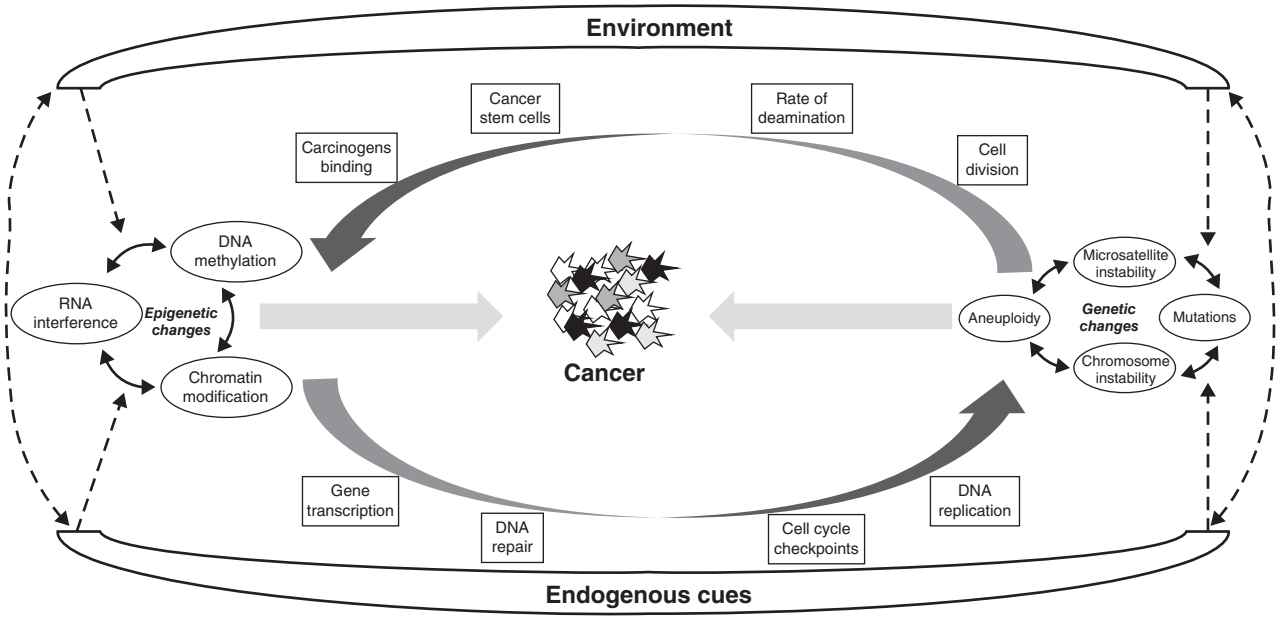


FIGURE 47.13. Epigenetic alterations, genetic changes, environmental exposures, and endogenous stimuli. Disruption of epigenetic mechanisms may cause abnormal phenotypes and cancer. Substantial cross-talk occurs between genetic and epigenetic alterations during the development and progression of cancer. The coexistence of genetic/epigenetic changes in all cancers and the complexity of the cross-talk between the two processes complicate the determination of primary and secondary events in tumorigenesis. (Adapted from Herceg et al.).[235]

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relatively nonspecific (e.g., global DNA hypomethylation) and common in many cancers, whereas other epigenetic changes involve more specific signaling pathways (e.g., increased potency of DNA binding at methylated CpG sites in certain codons).[238] Epigenetic mechanisms primarily involve the following three processes: 1) DNA methylation; 2) histone modifications; and 3) expression of noncoding RNA (microRNA, miRNA; long noncoding RNA, lncRNA), as displayed in Figure 47.14. The three common epigenetic pathways do not always act independently, similar to many cellular signaling pathways that influence other signaling pathways by "cross-talk."[239] Structurally diverse substances associated with epigenetic mechanisms include aflatoxins, 4-aminobiphenyl, asbestos, benzene, benzidine, benzo[α]pyrene, 1,3-butadiene, formaldehyde, metals (arsenic, beryllium, cadmium, hexavalent chromium, nickel), ionizing radiation, sulfur mustard, tobacco smoke, vinyl chloride, and biological organisms (human hepatitis B/C viruses, human papillomavirus, *Helicobacter pylori*).[235,240] In general, the extent of cancer promotion through epigenetic mechanisms depends on the amount and duration of exposure.[235] Although some epigenetic agents are also genotoxic, not all nongenotoxic agents are epigenetic carcinogens (e.g., dioxin acts on receptor-mediated pathways rather than epigenetic mechanisms). Furthermore, epigenetic pathways may be secondary mechanisms in tumors formed from some genotoxic epigenetic carcinogens (e.g., diethylstilbestrol, HBV, hexavalent chromium, ionizing radiation).[235]

Gene Expression

Epigenetic carcinogens produce changes in the regulation of gene expression (e.g., alterations in DNA methylation, translational control, posttranslational modifications, transcriptional activation).[28] These changes occur during normal development as well as during carcinogenesis. Epigenetic carcinogens increase the incidence of cancer in animal studies, usually because of prolonged, high-dose exposure that produces histological and biochemical changes in the animal.[241] Pathological signs of tissue damage include hydropic degeneration, cell necrosis, and fatty changes. In contrast to these abnormal pathological signs, evidence of more adaptive alterations includes organ enlargement, proliferation of cellular organelles (peroxisomes), and enzyme induction (e.g., mixed function oxidases).[242] Cell division is essential to the conversion of DNA

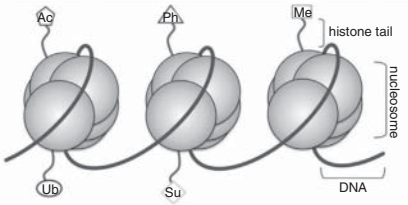
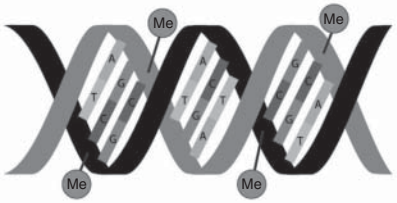
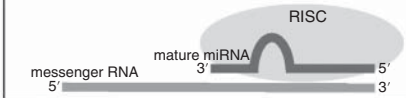
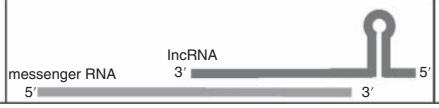
Epigenetic modifications			Commonly used evaluation methods
Histone modifications			• Western blot • Mass spectrometry • Chromatin immunoprecipitation (ChIP) - ChIP on chip (microarray) - ChIP sequencing
DNA methylation			• Methylation-specific PCR (MSP) whole-genome bisulfite sequencing (WGBS) • Reduced representation bisulfite sequencing (RRBS) • Bisulfite pyrosequencing • Combined bisulfite restriction analysis (COBRA) • Methylation DNA immunoprecipitation (MeDIP) • Mass spectrometry
Noncoding RNA	miRNA		• Single miRNA quantitative RT-PCR • smallRNA sequencing • miRNA microarray
	lncRNA		• Single lncRNA quantitative RT-PCR • RNA sequencing

FIGURE 47.14. Overview of main types of epigenetic mechanisms with simplified illustrations and commonly used methods to evaluate these mechanisms. (Adapted from Chappell et al.).[240]
Abbreviations: Ac = acetylation; Me = methylation; Ph = phosphorylation; Su = sumoylation; Ub = ubiquitination; IncRNA = long non-coding RNA; miRNA = microRNA; RISC = RNA-induced silencing complex; PCR = polymerase chain reaction.

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damage into inheritable mutations and the selection of altered phenotypes.

Epigenetic carcinogens represent a large, diverse category of compounds; these chemicals are not always easily distinguished from genotoxic chemicals. Animal studies identified a variety of epigenetic compounds, including mitogenic liver carcinogens (phenobarbital, polybrominated biphenyls), cytotoxic liver carcinogens (carbon tetrachloride), peroxisomal proliferators (clofibrate, di[2-ethylhexyl]phthalate, fenofibrate), cytotoxic stomach carcinogens (butylated hydroxyanisole), cytotoxic bladder promoters (saccharin, butylated hydroxytoluene), cytotoxic kidney carcinogens (chloroform, unleaded gasoline), hormones (diethylstilbestrol), solid-state carcinogens (asbestos), progressors (arsenic salts, benzene, hydroxyurea), and thyroid carcinogens (dietary deficiency of iodine).[243]

In animal studies, sustained tissue damage is an important mechanism for the induction of cancer by epigenetic chemicals; however, the action of epigenetic carcinogens probably results from both cytotoxicity and receptor-mediated cell proliferation, as demonstrated in Table 47.9. The former mechanism occurs at high doses, whereas the latter effect operates at high and low doses.[244]

Cytotoxic kidney carcinogens (unleaded gasoline, tetrachloroethylene, chloroform) produce cancer by the cytotoxic effects caused by the accumulation of a protein (alpha 2μ globulin) that is specific to male rats; however, humans do not produce this protein. Therefore, extrapolation of animal data to humans requires evaluation of the mechanisms associated with carcinogenesis and the use of different risk models.[245] The acceptance of the assumption that persistent cell damage produces tumors in rodents exposed to epigenetic carcinogens suggests the possibility of threshold doses for the carcinogenic effects and the establishment of safety margins;[242,243] however, this issue of threshold doses for certain carcinogens remains highly controversial.

DNA Methylation

DNA methylation involves the covalent modification of the CpG dinucleotide on the cytosine ring by adding methyl groups from the universal donor *S*-adenosyl-L-methionine to the DNA cytosine residues; the family of DNA methyltransferases catalyzes the covalent addition of a methyl group to the 5′ position of cytosine to form the fifth DNA base, 5-methylcytosine in cytosine-phosphate-guanosine (CpG) dinucleotide sequences (dyads). DNA methylation is a dynamic, well-balanced epigenetic process that occurs throughout the genome only at cytosine residues (CpG dinucleotides) in vertebrates; this process represses gene expression and helps regulate transcription, chromatin structure, chromosome integrity, and genomic imprinting (inheriting a gene from only 1 of 2 parents), resulting in gene silencing, histone modifications, and chromatin compaction.[246] The latter results from topological changes in chromatin confirmation. Regulatory processes are typically unmethylated when active.[247] Aberrant DNA methylation can disrupt any or all of these processes, causing gene activation and/or silencing with genomic instability contributing to carcinogenesis.[235] In tumor cells, DNA demethylation in genome-wide regions (global hypomethylation) is associated with genomic instability and cancer progression, whereas hypermethylation at localized promoter-associated CpG islands causes functional loss and transcriptional silencing of tumor suppressor genes as well as oncogene upregulation.[248]

TABLE 47.9. Pathological changes associated with chronic exposure of rodents to epigenetic carcinogens. (Adapted from Grasso et al.).[242]

Agent	Early Changes	Tumor Site	Threshold Dose
Solid implants (subcutaneous)	Fibrosis	Connective tissue	Yes (size)
Food coloring (subcutaneous)	Fibrosis	Connective tissue	Yes[a]
CCl_4, $CHCl_3$	Necrosis, regenerative hyperplasia	Liver	Yes
DEHP, fenofibrate	Hepatic hypertrophy, peroxisomal proliferation	Liver	Yes
Diethylene glycol	Hyperplasia, stones	Bladder	Yes
ESNS	Hyperplasia, stones	Bladder	Yes
H_2-antagonists	Hypergastrinemia/hyperplasia of ECL cells	Glandular stomach	Yes

Abbreviations: ECL = enterochromaffin-like; ESNS = 4-ethylsulfonylnaphthalene-1-sulfonamide.
[a] Related to the injected concentration.

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Although DNA methylation has some involvement in genome compartmentalization and chromosome stability, its primary supportive role is transcriptional regulation. Via the recognition of transcription factors, the DNA sequence accounts for a substantial part of the observed DNA methylation and chromatin patterns and, thus, the variation between cell types and individuals.[249] Typically, DNA hypermethylation represses gene expression (e.g., tumor suppressor genes in malignant tumors) by interfering with DNA binding of transcriptional activators and recruiting methyl CpG-binding transcriptional repressors, whereas DNA hypomethylation enhances gene expression and oncogene activation. There are short sequences of highly enriched CpG dinucleotides (CpG islands) near the 5′ regions of the genes that are resistant to methylation in normal tissues; most non-5′ regions outside the CpG islands are methylated. Typically, this methylation pattern is reversed in cancer cells. In contrast to histone modifications and noncoding RNAs, DNA methylation is the only epigenetic process that covalently binds to DNA. Global hypomethylation commonly occurs in cancerous cells along with locus-specific hypermethylation.[250] Methods to measure DNA methylation include whole-genome bisulfite treatment with sequencing (WGBS), combined bisulfite restriction analysis (COBRA) for gene-specific DNA methylation, mass spectrometry for global DNA methylation levels, and methylated DNA immunoprecipitation (MeDIP).[23]

Histone Modifications

In the chromatin of the human cell nucleus, special proteins (histones) package the DNA double helix into nucleosomes (i.e., chromatin structural units) that consist of DNA wrapped around repeated structural octamers of four core histone proteins (H2A, H2B, H3, H4) with 15–30 amino acid N-terminal tails protruding from the core assembly; most histone modifications occur in the tails. Posttranscriptional histone tail modifications can alter the access of chemicals and transcription factors to DNA, resulting in transcriptional changes that affect DNA damage/repair processes. Covalent modification of specific amino acid residues (e.g., lysine) on the histone tail involves a variety of processes (e.g., acetylation, methylation, phosphorylation, sumoylation, ubiquitination).[251] The integration of these processes either activates or silences the histones affecting events downstream (e.g., transcriptional activation or gene repression).

Chromatin Accessibility and Nucleosome Positioning

Higher-order chromatin is a complex spatial structure containing CpG-islands along with cis-regulatory regions or elements (e.g., proximal promoter, enhancer, insulator, silencer) that interact to control transcription and gene expression during the course of cell differentiation.[252,253] Mammalian cells have a large core (proximal) promoter region overlapping the first exon and upstream promoter elements, as displayed in Figure 47.15. In the core promoter region, hexagonal-shaped regulatory proteins help position RNA polymerase I adjacent to the transcription start site. Activated enhancers bind to pre-(transcriptional) initiation complexes or tethering elements in the proximal promoter region to upregulate transcription, whereas upstream silencers downregulate transcription by actively interfering with the preinitiation complexes.[254] Enhancers and silencers interact with multiple genes; however, another level of regulation and complexity results from special cis-regulatory DNA insulator regions that block those interactions.

In the nucleus, a compact nucleoprotein complex (chromatin) surrounds the DNA. The basic building block of the chromatin complex is a nucleosome comprised of 147 base DNA pairs wrapped around a histone octamer core and tail. Multiple nucleosomes assemble in a unidimensional shape resembling a string of

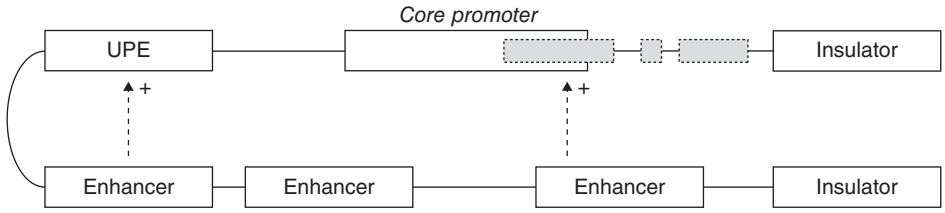


FIGURE 47.15. Mammalian transcription unit. The large core (proximal) promoter surrounds the transcription start site, overlapping the first exon and upstream promoter elements (UPE). Enhancers adjacent to the core promoter or upstream promoter elements brought close to the core promoter by the DNA loop can upregulate the gene transcription process. Silencers downregulate gene transcription, whereas insulators can block the actions of enhancers and/or silencers. (Adapted from Riethoven).[254]

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beads that fold into intragenic loops; the nucleosomes typically cover over 80% of the DNA-suppressing contact between DNA-binding proteins (e.g., DNA repair enzymes, transcription factors, polymerases) and the DNA.[255] In eukaryotic cell nuclei, chromatin folds multiple times into higher-order, 10 nm-chromatin fibers that form enhancer-promoter loops, insulated neighborhoods, and ultimately three-dimensional topologically associating domains (TADs), as displayed in Figure 47.16. Chromatin looping brings enhancers and promoters into close spatial proximity, stabilizing the loop and allowing communication between these two regulatory regions.[256] The folding of DNA into chromatin fibers and TADs compacts the genome and contributes to regulation of gene function.[257] These domains ultimately determine physical interactions (i.e., chromatin accessibility) between genomic regions and their regulatory elements (e.g., transcription factors, repair enzymes, polymerases). Some chromatin (heterochromatin) is highly condensed limiting chromatin access to regulatory elements, whereas other chromatin (euchromatin) has a loosely packaged, "beads on a string" shape that allows easier binding of regulatory proteins (e.g., transcription factors).[258,259] Nucleosome positioning along the DNA, methylation of cytosines within CpG dinucleotides, covalent histone modifications, and DNA-binding regulatory proteins (e.g., transcription factors) synergistically regulate chromatin conformation and DNA accessibility. Alterations in DNA accessibility and gene expression from cancer correlate to histone modifications and nucleosome positioning, particularly at transcription start sites or transcribed regions.[260] The TADs form nuclear compartments that vary in histone modifications and nuclear positions, resulting in either active or silent transcriptional sites on the chromosome.[261]

Functional sequence elements (e.g., transcription factor binding sites) in a genome are often associated with specific DNA sequence patterns called motifs. Different types of functional elements can have different motifs. CTCF binds a well-defined motif that forms specific loops and subsequently TAD boundaries with cohesin stabilizing the interactions of CTCF on enhancer- and promoter-bound transcription factors.[262] Cohesin is a multi-subunit, ring-shaped protein complex that binds DNA strands; normal chromosome segregation from the S-phase to cell division requires cohesin to mediate sister chromatid cohesion.[263]

A single genome can produce several hundred distinct cell types with identical genomes, but different epigenetic marks at regulatory elements, producing dissimilar gene expression. The two main types of regulatory elements in transcriptional activation

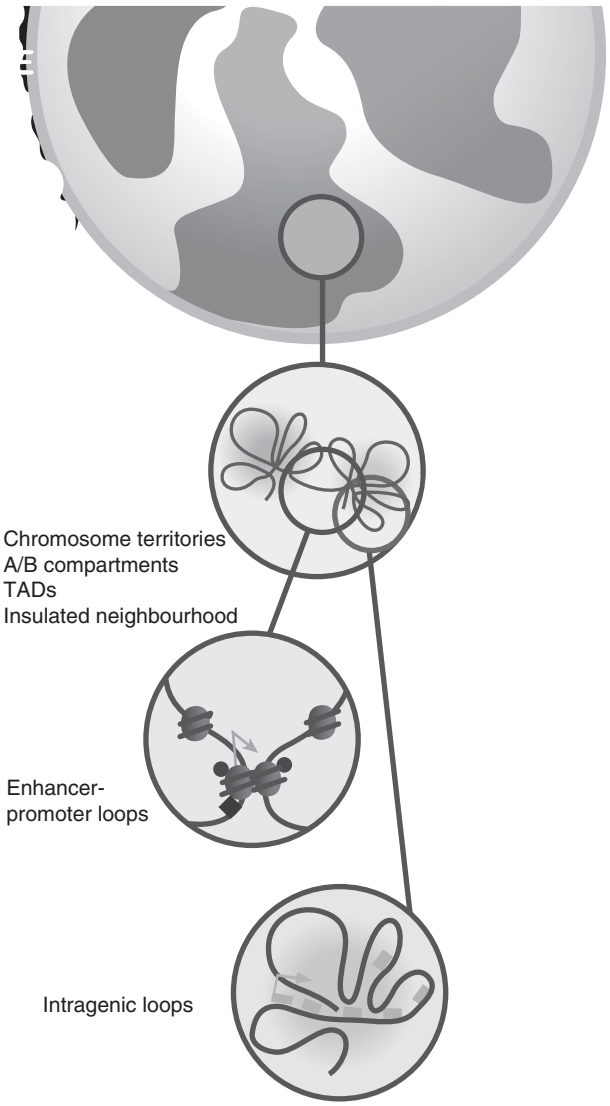


FIGURE 47.16. Schematic display of chromosomal structure. The smallest level of organization is the chromatin architecture in a single gene represented by intragenic loops of chromatin fibers at the functional level of transcriptional regulation. The intermediate level of organization involves enhancer-promoter loops and intra-TAD (topologically associated domains) that affect gene expression *via* distal regulatory networks. Large-scale chromatin organization in three dimensions divides the chromosome into megabase-sized active (open, A compartment) and repressed (closed, B compartment) territories that progressively subdivide into smaller and smaller subdomains (TADs). Physical interactions occur within the TADs with little contact outside the TAD boundary (isolated neighborhood). Histone modifications and nucleosome positioning are critical to chromatin accessibility and gene expression with alterations common in tumors. (Adapted from Ruiz-Velasco et al.).[262]

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are enhancers and promoters, with the prediction of carcinogenic changes in gene expression better for enhancers than promoters.[264,265,266] The latter regulatory element is a relatively small region surrounding a transcription start site necessary for initiating gene transcription, whereas enhancer elements contain multiple transcription factor-binding sites distant from the gene they regulate.[267] Enhancers do not always regulate the nearest gene; one enhancer may regulate many genes, or one gene may be regulated by multiple enhancers. Consequently, enhancers are numerous, with a given cell line sometimes containing thousands of enhancers. Using tumor profiling of breast, kidney, and prostate tumor tissues with DNA methylation data, Rhie et al. identified over 25,000 differentially activated enhancers, 1,200 transcription factors in the tumor-specific enhancer networks, and over 800,000 genome-wide links between genes and enhancers.[268] Genome-wide association studies indicate multiple single nucleotide polymorphisms (SNPs) are associated with increased cancer risks (i.e., susceptibility);[269] these SNPs exist within enhancers, DNase hypersensitive sites, and transcription factor-binding sites, primarily in noncoding regions of the genome.

CCCTC-binding factor (CTCF) is a master regulatory protein that bridges the gap between genome architecture and gene expression.[270] Arrangement of chromosomal architecture results from CTCF binding to various sites, including nuclear matrix and numerous genomic sites within active and inactive domain boundaries. CTCF helps control gene expression via insulation of enhancers, activation or repression of promoters, and regulation of distant chromatin interactions. CTCF can block the transcription of gene promoters or enhancers by binding to an insulator sequence, creating insulated neighborhoods.[271] A variety of factors affect CTCF activity including binding proteins and DNA methylation. CTCF alters higher-order chromatin structure, thereby controlling the inter- and intra-chromosomal distances between TADs. Figure 47.17 displays a schematic representation of CTCF and cohesion effect on gene expression.

Noncoding RNAs

Noncoding RNAs (ncRNAs) modulate chromatin regulation and gene expression in normal and cancerous cells, primarily involving transcriptional and posttranscriptional gene silencing. DNA damage from a variety of exogenous and endogenous sources produces several DNA lesions including base adducts, DNA mismatches, deletions/insertions, interstrand DNA cross-linking, and single-/double-strand breaks. The DNA damage response system responds to these abnormalities by initiating repair mechanisms before the damaged genes replicate. In addition to DNA damage response-activated gene transcription programs for protein-coding genes, DNA repair requires a subset of regulatory RNAs that do not produce proteins (noncoding RNAs).[272] The genome contains >60% RNA molecules transcribed into small ncRNAs of <200 nucleotides) and large ncRNAs (>200 nucleotides).[273] Various types of ncRNAs include DNA damage response RNAs (DDRNAs), double-stranded break-induced RNAs (diRNAs), promoter-associated RNAs (PARs), enhancer RNAs (eRNAs), long noncoding RNAs (>200 nucleotides, lncRNAs), and small ncRNAs. The latter includes microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), small nucleolar (snoRNA), small interfering RNA (siRNAs), and short hairpin RNAs (shRNAs).[274] Silencing (knockdown) of target gene expression involves the latter two double-stranded RNAs that degrade target mRNA during the process of RNA interference.[275] Over 1,000 miRNAs help regulate cellular processes, primarily via RNA polymerase-II by targeting multiple protein-coding transcripts that regulate the translation of an estimated 60% of the protein-coding genes in the human genome.[276,277]

LncRNAs are promoter- or enhancer-associated regulatory ncRNAs rather than housekeeping ncRNAs; the primary function of lncRNAs is the regulation of the expression of protein-coding genes in response to environmental factors. The lncRNAs can function as oncogenes or tumor suppressors, with significant numbers of these ncRNAs changing in cancer tissues.[278] Noncoding RNAs enhance genomic stability through extensive cross-talk with the DNA damage response signaling pathways, resulting in the expression of ncRNAs and posttranslational regulation of the DNA damage response genes. The ncRNA-regulated DNA damage response connects the fast phase of DNA damage response mediated by protein-induced translational modifications (acetylation, methylation, phosphorylation, sumoylation, ubiquitination) and the slow phase of the DNA damage response mediated at the transcriptional level of gene expression.[164]

Control of the DNA damage response genes occurs at multiple levels (transcriptional, posttranscriptional, RNA degradation). The small, double-stranded, non-(protein)-coding RNAs influence gene expression by posttranslational changes in chromatin confirmation or through posttranscriptional gene silencing by the formation of complementary (antisense-oriented),

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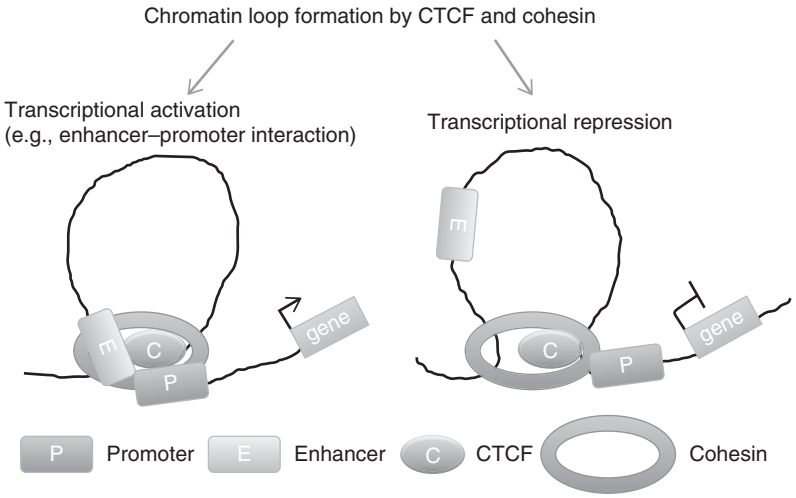


FIGURE 47.17. Chromatin loop function mediated by CTCF (CCCTC-binding factor) and the cohesin complex that produces transcriptional activation or repression depending on the binding site. CTCF and cohesin create a chromatin loop that encompasses the enhancer and promoter, resulting in transcriptional activation. Conversely, formation of a chromatin loop by CTCF and cohesin that blocks the enhancer from reaching the promoter represses gene expression. (Adapted from Kim et al.).[271]

small interfering RNAs (siRNAs).[279,280] Exogenous small ncRNA includes the endogenous 18–24 nucleotide microRNA (miRNA) and small interfering RNA (siRNA). Many small ncRNAs regulate gene expression, and ~60% of all coding protein genes use several mechanisms, including translational repression (miRNA) and mRNA degradation (siRNA). Some miRNAs function as oncogenes, whereas others act as tumor suppressor genes; human malignant tumors often contain many miRNA modifications.[281]

The classes of lncRNA include bidirectional, intronic, intergenic, sense, and antisense based on adjacent protein-coding genes. LncRNAs regulate gene expression through transcriptional regulation, mRNA processing, and chromatin modification, with RNA polymerase II transcribing most lncRNAs. Many lncRNAs are involved in epigenetic regulation of target genes by interacting with chromatin-remodeling or histone-modifying protein complexes (e.g., polycomb repressive complex 1/2, PCR1/2). In addition to providing molecular scaffolding to facilitate chromatin regulation, some lncRNAs (e.g., p21-associated ncRNA DNA damage activated, PANDA; long intergenic noncoding RNA-p21, linc-p21) are direct transcriptional targets of tumor suppressor proteins (i.e., p53) following initiation of the DNA damage response network.[282]

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B

Chemical Carcinogenicity

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Chapter 48

GENERAL PRINCIPLES

STATISTICS

The contribution of chemicals to cancer incidence remains controversial because of limitations in detecting the effect of chemical carcinogens on the multifactorial etiology of cancer, inconsistencies in the diagnosis and coding of cancer statistics, and confounding from associated risk factors. The latter includes the simultaneous exposure to multiple carcinogens. In general, exposure to carcinogens within the same class based on toxicological and physiochemical properties exerts additive effects on cancer risks, whereas carcinogenic mixtures of different carcinogen classes produce multiplicative effects on cancer risks.[1]

Overall

The lifetime probability of being diagnosed with invasive cancer is 45% in men compared with 38% in women; cancer causes ~1 of 4 deaths in the United States.[2] Although several thousand chemicals were synthesized annually from 1965–1985, the overall age-standardized mortality rates from cancer remained stable excluding lung cancer until 1991.[2,3] Since then, mortality rates have declined >30% from decreased smoking, improved treatment, and effective cancer screening; however, in high-income countries, cancer is the most common cause of disease-related death in adolescence and young adulthood.[4] Individuals with a previously diagnosed tumor are particularly vulnerable to developing a different tumor type. Based on population-based data from the Surveillance, Epidemiology, and End Results (SEER) program of cancer registries, ~25% of adults ≥65 years of age and 11% of younger adults will develop a new malignant tumor after their initial diagnosis with the prevalence rate ranging from ~4–37%, depending on the initial cancer type and age.[5] The SEER data exclude metastatic and recurrent tumors. Substantial geographical variation occurs in all cancer rates between various counties within the United States and between the United States and other countries.

Incidence

During the 1980s, the incidence rates for most cancers increased;[6] factors associated with this increase include improved detection (prostate, breast), increased smoking among women (lung cancer), increased rate of acquired immunodeficiency syndrome (non-Hodgkin lymphoma, Kaposi's sarcoma), and excessive exposure to sunlight (melanoma).[7] Data from the Surveillance, Epidemiology, and End Results (SEER) survey indicate the overall cancer incidence rate in the United States peaked in 1992.[8] By 1996, statistically significant decreases in cancer incident rates in males occurred for lung cancer, leukemia, colorectal cancer and cancer of the bladder, oral cavity and pharynx.[8] Similar decreases in cancer rates occurred for women except for lung cancer incidence. In the United States during 2009, the annual incidence rate of all invasive cancers was 459 cases/100,000 persons for a total of 1,476,504 cases.[9] Overall cancer incidence rates continued to decline in men in 2008–2014 at 2.2%/year, while the cancer incidence rates in women remained stable based on data from the Annual Report to the Nation on the Status of Cancer (American Cancer Society, Centers for Disease Control and Prevention,

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National Cancer Institute, North American Association of Central Cancer Registries).[10] Recently, the incidence of some cancers have begun increasing including breast, cervical, colorectal, HPV-associated oral, kidney, female liver, melanoma, and prostate cancers. In the Global Burden of Disease 2017 study, reported cancer incidence cases increased by 33% between 2007 and 2017 globally with the most developed countries accounting for the smallest increases.[11] Countries with the highest sociodemographic index reported 51% of the incident cancer cases but substantially fewer cancer deaths. Globally, there were 16.8 million reported incident cancer cases excluding nonmelanoma skin cancer; nonmelanoma skin cancers accounted for 7.7 million additional cancer cases. The highest 5-year survival rates (>90%) remain for melanoma and cancers of thyroid, prostate, and testis, whereas cancers of the esophagus, lung and pancreas produce the lowest 5-year survival rates (<25%).

Cancer Mortality

For the last 40 years, heart disease and cancer remained the top 2 leading causes of death with overall death rates similar for the last few years; mortality from cancer is slightly lower than that from cardiovascular disease as displayed in Figure 48.1.[12] In the United States, mortality from cardiovascular disease declined significantly as death from cancer rose, particularly from brain cancer and non-Hodgkin's lymphoma.[13] Death rates from cancer peaked in 1990 for men and 1991 for women. In contrast to cancer incidence rates in the 1980s, cancer mortality rates either stabilized or declined. By the late 1980s, cancer was the second leading cause of death in the United States, accounting for ~22% (i.e., ~550,000) of all reported annual US deaths.[14] During the late 1980s, the incidence cancer rate for people >54 years of age increased for most cancer types except for stomach and liver cancers; the latter two cancers began declining in the 1930s.[15] Worldwide, an estimated 10 million cancer-related deaths occur annually.

Figures 48.2 and 48.3 demonstrate the trends in the overall US death rates from selected cancers in men and women, respectively. Overall, cancer mortality decreased ~20% 1980–2014 with the cancer mortality rate decreasing annually by 1.8% for men, 1.4% for women, and 1.6% for children 2010–2014 as displayed in Figures 48.2 and 48.3.[10,16] During 2004–2008, cancer mortality decreased by 1.8%/year in men and 1.6%/year in women.[2] The mortality rates for the two sexes are slightly different; in 2014, the mortality rate for heart

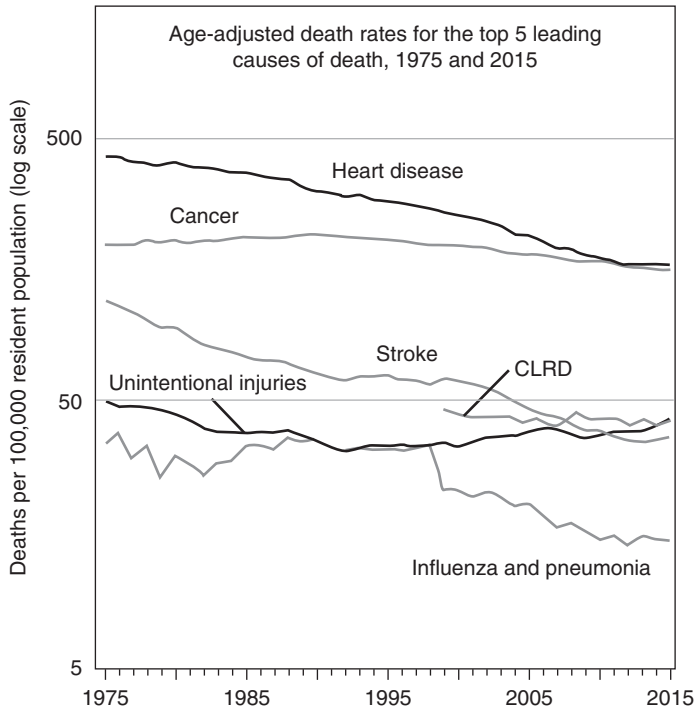


FIGURE 48.1. Leading causes of overall deaths in the United States per 100,000 residents, from 1975–2015. The five leading causes of death in 2015 were heart disease, cancer, chronic lower respiratory diseases (CLRD), unintentional injuries, and stroke. The age-adjusted death rate for heart disease stabilized from 2011–2015, whereas the rate for cancer steadily declined from 2000–2015. (Adapted from National Center for Health Statistics).[12]

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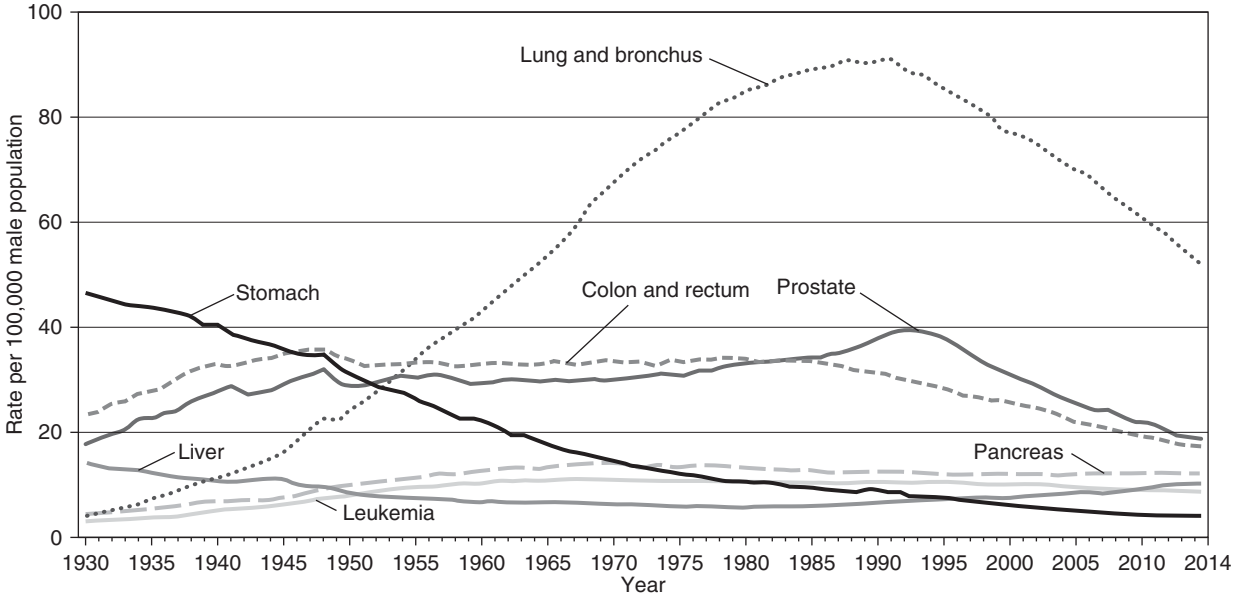


FIGURE 48.2. Annual 1930–2014 age-adjusted, cancer mortality rates per 100,000 men by common malignant tumor type. Currently, mortality for cancers of the liver and pancreas is increasing, whereas the other cancers noted in the figure are decreasing. SEER data indicate the overall age-adjusted death rates for pancreatic cancer increased annually ~0.1% from 2011 to 2020. From 2016 to 2020, the age-adjusted mortality rate for pancreatic cancer in men was 12.7/100,000 compared with 9.6/100,000 for women (https://seer.cancer.gov/statfacts/html/pancreas.html). ICD coding changes affect the mortality rates for cancers of the colon, liver, lung/bronchus, and rectum. (Adapted from American Cancer Society).[6]

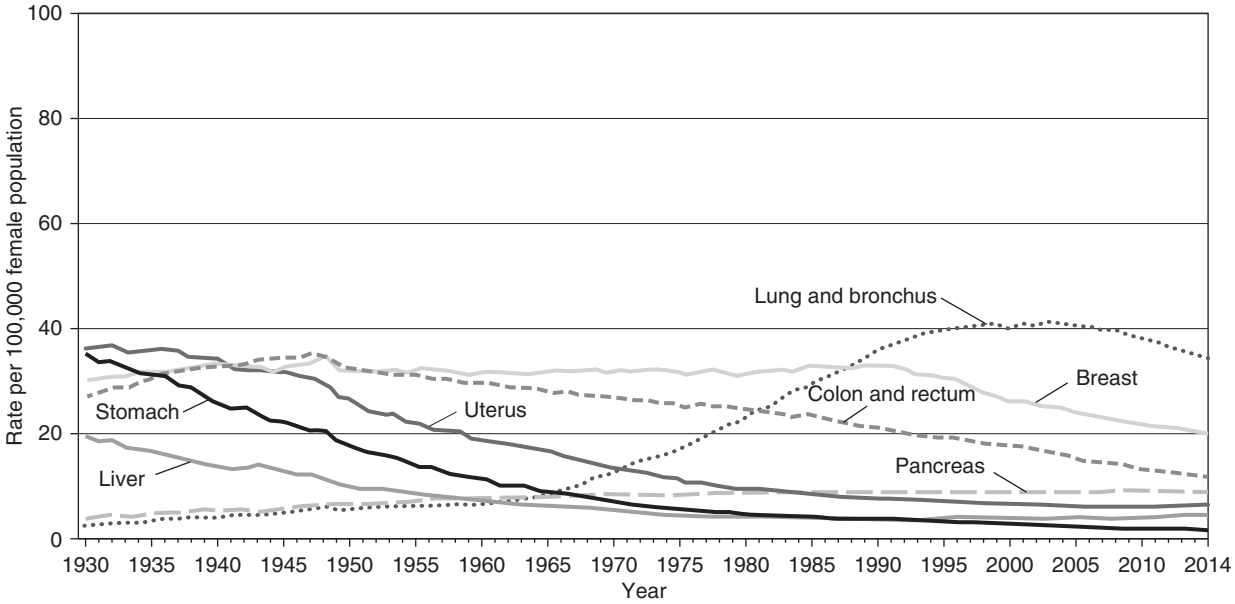


FIGURE 48.3. Annual 1930–2014 age-adjusted, cancer mortality rates per 100,000 women by common malignant tumor type. Currently, mortality for liver cancer is increasing, whereas the other cancers noted in the figure are decreasing. SEER data indicate the overall age-adjusted death rates from liver and intrahepatic bile duct cancer increased ~0.7% annually from 2011 to 2020. From 2016 to 2020, the age-adjusted mortality rate for liver and intrahepatic bile duct cancer was 5.2/100,000 in women compared with 14.1/100,000 in men (https://seer.cancer.gov/statfacts/html/livibd.html). ICD coding changes affect the mortality rates for cancers of the colon, liver, lung/bronchus, rectum, and uterus. Data on uterine cancer include cervical and corpus cancers. (Adapted from American Cancer Society).[6]

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disease in men was 24.5% compared with 22.3% for women.[17] Cancer accounted for 23.4% of deaths in men and 21.6% in women. Reductions in lung, prostate, and colorectal cancer deaths accounted for ~78% of the total decrease in men, whereas reductions in breast and colorectal cancer deaths accounted for ~56% of the total decrease in women. During this same period, the overall cancer incidence rate declined slightly (0.6%/year) in men, while remaining stable in women. Currently, almost ½ of all cancer survivors live ≥10 years after their initial cancer diagnosis with ~$^2/_3$ surviving at least 5 years.[18] In 2017, the Global Burden of Disease Study reported 9.6 million cancer-related deaths.[11] The vast majority of these deaths resulted in years of life lost (97%) rather than years lived with disability (3%). Countries with the highest sociodemographic index accounted for 30% of the cancer-related deaths but 51% of the reported incident cancer cases. The highest 5-year survival rates (>90%) remain for melanoma and cancers of thyroid, prostate, and testis, whereas cancers of the esophagus, lung and pancreas produce the lowest 5-year survival rates (<25%).

Tissue Sites

Incidence

In the United States over the last decade, the cancer incidence rate remained stable in women and declined annually by ~2% in men with the most common male cancers being prostate (19%), lung/bronchus (14%), and colorectum (9%) in men and breast (30%), lung/bronchus (13%), and colorectum (7%) in women.[19] The decline in cancer incidence in men results from continuing declines in lung and colorectum cancers along with sharp declines in prostate cancer incidence. The latter partially reflects changes in prostate cancer screening guidelines. Overall, during this period, cancer incidence rates declined for 11 of the 18 most common cancer sites in men and 7 of the 17 of the most common cancer types in women.[10] Cancer incidence increases progressively from childhood (≤14 years) to adolescence (15–19 years) and young adulthood (beginning at 20 years).[4] Embryonal tumors (medulloblastoma, hepatoblastoma, nephroblastoma, neuroblastoma, retinoblastoma) predominate in childhood, whereas sarcomas, Hodgkin and non-Hodgkin lymphomas are prevalent in adolescence and young adults.

The highest US cancer incidence rates involve the prostate (137.7/100,000 men), female breast cancer (123.1/100,000 women), and colorectal cancer (42.5/100,000 persons). Together, these three cancer types accounted for about ½ of all cancers diagnosed each year. Approximately ½ of newly diagnosed cancers in men are prostate, lung/bronchus, and colorectum cancers compared with breast, lung/bronchus, and colorectal cancers in women. Overall lung cancer incidence rates peaked in 1984.[8] In contrast to these major cancers, the overall incidence rates of human papillomavirus-related oropharyngeal cancers, esophageal adenocarcinoma, pancreatic cancer, melanoma, and cancers of the liver, intrahepatic bile duct, thyroid, kidney, and renal pelvis have increased over the last 10 years with some racial variation in the actual rates.[20] The incidence of thyroid cancer increased 3.6% annually from 1974–2013, driven largely by papillary thyroid cancer with annual mortality rates increasing 1.1% from 1994–2013.[21] Reductions in smoking prevalence (lung), increased screening and removal of premalignant lesions (colon, cervix), improved hygiene (stomach), and prostate-specific antigen testing have contributed to the decline in overall cancer incidence and death rates. Excluding nonmelanoma skin cancers (4.3 million incident cases), the most common global incident cancers in men during 2017 were tracheal-bronchus-lung cancer (1.5 million incident cases) and prostate cancer (1.3 million incident cases).[11] Globally, the most common cancers, excluding nonmelanoma skin cancers (3.3 million incident cases), in women were breast cancer (1.9 million incident cases) and colorectal cancer (0.819 million incident cases).

Cancer Mortality

Significant declines in cancer death rates continue for men and women; however, progress in reducing cancer mortality varies with specific tissue types. A review of cancer statistics in 15 industrialized countries between 1969–1986 indicates that cancer mortality in persons aged 45 years and older increased for lung, breast, and prostate cancers, while the mortality rate for stomach cancer decreased substantially.[22] Overall, the risk of dying from cancer has decreased by 32% since 1991. Cancer death rates continue to decline in the United States, including female breast, colorectal (men/women), lung/bronchus (men/women), and prostate. Although overall cancer mortality rates declined between 2010 and 2014, death rates for liver (men/women), pancreas (men/women), oral cavity/pharynx (men), soft tissue (men), uterus, and brain/nervous system (men/women) cancers have increased.[10,16]

Overall lung cancer mortality rates peaked in 1990;[8] however, lung/bronchus/tracheal cancer remains the leading causes of cancer mortality in men and women, accounting for ~29% of US cancer-related deaths.[23,24]

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TABLE 48.1. Five-year US cancer survival rates for four common tissue types, depending on stage I and IV diagnosed during the late 2000s and early 2010s, based on data from the Annual Report to the Nation on the Status of Cancer data.[10] Survival rates include men and women combined unless otherwise specified. The survival rates for lung/bronchus cancers remain higher for men than women. Newer treatment options (e.g., immunotherapy) have improved the survival rates for melanoma significantly.

Tissue Type	5-year Survival Stage I (%)	5-year Survival Stage IV (%)
Breast, female	100	26.5
Colorectal	88.1	12.6
Lung/bronchus	55.1	4.2
Melanoma	99.5	16

Although lung cancer mortality rates have fallen by 56% in men and 32% in women since 1990, lung cancer remains the leading cause of cancer-related deaths in the United States. Breast cancer and prostate cancer are the second-most common causes of cancer mortality in women and men, respectively. Overall, lung/bronchus (28%), colon/rectum (10%), prostate (6%), and female breast (8%) cancers account for the major portion of all cancer-related deaths.[23] Although there is little difference in the age-adjusted lung cancer mortality rates between white women and black women, these rates are much higher for black men compared with white men.[25]

Between 1980 and 2014, 5-year survival rates for stage I of six cancers (breast, Hodgkin lymphoma, melanoma, testicular, thyroid) exceeded 85%; however, cancer clusters of many cancers occur in individual US counties with especially high mortality including breast, liver, and kidney cancers.[23] Cancers with the lowest 5-year survival rates include brain, esophagus, liver, lung, pancreas, and stomach, with particular slow progress in treating lung and pancreatic cancers. During this period, pancreatic cancer and non-Hodgkin lymphoma mortality rates remained relatively constant, whereas liver cancer mortality increased by ~87%. For cancers diagnosed in the late 2000s and early 2010s, 5-year survival rates varied with tissue type and stage at diagnosis, as displayed in Table 48.1. Globally, the leading causes of cancer-related deaths in women during 2017 were breast cancer (0.601 million deaths), tracheal-bronchus-lung cancers (0.596 million deaths), and colorectal cancer (0.404 million deaths).[11] For men during 2017 globally, the most common causes of cancer-related deaths were tracheal-bronchus-lung cancers (1.3 million deaths), liver cancer (0.572 million deaths), and stomach cancer (0.542 million deaths).

ETIOLOGY

Chemical carcinogenesis is a multifactorial, multistep process that results from the complex interactions of endogenous/exogenous mutations (oncogenes, tumor suppressors, microRNAs) with genetic/epigenetic carcinogens. This process involves cellular control and repair pathways and cellular alterations of cell proliferation, adhesion, invasion, metastasis, and immune surveillance.

Interindividual variation in the response to carcinogens results from variation in several processes including metabolic activation (e.g., CYP2E1, *N*-acetyl transferase), detoxification (e.g., glutathione *S*-transferase 1), DNA repair, proto-oncogene types (e.g., *HRAS*, *c-MYC*), tumor suppressor genes (e.g., *TP53*), and immune function.[26] The lifetime risk of many cancer subtypes strongly correlates to the total number of divisions in normal, replicating stem cells that maintain tissue homeostasis; random DNA replication errors occurring during cell turnover account for the chance (i.e., "bad luck") events that increase organ-specific cancer risks.[27] A substantial percentage of these cancer-related deaths result from exposure to carcinogens associated with lifestyles (e.g., tobacco, alcohol) and environmental factors (e.g., viruses, radiation, natural and synthetic chemicals).[28] The exact portion of cancers attributable to the environment, heredity, and lifestyle factors compared with chance mutations of normal cells ("bad luck") remains unclear because of interactions between environmental and lifestyle carcinogens, variation in inter-country exposure patterns, and inadequate exposure data.

The cancer incidence rises sharply with advancing age; the cumulative cancer risks increase with ~4th power of age. At the end of our natural life span (i.e., typically 85 years), the cumulative risk (i.e., 30%) of acquiring cancer is similar to that of short-lived rodents at the end of their life span (i.e., 2–3 years).[29] The relationship between most cancers and advancing age reflects several factors, including the long latent period associated with solid tumors, cumulative effects of prolonged exposure to carcinogens,[30] and/or the procarcinogenic effect of aging (e.g., oxidative DNA damage).[29]

The population attributable fraction (PAF) quantifies the total effects of a cancer risk factor by providing a percentage or portion of avoidable cancers; however, the PAF does not necessarily indicate the percentage of cancers that can be prevented. The latter depends on the practicality of the preventive strategies and the uncertainties in the estimates Table 48.2 displays the PAF of cancer associated with 14 non-genetic risk

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TABLE 48.2. Estimates of the population-attributable fraction (PAF) of cancer associated with 14 major lifestyle, dietary, and environmental risk factors based on the 2010 UK study excluding nonmelanoma skin cancers. The optimum exposure levels indicate the ideal but not necessarily practical efforts to prevent cancer. The PAF for diet was 9.2% reflecting the interaction of multiple dietary factors in the overall impact of suboptimal diets on cancer rates. The dietary estimates do not specifically include the effects of early nutrition on cancer rate estimates. (Adapted from Parkin et al.).[31]

Exposure	Optimum Exposure Level	Estimated PAF (%)
Tobacco	None	19.4
Diet, total		9.2
Deficient fruit/vegetables	≥5 servings (400 g)/day	4.7
Red/processed meat	None	2.7
Deficit fiber	≥23 g/day	1.5
Excess salt	≤6 g/day	0.5
Overweight/obesity	≤25 kg/m^2 BMI	5.5
Alcohol	None	4.0
Occupation	None	3.7
Solar (UV) radiation	1903 birth cohort	3.5
Ionizing radiation	None	1.8
Infections	None	3.1
Physical exercise	≥30 minutes 5 times/week	1.0
Breastfeeding	6 months minimum	0.9
Postmenopausal hormones	None	0.5

factors). In a UK study of 14 major lifestyle, dietary, and environmental risk factors, the four most important cancer risk factors excluding nonmelanoma skin cancers were tobacco smoking, dietary factors, alcohol drinking, and body weight accounting for 34% of cancer cases occurring during 2010.[31] Because of the multifactorial causes of cancer, the same cancer may be attributed to several factors; thus, summing the PAF of individual factors overestimates the total burden of cancer attributable to the 14 risk factors. The overall estimate of the impact of the 14 factors on the overall cancer burden was 18% compared with 26% (range, 6–42%) for the 2009 American Institute for Cancer Research/World Cancer Research Fund study.

Occupation

Approximately 40% of the human carcinogens classified by the International Agency for Research on Cancer (IARC Group 1) are workplace chemicals or employed in specific occupations/industries. The proportion of cancer attributable to occupational exposure at a particular work site depends on carcinogenic potency, exposure duration, and the portion of the work force exposed to the carcinogen as well as study design (e.g., prevalence of exposed individuals within the general population, cancer type studied, proper classification of individuals within the exposed study group). Estimates of the overall proportion of cancer attributable to the work site typically range from ~2–8%[32,33] with a generally accepted level of ~4–5%.[28,34,35] The estimated population attributable fraction for men is ~3–14% compared with ~1–2% for women.[36] In a 2010 French study using a 1994 survey and other data along with relative risks for 23 exposure–cancer combinations derived from meta-analyses and pooled analyses, the estimated portion of cancers attributable to occupational exposures was 2.7% in men and 0.3% in women, whereas the cancer deaths attributable were 4.0% in men and 0.6% in women.[37] In certain cases of hazardous work sites (e.g., asbestos mining), the estimated proportion of cancers attributed to work site exposure ranges up to 40%.[38]

Most industrial-related cancers occurring among male workers develop in the lung and bladder. Of the total number of workers with these cancers, the estimated percentage of workers with industrial-related cancers ranges from ~10–20% and 21–27%, respectively.[39] In a French study of 4335 cancer cases in men and 403 cancer cases in women, lung cancer accounted

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for 75% of the overall cancer deaths.[37] The main occupational carcinogens were asbestos, polycyclic aromatic hydrocarbons, and hexavalent chromium in men and asbestos and involuntary smoking in women. Other important occupationally related cancers in men include nonmelanoma skin, mesothelioma, and sinonasal, whereas the main occupationally related cancers in women include lung, sinonasal, nasopharyngeal, and mesothelioma. In a study of six cancers (bladder, leukemia, lung, mesothelioma, nonmelanoma skin, sinonasal) in the United Kingdom, the estimated contribution of asbestos exposure to these cancers accounted for > ½ occupationally attributable deaths.[40]

The association between occupation-associated chemical exposure and cancers of the breast (except estrogens), ovary, prostate, and colorectal is not as strong as that between lung and bladder cancers.[41] The contribution of occupational exposures to female breast cancer remains unclear, depending on assumptions related to the effect of epigenetic factors (shift work, hormones, endocrine disruptors) on these estimates. A follow-up study on occupational cancer in 15 million inhabitants in 5 Nordic countries did not detect strong associations between occupational chemicals and breast cancer based on self-administered occupation questionnaires; the largest variation in breast cancer incidence occurred in women with their first children at an older age and women with a large average number of children.[42] Women in occupations requiring high educational level often have a higher age at first childbirth and an elevated breast cancer incidence. Prostate cancer in men is typically not associated with occupational exposures.

Environment

Evidence supporting the importance of environmental factors in cancer epidemiology includes the following: 1) the similar cancer risk in native and migrant populations (e.g., Japanese immigrants in California) adopting the habits of the host population over a generation; 2) larger differences in cancer incidence rates between countries than within different regions of the same country; and 3) substantial ethnic and racial differences in cancer incidence within countries (e.g., United States). Cancer rates vary by ~5-fold between industrialized countries and up to 30-fold between all countries.[15] Increasing cancer incidence or mortality rates do not necessarily imply environmental carcinogens are responsible for the increase because many factors influence cancer rates (e.g., aging, biological and epigenetic carcinogens).[43] Arsenic, asbestos, UV radiation, radon, and silica are common environmental carcinogens.

Air

Air pollution is a complex mixture of compounds, including multiple carcinogens from natural and anthropogenic sources (e.g., nitrosamines, benzene, vinyl chloride, asbestos, carcinogenic metals, formaldehyde, polychlorinated dibenzodioxins, polycyclic aromatic hydrocarbons) that varies substantially over time and space reflecting atmospheric processes (weather, oxidative reactions, pollutant interactions). The International Agency for Research on Cancer considers outdoor mixtures of air pollution and particulate matter human carcinogens (Group 1) based on sufficient evidence of increased risks of lung cancer in humans, sufficient evidence in animals, and strong mechanistic evidence (altered gene expression for DNA repair, epigenetic changes including altered DNA methylation, inflammation, oxidative stress).[44] For most pollutants, urban air contains pollutant concentrations several times greater than rural areas; however, concentrations of certain pollutants of concern near industrial sources may be several magnitudes higher than rural areas (e.g., arsenic, benzene, cadmium).[45]

Epidemiological evidence suggests urban air pollution near industrial sources (e.g., nonferrous smelters) increases the relative risk of lung cancer (i.e., 1.2–2.0);[46] however, the relatively low relative risks suggest uncontrolled confounding variables may significantly alter the determination of the contribution of air pollution to lung cancer. These findings are consistent with pooled analyses of European data and cohort studies in the United States.[47] In a prospective analysis of data obtained by the European Study of Cohorts for Air Pollution Effects using data from 17 cohort studies based in 9 European countries (4,013,131 person-years at risk), the meta-analyses demonstrated a statistically significant association between lung cancer and PM_{10} (hazard ratio = 1.22, 95% CI: 1.03–1.45)/10 μg/m^3.[48] There was no association between nitrous oxide and lung cancer. Quantitative risk estimates of airborne carcinogens suggest polycyclic organic matter forming during incomplete combustion is the major contributor in outdoor air to the increased human cancer risks.[49] Indoor air pollution is a significant risk factor for the development of cancer because of the presence of cigarette smoke, radon, benzene, and formaldehyde. Reviews indicate the relative risk of lung cancer is approximately 1.3 for nonsmokers living with smokers compared with nonsmokers living with nonsmokers.[50]

Cancer risks from pollution lie near the detection limit of epidemiological studies (i.e., RR = 1.5–2); below these levels, imprecise exposure data and confounding variables are potentially important sources of error.[46]

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Although suggestive of possible associations in the ESCAPE study with the exception of bladder cancer,[51] the hazard ratios for PM_{10} and nonpulmonary cancers (brain,[52] breast,[53] kidney,[53] liver[54]) were weak and statistically nonsignificant. Current analytical technology allows the detection of many trace pollutants in the air and water; however, few of these contaminants are routinely monitored. Estimates of human exposure to these pollutants frequently do not consider the wide geographical, individual, and economic variation in exposures.[55] Compared with the higher chemical concentrations at the work site, the lower exposure levels present in the environment create a greater probability of detecting an association generated by a confounding variable rather than an association with the variable under study.[56]

Drinking Water

Ecological studies suggest an increased risk of certain cancers from contamination of drinking water with hexavalent chromium (IARC Group 1), inorganic arsenic (Group 1), and nitrates (Group 2A), with some support from individual-based studies.[57] High inorganic arsenic concentrations in drinking water (i.e., >200 μg/L) are associated with elevated risks of skin, bladder, and lung cancers, whereas these associations are weaker at lower inorganic arsenic concentrations of <100–200 μg/L.[58] Although limited epidemiological evidence for ingestion of Cr^6 in drinking water suggests an increased risk for stomach and possibly lung cancers in Chinese and Greek ecological studies,[59,60] the quality of exposure information and lack of a dose-response relationship limit conclusions regarding causation.[61] A meta-analysis of highly Cr^6-exposed workers did not detect an elevated risk of gastrointestinal cancers, including stomach cancer (meta-standardized mortality ratio for stomach cancer = 1.09, 95% CI: 0.93–1.28) compared with the general population.[62] The primary issues regarding nitrates in drinking water result from the formation of *N*-nitroso compounds that potentially produce adverse effects from the complex interaction of nitrate concentrations and concomitant ingestion of nitrosation precursors/cofactors in susceptible subpopulations. Although the IARC lists ingested nitrates and nitrites as probable human carcinogens (Group 2A) under conditions of endogenous nitrosation based primarily on animal data and mechanistic considerations,[63] the causal role for nitrates and nitrites in the development of cancer remains controversial [inadequate epidemiology evidence for nitrates in food and drinking water, limited evidence for carcinogenicity in humans (i.e., stomach cancer) for nitrites in food].[64] Chlorination by-products form from the interaction of chlorine with naturally occurring fulvic and humic acids along with other organic chemicals. Chloroform (Group 2B) and other trihalomethanes are the most important organic chemical carcinogens found in chlorinated water; however, chlorination by-products are difficult to study because the chemical concentrations in this complex mixture of hundreds of halogenated chemical species vary significantly over time, source waters, and treatment practices.[65] Evidence of carcinogenicity is suggestive for bladder cancer and possibly colorectal cancer; overall, the evidence is inadequate to determine carcinogenicity because of inconsistent results and generally poor exposure data.

Lifestyle

The histological type of most cancers (i.e., >80%) is epithelial (i.e., uterus, rectum, colon, lung), typically in organs with exposure to environmental carcinogens and high cell proliferation/spontaneous mutation rates.[66] Determination of the contribution of diet to the overall cancer rate is the most uncertain of lifestyle factors because of the difficulty in obtaining accurate measures of dietary components, the long latency between dietary intake and clinical appearance of solid tumors (10–20 years), and the complex interaction of various dietary components. Tobacco smoking is clearly the most important lifestyle carcinogen; however, changes in smoking patterns and aging do not account for all the earlier increases in cancer rates. Since the 1960s, the prevalence of smoking in the general population has declined by ~½ to 23% in men and 19% in women aged 35–64 years by the early 2010s.[67] Despite the reduction in tobacco smoking prevalence, the overall cancer incidence attributable to smoking remains high at 29% (35% in men and 24% in women); the estimates for lung cancer attributed to smoking remain high at 84% among men and 81% among women, as more tumor types are associated with smoking (e.g., cervix, colon, acute myeloid leukemia, liver, stomach).

In an analysis of data from the Nurses' Health Study, the Health Professionals Follow-up Study, and US national cancer statistics, the population-attributable risk (PAR) was calculated for a low-risk group with a healthy lifestyle pattern (16,531 women, 11,731 men) and all other members of the cohorts (73,040 women, 34,608 men).[68] A healthy lifestyle included never or past smoking (<5 pack-years), no or moderate alcohol consumption (≤1 drink/day for women; ≤2 drinks/day for men), BMI 18.5–27.5, and at least 75 vigorously intense

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or 150 moderately intense minutes of aerobic physical activity/week. The estimated PAR for the overall incidence of total carcinomas attributable to unhealthy lifestyle factors studied was 41% for women and 63% for men; however, the relative reduction in cancer between the highest and lowest quintiles of the Nurses' Health and Health Professionals follow-up studies was relatively small (6–10%), indicating the attributable fractions specifically for diet were smaller, consistent with the 2010 UK estimates.[31,69] A meta-analysis of 314 observational and randomized clinical trials evaluated dietary risk factors for the five most common cancers (breast, colorectal, lung, prostate, stomach) based on predetermined guidelines to assess the strength of the evidence.[70] The authors reported convincing evidence for an association between alcohol/whole grains and colorectal cancer, whereas evidence was highly suggestive for heavy alcohol intake/breast cancer, fruit intake/lung cancer, and calcium/colorectal cancer. Large cohort studies have not detected overall protective effects of fruits/vegetables or vitamin A/β-carotene/retinol on lung or overall cancer rates.[71]

Additionally, the diet of an individual may contain a number of natural carcinogens (e.g., aflatoxin B_1, cycasin, safrole, pyrrolizidine alkaloids, natural pesticides). However, the contribution of synthetic pesticide residues to the overall incidence of cancer appears small, including in occupational settings where the evidence is weak and inconsistent due to the difficulty of study designs (bias, confounding, sample size, heterogeneous exposures).[55] The cooking of food generates a number of mutagens (nitropyrenes) and carcinogens (heterocyclic amines).

Infection

At least 10 infectious agents are established human carcinogens. These causal associations include *Helicobacter pylori*/stomach cancer, hepatitis B and C virus/liver cancer, Epstein–Barr virus/Burkitt's lymphoma, human herpesvirus type 8/Kaposi's sarcoma, human T cell lymphotropic virus/adult T cell leukemia and lymphoma, human papillomaviruses/cervix, penile, anal, and oropharyngeal carcinomas, *Schistosoma hematobium*/bladder carcinoma, *Clonorchiasis sinensis*/cholangiosarcoma of the bile duct, and AIDS/HIV-associated tumors. The attributable fraction varies with location, development status, and specific infectious rates. In a study of background infections with carcinogenic infectious agents and associated cancers using cancer incidence estimates from GLOBOCAN 2012, the attributable fraction varied from <5% in highly developed countries (the United States, Canada, Australia, New Zealand) to >50% in sub-Saharan African countries.[72] The overall global attributable fraction for infectious agents was 15.4% with the most important infectious agents globally being *H. pylori*, human papillomaviruses, hepatitis B virus, hepatitis C virus, and Epstein–Barr virus.

In Utero

Established human carcinogens following *in utero* exposure to diethylstilbestrol are vaginal adenocarcinoma in female offspring and squamous cell carcinoma of the cervix and testis.[73] The major childhood cancers are leukemia, lymphomas, Wilms' tumor, neuroblastoma, and brain tumors; almost all studies of parental exposures and childhood cancers use case-control designs because of the rarity of these cancers. A review of 24 case-control studies suggested an association between childhood brain cancer and hydrocarbon-associated occupations and between childhood leukemia and parental occupation in the paint industries; however, the limited study size and inaccurate exposure assessment in this study limit conclusions regarding causation.[74] Although reviews of other case-control studies also suggest the possibility of an association between childhood leukemia and several paternal exposures (paints, solvents, motor vehicle exhaust) and childhood nervous system cancers and paternal paint exposure,[75] significant limitations prevent definite conclusions regarding associations and/or causation.[76] These limitations include poor exposure assessments (self-reporting, interviews, birth certificates), recall bias, selective reporting bias, multiple comparisons, limited follow-up, little maternal data, and small sample size of cases.[77,78] Adequate exposure data from parents is a major limitation of these retrospective studies; the rarity of childhood cancers restricts the use of more definitive prospective studies.

GENERAL CAUSATION

Population data do not provide information on the etiology of disease in an individual. Although Japanese inhabitants have a higher stomach cancer incidence and eat more fish than Americans, this does not prove that fish in Japan causes stomach cancer. A large relative cancer risk in the study population may not significantly alter the cancer risk in the general population when the specific cancer rate is rare.

The multifactorial causes of cancer, the high prevalence of cancer in the general population, and the prolonged latency period between exposure and the

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clinical onset of cancer complicate the determination of causation in cancer patients with chemical exposures. Simple one-to-one correspondence between a specific factor and disease rarely, if ever, occurs so that the presence of the factor is necessary and sufficient; hence, even strong exogenous factors (e.g., long-term smoking, dominant breast cancer genes) do not always cause cancer when present.[79] Factors suggesting the possibility of an occupational cancer include the development of a cancer unique to the industry where the individual works (e.g., angiosarcoma/vinyl chloride exposure, mesothelioma/asbestos), an appropriate latency period between exposure and diagnosis of the specific type of cancer, and clinical evidence of exposure to a toxic dose of the carcinogen. Establishing contributory cause requires that the chemical exposure precedes the disease and that alteration of the chemical exposure changes the disease (rate). Contributory cause is neither sufficient nor necessary. Therefore, all subjects with a chemical exposure do not necessarily develop the disease and not every subject with the disease must be exposed to the compound. Determining a cause-effect relationship requires an experimental approach; thus, the use of epidemiological (observational) and animal data necessitates an evaluation of the *probability* of a causal relationship.[80] Observational human and experimental animal studies can demonstrate an association between a chemical and the increased incidence of cancer; however, the determination of a true cause-and-effect relationship requires a careful evaluation of the association.

There is no generally accepted consensus on the criteria for distinguishing positive from negative studies. The presence or absence of a statistically significant endpoint does not guarantee a causal relationship because the presence of certain factors (e.g., bias, confounding, inadequate sample size) may complicate the interpretation of the results. Reportedly negative studies should be evaluated for misclassification, dilution of the exposure group with unexposed subjects, omissions, adequate statistical power, and inadequate latent periods.[81] Factors favoring the validity of a positive result include dose-response relationship, strong association, lack of positive bias and confounding, and adequate exclusion of chance effects. Sir Austin Bradford Hill postulated nine characteristics of an association that suggest true causation.[82,83] None of the nine criteria of causation provide irrefutable evidence of a causal role, except for the presence of the disease before the exposure. However, the fewer criteria satisfied, the greater the probability that chance, bias, or confounding variables account for the association. The use of studies in this evaluation of chemical carcinogenicity assumes the studies are valid.

Other methods of determining causality include the Epidemiology-Toxicology ("Epid-Tox") framework involving: 1) collection of all relevant studies, 2) assessment of the study quality, 3) weight of evidence evaluation, 4) assignment of a scalable conclusion, and 5) placement of the conclusion regarding causal relationship on a grid that reflects the likelihood of a positive connection.[84] This approach reflects causality as an inference with varying degrees of certainty rather than absolute proof of a causal relationship. Epidemiological studies using a null hypothesis can fail to reject the null hypothesis as false; however, this type of postulate cannot establish that the variable has no effect on a health outcome. Ultimately, the determination of the presence or absence of a causal relationship between an exposure and a disease is a subjective process that evaluates the strength or likelihood that the exposure causes the effect of interest. A conclusion of a likely causal relationship between the environmental factor and the disease means the epidemiology and animal data provide consistent, reliable evidence of a causal inference (e.g., asbestos and mesothelioma; tobacco smoke and lung cancer). The causal relationship is uncertain when the epidemiology and animal data are inconsistent; in this situation, the weight of evidence from epidemiological studies demonstrates little or no evidence of any effect, although toxicological studies may suggest the plausibility of an effect in humans. The strength and primacy of epidemiology data may suggest a causal relationship in the absence of evidence supporting biological plausibility (Kaposi's sarcoma and HIV), particularly in the early phases of epidemiology studies and animal experiments. A causal relationship between the environmental factor and the disease condition is unlikely when epidemiological and toxicological evidence is compatible with the absence of effect (e.g., D-limonene and kidney cancer in male rats or phenobarbital and rodent liver cancers after negative epidemiology studies). The following is a list of characteristics for evaluating causal relationship of chemical exposures to a disease process in order of importance.[83]

Strength

A higher relative risk (rate ratio) indicates a stronger likelihood of a causal relationship. The studies should contain adequate sample sizes and substantial numbers of observed/expected cases to reduce random fluctuations due to chance. A relative risk of <2 may result from unrecognized bias or confounding variables, whereas a relative risk of >5 is unlikely to result from

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these factors.[85] A small relative risk does not necessarily imply lack of causality, particularly if the disease under study is common. Statistical significance implies the lack of an association is probably not missed rather than indicating a causal relationship exists; the size of the *P* value reflects the confidence to dismiss the null hypothesis. The *P* value is **not** a measure of the strength of the relative risk. Typically, the significance of the *P* value relates to one comparison, whereas multiple comparisons or tests weaken the significance of the *P* value. The ratio of a disease in two groups (exposed/unexposed) is probably more important in understanding a causal relationship than the absolute difference in the disease rate between the two groups.

Consistency

The similarity of results between studies of different designs, places, times, and populations supports a causal association; however, the occurrence of publication bias (i.e., nonpublication of negative studies) complicates the evaluation of consistency. The larger the number and type of studies reproducing the same results, the stronger the causal link and the less likely a constant error or fallacy accounts for the positive results. Consistency requires similar observations by multiple investigators using different methods at different times in different locations. Prospective studies provide more persuasive evidence of causation than retrospective or mortality studies. When discrepancies occur between studies, the studies with better methodology and exposure data should receive greater weight.

Specificity

Specificity is a measure of the uniqueness of the type of disease or the magnitude of the response. The latter implies causation when the magnitude of the disease is much higher for one disease (e.g., lung disease in smokers) than for other diseases (e.g., cardiovascular disease in smokers). Specificity is less common in chronic diseases with multifactorial etiologies than in infectious diseases. The development of hepatic angiosarcomas and mesotheliomas strongly suggests chemical exposure (vinyl chloride and asbestos, respectively) because of the single cause attributed to these diseases; however, the etiology of many diseases is multifactorial; each contributing cause adds a small portion to the risk of developing the disease. Hence, the demonstration of specificity strongly supports causation, but the absence of specificity does not negate a theory of causation.

Temporal Relationship

The cause or exposure *must* precede the development of the disease. When studying cancer with long latent periods, the exposure must occur earlier than one-half of the mean latent period. The latent period represents the time from initiation of the cancer cell to the presence of a clinically detectable tumor. Most of the latent period represents the promotion stage, when the initiated cell grows into a premalignant lesion. Consequently, disease induction and latent periods are important factors in the determination of cancer etiology in cohort studies that use exposure data to define exposure-response gradients.[86] Although minimum latent periods are necessary to establish a true causal link, the long latent period from induction of cancer to clinically apparent disease probably does vary substantially after similar exposure periods. Based on cancer data from atomic bombing victims, leukemia has the shortest latent period with the first evidence of excess leukemia cases appearing about 5–7 years postirradiation.[87] These studies indicate solid tumors have a longer latent period than leukemia with excess incidence of solid cancers persisting for 40 years and mean latency periods ranging from 5–30 years.[88] For analysis of data from radiation victims, the Committee on the Biological Effects of Ionizing Radiations assumes a minimum latent period of 2 years for leukemia and 10 years for tumors other than leukemia and breast cancer.[87] The latent period is age-dependent because the latent period is longer when exposure occurs at a young age.

Dose-Response (Biological Gradient)

The incidence of disease should increase with increasing exposure levels documenting the presence of a biological gradient. The demonstration of a true dose-response relationship and reduction in disease incidence following cessation of exposure strongly support a causal relationship. The presence of other carcinogens, poor exposure data, or the addition of confounding variables may obscure the dose-response relationship. Hence, the lack of a dose-response relationship does not exclude a causal link to the exposure.

Typically, exposure to genotoxic carcinogens demonstrates a dose-response effect; higher carcinogen concentrations produce: 1) an increased incidence and multiplicity of tumors; and 2) a reduction in the latent period. Genotoxic carcinogens exhibit a wide range of potencies. Strain A mice studies indicate a 30,000-fold difference in carcinogen potency for the development of pulmonary tumors.[89] Biotransformation frequently explains species- and dose-dependent

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differences in cancer rates as manifested by the shape of the dose-response curve. Furthermore, many chemicals may induce cancer following chronic exposure to near-toxic doses based on increased mitogenesis.[90] The issue of whether a threshold exists below which exposure to a carcinogen does not produce cancer remains controversial. Theoretically, the requirement for metabolic activation, the presence of saturated DNA repair processes, and dose-related latent periods may produce a no-observable-effect level.

Biological Plausibility

Biologically plausible depends on the extent of knowledge concerning the biological mechanisms of action; consequently, this characteristic involves toxicological corroboration of epidemiological evidence. The greater the biochemical data on the basis of the disease and the more extensive the pharmacokinetic information on the exposure, the more persuasive the evidence is for a causal role. Experimental animal data helps improve our understanding of the relationship between exposure and disease. The proposed causal relationship should not seriously conflict with data on the pharmacodynamics and toxicology of the substance. The use of frameworks for evaluating the human relevance of modes of action in the production of cancer in experimental animals improves the relevance of animal data to human cancer.[91,92]

Coherence of Evidence

The establishment of a cause-effect relationship should not conflict with apparent truths about the natural history or biology of the disease. Variation in the presence of a suspected environmental or occupational carcinogen should coincide with statistics on the prevalence of cancer in patients exposed to the carcinogen. The association of a carcinogen with a specific type of cancer should be consistent with known latent periods and the natural history of the type of cancer involved. Sound judgment requires the careful evaluation of unexpected associations; 1 in 20 associations will be statistically significant by definition. The incidences of most diseases are too low and the latencies too long to enroll a realistically large number of compliant volunteers for long periods of time. Confounding and bias complicate the interpretation of epidemiology studies.

Experimental Evidence

Although human carcinogens typically produce positive results in animal studies,[93] positive rodent studies do not always predict the carcinogenic potential of the chemical in humans, in part because high experimental doses do not reflect typical human exposures.[94] Interventional studies demonstrating an alteration in the disease corresponding to a change in the exposure strongly suggest a cause-effect relationship. Retrospective or prospective evaluation of changes in the concentration of a chemical that result from improved work practices provides important evidence to support causation, if the corresponding confounding variables are also controlled.

Analogy

If similar compounds produce the disease, the chemical exposure in question by analogy would cause the disease. Although the structure of chemical carcinogens diverges widely, the lack of an increased incidence of cancer in similar compounds argues against a causal role for the development of cancer.

CAUSATION AND INDIVIDUAL EXPOSURES

Establishment of a link between an individual exposure and a particular disease is very difficult to prove conclusively; however, several criteria establish a link between exposure and disease at the more likely than not degree. These criteria include: 1) the exposure is an established cause of the disease, 2) the exposure of the individual is similar (i.e., latency, intensity, duration) to the exposures of persons developing the disease, 3) the individual has a similar disease to persons etiologically linked to the exposure, 4) the individual was not exposed to another established cause of the disease, and 5) the adjusted relative risk of the disease among exposed individuals exceeds two. The latter value indicates the diseased individual is more likely than not to have developed the disease as a result of the specified exposure based on an excess risk being greater than the background risk (i.e., 1).[79] An odds ratio exceeding two suggests the results are quantitatively significant rather than simply statistically significant.[95] The development of cancer at a specific site should be consistent with known exposures and compatible latency periods.

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Chapter 49

EVALUATING CARCINOGENICITY

Chemical carcinogenesis is the induction or enhancement of neoplastic disease (benign or malignant) by xenobiotics. These substances are usually genotoxic, affecting specific organs and tissues (e.g., epithelial or other susceptible cells). Classification of the carcinogenic potential of specific xenobiotics involves evaluation of animal experiments, mechanisms of toxicity, and epidemiological studies. Signs of carcinogenicity in animal studies include increased frequency and types of tumors, decreased latency periods, and increased total tumors per animal. Experimental animal studies are the primary screening method for detecting environmental and occupational carcinogens; however, the use of maximum tolerated doses and interspecies variations require confirmation of carcinogenic effects in epidemiology studies. Chemical doses close to the maximum tolerated dose can induce mitogenesis, favoring mutagenesis and suggesting evidence of carcinogenesis when none exists. Each regulatory agency develops somewhat different methods for the assessment of cancer risks from xenobiotic exposures. Cocarcinogens (e.g., ethanol) may act at each stage of carcinogenesis; therefore, these xenobiotics increase the carcinogenic potential of other agents.[1] Cocarcinogens increase the effective concentration of the ultimate carcinogen through alterations of their kinetics; however, cocarcinogens are not genotoxic. These chemicals deplete the organism of endogenous detoxifying processes, including glutathione, induce oxidative and conjugating enzymes, inhibit DNA repair enzymes, and activate procarcinogens.[2,3] Cocarcinogens may be difficult to separate experimentally from tumor promoters that act through epigenetic mechanisms.

CHEMICAL STRUCTURE AND METABOLISM

A chemical carcinogen is a compound capable of producing a statistically increased incidence, type, onset, or multiplicity of neoplasms in *animals* when compared with animal controls. The issue of whether or not an animal carcinogen causes cancer in humans depends on a scientific evaluation of the appropriateness of extrapolating the animal data to humans (i.e., mechanism of action, route of exposure, interspecies variations, pharmacokinetics, dose, potency) and epidemiology data on human exposures.[4] Most chemical carcinogens are procarcinogens that undergo metabolic activation by the cytochrome P450 (CYP450) system or other metabolic pathways before these chemicals react with DNA or alter epigenetic mechanisms.[5] This process generates reactive intermediate metabolites that bind to nuclear and/or mitochondrial DNA and form DNA adducts (e.g., CYP2E1, CYP2A6, and CYP2D6 activation of *N*-nitrosamines; CYP2E1 activation of benzene to reactive benzoquinones). The latter is necessary but probably not sufficient for the development of cancer. Each class of genotoxic carcinogens reacts selectively with pyrimidine and purine bases to form DNA adducts. Aflatoxins, aliphatic epoxides, mustards, *N*-nitroso compounds, and polycyclic aromatic hydrocarbons (PAHs) transfer simple alkyl or aryl-alkyl groups to specific DNA bases, whereas azoamino dyes, aryl aromatic amines, and heterocyclic aromatic amines transfer arylamine residues to DNA. These genotoxic carcinogens are powerful mutagens that can produce nonsense or missense mutation by base pair mismatches or small

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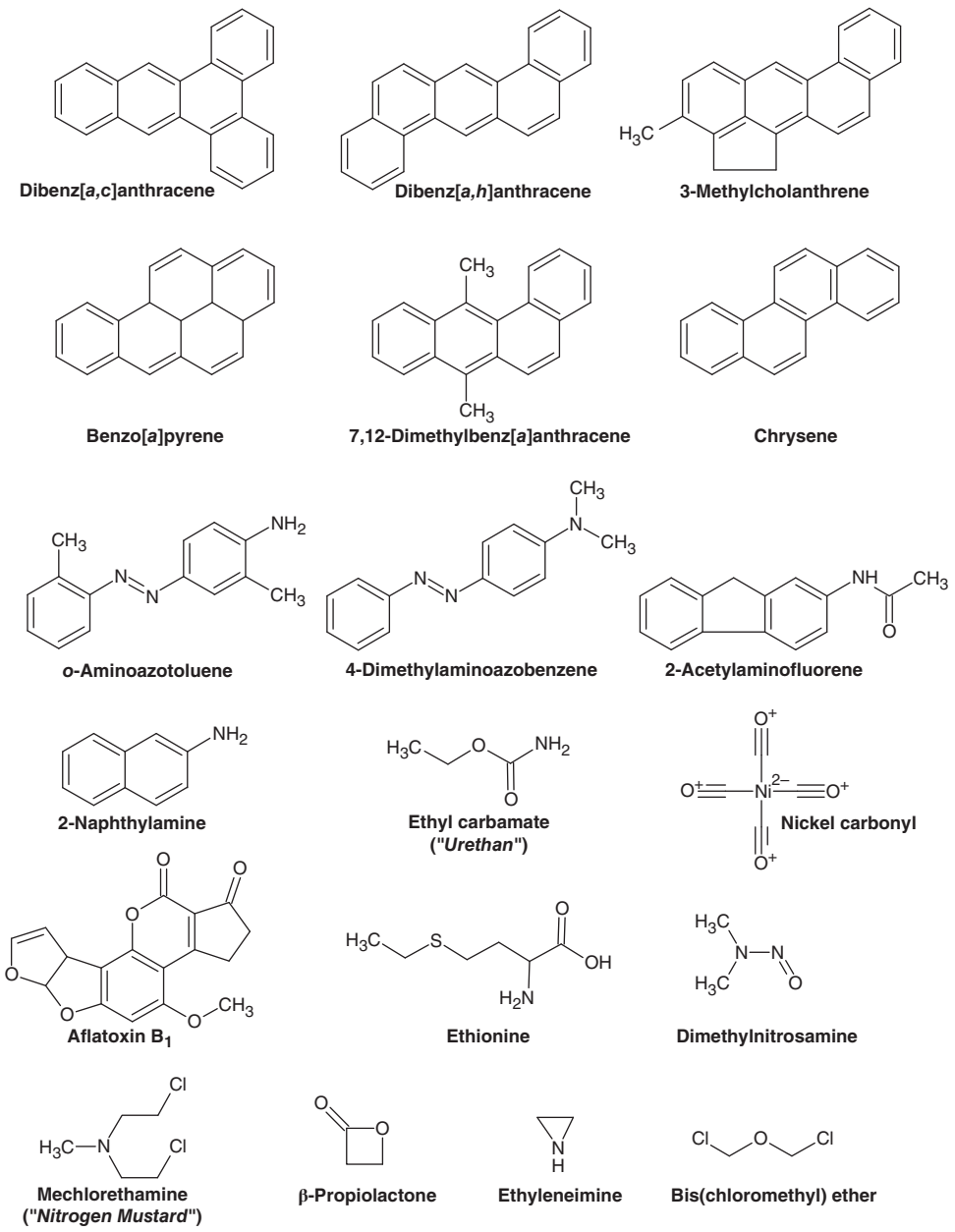


FIGURE 49.1. Diverse chemical structures of selected known and suspected chemical carcinogens.

deletions; other genotoxic chemical carcinogens can cause large deletions or chromosomal breaks. Many organic exogenous chemical carcinogens (e.g., PAHs and polyhalogenated aromatic hydrocarbons) accumulate in lipid stores that slowly release these chemicals into the blood; subsequently, following metabolic activation, these carcinogens travel to carcinogenic targets in peripheral tissues where the metabolic intermediates form DNA adducts.[6]

Some chemical carcinogens are not genotoxic; these carcinogens act at epigenetic sites usually at high doses and following prolonged exposure as detected in rodent studies via multiple mechanisms (e.g., DNA/histone methylation, DNA oxyradical damage, deamination of 5-methylcytosine, depurination, alteration of hormones, regenerative hyperplasia). Known and suspected chemical carcinogens display diverse chemical structures and divergent origins, as displayed in Figure 49.1.

Aromatic hydrocarbons were the first chemical group associated with cancer when Percival Pott linked the soot from the combustion of coal with scrotal skin cancer

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in chimney sweeps; however, the actual carcinogenic compounds (polycyclic aromatic hydrocarbons) were not identified until 150 years later. The pyrolysis of fossil fuels produces polycyclic aromatic hydrocarbons in automobile exhaust, factory emissions, and cigarette smoke. In 1935, Sasaki and Yoshida discovered the first carcinogen to act at a site remote from its application when they produced liver tumors in rats by feeding them the aminoazo dye, *o*-aminoazotoluene.[7] Rehn associated exposure to aniline dyes with the development of bladder cancer in 1895; subsequent[8] studies over the next 50 years revealed aromatic amines (e.g., benzidine [*p*-diaminodiphenyl], 1-naphthylamine, 2-naphthyhlamine) were the primary carcinogens in aniline dyes.

Highly reactive nitroso compounds (e.g., dialkylnitrosamine, dimethylnitrosamine) are potent liver carcinogens in animal studies; however, evidence for a causal link between dietary amines and an increased risk of stomach, brain, esophageal, or nasopharyngeal cancers is inconclusive.[9,10] Some chemotherapeutic agents are associated with increased cancer risks. An increased incidence of carcinomas of the bladder and acute nonlymphocytic leukemia occurs following chemotherapy with MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) and other alkylating agents (melphalan, cyclophosphamide).[11] Carcinogens of natural origin represent a significant source of exposure to known human carcinogens. Based on studies of the incidence of carcinomas in rodents exposed to various chemicals, 58% of the synthetic chemicals and 45% of the natural chemicals tested positive in at least one species.[12,13] Recognized human carcinogens of natural origin include both organic (e.g., aflatoxins, asbestos, mineral oils, shale oils, soot) and inorganic (e.g., arsenic, hexavalent chromium, nickel) compounds. The carcinogenic risk in the latter group depends on the metal species. The valence of the metal affects the compound's bioavailability; hence, the species determines the amount (i.e., absorbed dose) of the compound reaching the critical target organ.

EXPERIMENTAL CELL STUDIES

The Chemical Abstract Services Registry contains over 100 million unique chemical numbers (CAS RN). Over 100,000 chemicals are used in sufficient quantities to raise concern about their toxic effects. The purpose of animal studies and *in vitro* experiments with suspected chemical carcinogens is the identification of those chemicals producing significant risks of inducing human cancer. Human carcinogens predicted by experimental testing include vinyl chloride, 4-aminobiphenyl, *bis*(chloromethyl)ether, diethylstilbestrol, mustard gas, melphalan, and the combination of 8-methoxypsoralen and ultraviolet light.

There is no simple way to identify which environmental chemicals pose the greatest cancer hazard. Screening for suspected human carcinogenicity typically begins with short-term predictive tests (e.g., Ames test), followed by long-term bioassays in rodents and then epidemiology studies if the screening tests indicate the chemical is a potent carcinogen.

Table 49.1 lists the advantages and disadvantages of important methods for testing chemical carcinogenicity. The congruence of carcinogenicity testing and human epidemiology studies indicates these tests are sensitive; however, extrapolation of animal data to humans as a means to establish quantitative data rather than priorities for concern and regulation remains complicated and controversial.[14,15] Chemicals demonstrating potent or multiorgan effects in carcinogenicity studies signal the need for epidemiology studies; however, carcinogen potency in animal studies (e.g., dioxins) does not necessarily correlate with the induction of human

TABLE 49.1. Classical carcinogenicity testing. (Adapted from Shields and Harris).[14]

Method	Advantages	Disadvantages
In vitro testing	Economical, short-term with rapid results, human cells	Uncertain extrapolation to humans, frequent false positives/negatives, substantial inter-laboratory variation, mutagenicity does not imply carcinogenicity
Animal bioassay	Better predictive value than *in vitro* assay, elucidates species differences	Uncertain quantitative extrapolation to humans, higher doses than human exposure, species differences in DNA repair and metabolism
Molecular epidemiology	Measures internal dose, identifies individual risk and molecular pathways	Highly complex in a rapidly changing field
Classical epidemiology	Direct evaluation of human experience, examines confounders, provides dose-response data	Insensitive with unknown confounders limiting predictive value. Positive results suggest, but do not prove, carcinogenicity

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cancer. Issues surrounding animal studies include: 1) consequences of the study on environmental and economic matters, 2) appropriateness of using animals, 3) validity of the animal model, and 4) interpretation of the data.[16]

Mutations

Genotoxins are a broad spectrum of chemical or physical agents that disrupt cellular genetic material involving DNA; these agents can be mutagens, carcinogens, and/or teratogens. Genotoxic agents cause DNA damage including alterations in DNA structure from inaccurate replication of a portion of the genome that is not necessarily transmitted to the next generation of cells. Mutagens are chemical or physical agents that produce *transmissible* genetic alterations that are not necessarily carcinogenic, whereas carcinogens cause heritable genetic and/or epigenetic alterations resulting in autonomous tissue growth (neoplasia) and metastasis. Mutagenic chemicals may be direct mutagens or indirect mutagens that require metabolic activation. Most chemicals classified as human carcinogens or probable human carcinogens are mutagenic in mammalian cells *in vivo* and/or *in vitro*. Determination of mutagenicity or nonmutagenicity usually involves a minimal set of data, including gene mutations in bacteria and/or mammalian cells and *in vitro* and *in vivo* cytogenetics.[17] Mutagenic events result from: 1) carcinogen- or activated metabolite-induced DNA or chromatin modification or interference with other processes (spindle function, gene transcription); and/or 2) disruption of tissue homeostatic mechanisms (cell turnover, tissue necrosis, apoptosis, inflammation). The agreement between mutagenic activity and carcinogenic potential depends on the choice of databases. For the US National Toxicology Program (USNTP), the correlation between genotoxicity and carcinogenicity is ~60%, with the database containing many single-species or single tissue carcinogens.[18] Most chemicals in the IARC classification of carcinogens are multispecies or multitissue carcinogens. Compared with the USNTP, the correlation between carcinogenicity and genotoxicity is higher in the IARC database (e.g., Group 1, 80–93%; Group 2A, 84–90%; Group 2B, 50–90%).[19]

Most chemicals causing mutation in somatic or germ cells are positive in *in vitro* tests, including bacterial gene mutation (Ames test), mouse lymphoma assay, chromosomal aberration in cultured mammalian cells, hypoxanthine phosphorybosyl transferase (HPRT) gene mutation testing, and transgenic rodent studies (e.g., heterozygous p53-deficient, Tg.AC, Tg-Hras2 models).[20,21] Induction of micronuclei and chromosomal aberrations in rodent bone marrow supplements these tests. These tests primarily detect events causing cell initiation (i.e., mutation or clastogenicity) rather than mimicking all cancer stages. Although large differences may occur between mutagenic and carcinogenic potencies of a specific chemical, these assays are good screening tests for potential genotoxic carcinogens. The correlation between DNA reactivity, evidence of mutagenicity on the Ames test, and structural similarities to other known animal carcinogens is typically good.[22] Negative assays for mutagenicity in the presence of positive long-term bioassays in rodents suggest the chemical acts at a stage of carcinogenesis (e.g., promotion) other than initiation and displays epigenetic characteristics. Current standard genotoxicity test batteries are not highly sensitive to nongenotoxic (i.e., epigenetic) carcinogens.[23]

Table 49.2 lists some examples of chemicals recognized by the IARC as causes of human or animal tumors that are inactive in a variety of short-term genotoxic tests. These chemicals tend to produce tumors in susceptible tissue (e.g., mouse liver, rodent leukemogens, rodent thyroid gland, male rat kidney) and display diverse, unpredictable chemical structures.

Since the 1970s,[25] the most studied and best validated *in vitro* mutation assay has been the Ames test (*Salmonella* mammalian microsome mutagenicity assay);[26] this test uses special tester strains of *Salmonella typhimurium* requiring histidine for growth to detect the mutagenicity of physical agents, drugs, foods, natural substances, body fluids, and environmental chemicals/mixtures.[27] Newer approaches to carcinogenic testing based on emerging technologies in molecular biology, genomic sciences, and computer modeling include techniques based on computational methods, statistics-based (Q)SAR (Quantitative

TABLE 49.2. Some IARC-classified carcinogenic agents without genotoxicity. (Data adapted from Bartsch).[24]

Group 1[a]	Group 2A[a]	Group 2B[a]
Steroidal estrogen (17β-estradiol),	Anabolic steroids (testosterone),	Butylated hydroxyanisole, DDT, Di-(2-ethylhexyl) phthalate, hexachlorobenzene, hexachlorocyclohexane, nafenopin, phenobarbital, poly-brominated biphenyls, saccharin, TCDD
Oral contraceptives (norethisterone)	Polychlorinated biphenyls	

[a] International Agency for Research on Cancer (IARC) carcinogen classification.

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Structure-Activity Relationship), toxicogenomics and pharmacogenomics, *in vitro* assays, and high-throughput screening assays (e.g., US EPA ToxCast; US government regulatory/research entity, Tox21).[28,29]

The *Salmonella* assay (Ames test) detects the presence of either base substitution or frame shift reversion mutations by measuring the number of revertant bacteria capable of synthesizing histidine. Chemicals first recognized as animal carcinogens by screening with this test include the flame-retardant Tris, furylfuramide (a Japanese food additive), and hair dyes. The test uses the subcellular S-9 microsomal fraction of the rat liver that contains enzymes capable of activating procarcinogens; however, the conditions of the *Salmonella* assay may not exactly duplicate the milieu in an intact animal. A false positive test may occur in a *Salmonella* assay because of a lack of type II conjugation systems that allow the formation of DNA-reactive metabolites.[30] Prediction models based on the *Salmonella* assay with structural information provide information to determine the potential genotoxicity of industrial and pharmaceutical chemicals.[31,32] Chemicals producing tumors in more than one rodent species or more than one tissue site are more likely to test positive in the Ames test than single-species or single-site carcinogens.[33]

The utilization of mammalian cells in cell cultures is a complementary assay to the *Salmonella* assay, although the former test is more sensitive, expensive, and technically difficult than the latter. Completion times for mammalian mutation assays average 1–2 weeks. These tests detect forward mutations at one of several loci (e.g., thymidine kinase, hypoxanthine guanine, and phosphoribosyltransferase) by screening for loss of enzyme activity. Cell lines used in mammalian mutation assays include mouse lymphoma L5178Y, Chinese hamster ovary (CHO), and Chinese hamster V79. In cell cultures, the ability to interfere with the inhibitory effects of the gap junction and disrupt intracellular communication provides a test for the promoting activity of a suspected chemical carcinogen.

Short-Term Assays

Rapid *in vitro* assays provide a means to identify potential carcinogens from the plethora of chemicals involved with human exposure. Traditionally, the 2-year rodent bioassay was the primary vehicle for determining carcinogenicity; however, cost, time, and limited resources reduced emphasis on this type of experimental study in favor of short- and medium-term assays with endpoints of neoplasia or precursor lesions of neoplasia, particularly with advances in understanding chemical carcinogenesis and nongenotoxic mechanisms (e.g., inflammation, gap-junction intercellular communication inhibition, receptor-medicated effects). Short-term tests reflect underlying carcinogenic mechanisms; consistently, positive test results for mutations (point mutations, chromosomal rearrangements) usually indicate cancer potential.[34] The categories of tests include mutational assays in bacteria and cell lines, cell transformation assays, and cytogenetic assays.[35] These assays measure changes in the genome (e.g., mutations, chromosome damage, aneuploidy, DNA-adducts, sister chromatid exchange); however, these assays do not detect all genetic damage (e.g., gene amplification, insertion mutations, DNA methylation).[36] No single assay detects all carcinogens; therefore, carcinogen screening often uses assay panels with sequential *in vitro* and *in vivo* testing.[37] However, some studies indicate comparable results between *in vitro* assays (e.g., *Salmonella* and mouse lymphoma cell assays, chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells).[18] In comparison to rodent bioassays, short-term assays lack similar pharmacokinetics (i.e., metabolic activation and detoxification), involve short-term exposure, and fail to detect potent initiators specific to individual organs. These assays identify genotoxic chemicals rather than epigenetic carcinogens. Table 49.3 lists types of short-term assays based on the differences in the endpoint and source of genetic changes; regulatory agencies typically use a battery of tests to screen a chemical for genotoxicity, mutagenicity, and carcinogenicity.

Cell Transformation

Cell transformation assays involve the induction of certain phenotypic alterations related to neoplasms in cultured cells; these tests (e.g., Syrian hamster embryo cells, BALB/c3T3 mouse cell system) screen for potential carcinogens. The morphological transformation of mammalian cell lines (e.g., rodent 3T3 or 10T1/2) or human epithelial cell lines produces dense foci in cell cultures. These transformed cells lose the suppressive effects of contact inhibition and continue to divide. The injection of transformed cells into the appropriate strain of rodent will produce tumors. The procedures are technically difficult and require six weeks to complete; some chemical carcinogens (e.g., asbestos) are positive in cell transformation assays and negative in mutation assays.

Cytogenetic

All tumors contain chromosomal alterations (e.g., translocations, deletions, aneuploidy) with errors in

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TABLE 49.3. Short-term tests for mutations, genotoxicity, and/or carcinogenicity. The typical timeframe is several weeks to 1–3 months. (Adapted from Johnson).[20]

Type	System	Endpoint
	Gene Mutation Assays	
Prokaryotic mutagenesis *in vivo* (e.g., *Salmonella typhimurium*-Ames Test)	*In vitro*	Reverse or forward mutations in a bacterial strain
Chinese hamster ovary (CHO) and lung fibroblast (V79) cells	*In vitro*	Mutation in hypoxanthine guanine phosphoribosyltransferase
Mouse lymphoma thymidine kinase	*In vitro*	Mutation in thymidine kinase
Mouse spot test	*In vivo*	Somatic cell mutation for coat color variation
Mouse specific locus test	*In vivo*	Germ cell mutation for coat color and ear size
Transgene mutation induction	*In vivo*	Mutation in *LacI* gene (mouse or rat) or *LacZ* gene
Dominant lethal assay	*In vivo*	Death of fertilized egg in mammalian implanted species
	Chromosomal Abnormalities	
Yeast mitotic recombination, mitotic crossing over, or mitotic gene conversion	*In vitro*	Conversion of heterozygous alleles to homozygous state
Chromosomal aberrations	*In vitro*	Visible alteration in karyotype of cell lines (e.g., CHO, V79) and cultured lymphocytes
	In vivo	Rat bone marrow cells and spermatogonial cells
Sister chromatid exchanges		Visible exchanges of differentially labeled sister chromatids
Micronucleus test	*In vitro*	Micronuclei in cell lines
	In vivo	Micronuclei in bone marrow
Heritable translocation test	*In vivo*	Translocation-induced mouse germ cells
	Primary DNA Damage	
DNA damage	*In vitro*/ *in vivo*	Comet assay, alkaline elution assay, or ^{32}P-postlabeling for DNA damage in lymphocytes or cell lines (CHO, V79)
DNA repair	*In vitro*	Unscheduled DNA synthesis
Rodent liver unscheduled DNA synthesis induction	*In vivo*	Unscheduled DNA synthesis in primary rat hepatocytes
	Cell Transformation	
Induced cellular neoplastic transformation		Syrian hamster embryo cells, Balb/c3T3
	Drosophila Melanogaster Assays	
		Somatic mutations and germ cells
	Flow cytogenetics	
		Observation of DNA damage with flow cytometry

DNA replication and/or repair resulting in genomic instability. Clastogens are chemicals that induce structural chromosomal aberrations; chemicals producing DNA replication errors typically form DNA adducts, whereas ionizing radiation and chemicals disrupting DNA-enzyme complexes (e.g., topoisomerases) are associated with DNA repair errors.[17] Tests for genotoxicity include measures of chromosomal aberrations and changes in chromosomal structure with classification of chromosomal aberrations based on breaks (deletion, fragment) or rearrangements (translocation/inversion, exchange between chromatids/chromosomes). These assays use human lymphocytes, human fibroblasts, or rodent fibroblasts to detect abnormalities in chromosome numbers (polyploidy, aneuploidy) or chromosomal structure (translocations, fragmentation, rearrangement). The endpoint is the number of cells arrested in metaphase by colchicine.[35]

Sister chromatid exchange involves the detection of the reversal of loci from a sister chromatid that results from the breakage and symmetric rejoining of the sister chromatids within a single chromosome. These alterations are the end products of homologous recombination, necessitating differentiation of the sister chromatids. Although this exchange produces no alteration in morphology, florescent dye and Giemsa's stain allow documentation of the exchange.[38] Many chemicals that produce sister chromatid exchanges also

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cause DNA/chromosomal damage and gene mutations. This test is sensitive to genotoxic and epigenetic (e.g., saccharin, asbestos, phorbol esters) carcinogens; however, sister chromosome exchange is an indicator of exposure and not necessarily a mutagenic response. Sister chromatid exchange can be performed as an *in vivo* test in urine or blood from workers exposed to carcinogens; however, the results of testing in workers must be interpreted cautiously because of the lack of specificity of this test for carcinogens. Highly sensitive immunoassays for specific DNA-carcinogen adducts are available to test human exposure to genotoxic carcinogens, but these tests also should be interpreted with caution because of the presence of DNA adducts as part of natural DNA repair mechanisms.

Standard Genotoxicity Testing

Assessment of the genotoxicity of chemical and physical agents involves various *in vitro* and *in vivo* assays, with the former providing information regarding primary genotoxicity, whereas the latter assesses secondary genotoxic effects resulting from oxidative stress and inflammation.[39] No single screening test identifies all the chemicals that produce the most serious risk of human cancer; therefore, regulatory agencies require a battery or tier system to evaluate the carcinogenic potential of a chemical. Typically, the standard genotoxicity testing battery involves: 1) a bacterial gene mutation assay, 2) an *in vitro* mammalian mutation and/or chromosome (DNA) damage assay, and 3) an *in vivo* chromosome (DNA) damage assay.[40] The International Collaborative Programme for the Evaluation of Short-Term Tests for Carcinogens (IPESTTC) concluded that the Ames test was the most valuable *in vitro* screening test for genotoxicity.[41] The Ames test typically uses the presence and absence of an exogenous metabolic activation system to improve sensitivity. However, the test has limited sensitivity for inorganic metals and halogenated organic carcinogens along with relatively poor specificity for nitrogen- and sulfur-containing organic chemicals.[42] Overall, the Ames bacterial mutagenicity assay detects ~90% of known human carcinogens and predicts ~60% of rodent carcinogens.[43] A subsequent study (Collaborative Study on Short-Term Tests for Genotoxicity and Carcinogenicity) identified four *in vitro* assays (chromosomal aberrations, gene mutations, neoplastic transformation in cultured mammalian cells, and aneuploidy initiation in yeast) that improved the screening potential of the Ames test. This international study concluded that the combination of the Ames test and the chromosomal aberrations assay (i.e., microscopically visible alterations in chromosomal structure) was the most appropriate *in vitro* primary screen for the carcinogenic potential of new chemicals.[44] The second phase of this study confirmed the importance of *in vivo* assays as a means of identifying which *in vitro* genotoxic chemicals are active *in vivo* with the greatest potential human hazards. Based on this study, the mouse bone marrow micronucleus test was the best *in vivo* test of *in vitro* genotoxic compounds.[45] The latter detects genotoxicity but not mutagenicity, similar to DNA adduct or strand break analysis, chromosome aberration (abnormal chromosomes, chromosome/chromatid breaks, and translocations), Comet (single cell gel or micro-gel electrophoresis for DNA base damage, single/double-strand breaks), unscheduled DNA synthesis, and sister chromatid exchange assays. The uses of the latter two assays are very limited currently.[39]

The micronucleus assay detects genotoxicity including aneuploidy and clastogenicity *in vitro* and *in vivo*. Most clastogens produce lesions during G1 and S cell phases, with the formation of the micronuclei in the subsequent cell cycles, primarily during anaphase. The micronuclei are acentric chromosomal fragments and lagging chromosomes extruded from the nucleus during mitosis; the micronuclei are visible in cells from rodent bone marrow or mouse erythrocytes. These micronuclei represent chromosomal breakages, and their presence indicates genetic damage suggestive of carcinogenicity. The micronucleus assay is the only standard genotoxicity method for detecting aneuploidy (production of daughter cells with abnormal number of chromosomes) in somatic cells.[46] In germ cells, the dominant lethal assay can also detect aneuploidy as well as clastogenicity (mutations that break or rearrange genetic material in chromosomes).[47] Results from transgene mutation induction studies help differentiate initiating agents, tumor promoters, and complete carcinogens (e.g., Tg.AC mouse).[48] Chromatid aberrations and sister chromatid exchanges occur during the S phase in culture; consequently, their frequency reflects DNA damage remaining after *in vitro* replication and thus recent chemical exposure. Because the *in vivo* tests are somewhat insensitive, concluding a genotoxic chemical is inactive *in vivo* requires negative data from at least two *in vivo* assays in different tissues. Limited *in vivo* bioassays in rodents allow the testing of a promoter when the exposure to the chemical follows the administration of a carcinogen that is genotoxic for a specific target organ.

System Biology Framework

Classic genetic testing involving standard *in vitro* genotoxicity assays frequently generates false positive results

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that are not relevant to human cancer risk assessment and lead to expensive, 2-year animal studies. Other limitations include: 1) difficulty extrapolating *in vivo* experimental models with complex human systems; and 2) classifying genotoxic and nongenotoxic carcinogens based on pathological mechanisms. The system biology framework integrates the latest scientific data on genomics, including toxicogenomics, proteomics, metabolomics, computer modeling (*in silico* approaches), single cell genomics, and epigenomics to predict carcinogenicity.[39] Advances in techniques for gene expression analysis (e.g., high-throughput methods, 3-D culture systems, flow cytometric analysis) allow measurement of the multiplicity of chemical effects on the genome that cause mutations and cancer. Toxicogenomics uses global genomic technology and gene expression analysis in a single experiment to analyze the whole genome and identify genes responding to groups or categories of chemicals. The analysis of gene expression profiles (i.e., mRNA transcription) provides insights into the common molecular actions of different chemical carcinogens, identifies useful biomarkers of disease/cancer, and elucidates the relationship between human susceptibility and environmental factors.[49,50] Agent-specific gene expression profiles display both distinct and common features. Studies on ionizing radiation and genotoxic chemicals indicate genes susceptible to carcinogens involve cell growth arrest, cellular signaling DNA repair, and apoptosis via multiple pathways (e.g., p53 tumor suppressor pathway, NF-κB-dependent *AP1*, *GADD45G*, Cyclin E, *XPC* complex).[51] The gene expression profiles for DNA repair demonstrate relatively modest alteration of relatively few DNA repair genes compared with cell cycle control, inflammation, senescence, and apoptosis.[52] Information obtained from toxicogenomics helps predict the presence of carcinogenic mechanisms between carcinogens with similar structures. Proteomics and metabolomics are downstream events in the processes of genotoxicity and carcinogenicity. Proteomics focuses on the protein interactions in stem cell differentiation into various cell types and molecular mechanisms of carcinogen-induced DNA damage response to determine direct and indirect protein biomarkers for genetic damage. Metabolomics provides information on metabolic processes in the biological system that determine carcinogenic potential and individual susceptibility. *In silico* approaches involve the development of computer models to predict the carcinogenicity of chemicals based on molecular structure or structure-activity relationships (SARs). Quantitative SAR (QSAR) uses a variety of physicochemical parameters to identify the genotoxicity of a range of chemicals based on information from a variety of databases, including the US Tox21 Project, the National Institutes of Health Chemical Genomic Center, and the US EPA National Center for Computational Toxicology. The US FDA Center for Drug Evaluation and Research uses QSAR-based computational toxicology approaches to help evaluate drugs and drug-related genotoxic contaminants.[23]

The epigenome is the exceedingly complex physiological connection between the genome, transcriptional regulation, and the cellular environment. Processing large numbers of gene expression profiles by high-throughput, rapid techniques helps understand cell differentiation and the various signaling pathways activated by DNA damage during carcinogenesis; however, there currently is no clear, direct *in vitro*/*in vivo* relationship similar to DNA-reactive chemical carcinogens. Gene expression profiles indicating a strong DNA damage response suggest direct DNA modification, whereas increased expression of genes involved with cell cycle progression characterizes indirect-acting agents.[53] The latter indirect agents produce oxidative stress, aneuploidy, impaired DNA repair, or alteration of DNA methylation, whereas nongenotoxic (i.e., epigenetic) mechanisms involve changes in signal transduction pathways, disruption of gap junction intercellular communication, and inhibition of tubulin polymerization or topoisomerase activity as well as cell cycle progression that produce cell proliferation, differentiation, and metastasis.[54] Most epigenetic profiling studies focus on the identification of epigenetic changes associated with annotated genes (Gene Ontology Consortium, http://www.geneontology.org; Encyclopedia of DNA Elements, ENCODE, https://www.encodeproject.org).[55]

ANIMAL STUDIES

Although short-term assays for genotoxicity and carcinogenicity are efficient, inexpensive, and supplement animal bioassays, the long-term mammalian bioassay remains the gold standard for detecting chemical carcinogens. Most human cancers can be produced in animal models following chronic exposure to the carcinogen, even though the specific organ or exposure pathway may differ. Genetically modified mice enhance the understanding and sensitivity of rodent models by expressing human drug-metabolizing enzymes, specific human cancer syndromes, and models of preneoplastic/precancerous lesions.[56] Statistical considerations limit the sensitivity of these assays. These studies typically involve 50 control animals and groups of 50

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TABLE 49.4. Most common spontaneous neoplasm incidence rates in control (untreated) groups of Fischer 344 rats and B6C3F$_1$ mice in 2-year feeding and inhalation studies of the National Toxicology Program. The values in the table represent the proportion of tumor-bearing animals developing specific tumors, including tumors detected in rodents dying prior to euthanasia, whereas the values in parentheses denote the range of neoplasm rates detected among all control groups. (Adapted from Haseman et al.).[61]

Site	F344 Rats Male (%)	F344 Rats Female (%)	B6C3F1 Mice Male (%)	B6C3F1 Mice Female (%)
Adrenal gland pheochromocytoma	31.9 (13–63)	5.1 (2–12)	0.8 (0–5)	1.1 (0–4)
Liver adenoma/carcinoma	2.8 (0–10)	0.7 (0–6)	42.2 (10–68)	23.6 (6–56)
Lung adenoma/carcinoma	3.3 (0–14)	2.0 (0–10)	20.5 (4–32)	8.1 (2–26)
Malignant lymphoma	0.4 (0–6)	0.3 (0–2)	8.3 (2–20)	20.9 (6–42)
Mammary gland fibroadenoma	4.3 (0–12)	41.2 (8–60)	0	0.1 (0–2)
Leukemia (mononuclear cell)	50.5 (32–74)	28.1 (14–52)	0	0.1[a] (0–2)
Pituitary gland adenoma/carcinoma	31.0[b] (14–60)	54.5[b] (30–74)	0.7 (0–6)	15.4 (0–36)[b]
Testicular adenoma	89.1 (74–98)	—	0.4 (0–2)	—
Thyroid gland	16.9[c] (2–35)	13.7[c] (4–22)[c]	2.1 (0–4)	1.8 (0–8)

[a] All leukemias; [b] Almost exclusively pituitary adenomas of the pars distalis; [c] Mostly C-cell adenomas.

animals given different chemical doses. Even with the rare occurrence of no spontaneous tumors in the control group, a statistically significant result requires a 10% incidence of neoplasms in the treated animals.[57] To overcome these statistical limitations without using thousands of laboratory animals, these assays use the highest dose (i.e., maximum tolerated dose, MTD) of the chemical that will produce minimal toxicity (e.g., small reduction in body weight) with no increased mortality in the exposed group. Consequently, interpretation of the results and extrapolation of these results to humans require a careful evaluation of the experimental design and a cautious interpretation of the significance of the results. Long-term animal studies are usually sensitive, but not necessarily specific, indicators of human carcinogens. Most, if not all, human carcinogens produce tumors in laboratory animals; these studies usually demonstrate at least one common site of cancer in humans and animals.[58] Analysis of databases on 536 rodent carcinogens by computer information systems suggests there is no obvious association between chemical structure (i.e., chemical class), mode of action, and tumor profile.[59] A specific class of carcinogen typically produces tumors at a wide range of sites rather than a unique tumor pattern.

Design

Chemical carcinogenicity studies typically consist of four separate experiments involving one to two rodent strains of both sexes divided into three different exposure concentrations, including the maximum tolerated dose (MTD) and unexposed controls. Frequently, the goals of these studies are both detection of chronic toxicity and evaluation of chemical carcinogenic potential. The National Toxicology Program (NTP) uses Fischer 344 rats and B6C3F$_1$ mice exposed to the chemical for 2 years. Most carcinogenicity studies start with weanling animals to allow a sufficient latent period for neoplasm development. When determining the carcinogenicity of a chemical, the spontaneous rate of neoplasm formation in rodents is not usually considered; however, the production of benign neoplasms is evidence of carcinogenicity in these studies because no chemical to date has caused only benign neoplasms when administered to animals. In an evaluation of 471 NTP studies, the most common sites associated with carcinogenic effects in long-term rodent studies were the following: liver, 30%; kidney, 12.5%; lung, 10%; mammary gland, 7.4%; hematopoietic system, 7.2%; and forestomach, 6.4%.[60]

The spontaneous tumor incidences for ~100 tumor types examined in 2-year rodent studies are typically relatively low (i.e., <1–3%), with a few exceptions noted in Table 49.4.[61] Approximately 96% of untreated (control) male and female F344 rats developed a benign or malignant tumor during these long-term studies, whereas the presence of at least one malignant neoplasm occurred in 64% of male rats and 43% of female rats. About $^2/_3$ of the B6C3F$_1$ mice developed a benign or malignant tumor, whereas ~39% developed at least one malignant tumor. The tumor rates in the control rat groups from feeding studies and chamber (inhalation) studies were usually similar.

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TABLE 49.5. Design factors for animal studies. (Adapted from Goodman).[65]

Animal Data	Chemical Data
Animal models	Dose
Controls	Duration of test
Number of animals	Statistical tests
Age at onset of testing	Route of administration
Pathology protocols	Toxicity of chemical
Clinical observations/pathology	

For chronic (2-year) rodent studies, the US National Toxicology Program typically uses 50 male/50 female F344 rats and the same number of male/female $B6C3F_1$ mice; the most common tumors in the former control (untreated) are leukemias and tumors of the adrenal gland, pituitary gland, and testicle (males), whereas the most frequent tumors in the latter are hematopoietic, liver, and lung tumors. Several doses are administered with the highest dose being the maximum tolerated dose. Preneoplastic lesions in rodent livers are precursor lesions that progress to benign and malignant liver cell tumors; these lesions are endpoints in carcinogenicity testing when identified as hepatic foci by H&E (hematoxylin and eosin) stained sections.

The NTP considered replacing the $B6C3F_1$ mouse with a strain that produced a lower and less variable incidence of spontaneous tumors, but the extensive experience with good husbandry practices and the substantial amount of data on the incidences of natural diseases persuaded the group to retain this mouse strain.[62] Nutritional status is an important variable in these studies because excessive nutrients and subsequent endocrine dysfunction in some rodent strains produce high spontaneous tumor incidences in control animals.[63] A review of data from 53 rat studies and 55 mouse studies indicates a positive relationship between body weight and the incidence of the following tumors: liver in both sexes of mice, pituitary gland in both sexes of rats, and mammary gland tumors in female rats.[64] When the mean body weight of treated animals was 10% higher than that of control animals, the rates of false positive studies increased by up to 20–30%.

Table 49.5 lists the important design considerations for long-term carcinogenicity studies in animals. The sensitivity of long-term carcinogenicity tests in rodents depends on the background tumor incidence. The sensitivity improves as the incidence of spontaneous tumors approaches zero and the sample size increases.[66] The sample size should be large enough to reduce the likelihood of chance to a rarity while limiting excessive exposure of the subjects and avoiding the waste of resources. Power of a hypothesis test is the probability of obtaining a statistically significant result when there is a true difference between groups; thus, power is the complement of type II error.[67] For a 20% type II error and a difference in rates of size d (e.g., $P = 0.05$), there is a 20% chance a difference in size d will not be detected. The statistical power is the complement (e.g., 1–0.2) and indicates an 80% likelihood that the test will detect the difference. This analysis is specific to the parameters used. A power analysis helps interpret study findings when the results are not statistically significant.

Table 49.6 lists the sample size needed to detect a specific increase above background concentrations of the chemical, assuming the test has a power of 80% and a significance level of $P = 0.05$. These calculations assume the variation in tumor frequency is small.

Selection of Chemicals

The choice of which chemical to test depends on indications that the chemical might be carcinogenic based on structural similarities to known carcinogens and evidence of genotoxicity in short-term tests. Equally important are the extent of human exposure and the needs of government regulatory agencies. International cooperation in standardizing protocols, sharing

TABLE 49.6. Smallest number of animals required to detect a statistically significant increase above the background rate of tumors. (Adapted from Scales and Andrews).[66]

Baseline Tumor Rate (%)	1% > Baseline Rate	5% > Baseline Rate	10% > Baseline Rate	20% > Baseline Rate	50% > Baseline Rate
1	1,826	166	69	30	9
5	6,426	342	111	39	10
10	11,619	540	157	49	11
20	20,151	862	231	64	12
50	30,909	1,233	305	74	9
90	10,630	342	58	—	—

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TABLE 49.7. Major selection criteria for the determination of the route of chemical administration. (Adapted from Chabra et al.).[62]

Route	Major Criteria
Feed	Oral major route of human exposure, chemical easily absorbed by all routes, and least labor-intensive administration
Gavage	Limitations to use in feed (mucosal irritant, unpalatable, volatile, unstable, or non-uniform distribution in feed), limited amount of chemical, and containment of toxic chemical
Drinking water	Water-soluble and drinking water are major sources of human exposure
Inhalation	Inhalation is a major source of human exposure, and the lungs are the primary target organ
Dermal	Skin is the major source of human (occupational) exposure; skin is the primary target organ; and there are 2-stage initiation-promotion studies
Multiple routes	Major human exposure involves more than one route

information, and reducing costs by the elimination of duplicate studies helps to improve the amount and quality of data on carcinogenicity studies.[68]

Route of Exposure

The route of administration should be consistent with the most common route of exposure to the chemical in humans. Differences in pharmacokinetics and toxicokinetics between alternate exposure routes support studies that demonstrate up to a 10-fold variance in carcinogenic potency for compounds (e.g., asbestos, vinyl chloride, hydrazine).[69] Oral administration by gavage is an alternative method when the physical characteristics of the chemical preclude the use of more common exposure routes. In an evaluation of 400 carcinogenicity studies by the NTP, the administration of the chemical in feed accounted for 60% of the studies, whereas oral gavage accounted for ~27% of the studies.[16] Microencapsulation is a method for administering unstable, reactive, or unpalatable chemicals in the feed; this method avoids the complications of the gavage method.[70] Table 49.7 lists the criteria used for the selection of the route of administration.

Physiochemical Properties

The dose of the chemical at the critical target site in the animal depends partly on the physicochemical properties of the chemical. The stability and reactivity of the chemical during administration or storage may alter the amount of the chemical absorbed by the animal. Impurities may confound the results of long-term studies, particularly if commercial grades contain substances (e.g., dioxins) known to cause cancer in animals. Volatility of the chemical may change the dose absorbed by both the exposed and control groups, including chemicals administered in the diet or drinking water.

Dose

A major area of controversy is the selection of exposure concentrations that allow a reasonably normal life span while ensuring the emergence of obvious signs of chronic toxicity distinguishable from aging. Most long-term studies screen for chronic toxicity and carcinogenicity. Prechronic (14-day and 90-day) studies improve chronic study design by demonstrating frank toxicity concentrations and no observable adverse effect levels (NOAELs). Previously, most chronic carcinogenicity studies used a control group and two doses including: 1) the highest dose or maximum tolerated dose (MTD) capable of producing the greatest yield of tumors; and 2) one-half of the highest dose.

The selection of the MTD is an area of intense discussion because of the necessity to extrapolate the results to human exposures at much lower levels, particularly when the pharmacokinetics of the ultimate carcinogen may differ in humans. More recent long-term studies incorporate at least three dosage levels to delineate the dose-response curve. These studies include both interim sacrifices and autopsies of all deaths to determine the clinical effects at a particular dose.

Endpoints for selecting the proper dose include body weights, metabolism and disposition, organ weights, biochemical parameters, food/water consumption, pharmacological signs, gross pathology, clinical chemistry, histopathological changes, hematological changes, mortality, clinical signs, and toxicity. The guidelines of the National Cancer Institute indicate the MTD should not cause increased mortality or signs of clinical toxicity that would shorten the life span of the exposed group compared with the control group. Additionally, the MTD should not exceed 5% of the diet or cause more than a 10% reduction in weight in the exposed group compared with the control group. Clinical observation of food consumption, body weight, toxicity (diarrhea, coughing, convulsions), behavior, and mortality provides monitoring for chronic toxicity and intercurrent illness.[65] Special studies on metabolism, pharmacokinetics, biochemical abnormalities, interim necropsy, stop exposure groups, and immunotoxicology enhance the study design by improving the ability to extrapolate the results to different species.

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TABLE 49.8. US National Toxicology Program (NTP) criteria favoring positive results in animal bioassays for carcinogenicity. (Adapted from Huff et al.).[16]

Criteria Favoring Carcinogenicity
Occurrence of rare neoplasms
Progression toward more malignant lesions
Lack of regression of tumor
Mixture of benign and malignant lesions
Shorter latent period in tumor formation
Multiple tumors in the same tissue
Metastatic lesions
Few similar tumors in control animals
Statistically significant increase in the incidence of tumors
Similar tumors in other sites or experiments
Presence of dose-response effect
Similar mortality and morbidity between control and test animals
Adequate experimental design
Supportive evidence from structure–activity correlation
Positive genotoxicity studies

Interpretation

The determination of chemical carcinogenicity depends on the appearance of different histological tumor types at different pathological sites or on an increased incidence of neoplasms in exposed animals compared with control animals. Many factors (e.g., housing conditions, diet, duration of study) affect the rate of spontaneous tumor development in animals; therefore, the tumor incidence data must be compared carefully to concurrent and historical controls. The four major determinants providing evidence of carcinogenicity include: 1) increased neoplasm incidence consisting of a specific cell type at a specific site, 2) multiple neoplasms of the same cell type at a specific site, 3) reduction in the latent period, and 4) progression of benign lesions to malignant lesions.

Table 49.8 lists factors used in the determination of the carcinogenic potential of a chemical by the US National Toxicology Program. For statistical analysis, the occurrence of benign and malignant neoplasms of the same cell type at the same site is considered a group and an individual lesion because of the belief that benign neoplasms are an important indicator of rodent carcinogenicity.[71] The appearance of rare tumors at a specific site is a more important determinant of carcinogenicity than the same incidence of a common, spontaneous tumor at the same site. Chemicals causing tumors in several species and particularly tumors at the same site are greater cancer hazards than chemicals producing tumors in one tissue of one species.[33]

An unequivocally positive result on the animal bioassay demonstrates a clear, dose-related increase in tumor incidence at one or more sites in the exposed group compared with the control group. This dose-related increase should be linear and statistically significant. An equivocal result arises in the following circumstances: 1) the increased tumor incidence occurs in one strain or sex, 2) there is no obvious dose-response, or 3) the tumors develop at the same site as spontaneous tumors appear in the control group. Such circumstances are common following the development of tumors of the breast, pituitary, and thyroid in Fischer 344 rats and lymphomas, hepatomas, and lung tumors in $B6C3F_1$ mice.[72] Wide variation in the incidence and onset of tumors between species, sexes, strains, and ages raises concern about the validity of the results. A negative result in the bioassay means the chemical did not cause an increased incidence of neoplasms under the conditions of the experiment; this result does not exclude the potential for inducing cancer under other conditions. The lack of an effective dose, species, and/or strain resistance, excess mortality, or acute toxicity may limit the sensitivity of the bioassay.

Extrapolation

Compared with epidemiological studies, animal models of carcinogenesis have several advantages, including: 1) more precise exposure data; 2) adequate latent periods; and 3) early detection of potential carcinogens.[73] A positive bioassay in the carcinogenicity study indicates the chemical is carcinogenic in animals under the conditions of the study and the criteria used for positive tests (i.e., the number of positives required in different sexes and species); therefore, the chemical *may* represent a carcinogenic hazard to humans.[16] Typically, in the past, ~50% of chemicals tested in 2-year rodent bioassays in most databases were positive in one or both rodent species, including naturally occurring chemicals and pesticides.[74,75] As the criteria for a positive animal study strengthened and the testing selection criteria changed from an emphasis on highly suspicious carcinogenic chemicals to high-volume chemicals, the percentage of positive animal tests decreased significantly.[76] In a review of chemical carcinogenesis studies in nonhuman primates performed by the US National Cancer Institute at doses 10–40 times estimated human exposures, a variety of chemicals were tested, including 7 "classical" rodent carcinogens, 3 heterocyclic amines, 5 *N*-nitroso compounds, 6 chemotherapeutic agents, and 13 food-related compounds.[77] Most studies were inconclusive, except for

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2-amino-3-methylimidazo[4,5-f]-quinoxaline, diethylnitrosamine, methylnitrosourea, and procarbazine. Cyclamate and saccharine were not carcinogenic in these nonhuman studies.

Concerns for extrapolating animal testing to human exposures include the potential for testing at the maximum tolerated dose to screen for potent cytotoxins near the MTD rather than human carcinogenicity (i.e., false positives rather than false negatives), whereas almost all human chemical carcinogens produce positive results when tested in sufficient animal species.[78,79] This high positivity rate reflects selection toward suspected carcinogens, the use of rodents displaying high tumor rates (e.g., liver), and exposure to high doses of chemicals that promote rapid cell division. Consequently, rodent studies are subject to false positive results from the induction of mitogenesis and mutagenesis, when compared with epidemiology studies on the chemical concentrations present in the environment and workplace. Additional limitations to extrapolating positive rodent studies to human exposures include: 1) discordance in rodent bioassay results between species, strains, and genders of rodent and human exposures, 2) variable stresses in rodent studies involving restraint, handling, and administration of the chemical, 3) differences in toxicokinetics and routes of exposure between rodents and humans, and 4) variable responses of human and rodent organs to chemicals;[80] however, cancer bioassays remain a valuable and unique source of data to determine chemical carcinogenicity along with epidemiological and mechanistic information.

Animal carcinogens demonstrate a wide range of potencies. Based on the median daily dose (TD_{50}) as measured by the dose required to induce tumors in ½ of the animals that would normally remain tumor-free over their lifetime, the potency of animal carcinogens varies over 6–7 orders of magnitude.[74] The estimated TD_{50} usually ranges within a 30-fold factor of the MTD (i.e., the maximum dose used in the long-term studies).[81] Although gavage is somewhat more likely to produce cancer in rodents following exposure to chemicals with a low rather than high MTD, the absolute amount of the MTD is not usually a reliable predictor of rodent carcinogenicity.[82]

Evaluation of a potential hazard to humans from animal carcinogens requires extrapolation *down* the dose-response curve to concentrations encountered in environmental or occupational settings, as well as extrapolation *across* species from rodents to humans. Controversy remains regarding which animal carcinogens with high MTDs are human carcinogens at concentrations currently present in the workplace or the environment. For almost all known human cancers produced by chemicals, at least one common organ site of cancer occurs both in animals and humans following exposure to the chemical carcinogen; however, every animal carcinogen will not necessarily become a proven human carcinogen because the concordance from animal to human experience is variable.[58] Some animal tumors (e.g., Leydig cell adenomas) are not relevant in humans because of their unique hormonal effects in rodents and the rarity of these tumors in humans.[83] Although chemicals producing tumors in multiple species and multiple sites are more likely to cause human cancer,[33] some animal carcinogens produce multiple tumors in rodents, despite little evidence that the chemical causes human carcinogenicity when administered at doses sufficient to cause toxicity.[84]

Mathematical models aid extrapolation from high to low doses, depending on the validity of these models. Assessing human risks involves an analysis of the weight of the evidence of carcinogenicity in animal studies, human exposure data, epidemiology studies, and short-term tests. Table 49.9 lists the factors used for risk assessment; this analysis is discussed in the chapter on risk assessment.

TABLE 49.9. Factors used to assess risk in humans. (Adapted from Goodman).[65]

Risk Assessment Factors
Epidemiological data in humans
Positive animal studies (weight of evidence)
Number species/strains positive
Number of tumor sites
Dosage
Consistency of positive results between studies
Malignant potential of tumors
Time from first exposure to tumor (latent period)
Rarity of tumor type
Short-term tests
In vivo
In vitro (genotoxicity)
Supporting biological data
Extent of human exposure to chemicals

OBSERVATIONAL STUDY DESIGN

Because the development of cancer both in humans and in animals is a multistage process that is modulated by numerous environmental factors, the detection of a carcinogen by an epidemiological study requires prolonged exposure of a reasonably large sample to a

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TABLE 49.10. Comparison of epidemiological data. (Adapted from Derelanko).[86]

Study	Alternate Terms	Use
Cross-sectional	Prevalence, survey	Random sample of the prevalence of disease in population at one specific time. Best for studying common chronic diseases. Does not measure incidence, causal association, or temporal relationships.
Case-control	Retrospective, dose or case-referent	Compares exposure in subjects with and without a disease. Although selection of cases with and without disease is controlled, exposures are not controlled. Allows estimation of the relative risk of cases with and without exposure, but not absolute risk. Retrospective evaluation (recall bias, estimation of exposure) limits precision.
Cohort	Prospective, longitudinal, incidence	Observation of exposed subjects over time for onset of disease. Allows estimation of relative and absolute risk. Difficult to detect rare diseases. Prospective design reduces biases. Dose-response evaluation possible if data available.
Experimental studies		Controlled human exposures usually involve low doses. Useful for hazard identification, risk characterization, dose-response near threshold levels.
Case reports		Suggests association, but not proof or refutation of hazard.

potent carcinogen. No single study design or criterion establishes the link between exposure to a chemical and the development of cancer, and most governmental organizations use a subjective evaluation of the strength of the evidence to classify chemical carcinogens. A long latent period between exposure and the clinical occurrence of cancer, the high background incidence of cancer in the study population, and difficulty determining exact exposure data currently limit the sensitivity of the best-designed epidemiology studies to a risk ratio of approximately 1.5 and above.[57,85] Despite the limitations of epidemiology studies, proof that an animal carcinogen causes an increased incidence of cancer in humans requires epidemiological data (e.g., primarily mortality, cohort, and case-control studies). Randomized, controlled clinical trials are rarely feasible when studying potential chemical carcinogens; consequently, epidemiology studies on environmental factors are usually nonrandomized observational studies (i.e., ecological, case-control, cross-sectional, cohort designs).

Well-designed cohort or case-control studies easily detect relative risks of >10, whereas careful clinical observation can identify relative risks of >100, especially an association with a rare tumor. Table 49.10 outlines the differences between the types of epidemiology studies.

Exposure Assessment

The evaluation of the potential risk of cancer from environmental or occupational sources begins with a complete history and physical examination.

Table 49.11 lists important items to discuss in the medical history. Further information on potential carcinogens is available from sources listed in the appendix. The presence of a known or suspected carcinogen in the environment requires an evaluation of the dose of the chemical absorbed because the proximity of a carcinogen does not establish a causal link between the chemical and an increased risk of cancer. Table 49.12 records variables that affect the amount of chemical absorbed by a worker.

Chemical analysis of the blood and urine is available for the detection of some of the known and suspected carcinogens. However, the results must be carefully interpreted for biological half-lives, accurate population norms, potential contamination of the samples or containers, and confounding variables (e.g., cross-reacting metabolites and alternate sources of contamination such as food).

The risk of cancer depends on the intensity and duration of exposure as well as the natural history (e.g., induction time) of the disease and host factors. The chemical form of the substance, especially metals, affects bioavailability and the concentration of the carcinogen at the target site.[87] The solubility of a chemical (e.g., mercury, selenium, and arsenic) varies between the various forms (e.g., organic, inorganic, elemental); consequently, the medical effects of different forms of a chemical vary at divergent sites in the body. The ability of a chemical to damage the lungs will depend on particle size and density, water solubility, and inhaled concentration of the chemical. Compounds entering the gastrointestinal tract pass through the liver; therefore, other sites in the body may be exposed to an altered chemical (e.g., methylation of arsenic, binding of cadmium to metallothionein).

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TABLE 49.11. Medical history for environmental exposures. (Adapted from Shields and Harris).[14]

Category	History
Medical	Present illness, hospitalizations, radiation treatments, medical disorders associated with secondary malignancies, past chronic medications, disability, pre-employment physical exams
Family	Cancer, hereditary disorders associated with malignancy, household smokers, household occupations
Social	Tobacco and smokeless tobacco use, alcohol and substance use, hobbies, diet and nutrition (fads, special diets), foreign travel
Occupational	Job history, job hazards (chemicals, fumes, dusts, gases, odors), cancer clusters
Chemical hazards	Chemical name/CAS number, size of the work area, ventilation (engineering controls, natural flow (windows, doors, breezes, seasonal variations, location of work site in relation to chemical use), protective equipment, work practice (mechanism and duration of chemical exposure, accidental spills, daily amount used, storage of chemicals, changes in work practice during employment), industrial hygiene evaluations and measurements
Environmental	All residences and types of construction (building material, insecticide use), local point sources of pollution (industry, waste sites, agriculture), water source, cancer clusters

TABLE 49.12. Variables affecting the amount of the absorbed dose.

Variable	Covariable
Route of exposure	Skin, lungs, gastrointestinal tract
Duration of exposure	
Coworker exposure/effects	
Acute symptoms of overexposure	Sensory irritation, odors
Personal work habits	Protective equipment, personal hygiene, personal habits
Physical properties of chemicals	Volatility, evaporation rate, vapor density, odor threshold, particle size/type

For epidemiology studies, individual assessment of exposure usually is neither practical nor possible. Traditionally, job titles are used as a surrogate for exposure to chemicals. Job-exposure matrices (JEM) are alternatives to job titles as a means of improving the assessment of exposure. The JEM are cross-classification of job titles and/or industries based on the estimation of relative risk of exposure to chemicals. These estimates include probability of the use of the chemical, identification of exposure by decade, and correlating occupational codes with specific chemicals.[88]

Ecological Studies

Ecological studies compare the incidence of disease (e.g., over time) in geographically different populations or subpopulations with the presence or amount of exposure to an environmental factor. These studies ascertain exposure and disease for groups or whole populations rather than individuals. The validity of the exposure-disease relationships depends on several factors including: 1) large differences in exposure, 2) reliable assessment of environmental exposures, 3) minimal differences in confounding factors of the disease, and 4) reliable measures of the disease incidence. Limitations of ecological studies are substantial involving difficulty retrospectively evaluating exposures over time and among different population subgroups as well as complete ascertainment of the disease over time and place. The weaker the association, the more likely the association results from confounding and/or chance, particularly when comparing disparate geographical populations; however, ecological studies should detect the effects of common exposures (e.g., smoking and lung cancer). A statistically significant association does not necessarily indicate causation, depending on the presence of confounding, biases, or chance; however, causation is unlikely when the results are not statistically significant.

Mortality Studies

Mortality studies describe the pattern of death or cancer incidence in categories of workers exposed to specific chemicals. By demonstrating variations in risk between groups with different chemical exposures, these studies suggest, but do not determine, whether an association between a chemical and the occurrence of cancer is causal. Mortality statistics must be interpreted with caution as a result of concern over the validity of the following: 1) cause of death recorded on the death

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TABLE 49.13. Potential inaccuracies associated with mortality studies. (Adapted from Alderson).[89]

Inaccurate cause of death
Job misclassification
Job is poor measure of exposure
Inconsistency of job data between numerator and denominator
Selection bias
Confounding (e.g., smoking, diet, alcohol)
Aggregation of job classifications dilutes exposure data

certificate, 2) limited number of deaths in specific categories, and 3) relevance of the listed occupation to actual chemical exposure.[89] Table 49.13 lists limitations associated with the interpretation of data from mortality statistics.

Establishing databases improves the ascertainment of work histories; these databases prospectively gather information on present, past jobs, and exposure data. Although most occupational cancer studies rely on death certificates, the development of some tumors remains undetected because the worker dies of other causes. The incidence of cancer is a preferable measure of outcome compared with mortality.[90]

Proportional Mortality Ratio

Crude rates of incidence (i.e., the number of new cases per population per unit time) or prevalence (i.e., the number of existing cases per population at risk per unit time) are calculated irrespective of properties (e.g., age, sex) that differ within the populations. Incidence provides information about the risk of the disease in the defined population, whereas prevalence signifies the extent of the disease in the defined population. All measures of mortality require some adjustment to compare statistics from two populations. When the cancer incidence in a specific population is unknown, national figures determine if the percentage of cancer deaths from exposed workers exceeds the percentage in the larger population. The proportional mortality ratio (PMR) compares the proportion of deaths in a group of interest with the distribution of cancer deaths expected in the general population, as determined by Equation 49.1.

$$\text{PMR} = \frac{\text{Proportional mortality of exposed group}}{\text{Proportional mortality of unexposed group}}$$

$$= \frac{a/(a+b)}{c/(c+d)} \qquad \text{(Equation 49.1)}$$

where

a = deaths *observed* in exposed group from cause of interest,

b = deaths *observed* in exposed group from all other causes,

c = deaths in unexposed group from cause of interest from *statistical* data,

d = deaths in unexposed group from all causes determined by *statistical* data.

The PMR is adjusted for age and calendar year. If the cause of interest is common, local data help eliminate biases based on local factors (e.g., social class, environment). The use of the PMR has several limitations. Potentially, excess deaths from a major cause may mask the occurrence of excess cancer deaths. Furthermore, the PMR depends on the consistency of age-specific data between each category; therefore, the PMR is less reliable than the standardized mortality ratio (SMR).

Standardized Mortality Ratio

Standardization is the method used to produce an index that adjusts data from two populations for important variables such as age and sex. Equation 49.2 defines the standardized mortality ratio (SMR), which measures the number of deaths in the population of interest, with *expected* deaths obtained from mortality tables of the general population corrected for age and sex.

$$\text{SMR} = \frac{\text{Observed deaths (O)}}{\text{Expected deaths (E)}} \times 100$$

$$= \text{O/E} \times 100 \qquad \text{(Equation 49.2)}$$

where direct observation of a specific population provides O and mortality statistics from the general population determine E.

Because of the large number of statistics generated by mortality studies, some statistically significant increases will occur by chance only. A simple estimation of statistical significance of observed deaths in a small population is the determination of the number of expected deaths (E) within the 95% confidence limit (CI) of the observed deaths (O), as calculated by Equation 49.3.

$$\text{CI} = \text{O} \pm 2\sqrt{\text{O}} \qquad \text{(Equation 49.3)}$$

For example, if O = 16

$$\text{CI} = 16 \pm 2 \times 4 = 8 \text{ to } 24$$

Small sample size often complicates the evaluation of mortality data for statistical significance.

Table 49.14 lists the minimum number of deaths required to achieve statistical significance for an SMR of 100 at 2 probability levels (i.e., <0.05, <0.01). A SMR

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TABLE 49.14. Minimum number of deaths necessary to reach statistical significance from SMR 100 at $P < 0.05$ and $P < 0.01$. (Adapted from Alderson).[89]

SMR	$P < 0.05$	$P < 0.01$
105	1,614	2,796
110	423	732
115	197	340
120	116	200
125	77	133
130	56	96
135	43	73
140	34	58
145	28	48
150	23	40

of <100 indicates the selection of more fit workers compared with the general population; the presence of this SMR complicates the interpretation of the impact of the exposure on mortality.

Cross-Sectional (Prevalence)

These observational studies are identical to retrospective studies, except that study characteristics (e.g., disease) and the outcome (e.g., exposure categories) are evaluated at the same time. In contrast to the usual (termed inception) cohort studies that follow workers over a stipulated period, cross-sectional cohorts register only workers employed at a particular date without regard to the previous exposure concentration. Hence, cross-sectional studies enroll subjects with various exposure concentrations; these subjects are compared with one another in terms of an outcome. Like retrospective (case-control) studies, cross-sectional studies can investigate rare diseases that affect small numbers of individuals because the study *starts* with patients who have the disease; then, the study design analyzes differences in exposure (i.e., the study characteristic). Cross-sectional studies can easily estimate the prevalence of a disease in the population. Interpretation of the results from cross-sectional studies is difficult because selection factors may strongly influence the observed dose-response relationships. These types of studies traditionally help generate hypotheses and search for the etiology of a disease in an epidemic; however, cross-sectional studies do not definitively determine causation because disease incidence is not the outcome measure. Therefore, this type of study cannot determine whether the exposure preceded the disease.

The cross-sectional study is not a good design for cancer research because it requires a high prevalence of disease to separate exposure levels and sensitive laboratory methods to detect cancer early. Cross-sectional cohorts encounter chronology and selection biases. The former bias results from decreasing exposure concentrations over time. The latter bias produces problems interpreting the data because the cohort contains subsets of workers with different employment periods that may not reflect the exposure of the original cohort.[91] Cross-sectional studies are most effective when the following occurs: 1) exposure is continuous and steady up to the time of evaluation, 2) effects develop soon after exposure, and 3) the effect persists but does not cause loss of employment.[92]

Cross-sectional studies only suggest a cause–effect relationship because selection bias often masks true etiological factors and observation bias produces positive bias. Chronology and selection biases also overestimate risk in cross-sectional studies. Furthermore, poor exposure data and misclassification create negative bias by diluting broad categories. Longitudinal studies (cohort, case-referent, intervention) provide a better basis for establishing the etiology of cancer compared with cross-sectional studies.

Case-Control (Case-Referent) Studies

Case-control and cohort studies are analytical epidemiological studies that ascertain exposure and disease outcome in individuals. The former study design separates populations into groups based on the presence (case) or absence (control, referent) of *disease* and then retrospectively assesses the exposure rate to chemicals in each group. Among persons with a disease (cases), these studies ascertain the proportion of persons *previously* exposed to a chemical compared with a sample of persons in a group (controls) similar to the cases except for the exposure. Hence, exposure ascertainment is a potential source of bias because of the retrospective evaluation of the exposure. Nested case-control studies identify cases in a large cohort and a specified number of controls matching the cases for all characteristics except exposure; increasing the number of controls beyond the cases (e.g., 2:1, 3:1) improves precision.

The odds ratio (OR) measures the association between exposure and outcome, reflecting the occurrence of the disease in the two populations (i.e., exposed vs. nonexposed). The larger the OR, the stronger the association between exposure and disease, with an

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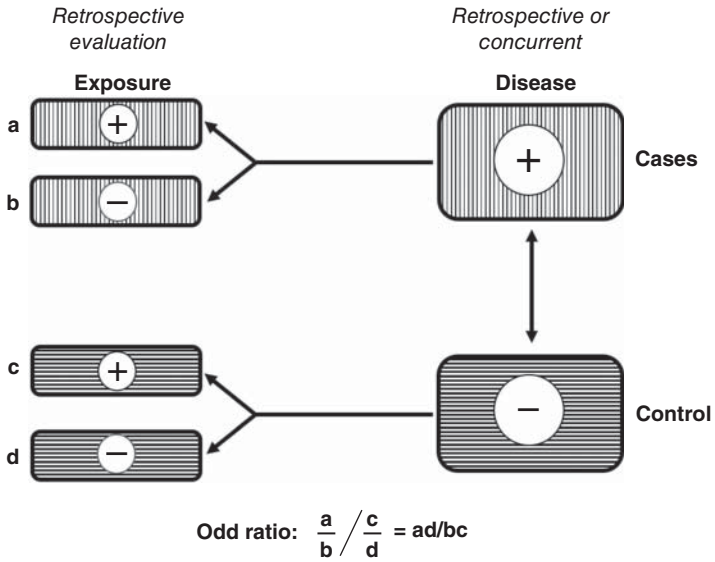


FIGURE 49.2. Calculation of odds ratio in case-control studies. Exposures in the cases are evaluated retrospectively, whereas the disease (e.g., cancer) may be defined retrospectively or concurrently. (Adapted from Hernberg).[92] *Abbreviations:* a = cases with exposure; b = cases without exposure; c = controls with exposure; d = controls without exposure.

OR of 1.5 indicating a modest association. Figure 49.2 outlines the method of calculating the odds ratio in case-control (case-referent) studies. These study designs investigate the etiology of diseases; therefore, validity of these studies depends on the ability to quantify the amount of exposure to a chemical and the influence of confounding factors on exposure. As defined in Figure 49.2, Equation 49.4 defines the odds ratio.

$$\text{Odds Ratio (OR)} = a/b \div c/d = ad/bc \quad \text{(Equation 49.4)}$$

An odds ratio of >1 indicates exposure is more common in persons with the disease (cases) than in the nonexposed group (controls), whereas an odds ratio of <1 indicates a less frequent exposure in the cases with the disease. The odds ratio is an *estimate* of the absolute disease risk in the exposed population because the cases are not representative samples of the exposed and unexposed populations. When the outcome of interest is common (i.e., >20% of subjects in any group), the odds ratio does not approximate the relative risk (risk ratio); however, the relative risks and odds ratios are similar when the absolute risk is low (e.g., mortality rate for most cancers) reflecting a rare outcome of interest. Because case-control studies estimate relative risk and not absolute risk, the interpretation of the importance of an elevated relative risk depends on the absolute risk as determined by other sources. Consequently, a relative risk of 10 may not be valid if the absolute mortality risk is very low (e.g., 10^{-7}).

Advantages

Case-control studies provide clues about the etiology of the disease studied and help quantify the risk of developing the disease after exposure to the chemical under study. This type of study provides circumstantial evidence of an association between exposure and disease (e.g., cancer); however, these studies do not infer temporal or causal relationships. The case-control study is the preferred type of study when the disease is rare because of the usual ease of accumulating a large number of cases quickly with relatively low expenses, particularly when follow-up is difficult. In this situation, the study characteristic is the disease; therefore, the study begins when enough persons with the disease are located. Additionally, the cost of the study is low, and the design is simple. Nested case-control studies are less expensive than full cohort studies because exposure assessment involves only the cases and selected controls. Relatively few subjects are necessary for the study compared with the number required for cohort studies. This type of study provides data about the etiology of disease; case-control studies can investigate multiple exposures as possible causal factors in the development of the disease.

Disadvantages

This type of observational study is useful only for a single endpoint that does not involve rare exposures; weaknesses include the inability to calculate absolute risks,

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incidences, or prevalence. Consequently, case-control studies cannot establish causality because of their inability to control unmeasured confounders.[93] Additionally, case-control studies are susceptible to unidentified and unpredictable biases including information bias from ascertainment of exposure data after disease occurrence and selection bias from suboptimal processes for controlling selection; however, both case-control and cohort studies are susceptible to chance and confounding. The disadvantages of case-control studies are similar to those of any retrospective study that relies on indirect measures of exposure and on the similarity of the control and case groups. Observer bias is the most common cause of positive bias when persons with the disease remember more about their exposure status than persons without the disease. Inaccurate or incomplete exposure data produces misclassification.

Ascertainment of exposure data almost always involves reported job history or recall of specific exposure rather than direct measurements; questionnaire-based methods of estimating exposure frequently do not produce valid or reliable results. Direct blood or tissue measurements of the chemical obtained after the diagnosis may not reflect prediagnosis values because the illness or treatment may alter these measurements. Increasing complexity of the occupational history, short duration of employment, and longer periods of recall reduce the validity and precision of exposure data.[94] The incorporation of industrial hygiene measurements from administrative exposure databases and expert assessment of direct measurement of study subjects (i.e., assuming a reasonable latency and biological half-life of the substance) improves the validity of the exposure data. Selection bias may arise when the exposed group contains individuals with multiple exposures and is not representative of the general population. Validation of information is difficult because of the retrospective nature of the study. Other sources of bias include diagnostic suspicion bias in case determination, exclusion bias in choosing controls, bias in the selection of cases and exposure ascertainment, and recall bias in the determination of exposure.

Cohort (Follow-Up) Studies

In this type of study, individuals are assigned to cohorts based on exposure (i.e., exposed, unexposed) and the outcome is mortality or incidence of the disease (e.g., cancer) in each group. Selection of subjects should proceed without knowledge of individual disease status; objective exposure criteria should be obtained. Options for objective exposure assessment include job category, environmental monitoring (exposure), and biological monitoring (dose). Exposure and dose should be considered separately because dose reflects intensity, duration of exposure, and personal factors (protective equipment, personal hygiene, activity, work schedule, and conditions). The cohort study may be either retrospective (historical) or prospective (concurrent), depending on whether the disease incidence is followed from some distant time in the past to the present (i.e., retrospectively) or traced from the present to a future time (i.e., prospectively). Prospective studies require highly reproducible and specific outcome measures to avoid a high rate of "false positive" tests. These tests should detect biologically significant differences.

Figure 49.3 outlines the configuration of a cohort study and the calculation of the rate ratio and rate difference. The cohort study is similar to an experimental study in which the investigator separates animals into exposed and unexposed groups and then measures the disease incidence. However, the environment, exposure intensity, and number of chemical exposures are less controlled in cohort studies than in experimental studies. Relative risk (RR) is a measure of the strength of an association and frequently refers to the rate ratio and the risk ratio. The rate ratio is a comparison of the rates of disease in the exposed and unexposed cohorts, as defined in Figure 49.3 by

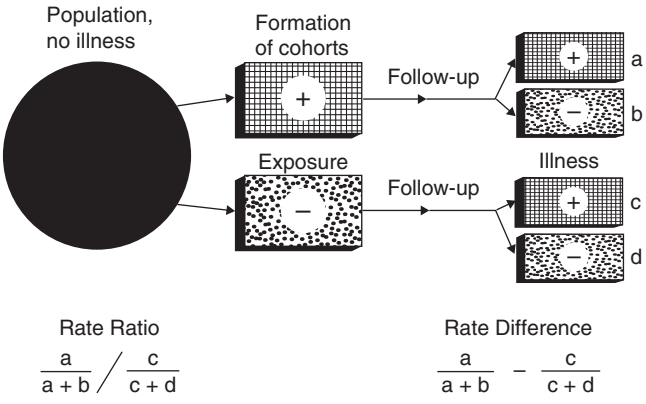


FIGURE 49.3. Calculation of rate ratio and rate difference in cohort studies. The cohort is divided based on exposure (exposed/unexposed groups) and then followed for a period of time. Only one exposure is usually studied, whereas several disease outcomes can be evaluated simultaneously. In contrast to experimental studies, confounding exposures may occur and exposures are not adjustable. (Adapted from Hernberg).[92] *Abbreviations:* a = exposed cohort with disease; b = exposed cohort without disease; c = unexposed cohort with disease; d = unexposed cohort without disease.

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Equation 49.5.

$$RR = a/(a+b) \div c/(c+d) \qquad \text{(Equation 49.5)}$$

An RR of >1 indicates a higher incidence of disease (i.e., times the risk) in the exposed group than the nonexposed group, whereas an RR of <1 demonstrates a lower disease incidence in the exposed group than the nonexposed group. If an unexposed cohort is not available for economic reasons and the standardized rates for age, sex, and calendar year from national statistics are used for the denominator, then the rate ratio for cancer mortality becomes the standardized mortality ratio (SMR). The rate ratio and risk ratio are closely related. The former is the ratio of the incidence rates in an exposed and unexposed comparison group, whereas the latter is a simple ratio that reflects the higher or lower probability of the risk occurring in the exposed group compared with the unexposed group.

Retrospective (inception) cohort studies help identify the potential etiology of various diseases, but these studies do not definitively establish causation because of the imprecise nature of the data on exposure. This type of study must be evaluated cautiously because of the following potential complicating factors: confounding of exposure between cohorts, dilution of the results from imprecise job classification, inadequate length of follow-up to detect the disease, and biases in the cohort over time. These biases include observation bias, loss by death in some categories, age at entry, entry of new workers, percent of original sample followed, and condition of cohort at the start of study. Inception cohort studies tend to underestimate the relative risk because of the presence of selection bias as a result of the healthy worker at hire and healthy worker survivor effects.

Prospective studies produce the best epidemiological data on the etiology of diseases such as cancer, but this type of study is less likely to uncover **new** causes of the disease compared with mortality or case-referent studies. These longitudinal studies eliminate the problem of interindividual and intraindividual variation because the members of the cohort act as their own controls. Because of the ability of this type of study to quantify exposure and study multiple medical factors, a prospective study can provide definitive answers about etiology and dose-response relationships. These studies are costly, require a stable industry, and need a high disease incidence in the population.

Advantages

The exposure-based design is most suitable for studies of rare exposures; the purpose of the study is to determine which disease results from exposure to a specific chemical with this study design allowing multiple endpoints. The advantages of a retrospective cohort study are the relative promptness of the results and the low cost of the project compared with concurrent prospective and intervention studies. Prospective studies offer the advantage that exposures are directly measured, confounding variables are more easily controlled, and the indicators of disease are better defined. Unlike cross-sectional studies that compare participants with various levels of exposure, prospective studies allow each participant to act as a control. Hence, prospective studies eliminate the normal variation between participants, allowing easier detection of small decrements in function over time. Several types of diseases can be evaluated in a cohort study at the same time, resulting in the examination of multiple effects from a given exposure. This study design allows the calculation of absolute risks, incidences, and prevalence.

Disadvantages

Retrospective cohort studies depend on the quality of prior exposure data and the ability to link that exposure with the development of a disease or diseases. Often, data on exposure, medical risk factors, and measures of disease are limited or unreliable. The presence of multiple chemical exposures, ascertainment of reliable prior work history, and other disease-causing exposures (e.g., smoking) complicate the interpretation of study results. Retrospective studies on cancer usually focus on mortality because little data are available on the medical conditions of the cohorts. The potentially long duration of follow-up increases the difficulty and cost of the project. A thorough study of the etiology of the disease is usually not possible, especially when the etiology is multifactorial.

Prospective studies provide more accurate data on exposure and disease, but this type of study requires large sample size, high cost, and prolonged follow-up for the long latent periods of cancer. The cohort design is not a good design for studying rare diseases.

Table 49.15 outlines the size of a cohort necessary to detect a specific relative risk given the incidence of the disease in the control population. This table demonstrates the difficulty of using the cohort design for rare diseases. The follow-up period for a cohort typically should be at least one-half the length of the latent period.[95] Because cohorts are divided on the basis of exposure, only one exposure can be studied at a time; however, by studying a large number of diseases potentially related to the exposure, some associations may occur solely on the basis of chance.

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TABLE 49.15. Approximate number of subjects required for detection of various relative risks of disease in a cohort study. (Adapted from Griffin and Weber).[95]

Prevalence of Disease in Controls	1.2:1[a]	1.5:1[a]	2:1[a]	3:1[a]	20:1[a]
1/100	57,000	10,000	3,000	1,000	50
1/500	288,000	52,000	16,000	5,000	300
1/1,000	577,000	105,000	31,000	10,000	600

[a] Relative risk of disease in exposed subjects and control subjects.

Interventional Studies

In contrast to the previous observational studies, an intervention study measures the effect of a *change* in the exposure of the exposed cohort; these studies are considered extensions of the cohort study. This type of study design is different from the clinical research trial, which is a true experimental study that randomizes subjects *before* exposure. Documented changes in the disease process following changes in exposure provide strong evidence of a causal link between the disease and the exposure; however, intervention study designs are rare.

Cancer Clusters

A cancer cluster involves a greater than expected number of cancer cases over a defined period of time, when compared with the same type of cancer in a similarly sized population (e.g., age, gender, race/ethnicity) over the same time. Historically, examination of cancer clusters resulted in the detection of several carcinogens including scrotal cancers in chimney sweeps (1775), osteosarcomas in radium dial painters (1929), lung cancers in asbestos workers (1965), hepatic angiosarcomas in vinyl chloride workers (1974), and vaginal clear cell carcinomas in daughters exposed to diethylstilbestrol *in utero* (1971). However, many perceived cancer clusters are not confirmed; chance remains a plausible explanation for most nonconfirmed cancer clusters, even though the cancer cluster meets statistical criteria.[96,97] Both the number of cancer cases in the cluster and the calculation of expected cases depend on the definition of the boundary of the geographical area; changing the boundaries may enhance or obscure the significance of the cancer cluster. Increasing public awareness of potential carcinogens in the environment contributes to an expansion in the number of anecdotal reports on cancer clusters. While improved health surveillance results in important discoveries of environmental causes of disease, intense surveillance produces many false alarms, and most investigations of clusters do not establish the presence of environmental carcinogens.[98,99] Multiple factors complicate the investigations of cancer clusters including: 1) the long latent period before the clinical appearance of cancer, 2) the limited number of cases available for study in a given situation, 3) the poorly understood etiology of most cancers with multiple multifactorial causes and few known risk factors, 4) the high incidence of cancer in the population, 5) migration producing alteration of the cumulative exposure profile of the population under study, and 6) the difficulty applying statistical analysis to the small size of most cancer clusters, particularly with rare cancers.[100]

In a random distribution of cancer cases over a geographical area, some cases will appear in close proximity based only on random statistical variation. The *post hoc* definition of the study population and a time frame including the initial cancer cluster cases may result in spuriously high rates of cancer types in that population. This approach is similar to the "Texas sharpshooter," who shoots at his object and then draws his target. Besides chance and exposure to a carcinogen, an excess cancer incidence may result from the presence of confounding variables (e.g., smoking, radiation, hereditary traits, infections). The determination of the cause of a cancer cluster is frequently difficult because of the intense emotional atmosphere surrounding these investigations and the presence of many design problems (small sample size, ascertainment bias, confounding variables, limited exposure data). Cancer is many different diseases with different causal mechanisms, contrary to the popular misconception that a single environmental contaminant causes any or many types of cancer. Investigation of these observations requires a multistage response to determine the extent of research necessary to establish causation.[101] Statistical methods (e.g., cluster analysis studies) are available to evaluate the spatial clustering of diseases based on Poisson distribution of cases.[102]

Table 49.16 outlines an approach to cancer cluster investigations. The Centers for Disease Control and Prevention (CDC) published guidelines focused specifically on cancer clusters in residential or community settings (https://www.cdc.gov/mmwr/pdf/rr/rr6208.pdf). The four-step approach for managing a reported cluster included: 1) initial contact and response, 2) assessment, 3) determining the feasibility of conducting an epidemiological study, and 4) conducting an epidemiological investigation. The CDC noted that only a small fraction of cancer cluster inquiries met the statistical and etiological criteria to support a cluster investigation as

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TABLE 49.16. Approach to the investigation of cancer clusters. (Adapted from Sullivan and Keiger).[103]

1. Identify and confirm each cancer case, including cancer type, with medical records and histopathology.
2. Document temporal relationship between diagnosis and exposure.
3. Compare observed overall number of cancer cases with expected rates based on cancer registries standardized for age. Calculate SMR.
4. Compare cancer types (organ, cell type) with expected rates. All cases must involve the same cancer type or types with the same cause.
5. Evaluate latency period (period of time between first exposure and clinical diagnosis) of each cancer. Typical latency period for hemological tumors is 5–10 years and for solid tumors, 15–20 years. The association of the exposure with a tumor is equivocal if the latency period is too short.
6. Evaluate confounding and contribution factors (smoking, substance abuse, familial history of cancer, other potential carcinogens, occupations associated with cancer).
7. Examine epidemiological data for elevated cancer rates for specific jobs or sites.
8. An excess of histologically similar cancer cases suggests the possibility of a causal relationship. Overrepresentation by a particular job, environment, or chemical exposure supports a causal relationship. The lack of a common exposure or excess of different histological types of cancer indicates a true cancer cluster is unlikely.
9. Environmental assessment and industrial hygiene review of area, with elevated cancer rates for the presence of potential carcinogens.
10. Conclusions include: a) absence of cancer cluster, b) possible presence of cancer cluster, but occupational or environmental source unlikely, c) cancer cluster is present and possibly related to occupational or environmental exposure, and d) cancer cluster is related to a specific chemical exposure.

outlined in these guidelines. Despite ascertainment bias (i.e., inclusion of index cases) and the lack of statistical power, the use of statistical significance is a useful tool to determine the preliminary probability of any health hazard.[104] Statistical methods indicate how unusual the cancer incidence is in a particular population; however, these methods do not determine the likely cause of the cancer cluster. A study of malaria would find a statistically significant association between marshy swampland and malaria. In fact, Hippocrates wrote that a poisonous cloud lifting up from marshy land caused malaria. Consequently, the establishment of a chemical as the cause of the cancer cluster requires careful evaluation of the exposure to determine the following: 1) the identified chemical causes human cancer, 2) an adequate exposure pathway existed, and 3) the dose of the chemical was sufficient to cause cancer.

After the preliminary investigation, the decision to continue the cancer investigation depends on an evaluation of the following three criteria: 1) high disease rate compared with age-adjusted cancer incidence in a similar (e.g., working) population and a sufficient latent period (i.e., 15–20 years for solid tumors, 5–10 years for hematological malignancies), 2) excessive, prolonged exposure (e.g., similar job classification, close proximity) to suspected carcinogens that correlates with the development of the cancer, and 3) biological plausibility.[105] The presence of two or three of these criteria indicates the need for further research. The predominance of a particular cancer type favors a chemical carcinogen as the etiology of the cancer cluster, particularly those cancers associated with well-recognized chemical carcinogens.[106] The discovery of several cases of hepatic angiosarcoma or malignant mesothelioma suggests the presence of excessive exposure to vinyl chloride and asbestos, respectively. The index cases should not be used in a study to test the hypothesis that a cancer cluster resulted from a chemical carcinogen because the addition of these cases will bias the results toward a positive result.[107]

OBSERVATIONAL STUDY INTERPRETATION

Time Dependency and Age

Latency describes the change in relative or excess disease rates with the time since exposure began. Determination of latency depends on several factors, including variation of exposure over time within the study group, the size of the group developing the disease of interest, the quality of the biomarkers of exposure, and the accuracy of exposure information. For most cancers, the cancer rates increase dramatically with age in any study group; therefore, age-related normalization of the cancer rates in the unexposed is necessary to assure the appropriate comparison of disease rates between the exposed groups and the aging control group with no exposure. Frequently, various timing factors (e.g., initial exposure time, duration, age at initial exposure,

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magnitude) are correlated to each other, requiring stratification or modeling to determine the effect of each factor depending on the quality of the exposure data. When investigating latency, changes in relative risks with time since exposure occurs later in mortality studies than incidence studies by approximately the average time from cancer detection to death. Exposure misclassification tends to bias the results of observational studies toward the null hypothesis (i.e., no association between exposure and disease) when a true association exists; however, the effect of misclassification on time-related factors is difficult to predict.

The appearance of excess cancer rates following exposure to chemical or physical carcinogens probably varies with the specific chemical agent and mechanism of action; some chemicals produce cancer rates resembling a unimodal pattern (e.g., leukemia in atomic bomb survivors), initially increasing after a latent period, then decreasing over time. In these situations, the mean or median latency period reflects the temporal relationship between the exposure and carcinogen; however, other chemical exposure-cancer relationships demonstrate a variable risk rate and latency reflecting the multicausal, multistep process of cancer development. Part of the difference in cancer risk with time results from study design, including time-related changes in exposure, short follow-up periods relative to the true latency period, and inclusion of subjects with variable *a priori* exposure (i.e., selected survivors).[108] The latter biases the observed latency period toward longer time intervals, whereas short follow-up periods bias the observed latency period to shorter intervals. The latency period also varies with the choice of outcome (e.g., symptoms onset, diagnosis, death).

Validity

The detection of an association between a disease and an exposure does not necessarily imply a true cause–effect relationship. Bias is a consistent error that causes either the overestimation (positive bias) or the underestimation (negative bias) of the true value of the outcome measure. The potential for systematic error (i.e., bias) is usually greater for observational than experimental studies. If proper statistical methods eliminate the likelihood of a chance association, the presence of a false positive association may result from: 1) selection bias, 2) information bias, and/or 3) confounding by a variable of the study characteristic that affects the outcome. The validity of a study is determined by the degree to which it accurately measures the true outcome; therefore, a valid study lacks bias. Statistical methods do not exclude the presence of bias. Precision (reliability) is a measure of the proximity of repeat samples to each other rather than a measure of the proximity of the samples to the true value; hence, a study may be reliable but not valid (i.e., not close to the true value of the observation) because of systematic bias.

Bias

Selection Bias

Selection bias occurs when the control (reference) group in case-control studies is not representative of the same population as the index subjects (e.g., when employed workers and members of the general population are matched for age and sex).[109] In practice, the effects of selection bias and confounding are similar, with the former usually referring to the lack of comparability of workers to the general population. The presence of selection bias indicates systematic error that results in the referral of subjects into the two study groups, depending on exposure or the disease studied, particularly when the participation rates between the two groups significantly differ. The first question is whether all employees were included in the study. Exclusion of workers may bias the results if the excluded workers are atypical of the workers in the study with respect to exposure, diseases, or associated risk factors for the development of the disease. Bias results may occur from several elements of study design, including selective referral patterns, use of volunteers, excessive dropout of workers during the study, uneven distribution of job skills (e.g., low psychomotor skills) that affect outcome measures (neuropsychological testing), and different methods of detecting disease in the two study groups.

Selection bias usually arises in case-control studies when different criteria of exposure separate cases and controls or in cohort studies when disease outcome influences the selection of exposed and unexposed subjects. Examples of selection bias include: 1) hospital admission bias or Berkson's bias, 2) prevalence or incidence bias, 3) detection bias, 4) volunteer bias, 5) healthy worker at hire and healthy worker survivor effects, 6) excessive losses to follow-up, and 7) membership bias.[110] Berkson's bias occurs when studies occur in the hospital setting and a spurious association between disease and exposure results from the different probability of admission between subjects with and without exposure. Mild or brief episodes of illness may be missed if the study focuses on the later period in the disease process, resulting in prevalence/incidence bias.

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Detection bias occurs when a nonspecific sign or symptom of disease is attributed to an innocuous exposure, resulting in a false association between exposure and disease. Volunteer and/or nonrespondent bias develops when these subjects are systematically different from other subjects in the study regarding health or exposure. Similarly, bias may result when group members have different health or exposure characteristics (membership bias, healthy worker at hire, healthy worker survivor effects) compared with the general population. Loss of follow-up may bias a study when those subjects lost to follow up differ from the study population.

Table 49.17 demonstrates the direction of selection and information biases. The physical requirements of a job may determine the disease pattern rather than any exposure in the occupational environment. Cancer is a disease with a long subclinical period; therefore, selection bias is seldom present. True selection bias occurs only when the disease under study affects the distribution of workers into groups. The issues of selection bias develop during the design phase; consequently, selection bias must be addressed during the design phase of the study.

Information Bias

A valid study requires similar collections of information from cases, controls, and exposed/unexposed groups. Information bias may occur in several situations including: 1) misclassification of exposure or disease, 2) inaccurate recall, 3) misinterpretation of assessment data, 4) inability to access important unpublished data from regulatory, chemical, and pharmaceutical organizations, or 5) inconsistent data obtained at different time periods. Information bias involves intra-interviewer/inter-interviewer bias, recall bias, questionnaire bias, and diagnostic or exposure suspicion bias.[110] The potential for recall bias is greatest when substantial concern about the potential adverse effects of an exposure exists, particularly as a result of media coverage, litigation, trade union negotiations, or passionate group discussions. *A priori* knowledge of subject classification may affect the intensity of the search for exposure or disease. These actions produce exposure suspicion bias. Most sources of information bias overestimate the relationship between exposure and disease.

In case-control studies, information bias results from the differential collection of exposure data from cases and controls. Observation bias most seriously affects case-control studies that often rely on information from questionnaires rather than direct measurements. Information bias also may occur in cohort studies when exposure status influences the collection of information on disease status. Retrospective cohort studies may also suffer from observation bias as a result of the tendency to more closely examine exposed populations. Prospective cohort studies can avoid observation bias by blinding the investigators.

TABLE 49.17. Direction of selection and information bias in epidemiological studies. (Adapted from Choi and Noseworthy).[110]

Type	Cross-Sectional	Case-Control	Retrospective Cohort	Prospective Cohort
		Selection Bias		
Berkson's	↑↓	↑↓	–	–
Prevalence, incidence	↑↓	↑↓	U	U
Detection	U	↑↓	↑↓	↑↓
Membership	↑↓	↑↓	↑↓	↑↓
Health worker effect	↓	↓	↓	↓
Volunteer	↑↓	↑↓	↑↓	↑↓
Lost to follow-up	–	–	↑↓	↑↓
		Information Bias		
Interviewer	↑↓	↑↓	↑↓	↑↓
Inter-interviewer	↑↓	↑↓	↑↓	↑↓
Questionnaire	↑↓	↑↓	↑↓	↑↓
Recall	↑↓	↑↓	–	–
Diagnostic suspicion	↑↓	↑↓	↑↓	↑↓
Exposure suspicion	↑↓	↑↓	–	–

Abbreviations: – = not possible; U = unlikely; ↑↓ = usually overestimate; ↑↓ = overestimate or underestimate; ↓ = underestimate.

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Reporting and Publication Bias

The systematic error of reporting bias occurs when researchers base their decision to publish certain results on the magnitude, direction, and/or statistical significance of their results, whereas publication bias refers to the systematic failure to publish certain types of studies. Additionally, authors or study sponsors may selectively report specific analyses or results (selective outcome reporting bias).[111] Publication is often less likely for negative than positive studies;[112,113] publication bias occurs when the direction and magnitude of the studies are more important determining factors for publication than quality, relevance, and/or study design.[114] Although asymmetry in funnel plots suggests the presence of publication bias, detecting publication bias is difficult in systematic reviews. The presence of bias reduces confidence in the estimates. Consequently, success in obtaining results of unpublished studies reduces the chance of publication bias and increases confidence in the estimates.

Potential Confounding Variables

Determination of causation requires an understanding of the role of confounding in observational study results. The presence of confounding distorts the results of these studies; the changes induced by confounding may weaken, strengthen, or reverse the true effect of an exposure, with the overall effect depending on the number and degree of confounders. Confounding variables (e.g., smoking) are outside factors that influence the assessment of the outcome under study, resulting in different risk factors for the outcome in exposed and unexposed groups. These causal risk factors are determinants of the disease associated with the exposure group and affect the development of the disease. A confounder meets the following criteria: 1) an independent risk factor for the outcome (causal or surrogate), 2) associated with the exposure, and 3) unaffected by the exposure.[115] A confounder is not usually an intermediate step in the causal pathway between the exposure and the disease (e.g., cancer).

Confounding results from a lack of comparability between exposed/unexposed groups, and the presence of confounding biases the estimation of the effect of exposure on the disease (e.g., cancer). In a cohort study, a confounding variable is a risk factor for the disease that is distributed asymmetrically between the exposed and unexposed groups. Conversely, in a case-control study, the confounding factor correlates with disease occurrence and is a determinant of exposure. Thus, the issue of confounding involves the comparability of the exposed and unexposed members of the underlying study population (exposed and unexposed subjects in the control group). Fundamental problems with case-control studies include estimates of exposure only for cases and a sample of noncases (controls). Selection bias also complicates the interpretation of case-control studies because of changes in residences or jobs. Confounding is usually a less serious problem in occupational studies compared with selection bias; however, lifestyle risk factors and prior or concomitant occupational exposures remain potential confounders, depending on the net effect of all factors, including confounding.[92]

Without limited opportunity to randomize exposure, confounding frequently occurs in observational studies; consequently, inaccurate estimates of the relationship between exposure and outcome may result from failure to adjust for confounding. Internal comparisons between groups classified by cumulative exposure may develop confounding issues due to time-related factors. Such confounding results from: 1) differences in cumulative exposure groups between generations, 2) differential health status at entry into the cohort, and 3) groups classified by cumulative exposure may become noncomparable with time due to the healthy worker survivor effect. These confounders attenuate the true dose-response relationship between cumulative exposure and disease.

Methods to control confounding during the design and data analysis phases include study design (matching on baseline characteristics, restriction, randomization when available, stratification of subjects, standardization of exposure categories, worst-case assumptions) and statistical procedures (linear or logistical regression modeling, stratified analyses, propensity scoring).[116] Study design alone is unlikely to fully resolve issues of confounding in nonrandomized studies. The propensity score ranging from 0–1 improves the estimate of a relationship between a nonrandomized factor (e.g., chemical exposure) and the outcome of interest (e.g., cancer) using multivariable statistical methods (e.g., logistic regression) based on available measured subject characteristics and the surrounding environment.[117] The probability is used to adjust for differences in the study populations (e.g., propensity score matching, stratification based on the propensity score, covariate adjustment of confounders using the propensity score), where a score of ≤ 0.1 is considered a negligible difference between groups. Statistical methods require the recognition and measurement of confounding variables; unmeasured confounders and inadequate quality or data size reduce the likelihood of effectively adjusting for confounding. Control of

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the confounding variables may be difficult when the confounding variable is large compared with the relative risk being studied.[118] Residual confounding may occur in observational studies when statistical analyses do not adequately adjust for confounding including the following: 1) unmeasured confounding, 2) overly broad categories for confounders, and 3) inaccurate or misclassified measures of confounder characteristics. The uniform distribution of confounding factors between the two study groups modifies, but does not confound, the incidence of the disease. Randomized controlled trials use randomization processes to limit all forms of confounding; therefore, this type of study does not use statistical methods to adjust for confounding.

Lifestyle Overview

Variation in cancer rates exists worldwide, with the highest overall age-standardized rates (i.e., ~300 cases/10,000 person-years) occurring in North America, Europe, New Zealand, and Australia.[119] Migrants from less-industrialized countries adopting Western lifestyles and diets develop cancer incidences similar to those of native members of developed countries.[120,121] The population attributable fraction (PAF) reflects the portion of cancers that would not occur with absent exposure to the causal factor under study. Lifestyle factors represent a large portion of avoidable cancers, including tobacco and alcohol use, solar ultraviolet radiation, body fatness, insufficient physical activity, and dietary factors (salt, inadequate fiber content, red and processed meat, insufficient fruit and/or vegetables) with the strength of the association with the latter three factors relatively small and subject to design issues. Typically, the relatively risks in positive studies evaluating diet, body fatness, and physical activity are below the commonly accepted level of >2 (particularly <1.5), leading to questions regarding the causality of the associations detected in observational studies. In the 1990s, evaluations of most case-control studies suggested vegetables and fruits provided some protection against certain cancers, leading to recommendations for ≥5 portions (i.e., >400 g) of fruits and vegetables daily;[122] however, evidence for an inverse relationship between total fruits and vegetable intake and overall cancer rates in subsequent cohort studies was less robust.[123] The relatively low relative risks reflect the wide variation in the prevalence and strength of modifiable factors (excluding tobacco and alcohol use) between countries, selected populations, cancer subtypes, sexes, and specific lifestyle factors. In a review of modifiable PAFs based primarily on case-control studies, tobacco smoking (larynx, lungs), excessive weight (gallbladder), and insufficient fruit intake (oral cavity/pharynx) account for the most avoidable cancers in women, whereas tobacco smoking accounts for a majority of avoidable tumors (lungs, larynx, esophagus, oral cavity/pharynx) in men.[124] Although some studies associate dietary vegetables and fruit, antioxidant vitamins, carotenoids, isothiocyanates, and physical exercise with reducing cancer risks, the overall protective effect of diet and exercise accounts for a small fraction of the total attributable risk associated with tobacco smoking. Thus, smoking cessation remains the most important intervention to reduce the high incidence of cancer among smokers.[125] Table 49.18 lists the factors associated with lifestyle that may confound cancer studies.

TABLE 49.18. Potential lifestyle factors associated with an increased risk of cancer based on sufficient epidemiological data. (Adapted from Pitot).[57]

Factor	Associated Tumor
Alcoholic beverages	Esophagus, larynx, liver, oropharynx
Aflatoxins	Liver
Betel chewing	Mouth
Diet[a] (fat, protein, calories, smoked/pickled foods)	Breast, colon, endometrium, gallbladder, gastric
Late age at first pregnancy	Breast
Nulliparous	Ovarian
Sexual promiscuity (human papillomavirus, HPV)	Cervix, vagina, vulva, penis, anus, oropharynx
Tobacco smoking	Bladder, esophagus, kidney (renal cell), larynx, lung, mouth, pancreas, pharynx
Smokeless tobacco	Larynx, mouth, pharynx

[a] The strength of the associations is relatively small, with potential methodological issues obscuring the true values.

Physical Activity

Energy consumption during an activity depends on the product of duration and intensity; the latter is measured by metabolic equivalents (METs) relative to the basal metabolic rate. Typically, descriptions of activity levels are light (≤3 METs), moderate (3–5.9 METs), and vigorous (≥6 METs). Alternatively, percentage of maximum aerobic capacity (i.e., the beginning of anaerobic metabolism) is a measure of activity levels defined by vigorous (≥80% maximum) and moderate (60–75% maximum); light physical activity involves minor changes in heart and respiratory rates with sedentary lifestyle involving no change in cardiorespiratory parameters. METs are usually converted to MET-hours/day or week to sum up daily or weekly physical activity, respectively.

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Physical activity (i.e., any movement using skeletal muscles) may modify some of the risk factors for colon, endometrial, and female breast cancer incidence and mortality by altering insulin-mediated pathways, energy balance, and/or circulating estrogen concentrations, particularly in postmenopausal, obese women.[126,127] A meta-analysis comparing high versus low physical activity in 33 studies involving 19,558 cases of endometrial cancer detected a statistically significant inverse relationship with endometrial cancer for postmenopausal women (RR = 0.81, 95% CI: 0.67–0.97) but not for premenopausal women (RR = 0.74, 95% CI: 0.49–1.1, $P_{\text{difference}} = -0.78$).[128] The inverse relationship with physical activity as statistically significant for overweight or obese women (RR = 0.69, 95% CI: 0.52–0.91), whereas the inverse relationship was not statistically significant for normal-weight women (RR = 0.97, 95% CI: 0.84–1.13). The World Cancer Research Fund/American Institute for Cancer Research (WCRF) concluded that the scientific evidence convincingly supported a lower colorectal cancer risk with higher overall physical activity levels and probably provides some protection for postmenopausal breast and endometrial cancers.[123] Reporting bias from self-reporting questionnaires, heterogeneity in study design, misclassification from measurement errors, and confounding of obesity with diabetes and cardiovascular diseases complicate firm conclusion regarding the quantitative effect of physical activity on cancer incidence and mortality.

Body Fat and Obesity

Excessive body fat is difficult to measure accurately and varies across different populations. Underwater weighing, computerized tomography, magnetic resonance imaging, and dual-energy X-ray absorptiometry are precise measures of body fat; however, these techniques are impractical in epidemiology studies because of cost and technical complexity. The BMI is a common measure of weight adjusted for height; however, very muscular and lean persons (e.g., athletes, manual laborers) have relatively high BMI with low fat stores; Asians typically have higher body fat stores at an equivalent BMI than European Caucasians.[129] The pattern of fat stores varies with gender, age, and genetic factors. The size of abdominal fat stores correlates to the risk of chronic diseases (e.g., cardiovascular diseases, diabetes) with the waist circumference (body roundness index) and the waist/hip ratio potentiality being better measures of metabolically active intra-abdominal fat stores and subcutaneous fat than BMI, but they lack strong validation.[130] The ideal body weight (BMI = 18.5–24.9) usually correlates to adult body fat of 15–20% in men and 25–30% in women.[131] The approximate equivalence of a BMI of 25 (upper ideal weight limit) and 30 (lower limit of obesity) is 37 in. (94 cm) and 40.2 in. (102 cm), respectively, in men and 31.5 in. (80 cm) and 34.6 in. (88 cm), respectively, in women. Adult weight gain typically involves the accumulation of fat rather than lean tissues.

In addition to BMI as an imprecise measure of obesity in population studies (e.g., BMI versus visual fat area reflected by waist circumference), methodological issues complicate interpretation of results on obesity and the risk of developing cancer, including obesity-associated detection bias, collider bias (i.e., unmeasured confounding induced by selection bias), reporting bias from use of self-reporting questionnaires, confounding, reverse causality, weight change over course of study, and the complexity of the relationship between obesity and associated comorbidities (diabetes, cardiovascular diseases);[132] some studies associate overweight and early obese states with improved cancer survival.[133] In 2002, the IARC determined the evidence was sufficient to conclude avoidance of weight gain reduced the risk of esophageal adenocarcinoma, colon cancer, renal-cell carcinoma, postmenopausal breast cancer, and cancer of the corpus uteri.[134] The IARC reassessed the preventive effects of weight control on cancer risks based on BMI; the review involved primarily observational studies because of the sparse number of studies on cancer risks following weight loss or weight-control interventions.[135] The IARC working group confirmed the original IARC findings, concluding the association between BMI and cancer risk was strong and dose-related for esophageal adenocarcinoma, colorectal cancer, and cancers of the gastric cardia, pancreas, liver, gallbladder, and kidney. These results were consistent across geographical regions and among sexes. The World Cancer Research Fund/American Institute for Cancer Research (WCRF) supported the IARC findings affirming convincing evidence for a dose-response relationship between body fatness as measured by the BMI and esophageal adenocarcinoma, colorectal cancer, postmenopausal breast cancer, and cancers of the endometrium, kidney, and pancreas.[123] The epidemiological evidence for an association between body fatness as measured by the BMI and gallbladder was probable, whereas the association between abdominal fatness using waist circumference, waist/hip ratio, and weight gain patterns was convincing for colorectal cancer and probable for pancreatic and postmenopausal breast cancers.

The strength of the association and dose-response between body fat and cancer remains variable and

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TABLE 49.19. Estimated relative risk of cancer in patients with elevated body-mass index (BMI) comparing the highest weight category (Overweight, 25.0–29.9; Class 1 Obesity, 30.0–34.9; Class II Obesity, 35.0–39.9; Class III Obesity, ≥40) based on World Cancer Research Fund/American Institute for Cancer Research evaluations and IARC Working Group review of observational studies on the most recent studies and meta-analyses. Sufficient evidence implies that chance, bias, and confounding were ruled out with confidence. (Adapted from Lauby-Secretan et al.).[135]

Cancer Site (Type)	IARC Human Evidence[a]	IACR Relative Risk (95% CI)[b]	WCRF/AICR Classification[c]
Breast, postmenopausal	Sufficient	1.1 (1.1–1.2)	Convincing[d]
Colorectal	Sufficient	1.3 (1.3–1.4)	Convincing
Esophageal adenocarcinoma	Sufficient	4.8 (3.0–7.7)	Convincing
Gallbladder	Sufficient	1.3 (1.2–1.4)	Probable
Gastric cardia	Sufficient	1.8 (1.3–2.5)	—
Kidney (renal cell)	Sufficient	1.8 (1.7–1.9)	Convincing
Liver	Sufficient	1.8 (1.6–2.1)	Convincing
Meningioma	Sufficient	1.5 (1.3–1.8)	—
Multiple myeloma	Sufficient	1.5 (1.2–2.0)	—
Ovary	Sufficient	1.1 (1.1–1.2)	Probable
Pancreas	Sufficient	1.5 (1.2–1.8)	Convincing
Prostate, advanced	—	—	Probable
Thyroid	Sufficient	1.1 (1.0–1.1)	—
Uterus, corpus	Sufficient	7.1 (6.3–8.1)	Convincing

[a] IARC evaluation of observational epidemiological studies; [b] International Agency for Research on Cancer relative risk with confidence interval of highest body-mass index (BMI) versus normal BMI (18.4–24.9); [c] WCRF/AICR = World Cancer Research Fund/American Institute for Cancer Research as measured by BMI; [d] Body fatness probably protects against premenopausal breast cancer.

relatively small compared with smoking and alcohol, depending on sex and cancer type. In random effects meta-analyses and meta-regressions of study-specific incremental estimates of cancer risk, the association between postmenopausal breast cancer and BMI was weakly positive with an increased relative risk of ~1.1/5 BMI units above normal weight (BMI = 18.5–24.9), whereas the risk of premenopausal breast cancer was inversely related to BMI.[136] Suspected mechanisms for this association included alteration of sex hormone metabolism and chronic inflammation disrupting the balance between cell proliferation and apoptosis.[137] In this study, the association between a 5-kg/m^2 increase in BMI for women was stronger for endometrial (RR = 1.59, $P < 0.0001$), gallbladder (RR = 1.59, $P = 0.04$), esophageal adenocarcinoma (RR = 1.51, $P < 0.0001$), and renal (RR = 1.34, $P < 0.0001$) cancers. Table 49.19 lists the cancer sites sufficiently associated with obesity and their estimated relative risks based on the IARC and WCRF reviews. The IARC considered the evidence limited for elevated body fatness-related increased risks for male breast cancer, fatal prostate cancer, and diffuse large B cell lymphoma, whereas the evidence was inadequate for squamous cell carcinoma of the esophagus, cutaneous melanoma, brain or spinal cord glioma, and cancers of the gastric noncardia, extrahepatic biliary tract, lung, testis, and urinary bladder.

Diet

Diet influences many types of cancer, depending on the cancer type and age at exposure;[138] however, the exact dietary components and the degree of influence remain unclear due to multiple methodological issues, including the complexity of chemical compounds in foods, difficulty classifying unique food groups, the absence of biomarkers to confirm exposure, reporting bias (self-reported questionnaires), collinearity of dietary and behavioral factors, confounding (e.g., smoking, fiber intake, body fatness) from nonrandom study designs, lack of uniformity in diets over time, and limited data on the influence of exposure timing on cancer incidence and mortality.[139] Consequently, nutritional studies are subject to cumulative biases, selective reporting, and extensive residual confounding, particularly following the use of big data to reach statistical significance at relatively modest absolute risk levels.[140] Separating the influence of a single dietary component on health outcomes is difficult when using limited self-reported nutrition data containing few questions to cover the exceedingly complex interactions of dietary items and multiple ingested chemicals.

Potential genotoxic carcinogens introduced during the consumption of processed food include polycyclic aromatic hydrocarbons (PAHs) from the effect of intense heat on fat extruded from meats or fish, heterocyclic amines from cooking meat or fish, nitrosamines

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from cured meat or fish products, and acrylamide from heat-induced reactions between carbonyl sugar groups (e.g., glucose) and free amino acid asparagine, including bread, potato chips, French fries, and baked goods. Additionally, diet and lifestyle may enhance epigenetic effects that promote tumor development by reducing the presence of anti-inflammatories, antioxidants, and endocrine disrupters.[141] Several studies in highly developed countries, including migrants immigrating to these countries,[142,143] suggest the consumption of promoting agents and dietary carcinogens along with poor dietary practices (e.g., inadequate nutrients, antioxidants, or fiber, excessive fat, or caloric intake) may increase the incidence of certain cancer types (e.g., breast, colon, endometrium, prostate);[144,145] however, analytical epidemiological studies indicate the association between diet and human cancer is relatively weak compared with other lifestyle factors (e.g., tobacco, alcohol) and biological agents (bacteria, viruses, parasites, aflatoxins), excluding obesity.[146]

A well-balanced diet remains the optimal approach to ensuring adequate intake of essential micronutrients for maintenance of overall health, including cancer prevention unless a person has vitamin or mineral deficiencies; typically, the absorption of micronutrients into the body is better through foods than supplements.[147] Most randomized clinical trials of vitamin and mineral supplements have not demonstrated definite benefits for cancer prevention in cancers unrelated to nutritional deficiencies.[148] Several clinical trials suggest supplementation of micronutrients in doses exceeding the recommended dietary allowance may increase cancer mortality, including β-carotene in smokers (i.e., ~18%),[149] folic acid, and vitamin E.[150]

Fat

In comparison with vegetables and fruits, fats are high energy-dense foods (i.e., >225–275 kcal/100 g). Meat, milk, and dairy products are significant sources of fat in high-income countries, with fat content being higher in most domestically bred than wild animals depending on animal type, rearing, processing, and preparation. Fatty acid classifications include saturated (solid at room temperature, typically of animal origin), unsaturated (liquid at room temperature, typically of plant or marine origin), and semisynthetic, partially hydrogenated *trans*-fatty acids (harder at lower temperatures than unsaturated fats). Complete hydrogenation of the latter converts the compound to saturated fatty acid, improving shelf life and increasing energy density and saturated fat consumption. Monounsaturated fatty acids have only one double bond, whereas polyunsaturated fatty acids have multiple double bonds. An "*n*" denotes the first double bond along the carbon chain of a polyunsaturated fatty acid (e.g., $n = 3$ for α-linolenic acid, omega 3′ fatty acid). Cattle and sheep contain more saturated fatty acids than poultry or pork. Dietary fat is necessary to absorb fat-soluble vitamins (A, D, E, K). The average Western diet contains 30–40% total fat, depending on the consumption of meat and dairy products. The average fat consumption in the United States is 36–38% of total caloric intake, whereas the National Cancer Institute (NCI) recommends an upper limit of 30% of total dietary calories.

Evidence suggesting diets high in fats and oils independently increase cancer incidence (e.g., colorectal, lung, postmenopausal breast cancers) is limited. Some epidemiology and animal studies suggest an association between increased dietary fat consumption and the incidence and mortality of some cancers (e.g., breast, colon, endometrium, prostate), primarily as a promoting rather than initiating agent. This association is strongest for breast cancer; however, the results are inconsistent, particularly with different estrogen-receptors and menopausal status.[151,152] Although some animal, ecological, and case-control studies suggest high total dietary fat content modestly increases breast cancer risks,[153] prospective cohort studies are inconsistent with positive results primarily in postmenopausal women.[154,155] Although most case-control studies support a modest association, less consistent cohort studies suggest the possibility of differences in the amount of fat consumption between international studies (i.e., as low as 15% fat in diet) and national studies (i.e., 34–44%).[156] An 8-year follow-up cohort study of 1,439 incident breast cancer cases (~54% postmenopausal) in the US Nurses' Health Study did not detect a positive association between total fat consumption and breast cancer comparing the highest and lowest quintiles.[157] Similarly, a prospective cohort study of 49,261 women aged 30–49 years at enrollment yielded 974 breast cancer cases with no association between total fat, monounsaturated fat, polyunsaturated fat, or saturated fat and breast cancer risks.[158] However, subgroup analysis suggested a reduced breast cancer risk after the age of 50 years, comparing the highest quintile of monounsaturated fat (HR = 0.45, 95% CI: 0.25–0.99) and polyunsaturated fat (HR = 0.54, 95% CI: 0.35–0.85) with the lowest quintile. Estrogen or progesterone status did not affect the hazard ratios.

Fiber

Fibers in the diet are complex carbohydrates typically classified as soluble and insoluble. Soluble fibers occur in fruits, vegetables, and particularly legumes (pulses) and certain minimally processed grains (e.g., oats), whereas

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insoluble fibers typically exist in bran cereals (e.g., rice, wheat).[159] The outer grain parts (bran, aleurone layer) contain nonstarch polysaccharides typical of carbohydrates that characterize dietary fiber. Soluble fibers undergo intestinal metabolism by bacterial enzymes to produce metabolites that moderately increase stool size; insoluble fibers substantially increase stool size and water content. Consequently, fiber dilutes fecal contents (e.g., short-chain fatty acids produced during gut fermentation), increases stool weight, and decreases intestinal transit time. Plant cells are the main dietary source of fiber; whole fruits and vegetables contain variable amounts of fiber; however, the fiber content of juices made from these foods is low. The daily fiber intake varies from 7–25 g with a typical intake of 10–13 g in Japan and the United Kingdom to ≥15–20 g in Africa and India.[160] The mean fiber intake of adult Americans is ~11 g/day, below the NCI recommended consumption of 20–30 g/day.

Studies of Western countries with high-fat, low-fiber diets demonstrate an increased colon cancer incidence compared with Asian countries (e.g., Japan) with low-fat, high-fiber diets.[161] Wheat bran is the most consistent product that reduces colon cancer incidence in experimental animals.[162] Although the findings could not exclude confounding, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) meta-analysis of 10 cohort studies on the influence of fiber on colorectal cancer concluded dietary fiber probably protected against colorectal cancer based on a consistent dose-response relationship and plausible mechanisms.[123] The summary effect estimate was 0.90 (95% CI: 0.84–0.99)/10 g daily increments with moderate heterogeneity. The funnel plot indicated that the relative risks in only one cohort study were statistically significant. The evidence for an inverse association between dietary fiber and esophageal cancer was considered limited and inconsistent. The Harvard pooled analysis of 13 prospective cohort studies with 725,628 participants and 8,081 colorectal cancer cases during 6–20 years of follow-up demonstrated a significant inverse association in the age-adjusted model (RR = 0.84, 95% CI: 0.77–0.92), but not after the inclusion of all risk factors (RR = 0.94, 95% CI: 0.86–1.03).[163] Fiber intake from cereals, fruits, and vegetables was not associated with colorectal cancer risk. In the European Prospective Investigation into Cancer and Nutrition (EPIC) study of >500,000 Western Europeans, the inverse association for cancer types comparing the highest and lowest quintiles of dietary fiber intake was statistically significant for colorectal (RR = 0.82, 95% CI: 0.72–0.96; n = 4,517; P_{trend} = 0.013)[164] and liver (RR = 0.51, 95% CI: 0.31–0.83; n = 191; P_{trend} = 0.013) cancer,[165] whereas the results for breast cancer were borderline (RR = 0.95, 95% CI: 0.89–0.101; n = 11,576; P_{trend} = 0.03).[166]

Fruits and Vegetables

Fruits and nonstarchy vegetables are usually low-energy-dense foods that contain fiber and a variety of bioactive compounds (e.g., minerals, vitamins, phytochemicals). The latter accounts for up to 100,000 different compounds categorized as glucosinolates, lectins, monoterpenes, phytoestrogens, phytosterols, polyphenols, protease inhibitors, sulfides, and terpenes.[123] Although some phytochemicals are antioxidants, these compounds are not essential dietary constituents. The specific composition of fruits and vegetables depends on species, strain, farming practices, environmental conditions, production processes, storage conditions, and cooking methods. Cooking usually reduces the total nutrient content of vegetables; however, cooking increases the bioavailability of some nutrients (e.g., lycopene in tomatoes).[167]

Vegetables are edible plant parts (bulbs, flowers, leaves, roots) classified as allium vegetables (e.g., garlic, leeks, onions), cruciferous vegetables (e.g., pok choy, broccoli, cabbage, watercress), and leafy vegetables (e.g., lettuce, spinach). Fruits are the seed-containing plant parts used for foods (e.g., apples, apricots, bananas, berries, citrus, figs, grapes including raisins, mangoes, melons). Some botanical fruits are usually included as vegetables when typically used in cooking as vegetables (cucumbers, peppers, squash, tomatoes). Legumes (pulses) are dried edible seeds from plants that produce pods as their fruits (e.g., beans, lentils, peanuts, peas), whereas nuts are edible seeds circumscribed by a dry, durable shell (e.g., almonds, chestnuts, hazelnuts, walnuts). Brazil nuts, cashews, and macadamia nuts botanically are seeds rather than nuts. Cereals (grains) are the seeds of cultivated grasses including barley, corn or maize, millet, wheat, oats, sorghum, rice, and rye. The food groups contain a variety of bioactive compounds, including carotenoids (α- and β-carotene, lycopene), water-soluble vitamins (folate, vitamin C), and fat-soluble vitamins (D, E).

Although the enhancement of total fruits and vegetables in the diet is a plausible means to reduce cancer rates because these foods are good sources of anti-proliferatives and antioxidants (i.e., fiber, vitamins, phytochemicals), cohort studies have not established a convincing causal association between fruit and vegetable consumption and overall cancer incidence. A review of case-control and cohort studies detected limited evidence for a cancer-preventive effect of fruit and vegetable consumption for cancers of the mouth

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and pharynx, larynx, esophagus, stomach, colorectum, lung, bladder (fruit only), kidney, and ovary (vegetables only).[168] The estimated population-preventable fraction for low fruit and vegetable intake was 5–12%. The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Report concluded that total fruit and vegetable consumption was not convincingly associated with reduced cancer risks in any tissues; however, decreased risks of cancer at some sites were probable or limited, as displayed in Table 49.20.

In a prospective cohort study of 49,261 Swedish women (2,347 cases of invasive cancer), the median daily intake of fruits and vegetables was 204 g with a 90th CI of 37–564 g.[170] The association between overall cancer incidence and total fruit and vegetable intake was not statistically significant. Comparing the highest and lowest quintiles, the incident rate ratio was 1.0 (95% CI: 0.88–1.16). A Japanese study of 191,519 participants (17,681 overall cancers) did not detect an association stratified for smoking and alcohol drinking between fruit or vegetable consumption and overall cancer rates.[171] The hazard ratios comparing the highest versus lowest quartiles of fruit intake for men were 1.03 (95% CI: 0.97–1.10; P_{trend} = 1.00) and 1.03 (95% CI: 0.95–1.11; P_{trend} = 0.97) for women. For vegetables, the hazard ratios were 1.07 (95% CI: 1.01–1.14; P_{trend} = 0.18) for men and 0.98 (95% CI: 0.91–1.06; P_{trend} = 0.99) for women. The European Prospective Investigation into Cancer and Nutrition (EPIC) study is a prospective cohort study involving 23 study centers in 10 Western European countries with >500,000 participants and substantial variation in diets.[172] The study compared incident cancer trends for quintiles of daily intake of total fruit (range, <89 g to ≥356 g), vegetable (range, ≤99 to ≥305 g), and fiber (range, ≤16.4 to ≥28.5 g) daily intake. The evidence for an inverse relationship between upper aerodigestive tract (mouth, pharynx, larynx, and esophagus) was weakly positive for total fruit intake and negative for total vegetable intake. Similarly, the data for combined fruit/vegetable intake and colorectal cancer were weakly positive, whereas the data for lung cancer were positive only for smokers. Overall, there was little evidence for an association between quintiles of vegetable intake and various cancer sites and small inverse associations between some cancer sites and fruit consumption. The study investigated total fruit and vegetable consumption; however, the study did not exclude an inverse association between cancer subtypes (e.g., estrogen receptor-negative breast cancer)[173] or fruit and vegetable subgroups (e.g., blueberries, nectarines, citrus).[174,175]

Evidence for an inverse association between breast cancer risk and total fruit and vegetable intake is inconclusive. Generally, reviews of case-control studies are positive, whereas cohort studies usually demonstrate a weakly positive or statistically insignificant association. In a systematic review and meta-analysis of 15 prospective studies comparing the highest and lowest intakes, the summary relative risk was weakly positive (RR = 0.89, 95% CI: 0.80–0.99, I^2 = 20%) for total fruits and vegetables, whereas the RR did not reach statistical significance for total fruits or total vegetables individually.[176] A review of 7,377 cases of invasive breast cancer did not detect statistically significant associations between consumption of total fruits (pooled multivariate RR = 0.93, 95% CI: 0.86–1.00) or total vegetables (pooled multivariate RR = 0.96, 95% CI: 0.89–1.04) and breast cancer.[177]

Meat

The carcinogenic effect of red and processed meats is difficult to separate from other dietary and lifestyle factors, considering the relatively weak observed effects and wide variation between studies. Epidemiological evidence for an association between overall red and processed (i.e., salted, cured, smoked) meat consumption and increased overall cancer rates is suggestive with the strongest evidence for colon cancer, whereas evidence for fish, eggs, and poultry is very limited.[133] Processed meats with preservatives (nitrites) typically include bacon, bratwurst, frankfurters, ham, pastrami, salami, and sausage; however, meats preserved only by refrigeration are usually not classified as processed meat, even if cooked. Plants naturally contain some nitrates with vegetables accounting for 70–97% of dietary nitrate consumption; the body converts ~5–20% of the absorbed nitrates to nitrites.[123] The curing process or *in vivo* metabolism can convert nitrates and intestinal degradation products of amino acids into *N*-nitroso compounds (e.g., nitrosamines). Heterocyclic amines and polycyclic aromatic hydrocarbons form in temperature-dependent processes during the cooking process (e.g., grilling, broiling, frying, barbecuing) because of the reaction of amino acids and creatine or the heat-induced degradation of fat, respectively.

Potential genotoxic mechanisms for developing gastrointestinal cancers from meats include: 1) mutagenic effect of heterocyclic amines contained in well-cooked meat processed at temperatures of >180°C for extended time periods and 2) endogenous formation of *N*-nitroso compounds in the gastrointestinal tract. Cured meats account for most of the dietary exposure to *N*-nitrosamine compounds, whereas fish and cheese contribute smaller nitrosamine exposures.[178]

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TABLE 49.20. Strength of evidence for *decreased* cancer risk at various sites for total vegetable and total fruit intake based on data from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and the European Prospective Investigation into Cancer and Nutrition (EPIC) study on dietary fruits, vegetables, and fiber. The EPIC study compared significant trends across quintiles of fruit, vegetable, and fiber intake, whereas the WCRF/AICR used meta-analysis techniques to develop categories reflecting the strength of the evidence of an inverse association or insufficient data.

Cancer Site	Total Non-starchy Vegetables		Total Fruits		Total Fiber	
	WCRF/AICR	EPIC	WCRF/AICR	EPIC	WCRF/AICR	EPIC
Mouth	Probable[a]	None[a]	Probable[a]	Significant[a]		Insufficient
Nasopharynx	Limited	–	Limited	–		–
Pharynx	Probable[a]	None[a]	Probable[a]	Significant[a]		Insufficient
Larynx	Probable[a]	None[a]	Probable[a]	Significant[a]		Insufficient
Lung	Limited	None	Probable	Significant		Insufficient
Esophagus	–[c]	None[a]	–[c]	Significant[a]		Insufficient
Stomach	Probable	None	Probable	None		None
Breast	–	None	–	None		Significant
Pancreas	Insufficient	None	Limited	None		Insufficient
Liver	Insufficient	Insufficient	Limited	Insufficient		Significant
Kidney	–	None	–	None		None
Colorectum	Limited	Significant[b]	Limited	Significant[b]		Significant
Bladder	–	None	–	None		None
Ovary	Limited	None	Insufficient	None		Insufficient
Endometrium	Limited	Insufficient	Insufficient	Insufficient		None
Cervix	–	None	–	None		Insufficient
Prostate	–	None	–	Possible small reduction		None

Abbreviations: Insufficient = inadequate data to calculate relative risks and confidence intervals; – = not reported in study.
[a] Combined cancer sites; [b] Combined total fruit and vegetable intake; [c] Subsequent analysis suggests an 11% reduction in esophageal adenocarcinoma per 100 g of vegetables/day in 3 studies and 16% reduction in esophageal squamous cell carcinoma per 100 g of fruit/day in 3 studies.[169]

N-nitrosation reactions between secondary or tertiary amines and nitrites (or other nitrosating agents) in cured meat cause the formation of *N*-nitrosamines (*N*-nitrosodimethylamine, *N*-nitrosopyrrolidine, *N*-nitrosoproline); these chemicals are recognized animal and probable human carcinogens. Nitrites, aldehydes, and quinones enhance nitrosation, whereas ascorbic acid, vitamin E, and polyphenols (found in vegetables and fruit) inhibit this process.[10]

Benzo(a)pyrenes and heterocyclic amines (MeIQ, IQ, Glu-P-1) occur in broiled or smoked meats; 2-amino-1-methyl-6-phenylimidao[4,5-*b*]-pyridine (PhIP) is an aryl amine formed in meat during cooking, particularly at high temperatures. The confounding factors in the evaluation of meat diets complicating the interpretation of studies associating PhIP with colon cancer include the presence of polyaromatic hydrocarbons, fat intake, and iron. PhIP and related heterocyclic amines (e.g., 2-amino-3,4-dimethylimidazo[4,5-*f*]quinolone, MeIQ; 2-amino-3,8-dimethylimidazo[4,5-*f*]quinolone, MeIQx) are mutagenic animal carcinogens that produce small and large intestine lymphomas and prostate tumors in experimental studies.

Trace amounts of animal carcinogens appear in food because of food processing; however, conclusions regarding positive epidemiology studies supporting a firm causal connection between well-done meats and cancer (e.g., breast, colon, stomach) remain controversial.[179] Some epidemiological evidence suggests that *N*-nitroso compounds contribute to the development of human cancers (e.g., esophageal cancer in high-risk Chinese areas, colorectal cancer in developed countries). These compounds are potential explanations for higher colon cancer incidences in

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studies of diet in developed countries (North America, Western Europe, Japan, Australia, New Zealand); however, interpretation of studies involving cancer and diet requires complex evaluations of numerous methodological issues, including measuring dietary patterns in different populations, standardizing food intake, defining food categories, determining proper outcomes, controlling bias, adjusting for confounding, predicting the effect of multicollinearity, determining genetic susceptibilities, developing statistical models, and evaluating differences in analytical metrics. Additionally, the typically weak magnitude of the observed effect between specific portions of the diet and cancer (i.e., relative risk 0.8–1.25) potentially allows confounding, exposure misclassification, and biases (information, selection, publication) to obscure the true effect.

In a meta-analysis of 21 studies comparing the highest versus lowest intake of red and processed meat with the risk of colorectal cancer, the summary relative risk (SRR) for colorectal cancer was 1.22 (95% CI: 1.11–1.34), whereas the SRR for red meat alone was 1.10 (95% CI: 1.00–1.21, statistically nonsignificant).[180] The mean for the highest category of red mean intake ranged from 26–197 g/day. The standardized measure for red meat in the meta-analysis was 50 g and 120 g for red/processed meat. Nonlinear dose-response analyses demonstrated increasing colorectal cancer risk up to ~140 g of red and processed meat/day, then the curve plateaued. The authors attributed substantial heterogeneity in the studies mostly to intake unit conversion in the meta-regression analysis. A subsequent meta-analysis of 27 independent prospective cohort studies using random effects models to examine red meat (beef, pork, lamb) and colorectal cancer risks demonstrated a summary relative risk of 1.11 (95% CI: 1.03–1.19).[181] There was substantial heterogeneity ($P = 0.014$, $I^2 = 33.60$) with no clear dose-response relationship. Nine studies reporting median red meat intake of <40 g/day have summary relative risk for colorectal cancer of 1.02 (95% CI: 0.98–1.07) without significant heterogeneity ($P = 0.014$, $I^2 = 0.0$). The authors noted that the association weakened over time.

Dysplastic changes in colorectal epithelium probably represent a stepwise progression from an adenoma to a malignant carcinoma, with the risk of an adenoma becoming malignant depending on the size, type, and number of adenomas.[182] Studies on the association between red meat and colorectal adenomas are limited. In a meta-analysis of 19 case-control studies and 7 prospective cohort studies of red or processed meat consumption and colorectal adenoma risk, the overall summary relative risk/daily consumption of 100 g red meat and colorectal adenomas was 1.27 (95% CI: 1.16–1.49, $I^2 = 5\%$, $n = 16$) and 1.29 (95% CI: 1.10–1.53, $I^2 = 27\%$, $n = 10$) per daily consumption of 50 g processed meat.[183] The results for red meat appeared stronger for case-control than cohort studies, whereas the opposite was true for the results involving processed meats. Linear dose-response analysis per 100 g red meat daily indicated a plateauing of the response near a relative risk of 1.5, with the greatest effect at the lower portion of the dose-response curve; most of these studies did not demonstrate a statistically significant difference between colorectal adenoma when comparing high and low red meat consumption. A meta-analysis of 19 studies of meat subtypes (5 beef, 5 pork, 2 lamb, 1 veal, 19 poultry) and colorectal cancers suggested different risks for various meat subtypes as well as variation between countries.[184] The colon cancer summary of relative risks was elevated comparing the highest and lowest intake categories for beef (RR = 1.24, 95% CI: 1.07–1.44); however, the Asian studies on beef demonstrated no statistically significant association between beef consumption and colon cancer risk. The studies on pork and poultry consumption did not demonstrate a statistically significant increase in the overall relative risk of colon cancer.

Pickled Vegetables

Investigations in areas with high esophageal and stomach cancer rates have not identified a specific dietary cause to account for these relatively high rates.[185] In a population-based case-control study of 250 lower esophageal cancer cases in 5 Chinese areas with high esophageal cancer rates using personal food interviews, multivariate logistic analysis identified multiple potential risk factors including not taking regular meals, overnight vegetable intake, GERD, hot food, passive smoking, pickled food, alcohol drinking, seldom eating breakfast, and false dining posture.[186] The odds ratio for pickled food was 2.273 (95% CI: 1.350–3.828) with a value less than several other identified factors (e.g., not taking regular meals, overnight vegetable intake, GERD, hot food). Statistical analyses for the multiple comparisons were not reported. A meta-analysis of 34 almost exclusively case-control studies on Asian pickled vegetable consumption and esophageal squamous cell carcinoma risks reported an overall random effects odds ratio of 2.08 (95% CI: 1.66–2.60, $P = <0.001$) and high heterogeneity (Q-statistic = 282.18, $I^2 = 88\%$).[187] A matched case-control study of 185 esophageal cancer cases from Yanting, Sichuan Province, reported a statistically nonsignificant odds ratio for frequent pickled vegetable intake of 2.12 (1.00–4.49) using conditional logistic regression.[188] Other identified risk factors with higher odds ratios included eating food rapidly

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(OR = 5.84, 95% CI: 2.05–16.7) and drinking shallow groundwater (OR = 4.18, 95% CI: 1.30–13.4). In contrast to most other countries in the world, the pickling processes in Japan and China use natural fermentation with an increased risk of fungal contamination.

Vitamins and Chemoprevention

Although some observational studies on diets high in fruits, vegetables, and antioxidants suggest these foods and nutrients may prevent cancer,[189] most randomized trials of the association between antioxidants and cancer incidence do not support the use of vitamin or mineral supplementation in primary cancer prevention in healthy adults. Several meta-analyses did not demonstrate a significant reduction in cancer rates with antioxidant vitamins, β-carotene, or mineral supplementation over 4–6 years, with the possible exception of a selenium-associated reduction in mortality.[190,191] Antioxidant supplementation did not significantly reduce total cancer incidence (RR = 0.99, 95% CI: 0.94–1.04) or mortality (RR = 1.03, 95% CI: 0.92–1.15), whereas β-carotene supplementation was associated with an increase in lung cancer incidence in current smokers (RR = 1.10, 95% CI: 1.03–1.10).[190] Selenium supplementation was associated with reduced cancer incidence in men (RR = 0.77, 95% CI: 0.64–0.92) but not in women (RR = 1.00, 95% CI: 0.89–1.13). The randomized, double-blind, placebo-controlled Women's Antioxidant Cardiovascular Study using 500 mg vitamin C qd, 600 IU vitamin E qd, and 50 mg β-carotene qod over a mean of 9.4 years detected no statistically significant effects of any antioxidant or any combination on total cancer incidence.[192] Most women were obese (mean BMI = ~30) and postmenopausal (77%) with only 27% reporting multivitamin use at baseline. A meta-analysis by the United States Preventive Services Task Force (USPSTF) did not find substantial evidence supporting the use of vitamin and mineral supplements to prevent cancer in healthy adults, although two trials demonstrated a small, borderline significant benefit from multivitamin supplements on cancer in men only.[147] Neither β-carotene nor vitamin E prevent cancer, whereas several studies suggest β-carotene supplementation increases lung cancer risk in smokers. The USPSTF concluded the evidence was insufficient to assess the balance between risk and benefit for single or multiple nutritional supplements in healthy adults with well-balanced diets, except possibly increased risks with β-carotene and vitamin E.[193] Consequently, they recommended against the use of vitamin E or β-carotene to prevent cancer.

Vitamin A

Vitamin A (retinol) is a generic term for retinoids (retinal, retinol, retinoic acid) derived from plant provitamin A carotenoids (e.g., β-carotene). A review of retrospective, mostly case-control epidemiology studies on the association between reduced vitamin A (retinol) intake and the overall cancer incidence suggested an ~2-fold increase in patients with low vitamin A consumption.[162] Recall bias and lack of control over other dietary and lifestyle factors (e.g., smoking) influencing cancer incidence limit interpretation of the validity of this study; subsequent observational studies do not support a consistent relationship between increased total cancer incidence and reduced vitamin A or β-carotene intake. Randomized clinical trials indicate β-carotene supplementation increases lung cancer risks in heavy current smokers with genetic susceptibilities (glutathione-*S*-transferase μ_1 variant, *GSTM1*; Arg/Arg genotype) based on subgroup analysis of a nested, case-control study of 29,133 white male Finnish smokers followed for 5–8 years.[194]

Vitamin D

Observational studies on the effect of vitamin D on cancer risk are limited and inconsistent, primarily focusing on colorectal and prostate cancer.[195] Limited data from several randomized clinical trials suggest high-dose vitamin D supplementation (i.e., 1,000 IU/day) reduces total cancer risk; however, observational studies suggest higher (25-[OH]D) concentrations are associated with an increased cancer risk. Mixed-effects dose-response meta-analysis data from 9 nested case-control studies of fair quality indicated a 10-nmol/L increase in prediagnosis blood 25-hydroxyvitamin D concentration and was associated with reduction in colorectal cancer risk of 6% (95% CI: 3–9%).[196] The results for a dose-response relationship between vitamin D and prostate or breast cancer risks were not statistically significant. Methodological issues limit conclusions, particularly potential residual confounding and the difficulty in determining true vitamin D status, including the contribution of endogenous vitamin D synthesis from sunlight; consequently, the US Preventive Services Task Force concluded that evidence is insufficient to determine the benefits or harms of vitamin D supplementation for cancer prevention. The Cohort Consortium Vitamin D Pooling Project of Rarer Cancers involving 10 international cohorts did not detect evidence of a protective association between higher concentrations of blood 25-hydroxyvitamin D (>75 nmol/L) and 7 cancer outcomes (endometrial, esophageal, gastric, kidney, non-Hodgkin lymphoma, ovarian, pancreatic).[197]

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Vitamin E

Evidence from observational studies on the role of vitamin E supplementation in reducing colorectal adenoma or cancer risks is equivocal. Most colorectal cancers arise from premalignant colorectal adenomas. In the randomized trial of Selenium and Vitamin E Cancer Prevention Trial (SELECT) enrolling 35,533 men over the age of 50–55 years, subgroup analysis identified 2,286 men with colorectal adenomas.[198] Vitamin E supplementation (400 IU α-tocopherol daily) did not affect the occurrence of colorectal adenomas compared with placebo (RR = 1.03, 95% CI: 0.96–1.10; $P = 0.38$). The lack of efficacy for reducing prostate cancer risk ended the trial early after 5.5 years, with overall follow-up ranging from 7–12 years after enrollment. Analysis of the data indicated a statistically significant increase in prostate cancer among healthy men on dietary supplementation with vitamin E compared with placebo (HR = 1.17, 99% CI: 1.004–1.36; $P = 0.008$).[199] The increased risk of prostate cancer first appeared 3 years after the trial began, with the hazard ratio increasing by 1.12–1.17 over the next 3 years. In the randomized, double-blind, placebo-controlled Women's Antioxidant Cardiovascular Study using 600 IU vitamin E qd for a mean of 9.4 years, vitamin E supplementation did not reduce the overall cancer incidence compared with placebo (RR = 0.93, 95% CI: 0.79–1.09).[192] Vitamin E (α-tocopherol) supplementation in the study on genetic susceptibilities in current smokers did not reduce lung cancer risks.[194]

Folic Acid

Folates are water-soluble B vitamins present in green, leafy vegetables, and cereals that provide 1-carbon units for cellular metabolism and are important coenzymes in genetic (e.g., nucleotide synthesis) and epigenetic (e.g., DNA methylation) pathways that prevent genomic instability and global DNA hypomethylation, respectively. The effects of folate deficiency on DNA methylation are highly complex and gene-/site-specific, depending on cell type, target organs, cancer stage, gene polymorphisms, and lifestyle factors.[200] Epidemiology studies suggest adequate folate consumption may slightly reduce colorectal cancer risk; however, confounding factors complicate the interpretation of these studies. A meta-analysis of 7 cohort and 9 case-control studies demonstrated a small reduction in the risk of colon cancer when comparing high and low intakes of dietary folate (RR = 0.75, 95% CI: 0.64–0.89), whereas the RR for colorectal cancer in groups with high and low intakes of *total* folate from food/supplements was not significantly reduced (RR = 0.95, 95% CI: 0.81–1.11).[201] Some studies suggest that high-dose folate supplements may increase the growth of precancerous lesions. In a nested, case-control study of Chinese men, plasma folate concentration was positively associated with colorectal cancer risk among men potentially with preneoplastic lesions based on the highest tertile of folate concentrations for men with late-stage colorectal cancer (OR = 2.66, 95% CI = 1.03–6.86).[202]

Coffee, Teas, and Caffeine

Coffee is a complex mixture of caffeine, acids (aliphatic, chlorogenic, citric, quinine), polysaccharides, proteins, lipids, and caramelized products, as well as endogenous (polycyclic aromatic hydrocarbons, heterocyclic amines, nitrosamines) and potentially exogenous contaminates (pesticides, mycotoxins, alkanes).[203] Although coffee contains hundreds of chemicals, the constituents in this beverage are not unique to coffee as a food product.[204] Some of these chemicals are possible carcinogens (caffeic acid, catechol, naphthalene), human carcinogens [benzo(*a*)pyrene], or mutagens (chlorogenic acid, naphthylglyoxal, caffeic acid),[205,206] whereas other constituents possess anticarcinogenic properties, including diterpenes (cafestol, kahweol), polyphenols (flavonoids, lignan phytoestrogens), and antioxidants (chlorogenic acid).[207,208] Most chronic animal studies on coffee did not detect carcinogenic effects.[209,210,211] The effect of coffee as a promoter is highly variable, with some studies demonstrating promoting effects and other studies demonstrating tumor-inhibiting effects.[203] Evidence indicating coffee consumption causes human cancer is weak.[212,213] An evaluation by an IARC Working Group found limited evidence for a weak correlation between coffee consumption and development of bladder cancer; however, the possibility of bias or confounding could not be excluded.[214] The evidence for an association with pancreatic and other cancers was inadequate. Consequently, the IARC lists coffee as unclassifiable (Group 3), with evidence suggesting lack of carcinogenicity in humans drinking coffee for cancers of the urinary bladder, female breast, pancreas, and prostate along with an inverse association with cancers of the liver and uterine endometrium.[214,215] Inadequate control for potential confounding, measurement error, selection bias, and/or recall bias, insufficient power, and inconsistent findings limited conclusions regarding brain, colorectal, esophageal, oral cavity, ovarian, oral cavity, and other cancers.

Although there is a correlation between national coffee consumption and US mortality rates for pancreatic cancer, evidence of a strong, dose-response relationship between coffee consumption and the occurrence of pancreatic cancer is weak.[216] Some ecological[217]

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and retrospective case-control studies[218] suggest an association with pancreatic cancer; however, most prospective studies demonstrate no association between coffee consumption and pancreatic cancer rates.[204,219] A meta-analysis of 40 prospective cohort studies relatively equally divided between the United States, Europe, and Asia using random effects meta-analyses and meta-regressions of study-specific incremental cancer estimates demonstrated a pooled relative risk of 0.82 (95% CI: 0.74–0.89) comparing high and non/lowest coffee drinker groups.[220] There was significant heterogeneity between studies (Q-statistic = 114.71, $P < 0.001$, $I^2 = 67.7\%$) reflecting international differences in coffee types, brewing methods, and serving sizes. An increase of 1 cup of coffee/day was associated with an overall 3% reduction (95% CI: 2–4% reduction) in cancer risk. Subgroup analyses demonstrated inverse associations with leukemia and breast, buccal/pharyngeal, colorectal, endometrial, esophageal, hepatocellular, pancreatic, and prostate cancers with no association for kidney, lung, and stomach cancers.

Teas are classified as black teas produced by an enzymatic oxidation process involving fermentation, whereas green tea is produced without fermentation. The latter is the most common tea accounting for ~80% of the world production.[214] Green tea contains polyphenols (catechins) including flavonols, flavandiols, flavonoids, and phenolic acids; catechins account for ~30% of the dry weight of these teas.[221] During the fermentation process for black tea, bisflavanols, theaflavins, and thearubigins form from the oxidative polymerization of monomeric flavan-3-ols. Caffeine accounts for ~3–4% of the dry weight (i.e., ~30–50 mg/cup).[214] Herbal teas contain various known and unknown components; their composition differs substantially from that of tea brewed from *Camellia sinensis*. Studies correlating cancer of the breast, intestine, larynx, lung, and colon with tea consumption are inconsistent; consequently, there is no clear association between tea and cancer development.[221] A Japanese study found an inverse association (HR = 0.43, 95% CI: 0.22–0.84) between the daily consumption of three cups of green tea and the risk of Stage I breast cancer recurrence.[222] The IARC classifies tea in Group 3 based on inadequate evidence of cancer in experimental animals and humans.[214]

Maté is an aqueous infusion of the herb *Ilex paraguayensis* prepared in a gourd, drunk hot (63–69°C) with a metal straw, and consumed primarily in South America; during the traditional drying process with burning organic material, polycyclic aromatic hydrocarbons enter the infusion in substantial concentrations.[223] Urinary concentrations of polycyclic aromatic hydrocarbon metabolites correlate with self-reported amounts of recent maté consumption.[224] Pooled results from two South American case-control studies demonstrate an odds ratio (OR) for esophageal squamous cell cancer comparing ever with never maté use of 1.60 (95% CI: 1.2–2.2); the OR increased linearly with cumulative maté consumption; however, the trend was statistically significant only for maté consumed hot or very hot.[225] The lack of studies demonstrating the carcinogenicity of cold maté and experimental animal studies demonstrating the tumor promoter properties of hot water at >65°C resulted in an IARC classification of Group 3 (unclassifiable) for not very hot maté and probable carcinogen (Group 2A) for drinking very hot beverages at >65°C.[215]

Tobacco

The IARC classifies tobacco smoke, environmental tobacco smoke, and smokeless tobacco as carcinogenic to humans (Group 1).[125] Tobacco smoke is a strong promoting agent (e.g., inflammation, oxidative damage) and complete carcinogen containing a complex mixture of procarcinogens, carcinogens, tumor promoters, and cocarcinogens; however, nicotine is not classified as a carcinogen.[226] Smokeless tobacco contains fewer identified carcinogens than cigarette smoke. Most carcinogens in tobacco smoke require metabolic activation, resulting in individual variation in susceptibility due to differences in metabolic activation and detoxification pathways. These genetic polymorphisms include *NAT2* slow acetylator genotype in bladder and breast cancer and *GSTM1* null genotype in combination with CYP1A1 polymorphism in lung cancer.

Genotoxic carcinogens react with nucleophilic sites in DNA to form covalent binding products (i.e., adducts). Tobacco smoking is associated with genotoxic effects in at least eight tissues (bladder/ureter, cervix, esophagus, myeloid organs, lung, oral/nasal, pancreas, pharynx/larynx).[227] Failure of DNA repair mechanisms to eliminate these adducts during DNA replication produces miscoding, and the insertion of wrong bases into the DNA strand causes permanent mutations. Dysregulation of cell cycle control occurs when these mutations appear in critical areas regulating cell growth (e.g., oncogenes, tumor suppressor genes). The specific gene mutations responsible for the development of tobacco-related cancer remain poorly defined; however, a meta-analysis of human epidemiology data demonstrated interindividual and histological differences in lung cancer mutations.[228] The odds of presenting with epidermal growth factor receptor (EGFR, a receptor tyrosine kinase) and the anaplastic lymphoma receptor tyrosine kinase-echinoderm microtubule-associated

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protein-like 4 (ALK-EML4) mutations were increased in: 1) never-smokers compared with ever-smokers and 2) patients with adenocarcinomas compared with nonsmall cell lung cancers, particularly adenocarcinomas.[229] These findings suggest key driver mutations in lung cancer patients may differ when developing in smokers from tobacco smoke or in never-smokers developing lung cancer after exposure to chromium, asbestosis, radon, or other nonsmoking-related lung carcinogens.

Composition

The physiochemical composition of the cigarette smoke depends on the origin and processing of the tobacco leaves, the porosity and treatment of the cigarette paper, the humidity, the age of the smoke as rapid coagulation of particles occurs, and the filter tip. The composition of cigarettes and cigarette smoke gradually changed over the last hundred years, resulting in particularly high tar concentrations prior to the introduction of "low-tar" cigarettes composed of filters with and without perforations, highly porous cigarette paper, and altered tobacco blends in the 1950s.[230,231] The latter resulted from changes in selection of tobacco types and varieties, incorporation of reconstituted tobacco into blends, opened and cut ribs, and "expanded tobacco" (i.e., tobacco with reduced weight and tar/cigarette resulting from cellular expansion and freeze drying). Variation in tobacco composition occurs between different countries. Figure 49.4 displays the modern commercial cigarette. Cigarette packages contain cigarette tar yields and nicotine concentrations in mainstream smoke as measured by smoking machines under highly standardized conditions using constituents identified by Dietrich Hoffmann and colleagues (Hoffmann analytes).[232]

The US sales-weighted average "tar" yields declined from 38 mg in 1954 to 12 mg in 1992 because of the changes listed above; during the same period, average nicotine yields declined from 2.7 to 0.95 mg.[233] In the United States, an increase in nitrate concentrations and enhancement of tobacco combustion accompanied these changes (i.e., 0.3–0.5 to 0.6–1.35%). More complete combustion decreases the carcinogenic polycyclic aromatic hydrocarbons (PAHs), whereas increased generation of nitrogen oxides produces higher concentrations of carcinogenic *N*-nitrosamines in cigarette smoke, particularly tobacco-specific *N*-nitrosamines.[234] Higher yields of the latter in mainstream smoke occur when smokers adjust to the lower nicotine yields by increasing smoking intensity (i.e., puff volume and frequency).

Tobacco smoke is a complex aerosol composed of a particulate phase (minute solid/liquid droplets) plus a vapor phase containing a mixture of gases (e.g., CO, CO_2, NO_x) and semivolatile compounds; tar refers to the particulate matter represented by the particulate phase minus nicotine and water.[235] During the burning of tobacco leaves, a variety of pyrolysis and reaction products form. Tobacco smoke contains over 5,000 chemical compounds, including over 80 carcinogens comprised of many genotoxic compounds (polycyclic aromatic hydrocarbons, heterocyclic amines, nitrosamines) and strong promoting agents in the acidic fraction.[236] The constituents of processed tobacco remain fairly constant over a variety of growing locations; however, the proportion of individual chemicals in tobacco including carcinogens depends on growing conditions and processing methods.[237] The lungs retain ~50–90% of the inhaled particulate matter in smoke, with most of the vapor phase constituents and gases reaching the alveoli.[238] The concomitant increase in tobacco-specific nitrosamines associated with increased use of blended tobaccos and the compensatory adjustment of smokers to lower nicotine intake complicate the analysis of the impact of reduced "tar" and filter-tipped cigarettes introduced in the 1950s. However, these changes in cigarette composition probably reduced lung cancer risks.[230] Regardless of tar content, the lung cancer risk is far greater in current smokers than in former or never-smokers.[239] Compared with nonmentholated

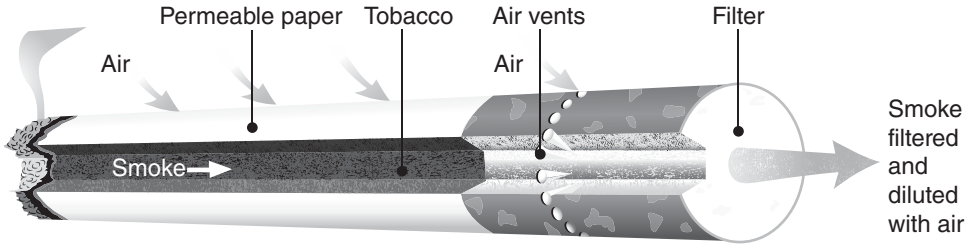


FIGURE 49.4. The modern cigarette contains a tobacco blend, paper, and usually a filter. The most common tobacco types worldwide are Burley, Oriental, and Virginia/Bright. Combustion occurs during a puff when the air drawn into the cigarette during inhalation forms mainstream smoke; combustion continues between puffs when the smoldering cigarette releases sidestream smoke into the environment from the lit cigarette end. After aging and dilution, the mixture of sidestream and exhaled mainstream smoke becomes environmental tobacco smoke (ETS). (Adapted from Thielen).[230]

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cigarettes, smoking mentholated cigarettes does not increase lung cancer risk above the rate for nonmentholated cigarettes after adjustment for total cigarette consumption (i.e., pack–years). In a case-control study of 693 lung cancer cases and 4,110 controls, the lung cancer risk for long-term smokers of menthol and nonmenthol cigarettes (≥20 years) was similar (odds ratio = 0.97, 95% CI: 0.70–1.34).[240]

Mainstream Smoke The chemicals in tobacco smoke either pass through the mouth-end cigarette condensing a short distance behind the burning cone (mainstream smoke), or exit the burning end into ambient air (sidestream smoke). Mainstream smoke becomes progressively stronger as the cigarette shortens from the addition of previously condensed material. The particulate phase accounts for 4.5–8% of mainstream smoke on a w/w basis, including nicotine, nitrosamines, metals (arsenic, beryllium, cadmium, nickel, zinc, ^{210}Po), polycyclic aromatic hydrocarbons (PAHs), and carcinogenic amines; the vapor phase accounts for ~5% on a w/w basis including ammonia, benzene, carbon dioxide, carbon monoxide, formaldehyde, hydrogen cyanide, *N*-nitrosodimethylamine, and *N*-nitrosodiethylamine.[241,242] Table 49.21 lists the main IARC Group 1 and 2A carcinogens in unburned tobacco and mainstream cigarette smoke.

Typically, stronger carcinogens (e.g., aromatic amines, metals, nitrosamines, PAHs) occur in relatively smaller amounts (0.001–0.2 μg/cigarette) than weaker IARC Group 2B carcinogens (~1,000 μg/cigarette).[179] The most prevalent carcinogens in unburned tobacco are nitrosamines (e.g., *N*′-nitrosonornicotine, NNN; 4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone, NNK).[243] Table 49.22 lists some reported ranges of selected human carcinogens released into mainstream smoke during cigarette smoking.

Sidestream Smoke Sidestream smoke differs from mainstream and environmental tobacco smoke in acute toxicity, chemical concentrations, and genotoxicity.[244] The generation of sidestream smoke occurs at lower burning temperature than mainstream smoke (i.e., 500–600°C vs. 850–950°C, respectively) in a reducing atmosphere. Sidestream smoke is slightly alkaline, whereas mainstream smoke from most common cigarettes is slightly acidic. Qualitatively, the composition is similar for sidestream and mainstream smoke; however, the yield/cigarette and the ratio of sidestream/mainstream concentrations of individual substances vary depending on specific physiochemical properties and cigarette construction. Sidestream smoke contains higher concentrations of some carcinogens than mainstream smoke (e.g., *N*-nitrosodimethylamine, *N*-nitrosodiethylamine, cadmium, nickel).[235] Table 49.23 displays estimated sidestream/mainstream cigarette smoke ratios of selected chemicals.

TABLE 49.21. Human (IARC Group 1) and probable human carcinogens (IARC Group 2A) reported in cigarette smoke and/or unburned tobacco. Cigarette smoke contains more carcinogens than unburned tobacco (i.e., cigarette tobacco and smokeless tobacco products including chewing tobacco and oral snuff) because of the formation of carcinogens during combustion. (Adapted from Borgerding and Klus).[241]

IARC Group 1 (Human Carcinogen)	IARC Group 2A (Probable Human Carcinogen)
4-Aminobiphenyl	2-Amino-3-methylimidazo (4,5-*f*)quinoline (IQ)
Arsenic	Acrylamide
Benzene	Dibenz[*a,h*]anthracene
Benzo[*a*]pyrene	Glycidol
Beryllium	Nitrogen mustard
1,3-Butadiene	*N*-Nitrosodiethylamine (DEN)
Cadmium	*N*-Nitrosodimethylamine (DMN)
Chromium (hexavalent)	Tetrachloroethylene
Ethylene oxide	
Formaldehyde	
N-Nitrosonornicotine (NNN)	
2-Naphthylamine	
Nickel	
o-Toluidine (2-methylaniline)	
^{222}Radon and decay (^{210}Po) products	
Trichloroethylene	
Vinyl chloride	

Environmental Tobacco Smoke Also known as second-hand, involuntary, or passive smoke, environmental tobacco smoke (ETS) is the aged, diluted mixture of exhaled mainstream and sidestream smoke released from the burning cigarette tip. ETS undergoes various physical and chemical changes during rapid diffusion and dispersion into the atmosphere, including reactions with chemicals in the atmosphere that are absent in tobacco smoke. Consequently, chemical concentrations in ETS vary with environmental conditions and time.[245] Although environmental tobacco smoke contains the same chemical compounds as mainstream and sidestream smoke, the concentrations, phase distributions, and component particle sizes of environmental tobacco smoke differ from mainstream and sidestream smoke.[246] Environmental tobacco smoke contains ~$^3/_4$ of the particulate matter in mainstream smoke along with very little formaldehyde; the latter reacts almost instantaneously with ammonia in the atmosphere to form hexamethylenetetramine.[241] Nicotine

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TABLE 49.22. Yield of several human carcinogens (IARC Group 1) reportedly released into mainstream cigarette smoke during smoking, expressed as μg/cigarette. (Adapted from Smith et al.).[242]

Substance	IARC Cancer Group	Reported Range (μg/Cigarette)
4-Aminobiphenyl	1	0.00019–0.005
Arsenic	1	0–1.4
Benzene	1	0.05–104
Beryllium	1	0–0.0005
Cadmium	1	0–6.67
Chromium	1	0.0002–0.5
2-Naphthylamine	1	0.0002–0.022
Nickel	1	0–0.51
Vinyl chloride	1	0.0013–0.0158

in ETS exists almost exclusively (i.e., ~95%) in the gaseous phase. Table 49.24 lists typical concentrations of selected constituents of ETS demonstrating the substantial quantitative differences in these constituents between ETS and other types of cigarette smoke. As the atmosphere dilutes sidestream smoke and ETS ages, nicotine evaporates from sidestream smoke.[247]

Smokeless Tobacco Smokeless tobacco refers to unburned tobacco that is applied to the gums or buccal mucosa, chewed (e.g., betel quid, areca nut, slaked lime, zarda), sucked (gutka, mawa, moist snuff, khaini, shammah, safa, snus, toombak), or insufflated as a fine powder (dry or liquid snuff). Most uses of smokeless tobacco involve placement of the material adjacent to the lips or between the gums and cheek rather than sniffing. The specific constituents of smokeless tobacco vary substantially by geographical region, with the largest medical literature on American and Swedish smokeless tobacco products; although the chemical concentrations within both individual contemporary products are relatively uniform, tobacco-specific nitrosamine concentrations are traditionally lower in moist Swedish snus than American snuff.[248,249] The American product contains lightly chopped, baked, or fire-cured tobacco leaves compared with finely chopped Swedish snus that contains moist, sun-cured, or air-fired tobacco leaves mixed with salts, humidifying agents, and substantially higher nicotine concentrations.[250]

The chemical composition of these tobacco products depends on the specific tobacco species/strain, growing conditions, processing/curing, and aging used to determine the pH and nicotine bioavailability.

TABLE 49.23. Estimated sidestream/mainstream ratios for the yield of some components of cigarette smoke. The actual yields depend on the physiochemical properties of the specific chemical and the cigarette construction (e.g., filter, paper, tobacco blend). (Adapted from Borgerding and Klus).[241]

Substance	Sidestream/ Mainstream Ratio
3-Methylvaleric acid	0.8–1.5
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	1–4
4-(*N*-Nitrosomethylamino) 1-(3-pydridyl)-1-butanone (NNK)	0.40
Acetaldehyde	1.4
Acetic acid	1.9–3.9
Acetonitrile	3–5
Acrolein	8–18
Ammonia	40–450
Aniline	30
Anthracene	30
Benzene	5–10
Benzo[*a*]pyrene	2–20
Cadmium	4–7
Carbon dioxide	8–11
Carbon monoxide	2.5–4.7
Catechol	0.6–0.9
Formaldehyde	36
Hydrogen cyanide	0.06–0.5
Isoprene	13–19
Methylamine	4.2–6.4
Naphthalene	17
Nicotine	2.6–7
N-Nitrosoanatabine	0.3–1
N-Nitrosodimethylamine	10–50
N-Nitrosonornicotine (NNN)	0.4–3
N-Nitrosopyrrolidine	6–30
Phenanthrene	2–30
Phenol	1.6–3.0
Pyridine	6.5–20
Quinoline	8–11
Toluene	6–8
Water	24–30

The pH influences nicotine absorption, whereas the nitrate/nitrite content affect nicotine-derived tobacco-specific *N*-nitrosamine concentrations.[251] These tobacco products contain at least 30 carcinogens, including tobacco-specific *N*-nitrosamines (e.g., *N*′-nitrosonornicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), *N*-nitrosamine acids (e.g., *N*-nitrososarcosine, *N*-nitrosoazetidine-4-carboxylic acid, 3-(methylnitrosamino)propionic acid, 4-(methylnitrosamino) butyric acid), volatile *N*-nitrosamines (*N*-nitrosodimethylamine, *N*-nitrosopyrrolidine, *N*-nitrosopiperidine), polycyclic aromatic hydrocarbons (benzo[*a*]pyrene, benz[*a*]anthracene, chrysene, benzo[*b*]fluoranthene, dibenz[*a*,*h*]-

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TABLE 49.24. Typical concentrations of some constituents of environmental tobacco smoke. (Adapted from IARC).[245]

Substance	Concentration ($\mu g/m^3$)
1,3-Butadiene	20–40
4-(*N*-Nitrosomethylamino) 1-(3-pydridyl)-1-butanone (NNK)	0.0007–0.023
Acetaldehyde	200–300
Benzene	15–30
Benzo[*a*]pyrene	0.00037–0.0017
Carbon monoxide	6,250–25,000
Formaldehyde	100–140
Nicotine	10–100
N-Nitrosonornicotine (NNN)	0.0002–0.0293

anthracene), and volatile aldehydes (acetaldehyde, formaldehyde).

Lung Cancer

Lung cancer is the leading cause of cancer-related deaths in men and women, with lung cancer mortality increasing in women from the 1930s until 2003; lung cancer mortality in men began decreasing in the 1980s.[252,253] The lung cancer incidence in women exceeded breast cancer for the first time in 1987. Approximately twice as many women as men with the same smoking history develop lung cancer; potential genetic susceptibilities in women include increased CYP1A1 expression and PAH metabolism, decreased glutathione S-transferase M1 and enhanced formation of reactive oxygen species, increased mutations of the tumor suppressor gene *P53*, and decreased activation of gastrin-releasing peptide receptor.[254] Occupational exposure to chemical carcinogens causes a relative small portion of lung cancers in men compared with tobacco smoking;[255,256] an acknowledged history of current or prior smoking occurs in ~85–90% of US lung cancer cases, primarily involving cigarette smoke.[257]

Smoking duration is the strongest determinant of lung cancer incidence; the risk is dependent, to a lesser extent, on intensity (i.e., daily cigarette consumption), based on studies using self-administered questionnaires.[258] Using questionnaire-based assessments of absolute, age-adjusted excess rates of lung cancer among smoking British physicians and multistage modeling, the hypothetical dose-response curve for absolute excess lung cancer rate fits a linear relationship to the fourth power of smoking duration and the second power (square) of smoking intensity.[259] For lung cancer and cigarette smoking, the lung cancer risk is monotonically related to cumulative smoking (pack-years). In contrast to low linear energy transfer radiation (e.g., fractionated X-ray exposure), modeling of excess odds ratios for total exposure based on pack-years suggests greater risk for a cumulative exposure delivered at a lower intensity (i.e., <20 cigarettes/day) for a longer duration than an equivalent cumulative exposure delivered at a higher intensity and shorter duration.[260] This difference may reflect different mechanisms involved with X-ray and cigarette smoke exposures. Using data from 15 case-control studies of cigarette smoking and lung cancer in the SYNERGY study, a flexible excess odds ratio model that was linear in cumulative exposure and nonlinear in exposure intensity also detected reduced effects of cumulative cigarette smoking on the higher portion of the dose-response curve (i.e., >20–30 cigarettes/day).[261] Studies using serum or urine cotinine concentrations to assess smoking intensity did not demonstrate a similar plateau on the upper portion of the dose-response curve. In a prospective study of 1,741 Norwegian volunteers with lung cancer and 1,741 matched controls (serum cotinine ≤5 ng/mL), the odds ratio of lung cancer increased linearly up to the highest exposure level (serum cotinine level of >378 ng/mL; OR = 55.1, 95% CI: 35.7–85.0).[262] These findings suggest altered smoking techniques (e.g., reduced inhalation/cigarette) and/or exposure misclassification may account for the differences in the models. Serum cotinine concentrations are measures of recent (i.e., few days) exposure, and pack-years of cigarette smoking have a limited sensitivity at lower smoking intensities.

Histology Lung cancer consists of four major histological subtypes: squamous cell carcinoma, adenocarcinoma, large cell carcinomas (primarily undifferentiated tumors), and small cell carcinomas. The first three tumor types are frequently classified together as non-small cell carcinomas. Most squamous cell and small cell carcinomas arise from the epithelial cells of the centrally located large- and medium-sized bronchi. In contrast, most adenocarcinomas arise from the epithelial cells in the peripherally located bronchioles and alveoli. Although cigarette smoking increases the risk of all histological types of lung cancer, the association is weaker between smoking and adenocarcinoma (i.e., relative risk, ~2–5) than squamous or small cell lung carcinomas. Histological patterns of smoking-related lung cancer in men and women have changed since the 1950s because of the increased incidence of adenocarcinoma compared with squamous cell carcinoma. A histological study of bronchogenic cancer in 1950 demonstrated that squamous cell carcinoma was ~17 times more common than adenocarcinoma.[263] A more recent study indicated the squamous cell carcinoma/adenocarcinoma ratio in male smokers decreased to 2.4:1 in 1970 and 1.4:1 by

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1986.[264] The ratio of women smokers decreased from 3.4:1 in 1950 to 0.57:1 by 1986. Adenocarcinoma is now the most common lung cancer type in the United States. Part of the increased prominence of adenocarcinoma may reflect the reduction in the risk of squamous cell carcinoma associated with changes in smoking habits (i.e., the lifelong use of filter cigarettes) and cigarette construction, particularly in women.[265] In a case-control study of 2,292 lung cancer patients, the odds ratio for squamous cell carcinoma in male lifelong filter and nonfilter cigarette smokers was not statistically different (OR = 0.8, 95% CI: 0.5–1.2); however, the odds ratio for squamous cell carcinoma in female lifelong filter cigarette smokers was significantly reduced (OR = 0.4, 95% CI: 0.2–0.8) compared with female lifelong nonfilter cigarette smokers. There was no reduction in the risk of adenocarcinoma for male and female lifelong filter cigarette smokers in comparison to the risks for nonfilter cigarette smokers.[266]

TABLE 49.25. Dose-response data on risk ratios for lung cancer and smoking. (Adapted from Damber and Larsson).[267]

Study	Study Type	Cigarettes/ Day	Risk Ratio
Doll and Peto[277]	Cohort	1–14	7.8
		15–24	12.7
		≥25	25.1
Hammond[275]	Cohort	1–9	4.6
		10–19	8.6
		20–39	14.7
		≥40	18.8
Cederlof et al.[276]	Cohort	1–7	2.3
		8–15	8.8
		≥16	13.9
Damber and Larsson[267]	Case-control	1–7	2.3
		8–15	7.3
		≥16	10.2

Mainstream Cigarette Smoke Tobacco smoking accounts for the vast majority of lung cancer mortality in the world.[255,267] In US birth cohorts over the last 75 years, lung cancer incidence and mortality primarily reflect patterns of active cigarette smoking.[268] The percentage of lung cancers associated with adenocarcinoma has increased dramatically since the 1980s, despite substantial reductions in the amount of tar and nicotine in cigarette smoke, partially reflecting the enhancement of nitrogen oxides and volatile tobacco-specific *N*-nitrosamines in cigarette smoke.[269] Factors contributing to lung cancer risks include coexposure to other potential carcinogens (e.g., arsenic, asbestos, cadmium, environmental tobacco smoke, PAHs, radon, vinyl chloride), diet, genetic susceptibility, hormonal influences/estrogen receptors in women with nonsmall cell lung cancer,[270,271] and chronic inflammation (e.g., HPV infections),[272] particularly in women without a smoking history.[254,257]

The risk of developing cancer from smoking is a dose-related phenomenon. Individuals smoking >40 cigarettes/day are high-risk candidates for lung cancer, whereas the increased risk in a person smoking <4 cigarettes/day is difficult to quantify. In a case–control study of 194 cases of lung cancer, the odds ratio (OR) for developing lung cancer in patients with a >40 pack-years history was 16.19 (95% CI: 5.1–51.33) compared with 8.33 (95% CI: 2.77–25.05) for smoking histories of >20–40 pack-years.[273] Cigar smoking is also causally associated with lung cancer; however, the risk of developing lung cancer is substantially lower for cigar smokers than for cigarette smokers.[235] Women appear more susceptible to the carcinogenic effects of cigarette smoke; the adjusted odds ratios for the major lung cancer subtypes at all smoking levels are consistently higher for women than men, particularly adenocarcinoma.[274] Table 49.25 enumerates the risk ratios between smokers and nonsmokers based on the number of cigarettes smoked per day in several studies.[275,276]

The risk of acquiring lung cancer from smoking declines beginning ~5 years after cessation of cigarette smoking, initially from elimination of the promoting effects of cigarette smoke.[278] Thereafter, the risk declines exponentially until mortality ratios of former smokers and nonsmokers are similar ~15–20 years after cessation of cigarette smoking.[277,279] The reduction in the elevated risk of lung cancer is partly dependent on the duration and intensity of previous smoking.

Mainstream Cigar/Pipe Smoking Although cigar, pipe, and cigarette smoke contain similar carcinogens, cigar and pipe tobacco consumption has increased while cigarette tobacco consumption has decreased. From 2000–2015, US cigarette tobacco consumption decreased by ~39% compared with increased large cigar (~180%) and pipe (~550%) tobacco consumption.[280] Most epidemiology studies indicate cigar and pipe smoking produce smaller, albeit significant lung cancer risk compared with cigarette smoking; potential factors contributing to the relatively lower risk associated with cigar/pipe smoking include less overall daily carcinogen exposure (e.g., inhalation depth, cigar size, smoking frequency, nicotine delivery).[281] Using Cox regression and random effects models in a meta-analysis of five prospective cohort studies from the

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United States, Netherlands, and Australia, the adjusted hazard ratio for lung cancer in exclusive cigar and/or pipe smokers was 2.04 (95% CI: 1.68–2.47) when compared with never-smokers of any tobacco product.[282] The risk of developing a smoking-related cancer in ever-smokers of cigars and/or pipes was also increased (overall HR = 1.07, 95% CI: 1.03–1.12). The US Cancer Prevention Study II recorded 23,589 deaths during an 18-year follow-up; Cox proportional hazard models demonstrated increased lung cancer mortality in current pipe smokers (adjusted HR = 5.00, 95% CI: 4.16–6.10) compared with never-smokers.[283] The increase in the relative risk was dose-dependent, characterized by a statistically significant increase with duration (smoking years) and intensity (pipefuls/day). The relative risk of lung cancer in exclusive pipe smokers was similar to or greater than that in cigar smokers.

Environmental Tobacco Smoke (ETS) In 1982, the IARC classified ETS as carcinogenic to humans (Group 1), with a causal association with lung cancer in adults. Estimates of the equivalency of ETS and mainstream cigarette smoking based on plasma cotinine suggest daily ETS exposure of a nonsmoking spouse to ETS from a smoking spouse ranges in a dose-dependent relationship from 0.1–1 cigarette, depending on the amount of the spouse's smoking.[284] In a population survey of English adults, the cotinine concentrations of nonsmoking spouses averaged ~0.6–0.7% of the smoking spouse.[285] The distribution of cotinine values in nonsmokers was positively skewed, with the geometric mean ranging from 0.31 ng/mL in nonsmoking households to 1.99 ng/mL when the other spouse reportedly smoked ≥30 cigarettes daily. Physical differences (e.g., age, cytotoxicity, particle size and deposition, inhalation pattern, clearance mechanism, pH, enzyme induction) between mainstream and ETS smoke and questions regarding the exposure necessary for ETS to induce and/or promote the carcinogenic effects observed in epidemiological studies complicate the extrapolation of ETS risks based on mainstream smoking data.[286,287]

Several analyses of epidemiology studies of nonsmoking spouses living with cigarette smokers indicate ETS smoke increases lung cancer risk in the nonsmoking spouse when compared with spouses living with nonsmokers.[288] These studies indicate the association between a lifelong nonsmoker living with a smoking spouse and lung cancer is relatively small (i.e., RR = ~1.1–1.3) compared with mainstream smoke and consistent with some evidence suggesting the lung cancer risk decreases significantly when the first exposure occurs after the third decade of life.[289] In a meta-analysis of 33 case-control and 4 cohort studies of lifelong nonsmokers living with smoking spouses, the estimated pooled relative risk for lung cancer in nonsmoking spouses was 1.24 (95% CI: 1.13–1.36).[290] Although most case-control and cohort studies adjusted for confounding variables did not reach statistical significance, the authors believed strongly that heterogeneity, misclassification bias, and/or confounding did not account for the elevated pooled relative lung cancer risk. Other authors disagreed with the conclusions regarding the importance of bias and confounding factors.[291,292] In a meta-analysis of 7 cohort, 25 population-based case-control, and 23 hospital-based case-control studies, the pooled relative risk for lung cancer in never-smoking spouses of tobacco smokers was 1.27 (95% CI: 1.17–1.37).[293] A meta-analysis of 22 studies of workplace environmental tobacco smoke exposure from multiple locations worldwide and lung cancer risk demonstrated similar relative risks. This study by Stayer and Bena et al. published in 2007 reported a 24% increase in lung cancer risk among workers exposed to environmental tobacco smoke (RR = 1.24, 95% CI: 1.18–1.29) with a 2-fold increased risk for workers classified as highly exposed to ETS (RR = 2.01, 95% CI: 1.33–2.60).

Smokeless Tobacco The association between lung cancer and smokeless tobacco products is relatively weaker compared with tobacco smoking.[294] In the prospective US Cancer Prevention cohort study of exclusive snuff and chewing tobacco users followed from 1982–2000 (CPS-II), the multivariate-adjusted hazard ratio for lung cancer mortality in current chew/snuff users was statistically significant (HR = 2.00, 95% CI: 1.23–3.24; n = 18) compared with nontobacco users based on questionnaires.[295] The first Cancer Prevention Study (CPS-I 1959–1972) did not detect a similar elevated risk of lung cancer mortality in current chew/snuff users (HR = 1.08, 95% CI: 0.64–1.83; n = 18). The Mumbai cohort study of 33,682 exclusive smokeless tobacco male users followed for an average of 5.5 years did not demonstrate an elevated risk of developing bronchial or lung cancer when compared with nontobacco users (adjusted HR = 1.59, 95% CI: 0.87–2.90; n = 34).[296] Similarly, the Swedish cohort study of 279,897 male construction workers followed from 1969–1992 did not find an elevated rate of lung cancer in current exclusive snuff (snus) users compared with never-tobacco users (RR = 0.8, 95% CI: 0.4–1.3; n = 15).[297]

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Nonpulmonary Cancers

Mainstream Cigarette Smoke Nonpulmonary sites causally associated with cigarette smoking include the mouth, larynx, nasal cavity (squamous cell carcinoma), nasopharynx, esophagus, stomach (adenocarcinoma), pancreas, kidney, and urinary bladder.[235] Mouth, larynx, and esophagus (squamous cell and adenocarcinoma) cancers are strongly correlated to tobacco consumption; studies of mouth, pharyngeal, and laryngeal cancers indicate cessation of smoking reduces cancer risks to near unity after ≥10 years compared with nonsmokers. In a Brazilian case-control study of 784 cases of mouth, pharynx, and larynx cancers and 1,578 noncancer controls, the relative risk of all upper aerodigestive tract cancers for ex-smokers was 1.98 (95% CI = 1.0–3.8) compared with never-smokers.[298] After quitting commercial cigarettes for >10 years, the relative risk was nonsignificant (RR = 1.45, 95% CI: 0.7–3.0) when compared with never-smokers. The relative risk of current smokers was ~6. In comparison with pharyngeal and laryngeal cancers, the relative risks for esophageal cancer based on smoking duration and intensity are somewhat lower.

Tobacco smoking is a significant contributory cause of pancreatic, bladder, and renal cell cancers.[299] In a meta-analysis of 82 published studies (1950–2007) containing epidemiological information about smoking and pancreatic cancer, the overall pancreatic cancer risk for current smokers was 1.74 (95% CI: 1.61–1.87) and 1.2 (95% CI: 1.11–1.29) for former smokers, with substantial heterogeneity between studies.[300] The results of studies on smoking and renal-cell cancer are somewhat inconsistent. In a meta-analysis of 19 case-control and 5 cohort studies, the relative risk for smoking men was 1.54 (95% CI: 1.42–1.68) and 1.22 (95% CI: 1.09–1.36) for smoking women, with a dose-response relationship between cumulative smoking history and the risk of renal-cell cancer. In an update of a prospective cohort study of 17,363 London-based male government employees (age 40–69 years) followed for 38 years, the hazard ratio for 68 deaths from kidney cancer was 0.64 (95% CI: 0.32–1.26) for former smokers and 1.29 (95% CI: 0.69–2.41) for current smokers.[301] Smoking increases the risk of transitional cell and squamous cell carcinomas of the bladder, ureter, and renal pelvis in men and women; the relationship is dose-dependent. In the 50-year follow-up of British physicians, the mortality rates/100,000/year for bladder cancer were 13.7 in never-smokers, 37.7 in smokers of 1–14 cigarettes/day, 31.8 in smokers of 15–24 cigarettes/day, and 51.4 in smokers of ≥25 cigarettes/day based on 220 bladder cancer-related deaths.[302] The mortality rate for bladder cancer in lifelong nonsmokers was 13.7.

Weaker, but significant, associations also occur between tobacco smoking and myeloid leukemia, stomach cancer, and liver cancer.[303] The risk of myeloid leukemia increases with the amount of tobacco smoked in studies with adequate design. A cohort study of 330,000 Swedish construction workers included 372 incident cases of acute and chronic myeloid leukemias.[304] The association between acute myeloid leukemia and smoking intensity was statistically significant in current smokers (RR = 1.5, 95% CI: 1.06–2.11), whereas there was no statistically significant association between smoking and chronic myeloid leukemia. When compared with never-smokers, current smokers have ~50% increased risk of developing stomach cancer. In a meta-analysis of high-quality gastric cancer studies (1997–2006), the odds ratios of current and ever-smokers developing gastric cancer were 1.57 (95% CI: 1.24–2.01) and 1.48 (95% CI: 1.28–1.71), respectively, compared with never-smokers.[305] After quitting for 5–15 years, the difference in gastric cancer incidence between never-smokers and ex-smokers becomes statistically non-significant.[306] In a meta-analysis of 38 cohort and 58 case-control studies, almost exclusively from Asia, the adjusted summary relative risk of liver cancer for current smokers was 1.51 (95% CI: 1.37–1.67) and 1.12 (0.78–1.60) for former smokers compared with never-smokers.

The risk of developing colorectal cancer from cigarette smoking is relatively small. A meta-analysis of 36 cohort studies demonstrated a 15% increase in colorectal cancer incidence and a 27% increase in colorectal cancer mortality, with the association stronger for rectal than colon cancer. Data suggest the association between colorectal cancer and smoking may primarily result from a subtype of colorectal cancer developing during hyperplastic polyp progression.[125] The association between breast cancer and tobacco smoking is weaker and less consistent than that between most other smoking-related cancers, with relative risks ranging from 1.2–1.3. Tobacco smoking does not significantly affect the cancer incidence of the postmenopausal uterus, prostate, or thyroid.[125] Confounding factors associated with cigarette smokers when compared with nonsmokers in epidemiology studies include higher alcohol consumption, physical inactivity, lower fruit/vegetable consumption, higher fat/meat consumption, and less screening for colorectal cancer.

Mainstream Cigar/Pipe Smoke The risk of developing nonpulmonary cancers is substantially lower in cigar/pipe smokers than in cigarette smokers.[280] Although the risk of lung cancer is considerably lower for cigar smokers than for cigarette smokers, cigar smoking is causally

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associated with cancer of the oral cavity, pharynx, pancreas, and urinary bladder.[307] In an analysis of pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium comprising 13,935 cases and 18,691 controls in 19 studies from 1981–2007, the risk of developing head and neck cancer in exclusive cigar smokers was 3.49 (95% CI: 2.58–4.73; n = 110 cases) and 3.71 (95% CI: 2.59–5.33; n = 77 cases) in exclusive pipe smokers.[308] The study excluded esophageal, nasopharyngeal, and salivary gland cancers. A meta-analysis of five cohort studies indicated exclusive cigar and/or pipe smoking is associated with a statistically significant increase in the risk for head and neck cancers (HR = 1.51, 95% CI: 1.22–1.87) and liver cancers (HR = 1.56, 95% CI: 1.08–2.26) when compared with never-smokers based on questionnaire data.[282] The hazard ratios for pancreatic cancer (HR = 1.19, 95% CI: 0.91–1.57; n = 128 cases) and bladder cancer (HR = 1.16, 95% CI: 0.98–1.37; n = 242 cases) were not statistically different than never-smoker rates. The US Cancer Prevention Study II detected statistically significant increases in multivariable-adjusted hazard ratios in current exclusive pipe smokers for death from oropharyngeal cancer (HR = 3.90, 95% CI: 2.15–7.08; n = 15 cases), laryngeal cancer (HR = 13.1, 95% CI: 5.2–33.1; n = 10), and pancreatic cancer (HR = 1.61, 95% CI: 1.24–2.09; n = 64) compared with never-smokers.[283] The hazard ratio for bladder cancer was not statistically different from never-smokers (HR = 1.50, 95% CI: 0.94–2.39; n = 20 cases).

Environmental Tobacco Smoke The associations between environmental tobacco smoke and risk of nonpulmonary cancers are relatively weak and inconsistent, including cancers of the nasopharynx, brain and central nervous system, stomach, colon, rectum, pancreas, liver (hepatocellular carcinoma), kidney (renal cell carcinoma), urinary bladder, cervix, ovary, and testes.[309] Although large cohort studies in Europe and North America do not support an association between ETS and breast cancer,[310,311] subgroup analysis of some case-control studies suggests an increased breast cancer risk in premenopausal women exposed to ETS;[312] however, weaker association of cohort studies and lack of a plausible explanation why the effect on lung cancer risk would be much greater for ETS than mainstream smoking limit conclusions regarding causation.

Major childhood cancer sites are extremely heterogeneous, and subtypes are difficult to study because of the lack of adequate sample sizes and exposure assessments. Although these studies suggest the possibility of an association between preconception paternal and/or maternal smoking and several childhood cancers (e.g., hepatoblastoma, RR ≅ 2.0–5.5;[313] leukemia, RR ≅ 1.5–4),[314] conclusions regarding causality are limited by small sample sizes, adequate adjustment of cofounders (e.g., socioeconomic status, race, parental age, sex, birth weight, gestational age, age at exposure), and potential recall bias. Maternal tobacco smoking during pregnancy generally demonstrated inconsistent results, including modest increases in risk, null results, and inverse relationships. Most evidence associating other childhood cancers is inconsistent or null, including brain cancer, Ewing's sarcoma, germ cell tumors, neuroblastoma, rhabdomyosarcomas, reticuloendothelial sarcomas, soft tissue sarcomas, and Wilms' tumor.[125]

Smokeless Tobacco Several factors complicate the determination of the magnitude and significance of the cancer risk following the use of smokeless tobacco products including small case numbers and inconsistent results, recall bias from the use of questionnaires, potential misclassification of cancer coding and smoking status, inconsistent definitions of exposure, and wide variation in the carcinogenic potency of smokeless tobacco products. Analysis of 53 oral tobacco products from 5 World Health Organization regions detected an ~500-fold variation in unionized nicotine content (0.2–99.1%) and extremely large variations in tobacco-specific *N*-nitrosamines with 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) ranging from 0.0045–516 μg/g product.[315] The latter carcinogen exists in some products (e.g., khaini, toombak, zarda) in particularly high concentrations. Consequently, the results of studies differ between countries.

The association between smokeless tobacco use and cancer is strongest for oropharyngeal cancer in the United States, whereas the association is weaker for the use of Scandinavian snuff.[294] In a US population-based case-control study of 1,046 cases and 1,239 frequency-matched controls, the association between ever-smokeless tobacco use and squamous cell carcinoma of the head and neck was not statistically significant (OR = 1.20, 95% CI: 0.67–2.16).[316] The association was statistically significant comparing lifetime smokeless tobacco users with ≥10 years of use and never-users (OR = 4.43, 95% CI: 1.47–13.36; n = 16 cases); however, the wide confidence intervals suggest design issues (recall bias, confounding). Although a meta-analysis of US and Asian epidemiological data found an increased risk of oral cancer (overall RR = 2.6, 95% CI: 1.3–5.2), northern European studies did not confirm the increased risk (RR = 1.0, 95% CI: 0.7–1.3).[317] Analysis of pooled data from 11 US

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case-control studies from 1981–2006 in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium demonstrated a statistically significant difference in the risk of head and neck cancer between never-cigarette smoking snuff users and nontobacco users (OR = 1.71, 95% CI: 1.08–2.70; $n = 44$ cases), but not among never-cigarette smoking, chewing tobacco users (OR = 1.20, 95% CI: 0.81–1.77; $n = 61$ cases).[318] The study did not detect a dose-response relationship between the intensity of snuff use or tobacco chewing and the development of head and neck cancer. The association was strongest for oral cancers in ever snuff users (OR = 3.01, 95% CI: 1.63–5.55; $n = 20$ cases) and ever chewing tobacco users (OR = 1.81, 95% CI: 1.04–3.17; $n = 23$ cases); however, the dose-response relationship was not statistically significant. Mortality from oropharyngeal cancers was not increased in exclusive US snuff and chewing tobacco users in the Cancer Prevention Studies when compared with never-tobacco users based on questionnaire responses.[295] Oral cancer was not associated with Scandinavian moist snuff (snus) when comparing current male construction workers using snus with never-users of any tobacco products (RR = 0.9, 95% CI: 0.4–1.8; $n = 9$ cases).[297] Similarly, in a prospective study of 10,136 Norwegian men enrolled since 1966, the incidence of oropharyngeal cancer was not increased in current snus users compared with never-tobacco users (RR = 1.13, 95% CI: 0.45–2.83; $n = 6$).[319] The relative risk of pancreatic cancer was borderline significant in current snus users (RR = 1.60, 95% CI: 1.00–2.55; $n = 27$ cases).

Alcohol

Exposure

Most alcoholic beverages contain primarily ethanol and water along with volatile and nonvolatile flavoring compounds and contaminants. Although the exact constituents of many alcoholic beverages are trade secrets, potential carcinogens include acetaldehyde (a metabolite that disrupts DNA repair, methylation, and synthesis.), aflatoxins, arsenic, asbestos, nitrosamines, and ethyl carbamate (urethane); the latter is an IARC Group 2A carcinogen present in alcoholic beverages (whisky, wine) and fermented food products (e.g., bread, cheese, soy sauce).[320] These alcohol contaminants are usually present in relatively low concentrations, particularly in more current times.[321] Typically, the ethanol source in alcoholic drinks is biological rather than synthetic because of the potential presence of impurities in ethanol produced from ethylene. In the general population, individual-level alcohol consumption data are preferred to sales data as an exposure measure; the former allows comparison of drinking patterns between population subgroups and evaluation of medical consequences after adjustment for confounders and individual characteristics. However, self-reported alcohol consumption accounts for only 40–60% of total alcohol sales, particularly among heavy drinkers.[322,323] In addition to recall bias, general population surveys usually canvas private households rather than populations without permanent locations (e.g., homeless, institutionalized residents, prisoners, students, military personnel); these groups are often associated with heavy drinking patterns.[324] Factors important in the evaluation of alcohol consumption include average volume, alcohol consumption status, frequency, and occurrence/volume of binge drinking. The alcohol content in standard measures for most alcoholic drinks (e.g., wine, beer, spirits) ranges from 10–14 g; however, these measures vary between countries. The US Department of Agriculture food consumption tables list the following ethanol content for standard alcoholic drinks: wine, 11.3 g; regular beer, 12.8 g; light beer, 11.3; and hard liquor, 14.0 g.[325] The Dietary Guidelines for Americans define 14 g of ethanol as a standard drink, equivalent to approximately 12oz of beer, 5 oz of wine, and 1.5 oz of distilled spirits. In Canada, the standard drink typically contains 13.6 g compared with 8 g in the UK and 10 g in Australia and New Zealand; however, several studies indicate actual serving sizes of drinks vary substantially from the "standard drink."[326] Assuming a standard drink contains 14 g of ethanol, the corresponding volumes are typically 330 mL of beer, 150 mL of wine, and 36 mL of hard liquor. The definition of heavy drinking varies between institutions and regions, with heavy drinking variously defined as ≥5 drinks or >50–60 g of alcohol.[327,328] Drinking in moderation typically is a daily drinking pattern not exceeding two drinks in men and one drink in women. Evidence is insufficient to support an association between daily alcohol consumption in men drinking ≤2 standard drinks or women drinking ≤1 standard drink and cancers of the esophagus, larynx, oral cavity, or pharynx.

Cancer Sites

The US National Toxicology Program (USNTP) lists alcohol beverage consumption as a known carcinogen based on sufficient evidence of carcinogenicity from human studies. IARC classifies alcoholic beverages as human carcinogens (Group 1) based on sufficient evidence in humans and experimental animals, including sufficient evidence of carcinogenicity in experimental animals for the carcinogenicity of the ethanol metabolite, acetaldehyde. The biological basis underlying the association between alcohol consumption and cancer is

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not well defined; potential mechanisms include reactive metabolites, acetaldehyde-induced cell proliferation from disruption of DNA synthesis, methylation, and repair, oxidative stress with lipid peroxidation, reduced retinoic acid concentrations, alteration of hormone levels/estrogen receptors, and epigenetic influences (e.g., decreased methylation). Both organizations categorize oral cavity, pharynx, larynx, and esophagus as sites of alcohol-related cancers. Genetic epidemiological studies suggest alcohol dehydrogenase 1B variant (*ADH1B*1/*1*) polymorphism and the heterozygous aldehyde dehydrogenase 2 (*ALDH2*) genotype increase interindividual susceptibility to esophageal cancer and cancers of the upper aerodigestive tract combined, particularly the hypopharynx in Japanese studies with a high prevalence of *ALDH2* genotype.[329] These studies indicate the importance of the variant allele and elevated acetaldehyde concentrations in the development of head and neck cancers. East Asians and Caucasians with the *ADH1B*1/*1* genotype have an elevated risk of excessive alcohol consumption because of less active alcohol dehydrogenase.[330]

The IARC also associates alcohol beverages with cancer in the colorectum, liver, and female breast, whereas the NTP considers the evidence supporting cancer in the latter two sites weaker than the above four cancer types and possibly causal. Studies associating other cancer sites are inconsistent and/or limited in determining a causal relationship including bladder, brain, cervix, endometrium, Hodgkin disease, leukemia, lung, melanoma, multiple myeloma, ovary, pancreas, prostate, stomach, testis, thyroid, vagina, and vulva.[321] The risks of developing alcohol-related cancers do not typically vary significantly by beverage type or sex.

Many studies evaluate current drinking patterns (e.g., alcohol use at the beginning of a cohort or prior to diagnosis in case-control studies); however, lifetime alcohol consumption is also associated with elevated risks of cancer at multiple sites. A meta-analysis of long-term alcohol consumption and cancer comparing the highest and lowest intake categories demonstrated elevated adjusted, pooled relative risks for oral cavity and pharynx (RR = 4.84, 95% CI: 2.51–9.32), larynx (RR = 2.25, 95% CI: 1.49–3.42), esophagus (RR = 6.71, 95% CI: 4.21–10.70), and colorectal (RR = 1.45, 95% CI: 1.22–1.71) cancers.[331] The association between breast cancer and cumulative alcohol consumption was weak and nonlinear, whereas the dose-response relationship for colorectal cancer was modest and linear. In the National Institutes of Health-AARP Diet and Health Study of ~500,000 persons, the hazard ratio comparing light (0.5–>1 drink/day) and nonalcohol drinkers was 0.89 (95% CI: 0.82–0.96), whereas the hazard ratio for heavy alcohol drinkers (>7 drinks/day) was not statistically significant at 1.11 (95% CI: 1.00–1.24).[332] The authors noted a modest increase in adenocarcinoma among heavier drinkers and a nonlinear reduction in squamous cell carcinoma that attenuated with increasing alcohol consumption.

Oral Cavity/Pharynx Cancers of the mouth and pharynx are consistently and strongly associated with alcohol consumption and tobacco smoking in a dose-related relationship across various regions and populations after adjustment for confounding (e.g., smoking), particularly among heavy drinkers. Compared with nondrinkers, the risk for these cancers in heavy drinkers (i.e., regular consumption of ~50 g ethanol daily) is ~3-fold with a range of ~4–8.[321] Risks of developing these cancers is small and difficult to detect in light alcohol drinkers (<1–2 drinks daily).[333,334] Elevated risks of mouth and pharyngeal cancers occur in nonsmoking and smoking drinkers of alcoholic beverages; the risk of these cancers with smoking and drinking alcoholic beverages is multiplicative, characterized by higher risks than nondrinking smokers or nonsmoking drinkers. Most studies demonstrate synergistic effects of cigarette smoking and alcohol consumption, primarily as a multiplicative interaction.[335] Heterogeneity among studies, small number of cases in nondrinking, nonsmoking individuals, and difficulty identifying the amount of each type of drink consumed complicate the determination of risks associated with each type of alcoholic beverage. In US studies, beer consumption has the highest risk of developing oral cavity/pharyngeal cancers,[336] whereas wine and hard liquor have the highest risks in Italy[337] and Latin America,[335] respectively. The risk of these cancers is lower in former than current alcoholic beverage drinkers, with risks returning to levels associated with nondrinkers after 10–20 years.[338]

Larynx Multiple studies across various populations throughout the world associate laryngeal cancer with alcohol consumption and tobacco smoking; this relationship is dose-dependent with an ~2-fold increased risk when comparing heavy drinkers (>50 g alcohol daily) with nondrinkers and light drinkers.[321] In a meta-analysis of 38 case-control, 2 cohort studies, the relative risk of developing laryngeal cancer was 1.90 (95% CI: 1.59–2.28) for alcohol drinkers compared with nondrinkers.[339] The risk of light alcohol drinking (≤1 drink/day) was not statistically significant (RR = 0.88, 95% CI: 0.71–1.08), whereas elevated relative risks were detected in moderate drinkers (>1–<4 drinks/day; RR = 1.47, 95% CI: 1.25–1.72) and heavy drinkers (≥4 drinks/day; RR = 2.62, 95% CI:

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2.13–3.23). Tobacco smoking is a strong risk factor for developing laryngeal cancer with the interaction of tobacco smoking and heavy alcohol drinking being multiplicative.[340] Increased risk of laryngeal cancer occurs in alcohol drinkers and abstainers. In a pooled analysis of never-tobacco users, the odds ratio for laryngeal cancer in heavy drinking (≥5 drinks/day) never-tobacco users was 2.81 (95% CI: 1.49–5.27; $n = 65$).[341] Based on limited information, data suggest the most frequently consumed beverage in each population is usually associated with the highest risk of developing laryngeal cancer.[342]

Esophageal The risk of developing esophageal squamous cell carcinoma is consistently elevated in most studies worldwide, with an overall ~2-fold increase in heavy alcohol drinkers (>50 g alcohol/day) compared with nondrinkers after controlling for tobacco smoking. The specific risk varies with study type, outcome measures, drinking intensity, population characteristics, and histological type. Most studies demonstrate a dose-response relationship between alcohol consumption and the risk of esophageal squamous cell cancer. In a prospective cohort study on *mortality* from esophageal cancer in the American Cancer Society Cancer Prevention Study I, the adjusted relative risk for 6 drinks daily was 5.79 (95% CI: 3.44–9.74, $n = 22$) compared with 1.61 (95% CI: 0.94–2.77, $n = 18$) for 2 drinks daily.[332] Elevated risks of esophageal squamous cell cancer are not consistently related to beverage type.[343]

Studies of the interaction of tobacco smoking and alcohol consumption indicate the relationship is usually multiplicative, with a few studies suggesting a relationship between additive and multiplicative. Compared with never-users, the adjusted risk of esophageal squamous cell carcinoma is significantly elevated in heavy Swedish users of tobacco and alcohol (OR = 23.1, 95% CI: 9.6–56.0).[343] The presence of the heterozygous aldehyde dehydrogenase two genotype increases acetaldehyde concentrations in blood and saliva; this polymorphism increases the susceptibility of these individuals to the development of esophageal squamous cell carcinoma, particularly in Asian studies where this polymorphism and cigarette smoking are relatively high.[344,345] The association between alcohol and esophageal squamous cell carcinoma is relatively weak in the absence of tobacco use. European case-control studies of former drinkers indicate that the risk of squamous cell carcinoma decreases after 10 years of abstinence.[346] Compared with nonsmoking, current drinkers, the risk of esophageal cancer decreased significantly after 10 years of abstinence (OR = 0.37, 95% CI: 0.14–0.99).[347]

Adenocarcinoma accounts for ~5% of esophageal cancers; in comparison to esophageal squamous cell carcinoma, the association between alcohol consumption and esophageal adenocarcinoma is weak and inconsistent.[321] Most case-control studies of esophageal cancer do not demonstrate a statistically significant increased risk of esophageal adenocarcinoma, even with high alcoholic beverage consumption levels. In a Swedish population-based, case-control study, the multivariately adjusted risk of developing esophageal adenocarcinoma in heavy drinkers (>70 g alcohol/day) was not significantly elevated compared with never-alcohol users (RR = 0.6, 95% CI: 0.3–1.1).[343]

Colorectum Cohort studies and meta-analyses suggest a modestly increased colorectal cancer risk with the consumption of alcoholic beverages, primarily with moderately heavy alcohol consumption (e.g., >30 g alcohol/day).[348] In a meta-analysis of eight European and North American prospective cohort studies, increased colorectal cancer risk was limited to persons consuming ~≥2 drinks daily.[349] Compared with nondrinkers, the adjusted, pooled multivariate relative colorectal cancer risk for consumers of 2–3 drinks daily was 1.16 (95% CI: 0.99–1.36) and 1.41 (95% CI: 1.16–1.72) for persons consuming ≥4 drinks daily. Adjustment for the multivariate analysis included age, family history of colorectal cancer, height, education, physical activity, tobacco smoking, body mass index, use of nonsteroidal anti-inflammatory drugs/multivitamins, and energy intake/intake. In a meta-analysis of 27 cohort and 34 case-control studies using the random effects model and nondrinkers or occasional alcohol drinkers as referents, the estimated summary relative risk for moderate drinkers (2–3 drinks/day) was 1.21 (95% CI: 1.13–1.28) and 1.52 (95% CI: 1.27–1.81) for heavy drinkers (≥4 drinks/day).[350] The RR for light drinkers (≤1 drink/day) was 1.00 (95% CI: 0.95–1.05). For heavy drinkers, the association between colorectal cancer and alcohol consumption was stronger in Asian compared with Western populations (RR = 1.81, 95% CI: 1.33–2.46). A majority of prospective cohort studies of alcohol consumption and colorectal cancer did not detect statistically significant associations, while most positive cohort studies evaluated Japanese men or men of Japanese descent.[321]

Studies on the dose-response relationship between colorectal cancer and alcohol consumption are inconsistent; tobacco smoking does not appear to affect the relationship between colorectal cancer and alcohol use. Some studies suggest the possibility of a J-shaped dose-response curve for moderate alcohol consumption (≤3 drinks/day). In a Greek case-control study of 250

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consecutive patients initially diagnosed with colorectal cancer and matched community controls, the odds ratio for moderate alcohol intake in men (12–35 g alcohol/day) was 0.35 (95% CI: 0.16–0.74) compared with controls (<12 g/day); the odds ratio for moderate intake in women was 0.40 (95% CI: 0.18–0.91).[351] The odds ratio for heavy drinkers (>48 g/day) was statistically significant only in men (OR = 3.45, 95% CI: 1.35–8.83).

Liver Heavy, but conceivably not light, consumption of alcoholic beverages is an independent risk factor for the development of primary liver cancer (hepatocellular carcinoma, HCC) based on worldwide cohort and case-control studies. Potential recall bias and altered ethanol intake from alcohol-related illness (e.g., cirrhosis) prior to the development of liver cancer complicate the interpretation of the precise risks associated with alcohol intake and liver cancer;[352] however, the risk from alcohol consumption is more moderate for liver cancer than upper aerodigestive tract cancers.[353] In a meta-analysis of six primarily nested case-control studies, the pooled relative risk (RR) for HCC in heavy drinkers (≥6 drinks/day, >75 g ethanol/day) compared with nondrinkers was 1.22 (95% CI: 1.10–1.35) with no significant heterogeneity ($I^2 = 0\%$, $P = 0.786$).[354] The pooled RR for moderate drinkers (<3 drinks/day) and HCC was not statistically significant (RR = 0.91, 95% CI: 0.81–1.02), based on 16 studies with significant heterogeneity ($I^2 = 65.6\%$, $P < 0.001$). In a meta-analysis of 2,294 cases from 17 case-control and 3 cohort studies, the pooled RR for liver cancer in heavy drinkers (≥~7 drinks/day) was 1.86 (95% CI: 1.53–2.27) compared with a RR of 1.17 (95% CI: 1.11–1.23) for light drinkers (<2 drinks/day).[352] A meta-analysis of light drinkers in 7 cohort and 13 case-control studies did not detect a statistically significant risk of liver cancer (RR = 1.03, 95% CI: 0.90–1.17).[355]

Confounders for HCC include tobacco smoking, aflatoxin-contaminated food, nonalcoholic fatty liver disease, and hereditary hemochromatosis. Most, but not all, cases of HCC involve cirrhotic livers with the cirrhosis being part of the pathogenic process of liver carcinogenesis. Chronic infections by hepatitis B and C viruses (HBV, HCV) are major confounders in studies of liver cancer, with an estimated 20-fold increase in HCC risks.[356] In a meta-analysis of 32 case-control studies, the odds ratio (OR) for HBsAg positivity and anti-HCV/HCV RNA negativity was 22.5 (95% CI: 19.5–26.0), whereas the OR for anti-HCV/HCV RNA positivity and HBsAg negativity was 17.3 (95% CI: 13.9–21.6). The increased risk of primary liver cancer occurs in HBV/HCV infected and uninfected individuals.

Female Breast Most recent case-control and cohort studies on the association between breast cancer and ethanol suggest moderate and heavy alcohol consumption (i.e., >1–2 drinks/day) increases the relative risk of breast cancer ~50–100%.[157,357] A pooled analysis of 6 cohort studies revealed a multivariate-adjusted relative risk of 1.41 (95% CI: 1.18–1.69) for 2–5 drinks/day compared with nondrinkers as measured by dietary questionnaire.[358] The risk was not linear as the risk of breast cancer was not significantly increased in women consuming >5 drinks/day; however, in a pooled analysis of 58,515 women with breast cancer (Collaborative Group on Hormonal Factors on Breast Cancer), the risk of breast cancer increased linearly with increasing alcohol consumption.[359] Compared with abstainers, the pooled RR was 1.32 (95% CI: 1.19–1.45, $P < 0.00001$) for women consuming 3–4 drinks daily, whereas the risk of breast cancer in women drinking >4 drinks (median = 58 g ethanol) daily was 1.46 (95% CI: 1.33–1.61, $P < 0.00001$). The relative risk of breast cancer for women consuming 1½ drinks/day was slight (RR = 1.13, 95% CI: 1.07–1.20). Smoking status (i.e., ever-smokers vs. never-smokers) did not affect breast cancer rates in alcohol consumers.

Most case-control studies have not demonstrated a dose-response relationship between female breast cancer and cumulative alcohol consumption,[360,361,362] with the exception of the Longnecker et al. study of non-Hispanic white and Hispanic women in the Cancer Surveillance Program of Los Angeles County.[363] The latter study demonstrated a linear dose-response relationship between alcohol consumption and breast cancer risks, with the exception of women consuming ≥46 g of alcohol daily for a lifetime (OR = 0.94, 95% CI: 0.46–1.93; $n = 16$ cases).

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, the incidence rate ratio per 10 g of alcohol/day increasing recent alcohol intake for 4,285 cases of invasive breast cancer followed for an average of 6.4 years was 1.03 (95% CI: 1.01–1.05).[364] When adjusted for confounding, the risk of breast cancer did not correlate to lifetime alcohol intake. The risk of breast cancer in women using alcoholic beverages does not vary with age at diagnosis, beverage type, oral contraceptive use or hormone replacement, family history of breast cancer, tobacco smoking, menopausal status, or child-bearing patterns.[321]

Pharmaceutical Preparations

The successful treatment of cancer patients and some nonmalignant conditions revealed that certain chemo-

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therapeutic agents produce hematopoietic and lymphatic cancers.

Table 49.26 lists the therapeutic agents associated with recognized or suspected human cancers. Radiation and chemotherapeutic drugs are frequent adjunctive agents.[365] Breast, thyroid, and bone marrow are the most susceptible organs to radiation carcinogenesis, whereas bone marrow is frequently susceptible to adverse effects from chemotherapy with the combination of intensive radiotherapy and chemotherapy, particularly leukemogenic.[366] Coal tar is a complex mixture of polycyclic aromatic hydrocarbons (PAHs) and tumor initiators used for >100 years in various vehicles for the treatment of psoriasis; potent corticosteroids have replaced pharmaceutical coal-tar preparations because of their far superior efficacy and limited safety data on the latter.[367] Some,[368] but not all,[369,370] studies of the application of coal tar prior to UV radiation treatment of psoriasis (Goeckerman therapy) associate the treatment with an increased risk of skin cancer. Therapeutic drugs associated with cancer in experimental animals but with inadequate human epidemiological evidence (IARC Group 2B, possible carcinogen) include dantron, digoxin, hydrochlorothiazide, methylthiouracil, metronidazole, mitoxantrone, niridazole, panfuran S, pentosan polysulfate sodium, phenazopyridine, phenoxybenzamine, phenobarbital, phenolphthalein, phenytoin, primidone, propylthiouracil, sulfasalazine, triamterene, zalcitabine, and zidovudine (AZT).[371] Some of these agents are suspected tumor promoters (e.g., digoxin with its structural homology to steroid hormones and association with breast cancer). Tumors associated with hormone therapy typically occur in organs responsive to hormonal stimulation. Diethylstilbestrol (DES) acts transplacentally on the vagina and cervix of female offspring; DES may also affect the testicle of male offspring of mothers exposed *in utero* to DES. Epidemiology studies suggest estrogen replacement therapy and sequential oral contraceptives increase the incidence of endometrial cancer, whereas anabolic steroids probably increase the incidence of liver cancer (IARC Group 2A).[372] The IARC classifies phenobarbital as a possible carcinogen (Group 2B) based on inadequate evidence in humans and sufficient evidence in rodents. In mice, phenobarbital consistently produces hepatocellular adenomas and carcinomas, whereas rats less consistently develop hepatocellular adenomas. The sequential administration of phenobarbital and carcinogens enhances the incidence of hepatocellular preneoplastic foci, adenomas, and carcinomas, consistent with epigenetic effects. *In vitro* and *in vivo* studies of phenobarbital demonstrate proinflammatory effects on hepatic mesenchyme and mesenchymal-epithelial interactions along with the release of tumor necrosis factor alpha from mesenchymal cells and inhibition of apoptosis in hepatocytes.[373]

Natural Carcinogens

Potential environmental carcinogens include naturally occurring, semisynthetic, and synthetic chemicals, radiation (fallout, solar, radon), and some biological agents (viruses, bacteria, fungi, parasites).[374] Although the environment contains many substances that increase cancer incidence in laboratory animals following exposure to high carcinogen doses, only a few of these animal carcinogens (e.g., tobacco, asbestos, aflatoxin-contaminated food) contribute significantly to human cancers based on our present knowledge. The risk of human cancer from these agents at doses typically encountered in the environment is not well defined, except for biological agents, tobacco use, and heavy contamination with aflatoxins, particularly with hepatitis B virus (HBV) coinfection.

Biological Agents

Epidemiological studies associate certain retroviruses with several hematological malignancies, including human T-lymphocyte viruses and T cell malignancies,[375] human immunodeficiency viruses and AIDS-associated lymphomas,[376] hepatitis B/hepatitis C, viruses, and liver cancer,[377] and Epstein–Barr virus with nasopharyngeal cancer.[378] Hepatitis D is not considered a carcinogen (IARC Group 3). Table 49.27 lists some biological agents associated with human cancers by the International Agency for Research on Cancer (IARC).

Epstein–Barr virus (EBV) was the first oncogenic virus discovered when Epstein et al. demonstrated EBV particles in cultured lymphoblasts from Burkitt's lymphoma.[379] Other cancers associated with EBV include Hodgkin lymphoma, immunodeficiency-related non-Hodgkin lymphoma, nasopharyngeal carcinoma, and nasal-type extranodal natural killer (NK)/T cell lymphoma. Human immunodeficiency virus type 1 (HIV-1) is associated with increases in the risks of Hodgkin lymphoma, genital cancers including invasive anal, vaginal, vulvar, and penile cancers, conjunctival eye cancer, nonmelanoma skin cancer, non-Hodgkin lymphoma, Kaposi sarcoma, and cervical cancer.[380] The latter three are AIDS defining cancers used to diagnose acquired immunodeficiency syndrome (AIDS). Most of the cancers associated with HIV-1 occur after coinfection with another cancer-causing virus. Human T cell lymphotropic virus type 1 (HTLV-1) causes adult T cell leukemia/lymphoma, with a high percentage of patients demonstrating high anti-HTLV-1 antibodies

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TABLE 49.26. Therapeutic agents associated with (Group 1, carcinogenic) or suspected of (Group 2A, probable) causing an increased risk of human cancer in specific tissues based on epidemiological studies, animal data, and specific IARC criteria for each classification and group (https://monographs.iarc.fr/agents-classified-by-the-iarc/). (Adapted from Agents Classified by the IARC Monographs, WHO).

Agent	Associated or Suspected Neoplasm	IARC Classification of Epidemiological Evidence[a]	IARC Group[a]
Alkylating agents (busulfan, cyclophosphamide, melphalan, methyl-CCNU[b])	Acute myeloid leukemia, bladder	Sufficient	1
Inorganic arsenicals	Skin, liver	Sufficient	
Azathioprine	Non-Hodgkin's lymphoma, squamous cell skin carcinoma	Sufficient	1
Chlornaphazine	Bladder	Sufficient	1
Chlorambucil	Acute myeloid leukemia	Sufficient	1
Coal tar	Nonmelanoma skin cancer	Sufficient	1
Cyclosporin	Non-Hodgkin's lymphoma, squamous cell skin carcinoma, enhanced risk at multiple sites	Sufficient	1
Diethylstilbestrol (nonsteroidal estrogen)	Vaginal/cervix (clear cell adenocarcinoma) cervix/testis (squamous cell carcinoma) from *in utero* exposure; female breast cancer from exposure during pregnancy; endometrium	Sufficient	1
Estrogen – menopausal			
Estrogen-only	Endometrium, ovary, female breast	Sufficient	1
Estrogen and progesterone	Endometrium, female breast	Sufficient	1
Estrogen and progesterone – premenopausal contraceptives	Female breast, cervix, liver	Sufficient	1
5-Methoxypsoralen with UV light	Squamous cell skin carcinoma	Sufficient	1
MOPP chemotherapy (combined mechlorethamine, vincristine, procarbazine, prednisone)	Acute myeloid leukemia, lung	Sufficient	1
Phenacetin-containing analgesic mixtures	Renal pelvis, ureter	Sufficient	1
Tamoxifen	Endometrium	Sufficient	1
Thiotepa	Leukemia	Sufficient	1
Thorotrast	Hepatic angiosarcoma	Sufficient	1
Treosulfan	Acute myeloid leukemia	Sufficient	1
Androgenic (anabolic) steroids, oxymetholone	Liver	Limited	2A
Chloramphenicol	Aplastic anemia, leukemia	Limited	2A
Etoposide[c]	Acute myeloid leukemia	Limited	2A
Nitrogen mustard	Squamous cell skin cancer, possibly leukemia	Limited	2A
Pioglitazone	Bladder	Limited	2A
Teniposide (semisynthetic podophyllotoxin derivative)	Acute myeloid leukemia	Limited	2A

[a] International Agency for Research on Cancer classification; [b] Methyl-CCNU = 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea; [c] Etoposide with cisplatin and bleomycin is classified as a Group 1 (human) carcinogen increasing the risk of acute myeloid leukemia.

and host cells (CD4 T cells) producing oncogenic viral proteins; this retrovirus infection precedes diagnosis of adult T cell leukemia/lymphoma based on examination of monoclonal insertion sites in tumors.[381] The association between human papilloma virus and cervical cancer is strongly based on epidemiological studies and mechanistic data. HPV 16 and 18 are also associated with cancers of the vulva, vagina, penis, anus, and oral cavity.[382] Infection with Kaposi sarcoma-associated herpesvirus causes Kaposi sarcoma, a plasmablastic variant of multicentric Castleman disease, and primary effusion lymphoma primarily in immunosuppressed patients.

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TABLE 49.27. Some biological agents associated with human cancers using criteria established by the International Agency for Research on Cancer (IARC) and the US National Toxicology Program (USNTP). (Adapted from Lagiou et al.).[146]

Cancer Site	Biological Agent
Anal cancer	Human papilloma viruses (HPV 16, 18, 33), human immunodeficiency virus 1
Bladder, urinary	*Schistosoma hematobium*
Cervical cancer	Human immunodeficiency virus type 1, human papilloma viruses 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, but not types 6 or 11[a]
Cholangiocarcinoma	*Clonorchis sinensis*, *Opisthorchis viverrini*
Leukemia, adult T cell	Human T cell lymphotropic virus type 1
Liver	*Aspergillus flavus*/*parasiticus* (Aflatoxins B1, B2, G1, G2), Hepatitis B/C viruses
Lymphoma, non-Hodgkin's	Human Epstein–Barr virus (immunosuppression-related), human immunodeficiency virus type 1, but not type 2
Lymphoma, Burkitt's, extranodal NK/T cell, and Hodgkin	Human Epstein–Barr virus (human herpesvirus 4)
Lymphoproliferative diseases	Human Epstein–Barr virus (human herpesvirus 4)
Nasopharyngeal cancer	Human Epstein–Barr virus (human herpesvirus 4)
Sarcoma, Kaposi	*Herpes simplex* virus 8 (HHV-8), human immunodeficiency virus 1,
Skin cancer, Merkel cell carcinoma	Merkel cell polyomavirus[b]
Stomach	*Helicobacter pylori*

[a] Human papillomavirus types 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, 97 are classified as possibly carcinogenic (IARC Group 2B);
[b] Merkel-cell virus is common, whereas skin cancer is much less common; hence, other risk factors are necessary to cause cancer.

These viruses produce RNA and protein products that transform host cells and promote the survival and growth of transformed cells.[383]

Mycotoxins

Aflatoxins are the most important natural carcinogens in food; these hepatocellular carcinogens are highly substituted coumarin metabolites of *Aspergillus flavus* (B1, B2) and the closely related species *Aspergillus parasiticus* (B1, B2, G1, G2), classified by their blue fluorescence (B1, B2) and green-yellow fluorescence (G1, G2) under ultraviolet light.[380] These four aflatoxins are listed by the IARC as human (Group 1) carcinogens. Aflatoxin B1 is the most potent hepatocellular carcinogen in animal studies and the most common aflatoxin contaminant of human foods, whereas aflatoxin M1 (a metabolite of B1) is listed as a possible carcinogen (IARC Group 2B). The highest contamination of food sources with aflatoxins occurs in maize, beans, grains, and groundnuts stored in hot, humid conditions common in subsistence farming communities in tropical and subtropical areas in Eastern Asia, sub-Saharan Africa, and parts of South America. Milk consumption from cows fed aflatoxin B1-contaminated feed is an additional source of aflatoxin exposure.

Normal cooking processes do not destroy aflatoxins. Implementation of food monitoring and rapid use of optimal drying and storage facilities (i.e., <10% moisture) substantially reduced harmful aflatoxin exposure in developed countries. Cytochrome P450 enzymes (i.e., 3A4, 1A2, 3A5, 3A7) metabolize aflatoxins to highly reactive exo-epoxides that ultimately form adducts and DNA mutations including alteration of the p53 tumor suppressor gene.[384,385] The multiplicative interaction between aflatoxin B1 and HBV contributes significantly to the high incidence of hepatocellular carcinomas in Africa and East Asia.[386]

Other natural substances are animal carcinogens including fumonisins, ochratoxin A, and sterigmatocystin; however, human data are limited with insufficient data to conclude these substances contribute to human cancers (IARC Group 2B, possible carcinogens). Fumonisins are mycotoxins produced by some strains of *Fusarium* (e.g., *Fusarium moniliforme*) that occur primarily in corn (maize) and corn products; fumonisin B1/B2 and fusarin C are classified as possible carcinogens (IARC Group 2B) based on inadequate human studies and sufficient evidence in experimental animals. *Fusarium graminearum*, *Fusarium culmorum*, and *Fusarium crookwellense* strains producing deoxynivalenol, fusarenon X, nivalenol, or zearalenone are considered noncarcinogenic. *Penicillium verrucosum*, *Aspergillus ochraceus*, and rare *Aspergillus* species (*Aspergillus alliaceus*, *Aspergillus melleus*, *Aspergillus sclerotiorum*, *Aspergillus sulphureus*) produce ochratoxin A; many commodities contain this mycotoxin including pork, grains, cereals, peas, coffee beans, corn, and flour, particularly wheat and barley from northern temperate zones.[387] The IARC considers ochratoxin A possibly carcinogenic (Group 2B) based on inadequate human studies (i.e., ecological studies associating urothelial urinary tract tumors and high ochratoxin A in patients with Balkan endemic nephropathy) and sufficient evidence in experimental animals (hepatocellular tumors in mice, renal cell adenomas, and carcinomas in rats and mice). Sterigmatocystin is a metabolite of *Aspergillus versicolor* that is structurally similar to aflatoxins; hosts for this mycotoxin include salami,

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ham, grains, corn, bread, cheese, spices, soybeans, pistachio nuts, animal feed and silage, green coffee beans, and wheat.[388] The IARC classifies sterigmatocystin as a possible carcinogen (Group 2B) based on suggestive experimental animal data and no evidence of carcinogenicity in humans.

Plants and Medicinal Herbs

Foods Based on animal studies, a genotoxic cycasin metabolite glycoside (methylazoxymethanol) and a nor-sesquiterpene glucoside (ptaquiloside) derived from the bracken fern, *Pteridium aquilinum* are potent plant carcinogens.[389] Foods derived from seeds, roots, or leaves of cycad plants (Cycadaceae family) found in tropical and semitropical regions contain methylazoxymethanol along with starch depending on preparation processes; hepatocellular carcinoma developed in 2 of 9 monkeys receiving oral cycasin or methylazoxymethanol acetate doses over a mean of 57 months (range, 2–133 months) sufficient to cause hepatitis and cirrhosis.[390] There were no controls. Ptaquiloside forms an unstable dienone that develops covalent DNA adducts, with guanine and adenine causing subsequent breaks in DNA strands and apoptosis in cell cultures; very limited studies suggest ptaquiloside exposure causes mammary, intestinal, and urinary bladder cancer in several animal species,[391] and esophageal cancer in humans.[392] A Japanese case-control study of 98 cases of esophageal cancer and 476 controls reported a relative risk of 2.7 for the daily consumption of bracken fern; however, limited data on confidence intervals, potential information/selection bias, and a lack of adjustment for confounders complicate the determination of the results validity.[393] The IARC classifies cycasin and bracken fern consumption as possible carcinogens (Group 2B) based on animal data and insufficient (weak) human data.

Safrole (shikimol) is a component of certain essential oils (star anise, camphor, sassafras, cinnamon leaf) and spices (mace, ginger, cinnamon, nutmeg, black pepper, California bay laurel). The highest safrole concentration occurs in sassafras root. Relatively high amounts of safrole produce liver tumors in rats; subsequently, safrole was removed as a flavoring agent from the Generally Recognized As Safe (GRAS) list by the US Food and Drug Administration (FDA). The IARC classifies safrole, cycasin, and ptaquiloside in Group 2B as possible human carcinogens. Betel quid with or without tobacco in nonsmokers is a human carcinogen (oral/pharyngeal cancers, oral potentially malignant disorders, nitrosation to stomach carcinogens)[394] that contains high concentrations of safrole and potentially safrole-DNA adducts;[395] however, the contribution of safrole to the betel quid carcinogenicity remains unclear.

Herbs and Dietary Supplements Several species in the *Aristolochia*, *Asarum*, and *Thottea* genera from the *Aristolochiaceae* family contain aristolochic acid I and the de-methoxylated metabolite (aristolochic acid II); for a wide variety of illnesses, traditional Chinese medicine uses these ingredients in many herbal medicines, including Guang Fang Ji (*Aristolochia fangchi*), particularly in Taiwan.[396] In the 1990s, over 100 cases of interstitial renal fibrosis frequently progressing rapidly to kidney failure and urothelial carcinomas (i.e., ~40%) appeared in Belgian women using slimming agents containing Guang Fang Ji.[397,398] Subsequent studies in Taiwanese herbalists using aristolochic acid-containing herbs confirmed the increased risk of renal failure and upper tract urothelial carcinomas following exposure to these herbs. The IARC upgraded aristolochic acid to a Group 1 carcinogen based on strong mechanistic evidence (e.g., aristolactam-DNA adducts, TP53 suppressor gene mutations, apoptosis, and interstitial cell proliferation), sufficient evidence in experimental animals, and consistent data (e.g., DNA adducts, A to T mutations) in patients with urothelial (renal pelvis, ureter) cancers and either Balkan endemic or aristolochic acid nephropathy in areas where aristolochic acid-containing plants contaminate wheat fields.[399,400]

Animal studies suggest the possibility of carcinogenicity (i.e., IARC Group 2B) from exposure to several herbs, including *Aloe vera* whole leaf extract, coltsfoot (*Tussilago farfara*), comfrey (*Symphytum officinale*), *Ginkgo biloba*, goldenseal (*Hydrastis canadensis*), gordolobo yerba, (*Senecio vulgaris*, *Senecio riddellii*), groundsel (*Senecio flaccidus*), and kava extract (*Macropiper methysticum*); however, epidemiology data are insufficient to link these herbs to human carcinogenicity. In rodent studies, *A. vera* whole-leaf extract is an intestinal irritant producing goblet cell hyperplasia of the large intestine during a 13-week study involving oral doses of 1, 2, and 3%.[401] Subsequent studies of $B6C3F_1$ mice and F344/N rats gavaged with daily doses of 0.5, 1, and 1.5% *A. vera* whole-leaf extract demonstrated no large intestine neoplasms in controls, mice, or the 0.5%-dose group of rats; however, a dose-related increased incidence of large intestinal tumors developed in male and female rats fed 1 and 1.5% *A. vera* whole-leaf extract. Compared with controls, survival decreased in the 1.5% dose group of female rats, and intestinal hyperplasia occurred in all groups receiving 1 and 1.5% *A. vera* whole-leaf extract. Epidemiological studies of *G. biloba* are limited and inconsistent with substantial methodological flaws (e.g., low participation

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rates, low statistical power, relatively weak hazard ratios with wide confidence intervals including 1, potential exposure misclassification) to establish this herb as a human carcinogen. Rodent studies suggest the possibility of liver cancer based on the increased incidence of hepatoblastomas and hepatocellular carcinomas; however, the findings are not consistent between species and sexes.[402]

Coltsfoot, comfrey, gordolobo yerba, and groundsel contain pyrrolizidine alkaloids associated with liver inflammation and hepatocellular carcinomas in rodents. Inadequate data are available to evaluate the human carcinogenic risk from this widespread group of plants containing a pair of linked pyrrole rings (pyrrolizidine alkaloids). Riddelliine (IARC Group 2B) is a genotoxic pyrrolizidine alkaloid present in many western US plants that is mutagenic in rat liver cells.[403,404] Goldenseal roots contain isoquinoline alkaloids (e.g., berberine, canadine, hydrastine). In a 2-year study of $B6C3F_1$ mice and F344/N rats fed *ad libitum* diets containing 0 (control), 3,000, 9,000, or 25,000 ppm goldenseal root powder, the incidence of hepatoblastoma and hepatocellular adenoma increased in male but not female mice.[405] In male and female rats, the incidence of hepatocellular adenoma increased, and one case of hepatocellular carcinoma occurred (a rare tumor in F344/N rats). Human data on the carcinogenicity of goldenseal root powder is unavailable.

Kavalactones (e.g., α-pyrones, kavapyrones) are the active ingredients in kava rhizomes widely cultivated in Oceania for use as ritual beverages to promote a sense of well-being and relaxation. Epidemiological data on kava consumption and cancer are primarily ecological with significant methodological flaws (crude exposure and outcome measures, inadequate adjustment for confounding). In rats and mice administered Kava Kava (27% kavalactones) up to 1 g/kg body weight for 2 years, examination of male mice demonstrated a significant dose-related increase in the incidence of hepatoblastomas, whereas female mice demonstrated a significant increase in the combined incidence of hepatocellular adenoma and carcinoma in the low- and mid-dose but not the high-dose groups.[406] Treatment-related increases in carcinogenic activity were not observed in male or female rat livers. In these chronic studies, dose-related increases in the incidences of hepatocellular hypertrophy and centrilobular fatty change developed.

The madder root (*Rubia tinctoria*) contains red coloring material used as a dye; the extract contains several hydroxyanthraquinones (e.g., purpurin, rubiadin). Inadequate animal and human data are available to classify this herb as a carcinogen (IARC Group 3).[407]

Methoxsalen (8-methoxypsoralen) with ultraviolet A radiation is a recognized human carcinogen (IARC Group 1) and 5-methoxypsoralen is a probable carcinogen, whereas other psoralens (3-carbethoxypsoralen, 7-methylpyrido [3,4-*c*] psoralen, pyrido [3,4-*c*] psoralen, 4,5′,8-trimethylpsoralen) are not classifiable by their carcinogenicity (IARC Group 3).

STATISTICS

Statistical Significance and *P* Value

The *P* value is a measure of the chance variation of the results; therefore, this statistical measure does not quantify the actual risk of developing the disease and does not convey information regarding the strength of the respective association. However, a causal association is unlikely if the *P* value in non-significant. When the sample size is large, small and clinically non-significant differences may yield statistically significant differences. *P*-values are numerical fractions of 1 with a value of 0.05 indicating a 5% or less chance the association would occur when there was no true association. Traditionally, most medical research accepts a *P*-value of ≤0.05 as evidence the observed association did not arise from chance; however, small *P*-values (i.e., <0.05) do not guarantee an association is genuine or causal. Highly unlikely events associated with extremely small *P*-values can occur by chance, particularly when the study examines multiple comparisons. The respective *P*-values lose their collective interpretability in the presence of multiple tests and/or comparisons.[146] The odds ratio is a more informative measure of the strength of the association between the disease and an exposure compared with the *P*-value. No test of statistical significance separates unidentified bias or residual confounding from true effect in observational epidemiology studies. In contrast to more homogeneous experimental studies, normal (Gaussian) distribution is less applicable to epidemiology studies that include subjects with substantial genetic variability and highly variable exposure scenarios. Consequently, statistical significance may overstate the real significance of the results of observational epidemiology studies.[408]

When study results indicate a true difference exists between two populations under study, the next question is whether the difference is clinically significant and what degree of overlap occurs between the two groups. Statistical significance is not equivalent to clinical significance.[409] The *P*-value is a measure of the probability that a test outcome results from chance rather than an indication of a strong association or an important clinical difference. A weak, inconsequential association may

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be highly statistically significant in a large study, whereas a strong association may be statistically nonsignificant in a small, underpowered study. The confidence interval and *P*-value are intimately linked. The 95% confidence interval of a statistically significant association ($P < 0.05$) does not include the null value (i.e., 1 for relative risk) 95% of the time; however, normal (Gaussian) distribution is less applicable to heterogeneous human populations than inbred experimental animals. Thus, the use of normal distributions may overstate statistical significance unless higher standard errors than the usual ±1.96 standard errors are used to generate genuine 95% confidence intervals.[408] Confidence intervals (CI) provide all the information a *P*-value does. Additionally, the CI provides information about precision of the observed estimate (e.g., the inclusion of 1 indicates the results are statistically nonsignificant) with the range determining if clinically significant values are compatible with the results.[410] The complete overlap of confidence intervals indicates little difference between the two groups or subgroups. Effect sizes (e.g., odds ratios) also help determine the clinical importance of study results as measures of the amount and utility of the difference between two groups. The upper bound of the CI indicates if the data are compatible with clinically significant effect, particularly when the CI is precise (i.e., narrow).

Logistic Regression and ROC Curve

Logistic regression is a common statistical method that quantifies the relationship between individual characteristics and the outcome of interest. This method demonstrates which factors (independent variables) have the strongest association with an outcome of interest (dependent variables), while providing a measure of the magnitude of the factors effect on the outcome. The ability to adjust for confounding factors that are associated with both independent and dependent variables provides a mechanism to limit the influence of confounders. The validity of a logistic regression model depends on the following: 1) the number and suitability of the measured independent variable, 2) the variables remain constant across the range of values for the variable, and 3) the absence of an interaction between independent variables.[411] A receiver operating characteristic (ROC) curve can assess the ability of a logistic regression model to predict outcomes. The ROC curve is a plot of sensitivity of the model on the vertical axis and 1 minus the specificity on the horizontal axis for all possible cutoffs used to separate patients. The area under the ROC curve (C statistic, concordance) reflects the difference between the model estimates of risk and the observed risk with a range of 0–1. One indicates the model has perfect sensitivity and specificity, whereas 0.5 implies the model produces results no better than chance. Typically, a C statistic below 0.7 indicates the model is not clinically useful, a higher than 0.7 implies fair predictive value, and a 0.9 indicates a well-calibrated model.[412]

Population Attributable Fraction

The population attributable fraction helps policymakers understand the effects of public health interventions and policies on exposed populations. The population attributable fraction is the amount of a specific disease burden that could be eliminated by the eradication of certain causal factors (i.e., exposures) from the population. This value reflects the estimated population attributable risk fraction rather than the etiological fraction,[413] which cannot be estimated in an individual without robust biological assumptions.[414] Consequently, the population attributable fraction is the proportional reduction in the average disease risk over a specified time interval resulting from the elimination of the specified causal exposure(s), while the other disease risk factors in the population remain unaffected.[415] Population attributable risk proportion implies the subjects in the numerator are part of the population in the denominator, whereas the excess fraction may not include the subjects in nominator in the denominator (i.e., whole population). Statistical methods can adjust for confounding when estimating attributable risk from retrospective data; however, some attributable fraction formulas require the absence of confounding in the exposure-disease association.[416]

The population attributable fraction may be divided into exposure-category-specific attributable fractions that sum to the population attributable fraction.[415] For a specific disease with multiple causal factors, the sum of each single attributable fraction may exceed 1; hence, the use of broad factors (e.g., unknown causes) to sum to 1 is inappropriate. Furthermore, the population attributable fraction does not determine the probability that a specific case was or was not caused by the exposure; similarly, estimation of the attributable fraction does not identify which cases were or were not caused by the exposure. The attributable fraction is most useful for strong causal relationships that are amenable to interventions (e.g., smoking and lung cancer). In these situations, the risk factor should be immediately modifiable and the unexposed setpoint should be established at a realistically attainable exposure value for

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the exposed population. The use of broad exposure definitions also reduces the precision and increases the standard error of the attributable fraction, particularly when the proportion of exposed cases and controls exceeds 50%.[417]

Systematic Reviews and Meta-analyses

Determination of the true effect of chemical exposure on cancer risks depends on the totality of evidence rather than on an individual study because single studies may be misleading and unrepresentative of the totality of the evidence.[418] Systematic reviews are research summaries focusing on a clinical question by a structured, reproducible approach; often, a statistical pooling of results from various studies (i.e., meta-analysis) accompanies the review.[419] The latter provides a single estimate of effect. The role of meta-analyses remains controversial because no statistical summarization can account for problems caused by unidentified bias, residual confounding, or selective presentation of data.[420] These techniques address the issue of chance; however, meta-analyses do not guarantee the absence of bias, unrecognized confounding, or selective reporting. To reduce error and subjectivity, systematic reviews usually include two or more reviewers along with a measure of agreement on study selection and quality appraisal (e.g., κ statistic). Several guidelines are available for evaluation of the quality of evidence, including those from Oxford Centre for Evidence-Based Medicine, the American Heart Association,[421] and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). The latter categorizes confidence in very low, low, moderate, and high categories.[422] Increasing confidence ratings is unusual, primarily involving observational studies with large effect sizes. Table 49.28 lists important questions to evaluate the credibility and validity of systematic reviews and meta-analyses.

TABLE 49.28. Questions for the evaluation of results from a systematic review and meta-analysis. (Adapted from Murad et al.).[419]

Judgment	Questions
Credibility of methods	1. Was the review evaluating a sensible question?
	2. Did the search include a representative or complete sample of available eligible studies?[a]
	3. Were study selections and assessments reproducible?
	4. Are results applicable to the environmental or occupational question?
	5. How confident were the authors in their estimates of effect?
Confidence in effect estimates	1. How serious was the risk of bias?
	2. How consistent are the results across studies?
	3. How precise are the estimates?
	4. How serious are reporting and publication biases?
	5. Should the confidence rating be changed?
	6. Do the results answer the question in a quantitatively important way?

[a] Typically, the minimum requirements for most questions include Medline, Embase, and the Cochrane database.

Effect Size

Systematic reviews and meta-analyses provide a synthesis of available evidence to help understand the relationship between chemical exposure and cancer, as well as other focused clinical questions. The credibility of the review process depends on appropriate eligibility criteria, exhaustive literature search, and optimum summarization of the results, whereas the quality of evidence depends on the exclusion of biased studies, consistent results (i.e., homogeneity), and adequate sample size to produce precise estimates of effect size. The latter is a statistical measure for the magnitude of the difference between two outcomes adjusted for an estimate of variability; effect size measures dichotomous (binary) and continuous data. The latter includes the difference between the mean values and standardized difference between mean values, whereas the former includes relative risk, odds ratio, and absolute risk difference. In contrast to the absolute risk difference, the relative risk and odds ratio rely less on the underlying risk. For rare events, the odds ratio and relative risk are similar; however, the odds ratio is significantly greater than the relative risk for more frequent events (i.e., >20%), resulting in overestimation of risk (e.g., the number of patients with a disease/total number of patients); additionally, the odds ratio displays a greater risk compared with the relative risk when the effect size is <2.[423] Effect sizes of large trials in the same direction and within 30% of the pooled values in meta-analyses are usually considered concordant.[424,425]

Meta-analysis results are usually displayed as forest plots with the confidence interval as a horizontal line, the point estimate as a square with the size proportional to the weight of the study, and the pooled estimate as a diamond. Large differences in point estimates and

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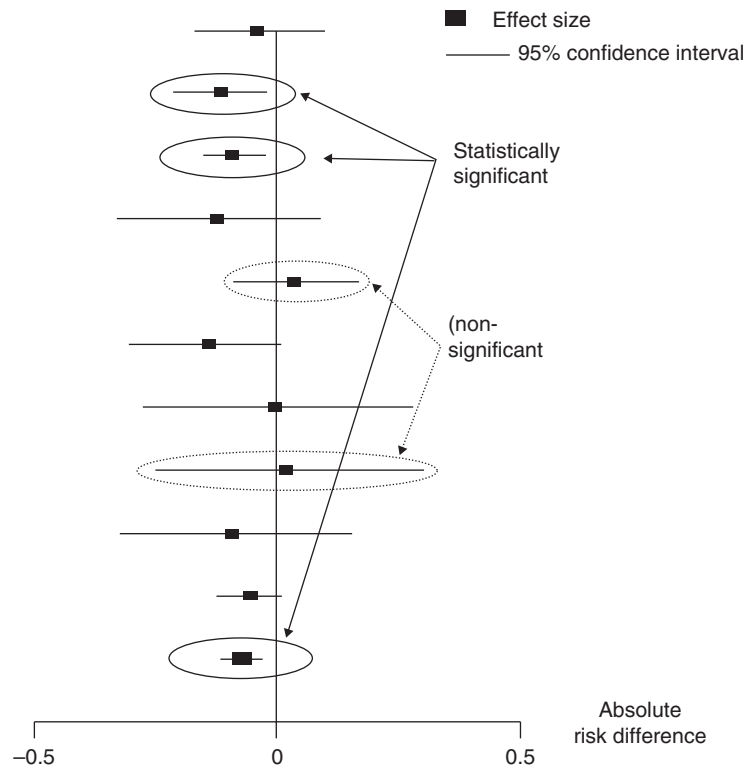


FIGURE 49.5. Forest plot. The effect size in this forest plot is the absolute risk difference between two different interventions. Failure of the confidence interval to cross zero on the *y*-axis indicates a statistically significant outcome. (Adapted from Leucht et al.).[423]

confidence intervals that do not overlap on the forest plot reduce confidence in the pooled estimates by suggesting random error is unlikely (i.e., low *P* value).[419] Figure 49.5 is a forest plot summarizing the effect size (pooled absolute risk difference) for a meta-analysis of 11 studies on 2 types of intervention. The size of the square reflects effect size, whereas the horizontal line through the square represents the 95% confidence interval. Failure of the 95% confidence interval to intersect zero on the *y*-axis indicates a statistically significant outcome. Small and/or imprecise studies typically have large confidence intervals, whereas large studies usually have smaller confidence intervals.

Publication Bias

Assessing the risk of bias is problematic with no single correct method; the review/meta-analysis should include an overall assessment of bias with a corresponding alteration of the confidence in estimates as needed. The results of the systematic review and meta-analysis are only as reliable as the quality of the studies summarized. Publication bias represents a serious concern for evidence-based medicine because of the tendency to publish positive rather than negative studies, particularly if a study reports a selected subset of significant predictors. This tendency creates a systematic bias against the null hypothesis raising the potential for false positive studies and limiting the validity of the meta-analyses that do not require comprehensive reporting, including preregistered hypotheses and disclosure of the number of tests conducted. Several factors contribute to publishing false positive findings including: 1) small sample size, 2) increased pursuit of novelty, 3) various forms of multiple testing and researcher flexibility, and 4) incorrect *P*-values from lack of independent data points (clustered data).[426] HARKing[427] is the use of Hypothesizing After the Results are Known and hindsight bias (knew-it-all-along)[428] contributes to the publication of false positive studies; the latter overestimates the plausibility of the "*post hoc* hypotheses" derived from data rather than the testing. Although data exploration is not fundamentally inappropriate, these analyses may cause an array of relationships and interpretations that are difficult to objectively correct for multiple testing.[429] Such exploratory work should be published in the Results section rather than the

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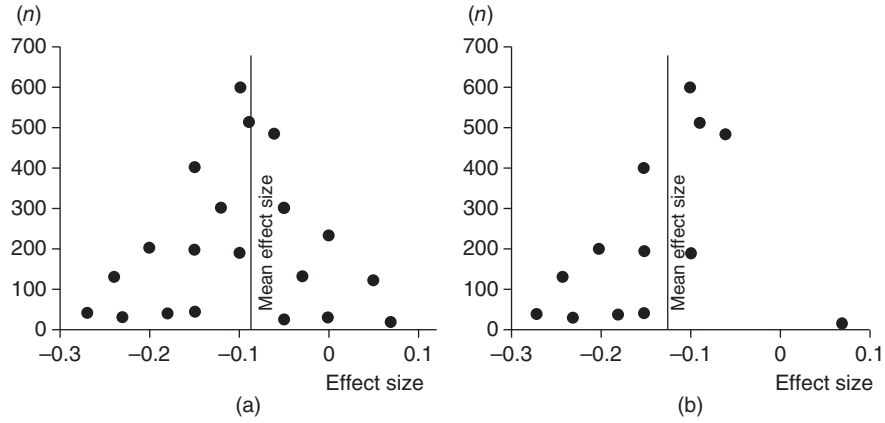


FIGURE 49.6. Hypothetical funnel plots graph study size n (*y*-axis) and effect size (*x*-axis). Graph (a) is a symmetric plot demonstrating an inverted funnel characteristic of a meta-analysis with publication bias unlikely, whereas graph (b) is asymmetric in the region of smaller studies on the lower right of the graph. The absence of published studies in this region indicates the presence of publication bias. (Adapted from Leucht et al.).[423]

TABLE 49.29. Sources of funnel plot asymmetry. Bias indicates the presence of systematic, non-random errors. (Adapted from Egger et al.).[424]

Source	Explanations
Selection bias	Publication bias, location bias (English language, multiple publications, citation)
True heterogeneity	Effect size varies by study size (intensity of intervention, underlying risk differences)
Data issues	Methodological problems with small studies, inadequate analysis, misrepresentation
Artifactual Chance	Inappropriate choice of outcome measure

Introductory section to prevent misinterpreting the hypothesis as *a priori* rather than *post hoc*.

The funnel plot graphically represents effect sizes of individual studies against precision or the number of participants; larger studies with higher precision appear at the top of the graph. The basis for interpreting funnel plots is the assumption that small negative studies are less likely to be published, resulting in an asymmetric plot, as displayed in Figure 49.6. Table 49.29 lists potential sources of asymmetry in funnel plots.

Heterogeneity

Heterogeneity in a meta-analysis partially determines the validity of study conclusions. Certain statistical evaluations help determine the degree of heterogeneity (e.g., Cochran Q test); however, this test does not easily detect true heterogeneity, particularly when the meta-analysis includes small studies with low power.[430] The I^2 statistic is a calculated measure of heterogeneity that reflects the magnitude of the variability in studies included in a meta-analysis, with less dependence on power and statistical significance than the Cochran Q test.[431,432] The value of I^2 statistic ranges from 0–100%, with 0% indicating no heterogeneity and chance explaining variability in the point estimates. As the I^2 increases progressively, heterogeneity and concern about variability increase. The confidence interval includes the range where the value of the true effect plausibly lies; consequently, the confidence interval reflects the precision of the estimate (i.e., how closely individual estimates are to each other). The weight of an individual study depends on its precision.

Subanalyses

Systematic reviewers may use subgroup analyses to identify groups of subjects responding differently to an exposure or treatment than the whole group; however, compelling subgroup effects are often spurious. Criteria for assessing the validity of subgroup analyses include: 1) identification of the hypothesis as an effect *before* the study began, 2) the possibility of chance explaining the effect, 3) consistency of the effect across studies, 4) strong preexisting biological support for the effect, and 5) evidence supporting the effect based on within- or between-study comparisons (systematic reviews only).[433] The credibility of apparent subgroup differences arising *post hoc* rather than *a priori* is suspect.

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TABLE 49.30. Calculation of test characteristics.

Test Outcome	Value	Disease (Carcinogen) Present	Disease (Carcinogen) Absent
Test positive		A (true positive)	B (false negative)
Test negative		C (false positive)	D (true negative)
Sensitivity	A/(A + C)		
Specificity	D/(B + D)		
Total positive tests	A + B		
Total negative tests	C + D		
Total tests	A + B + C + D		
Positive predictive value	A/(A + B)		
Negative predictive value	D/(C + D)		
Accuracy (concordance)	(A + D)/A + B + C + D		

Abbreviations: A = true positive; B = false negative; C = false positive; D = true negative.

Negative Studies and Predictive Values

Sensitivity measures the *proportion* rather than the *absolute* number of subjects with the condition detected by the test, whereas specificity is the proportion of subjects without the condition that have a negative test. The actual number of individuals with the condition missed by the test is highly dependent on the prevalence of the condition in the studied population. The predictive value measures the actual number of subjects missed by the test. *Positive predictive value* describes the probability that a positive test result will be a true positive, whereas *negative predictive value* describes the probability that a negative test result will be a true negative. If the sensitivity and specificity are constant, the positive predictive value increases as the prevalence of the condition increases. The negative predictive value decreases as the prevalence increases. Table 49.30 outlines the calculation of these test characteristics. Accuracy (i.e., total true tests/total tests) measures how often the tests are correct (i.e., true values) in contrast to precision that measures how closely values are to each other.

A true negative study requires the following: 1) a large sample size with sufficient follow-up and disease prevalence in a cohort study or adequate case size and common exposure in a case-referent study, 2) a sensitive measure of outcome (e.g., disease in a cohort study or exposure in a case-referent study, and 3) accurate exposure data.[434] The statistical power of a study is the chance of detecting a specific outcome when the outcome truly occurred in the population given a specified level of significance (usually, $\alpha = 0.05$) and a probability of failing to detect the true difference (usually, $\beta = 0.2$). Hence, a negative study with good statistical power indicates the lack of a correlation in the test population between the study variable and the outcome. Nomograms are available to aid in the calculation of the power of a study.[435] Given the conditions of exposure and the biases in a study, the results can exclude a rate ratio above the upper confidence limit. Difference in the dose frequently explains the apparent conflict between "positive" and "null" studies using the same chemical. This difference in dose often outweighs other sources of variability.[436]

EXTRAPOLATION

Extrapolation of test results from an observational study population to another population requires an analysis of potential errors including: 1) extrapolation of results to a population with a different prevalence of disease or exposure, 2) failure to account for confounding factors in the general population affecting the outcome, 3) using population data to reach conclusions about individuals, and 4) extrapolation beyond or below the exposure range.[437] Causation in cancer studies is typically multifactorial, with no single factor both necessary and sufficient for cancer occurrence; furthermore, no single factor is usually sufficient (albeit not necessary) to cause cancer in a particular individual. Despite the presence of strong carcinogens or susceptibility factors (e.g., long-term, heavy smoking, dominant breast cancer genes) in individuals, not all individuals will develop cancer. Although observational epidemiological studies suggest a causal relationship between chemical exposure and an increased cancer risk in a selected population, attributing causality to an association between cancer and a chemical exposure in an individual within the population is complicated, depending on the individual cumulative dose and latency.[438] Criteria for determination of causation in an individual following a chemical exposure include: 1)

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the chemical is an established carcinogen with strong epidemiological evidence, an appropriate, reproducible animal model, and some insight into the underlying carcinogenic process; 2) the individual exposure is comparable (e.g., latency, duration, intensity); 3) the cancer type is etiologically linked to the exposure; 4) the individual was not exposed to another established or likely cause of the specific cancer type; and 5) the fully adjusted relative risk of the individual's cancer type following similar exposure is >2.[146] A relative risk of >2 suggests the excess risk due to the exposure (i.e., >1) is larger than the background risk of 1 and the individual is more likely than not to develop cancer from the exposure rather than the background causes of the cancer type. This magnitude of relative risk suggests the results are quantitatively rather than statistically significant, allowing for the possibility of unidentified bias and residual confounding.[439]

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Chapter 50

CARCINOGEN CLASSIFICATIONS

Several public health organizations (e.g., World Health Organization's International Agency for Research on Cancer, IARC; the United States National Toxicology Program, NTP), and governmental agencies (e.g., the United States Environmental Protection Agency, USEPA) review the available evidence on carcinogenicity and then categorize chemicals based on the evaluation of the probability the chemical causes human cancer. The US National Institute for Occupational Safety and Health (NIOSH) classifies occupational carcinogens by evaluating existing cancer hazard assessments from NTP, USEPA, and IARC.[1] This determination depends on one of the following methods: 1) evaluation of chemical carcinogen hazard assessments by the US Department of Health and Human Services' National Toxicology Program (NTP), the Integrated Risk Information System (IRIS) from the USEPA, or the IARC; 2) nomination by NIOSH for classification by NTP; or 3) classification by NIOSH. When developing a new chemical carcinogen classification, NIOSH uses the United Nations' Globally Harmonized System for Classification and Labelling of Chemicals (GHS) as interpreted by the US Occupational Safety and Health Administration (OSHA). NIOSH designates a substance an occupational carcinogen if the evidence meets GHS classes 1A, 1B, or 2.

Although all these agencies rely on a qualitative evaluation of the *weight* and *strength* of the evidence on potential carcinogenicity hazards, each of these organizations emphasizes different aspects of the carcinogen evaluation process. These classification systems typically do not consider potency as a criteria for determining carcinogenicity;[2] however, some governmental agencies have developed databases integrating data on carcinogenic risks (e.g., NTP Carcinogenic Potency Database, CPDB, https://healthdata.gov/dataset/Carcinogenic-Potency-Database-CPDB-/sqjy-rr5s/about_data; USEPA Integrated Risk Information System, IRIS, https://www.epa.gov/iris) to help set exposure standards for chemical carcinogens. The CPDB provides current historical information involving the interpretation/experimental details of bioassays, TD_{50s}, and calculation of carcinogenic potency. Besides potency, the relationship between cancer risk and exposure to a carcinogen in an individual depends on several other factors specific to the individual, including internal dose and susceptibility.

NATIONAL TOXICOLOGY PROGRAM

The NTP classifies carcinogens based on internally derived experimental data, published scientific studies, and reviews by nongovernmental expert panels. Five categories (i.e., clear, some, equivocal, no, inadequate) of evidence summarize the carcinogenic activity demonstrated in each study. Positive (clear, some) results indicate a potential cancer hazard from exposure to the chemical based on animal studies, whereas negative (no) studies indicate the lack of an increased tumor incidence under the experimental conditions.

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Hence, negative studies do not necessarily eliminate the potential for a chemical to cause cancer. The difference between clear and some evidence of carcinogenicity reflects a dose-related increase in tumor incidences in the former and only a chemically related increase in tumor incidences in the latter. Equivocal studies demonstrate a marginal increase in tumor incidences in contrast to inadequate studies that contain major design flaws preventing proper interpretation of the data.

Based on the weight of the evidence from these studies, chemicals are classified into two categories: 1) substances known to be human carcinogens, and 2) substances reasonably anticipated to be human carcinogens, as displayed in Table 50.1. Evidence supporting inclusion in these categories includes traditional cancer epidemiology studies, clinical studies, and/or *in vivo* studies clarifying the chemical-induced carcinogenic mode of action (i.e., the sequence of events from chemical absorption to ultimate effect). The former category implies the existence of sufficient evidence of carcinogenicity in epidemiology studies that indicate a causal relationship between human cancer and exposure to the agent, substance, or mixture. The latter includes several types of evidence including: 1) limited evidence of carcinogenicity from human studies that indicates a credible causal interpretation; however, alternative explanations (e.g., bias, chance, confounding) could not be excluded; 2) evidence in human or laboratory animal studies is less than sufficient; however, the agent, mixture, or substance belongs to a well-defined, structurally related substance listed as a potential carcinogen in previous reports or the existence of convincing mode of action data indicates the substance is a likely human carcinogen; or 3) sufficient evidence of carcinogenicity from experimental animal studies indicates an increased incidence of malignant and/or a combination of malignant/benign tumors in: a) multiple species or multiple tissue sites; b) multiple exposure routes; or c) an unusual degree of tumor incidence, site, type, or age at onset.[3] Table 50.2 lists the chemicals assigned by the NTP to these two categories. The NTP publishes the results of their reviews in the congressionally mandated Report on Carcinogens involving 243 substances by 2014, and updated in 2021, as displayed in Table 50.2.[3]

TABLE 50.1. National Toxicology Program (NTP) carcinogen classifications with criteria.

Classification	Criteria
Known to be a human carcinogen	Sufficient evidence of human carcinogenicity in epidemiology studies demonstrates a causal relationship
Reasonably anticipated to be a human carcinogen	1) Limited human evidence indicating a credible causal relationship, but an alternate explanation (bias, chance, or confounding factors) cannot be excluded or 2) Sufficient animal evidence of carcinogenicity indicating increased malignant and/or malignant plus benign tumors in: a) multiple species or multiple tissues; b) multiple exposure routes; or c) unusual incidence, onset, site, or tumor type or 3) Convincing mechanistic data on carcinogenicity likely to cause human cancer or less than sufficient animal or human data for a chemical with a well-defined, structural relationship to a previously recognized human carcinogen

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

Rather than relying only on internal data, the International Agency for Research on Cancer (IARC) produces comprehensive evaluation of ~1,000 chemicals based on reviews of all published experimental and epidemiological data (https://monographs.iarc.fr/agents-classified-by-the-iarc/). Selection of chemicals for review depends on the results of questionnaires sent to governments involved in the organization. The IARC does not produce experimental data; therefore, IARC publications rely on expert analysis and interpretation of available data rather than new experimental data.[4] The overall IARC evaluation involves human, animal, and mechanistic data, with strong mechanistic data providing evidence for raising or lowering the category, as displayed in Table 50.3.

Many human carcinogens produce various biological changes in the multi-stage process of carcinogenesis; these changes involve modification of cell signaling and gene expression that govern the creation and maintenance of cell identity (i.e., epigenetic mechanisms) as well as the previous emphasis on altered morphology and genotoxicity (alteration of DNA sequences).[5] The role of epigenetic changes in classifying carcinogens in previous monographs has been modest.[6] To identify and organize the plethora of mechanistic data including

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TABLE 50.2. US National Toxicology Program Summary of 243 known and suspected human carcinogens as listed in the 15th Report on Carcinogens. (https://ntp.niehs.nih.gov/ntp/roc/content/listed_substances_508.pdf, NTP).[3]

Known to Be Carcinogenic	Reasonably Anticipated to Be Carcinogenic
Aflatoxins	Acetaldehyde
Alcoholic beverage consumption	2-Acetylaminofluorene
4-Aminobiphenyl (4-aminodiphenyl)	Acrylamide
Analgesic mixtures containing phenacetin	Acrylonitrile
Aristolochic acids	Adriamycin® (doxorubicin hydrochloride)
Arsenic compounds, inorganic	2-Aminoanthraquinone
Asbestos	*o*-Aminoazotoluene
Azathioprine	1-Amino-2,4-dibromoanthraquinone
Benzene	1-Amino-2,4-methylanthraquinone
Benzidine	2-Amino-3,4-dimethylimidazo(4,5-f)quinoline
Beryllium and beryllium compounds	2-Amino-3,8-dimethylimidazo(4,5-*f*)quinoxaline
bis(Chloromethyl) ether and technical-grade chloromethyl methyl ether	1-Amino-2-methylanthraquinone
1,3-Butadiene	2-Amino-3-methylimidazo(4,5-*f*)quinoline
1,4-Butanediol dimethylsulfonate	2-Amino-1-methyl-6-phenylimidazo (4,5-*b*)pyridine
Busulfan (Myleran®)	Amitrole
Cadmium and cadmium compounds	*o*-Anisidine and its hydrochloride
Chlorambucil	Antimony trioxide
1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea	Azacitidine (5-azacytidine®,5-AzaC)
Chromium hexavalent compounds	Basic Red 9 monohydrochloride
Coal tars and coal-tar pitches	Benz[*a*]anthracene[b]
Coke oven emissions	Benzo[*b*]fluoranthene[b]
Cyclophosphamide	Benzo[*j*]fluoranthene[b]
Cyclosporin A	Benzo[*k*]fluoranthene[b]
Diethylstilbestrol	Benzo[*a*]pyrene[b]
Dyes metabolized to benzidine (Benzidine Class Dyes, Direct Black 38/Blue 6)	Benzotrichloride
Epstein–Barr virus	2,2-Bis(bromomethyl)-1,3-propanediol (technical grade)
Erionite	Bis(chloroethyl) nitrosourea
Estrogens, steroidal	Bromochloroacetic acid
Ethylene oxide	Bromodichloroacetic acid
Formaldehyde	Bromodichloromethane
Helicobacter pylori (Chronic infection)	1-Bromopropane
Hepatitis B virus (HBV)	Butylated hydroxyanisole (BHA)
Hepatitis C virus (HCV)	Captafol
Human immunodeficiency virus Type 1 (HIV_1)	Carbon tetrachloride
Human papilloma virus (HPV)	Ceramic fibers (respirable size)
Human T-cell lymphotrophic virus Type 1	Chloramphenicol
Kaposi Sarcoma-associated Herpes virus	Chlorendic acid
Melphalan	Chlorinated paraffins (C12, 60% Chlorine)
Merkel cell polyoma virus	Chlorodibromoacetic acid
Methoxsalen with ultraviolet A therapy (PUVA)	1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea
Mineral oils, untreated/mildly treated	Chloroform
Mustard gas	3-Chloro-2-methylpropene
2-Naphthylamine	4-Chloro-*o*-phenylenediamine
Neutrons	Chloroprene
Nickel compounds	*p*-Chloro-*o*-toluidine and its hydrochloride
Radon	Chlorozotocin
Silica, crystalline (respirable size)	Cisplatin
Solar radiation including broad-spectrum ultraviolet radiation and exposure to sunlamps or sunbeds	Cobalt and cobalt compounds releasing cobalt ions *in vivo*
Soots	Cobalt–tungsten carbide powder/hard metals
Strong inorganic acid mists containing sulfuric acid	*p*-Cresidine

(Continued)

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TABLE 50.2. (Continued)

Known to Be Carcinogenic	Reasonably Anticipated to Be Carcinogenic
Tamoxifen	Cumene
Tars and mineral oils	Cupferron
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD); dioxin	Dacarbazine
Thiotepa	Danthron (1,8-Dihydroxyanthraquinone)
Thorium dioxide	2,4-Diaminoanisole sulfate
Tobacco smoking, environmental tobacco smoke, smokeless tobacco	2,4-Diaminotoluene
o-Toluidine	Diazoaminobenzene
Trichloroethylene	Dibenz[*a,h*]acridine[b]
Vinyl chloride	Dibenz[*a,j*]acridine[b]
Wood dust	Dibenz[*a,h*]anthracene[b]
X-ray and gamma radiation	7H-Dibenzo[*c,g*]carbazole[b]
	Dibenzo[*a,e*]pyrene[b]
	Dibenzo[*a,h*]pyrene[b]
	Dibenzo[*a,i*]pyrene[b]
	Dibenzo[*a,l*]pyrene[b]
	1,2-Dibromo-3-chloropropane
	1,2-Dibromoethane (ethylene dibromide)
	2,3-Dibromo-1-propanol
	Dichloroacetic acid
	1,4-Dichlorobenzene
	3,3′-Dichlorobenzidine and its dihydrochloride
	Dichlorodiphenyltrichloroethane
	1,2-Dichloroethane (ethylene dichloride)
	Dichloromethane (methylene chloride)
	1,3-Dichloropropene (technical grade)
	Diepoxybutane
	Diesel exhaust particulates
	Di(2-ethylhexyl) phthalate
	Diethyl sulfate
	Diglycidyl resorcinol ether
	3,3′-Dimethoxybenzidine and its dihydrochloride[a]
	4-Dimethylaminoazobenzene
	3,3′-Dimethylbenzidine
	Dimethylcarbamoyl chloride
	1,1-Dimethylhydrazine
	Dimethyl sulfate
	Dimethylvinyl chloride
	1,6-Dinitropyrene
	1,8-Dinitropyrene
	1,4-Dioxane
	Disperse Blue 1
	Epichlorohydrin
	Ethylene thiourea
	Ethyl methanesulfonate
	Furan
	Glass wool fibers (some respirable sizes)
	Glycidol
	Hexachlorobenzene
	Hexachloroethane
	Hexamethylphosphoramide
	Hydrazine and hydrazine sulfate
	Hydrazobenzene
	Indeno(1,2,3-cd)pyrene[b]

(Continued)

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TABLE 50.2. (Continued)

Known to Be Carcinogenic	Reasonably Anticipated to Be Carcinogenic
	Iron dextran complex
	Isoprene
	Kepone® (chlordecone)
	Lead and lead compounds
	Lindane, hexachlorocyclohexane (technical grade), and other hexachlorocyclohexane isomers
	2-Methylaziridine (propyleneimine)
	5-Methylchrysene[b]
	4,4′-Methylenebis(2-chloroaniline)
	4-4′-Methylenebis(*N*,*N*-dimethyl)benzenamine
	4,4′-Methylenedianiline and its dihydrochloride
	Methyleugenol
	Methyl methanesulfonate
	N-Methyl-*N*′-nitro-*N*-nitrosoguanidine
	Metronidazole
	Michler's ketone [4,4′-(Dimethylamino)benzophenone]
	Mirex
	Naphthalene
	Nickel, metallic
	Nitrilotriacetic acid
	o-Nitroanisole
	Nitrobenzene
	6-Nitrochrysene
	Nitrofen
	Nitrogen mustard hydrochloride
	Nitromethane
	2-Nitropropane
	1-Nitropyrene
	4-Nitropyrene
	N-Nitrosodi-*n*-butylamine
	N-Nitrosodiethanolamine
	N-Nitrosodiethylamine
	N-Nitrosodimethylamine
	N-Nitrosodi-*n*-propylamine
	N-Nitroso-*N*-ethylurea
	4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone
	N-Nitroso-*N*-methylurea
	N-Nitrosomethylvinylamine
	N-Nitrosomorpholine
	N-Nitrosonornicotine
	N-Nitrosopiperidine
	N-Nitrosopyrrolidine
	N-Nitrososarcosine
	o-Nitrotoluene
	Norethisterone
	Ochratoxin A
	4,4′-Oxydianiline
	Oxymetholone
	Pentachlorophenol and synthesis by-products
	Phenacetin
	Phenazopyridine hydrochloride
	Phenolphthalein
	Phenoxybenzamine hydrochloride

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TABLE 50.2. (Continued)

Known to Be Carcinogenic	Reasonably Anticipated to Be Carcinogenic
	Phenytoin and phenytoin sodium
	Polybrominated biphenyls (PBBs)
	Polychlorinated biphenyls (PCBs)
	Procarbazine and hydrochloride
	Progesterone
	1,3-Propane sultone
	β-Propiolactone
	Propylene oxide
	Propylthiouracil
	Reserpine
	Riddelliine
	Safrole
	Selenium sulfide
	Streptozotocin
	Styrene
	Styene-7,8-oxide
	Sulfallate
	Tetrachloroethylene (perchloroethylene)
	Tetrafluoroethylene
	Tetranitromethane
	Thioacetamide
	4,4′-Thiodianiline
	Thiourea
	Toluene diisocyanates
	o-Toluidine and *o*-toluidine hydrochloride
	Toxaphene
	Tribromoacetic acid
	2,4,6-Trichlorophenol
	1,2,3-Trichloropropane
	Tris(2,3-dibromopropyl) phosphate
	Ultraviolet radiation A, B, and C
	Urethane
	Vinyl bromide
	4-Vinyl-1-cyclohexene diepoxide
	Vinyl fluoride

[a] Including dyes metabolized to 3,3′-dimethoxybenzidine. [b] Polycyclic aromatic hydrocarbons.

epigenetic alterations (i.e., inherited, stable changes in gene expression and chromatin organization independent of DNA sequences), the IARC convened two workshops in 2012 that identified 10 key mechanistic characteristics of established human carcinogens, as displayed in Table 50.4.[7] Consideration of these characteristics facilitates the evaluation of experimental data by upgrading or downgrading the animal data according to the strength of the mechanistic data. Evaluating the mechanistic information involves: 1) identifying relevant information through comprehensive searches of the medical literature for end points associated with key characteristics following exposure to the agent and metabolites; 2) screening and organizing the results by population (animal, human) end points related to key characteristics and toxicokinetics; and 3) synthesis of mechanistic information and development of adverse outcome networks using key characteristics to evaluate evidence for mechanistic events as a function of relevant features (dose, temporal relationship, species).[8]

Morphological evidence for human carcinogenicity is stronger if based on cohort studies than case-referent studies and only suggestive if based on case series, ecological, or mortality studies. Sufficient data in animal studies requires positive results in ≥2 studies or species, whereas positive results in one study or species provide limited data. Table 50.5 outlines the criteria for epidemiological evidence, and Table 50.6 summarizes the assessment of animal data.

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TABLE 50.3. International Agency for Research on Cancer (IARC) classifications and criteria.

Category	Classification	Criteria
Group 1	Carcinogenic to humans	Sufficient causal evidence in humans or Sufficient animal evidence and strong mechanistic evidence through a carcinogenic mode of action relevant to exposed humans
Group 2A	Probably carcinogenic to humans	Limited human evidence and sufficient experimental animal evidence or Inadequate human evidence and sufficient experimental animal evidence along with strong mechanistic evidence in exposed humans
Group 2B	Possibly carcinogenic to humans	Limited human evidence and less-than-sufficient animal evidence or Insufficient human evidence and sufficient animal evidence or Limited animal evidence and other supporting data.
Group 3	Not classifiable as to carcinogenicity to humans	Inadequate human evidence and inadequate or limited animal evidence or Sufficient animal evidence and strong mechanistic evidence the chemical does not act on humans
Group 4	Probably not carcinogenic to humans	Strong and consistent evidence of lack of carcinogenicity in humans and animals (rare)

TABLE 50.4. Summary of key mechanistic characteristics associated with human carcinogens. The presence of multiple characteristics (e.g., genomic instability, oxidative stress, chronic inflammation) rather than single processes (e.g., oxidative stress) provides stronger evidence of a carcinogenic process. (Adapted from Smith et al.).[7]

Characteristic	Relevant Examples
Electrophilic structure	Parent compound or metabolite possesses electrophilic properties, forming DNA or protein adducts (e.g., epoxide, quinone)
Genotoxicity	Causes DNA damage (DNA-protein crosslinks, strand breaks, unscheduled DNA synthesis), cytogenetic changes (chromosome aberrations, micronuclei), gene mutations
Genomic instability, altered DNA repair processes	Abnormal DNA replication/repair (double-stranded breaks or base-excision repair, topoisomerase II)
Epigenetic alterations	DNA methylation, histone modification, miRNA expression
Oxidative stress	Macromolecular oxidative damage (DNA, lipids), oxygen free radical formation
Chronic inflammation	Altered cytokine and/or chemokine production, leukocytosis, increased myeloperoxidase activity
Immunosuppression	Immune dysfunction, ↓immunosurveillance
Altered receptor function	Modulation of endogenous ligands (e.g., hormones), ↓↑ receptor activation (e.g., estrogen, peroxisome proliferation/activation, aryl hydrocarbons)
Immortality	Cell transformation, ↓ senescence
Modulation of nutrient supply, cell proliferation, cell death	↑ Angiogenesis, alteration of cell replication and cell cycle control pathways, ↑ cell proliferation, ↓ apoptosis

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TABLE 50.5. International Agency for Research on Cancer (IARC) assessment of human evidence of carcinogenicity in case-control and cohort studies. (Adapted from Richter and Goldsmith).[4]

Strong Association	Negative Association
No positive bias	No negative bias
No positive confounding	No negative confounding
Chance unlikely	Misclassification of exposure or outcome
Dose-response relationship	Type B error minimized
Many positive studies	Many negative studies
Latency period consistent	Latency not considered

TABLE 50.6. International Agency for Research on Cancer (IARC) assessment of animal studies for carcinogenicity. (Adapted from Richter and Goldsmith).[4]

Category	Definition	Criteria
Sufficient	Causal relationship between agent and human cancer	Positive results from two or more studies or species
Limited	Causal relationship credible, but chance, bias, confounders may explain relationship	Positive result from one study or species
Inadequate	Data insufficient or studies negative	

All agents classified as human carcinogens also produced positive results in at least one animal experiment based on 2006 criteria. The IARC does not include short-term (*in vitro*) testing in the classification scheme, but positive results in such studies may result in a higher classification. The IARC categorizes ~1,000 agents divided into 122 Group 1 (human) carcinogens (Table 50.7), 93 Group 2A (probable human) carcinogens, 319 Group 2B (possible human) carcinogens, 501 Group 3 (not classifiable), and 1 Group 4 (probably not a carcinogen).[9] In contrast to the USEPA, the IARC does not include chemicals with limited evidence in animals and limited evidence in humans as probable human carcinogens (IARC Group 2A).

Tables 50.8 and 50.9 list IARC Group 1 carcinogens for chemical mixtures and specific exposures (industrial processes and byproducts). Epidemiological studies of foundry workers consistently demonstrate a relative risk of lung cancer of 1.5–2.5 compared with the general population.[10] Chromium and nickel fumes are additional lung carcinogens in steel foundries. Most of the epidemiological studies have not measured the relationship between exposure to these suspected carcinogens and excess mortality from lung cancer. In a meta-analysis of 27 studies (cohorts, record linkage, case-control) of lung cancer among painters, the summary relative risk of lung cancer in painters was 1.35 (95% CI: 1.21–1.51) after controlling for smoking.[11] Exposure-response analyses suggested that the increased duration of employment as a painter increased the lung cancer risk.

Table 50.10 lists Group 2A (probable human carcinogens) for chemicals, mixtures, and specific exposures. Although these classification schemes now include mechanism of action data in the carcinogen classification, these databases do **not** typically include biological data (e.g., route of exposure, pharmacokinetics, mechanism of tumor induction, cell proliferation) that allow an estimation of the potential cancer risk in an individual.[2]

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Table 50.11 outlines the 1986 alphanumeric cancer classification of the US Environmental Protection Agency (USEPA). The USEPA revised those guidelines in 2005; however, the USEPA did not reclassify all chemicals previously classified under the 1986 guidelines. Information used to categorize chemicals into the 1986 classification scheme includes human data, animal data, and supporting data using a weight-of-evidence approach. First, a chemical is assigned a category based on an evaluation of human and animal data on the specific chemical. The following terms describe the weight-of-evidence for the chemical: sufficient, limited, inadequate, no data, and no evidence of carcinogenicity. The preliminary classification is revised based on an evaluation of the supporting data (e.g., genotoxicity, toxicokinetics, and mechanistic data).[13] The USEPA cancer classifications of over 540 potential carcinogens have evolved from the alphanumeric categories listed in

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TABLE 50.7. International Agency for Research on Cancer (IARC) list of Group 1 human carcinogens based on IARC volumes 1–125, including biological organisms, chemicals/mixtures, dusts/fibers, metals, personal habits, pharmaceuticals, and radiation. Other categories include occupations and occupational processes. The IARC frequently updates the classification of carcinogens through the publication of new volumes with a complete list of all chemicals in Groups 1–4 available on their website. (https://monographs.iarc.who.int/agents-classified-by-the-iarc/). (Adapted from Cogliano et al.).[10]

Substance [CAS Number]	Main Tissue Tumor Types
Acetaldehyde in alcoholic beverages	Esophagus, upper aerodigestive tract
Acid mists, strong inorganic	Larynx
Aflatoxins	Liver, hepatocellular carcinoma
4-Aminobiphenyl [92-67-1]	Bladder
Aristolochic acid [313-67-7][a]	Renal pelvis[b], ureter[b]
Aristolochic acid, plants containing	Renal pelvis, ureter
Arsenic [7440-38-2] and arsenic compounds[c]	Lung, skin, bladder
Asbestos [1332-21-4]	Lung, pleural/peritoneal mesothelioma, ovary
Azathioprine [446-86-6]	Non-Hodgkin lymphoma, squamous cell carcinoma, skin
Benzene [71-43-2]	Leukemia
Benzidine [92-87-5]	Bladder
Benzo[*a*]pyrene [50-32-8][a]	—
Beryllium [7440-41-7] and beryllium compounds[a, c]	Lung
N,*N*-Bis(2-chloroethyl)-2-naphthylamine (chlornaphazine) [494-03-1]	Bladder
Bis(chloromethyl)ether [542-88-1] and chloromethyl methyl ether [107-30-2] (technical-grade)	Lung
Busulfan (Myleran®)	Acute myeloid leukemia
1,3-Butadine [106-99-0]	Hemolymphatic system
1,4-Butanediol dimethanesulfonate (Busulphan; Myleran) [55-98-1]	Hematopoietic system
Cadmium [7440-43-9] and cadmium compounds[c]	Lung
Chlorambucil [305-03-3]	Acute myeloid leukemia
Chlornaphazine [494-03-1]	Bladder
1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (methyl-CCNU; semustine) [13909-09-6]	Hematopoietic system
Chromium[VI] compounds[c]	Lung
Clonorchis sinensis, chronic infection	Cholangiocarcinoma
Coal, indoor emissions from combustion	Lung
Coal tar pitch	Skin, lung
Cyclosporin [79217-60-0]	Non-Hodgkin lymphoma, non-melanotic skin
Cyclophosphamide [50-18-0]/[6055-19-2]	Acute myeloid leukemia, bladder
Diethylstilbestrol [56-53-1], during pregnancy	Breast
Diethylstilbestrol [56-53-1], *in utero*	Cervical clear cell adenocarcinoma, vaginal clear cell adenocarcinoma

(Continued)

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TABLE 50.7. (Continued)

Substance [CAS Number]	Main Tissue Tumor Types
Epstein–Barr virus	Burkitt lymphoma, extranodal NK/T-cell lymphoma, Hodgkin and non-Hodgkin (immune suppression related) lymphoma, nasopharynx
Erionite [66733-21-9]	Pleural/peritoneal mesothelioma
Estrogen menopausal therapy	Endometrium ovary
Estrogen-progestogen contraceptives	Breast, cervix, hepatocellular liver carcinoma
Ethylene oxide [75-21-8]	Hematopoietic system[b]
Etoposide [33419-42-0] in combination with cisplatin and bleomycin	Acute myeloid leukemia
Fission products including ^{90}strontium	Leukemia, solid cancers
Formaldehyde [50-00-0]	Nasopharynx, leukemia
Helicobacter pylori chronic infection	Stomach
Hepatitis B virus (chronic infection)	Liver-hepatocellular carcinoma
Hepatitis C virus (chronic infection)	Liver-hepatocellular carcinoma, non-Hodgkin lymphoma
Herpesvirus, Kaposi sarcoma	Kaposi sarcoma, primary effusion lymphoma
Human immunodeficiency virus type 1 (infection)	Anus, cervix, eye-conjunctiva, Hodgkin and non-Hodgkin lymphoma, Kaposi sarcoma
Human papillomavirus type 16	Anus, cervix, oral cavity, oropharynx, penis, tonsil, vagina, vulva
Human papillomavirus type 18, 31, 33, 35, 45, 51, 52, 56, 58, 59	Cervix
Human T cell lymphotropic virus type 1	Leukemia, T-cell lymphoma-adult
Kaposi sarcoma herpes virus	Kaposi sarcoma, primary effusion lymphoma
Melphalan [148-82-3]	Acute myeloid leukemia, lung
8-Methoxypsoralen (methoxsalen) [298-81-7] plus ultraviolet A radiation	Skin squamous cell carcinoma
4,4′-Methylenebis(2-chloroaniline) (MOCA) [101-14-4][a]	—
Mineral oils, untreated/mildly treated	Skin
MOPP and other combined chemotherapy including alkylating agents	Acute myeloid leukemia
Mustard gas (sulfur mustard) [505-60-2]	Pharynx, larynx, lung
2-Naphthylamine [91-59-8]	Bladder
Nickel compounds[c]	Lung, nasal cavity, paranasal sinuses
N′-Nitrosonornicotine (NNN) [16543-55-8][a]	—
4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) [64091-91-4][d a]	—
Opisthorchis viverrini, chronic infection	Liver-cholangiocarcinoma
3,4,5,3′,4′-Pentachlorobiphenyl (PCB-126) [57465—28-8][a]	—
2,3,4,7,8-Pentachlorodibenzofuran [57117-31-4][a]	—
Pentachlorophenol [87-86-5]	—
Phenacetin [62-44-2]	Renal pelvis, ureter

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TABLE 50.7. (Continued)

Substance [CAS Number]	Main Tissue Tumor Types
Polychlorinated biphenyls (PCBs 77, 81, 105, 114, 118, 123, 126 156, 157, 167, 169, 189)[a]	Melanoma
^{32}Phosphorus	Acute leukemia
Plutonium	Bone, liver, lung
Radioiodines including ^{131}Iodine	Thyroid
^{222}Radon [10043-92-2] and its decay products	Lung
^{224}Radium and decay products	Bone
^{226}Radium and ^{228}Radium plus decay products	Bone, mastoid process, paranasal sinus
^{232}Thorium and decay products	Bile duct, gall bladder, leukemia except chronic lymphocytic leukemia, liver hemangiosarcoma
Schistosoma haematobium, chronic infection	Bladder
Semustine (methyl-CCNU)	Acute myeloid leukemia
Silica dust, crystalline [14808-60-7] (occupational exposure to inhaled quartz/cristobalite)	Lung
Solar radiation	Skin
Soot	Skin
Sulfur mustard	Lung
Talc containing asbestiform fibers	Lung
Tamoxifen [10540-29-1] [d]	Endometrium
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin [1746-01-6]	Overall cancer rate
o-Toluidine [95-53-4]	Bladder
Thiotepa [52-24-4]	Leukemia
Treosulfan [299-75-2]	Acute myeloid leukemia
Trichloroethylene [79-01-6]	Kidney
Vinyl chloride [75-01-4]	Liver, angiosarcoma, hepatocellular
Gamma (γ)-, X-ray radiation	Bladder, bone, brain and central nervous system, breast-female, colon, esophagus, kidney, leukemia except chronic lymphocytic leukemia, lung, salivary gland, skin-basal cell carcinoma, stomach, thyroid
Ultraviolet radiation (UVA, UVB, UVC), tanning devices	Skin-basal cell carcinoma, melanoma (eye), squamous

[a] Upgraded to Group 1 based on mechanistic and/or other relevant data rather than sufficient human data alone. [b] Limited evidence only. [c] Evaluation applies to the group of compounds as a whole and not necessarily to all individual compounds within the group. Metallic nickel and nickel alloys are classified as Group 2B. [d] There is also conclusive evidence that this agent (tamoxifen) reduces the risk of contralateral breast cancer.

Table 50.11 to a narrative paragraph with standardized descriptions based on guidelines published in 1996, 1999, and 2005. These guidelines permit consideration of the relevance of bioassays to human exposures, including analysis of the mode of action and similarity of the routes of exposure, with preference given to peer-reviewed scientific journals.

The USEPA scheme is more rigorous than the IARC classification because the probable human carcinogen and the noncarcinogenic categories require human data; however, the USEPA tends to classify animal carcinogens into higher cancer categories in the absence of human data consistent with their primary goal of protecting human health as described

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TABLE 50.8. International Agency for Research on Cancer (IARC) Group 1 human carcinogens associated with specific exposures (industrial processes, by-products, environmental carcinogens) with suspected carcinogens. Other chemicals may contribute to the carcinogenic process (e.g., chromium/nickel fumes contribute to lung cancer in steel foundries).[12] IARC frequently updates the classification of carcinogens through the publication of new volumes. For the most current list of Group 1 carcinogens, refer to the IARC website at https://monographs.iarc.who.int/wp-content/uploads/2019/12/OrganSitePoster.PlusHandbooks.pdf. (Adapted from IARC).[9]

Specific Exposure	Main Tumor Tissue Types
Acheson process, occupational exposure	Lung
Aluminum production (PAH, tar volatiles)	Lung, bladder
Auramine manufacturing (auramine, aromatic amines)	Bladder
Coal gasification	Ling
Coal-tar pitches [65996-93-2]	Skin, lung
Coal tar [8007-45-2] distillation	Skin
Coke production	Lung
Diesel engine exhaust	Lung
Fluoro-edenite fibrous amphibole	Mesothelioma
Furniture and cabinet making (wood dust)	Nasal cavity
Hematite underground mining (radon exposure)	Lung
Iron and steel founding	Lung
Isopropanol manufacture (strong-acid process)	Nasal cavity and paranasal sinuses
Leather dust	Nasal cavity and paranasal sinuses, nasopharynx
Magenta, manufacture of	Bladder
Mineral oils, untreated and mildly treated	Skin
Painter, occupational	Bladder, lung, mesothelioma
Rubber industry (benzene, aromatic amines)	Bladder, leukemia, lymphoma, lung, stomach
Shale oils [68308-34-9]	Skin
Strong inorganic acid mists containing sulfuric acid (occupational exposure)	Larynx
Welding	Eye-melanoma

Abbreviation: PAH = polycyclic aromatic hydrocarbons.

TABLE 50.9. IARC Group 1 human carcinogens associated with mixtures of chemicals. IARC frequently updates the classification of carcinogens with the publication of new volumes. For the most current list of Group 1 carcinogens, refer to the IARC website https://monographs.iarc.who.int/agents-classified-by-the-iarc/. (Adapted from IARC).[9]

Mixtures	Main Tumor Tissue Type
Air pollution/particulate matter, outdoors	Lung
Alcoholic beverages	Female breast, colorectum, esophagus, larynx, hepatocellular liver, oral cavity, pharynx
Betel quid without tobacco	Esophagus oral cavity
Betel quid with tobacco	Esophagus, oral cavity, pharynx
Salted fish (Chinese-style)	Nasopharynx
Solar radiation	Skin
Soots associated with chimney sweeps	Skin, lung
Tobacco, environmental	Lung
Tobacco smoking	Oral cavity, pharynx, esophagus
Tobacco smoke	Bladder, cervix, colorectum, esophagus (adenocarcinoma, squamous cell carcinoma, kidney, myeloid leukemia, larynx, liver, lung, nasal cavity/paranasal sinus, ovary, pancreas, pharynx, stomach, ureter pharynx, larynx, esophagus, pancreas, kidney)
Tobacco, smokeless	Esophagus, oral cavity, pancreas

in Table 50.12.[14] The weight-of-evidence does not correspond to a specific quantitative probability of chemical carcinogenicity as a result of the difficulty in assigning a probably from supportive data. However, the USEPA database provides quantitative estimates of carcinogenic risk for oral and pulmonary routes of exposure as well as reference concentrations and doses that estimate the daily oral or continuous inhalation exposure that is unlikely to produce an appreciable risk of deleterious effects during a lifetime for the human population including sensitive subgroups.[15]

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TABLE 50.10. IARC list of Group 2A carcinogens (probable human carcinogens). A complete listing of chemical substances and mixtures is available on the IARC website (https://monographs.iarc.who.int/agents-classified-by-the-iarc/).

Substance	CAS No.
Chemicals	
Acrylamide	79-06-1
Adriamycin	
Androgenic (anabolic) steroids	23214-92-8
Azacitidine	320-67-2
Bischloroethyl nitrosourea (BCNU)	154-93-8
Captafol	2425-06-1
Chloral	75-87-6
Chloral hydrate	302-17-0
Chloramphenicol	56-75-7
α-Chlorinated toluenes combined exposure ((benzal chloride [98-87-3], benzotrichloride [98-07-7], benzyl chloride [100-44-7]), and benzoyl chloride [98-88-4])	
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)	13010-47-4
p-Chloro-*o*-toluidine and its strong acid salts[a]	95-69-2
Chlorozotocin	54749-90-5
Cisplatin	15663-27-1
Cobalt metal (7740-18-4) with tungsten carbide	12070-12-1
Cyclopenta[*c*,*d*]pyrene[b]	27208-37-3
Diazinon	333-41-5
Dibenz[*a*,*j*]acridine	224-42-0
Dibenz[*a*,*h*]anthracene	53-70-3
Dibenzo[*a*,*l*]pyrene	191-30-0
4,4′-dichlorodiphenyltrichloroethane (DDT)	50-29-3
Dichloromethane (methyl chloride)	75-09-2
Dieldrin (60-57-1) and aldrin (309-00-2) metabolized to dieldrin	
Diethyl sulfate	64-67-5
Dimethylcarbamoyl chloride	79-44-7
Dimethylformamide	68-12-2
1,2-Dimethylhydrazine	540-73-8
Dimethyl sulfate	77-78-1
Epichlorohydrin	106-89-8
Ethyl carbamate (urethane)	51-79-6
Ethylene dibromide	106-93-4
N-Ethyl-*N*-nitrosourea	759-73-9
Glycidol	556-52-5
Glyphosate	1071-83-6
Human papillomavirus type 68	
Hydrazine	302-01-2
Indium phosphide	22398-80-7
IQ (2-Amino-3-methylimidazo[4,5-*f*]quinoline)	76180-96-6
Lead compounds, inorganic	
Malaria, infection by *Plasmodium falciparum* in holoendemic area	
Malathion	121-75-5
2-Mercaptobenzothiazole	149-30-4
Merkel cell polyomavirus (MCV)	
5-Methoxypsoralen	484-20-8
Methyl methanesulfonate	66-27-3
N-Methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG)	70-25-7
N-Methyl-*N*-nitrosourea	684-93-5
Nitrite/nitrate from endogenous nitrosation	
6-Nitrochrysene	7496-02-8

(Continued)

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TABLE 50.10. (Continued)

Substance	CAS No.
Nitrogen mustard	51-75-2
1-Nitropyrene	5522-43-0
N-Nitrosodiethylamine	55-18-5
N-Nitrosodimethylamine	62-75-9
2-Nitrotoluene	88-72-2
Pioglitazone	111025-46-8
Polybrominated biphenyls	59536-65-1
Procarbazine hydrochloride	366-70-1
1,3-Propane sultone	1120-71-4
Styrene	100-42-5
Styrene-7,8-oxide	96-09-3
Teniposide	29767-20-2
Tetrabromobisphenol A	79-94-7
3,3′,4,4′-Tetrachloroazobenzene	14047-09-7
Tetrachloroethylene	127-18-4
1,2,3-Trichloropropane	96-18-4
Tetrafluoroethylene	116-14-3
Tris(2,3-dibromopropyl) phosphate	126-72-7
Vinyl bromide	593-60-2
Vinyl fluoride	75-02-5
Mixtures	
Bitumens, occupational exposure to oxidized bitumens and emissions during roofing	64742-93-4
Creosotes	8001-58-9
Non-arsenical insecticides, occupational exposures in spraying and application	
Very hot beverages (>65°C) including hot mate	
Exposure	
Art glass, glass containers, and pressed ware manufacturing	
Biomass fuel, primarily wood with indoor emissions from combustion	
Carbon electrode manufacture	
Frying, high-temperature emissions	
Hairdresser or barber, occupational exposure	
Petroleum refining, occupational exposure	
Red meat consumption	
Shiftwork involving circadian rhythm disruption	
Silicon carbide whiskers 409-21-2	

[a] Evaluated as a group. [b] Upgraded to 2A based on supporting evidence from other data.

EUROPEAN GLOBALLY HARMONIZED SYSTEM

As a method to standardize the carcinogenic hazards of chemicals, the United Nations Conference on Environment and Development (UNCED) developed the Globally Harmonized System (GHS) to classify chemical carcinogenicity; this system uses two categories of known or presumed human carcinogens (Categories 1A, 1B) and suspected human carcinogens (Category 2), as displayed in Table 50.13.[16] Allocation of substances to these categories depends on an evaluation of the inherent properties of the chemical or mixture, including the strength of human/animal evidence and a weight-of-evidence approach to additional information relevant to the potential of these substances to produce cancer. Although determination of the category may be specific to the route of exposure, these categories do not necessarily provide information about potency, risk, or exposures relevant to humans.[17] The GHS considers a chemical demonstrating evidence of carcinogenicity in a well-designed experimental study as a presumed or

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TABLE 50.11. 1986 United States Environmental Protection Agency (USEPA) classification of carcinogenicity and cancer types associated with human and probable human carcinogens based on epidemiological evidence. The cancer type associated with a specific chemical depends on the route of exposure (see IRIS database for specific details on individual chemicals). The latest USEPA guidelines allow multiple descriptors for individual chemicals or mixtures (e.g., hexavalent chromium). From USEPA Integrated Risk Information System (IRIS) Database (https://cfpub.epa.gov/ncea/iris/search/index.cfm). (Adapted from IRIS Advanced Search, USEPA).

Carcinogen Group	Description of Evidence	Chemical (Cancer Type – Human or Animal)
A (Human)	Sufficient human	Arsenic, inorganic (skin, lung); asbestos (lung, mesothelioma); benzene (leukemia); benzidine (bladder); bis(chloromethyl)ether (respiratory tract); chromium VI (lung); coke oven emissions (respiratory); nickel subsulfide or refinery dust (lung); vinyl chloride (liver angiosarcoma, hepatocellular carcinoma)
B1 (Probable Human)	Limited human	Acrylonitrile (brain or spinal cord astrocytomas, Zymbal's gland carcinoma, stomach papillomas, and carcinomas/respiratory); beryllium and compounds (lung); cadmium (lung, trachea, bronchus); formaldehyde (squamous cell carcinoma)
B2 (Probable Human)	No or inadequate human data and sufficient animal	Acetaldehyde, aldrin, aniline, aramite, azobenzene, benzotrichloride, benzyl chloride, bis(chloroethyl)ether, bromate, bromodichloromethane, bromoform, chlordane, chloroform, di(2-ethylhexyl)phthalate (DEHP), 3,3′-dichlorobenzidine, *p*,*p*′-dichlorodiphenyldichloroethane (DDD), dichlorodiphenyldichloroethylene (DDE), dichlorodiphenyltrichloroethane (DDT), 1,2-dichloroethane, 1,3-dichloropropene, dichlorvos, dieldrin, 2,4/2,6-dinitrotoluene mixture, 1,2-diphenylhydrazine, epichlorohydrin, furmecyclox, heptachlor, hexachlorobenzene, hexachlorocyclohexane, hexachlorodibenzo-*p*-dioxin mixture, hydrazine/hydrazine sulfate, 4,4′-methylene bis(*N*,*N*′-dimethyl)aniline, *N*-nitroso-*N*-methylethylamine, *N*-nitroso-di-*n*-butylamine, *N*-nitrosodi-*N*-propylamine, *N*-nitrosodiethanolamine, *N*-nitrosodiethylamine, *N*-nitrosodimethylamine, *N*-nitrosodiphenylamine, *N*-nitrosopyrrolidine, polychlorinated biphenyls (PCBs), propylene oxide, quinoline, toxaphene, 2,4,6-trichorophenol
C (Possible human)	No human and limited animal	Di(2-ethylhexyl)adipate, dibromochloromethane, hexachlorobutadiene, β-hexachlorocyclohexane, hexahydro-1,3,5-trinitro-1,3,5-triazine, isophorone, prochloraz, 1,1,1,2-tetrachloroethane, 1,1,2-trichloroethane, trifluralin, 2,4,6-trinitrotoluene (TNT)
D (Not classifiable)	No or inadequate human and animal	Chromium VI inhalation
E (Noncarcinogenic)	At least two negative animal studies or negative human and animal studies	None

suspected human carcinogen unless the mechanism of tumor formation is not relevant to humans.

Additional information via a weight-of-evidence evaluation may increase or decrease the likelihood that the substance is a human carcinogen and elevate the suspected carcinogen to Category 1. Typically, the requirement for changing a category is more stringent for decreasing than increasing the level of concern. The weight-of-evidence evaluation involves multiple factors including tumor type, number, background incidence, latency, progression, routes of exposure, structural similarity to known carcinogens, relevance of toxicokinetics of test animals to humans, carcinogenic responses of multiple species and sexes, dose-response, and relevance of mode of action to humans.

AMERICAN CONFERENCE OF GOVERNMENTAL AND INDUSTRIAL HYGIENISTS

The American Conference of Governmental and Industrial Hygienists (ACGIH, https://www.acgih.org/) is a private US organization that classifies potential carcinogens into five categories, as displayed in Table 50.14, based on their evaluation of evidence. In evaluating occupational carcinogens, ACGIH places

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TABLE 50.12. 2005 US Environmental Agency (USEPA) criteria for classification of carcinogenicity. More than one descriptor can apply to a chemical exposure when the carcinogenic effect differs by internal dose (e.g., poor absorption) or route of exposure. (Data adapted from Environmental Protection Agency).[15]

Descriptor	Weight-of-Evidence	Description of Evidence
Carcinogenic to humans	Strong evidence in humans	Convincing epidemiological evidence of causal association or Lesser epidemiological evidence with strong association, extensive animal evidence, identified mode of action, **AND** consistent biological mechanisms in animals and humans
Likely to be carcinogenic to humans	Adequate carcinogenic potential with likely rather than strong evidence in humans[a]	Broad spectrum including plausible, but not causal association in epidemiology studies with supporting biological or experimental evidence, strongly positive animal evidence (<1 study type) with/without human evidence, strongly positive tumor study with highly malignant, early tumor onset, or relevant rare response, The A positive tumor study with a supportive mechanistic or epidemiological data
Suggestive evidence of carcinogenic potential	Suggestive without sufficient evidence for stronger association	Varying concerns for carcinogenicity including small increased tumor incidence in single animal or human study less than likely category, small increased tumor rate with high background rate with inability to exclude alternative to chemical carcinogenicity, or Evidence of positive study with design flaws or no dose-response
Inadequate information to assess carcinogenic potential	Inadequate information to assess carcinogenic potential	Little or no information, conflicting evidence, or negative study without sufficient evidence to raise descriptor to suggestive level
Not likely to be carcinogenic to humans	Robust data indicating no human carcinogenic hazard	Extensive, convincing evidence that a chemical is not carcinogenic by exposure route, above threshold, or Strong evidence of lack of animal carcinogenicity with no human data suggesting carcinogenic effect

[a] The term does not imply a quantifiable probability.

TABLE 50.13. Carcinogenic categories of the UN Globally Harmonized System of Classification and Labelling of Chemicals. Sufficient evidence indicates a causal association between the substance and cancer development, whereas limited evidence implies a positive association between the exposure and the substance that is not definitely causal. (Adapted from United Nations).[16]

Category	Classification	Criteria
1A	Known human carcinogen	Based primarily on epidemiology data demonstrating a causal relationship between exposure and tumor formation.
1B	Presumed human carcinogen	Based primarily on sufficient evidence from animal studies. Depending on a weight-of-evidence evaluation of additional information, a substance may be elevated to a higher category with limited evidence of carcinogenicity in humans and experimental animals.
2	Suspected human carcinogen	Limited evidence in human and/or animal studies with insufficient evidence to place substances in category 1.

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TABLE 50.14. American Conference of Governmental and Industrial Hygienists (ACGIH) classification of carcinogens.

Category	Classification	Criteria
A1	Confirmed human carcinogen	Carcinogenic to humans based on weight-of-evidence from epidemiological studies.
A2	Suspected human carcinogen	Human data is adequate but conflicting (insufficient) to elevated to A1 or An experimental animal carcinogen (sufficient) at relevant occupational exposures.
A3	Confirmed animal carcinogen with unknown relevance to humans	Animal carcinogens at doses, routes or Mechanisms not relevant to occupational exposures and unlikely to cause human cancers.
A4	Not classifiable as a human carcinogen	Agents of concern without adequate data including lack of animal data.
A5	Not suspected as a human carcinogen	Existing studies of sufficient quality demonstrate no significant cancer risk or lack of experimental animal data supported by mechanistic data. This category also contains substances with no reported human or experimental animal carcinogenicity.

greater emphasis on human evidence in order of preference beginning with cohort studies and then case-control studies, case reports, and descriptive studies. The criteria for interpreting these epidemiology studies include strength of statistical association, dose-response relationships, temporal relationship between exposure and disease, consistency with previously reported epidemiological studies, coherence with known biological mechanisms, specificity of risk in high-exposure workplaces, and statistical significance. The ACGIH considers experimental animal data preferring long-term bioassays in two mammalian species at doses and routes relevant to workplace exposures.

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Chapter 51

RISK ASSESSMENT

BACKGROUND

Risk assessment provides a conceptual framework for the structured review of chemical toxicity and adverse health effects that could potentially result from chemical exposure by evaluating the hazard (toxicity) and exposure to the chemical, compound, or mixture.[1] Toxicity is an inherent property of all chemicals; consequently, all chemicals are hazardous depending on the dose necessary to develop adverse effects. A hazard connotes the *potential* to produce an adverse effect. The Environmental Protection Agency and the International Agency for Research on Cancer identify cancer hazards by classifying the potential of a chemical to cause cancer based on animal, human, and computational data. Risk is the *probability* that an adverse effect (e.g., cancer) will occur. This probability depends on the dose delivered to the critical target organ and the carcinogenic potency;[2] hence, the presence of an environmental carcinogen does not necessarily imply cancer will develop. Risk assessment determines the likelihood of an adverse effect (e.g., cancer) given the uncertainties involved in the analysis.

Risk assessment possesses no units of measure. Numerical risk values range from zero (i.e., no chance of occurrence) to one (i.e., absolute certainty). Chemical use produces risks of adverse health effects including cancer; however, the reduction of the risk to zero is not possible because many carcinogens occur naturally. Consequently, the presence of these chemicals cannot be completely eliminated without unacceptable social and economic costs.[3] The concept of acceptable risk recognizes the impracticality of eliminating all cancer risks as an alternative to the concept of zero risk.

The US regulatory agencies (Food and Drug Administration, FDA; Environmental Protection Agency, USEPA) establish carcinogen exposure concentrations in food, consumer products, water, and the environment based on the Acceptable Risk Concept.[4] Therefore, governmental agencies balance relatively small cancer risks with public interests by establishing exposure concentrations that produce negligible or *de minimus* risk.[5] Typically, these agencies set the acceptable level at 1 excess cancer death/1,000,000 lifetime exposures. An acceptably low risk (i.e., 1×10^{-6}) rather than an absolute absence of risk (i.e., 0) defines a safe risk.

EPA and Quantitative Risk Assessment

Risk assessment quantifies the probability that an adverse effect will occur by using mathematical models to extrapolate high-dose animal exposures to the low-dose exposures present in the human environment. Consequently, qualitative risk assessment depends on the validity of the mathematical assumptions used in the modeling process rather than on epidemiological data.[6] The critical data points define the slope of the dose-response curve rather than the NOAEL; the latter approximates the threshold for adverse health effects. Although the appropriate methodology and modeling for the estimation of these critical data points are somewhat controversial, the linear, no-threshold model that extrapolates relevant animal exposure data to humans

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remains the default method for evaluating carcinogenic risk given the concern for safety and existing uncertainty.[1] Health protective risk assessment procedures, as described in the USEPA cancer guidelines, mean cancer estimates contain some uncertainty; however, these estimates are more likely to overstate than understate hazard and/or risk.[7]

Most US government agencies use this methodology to estimate the risk of exposure to suspected carcinogens. This process depends on the potency of the chemical and the amount of absorbed dose and uses four steps: 1) hazard identification – what is the identity and circumstances of the suspected human carcinogen based on existing scientific evidence? 2) exposure assessment – what are the conditions (amount, frequency, duration) of human exposure? 3) dose-response assessment – what effects occur at the estimated exposure level based on human, extrapolated animal, *in vitro*, and mechanistic data? and 4) risk characterization – what is the summarized character of the risk and validity of supporting data (extent, nature) for the estimated risk to the suspected carcinogen including the uncertainty? Risk assessments are conducted without consideration of the consequences of regulatory action; however, risk management combines risk assessment with the directives of legislation to determine the necessity to control specific chemical exposures. Other factors involved with the determination of final policies regarding chemical exposure include socioeconomic values, cost, technical feasibility, duration and magnitude of risk, and the population at risk as well as political and trade considerations.

The USEPA Integrated Risk Information System (IRIS) assessment program evaluates the quantitative and qualitative risk information on >540 potential environmental contaminants for hazard identification and dose-response evaluation.[8] These hazard assessments provide quantitative data for noncarcinogens (oral/inhalational reference doses) and carcinogens (oral slope factors, inhalation unit risks). For the latter, the USEPA uses a weight-of-evidence approach based on animal, human, pharmacokinetic, and mechanistic (mode-of-action) data, including analysis of study design (e.g., appropriate statistical analysis), as outlined in Figure 51.1. The use of mode-of-action in the potential carcinogen assessment is a primary focus of USEPA

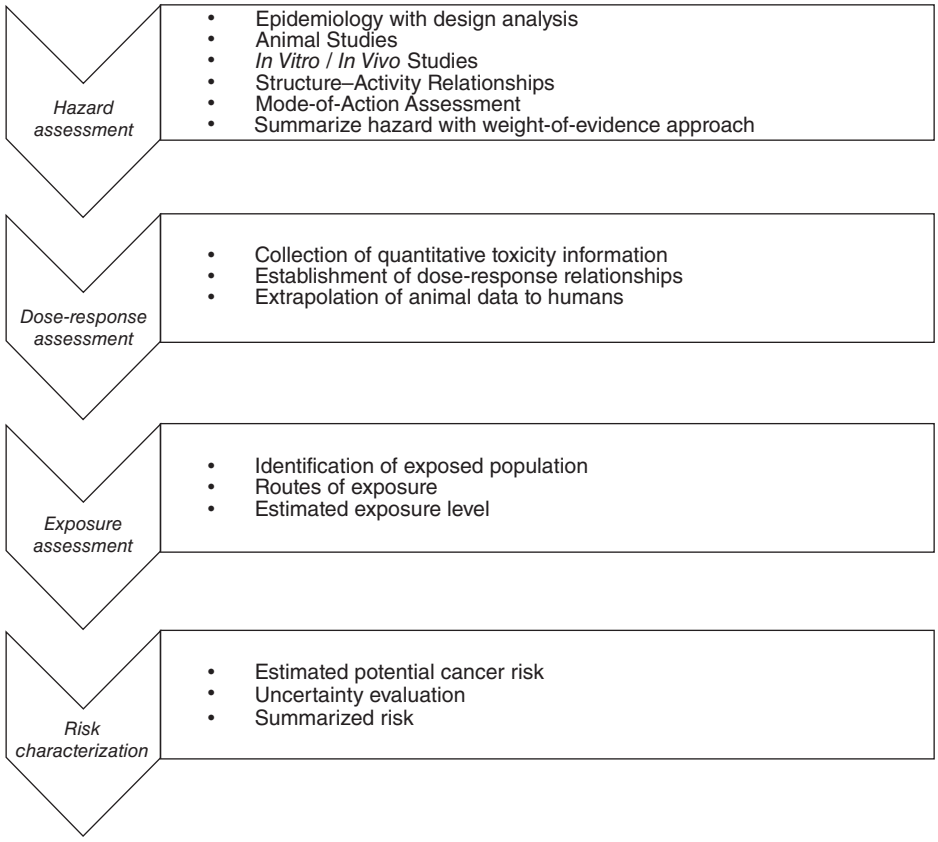


FIGURE 51.1. Four main elements of risk assessment with descriptors. (Adapted from Derelanko).[10]

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cancer guidelines to integrate recent significant scientific advances involving the causation of cancer into the risk assessment process. The mode-of-action represents the sequence of key events and processes (e.g., mutagenicity, mitogenesis, cytotoxicity with subsequent cell proliferation, inhibition of cell death, immune suppression) that proceeds from the initial cell–agent interaction through anatomical and operational alterations to malignant tumor formation. Understanding these processes helps identify susceptible populations and life stages. The weight-of-evidence approach summarizes the results of hazard assessment by providing conclusions regarding the likelihood of human carcinogenic effects and the conditions necessary for cancer formation, including an analysis of the data (i.e., strengths, limitations, significant issues). The standard hazard descriptors with the older alphanumeric group classification include: 1) carcinogenic to humans – Group A, 2) likely to be carcinogenic to humans – Group B, 3) suggestive evidence of carcinogenic potential – Group C, 4) inadequate information to assess carcinogenic potential – Group D, and 5) not likely to be carcinogenic to humans – Group E.[7,9]

Most risk assessments of low-dose exposure to chemical carcinogens accept conservative assumptions designed to overestimate the true risk in order to provide an extra margin of safety.[11] These conservative assumptions include the following: 1) the risk to humans is similar to the risk of the most sensitive animal species, 2) benign tumors are included in the assessment, unless there is scientific evidence to the contrary, 3) there is no threshold dose, 4) cross-species scaling factors (e.g., $(\text{body weight})^{3/4}$) are appropriate, and 5) mathematical models accurately predict the dose-response curve at levels of exposure below the lowest experimental dose. Hence, chemical exposure at concentrations near regulatory levels does not necessarily imply cancer will develop.

The accuracy of risk assessment depends on the adequacy of the data, the appropriateness of the extrapolation from experimental data to actual situations, and the extent of our understanding of the biological mechanisms and modes of action that relate exposure to cancer outcomes. Two priorities of the EPA are the development of more accurate models (e.g., biologically based dose-response models) and a better estimation of the amount of chemical exposure in the environment.

Safety Factor Analysis

The safety factor technique for food additives, drinking water, and air is an alternative to quantitative risk assessment as a method to establish safe chemical concentrations without properties of germ cell mutagens or genotoxic carcinogens; this method uses a variety of indices to determine safety including acceptable daily intake (ADI), reference dose, tolerable daily intake, potency index, minimal risk level, and hazard index. This semiquantitative approach for noncarcinogens assumes the presence of a threshold level (i.e., the no observable adverse effect level, NOAEL) determined by animal testing below which adverse health effects do not occur. The NOAEL is an experimentally derived value with biological variability rather than an absolute value; consequently, the chemical concentration defining the NOAEL depends on the sample size of the study. Furthermore, the estimated NOAEL for a rare toxicological event in the study population usually lacks precision. The major limitation of safety indices is the lack of information on the likelihood of adverse effects following exposure to concentrations exceeding the index value for carcinogens and noncarcinogens.[12]

A safety or uncertainty factor provides a protective margin to account for extrapolation from animal models to humans while protecting susceptible segments of the population.[13] Hence, wide safety margins for the protection of public health should not be confused with the establishment of causation when exposures exceed the regulatory limits.[14] Equation 51.1 describes the relationship between the safety factor and the acceptable level as defined by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO).

$$\text{Acceptable daily intake (ADI)} = \frac{\text{NOAEL (animal data)}}{\text{Safety factor}} \qquad \text{(Equation 51.1)}$$

The uncertainty factor is usually 10-fold, with the size of this factor depending on an evaluation of chronic bioassay data, chemical properties, and interspecies variability. The USFDA adds an additional 10-fold factor when only subchronic studies are available to establish the NOAEL. The addition of a 10-fold factor for individual human variability means that an acceptable margin of safety is 100. Table 51.1 lists factors that increase or decrease the safety factor. Both the US EPA and the FAO/WHO initially used the ADI-derived method to establish safe concentrations of chemicals for adverse effects **other than** carcinogens and mutagens. The acceptable daily intake (ADI) is an estimate (i.e., within an order of magnitude) of the daily uptake in a human population, including sensitive people, that would not result in an appreciable risk of deleterious effects over a lifetime exposure.[15] The USEPA redefines the ADI as the reference dose (RfD) and the

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TABLE 51.1. Factors modifying the value of the safety factor.

Factor	Increase	Decrease
Mechanism of action	Unknown	Known
Evidence of threshold effect	Absent	Present
Human evidence	Limited	Substantial
Human exposure	Continuous	Intermittent
Human elimination	Slow with accumulation	Rapid
Most sensitive species	Man	Animal
Test species	Not most sensitive	Most sensitive
Induction of adverse effects	Several species	One species
In vitro tests	Genotoxic	Nongenotoxic
Majority of tumors	Malignant with rapid metastasis	Benign
Tumor sites	Multiple	Single
Tumor development	Both sexes	One sex
Tumor type	Rare	Common

safety factor as the uncertainty factor. Although the safety factor process assumes a threshold exists below which exposure to the chemical produces no adverse effect, chemical exposures to concentrations near the RfD (i.e., ADI) level do not necessarily cause adverse effects because of the addition of the safety factor. Figure 51.2 displays the dose-response curve from a typical (noncarcinogenic) toxicology study.

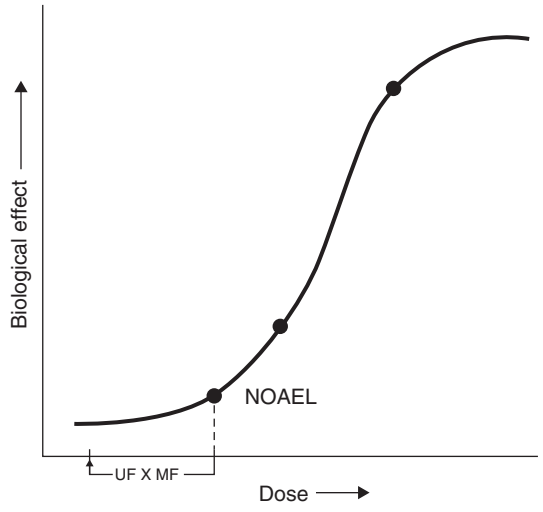


FIGURE 51.2. Schematic representation of noncarcinogenic dose-response curve displaying the relationship between the RfD (reference dose) or RfC (reference concentration) and the No Observable Adverse Effect Level (NOAEL) usually derived from animal data. The RfD and RfC assume a threshold value and include a safety factor derived from the product of an uncertainty factor (UF) and modifying factor (MF) that may deviate from the NOAEL by several orders of magnitude, depending on the quality of the data and modifying factors listed in Table 51.1. (Adapted from Derelanko).[10]

Risk Management

Risk management is a political process that integrates social, economic, and technical considerations with the scientific estimation of health risk to reach a decision on the extent to which chemical exposure is controlled. This decision-making process evaluates alternative regulatory actions and selects the appropriate response based on socioeconomic and political considerations. Defining strategies to control chemical exposures involves a value judgment regarding the acceptability of risk. Traditionally, the acceptable risk for a carcinogen is 1×10^{-6} or one excess cancer death per 1 million lifetime exposures.

Risk Communication

Risk is an inescapable part of life; risks are considered acceptable when the benefits outweigh the risk. However, the risk of exposure to a chemical often is not shared proportionally with the benefits associated with the chemical. Furthermore, involuntary exposure issues are compounded by the inability to decide the extent of exposure; this situation results in highly emotional debates when strongly held perceptions are not consistent with scientific reality. In such settings, the communication of factual information should be done by comparison of relative risks of similar situations. Acceptance of risk depends on factors (e.g., severity of outcome, perceived probability of occurrence, peer pressure, ability to control exposure, suffering associated with outcome, visibility of alternate source to blame, perceived benefit, and degree of uncertainty.[16]

The acceptance of risk for an undesirable outcome from a chemical exposure or an activity is specific to the individual (e.g., smoking, riding a motorcycle). When the

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individual does not accept the risk and the undesirable outcome occurs, the situation may provoke emotional distress and rage in the individual. This situation should be considered when communicating the risks of an outcome to an audience. Table 51.2 presents comments on the important factors that affect risk communication.

HAZARD IDENTIFICATION

Hazard identification is a *qualitative* risk assessment process that first determines which chemicals are present in the environment and then evaluates the potential of the chemicals to produce cancer or another adverse effect, including the circumstances necessary to express that potential risk.[9] The hazard identification process answers the following two questions: 1) does the chemical cause cancer or another health hazard? and 2) when does the identified hazard appear? A weight-of-evidence approach assesses the available data, including the quality and results of animal and epidemiological studies, *in vitro*/*in vivo* data, structure–activity relationships, and modes of action.[1] The ability of a chemical to cause cancer depends on its ability to reach the appropriate site in a biologically active form. Part of the hazard identification process includes an analysis of the physiochemical, metabolic, and pharmacokinetic properties as well as the routes and patterns of exposure to determine the extent a chemical presents an environmental carcinogenic hazard. The result of the hazard identification process is a scientific judgment on the potential of a chemical to cause human cancer or another adverse event.

Physiochemical Properties

Although this section intuitively seems to be part of exposure assessment, both the toxic potential and the physicochemical properties are considered together because both factors help determine the potential for a health hazard.[17] Figure 51.3 demonstrates the passage of chemicals through the environment. The physicochemical properties of a chemical determine the fate of a chemical in the environment by altering its migration, accumulation, and degradation in various media; however, direct measurements of the fate of a particular chemical in a specific medium are the most accurate estimation of the presence of the chemical in a similar environment. The Hazardous Substances Data Bank (HSDB) and the USEPA Environmental Fate Database have been combined with the National Library of Medicine's PubChem. The new PubChem database (https://pubchem.ncbi.nlm.nih.gov/) contains specific information on the fate of many chemicals.

Water Solubility

Highly water-soluble chemicals tend to remain dissolved in water rather than in soil and sediment. This type of chemical does not typically accumulate in aquatic organisms, with volatilization into the air being relatively less common depending on their vapor pressure. Highly water-soluble compounds usually biodegrade more readily than chemicals with less water solubility. Many environmental contaminants (e.g., dioxin, DDT, polychlorinated biphenyls) are chemicals with low water solubility; these chemicals are relatively more resistant to degradation in soil and water.

Vapor Pressure

Equilibrium vapor pressure (i.e., the solubility of a chemical in the air) is an important determinant of the transport of the chemical to the air; this physical property is a function of the inherent properties of the chemical and temperature. The volatility of a chemical in water varies with the vapor pressure and water solubility. Even though low water solubility and low vapor pressures discourage volatilization from water, some environmental contaminants (e.g., DDT) volatilize from concentrated areas because of the low concentrations in the environment. Chemicals with vapor pressures of $<10^{-6}$ exist mostly in particulate matter rather than air.[19]

Dissociation Constant

The dissociation constant (pK_a) is the pH at which 50% of the chemical exists in the ionized form; this value measures the extent to which the chemical breaks into charged forms. The ionic charge of a chemical affects its binding to soil and sediment. Most soils are negatively charged and bind chemicals with positive charges more effectively. Chemicals (e.g., paraquat, diquat) that form cations at existing soil pH generally adsorb strongly to soil materials (e.g., clay). The dissociation constant also affects the ability of the chemical to penetrate biological membranes because only the nonionized form can penetrate lipid membranes.

Log Octanol/Water Partition Coefficient

This physical property (K_{ow}) is the ratio of the chemical concentration in octanol divided by the concentration of the chemical in water at equilibrium. Chemicals with high K_{ow} display hydrophobic properties, tend to partition away from water, and distribute into aquatic organisms. For nonionized chemicals, this ratio correlates well with bioconcentrations in aquatic organisms and adsorption to soil or sediment;[20] however, the K_{ow} explains only part of the bioconcentration of chemicals

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TABLE 51.2. Observations on risk and risk communication. (Adapted from Cox and Strickland).[16]

Issue	Observation
Risk	1. Life involves risk.
	2. Societies require risk to grow and prosper.
	3. Beneficial actions require some risk.
	4. All societies require change, and change involves risk.
	5. Proving the absence of risk is very difficult, even though such risks are inconsequential, whereas proving the presence of risk is much easier.
	6. Although the risk of harm in our society is lower, the acceptance of risk is also lower.
Emotion	1. Risk intensifies one of the strongest human emotions, fear.
	2. Uncertainty strengthens emotions related to risk.
	3. Risk implies uncertainty, which is uncomfortable for most people.
	4. Lack of scientific understanding reduces the willingness to accept risk, assuming that benefits and risk remain constant.
	5. Risk should be analyzed in the whole context of all alternatives to actions and inactions.
Individuals	1. Freedom of an individual directly relates to the responsibility accepted for individual actions.
	2. The ability to manage risk requires experience with uncertainty and responsibility for the consequences of risk.
	3. Individuals accept greater risk when comfortable rather than when struggling for survival.
	4. Individuals will accept risks considered unacceptable by society when they believe in substantial personal benefit.
Society	1. Society determines reasonable risk based on benefits to many and risks to individuals.
	2. Societal benefits do not justify excessive individual risks without individual benefits.
	3. Society values indicate that involuntary risk should be compensated by society or involved entities.
	4. Older individuals usually accept less risk than younger individuals, and as the population ages society's acceptance of risk probably will decrease.
	5. As the industrial base of society decreases, the acceptance of risk also decreases.
Perception	1. Public perception requires evaluation and appropriate actions, even though the perceptions are not scientifically based.
	2. Most individuals consider risk undesirable.
	3. Problems require both technical and political solutions.
	4. Achieving technical solutions during a political crisis is difficult. Political action responds to crises, whereas technical solutions require a dispassionate logic that is usually not present during a political crisis.
Communication	1. Communicating a positive concept (e.g., degree of safety) is easier than a negative concept (e.g., risk).
	2. Numerical calculations should not be used to communicate risk because of the focus on large numbers rather than small risks.
	3. The risk communicator must be a knowledgeable, skilled communicator.
	4. The media tends to focus on controversial issues rather than a dispassionate analysis of the scientific issues of risk. Good risk communication creates little reaction.
	5. The media reports what is wrong rather than what is right.
	6. Activists create stories that emphasize risk rather than safety, but the media generally does not report stories that emphasize industrial safety.
	7. Issues are much easier to resolve before extensive media coverage crystalizes public opinions.

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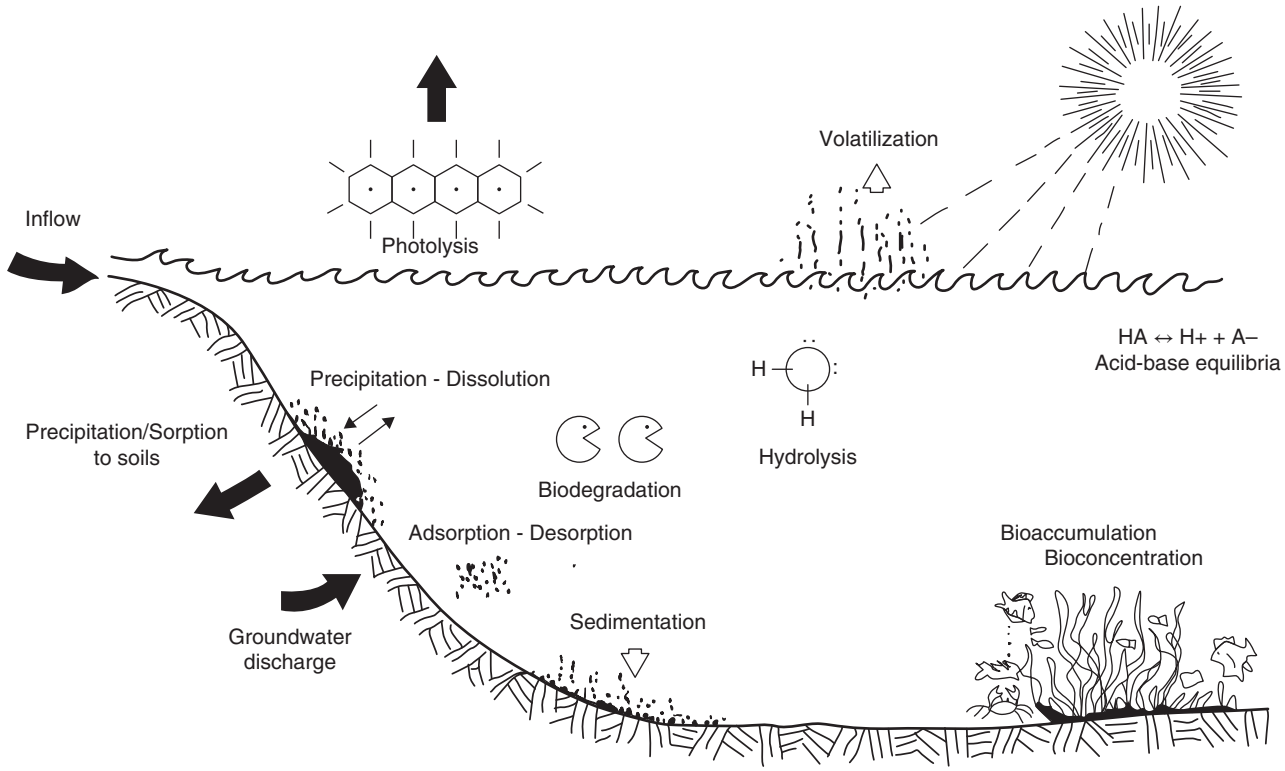


FIGURE 51.3. Schematic representation of the environmental fate of chemical carcinogens. (Adapted from Paustenbach).[18]

in the environment. Other factors contributing to bioconcentration and biomagnification (i.e., the transfer of the chemical up the food chain) include the type of food chain, metabolism, bioavailability, and persistence of the chemical in the environment.[18] The K_{ow} does not accurately predict the adsorption or bioaccumulation of metallic organic complexes, ionic compounds, or inorganic chemicals.

Henry's Law Constant

Henry's law constant is the air/water partition coefficient at equilibrium; this constant expresses the rate of evaporation of a chemical from water. Chemicals with a Henry's Law constant below the constant for water (i.e., 10^{-7} atm-m^3/mol) tend to concentrate in water, whereas chemicals with Henry's Law constants above 10^{-3} atm-m^3/mol volatilize rapidly. Other factors in the environment affecting the volatilization of chemicals include water depth, flow rate, sediment and organic material content, turbulence, adsorbents, emulsions, and electrolytes. A slow river model is available to estimate the volatilization of chemicals that requires only the Henry's Law constant and the molecular weight of the chemical;[21] however, this model overestimates the volatilization from ponds, lakes, and deep rivers.

Ultraviolet–Visible Absorption Spectrum

The ultraviolet–visible absorption spectrum (UV–Vis) is a measure of the ability of a chemical to absorb radiation in this wavelength region (200–750 nm). Chemicals that cannot absorb sunlight cannot undergo direct photodegradation. Indirect photodegradation forms reactive intermediates (e.g., hydroxyl radicals) and is the main process of degradation in the atmosphere. Biodegradation results from the metabolic activity of microorganisms (e.g., fungi, bacteria). This process is the main metabolic pathway in soil because ultraviolet light does not penetrate below the top centimeter of the surface. Chemical hydrolysis is an important degradation process in aqueous environments; this process is independent of the presence of sunlight, microorganisms, or oxygen.

Data Validation

Toxicological data vary in quality, resulting in the need for criteria on objective and standardized methods to evaluate data quality, especially when deciding which data to include in systematic reviews, meta-analyses, public databases (e.g., Chemical Effects in Biological Systems, CEBS, https://cebs.niehs.nih.gov/cebs/),

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and globally harmonized system (GHS) classifications. Although major chemical assessments are still driven primarily by traditional data, collaboration between organizations involved in risk assessment (e.g., Next Generation of Risk Assessment, NexGen, https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=286690) is improving approaches to risk assessment, including adverse outcome networks (AON) and pathways (AOP) that better define modes of action and causal relationships.[22]

Quality criteria systems exist to help evaluate individual sites and the appropriateness of including these studies in the overall body of evidence, as listed in Table 51.3. These systems share common areas to consider while assessing study quality including adequate details on study conditions, design, and protocols; selection/randomization of study groups; validity and reliability of outcome assessment methods; approach to avoid selective reporting; and evaluation of potential confounders and/or bias.[23] The latter implies potential systematic or directional error rather than imprecision of test results from statistical fluctuations produced by design flaws (e.g., inadequate exposure control, small study numbers). Assessing study quality is not equivalent to evaluating the risk of bias in the study; this risk reflects the internal validity of the study as a result of study design that introduces a systematic error affecting the value of outcome measures.

The Navigation Guide is a systematic review process to synthesize scientific evidence from human and nonhuman research to reach overall conclusions regarding strength of evidence in the hazard identification part of risk assessment. This process involves: 1) specifying the study question, 2) selecting the evidence, and 3) rating the quality and strength of the evidence.[35] Figure 51.4 demonstrates the integration of the risk of bias assessment with determination of the quality and strength of evidence to reach conclusions regarding hazard identification.

Observational Studies

Transparency and harmonization in publications and data exchanges between collaborators require the inclusion of information useful to determine the reliability of study data. Important components of information about observational epidemiological investigations include: 1) subject characteristics (age, sex, race/ethnicity, medical history, disease description) and procedures applied to subjects (observational place/time), 2) study design

TABLE 51.3. Study quality criteria systems. Lynch et al. provide an overview of guidance systems for the evaluation of the quality of human studies, including over 40 specific areas involved in the evaluation. Answers to questions regarding these areas involved reporting requirement, scoring for category based on the extent issues were addressed (e.g., definitely low, probably low, probably high, definitely high risk of bias), or fulfillment of yes/no criteria. (Adapted from Lynch et al.).[23]

Study Quality Criteria System	Publication Year	Applicable Studies
Integrated Risk Information System (IRIS) Risk of Bias (RoB) evaluation	2013–2014	Human, animal, systematic reviews
National Toxicology Programs (NTP) Office of Health Assessment and Translation (OHAT) approach[24]	2013, 2015	Human, animal, systematic reviews
Navigation Guide[25]	2013–2014	Human, animal, systematic reviews
Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) system[26]	2007	Human
Money et al.[27] adaptation of Lavelle et al.[28]	2013	Human
Klimisch System[29]	1997	Animal, *in vitro*
Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines[30]	2010	Animal, *in vitro*
Organization for Economic Cooperation and Development (OECD) Guidance Document 34[31]	2005	Animal, *in vitro*
Toxicological Data Reliability Assessment Tool (ToxRTool)[32]	2009	Animal, *in vitro*
Assessment of Multiple Systematic Reviews (e.g., AMSTAR)[33]	2007	Systematic reviews
Risk Of Bias In Non-randomized Studies (ROBINS-I)[34]	2016	Systematic reviews involving bias in observational and interventional studies

Abbreviation: AMSTAR = A MeaSurement Tool to Assess systematic Reviews.

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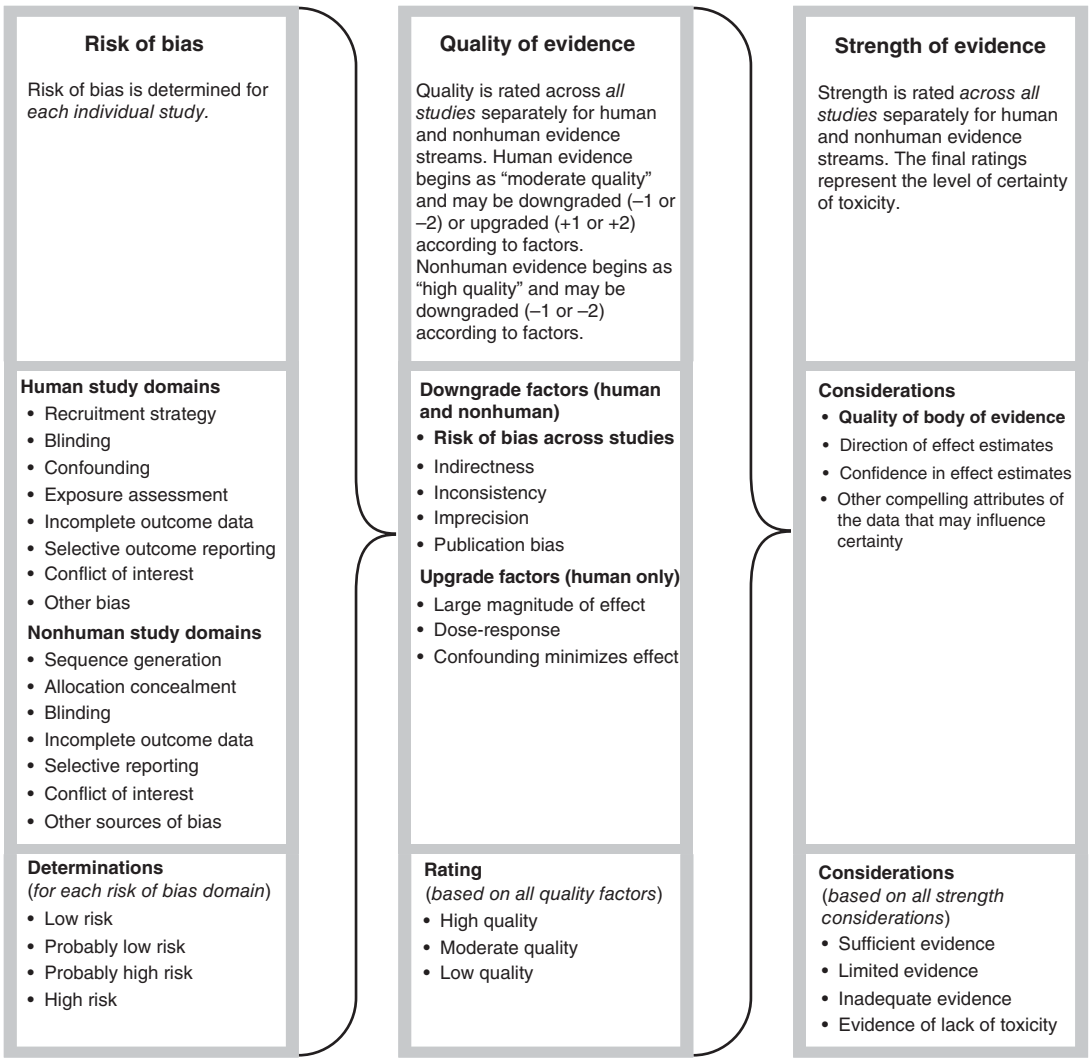


FIGURE 51.4. Navigation Guide systematic review process overview outlining evaluation of risk of bias, quality of evidence, and strength of evidence during the hazard identification part of risk assessment. (Adapted from Lam et al.).[35]

and implementation (classification, timeline, organization), 3) biomaterials collected and preserved with description of methods, and 4) assays performed and results obtained (method, unit of measure, values).[36] The exact checklist depends on the study design and subject characteristics; no single criterion determines the overall adequacy of a study.

The primary objective of a quality evaluation is the determination of the internal validity of the study as demonstrated by the lack of ambiguity about the study results achieved by controlling all potential influences other than the intended outcome. For observational epidemiological studies, this objective involves the careful identification and selection of study population, investigating and adequately controlling confounding factors, and avoiding selective reporting.

Well-documented analytical (cohort, case-control) epidemiological studies provide more relevant data for the hazard identification process than ecological epidemiological studies or animal data. Reasons for preferring epidemiological data include the inclusion of heterogeneous human populations, the avoidance of extrapolation from animal to human species, and the inclusion of concomitant risk factors (e.g., smoking, diet). Case-control and cohort studies are more reliable studies for hazard identification because they allow better control of confounding factors than other observational studies. Analytical studies with precise exposure estimates and specific biomarkers have greater weight than less well-designed studies. Case reports or case series describe a particular effect (e.g., cancer cluster) in a group of patients as observed by one or

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several health professionals. Usually, these case reports are highly selective and anecdotal. The lack of statistical stability limits the usefulness of this type of data for incorporation into hazard identification. These descriptive studies generate hypotheses about exposure factors; however, subsequent analytical designs are necessary to determine causality. The presence of dose-response effects is particularly helpful for hazard identification. If well-designed epidemiological studies with good exposure data demonstrate no effects at a specific level of exposure, then the overall weight-of-evidence indicates the agent is potentially carcinogenic in humans, including the correlation of upper estimates of the potential human risk with estimates from animal data.

Bias

Integrating the use of systematic reviews into risk assessment helps modernize evidence-based decision-making and strengthen the process of developing safe chemical limits. The National Academy of Science recommends risk of bias assessment (i.e., credibility of the relationship between exposure and outcome) to verify the internal validity of studies used to formulate hazard identification and dose-response assessment for the development of oral and inhalational reference doses.[37] The assessment of risk of bias involves the use of a formal process to critically appraise the study quality and potential of the study design to compromise the credibility of the relationship between exposure and outcome (i.e., the presence of systematic error that causes deviation from the true effect). Several agencies have developed tools for risk of bias analysis on environmental health hazard assessments, including the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group, the Navigation Guide, the National Toxicology Program Office of Health Assessment and Translation (OHAT, https://www.niehs.nih.gov/research/atniehs/labs/iha/ohat/index.cfm#:~:text=The%20Health%20Assessment%20and%20Translation,health%20research%20and%20regulatory%20agencies) and Office of the Report on Carcinogens, and the Integrated Risk Information System (IRIS) of the US Environmental Protection Agency.[38] The OHAT is a risk of bias rating tool for six types of bias (selection, confounding, performance, attrition/exclusion, detection, selective reporting) in human and animal studies;[39] this tool consists of 11 questions (domains) designed to detect different types of bias and determine the suitability of the study for inclusion in the risk assessment process, as displayed in Table 51.4. Each question is rated on a 4-point scale (definitely low, −; probably low, −/NR; probably high or not reported, +; definitely high, ++) with higher methodological quality producing lower scores.

The core questions are unique to the systematic review; consequently, the investigator adapts the questions to the specific research hypothesis.

Animal/In Vitro Data

Animal data are important for hazard identification because of the lack of adequate epidemiological data for many chemicals. Assays in genetically engineered rodents (e.g., transgenic, knock-out strains) provide insight into the chemical and gene interactions involved in carcinogenesis.[40] Current standardized rodent carcinogenicity studies require at least 50 animals/sex/dose group in each of the 3 treatment groups and a concurrent control group followed long-term (18–24 months) for neoplasms. Although toxicological results from animal studies anticipate effects in humans, both negative and positive results are difficult to interpret when the animal studies are inadequately designed. The high dose in long-term studies typically should detect treatment-related carcinogenic effects without compromising the outcome of the study through excessive toxicity or inducing inappropriate toxicokinetics; the two or more lower doses help define the shape of the dose-response curve. Considerations for the relevance of an animal study to human exposure include the size of groups, statistical analysis, reliability of end-points, physicochemical properties of substances, adequate or excessive doses, relevance of route of exposure, intensity of exposure compared with humans, and consistency of applied dose. The doses should be chosen to produce a graded response including the expected NOAEL. Whenever species-specific pharmacokinetics vary, the animal species with pharmacokinetics most similar to humans should be selected.

In 1997, Klimisch et al. published a system for categorizing the reliability of animal and *in vitro* studies into four classifications based on: 1) reliability (inherent quality of the study to provide clarity and plausibility to the study results), 2) relevance (suitability of the results to hazard identification or risk characterization), and 3) adequacy (usefulness of data for hazard or risk assessment with greater weight for more reliable and relevant data).[29] Table 51.5 describes the definition of the four categories of reliability defined by Klimisch et al.

Data from reliability categories 1 or 2 are sufficient as stand-alone information on the specified outcome, whereas category 3 data serve only as additional data in weight-of-evidence evaluations. A reliability assessment tool (Toxicological data Reliability assessment Tool, ToxRTool) is available to improve the reliability

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TABLE 51.4. Eleven questions (domains) of the National Toxicology Program Office of Health Assessment and Translation (OHAT). (Adapted from Office of Health Assessment and Translation).[39]

Question Number	Description	Subdomain	Bias Type
1	Was administered dose or exposure level adequately randomized?		Selection
2	Was allocation to study groups adequately concealed?		Selection
3	Did selection of study participants result in appropriate comparison groups?		Selection
4	Did the study design or analysis account for important confounding and modifying variables?		Confounding
5	Were experimental conditions identical across study groups?		Performance
6	Were the research personnel and human subjects blinded to the study group during the study?		Performance
7	Were outcome data complete without attrition or exclusion from analysis?		Attrition or Exclusion
8	Can we be confident in the exposure characterization?		Detection
9	Can we be confident in the outcome assessment?		Detection
10	Were all measured outcomes reported?		Selective reporting
11	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?		Other
11a		Were statistical methods appropriate?	Other
11b		Did researchers adhere to the study protocol?	Other
11c		Did the study design or analysis account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	Other

TABLE 51.5. Reliability categories defined by Klimisch et al. (Adapted from Klimisch et al.).[29]

Number	Descriptor	Definition
1	Reliable without restrictions	Implemented with generally valid and/or internationally/nationally accepted testing guidelines according to good laboratory practice or closely related/comparable guidelines.
2	Reliable with restrictions	Implemented with test parameters not totally complying with specific testing guidelines (e.g., good laboratory practice), but sufficient to accept as a well-documented, scientifically acceptable testing guideline.
3	Unreliable	Literature/reports indicate interferences between measuring system and test substance; organisms/test systems used are not relevant to exposure and/or implemented with a method inadequate to evaluate outcome measure based on expert judgment.
4	Unassignable	Study or medical literature contains insufficient experimental details or data to evaluate outcome measures.

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assessment of toxicological data (https://joint-research-centre.ec.europa.eu/scientific-tools-and-databases/toxrtool-toxicological-data-reliability-assessment-tool_en).[32]

Toxicogenomics

Toxicogenomics refers to the global analysis of toxin-induced modifications of biomolecules (genome, transcriptome, metabolome, proteome) involved in pathways causing toxicity; this approach helps improve the risk assessment process by increasing knowledge on low-dose responses, exposure assessment, dose-response modeling, intra/interspecies extrapolation, and genetic variability.[41] High-throughput and high-content assays along with robotic implementation generate data at unprecedented speeds along with advances in molecular, computational, and systems biology. Consequently, the amount of existing toxicological and toxicogenomic data has increased exponentially in the last several decades, particularly since the completion of the Human Genome Project.

Transcriptomic studies differ substantially from whole-animal toxicity studies evaluated by criteria systems (e.g., ToxRTool) in Table 51.3. Specialized assessment tools (e.g., Systematic Omics Analysis Review tool, SOAR, https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0110379&type=printable) are available to assess the quality of transcriptomic studies using established community standards (e.g., Minimum Information About a Microarray Experiment standard, MIAME).[42] The SOAR tool focuses on data analysis and study design of transcriptomics RNA microarray studies.[43]

Systematic Reviews

A MeaSurement Tool to Assess systematic Reviews (AMSTAR, https://amstar.ca/Amstar_Checklist.php) was published in 2007 as a practical and critical appraisal method for evaluation of the rapid assessment of the quality of systematic reviews involving randomized, controlled studies;[44] however, a substantial number of published systematic reviews include nonrandomized studies, particularly studies involving environmental exposures. These studies require different risk of bias assessments because nonrandomized studies potentially contain a range of biases that are much less prominent in randomized studies. Additionally, observational studies often contain very large populations that generate precise estimates of effects that may be inaccurate because of residual biases, resulting in meta-estimates weighted toward the observational study estimates. Consequently, AMSTAR was revised (AMSTAR 2, Figure 51.5) to include 16 questions relevant to randomized and nonrandomized study evaluations.[45]

Although all questions are important steps to conducting a systematic review and meta-analysis, seven domains are critical to the validity of the conclusions, as listed in Table 51.6.

Rather than creating an overall score, the authors of AMSTAR 2 recommend using the following scale: 1) high – no or 1 noncritical weakness, 2) moderate – more than 1 noncritical weakness, 3) low – 1 critical flaw with or without noncritical weaknesses, and 4) critically low – more than 1 critical flaw with or without noncritical weaknesses, as outlined in Table 51.7. The presence of several noncritical weaknesses may reduce confidence in the review, resulting in a reduction in the rating. The AMSTAR 2 broadly assesses study quality, including flaws introduced through poor conduct of the review. In contrast to the more general approach of AMSTAR 2, the Risk Of Bias In Systematic (ROBIS) review focuses specifically on the risk of bias introduced by conducting reviews of nonrandomized intervention studies.[34] Interpretation of the outcome of the review involves judgment on low, moderate, serious, critical, or inadequate information on risks of bias based on seven domains; these domains include bias from confounding, selection of study participants, classification of interventions, deviations from intended interventions, missing data, outcome measurements, and selective reporting.

Alternative methods to systematic review tools include scoping reviews that rapidly map available evidence on a particular topic or research area to identify data gaps, key concepts, and sources of evidence.[46] The depth of coverage of available literature depends on the purpose of the review. Purposes of scoping reviews include summarizing and disseminating research discoveries, examining the range, extent, and type of research activity, identifying research needs, and determining the value of a full systematic review.[47] The latter focuses on well-defined questions using appropriate, predetermined study designs, whereas scoping reviews use different study designs as needed to cover broader topics. Systematic reviews also answer questions based on a relatively narrow range of quality studies, while scoping reviews focus less on specific questions or study quality; however, study details should be sufficient to allow replication of the scoping review by other researchers. The methodological framework of a scoping review includes the following: 1) identifying the research question, 2) determining relevant studies, 3) selecting appropriate studies for research question, 4) charging the data, and 5) collating, summarizing, and reporting the results.[47]

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AMSTAR 2

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

☐ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☐ Partial Yes
☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

☐ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (eg, language)

For Yes, should also have (all the following):
- ☐ searched the reference lists/bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

☐ Yes
☐ Partial Yes
☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder selected by one reviewer

☐ Yes
☐ No

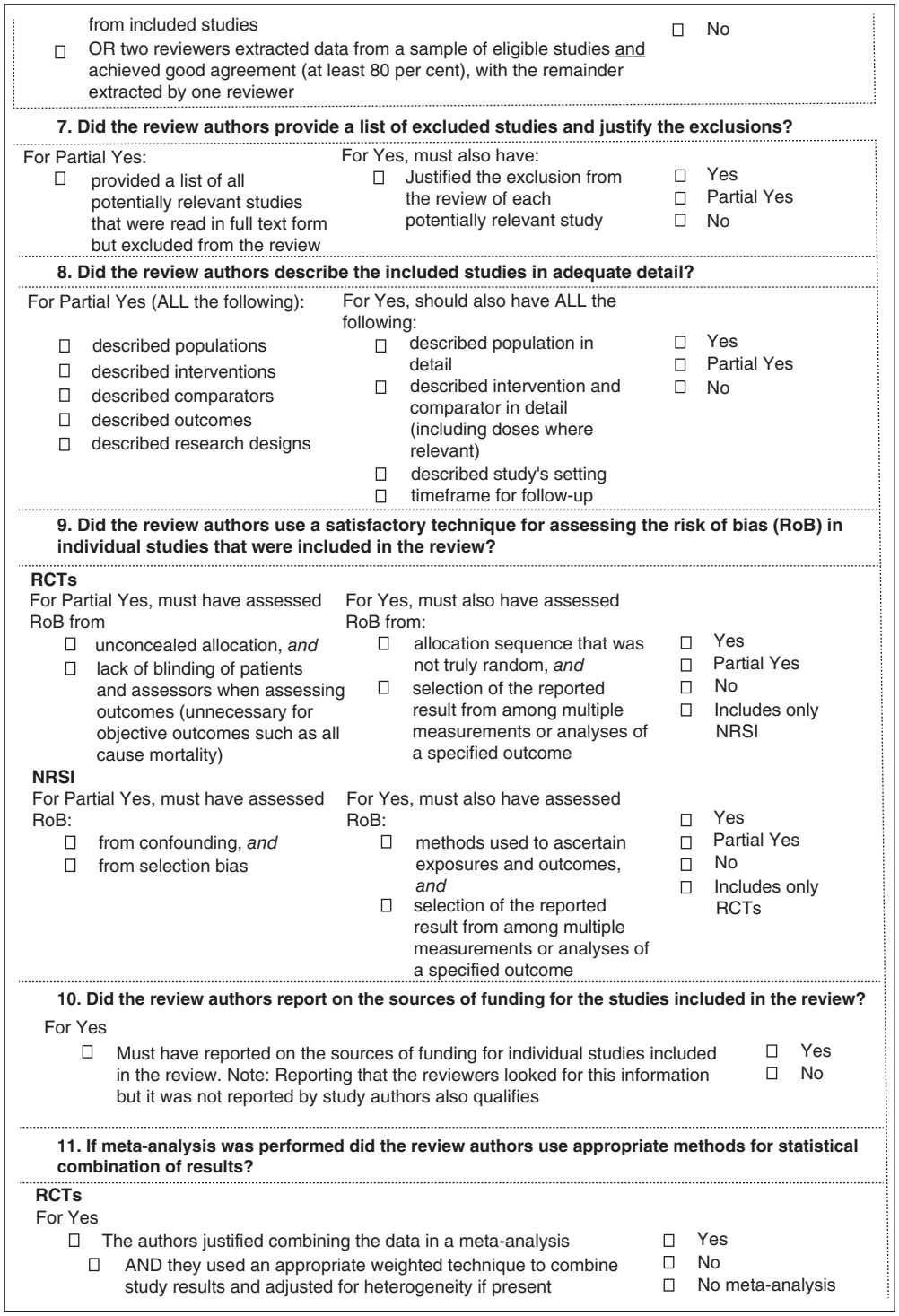
6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers achieved consensus on which data to extract

☐ Yes

FIGURE 51.5. For evaluation purposes, items 2, 4, 7, 9, 11, 13, and 15 are considered critical domains (denoted by asterisks), whereas items 1, 3, 5, 6, 8, 10, 12, 14, and 16 are noncritical domains. This appraisal tool for randomized and nonrandomized studies is not designed to generate an overall numerical score.
Abbreviation: PICO = Population, Intervention, Comparator, and Outcome framework.

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from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder extracted by one reviewer

☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- ☐ provided a list of all potentially relevant studies that were read in full text form but excluded from the review

For Yes, must also have:
- ☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes
☐ Partial Yes
☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- ☐ described populations
- ☐ described interventions
- ☐ described comparators
- ☐ described outcomes
- ☐ described research designs

For Yes, should also have ALL the following:
- ☐ described population in detail
- ☐ described intervention and comparator in detail (including doses where relevant)
- ☐ described study's setting
- ☐ timeframe for follow-up

☐ Yes
☐ Partial Yes
☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from
- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality)

For Yes, must also have assessed RoB from:
- ☐ allocation sequence that was not truly random, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:
- ☐ from confounding, *and*
- ☐ from selection bias

For Yes, must also have assessed RoB:
- ☐ methods used to ascertain exposures and outcomes, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes
- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

☐ Yes
☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes
- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present

☐ Yes
☐ No
☐ No meta-analysis

FIGURE 51.5. (*Continued*)

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☐ AND investigated the causes of any heterogeneity	conducted
For NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☐ No meta-analysis conducted
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect	☐ Yes ☐ No ☐ No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☐ Yes ☐ No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☐ Yes ☐ No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☐ No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☐ Yes ☐ No

FIGURE 51.5. (*Continued*)

Carcinogenic Potential

Previously, the USEPA used a weight-of-evidence approach to characterize the extent and strength of the evidence for chemical carcinogenesis, as described under the section on Qualitative Classification Schemes of Cancer.[9] This scheme is a continuum of the carcinogenic potential of a chemical based on scientific judgment, and classification ranges from definite (Group A) to no evidence (Group E). The weight-of-evidence approach depended primarily on long-term animal data at or near the maximum tolerated dose to evaluate the potential of a chemical to cause cancer. This process did not assess the potency of the chemical to induce tumors, even though the actual risk of cancer depends

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TABLE 51.6. Seven critical domains in an AMSTAR 2 evaluation. The prominence of risk of bias reflects the potential impact of nonrandomized studies in systematic reviews. (Adapted from Shea et al.).[45]

Question	Description
2	Protocol registered before commencement of review
4	Adequacy of literature search
7	Justification for excluding individual studies
9	Risk of bias in studies included in review
11	Appropriateness of meta-analytical methods
13	Consideration of risk of bias during interpretation of review results
15	Assessment of the presence and impact of publication bias

TABLE 51.7. Overall rating and outcome of systematic reviews involving randomized and nonrandomized healthcare intervention studies using AMSTAR2 questions. The purpose of the evaluation is to recognize high-quality systematic reviews; however, the overall evaluation does not generate an overall score to compare individual studies within a specific category. Table 51.6 identifies the seven critical domains. (Adapted from Shea et al.).[45]

Category	Overall Number of Weaknesses	Descriptor
High	≤1 noncritical with no critical flaws	Accurate/comprehensive summary of studies that addresses outcome of interest
Moderate	>1 noncritical with no critical flaws	May provide an accurate summary of available studies in the review
Low	1 critical with/without noncritical flaws	Critical flaw may not provide an accurate and comprehensive summary of studies on outcome of interest
Critically low	>1 critical with/without noncritical flaws	Does not provide an accurate/comprehensive summary of study results

on absorbed dose and potency. The potency of individual carcinogens varies substantially, as indicated by four orders of magnitude variation in the USEPA potency estimates for IARC Group 1 (human carcinogens).[48] Other factors relevant to the weight-of-evidence approach include the results of short-term test (e.g., point mutations, DNA damage/repair), the presence of toxic effects that enhance carcinogenesis (e.g., immunosuppression, endocrine abnormalities), mode-of-action, and the appearance of structure–activity relationships to known carcinogens. Key questions regarding hypothesized mode-of-action involve the strength of supportive animal evidence, its relevance to humans, and susceptible populations or life stages. Currently, the USEPA uses a weight-of-evidence narrative describing conclusions regarding weight-of-evidence of carcinogenic potential and a summary of the data forming the basis for the conclusions.[7] This brief summary with the hazard characterization (e.g., carcinogenic to humans – not likely to be carcinogenic to humans) replaces the alphanumeric classification system of Groups A–E used in the 1986 USEPA cancer guidelines.

Chemical carcinogens display a wide spectrum of activity ranging from direct DNA damage (genotoxic mechanisms) to epigenetic mechanisms (e.g., recurrent cytotoxicity and cell proliferation). Many recognized carcinogens act through genotoxic mechanisms; these carcinogens do not depend on the development of tissue toxicity at the maximum tolerated dose.[49] Animal data suggest the existence of at least eight pathophysiological classes of animal carcinogens including: 1) cytotoxic kidney, 2) cytotoxic bladder, 3) cytotoxic liver, 4) mitogenic liver, 5) peroxisome proliferating/mitogenic liver, 6) solid state, 7) promoters, and 8) genotoxic.[50] Not all of these mechanisms produce the same cancer risks in humans; kidney tumors in male rats do not accurately predict human carcinogenicity because of the unique accumulation of an $\alpha_{2\mu}$-globulin–metabolite complexes in the rat kidney that causes proximal tubule damage.[51] Evidence on mode(s)-of-action preceding tumor development (e.g., mutagenesis, receptor activation, alteration of signaling pathways, increased cell proliferation, apoptosis) could potentially help determine the likelihood of a cancer hazard and the dose-response relationship below the range of observable tumor

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response. Key questions involve the potential of the chemical or the activated metabolite to produce mutations by interacting directly with DNA (genotoxic) or causing mutations in gene expression via epigenetic processes. The significance of different mechanisms of carcinogenesis (e.g., genotoxic vs. epigenetic) to risk assessment is the possible existence of a threshold and the necessity of using several models to describe the true risk of developing cancer. Experience at the National Toxicology Program (NTP) suggests DNA-reactive substances that produce gene mutations causing tumors are often unique, in certain anatomical sites, whereas tumors at other sites may develop from both mutagenic and/or epigenetic influences.[52]

DOSE-RESPONSE ASSESSMENT

The second step of risk assessment for carcinogens is the estimation of the relationship between a particular exposure level of interest and the subsequent potential human risk based on the mode(s)-of-action for each tumor type and the strength of human and experimental data. Mathematical modeling helps incorporate a wide range of experimental data into the dose-response assessment; the dose-response assessment usually involves agents considered carcinogenic to humans or likely to be carcinogenic to humans.[7] The dose-response assessment involves the following two steps: 1) the derivation of a point of departure (POD) from the observed range of human and experimental data, and 2) the extrapolation of the relationship to levels below the POD as necessary. The POD is the starting point for subsequent extrapolations and analyses that calculate a slope factor for linear extrapolation commonly used in cancer risk assessment and a reference dose or concentration used for nonneoplastic risk assessment. The use of the POD below all observed data points introduces model inaccuracy and parameter uncertainty (i.e., lack of knowledge about the values of a model's parameters) along with issues related to human variability that increase with the distance between the lowest observed data points and the POD.

The POD is an estimated dose near the lower end of the observed range without significant extrapolation to lower doses as expressed in human-equivalents.[7] Exposure refers to the amount of substance in contact with the outer boundary of the organism, whereas dose is the amount of substance available to interact with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism. The dose may be applied (available for absorption), absorbed (amount crossing a specific area of the organism), internal (general term used without respect to specific absorption barriers or exchange boundaries), and delivered (amount available for interaction with specific cell or organ). Without evidence to the contrary, the recommended long-term measure of exposure to a carcinogen is the cumulative dose received over a lifetime expressed as average daily exposure prorated over a lifetime with an assumption that a high dose of a carcinogen received over a short time is equivalent to a corresponding low dose spread over a lifetime.[7] Variable lifetime exposures to carcinogens are summed to express the cumulative exposure as an average daily exposure.

Data from epidemiological studies with sufficient quality are preferred to extrapolation of animal data using toxicokinetic information for cross-species dose scaling or appropriate default values. When using tumor data from long-term cancer bioassays with ~50 animals, empirical modeling usually supports extrapolating increased tumor incidences to 1–10%, whereas large epidemiological studies support increased tumor incidences below 1%.[7] The default procedure is the standard USEPA model unless sufficient quantitative and mode-of-action data are available to develop a biologically based model. The POD for extrapolating to an environmental exposure of interest outside the range of observed data is usually the lower 95% confidence limit on the lowest dose level supported by mathematical or biological models of the data. When a chemical produces multiple tumor types, the dose-response assessment analyzes all tumor types, followed by the synthesis of strength of mode-of-action evidence, characterization of individual tumor risk estimates, and evaluation of the relevance of each tumor type to all human populations including susceptible ones. A NOAEL is not usually used for assessing the carcinogenic potential when one or more empirical models fit the data unless the data support a nonlinear mode-of-action.

The ultimate purpose of the dose-response assessment is to determine a safe dose that does not produce a significant increase in the risk of human cancer. The distinction between dose-response relationships between genotoxic carcinogens and other types of toxic reactions is based on the premise that genotoxic events (e.g., *in vitro* activation, covalent binding) are linear over many orders of magnitude. This assumption implies the lack of a threshold; however, this assumption remains unproven experimentally. Consequently, such estimates require extrapolation outside the range of the experimental data (i.e., from high-dose animal experiments to low-dose levels present in the environment). Such an extrapolation involves biological and statistical uncertainties. Because the incidence of tumors is so small at these low doses, testing would require

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prohibitively large numbers of animals; therefore, mathematical models must be used to estimate the risk of cancer.

Thresholds

Regulatory agencies generally adhere to the policy that carcinogens do not display a threshold effect; these agencies use linear models to describe the risk of a chemical causing cancer. Based on computer models, these agencies extrapolate data from human studies (e.g., BEIR VII) or rodent experiments using maximum tolerated doses for their lifetime (2 years) to the relatively low chemical doses absorbed by humans from the environment. This extrapolation frequently spans four to five orders of magnitude; differences exist between the nonlinear slopes seen in animal studies and the relatively linear dose-response curves seen in epidemiological studies of humans exposed to carcinogens.

A major concern in risk assessment is an accurate description of the dose-response curve at low doses. A low-dose linear model assumes no threshold exists and small increases in dose at a low exposure concentration cause a proportionate increase in the risk of developing tumors, whereas a nonlinear model exhibits a threshold effect so that a small increase in dose at low exposure levels does **not** increase the incidence of tumors. The linear approach is preferred in the absence of sufficient information regarding modes-of-action or mode-of-action evidence indicates the dose-response curve at low doses is or probably is linear.[7] The choice of a linear model when the carcinogen demonstrates a true threshold effect would result in an overestimation of the true risk of inducing a tumor, whereas the choice of a nonlinear model when there is no threshold would underestimate the true risk at low doses. Unfortunately, standard experimental designs currently do not differentiate between promoters (epigenetic carcinogens) that exhibit nonlinear dose-response curves and initiators (genotoxic carcinogens) that demonstrate a linear dose-response curve.[53]

The principal argument favoring the lack of a threshold is the description of cancer as a disease that begins with the heritable alteration of a single cell by the interaction of a chemical carcinogen with DNA or other intracellular molecules. The dose-response curve for radiation-induced cancer does not display a threshold effect. Evidence supporting the existence of a threshold includes the following: 1) some chemical carcinogens (e.g., promoters) require tissue damage before cancer appears, 2) integrity of the immune system affects the formation of tumors, 3) reduction of the latent period with decreasing dose may extend the latent period beyond the life of the animal, 4) alteration in the homeostasis of the animal modulates the response to the carcinogen, and 5) interference with a specific stage of the multistage process of cancer may limit the emergence of a tumor.[54] Low-dose threshold would most likely occur when the carcinogen has no endogenous counterpart.[55]

Thresholds detected in human or animal studies occur at lower levels following exposure to genotoxic than epigenetic carcinogens, probably because of pharmacological and toxicological effects. The classic S-shaped dose-response curve with a high threshold describes the carcinogenic effects of epigenetic carcinogens.[56] A no-effect level does occur in rodent assays (i.e., the application of a suspected promoter after administration of a genotoxic carcinogen) following administration of promoting agents (e.g., saccharin,[57] phenobarbital, butylated hydroxytoluene);[58] consequently, thresholds of dose or exposure duration may exist for certain carcinogens that do not produce irreversible disease below the threshold.[59]

In 2006, the National Academies Biological Effects of Ionizing Radiation (BEIR) VII Committee concluded the available scientific evidence was consistent with a linear dose-response relationship between ionizing radiation and the development of human cancers.[60] These conclusions were based primarily on mechanistic and animal studies combined with epidemiological data from ionizing radiation exposures mostly above 100 mGy. The report acknowledged the difficulty of conducting very large epidemiological studies to detect very small cancer risks associated with ionizing radiation exposures of <100 mGy. In 2018, the National Council on Radiation Protection (NCRP) published a critical review of 29 high-quality epidemiological studies on leukemia and total solid cancers in populations exposed to low-dose LET ionizing radiation reported in the medical literature from 1999–2017.[61] The interdisciplinary committee considered support for the linear-nonthreshold model strong in five studies (Life Span Study,[62] pooled childhood thyroid cancer,[63] tuberculosis fluoroscopic examinations and breast cancer, INWORKS, occupational solid cancers[64]), moderate in six studies, weak-to-moderate in nine studies, and no support in five studies (Mayak and Techa River, Hanford ^{131}I fallout, Kerala, India high background radiation, Canadian worker study, US nuclear weapons test participants). Three studies were inconclusive. The committee concluded that recent epidemiological studies support the continued use of the linear-nonthreshold model for radiation protection. A US National Cancer Institute international committee

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conducted a systematic review of recent epidemiological studies to assess the magnitude and direction of potential biases in recent studies of excess cancer risks from low-dose (<100 mGy) ionizing radiation, particularly in sensitive populations (e.g., childhood leukemia and thyroid cancer, breast cancer).[65] The 26 eligible studies included 8 environmental, 4 medical, and 14 occupational exposures published from 2006–2017 involving 91,000 solid cancers and 13,000 leukemias with mean doses ranging from 0.1–82 mGy. Most studies reported positive dose-response relationships for solid cancer and/or leukemia risks.[66] For childhood exposures, the metaERR$_{100\,mGy}$ for leukemia was 2.84 (95% CI: 0.37–5.32). For adult exposures, metaERR$_{100\,mGy}$ for leukemia was 0.16 (95% CI: 0.07–0.25) and 0.29 (95% CI: 0.011–0.047) for solid cancers. A systematic assessment for biases (selection bias, confounding, misclassification of outcome) suggested a few positive studies were biased away from the null. The authors concluded that the magnitude of the cancer risks from low-dose LET radiation was compatible with the 95% confidence limits of solid cancers and leukemia risks extrapolated from atomic bomb survivors.

Nonneoplastic Effects

For nonneoplastic, toxic effects, the experimentally derived, no observable adverse effect level (NOAEL) is divided by an uncertainty factor to provide a margin of safety for exposures at concentrations present in the environment. Increasingly, models are being used to estimate a "benchmark dose" as a substitute for the NOAEL based on an estimate (i.e., lower confidence limit) of a particular incidence level (e.g., 5%) associated with a critical effect;[1] this benchmark dose usually exists in or near the observed experimental dose range. Prior to the 1990s, the USEPA determined reference doses (RfD), reference concentrations (RfC), and cancer slope factors from NOAELs or the lowest-observed-adverse-effect levels (LOAEL) with enhanced safety factors in the absence of NOAELs. Together with other scientific information, the USEPA uses these data for setting public health standards regarding chemical exposures. Several limitations of the NOAEL approach involve the inability to account for variability in the dose-response (e.g., estimate, slope), the use of a single dose dependent on study design, and the absence of a NOAEL other than using an uncertainty factor. In the later 1990s, the USEPA developed the benchmark dose (BMD) method to replace NOAELs; this method is more independent of study design.[67] The BMD uses mathematical modeling of dose-response data to select a BMD associated with a predetermined benchmark response (e.g., 1–10% increased incidence of a pathological lesion).

Animal studies usually involve chemical exposures at doses near toxic concentrations, whereas human exposures typically occur at chemical concentrations near values of 1/100–1/1,000th of the NOAEL as determined in rodent bioassays. In contrast to the estimation of the NOAEL as an approximation of the threshold, the critical data point for the dose-response of carcinogens is the slope of the dose-response curve. Because of the uncertainty in low-dose risk extrapolation, there is increasing reliance on specification of the margin between potency in the experimental range and estimation of exposure.[68]

Substantial variation exists between humans and experimental animals in how they interact with exposure to a toxicant. Toxicokinetics represents what the body does to the toxic agent (i.e., the fate of the toxicant in the body), whereas toxicodynamics involves what the toxic agent does to the body (i.e., injury, adaptation, repair).[69] Examples of toxicokinetic processes include absorption, distribution, elimination, and biotransformation of the toxicant. Toxicodynamics involves the effect of the toxic agent on multiple biological processes, including interference with metabolic systems, formation of reactive oxygen species and DNA adducts, and alteration of signal transduction and apoptosis. Toxicokinetic effects depend on the external and internal dose (i.e., absorption from the exposure site, distribution, elimination), whereas toxicodynamic effects depend primarily on toxicant concentration in the target organ and receptor site sensitivity. Factors that affect interspecies and intraspecies variability in toxicokinetics include differences in physiological function (e.g., blood flow, filtration rate, gastric pH) of various organs, anatomy, and metabolic kinetics. Common areas of variability between species include liver enzymes, detoxification processes, gastrointestinal tract enzymes, and hormone levels. Physiological and anatomical differences also account for some of the variability in toxicodynamics. The extrapolation of animal data outside the range of observation requires the acceptance of unverifiable assumptions about the mathematical character of the dose-response curve near the zero-dose concentration. An additional uncertainty factor is the interspecies extrapolation from rodent data to humans that involves dose scaling of body weight and total body surface area along with species differences in metabolism and oncogene suppression/enhancement.[70] Unfortunately, there is no consistently reliable scaling factor. Determinants other than body weight (metabolic

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rate, species lifetime) may more accurately extrapolate chemical doses across species weight.[71] Modifying factors for adverse health effects at a given dose include sex, age, and lifestyle.

Various national and international agencies have developed comparable schemes for determining the exposure level that causes minimal or no risk of producing nonneoplastic effects in the general population. These schemes include minimal risk levels (US ATSDR), reference dose/concentrations (US Environmental Protection Agency), Tolerable/Acceptable Daily Intakes (IPCS), and tolerable daily intakes/concentrations (Health Canada). These schemes use the NOAEL of the benchmark data as an estimate of the highest dose that does not produce a statistically significant increase in the incidence of physiological or pathologically significant effects when compared with unexposed control groups. The NOAEL is an estimate of an observed value; this value may overestimate or underestimate the true biological threshold. The NOAEL does not account for the steepness of the dose-response level. Dividing the NOAEL by an uncertainty factor that accounts for variabilities and uncertainties produces a tolerable daily intake (ADI). This uncertainty factor accounts for uncertainties in interspecies (default factor 10) and intraspecies (default factor 10) variations. Additional factors that may modulate the uncertainty factor include the adequacy of the database, the severity of the effect, extrapolation from a LOAEL to a NOAEL, and the use of subchronic exposure data rather than chronic exposure data.

Neoplastic Effects

Traditionally, extrapolation of the dose-response of genotoxic neoplastic effects from high-dose experimental animal studies to the low-dose range involves the use of linearized mathematical models (e.g., linearized Armitage–Doll multistage model). The validity of linear models is difficult to prove or disprove experimentally, even when using bioassays with extremely large numbers of animals.[72] Although some authors criticize linear models as being too conservative,[73] the precision of the risk estimates is probably low.[1] Measures of dose-response other than linear models include estimation of carcinogenic potency in the experimental range, division of the carcinogenic effect level by a margin of protection, and calculation of margins of exposure based on T25 (daily dose in mg/kg body weight obtained by linear extrapolation) or BMDL10 (a mathematically derived value calculated from lower 5% confidence bound on a dose resulting in a 10% increase in experimentally derived tumor incidence above background).[74]

Tumor Incidence Models

The USEPA modeling process assumes a measure of dose (equivalent dose, ED) exists for which the tumor-onset rate in animals and humans is equivalent. To relate the dose of a carcinogen in animals and humans, the following two classes of models are necessary: 1) species extrapolation and 2) tumor incidence.[75] The former relates the administered dose in animal studies or the exposure level in humans to an equivalent dose; the model corrects for differences in production of the active carcinogenic agent across species. The latter class of models correlates the equivalent chemical dose to the probability of developing cancer. Several types of tumor incidence models establish the equivalent dose-response (i.e., tumor incidence) curve by formulating different mathematical functions that fit experimental animal data. The two major categories of these mathematical models are mechanistic and tolerance distribution models.

These models predict the safe equivalent dose defined as the dose predicted by the tumor incidence model that results in a negligible increase in the tumor incidence compared with the spontaneous tumor rate in animals. The equivalent dose in animals and humans is considered safe in both. The safe equivalent dose is then converted to safe concentrations for human exposure by extrapolation with models similar to species extrapolation models used to convert the administered dose in animal studies to an equivalent dose (ED) in humans. Table 51.8 outlines the steps in the modeling process that determine a safe exposure level.

TABLE 51.8. Method for determination of a safe exposure level. (Adapted from Portier et al.).[75]

Consider Mechanism of Toxicity
Estimate equivalent dose (ED)
Determine appropriate tumor incidence model
Estimate relationship between administered dose and equivalent dose in animal model
Express administered dose in carcinogenicity experiment as units of equivalent dose
Estimate parameters of tumor incidence model as function of equivalent dose
Determine safe equivalent dose level
Estimate relationship between equivalent dose and human exposure
Express human safe equivalent dose in units of exposure/dose

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Mechanistic Models

Mechanistic models include one-hit, multi-hit, multistage, and linearized multistage models. These mechanistic models depend on the assumption that tumors originate from a single, damaged cell; however, these models use divergent equations to describe the tumor incidence curve. Although these models predict substantially different risks as the dose approaches zero, they usually fit the observed data well.[76] A major issue regarding the accurate estimation of the true risk of developing cancer is the shape of this curve in the low-dose region, because a low-dose linear model predicts a much smaller safe dose compared with a low-dose nonlinear model as demonstrated in Figure 51.6.

The use of a nonlinear model when the true tumor incidence curve is linear would underestimate the true risk to the human population, whereas the use of a linear model when the real low-dose curve is nonlinear would overestimate the true risk. The former situation would increase the cancer risk in the exposed population; the latter situation could result in the exclusion of a useful chemical from the marketplace. The USEPA prefers a low-dose linear model when data are limited, unless this type of model conflicts with known data.[9]

Many regulatory agencies including the USEPA use a modification of the multistage model called the linearized multistage model. The multistage model assumes that the induction of cancer results from a number of random molecular events that occur in linear relation to the carcinogen dose.[77] To account for biological variability in animal studies, the linearized multistage model uses the 95% **upper** (but not the lower) confidence limit of tumor incidence; thus, this model produces conservative, upper bound estimates rather than point estimates.[13] The net effect of the linearized multistage model assumptions is the resemblance of the one-hit model at low-dose and linearity at doses near zero. This model produces a large, but indeterminate, overestimate of the actual risk of human cancer with the virtually safe dose (VSD) being dependent primarily on the chemical dose used in the study rather than actual experimental results.[78]

Tolerance Distribution Models

This class of models includes log-probit (probit), logit, Weibull, and γ-multi-hit. These models assume that human cancer develops when chemical exposure exceeds a critical level. The range of threshold values for an individual within a population includes zero; different model types in this class of models use divergent mathematical functions to describe the probability distributions of individual tolerance to the development of cancer within a population. The tolerance distribution models produce similar shapes within the range of experimental data, but they differ substantially in the low-dose range.[13] Table 51.9 describes the comparative range of potential risks predicted by various models.

The time-to-tumor model is another class of model that includes the log-normal distribution, Weibull distribution, Armitage–Doll, and Hartley–Sielken models. These models attempt to characterize the cancer process by mathematically describing the relationship between dose and tumor latency. Therefore, these models require a large set of biological data that frequently are incomplete.

Biologically Based Models

The statistical "curve-fitting" models described above do not consider biological changes (e.g., pharmaco-

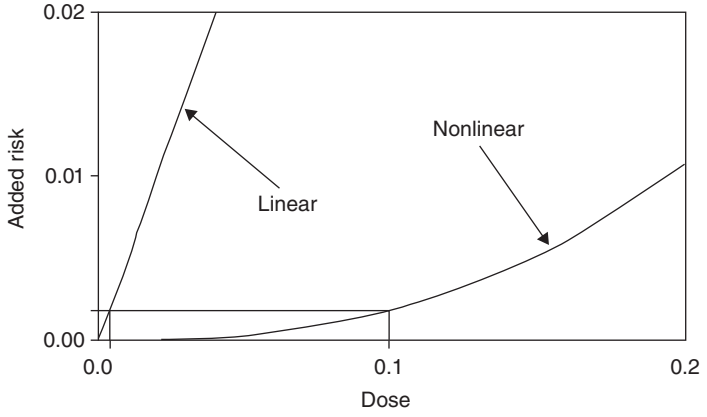


FIGURE 51.6. Linear and nonlinear dose-response curves in the low-dose range. (Adapted from Portier et al.).[75]

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TABLE 51.9. Relative differences in relative risk estimates between various models compared with actual risks. (Adapted from Johannsen).[13]

Model	Model Classification	Comparative Risk Estimate
Linearized Multistage	M	High
One-Hit	M	High
Linear	L	High
Multistage	M	High
Weibull	TD	Medium
Multi-hit	M	Medium
Logit	TD	Low
Probit	TD	Low

Abbreviations: L = Linear; M = Mechanistic; TD = Tolerance Distribution.

kinetics, metabolism, and mechanism); these factors may modify the tumor incidence predicted by these empirical models in the low-dose range. The Moolgavkar–Venzon–Knudson (M–V–K) model[79] attempts to incorporate biological data on cell proliferation and transformation into a 2-stage (mutation) stochastic carcinogenesis model. The first stage produces an intermediate cell type that alters growth characteristics, whereas the second mutational event produces malignant transformation.[80] The cancer incidence is related to the birth, death, mitotic, and transition rates of normal, initiated, and transformed cells.

The cancer incidence rate varies with a power of age for epithelial cancers.[81] The biologically based dose-response models provide the best method of estimating the relationship between **delivered** dose and health effects.[82] Although multistage mechanistic models (e.g., Armitage–Doll) partially account for age variation in cancer incidence for adult epithelial cancers, the model uses unrealistically large numbers of stages (e.g., 5–7) to fit cancer data (e.g., colorectum).[83] In contrast to mechanistic models, the M–V–K model allows consideration of the effects of cocarcinogens, promoters, and initiators,[84] resulting in better statistical fits for biological models than mechanistic models, particularly for processes involving genomic instability.[85] Various revisions of the existing biological model were developed to describe the dose-response curve for specific types of cancer. Moolgavkar and Leubeck developed a 3-mutation model to fit colorectal incidence data with plausible mutation rates without accounting for genomic instability,[86] whereas Little fit solid tumor and leukemia mortality rates in Japanese atomic bomb survivors[87] and lung cancer mortality in Colorado Plateau uranium miners[88] with a 2- or 3-mutation M–V–K model assuming genomic destabilization. In the latter model, the fit was superior for the 3-mutation model to the 2-mutation model.

Pharmacokinetic Models

Pharmacokinetic models describe the compartmental disposition of a chemical and metabolite in the body over time by **mathematical** analysis of the processes of absorption, distribution, metabolism, and excretion. The advantage of this model type is the calculation of an internal dose present at the target site rather than an administered dose or an ambient air concentration. This nonlinear exponential model correlates tissue concentration and time profile of the active carcinogen with the administered dose of the parent chemical.

Pharmacokinetic models improve extrapolation across different exposure routes and among various animal species by calculating the difference between the administered dose in animals and the equivalent dose (ED) in humans.[89] Such models help evaluate the impact of the pharmacokinetic process (e.g., metabolic saturation) across different species that may produce nonlinear risk estimates at the low-dose range; however, this model lacks the ability to account for intraspecies differences in pharmacokinetic parameters, with subsequent limitations on the extrapolation of dose-related tumor incidence to humans.

Physiologically based pharmacokinetic models differ from pharmacokinetic models because the former models depend on actual **physiological** measurement of pharmacokinetic data in test species rather than mathematical calculations. The actual measurement of the physiological deposition of the chemical and the use of mass balance equations allow more accurate extrapolation from high dose to low dose within the same species. The physiologically based pharmacokinetic models provide the best method for converting the **applied** dose into the **delivered** dose at the target organ.[82] Potentially, these biologically based *deposition* models can simulate the behavior of the chemical in different biological systems. Additionally, these models account for such differences as saturation (zero order) and Michaelis–Menten kinetics, nonlinear tissue binding, enzyme induction and inhibition, hepatobiliary circulation, receptor affinity, and unequal diffusion across cell membranes.[90] This model also

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allows cross-species extrapolation by adjusting the appropriate constants permitting modeling of other routes of administration by adding the appropriate equations. Substantial differences in calculated risk may result from the use of this model compared with the risk estimated from linearized multistage model (LMS). For a lifetime exposure to 1 μg dichloromethane/m^3 air, the estimated risk of cancer was two orders of magnitude lower for the PBPK model compared with the LMS model.[91]

Potency Estimation and the Experimental Range

Under the Canadian Environmental Protection Act, the measure of dose-response for genotoxic carcinogens is the tumorigenic dose or concentration$_{05}$ (TD5).[92] This dose is associated with a 5% increase in the tumor incidence in experimental or epidemiological studies. The exposure/potency index (EPI) is the estimated daily human intake divided by the TD5. An EPI of 10^{-6} represents a 1-million-fold difference between human exposure and the lower end of the dose-response curve (i.e., TD5). The choice of the model is not critical because of the use of data within the experimental range.

In contrast to Canada and Europe, the USEPA uses the linear model as the default model when the mode-of-action is not established, or the dose-response curve has a linear component below the POD. Evidence of nonlinearity is necessary to use an estimation of a margin of exposure (EPI). The dose-response curve is usually nonlinear in the high-dose range. The slope of the dose-response curve is the slope factor; this value is an upper-bound estimate of risk/dose increment used to estimate risk probabilities for different exposure levels. The slope factor is equal to 0.01/LEDxx (lower bound xx of the central estimate) when LEDxx is used as the POD and xx typically ranging from 1–10% increased tumor incidence.

Calculated slope factors may overestimate the true slope factor when using the largest of several slope factors, the default linear extrapolation model extends over several orders of magnitude, or the slope factor is based on highly susceptible animal strains. Underestimation of the slope factor may occur when the study design did not include exposure during a susceptible life stage, the study population does not reflect the general population (e.g., healthy workers), the existence of random exposure misclassification/measurement error, or the slope factor is derived from a subset of several tumor types.

The USEPA defines potency (q_1) as the quantitative expression of increased tumorigenic response per unit dose rate at very low dose levels (i.e., levels well below experimental data). For regulatory purposes, the lifetime increased cancer probability following exposure to a carcinogen at a lifetime, time-weighted average dose rate (D) is approximately equal to the product of $q_1 \times D$.

EXPOSURE ASSESSMENT

The objective of this process is a qualitative and quantitative determination of the amount of a chemical in contact with the body over a specified period of time by assessment of magnitude, frequency, exposure duration, and internal dose. Factors in this evaluation include important sources, pathways, and routes (air, soil, food, and water), intensity, frequency, and duration of contact, potential dose, and rate of uptake.[1,93] This analysis also includes separate analyses of susceptible subgroups within the population of interest (e.g., life stages, pregnant women, genetic susceptibility). Figure 51.7 displays how the terms of exposure and dose relate to chemical transport through the body after contact with the chemical in the environment. Exposure assessment typically involves four major steps: 1) elucidating the assessment questions, 2) defining the conceptual and mathematical models, 3) evaluating and collecting available data, and 4) exposure characterization.[7] Carcinogen risk assessment models usually assume the risk is proportional to the lifetime cumulative exposure expressed as a lifetime average daily dose; however, short-term, less-than-lifetime exposure estimates may be more appropriate when the data fits nonlinear dose-response curve.[9]

Childhood and adult exposures differ substantially, including age-specific exposure pathways (e.g., transplacental exposures *in utero*, breast milk consumption, enhanced hand-to-mouth exposures from crawling).[94] Additionally, relatively increased childhood exposures may result from their higher respiratory rates, large food and water intakes, and high surface area to body weight ratios compared with adults. The metabolic pathways of children are age-dependent, particularly *in utero* and the first months of life when their organs are very immature.[95] Age-specific developmental stages result in periods of susceptibility defined by critical windows of exposure, critical windows of development, and windows of vulnerability. The long lifespan of children allows more time to develop chronic diseases initiated by early environmental exposures.

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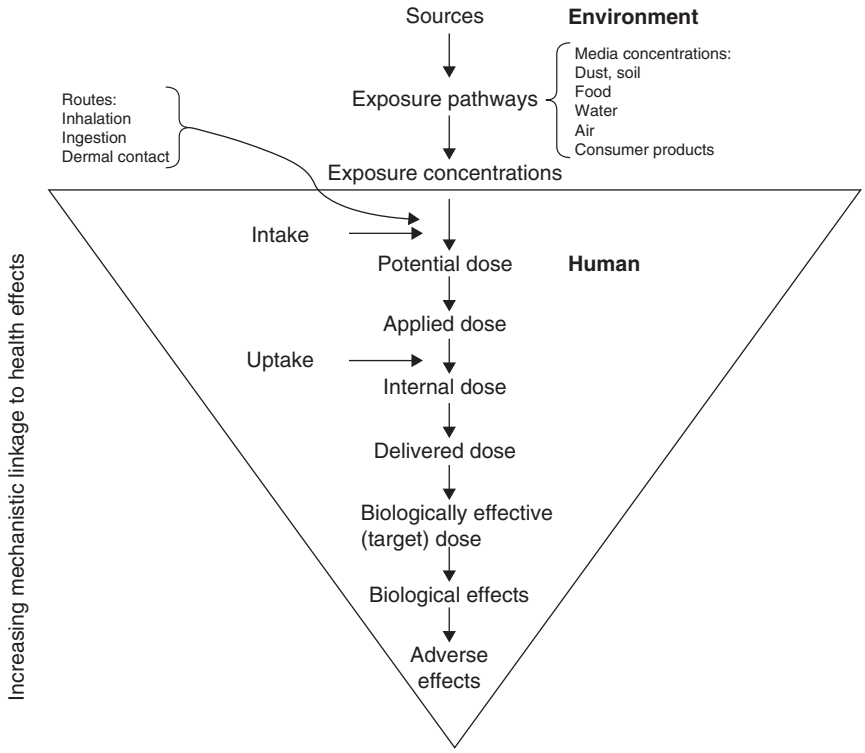


FIGURE 51.7. Paradigm of chemical transport from the environment through the body. (Adapted from IPCS).[1]

Exposure

Exposure is the amount of a chemical in contact with the outer surface of the organism.[96] Although there is some ambiguity about the location of this contact, USEPA guidelines define contact as the visible exterior (i.e., outer boundary) of the person rather than the exchange boundaries where absorption occurs.[97] The outer boundary of the person is the skin, mouth, and nostrils. The *dose* is the amount of the chemical that crosses the outer boundary of the organism after contact. A complete exposure assessment will provide information on the duration, intensity, frequency, exposure routes, and characteristics (such as size, sex, number, health status [e.g., obesity, chronic diseases], lifestyle [e.g., physical activities, personal habits], local environment, hobbies, para-occupational exposure) of the populations exposed to the chemical. Additional factors include work practices (e.g., control measures, handling procedures, personal protection, pattern and amount of chemical use, potential for misuse or accidental exposure), and physiochemical properties.

Dose

Potential dose is the amount of chemical present at the site of contact (skin, mouth, nares), whereas the *applied dose* is the amount of chemical present at the site of absorption (skin, lung, gastrointestinal tract). The applied dose frequently is difficult to measure because the site is usually inside the body; therefore, the potential dose (i.e., amount of chemical ingested, inhaled, or applied to the skin) is the surrogate measure for the applied dose. The applied dose is usually smaller than the potential dose, depending on the chemical characteristics and bioavailability. These parameters vary between different routes of exposure (e.g., anaerobic conditions in the colon may alter chemical bioavailability prior to absorption).

The *internal dose* is the amount of the applied dose that crosses the site of absorption and subsequently is available to interact with the receptors in the body. Once absorbed, the chemical undergoes metabolic transformation followed by transport throughout the body. The amount delivered to a specific site of interest

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(e.g., tissue, organ, fluid) is the *delivered dose*; this value is substantially smaller than the internal dose. The *biologically effective dose* is the amount of the chemical reaching the site (e.g., cell, membrane) where adverse effects occur. The biologically effective dose is often smaller than the delivered dose, depending on the ability of the chemical to diffuse across membranes to the site of interaction.

Exposure Estimates

Estimation of the total daily intake (i.e., μg/kg body weight) of a substance is critical to assessing the true magnitude of the cancer risk following contact with a particular substance. The major routes of chemical exposure for humans include ingestion of dust/soil or contaminated food and water; inhalation of dust, vapors, or aerosols; and the direct dermal absorption of liquids or contaminated solids. Computer programs (e.g., USEPA Risk Assistant) are available to conduct site-specific risk assessments for environmental chemicals. These programs prompt the user to identify the chemicals of concern, automatically list exposure pathways, and set default assumptions for exposure parameters that are modified as needed. The distribution of contaminants in soil, air, water, and food usually follows a log-normal rather than a normal distribution, as displayed in Figure 51.8; hence, statistical analysis of these distributions requires geometric means and geometric standard deviations. Table 51.10 lists the factors to consider when estimating the exposure (potential dose) of a chemical.

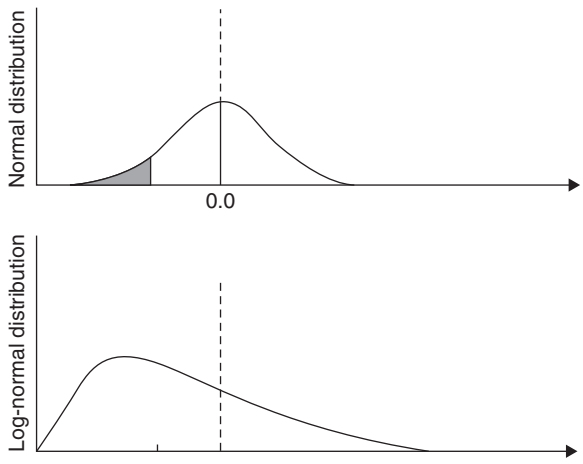


FIGURE 51.8. Schematic representation of normal and log-normal distributions. Log-normal distributions contain only positive numbers, whereas normal distributions may contain negative numbers. Additional, the mean of a log-normal distribution is always higher than the symmetrical normal distribution. (Adapted from Paustenbach).[18]

TABLE 51.10. Factors used to estimate uptake of a contaminant. (Adapted from Paustenbach).[18]

Route	Factor
Lungs	Ambient concentration, particle size distribution, concentration in dust, respiratory rate, duration of exposure.
Skin	Concentration in soil/dust, deposition rate on skin (direct and soil/dust), area of exposed skin, duration of exposure.
Gastrointestinal tract	Daily amount of contaminated source, concentration of contaminated source.

Evaluation of the potential dose usually involves: 1) measurement of the chemical at the point of contact with the outer boundary of the body over a period of time (point-of-contact or personal measurement); or 2) separate measurement of environmental concentrations of the chemical and the time of contact (scenario evaluation).[1] The data should be evaluated for quality and reflect the risks in the population of interest, including adjustment for susceptible, age/sex-related, and highly exposed subgroups. The potential dose also can be estimated from an analysis of internal indicators (biomarkers, body burden, biological fluids) after exposure (reconstruction). Point-of-contact exposure measurements provide the most accurate value for the potential dose because this value reflects a direct measurement of the chemical concentration at the interface of the person and the environment over a period of time. Instruments for these measures include radiation dosimeters, carbon monoxide monitors, and absorbent pumps for hydrocarbons; however, these devices are not source-specific, and some assumptions are necessary to extrapolate these short-term measurements to lifetime exposures. Scenario evaluation involves estimation of the concentration at the point-of-contact by modeling or indirect measurements of the environmental chemical rather than at the point-of-contact. When monitoring data are inadequate, environmental fate models are used to estimate chemical concentrations. These models involve a wide range of complex analyses of spatial dimensions and temporal changes; these fate models include transport models, dispersions models, equilibrium models, and simple dilutions models. The reliability of these estimates depends on the validity and uncertainty of the underlying assumptions, reliability of

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TABLE 51.11. Respiratory volumes based on age and sex. (Adapted from Paustenbach).[18]

Value (Units)	Adult Male	Adult Woman	Child (10 years)	Infant (1 year)	Newborn
Resting (L/min)	7.5	6.0	4.8	1.5	0.5
Light activity (L/min)	20.0	19.0	13.0	4.2	1.5
8-hour light activity[a] (L)	9,600	9,100	6,240	2,500[c]	90[d]
8-hour normal activity[b] (L)	9,600	9,100	6,240	—	—
8-hour rest (L)	3,600	2,900	2,300	1,300[c]	690[d]
24-hour total (L)	23,000	21,000	15,000	3,800[c]	800[d]
% Occupational	42%	43%	—	—	—

[a] Work or home. [b] Nonoccupational. [c] Based on 10 hours light activity and 14 hours rest. [d] Based on 1 hour of light activity and 23 hours rest.

the model under similar conditions, and quality of the input data. Confidence in the validity of the exposure estimates increases with more knowledge about these parameters. Reconstruction is the third option for estimating the potential dose using biomarkers of internal dose. The use of biomarkers requires a thorough understanding of the relationship between the internal and potential doses along with the exclusion of interfering reactions from the metabolism of unrelated chemicals. Optimization of sampling conditions (e.g., timing of the sample) is necessary to correlate exposure with the biomarker. Unfortunately, these conditions exist for relatively few chemicals.

If the chemical contaminant is a vapor, the most direct estimation of the concentration is an actual measurement, particularly in the occupational setting where more data are available than in environmental locations. The suitability of estimating exposure data for a specific population depends on how closely the data represent actual concentrations, time periods, and processes of the selected worker groups. The most common measure of exposure is cumulative exposure (average intensity multiplied by time); however, these measurements do not incorporate intermittent peak exposures that may alter the response to a given exposure.[98] In the absence of direct measurements, computer models can estimate the ambient concentration of a contaminant from volatilization of the chemical from water or soil to the air. The amount of contaminant absorbed from nonvolatile chemicals depends on the inhalation of respiratory particles (i.e., aerodynamic diameter <20 μm) that contain the chemical. Published data provides the total amount of particulates in air at a particular location. Once the amount of a chemical in a volume of air is determined, the systemic uptake can be estimated from assumptions about the pulmonary bioavailability of the chemical and the respiratory rate, as demonstrated in Table 51.11.

Assessment of chemical exposure in consumer products involves the combination of contact parameters and estimates of chemical concentrations. Data important for the development of realistic exposure assessments for consumer products are listed in Table 51.12. A variety of information sources are available to assess common exposure scenarios for consumer products.[99]

Table 51.13 lists average values recommended by the USEPA for parameters used in the risk assessment of exposures to contaminants in the air, soil, and water. The daily sum of maximum dermal, pulmonary, and oral doses represents an average daily exposure prorated over a lifetime to approximate the cumulative carcinogen dose. For risk assessment, the USEPA assumes from a risk assessment perspective that a high dose of

TABLE 51.12. Important data on the assessment of exposure to consumer products. (Adapted from International Programme on Chemical Safety, IPCS).[1]

Information Type	Important Parameters
Contact	1. Frequency of use. 2. Duration of use per event. 3. Area of use (e.g., room size). 4. Air exchange rate.
Concentration	1. Weight fraction of chemicals in the product. 2. Concentration of chemical at body interface (after dilution or evaporation).
Product use	1. Physical form. 2. Amount of product used per event. 3. Contact surface. 4. Intended use of product.

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TABLE 51.13. USEPA Recommended human parameters for risk assessment. (Adapted from USEPA).[101]

Parameter	Value
Body Weight (kg)	
2–5 years	13.2
6 years	20.8
Adult	70
Lifespan (years)	75
Exposed Skin Surface (m^2)	
Adult	0.20
Worst case	0.53
Swimming or bathing	1.94 (♂), 1.69 (♀)
Respiratory Volume (m^3/day)	
8-hour work shift	10
Average adult	20
Worst case	30
Drinking Water (L/day)	
Adult (average)	1.4
Adult (worst case)	2.0
Infant (≤10 kg)	1.0
Showering (minutes [gallons used])	
Median	7 (56)
90th percentile	12 (96)
Average Food Consumption (Worst Case)	
Adult total (g/day)	2000
Beef (g/day)	100
Dairy (g/day)	400
Fruit (g/day)	140
Vegetable (g/day)	200
Sport fish (g/day)	30 (140)
Soil Ingestion (≤7 years)	
Average (g/day)	0.2
90th percentile (g/day)	0.8

a carcinogen over a short period of time is equivalent to a low dose over a correspondingly longer period of time.[9] Worst-case scenarios involving maximally exposed individuals (i.e., 95th–99th percentile exposure) to all contaminated media are useful as screening tools to dismiss insignificant hazards; however, this type of estimation does not accurately estimate real risks. A more practical approach is the use of a single 95th percentile exposure (i.e., food source, residence, **or** childhood ingestion) as a measure of the maximally exposed individuals in the population.[100]

Dose Estimation

Most risk assessments use the potential internal dose for estimation of dose-response relationships because of the lack of adequate toxicokinetic data to estimate the delivered or biologically effective dose. The internal dose depends on the chemical concentration in a particular medium and chemical characteristics. These doses are usually measured as dose rates (i.e., amount of dose/unit time). These intake rates represent units of mass/time (e.g., mg/day); they usually vary over a period of time. Hence, many risk assessments use average intake (potential dose) rates or average uptake (internal dose) rates.

The intake of chemicals in vapors is usually insignificant from dermal exposures compared with inhalation. The dermal intake of chemicals from soil depends on the physicochemical properties of the contaminant and the soil, in addition to factors listed in Table 51.10. Typically, dermal exposures in the occupational setting involve the hands and forearms (i.e., ~2000 cm^2). Oral bioavailability of chemical contaminants also varies widely, depending on the same factors listed above. The bioavailability of chemicals in liquids is usually much higher for oral than dermal absorption.

Estimation of the daily or lifetime intake of chemicals is a complex process because this analysis requires consideration of multiple factors. These factors include bioaccumulation, dermal uptake, degradation, environmental migration through soil and air, deposition of particulates and dust, and ingestion of contaminated foods (e.g., plants, milk). Pharmacokinetics and consumption patterns over a lifetime frequently vary.[18] For cancer, lifetime probabilities usually describe the biological response. In these cases, the dose is described as a lifetime average daily dose, even though the exposure does not occur over the entire lifetime.[1] In some experimental animals administered high-dose potent carcinogens rather than doses commonly present in the environment, single-dose exposures to carcinogens can produce an increased tumor incidence.[102,103]

Oncogene proteins appear in the extracellular environment; therefore, immunoprecipitation techniques can detect these proteins in biological fluids. The challenge of developing reliable markers of oncogene activation remains; however, the identification of such markers provides valuable insights into the cause of occupational cancer and the true cancer risk in an individual worker. The efficacy of biological monitoring (sister chromatid exchange, oncoproteins, miRNA, DNA methylation, signaling pathway inhibition, tumor suppressor gene products) of workers exposed to

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carcinogens depends on a better understanding of confounding variables, prognostic value, and the outcome of early screening and treatment.[104,105,106]

Variation, Uncertainty, and Exposure Characterization

Variation in exposure estimates results from variability in the exposure of individuals within the population and uncertainty about the correct value for a specific exposure measure. Most risk assessments evaluate exposure variability and, less often, the uncertainty involved with these estimates. Characterization of the variability and uncertainty of the internal dose is more difficult because of more limited data. Depending on the complexity of the risk assessment, evaluation of the uncertainty in exposure risk assessments may involve only the qualitative discussion of the reasons for the selection of specific data or scenarios. Quantitative assessment of uncertainty includes: 1) scenario uncertainty – missing or limited information needed to define exposure, 2) parameter uncertainty – inadequate data on some parameters, and 3) model uncertainty – gaps in the scientific theory required to mathematically predict certain events.[1] Historically, many risk assessments used worst-case scenarios rather than realistic estimations of variability and uncertainty of the risk calculations. In these situations, the use of highly exposed individuals and upper confidence bounds on physical data implies that the risk estimates do not exceed the upper bound during exposure to highly exposed individuals. The true risks are probably much lower for individuals with exposures near the group mean.

RISK CHARACTERIZATION

Risk characterization is a summary review of the major scientific evidence and reasoning of a risk assessment that quantifies the likelihood of the development of adverse effects including cancer in a population exposed to certain chemicals.[107] This final step in the risk assessment process summarizes the preceding three steps by presenting the following: 1) a numerical risk estimate and 2) a discussion of validity and significance of the risk estimate. The risk characterization process estimates the risks associated with a range of exposures to help risk managers decide on appropriate regulatory, economic, and technological options. Risk assessment is only one part of the decision-making process for these options. Other considerations include political implications, trade impact, cost, socioeconomic values, feasibility, duration and magnitude of the risk estimate, populations at risk, and risk comparisons.[1] Risk estimates are expressions of uncertainty; these estimates change as knowledge regarding risks improves. Estimates of carcinogenic risk involve risk by analogy to animal data.[108] This process requires the comparison of carcinogenic potency in animals and humans along with extrapolation of high-dose animal data to low-dose human exposures. In relation to dose-response and exposure assessments, the major assumptions, uncertainties, scientific judgments, and relevant biological information should be analyzed to evaluate the risk estimates in relation to the actual risks in the environment.[109] Estimation of these risks improves the decision-making process regarding the hazards by understanding the cause and magnitude of the risks. Table 51.14 lists the important areas to evaluate during the risk characterization process.

Individual and Population Risks

With linear extrapolations associated with cancer risks, risk below the POD is typically approximated by multiplying the slope factor by an exposure estimate (i.e., Risk = Slope Factor × Exposure). The risk characterization should include expected or central estimates of risk, upper and lower bounds (e.g., confidence limits) based on the point of departure (POD) along with

TABLE 51.14. Areas pertinent to the evaluation of a risk assessment. (Adapted from International Programme on Chemical Safety, IPCS).[1]

Pertinent Areas to Evaluate
1. Conclusions and confidence in the existence and magnitude of risk
2. Identification of specific exposure in general population causing risk and evaluation of true exposure (body burden)
3. Presence of sensitive subgroups and evidence for true increased risk in these populations
4. Range of uncertainty and magnitude of risk near likely exposure levels
5. Likelihood of zero risk
6. Presence or absence of adequate information for regulatory decisions
7. Presence and importance of data gaps
8. Source and precision of key parameters that drive risk analysis
9. Results of peer review, if any
10. Presence of relevant ongoing research
11. Importance and validity of studies excluded from analysis

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characterization of uncertainty of the risk. For exposure levels above the POD, a point in the curve of the dose-response model provides the value rather than a calculated estimate. With nonlinear extrapolations, the risk assessment approach depends on the chosen procedure. When the nonlinear dose-response curve is available, the risk is a function of the expected exposure and the value at the appropriate point on the curve. Calculation of a reference dose (RfD) or reference concentration (RfC) allows the expression of a hazard quotient (HQ) defined as HQ = exposure estimate/(RfD or RfC).

Regulatory agencies traditionally accept assumptions that are least likely to underestimate the actual risk to human populations; therefore, the risk estimates are usually conservative as a means to protect vulnerable subpopulations.[110] The USEPA uses an upper bound (95%) confidence limit around the best estimate of risk rather than the maximum likelihood or central tendency (e.g., mean). The USEPA then applies this upper bound risk estimate to the maximum exposed individual (i.e., 24 hour/day over 70 years of maximum exposure, 2 L of water/day, 20 m^3 inhaled air/day, 100 mg ingested soil/day, 100% bioavailability). In the absence of contrary data, the USEPA also uses conservative quantitative assumptions for all dose-response assessments. These assumptions include: 1) surface area as a scaling factor for extrapolation from animals to humans, 2) low-dose linear models without thresholds, 3) the combination of malignant and benign tumors in the calculation of tumor incidence, and 4) positive results from the most sensitive species or strain.

Individual risk is the probability that a specific person or subgroup of a population will develop adverse health effects from exposure to a chemical over an established period. Individual risk requires the presence of carcinogenic (i.e., stochastic) effects or noncarcinogenic (nonstochastic) effects at concentrations above threshold values. Individual risks vary within a population. Identification of individuals with high risk depends on the degree of susceptibility, the exposure level relative to the population average, and the probability of developing an adverse health effect at a given exposure level. Factors predisposing individuals within a population to an increased risk of adverse health effects include preexisting diseases, lifestyle (tobacco, alcohol consumption), nutritional deficiencies, developmental processes, and prior or concurrent chemical exposure.[1]

Determining individual risks from these models requires careful analysis of the assumptions used to develop the models. Quantitative risk assessment evaluates the risks in a theoretical population; consequently, these risk estimates should not be applied directly to an individual.[111] The risk assessment process provides a good scale to compare the upper bound risk of different chemicals or mixture of chemicals with various exposures in a population; however, these risk estimates do not have precisely defined endpoints.[112] The true risk of an **individual** exposed to a chemical would not be higher than the estimated risk; the true risk probably would be much lower (and, if fact, may be zero). The true risk depends on the actual individual exposure, the susceptibility of the host to cancer, and the validity of

TABLE 51.15. Comparison of the annual risk of death from common actions and exposures in the United States during the 1980s. (Adapted from Wilson and Crouch).[108]

Action	Annual Risk ($\times 10^{-6}$)	Uncertainty
Cigarette smoking (1 ppd)	3,600	3
All cancer	2,800	10%
Mountaineer	600	50%
Motor vehicle accident	240	10%
Police, killed in line of duty	220	10%
Home accident	110	5%
Frequent flying professor	50	50%
Sea-level background radiation	20	3
4 Tablespoons peanut butter/day	8	3
Electrocution	5.3	5%

Abbreviation: ppd. = pack per day.

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the assumptions that extrapolate risk from animal data to the specific exposure level in humans. Major factors influencing the validity of the assumptions involved in risk assessment include: 1) variation in the environment, population, and exposure level, 2) multiple exposures, 3) species differences, 4) absorbed dose, 5) dose calculations based on body weight vs. surface area, 6) use of statistical rather than biological significance, 7) wide confidence intervals, 8) uncertainty factors, and 9) extrapolation from high-to low-dose.[10]

Risk Comparisons

Risk implies uncertainty, whereas understanding the meaning of a risk requires knowledge of the concept of probability that compares calculated and background risks. There is no consensus about the appropriate background risks to compare the output of risk assessment, particularly involuntary assumed risks. Many people do not perceive various risks as simply a matter of probability, particularly when comparing choices in personal lifestyle (smoking, motorcycle riding) with risks from unintentional chemical exposures.[113] Different people perceive risk differently depending on the seriousness of the effect, the theoretical benefit of the risk, the likelihood of the adverse effect, the individual at risk, their familiarity with the adverse effect, and how the hazard affects them personally.[114] For comparison, Table 51.15 lists the annual risk of death from common actions or exposures along with estimates of uncertainty based on data from the 1980s.

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Chapter 52

CANCER SURVEILLANCE

Most human cancers occur in epithelial tissue (carcinomas) from the interaction of a variety of host factors (genetic susceptibility, health, lifestyle) and the external environment.[1] Although mortality from cardiovascular diseases, infectious diseases, and many cancer types (e.g., hematopoietic) has steadily declined over the last 50 years, many advanced epithelial (carcinomas) and mesenchymal (sarcomas) tumors remain mostly incurable.[2] Consequently, monitoring individuals at risk (e.g., carcinogen-exposed workers, susceptible patients) is important to identifying early biological changes, when medical therapy has the best chance of reducing morbidity and mortality during the preclinical stage of cancer. The chapter on Qualitative Carcinogen Categories lists human carcinogens and recognized target organs based on information in public databases (IARC, USNTP, USEPA, GHS). These databases provide a plethora of information on proteins involved in signal transduction pathways that enable movement of external signals from cell surface rectors to enhancer-promoter regions along the chromosomes. These growth factors regulate gene expression required for cell growth, differentiation, and death (apoptosis), with crosstalk among the pathways exponentially increasing the complexity of the molecular and biochemical changes associated with cancer. Alterations of these pathways occur during the multiple stages of cancer, including the development of the increasing resistance of late-stage cancer cells to chemotherapeutic and radiation treatments as a result of genomic instability causing new pathways of epithelial-to-mesenchymal cell transitions. These free-floating, amoeba-like mesenchymal cells develop resistance to the hypoxic tumor microenvironment surrounding neoplasms and targeted chemotherapeutic drugs allowing proliferation and metastasis to noncancerous tissues (brain, liver, lungs).

MEDICAL SCREENING

Medical screening involves the application of population-wide tests to identify *asymptomatic*, at-risk persons (e.g., age, sex, family history) requiring further testing or preventive action to improve their outcome compared with no interventions.[3] Criteria for cancer screening include: 1) an important medical condition, 2) availability of effective treatment, 3) access for diagnosis and treatment of the cancer, 4) latent period between screening and cancer treatment sufficient for an improved outcome compared with treatment at clinical presentation documented by large, randomized clinical trials, 5) availability of a sensitive, specific test acceptable to the population tested, 6) adequate knowledge of cancer progression and presentation, 7) a well-defined policy for treatment options, 8) benefit of the screening program should outweigh harm from the screening, and 9) the cost–benefit compares favorably with other medical expenditures.[4] Despite the dramatic increase in knowledge regarding genetic and epigenetic molecular pathways through whole-genome, high-input screening of over 200 human genes (e.g., *TP*53 tumor suppressor genes, *KRAS* oncogenes) involved as drivers of carcinogenesis, most population-based screening techniques for early cancer detection remain investigational.[2] Using next-generation sequencing-by-synthesis technologies to examine tissues from 24 pancreatic

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tumors, Jones et al. identified 63 genetic alterations (primarily point mutations) in 12 cellular signaling pathways and processes.[5]

The common, effective cancer screening techniques include fecal occult blood testing and flexible sigmoidoscopy for colorectal cancer at ≥50 years of age,[6] Papanicolaou (PAP) test for cervical cancer in women of >21 years of age and HPV DNA test at >30 years of age, mammography for breast cancer in women at >45 years of age, human chorionic gonadotropin (HCG) for gestational trophoblastic disease in pregnant women, and low-dose computed tomography for lung cancer in high-risk persons (age 55–74 years in good health with ≥30 pack-year history).[7] Table 52.1 lists the 2020 United States Preventive Services Task Force (USPSTF) recommendations for cancer screening.

Common cancer screening tests without unequivocal validation in large clinical trials include α-fetoprotein (AFP) for hepatocellular cancer in high-risk persons, prostate-specific antigen (PSA) for prostate cancer in men aged ≥50 years, homovanillic and vanillylmandelic acid for newborn neuroblastoma, and cancer antigen 125 (CA-125) with ultrasound for ovarian cancer.

Limitations for the development of early screening tests involve low prevalence of specific cancer types in asymptomatic persons along with poor sensitivity and specificity. The receiver operating characteristic (ROC) curve is a measure of the ability of the dichotomous biomarker to accurately classify tumor and nontumor tissue. The ROC curve plots the sensitivity versus 1 minus the specificity of biomarker while varying the threshold to designate the biomarkers as positive. The area under the curve (AUC) of an ROC curve determines the accuracy of classifying tumor and nontumor tissues, with 1 being a perfect marker and 0.5 being an uninformative biomarker. Realistically accurate biomarkers have values of 0.80–0.90, with 0.70 being a fairly accurate biomarker.

Preemployment Physical Exam

Currently, validated, sensitive, and specific techniques to identify which workers will develop cancer following exposure to carcinogens are unavailable. Preemployment physical examinations can detect certain risk factors (smoking, family history, nutrition status, preexisting disease) depending on the cancer type associated with the associated industrial process. Counseling workers with known risk factors may help mitigate their exposure to carcinogens by encouraging them to use appropriate personal protective equipment, observe standard work site techniques, and modify their lifestyles. Individual susceptibility may result from variations in metabolism (cytochrome P-450, aryl hydrocarbon hydroxylase, debrisoquine hydroxylase, *N*-acetylation)[8,9] or the presence of certain diseases (e.g., xeroderma pigmentosum with UV-induced skin cancer). Preexisting conditions (e.g., nutritional deficiencies) may render DNA more susceptible to point mutations or translocations associated with cancer initiation. More data are necessary to accurately identify the genetic and/or epigenetic processes that enhance susceptibility to cancer.

Screening Examinations

Agencies listing known carcinogens include: the European IARC, the European Globally Harmonized System of Classification and Labelling of Chemicals (GHS), the US National Toxicology Program (US Department of Health and Human Services), the US Environmental Protection Agency (USEPA), and the American Conference of Governmental and Industrial Hygienists (independent, non-governmental body). Exposure to known carcinogens should be minimized with exposure never exceeding regulatory standards or recommended threshold limit values (e.g., TLV); however, exposure to concentrations above these standards does **not** imply that cancer will necessarily result because of the safety factors built into these standards.[10]

Older screening tests for lung cancer (sputum cytology, chest X-ray) and bladder cancer (urine cytology, urinalysis for red blood cells) are not valid biomarkers for early cancer detection. The formulation of a specific program for employees depends on the potency (known vs. suspected) of the carcinogen, the extent of exposure, and the documented efficacy of the outcome of screening. Numerous genetic and epigenetic markers are being tested based on data from molecular and biochemical studies on carcinogenesis.

BIOMARKERS

Analysis of chemical concentrations in air determines the **potential** amount (i.e., applied dose) of a carcinogen available for uptake into the body. Therefore, chemical concentrations in ambient air are an indirect measure of carcinogen uptake into the blood (i.e., internal dose) or the amount (i.e., biologically effective dose) of the carcinogen present at the site of action in the cell nucleus or cytoplasm.[11] The amount of carcinogen transferred from the external environment to nuclear DNA depends on the

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TABLE 52.1. United States Preventive Services Task Force (USPSTF) 2020 recommendations for cancer screening. (Based on Smith et al.).[7] These recommendations are updated as new evidence becomes available.

Cancer	Description	Grade
Bladder	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for bladder cancer in asymptomatic adults.	I
BRCA risk assessment and genetic counseling/testing	The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility 1 and 2 (BRCA1/2) gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing.	B
Breast	The USPSTF recommends screening mammography for women, with or without clinical breast examination, every 1–2 years for women aged 40 years and older.	B
Cervical	The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women aged 21–29 years. For women aged 30–65 years, the USPSTF recommends screening every 3 years with cervical cytology alone, every 5 years with high-risk human papillomavirus (hrHPV) testing alone, or every 5 years with hrHPV testing in combination with cytology (cotesting).	A
Colorectal	The USPSTF recommends screening all adults for colorectal cancer starting at age 50 and continuing until age 75. The USPSTF also recommends screening for adults 40 to 49 years. For adults aged 76 to 85, the USPSTF recommends selective screening for colorectal cancer based on patient's prior screening history, overall health, and preferences.	A B C
Lung	The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults aged 50–80 years who have a 20-pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years, develops a health problem that substantially limits life expectancy, or the has ability or willingness to have curative lung surgery.	B
Oral (asymptomatic adults)	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults.	I
Ovarian (asymptomatic adults)	The USPSTF recommends against screening for ovarian cancer in asymptomatic women who are not known to have a high-risk hereditary cancer syndrome.	D
Pancreatic (adults)	The USPSTF recommends against screening for pancreatic cancer in asymptomatic adults.	D
Prostate (55–69 years)	For men aged 55–69 years, the decision to undergo periodic prostate-specific antigen (PSA)–based screening for prostate cancer should be an individual one based on a discussion of the potential benefits and harms. Over the age of 70, prostate cancer screening is not recommended (category D).	C
Skin cancer (asymptomatic adolescents and adults)	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults.	I
Behavioral counseling	The USPSTF recommends counseling young adults, adolescents, children, and parents of young children about minimizing exposure to ultraviolet (UV) radiation for persons aged 6 months to 24 years with fair skin types to reduce their risk of skin cancer.	B

Abbreviations: A = recommends the service with high certainty that the net benefit is substantial; B = recommends the service with high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial; C = recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small; D = recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits; I = the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

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physiochemical properties (e.g., volatility, solubility) of the chemical, toxicokinetic characteristics (absorption, metabolism), and the route of exposure as well as individual susceptibility. Potential tumor-associated markers include: proteins (metabolites, cell surface receptors (e.g., receptor-tyrosine kinases),[12] serum proteins/enzymes, oncoproteins, carcinoembryonic proteins); circulating cell-free DNA including methylated DNA markers, histone modification patterns, microRNAs, and other RNA subtypes; and circulating tumor cells encoded by promoter/suppressor genes.[13] Of these tumor-associated biomarkers, DNA methylation has significant advantages (e.g., restriction to limited genome locations, amplification at relatively low costs, stability).[14] Advantages of cancer-associated biomarkers include relatively easy access (e.g., urine, blood), automated, high-throughput, relatively inexpensive assays, and quantitative data with objective endpoints; however, there is a lack of sensitive assays with high specificity for early malignancy in asymptomatic persons in populations with a low prevalence of cancer. The Early Detection Research Network (EDRN, https://edrn.nci.nih.gov/) is a research consortium established in 1999 by the US National Cancer Institute with the mission of translating promising cancer biomarkers to clinics for use in assisting with medical decisions.[15]

Table 52.2 outlines the role of biomarkers in the multistage process of carcinogenesis that results in difficulty separating external exposure, internal dose, and the biologically effective dose.[16] Emerging technologies include genomics (copy number, heritable variation, somatic mutations); epigenomics; proteomics (protein measurement); transcriptomics (mRNA and microRNA expression); and metabolomics (small metabolite concentrations).[17] However, effects of exposure to chemical carcinogens are not simply additive because of nonlinear relationships in signaling pathways between genotype and phenotype along with the biological complexity of nonlinear interactions at a molecular level between multiple genes, environmental risk factors, and epigenetic changes.

The National Research Council Committee on Biological Markers divided biomarkers into measures of **exposure**, **effect**, or **susceptibility**;[18] however, a biomarker does not always measure a single carcinogenic exposure or effect because of the complexity of signaling pathways and the cross-talk between them during the multistate process of cancer.[19] Figure 52.1 illustrates an overview of biomarker types and the interactions of various biomarkers during carcinogenesis. Biomarkers of exposure measure a chemical, metabolite, or product of the interaction of the chemical with a target molecule in the exposed individual, whereas a biomarker of effect measures a biochemical, behavioral, physiological, or other alteration in the person associated with a suspected or established disease process. Biomarkers of susceptibility assess the acquired or inherent ability of a person to respond to a specific chemical exposure. Typically, these biomarkers focus on the early stages of the exposure-response process (internal dose, biological effective dose, early biological effects), when an intervention is most likely to be successful.[20] Internal dose is the amount of chemical and metabolite found in the person, whereas biologically effective dose represents the integration of external exposure, toxicokinetics, and chemical interaction with the target site (e.g., DNA, essential enzyme). The early biological effect correlates to a specific health effect (e.g., lymphocyte chromosomal aberrations) caused by the exposure.

Many biomarkers are not unique to malignant neoplasms. Lipid peroxidation continuously produces substantial amounts (e.g., 5,400 adducts/cell) of DNA modification in healthy persons.[21] Consequently, the presence of carcinogen-DNA adducts is a necessary but not sufficient condition for the initiation of chemical carcinogenesis because tumors do not always develop in tissues that contain these adducts. Chemical carcinogenesis develops along a

TABLE 52.2. Biomarkers and their relation to the stages of carcinogenesis.

Biomarker	Site	Carcinogenic Equivalent
Susceptibility	Preexposure metabolism or DNA repair capacity	Enhancement of the progression of cancer stages
Exposure	Toxin–body interface	External dose of pro-carcinogen or direct carcinogen
Internal dose	Body fluids (blood, urine) or exhaled air	Ultimate carcinogen
Biologically effective dose	Sub-cellular level	Initiate cell
Early biological effect	Sub-clinical tumor	Pre-neoplastic lesion
Clinical disease	Altered structure or function	Malignant tumor

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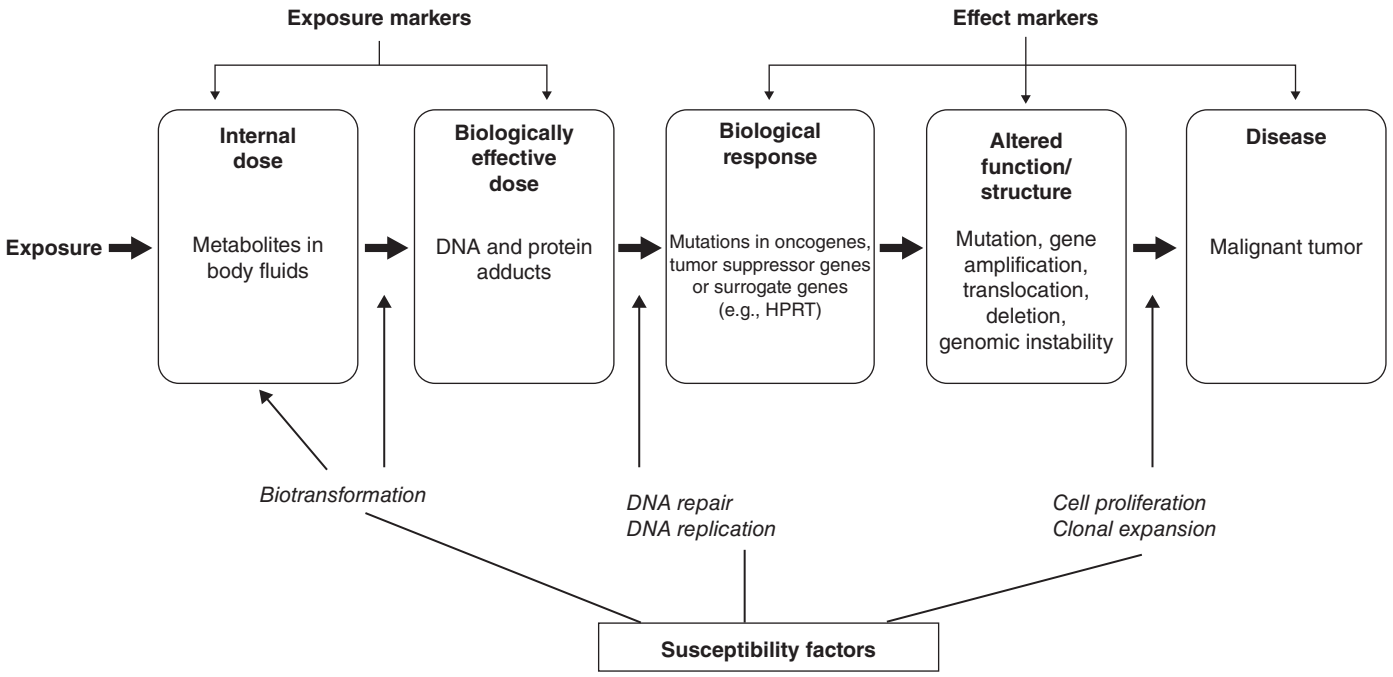


FIGURE 52.1. Schematic overview of biomarker types and interactions during carcinogenesis. (Adapted from Soderkvist and Axelson).[19] *Abbreviation:* HPRT = hypoxanthine-guanine phosphoribosyl transferase.

continuum from environmental contamination to clinically apparent disease, as reflected in Figure 52.1; the classification of a biomarker depends on events in this sequence that approximate the biomarker. The goal of biomarker development focuses on a molecular biology approach (epigenomic, genomic, transcriptomic, proteomic, metabolomic) that detects cancer during the preclinical phase, when treatment is most effective. With the exception of some measures of internal dose and cytogenic techniques,[1] the principle limitation to biomarker effectiveness among the plethora of potential biomarkers currently is the lack of adequate validation through molecular cancer epidemiological studies with sufficient power, especially given the diversity of individual lifestyle, environment, and occupation.[22] Other potential limitations of epidemiological biomarker studies include small sample sizes, selection bias, information bias (measurement error), false positives from multiple comparisons when using genome-wide scans, and confounding.[23,24] The latter bias complicates the interpretation of these studies because biomarkers are measures of exposure and outcome. Effective biomarkers of genetically susceptible populations should demonstrate the lowest risk for nonsusceptible, nonexposed groups and the highest risk for susceptible, exposed groups. Although there are a variety of biomarkers for exposure, response, and susceptibility, distinguishing adaptive and reversible responses from irreversible pathological changes is difficult.

Exposure

Biomarkers of exposure indicate the presence or the likelihood of previous exposure to a chemical or to alterations (e.g., DNA adducts, oncogene protein products, chromosomal aberrations) of the target organs from the chemical; potential biomarkers include measurements of external exposure, internal dose, biologically effective dose (e.g., level of DNA damage), and markers of harm. The latter three biomarkers quantify exposure at the cellular level, allowing characterization of exposures in low-risk populations. Biomarkers of gross chromosomal mutations from the formation of DNA adducts include chromosome breaks, gaps, and translocations; however, no single biomarker is sufficiently validated to determine the cancer risk in all individuals exposed to a chemical carcinogen.[25] Occupation is often a proxy for exposure to specific chemical carcinogens.[26] Assessment of exposure includes historical data (questionnaires, interviews), personal monitoring,

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and measurements of the carcinogen in the ambient environment. The latter is complicated by the changing distribution of chemicals in samples over time. Other biomarkers of exposure include biologically active substances absorbed from the environment (e.g., blood and urinary cotinine for quantitating cigarette smoke exposure). Tobacco-specific nitrosamines (e.g., 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone, NNK) and polycyclic aromatic hydrocarbons (e.g., benzo[*a*] pyrene) are recognized human carcinogens present in cigarette smoke. 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and the glucuronidated conjugates are metabolic biomarkers of NNK exposure, whereas urinary concentrations of 1-hydroxypyrene and tetraol, *r*-1,*t*-2,3,*c*-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT) are biomarkers of exposure to polycyclic aromatic hydrocarbon.[27] These urinary metabolites are biomarkers of internal dose.[28] Current data on the influence of genetic variation in PAH metabolism on urinary metabolite biomarkers are variable and inconclusive.[29]

Internal Dose

The internal dose represents the amount of carcinogen absorbed into the body as measured in body fluids (blood, urine, exhaled air, breast milk, adipose tissue, nails, hair). Consequently, the internal dose is a more accurate determination of the actual amount of the chemical transferred from the external environment to sites of action compared with measurements of concentrations in ambient air. However, these body fluids are usually not the target organs. Hence, measures of internal dose do not directly reflect the molecular interaction between the chemical and the macromolecules of the cell that initiate or promote carcinogenesis. Unless bioaccumulation occurs, measures of internal dose represent recent exposure only. Glutathione detoxifies reactive chemicals following exposure, and measurement of specific metabolites (e.g., mercapturic acids) is a good biomarker of internal dose;[11] however, such testing requires knowledge of the kinetics of individual carcinogens and sophisticated analytical techniques.

Biologically Effective Dose

Biomarkers of the biologically effective dose measure the interaction of a chemical with cellular macromolecules in the target organ or a surrogate (e.g., blood, urine). These biomarkers indicate the chemical reached a toxicologically significant site and produced damage to critical macromolecular targets. The advantage of biomarkers of effective dose is their independence from interindividual differences in metabolism. The determination of an effective dose for carcinogens often involves measuring DNA changes in body fluids. Methods for the detection of the effective dose may be chemically specific (e.g., hemoglobin, protein or DNA adducts) or a nonselective measure (e.g., rate of DNA repair, oxidative DNA damage, adduct formation).[30] The carcinogen-DNA adducts result from the covalent binding of electrophilic chemicals with DNA; this interaction is a necessary but not sufficient condition for the initiation of cancer. DNA adducts indicate chemical-induced mutagenicity and an elevated cancer risk. However, carcinogen-protein adducts, particularly Hb adducts (e.g., alkylating agents, aromatic amines, nitroaromatic compounds), are surrogates for carcinogen-DNA covalent binding and effective dose when detectable in body fluids; estimates for cancer risks are more accurate based on these adducts than measuring genotoxic substances and their metabolites in human body fluids.[31] Nonselective measures of the effective dose (e.g.,^{32}P postlabeling assays, immunoassays) indicate the occurrence of a reaction at the target site; the test does not provide information regarding the structure or nature of the chemical interaction. These techniques are very sensitive for DNA adduction monitoring and correlate on a group level; however, these tests lack specificity, do not reflect the current cancer status, and do not correlate well on an individual level.[32,33]

Macromolecular (i.e., DNA, protein) adduct levels depend on several factors, including the amount of external contamination, absorption and distribution of the carcinogen, metabolic activation of the carcinogen, stability of the carcinogens or metabolites and their adducts, and DNA replication and repair.[34] Interpretation of macromolecular adduct data is complicated when the carcinogen requires metabolic activation or produces different adduct concentrations in the target organs than in body fluids. Methods for detecting DNA and protein adducts include the following: synchronous fluorescence spectrophotometry; high-performance liquid chromatography with electrochemical or fluorescent detection; gas chromatography/mass spectrometry; liquid chromatography/tandem mass spectrometry; immunoassays using polyclonal or monoclonal antibodies; and ^{32}P-postlabeling. The latter two techniques are the most common and sensitive methods, but the ability to identify a particular type of adduct using strict structural criteria (i.e., specificity) remains problematic.[35] Monoclonal antibodies offer greater specificity than ^{32}P-postlabeling, but substantial cross-reactivity still occurs with these antibodies.

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DNA Adducts

DNA adducts are molecular dosimeters (biomarkers of exposure) and measures of the genotoxic potential of chemicals (biomarkers of effect).[36] Some DNA adducts produce mutations, whereas others do not; furthermore, some DNA adducts occur in healthy persons because of lipid peroxidation. Carcinogen-DNA adducts are detectable by current laboratory techniques involving a variety of agents, including aflatoxin B_1, vinyl chloride, aromatic compounds, 8-methoxypsoralen, cisplatin, melphalan, and UV light. Monitoring DNA adducts in the work environment primarily involves workers exposed to PAHs; dihydrodiol epoxide metabolites of these compounds form the adducts. A study of foundry workers demonstrated a good correlation between ambient air levels of polycyclic aromatic hydrocarbons (PAHs) and PAH-DNA adducts in workers; however, the adduct concentrations of local controls living near the cokeries were similar to those of workers rather than rural controls.[37,38] Extensive interindividual variation in PAH-DNA binding complicates the interpretation of these studies and the ability of these tests to separate environmental, occupational, and background contributions to measured PAH-DNA adduct concentrations. Factors contributing to the large interindividual variation include work habits, safety equipment use, diet (broiled, barbecued, smoked meat, or fish), smoking, outdoor exposure (forest fires, coke production, motor vehicle exhaust, coal combustion), and age.[39]

A consistent decrease in PAH-DNA adduct concentrations occurs within several weeks; therefore, samples should be collected during a period of constant PAH exposure.[40] Interindividual variations in the background macromolecular adduct concentrations depend primarily on differences in carcinogen toxicokinetics (e.g., absorption, metabolism) and the efficiency of DNA repair processes; genetic polymorphisms explain only part of the interindividual variation.[34,41] The formation and persistence of adducts also vary within different organs and different cell types within the same organ. Most tissues contain multiple cell types that differ in their ability to form DNA reactive species and produce DNA adducts. The presence of differences in the background adduct concentrations and interindividual variation suggests biological monitoring has advantages over environmental monitoring of large populations.[42,43] The major issue concerning DNA adducts at the present time is the clinical prognostic value of the presence of damaged DNA. Certain individuals possess heritable genes that increase cancer risk (e.g., *MSH2* gene for colon cancer, *BRCA1/2* gene for breast cancer). Although breast cancer is relatively common, only about 5–10% of breast cancer cases result from the inheritance of highly penetrant cancer susceptibility genes. The cloning of the *BRCA1/2* genes indicates these genes contain over 1,000 mutations with no test detecting all mutations in *BRCA1* or *BRCA2* genes. The presence of these gene mutations confers a seriously increased risk of breast and ovarian cancers in women with these mutations;[44] consequently, the National Comprehensive Cancer Network guidelines recommend criteria/family history-based *BRCA1*/*BRCA2* testing in women meeting these guidelines. The issue of screening the general population of women for breast and ovarian risk factors (*BRCA1/2, RAD51C/D, BRIP1, PALB2*) remains unresolved.[45,46]

Protein Adducts

Similar to DNA adducts, the suitability of a carcinogen-protein adduct depends on the degree of carcinogen-protein adduct binding, the background DNA adduct concentrations, and the stability of the DNA adducts. In some instances, carcinogen-protein adducts are satisfactory surrogates for DNA binding. The most commonly studied classes of proteins are hemoglobin and albumin. The use of hemoglobin for dose monitoring offers several advantages over DNA adducts, including a specific lifespan not affected by repair processes, accessibility, and reliable methods of chemical identification.[47] For adducts attached to hemoglobin and albumin in the blood, the information about past exposure to carcinogens is limited by the half-life (125 days, 25 days, respectively) of these two compounds. 4-Aminobiphenyl is a human bladder carcinogen that forms a large amount of hemoglobin adducts; urinary concentrations of 4-aminobiphenyl correlate with tobacco smoke exposure. Although preliminary studies of tobacco smokers indicated a 3–5-fold increases in hemoglobin adducts of 4-aminobiphenyl,[48] the biomarker of effective dose (4-aminobiphenyl-Hb adducts) weakly correlates with the biomarker of internal dose (urinary 4-aminobiphenyl) as a result of variations in accumulation and elimination rates.[49] To the extent that protein adducts quantify genotoxicity in the target organ, these adducts will reflect the magnitude of the process of initiation. If initiation is the rate-limiting step in the development of carcinogenesis following carcinogen exposure, the adduct concentrations should estimate the relative cancer risk; however, if later stages (promotion) are more important than initiation, then molecular adduct concentrations will not be proportional to the cancer risk.

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Early Biological Effect

Biomarkers of response range from simple measures (weight, histopathology, mortality) to sophisticated determination of isoenzyme induction and molecular genetics/epigenetics. These biomarkers predict the development of subsequent health impairments, including subcellular histological abnormalities and clinical functional changes in gene expression. The value of a biomarker of response depends on the sensitivity and specificity of the test for the presence of toxicologically significant changes. Biomarkers of early biological effects include cytogenic techniques and oncogene protein products. These biomarkers of early biological effects detect **irreversible** damage to the genome or epigenome in contrast with biomarkers of the biologically effective dose (carcinogenic-DNA, carcinogenic-protein adducts) that reflect a potentially repairable interaction with critical macromolecules. Both biomarker types provide a summation of the biological processes that result from a carcinogenic exposure; however, carcinogen-DNA and carcinogen-protein adducts are **chemical**-specific markers, whereas biomarkers of biological effect (cytogenic and oncogene protein products) are nonspecific markers of the response of an organism to all carcinogens.

Markers of biological effect detect the changes in the target cells that commit the cell to the development of malignant disease. These markers have difficulty distinguishing background by-products of the DNA repair process from products of the initiation and promotion stages of carcinogenesis. In contrast to studies on radiation that indicate the presence of dicentric chromosomes is a specific marker of effect, studies with chemicals have not identified a unique chromosome marker. The advantage of monitoring workers with biomarkers of biological effects is the use of a single test, in contrast to chemical-specific biomarkers (e.g., adducts) that require a test for each carcinogen. Data from chromosome studies on the effects of chemicals must be interpreted on a group basis rather than as a specific marker of chemical exposure pending further research. Although molecular epidemiology studies have identified many promising biomarkers, including alteration of gene expression and DNA methylation, these newer biomarkers require validation and documentation of their role in causing cancer.[50]

Cytogenic Techniques

Cytogenic techniques identify and quantify chromosomal changes, including abnormalities of chromosome numbers, breakage, rearrangements, and exchanges. **Chromatid** aberrations include chromatid breaks, exchanges, and intra-exchanges, whereas **chromosomal** aberrations include acentric fragments, dicentric chromosomes, and ring chromosomes. Cytogenic techniques include sister chromatid exchanges, micronucleus tests (fragments of nuclear material present in the cytoplasm after mitosis), and measurements of single-strand breaks in lymphocyte DNA or DNA hyperploidy. The micronucleus and chromosomal aberrations assays in peripheral blood lymphocytes and exfoliated epithelial cells gradually replaced sister chromatid exchange tests as the most frequently used cytogenetic endpoints in human population studies.[51] Chromosomal aberrations and micronucleus assays are common biomarkers of genotoxicity in workers exposed to radiation, organic chemicals (benzene, styrene, ethylene oxide, polycyclic aromatic hydrocarbons), and metals (uranium, chromium, lead, nickel, pesticides, antineoplastic drugs). Although many human carcinogens increase chromosomal damage in persons exposed to these chemicals,[52] interindividual variation and the complexity of changes involved with the multistage process of carcinogenesis complicate the establishment of a direct causal relationship between specific levels of chromosomal aberrations and cancer risks.

Several studies comparing groups with high and low micronucleus and chromosomal (but not chromatid) aberration frequencies in healthy subjects suggest a significant association between increased frequencies and cancer risk (i.e., early events in carcinogenesis);[53] however, interindividual variability and preventive strategies in high-risk groups require further study.[54] Intra- and interindividual variations occur in baseline frequencies of cytogenetic end points in lymphocytes from human populations with a significant portion of the variation resulting from personal characteristics (e.g., sex, smoking, environmental/occupational exposures). Age is an important confounding factor in determining the results from cytogenic studies resulting from age-related increases in micronucleus (MN) and chromosomal aberration (CA) frequencies. In Poisson regression analysis of 2,000 MN tests, the frequency ratio comparing the 50–59-year-old subgroup with the 1–19-year-old subgroup was 1.97 (95% CI: 1.43–2.71); the MN frequency ratios remained similar comparing older subgroups (>59 years) with the young subgroup.[55] Results for CA assays were similar, except the frequency ratios continued to increase in subgroups of >59-year-olds. Although the presence of a positive association between a chemical exposure and CA or MN frequency may suggest an increased cancer risk, a null association does not exclude a carcinogenic exposure

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if the mechanism of action operates through processes that do not currently produce CAs or micronuclei (e.g., epigenetic or receptor pathways). Unstable CAs and micronuclei usually persist for a few months, whereas translocations could exist for years.[56]

Oncogene/Tumor Suppressor Protein Products

Activation of oncogenes results from gene mutations, chromosomal breaks, and rearrangements of chromosomes. Immunoblotting or polymerase chain reaction techniques can detect the activation of oncogenes following exposure to environmental carcinogens (e.g., benzo[*a*]pyrene, *N*-nitroso compounds, PAH).[57,58] The *RAS* gene is a potential early marker of carcinogenicity along with the *p21* protein product of this gene because of the important role this gene plays in the control of cell proliferation. A small study of 40 volunteers without exposure to known carcinogens other than smoke indicated that smoking is unlikely to confound human monitoring studies using oncoprotein levels.[59]

A variety of different cancer types contain mutations of the TP53 gene, which codes for the tumor suppressor protein p53.[60] Tumorigenesis typically involves only a relatively small number of mutations. Although most mutations in tumors are unlikely to affect the initiation or progression of cancer particularly mutations affecting the third codon base,[61] high-throughput sequencing of cancer genomes indicates certain mutations frequently occur in specific tumors as fingerprints of the impact of environmental factors.[62] Most tumor-specific mutational signatures have two or more signatures. Sequence analysis of TP53 gene mutations in UV-induced nonmelanoma skin cancers (basal/squamous cell carcinomas) indicates a substantial percentage (e.g., >50%) of these skin cancers are associated with C → T transitions at dipyrimidine sites including CC → TT tandem mutations.[63] Lung cancers frequently contain TP53 mutations characterized by G → T transversions, particularly in tumors associated with exposure to tobacco smoke and benzo[*a*]pyrene.[64] Aristolochic acid forms DNA adducts at adenine bases after metabolic activation. A → T mutations comprise >70% of the mutations in aristolochic acid-induced urothelial cell carcinomas, with the A → T transversion being a characteristic mutation of aristolochic acid in experimental systems.[65,66]

Patients living in areas with high aflatoxin levels are more likely to have TP53 mutations (e.g., codon 249 G > T transversions) compared with patients living in areas with low aflatoxin concentrations;[67] however, multiple genetic and epigenetic changes are involved in the molecular pathogenesis of hepatocellular cancer (HCC) beside somatic mutations in the TP53 tumor suppressor gene, including activation of the Wnt signaling pathway involved with apoptosis complicating the use of this biomarker alone as a surrogate for HCC risks.[68,69] Additionally, the prevalence of TP53 mutations varies significantly between various geographical locations and tumor types. In a Chinese case-series of hepatocellular carcinoma, the prevalence of this mutation ranged from 36–54%, whereas the prevalence of a codon-249 TP53 mutation in patients with hepatocellular carcinoma was much lower in Egypt.[70,71] The apparent association of p53-specific mutations with aflatoxin probably results from the selective advantage of HBV-mutated cells rather than a causal event in the pathological process of aflatoxin-induced HCC. Numerous issues complicate the use of human cancer gene fingerprints including the following: 1) multifactorial process of human cancer, 2) individual variation in DNA repair mechanism, 3) confounding of biological (e.g., grading, staging) and clinical (e.g., treatment) factors, 4) variation in temporal sequences in the activation and deactivation of cancer genes, 5) high frequency of cancer gene mutations from genomic instability unrelated to an exposure, and 6) several different carcinogens may induce the same TP53 mutations.[50]

Cell-Free Circulating Tumor DNA

Most circulating cell-free DNA (cfDNA) in the blood stream results from the rupture of nonmalignant, germline cells, whereas the subset (ctDNA) of cfDNA derives from tumor-specific DNA abnormalities. Next-generation sequencing provides high-throughput analysis of cfDNA in circulating blood to detect ctDNA using a digital polymerase chain reaction to amplify cfDNA fragments and quantify specific alterations in ctDNA; typically, the latter represents <1% of the circulating cell-free DNA.[72] The Cobas EGFR Mutation Assay is a US Food and Drug Administration (FDA)-approved ctDNA analytical technique to initially genotype tumors in lung cancer patients when adequate amounts of tissue are unavailable to characterize the tumor tissue.[73] Other potential uses for this biomarker in addition to noninvasive cancer detection and characterization include monitoring of disease relapse, prediction of tumor response, and detection of tumor resistance.

Epigenetic

The epigenome is the combination of epigenetic information including DNA methylation, histone modification (e.g., acetylation, methylation, phosphorylation), nucleosome positioning, chromatin

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modification, and miRNA expression. Dysregulation of the epigenome involves the following: 1) DNA alteration and histone modification, 2) changes in somatic epigenetic proteins, and 3) altered expression of epigenetic proteins, resulting in a vast array of potential biomarkers.[74] Potential epigenetic markers of cancer diagnosis and prognosis include DNA methylation, histone modification patterns, and miRNAs. Of these potential biomarkers, DNA methylation is the best studied involving DNA methylation (5-methylcytosine) at the CpG dinucleotides, primarily concentrated in the CpG islands within core promoter regions or the first exon.[75] DNA methylation biomarkers include quantitative methylation-specific PCR, a 1-step methylation-specific polymerase chain reaction assay, and MethyLight assay. Potential biomarkers of cancer genes include methylation of *BRCA1* gene in breast cancer, *MGMT* gene in glioblastoma, and *MLH1* gene in colon cancer. *SEPT9* is the first USFDA-approved, blood-based methylated biomarker for colon cancer diagnosis.[76] Post-transcriptional gene regulation by miRNAs includes editing, splicing, transport, storage, and translation of mRNA through downregulation of gene expression by complementary binding to the 3′-UTR region of the target genes.[77] The dicer gene codes for an enzyme that cleaves dsRNA and pre-miRNA into small interfering RNA and miRNA, which are essential for development of the female reproductive tract. Dysregulation of miRNAs (e.g., *miR*-379, *miR*-15b, *miR*-691, *miR*-872, *miR*-1897) is associated with ovarian toxicity and potentially mitogen-activated protein kinase signaling pathways involved in cancer.[78]

In 2007, the American Academy of Cancer Research began collaboration on biomarker research by forming the AACR-FDA-NCI Cancer Biomarkers Collaborative with the US Food and Drug Administration (FDA) and National Cancer Institute (NCI). The purpose of the collaboration was to accelerate the translation of cancer therapeutics into the clinic by shaping the processes for the effective development of validated biomarkers and to use the clinical trials to maximize patient benefit.[79] The CBC identified and provided recommendations for eight critical areas for the development of biomarkers for the rapidly expanding field of epigenetic modification associated with cancer including biospecimens (i.e., quality of sample material), analytical performance, bioinformatics, and collaboration with data sharing. Identification of accurate epigenetic biomarkers awaits further validation studies.

Susceptibility

Some individuals are more susceptible to environmental exposures that result from genetic predisposition or other factors (age, gender, ethnicity, health impairment, nutritional deficiencies). Genetic variation may modulate the susceptibility of an individual to a toxin (e.g., differences in the toxicokinetics of the specific chemical).[80] Genes vary in their penetrance (i.e., the frequency of the expression of a specific genotype given a certain environmental condition). The most important sources of variability involve variations in DNA repair and metabolic genes (polycyclic aromatic hydrocarbon-associated lung cancer).[11,81] The ability to acetylate aromatic amines, hydrazines, and sulfonamides is genetically determined; ethnicity has a significant impact on the number of individuals with a specific acetylator phenotype. Cytochrome P450 enzymes activate a wide range of environmental carcinogens to reactive intermediates; however, amounts of these enzymes vary substantially between individuals. Urinary caffeine is a biomarker for the activity of CYP1A2 that catalyzes the *N*-oxidation of several aromatic and heterocyclic amines to reactive carcinogens.[82] Most genes act in a sequence or cascade. Although a large number of studies examine the role of signal nucleotide polymorphisms (SNPs), relatively few SNPs are clearly associated with increased cancer risks across different populations (e.g., methylenetetrahydrofolate reductase [*MTHFT* gene] deficiency and colorectal cancer).[83]

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Tumor Sites

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Chapter 53

RESPIRATORY TRACT

Lung cancer is the leading cause of cancer-related deaths among men and women in the United States, with 5-year survival rates remaining very low despite some improvement recently. From 2014–2018, the overall 5-year survival rate increased from 21–25%. Other less common tumors of the respiratory tract include sinonasal cancer, laryngeal cancer, and mesotheliomas. Table 53.1 lists the strength of the human evidence (i.e., sufficient, limited) for carcinogenic agents and processes associated with respiratory tract cancers based on evaluations by the International Agency for Research on Cancer (IARC).[1,2] The carcinogenic potential of these agents/processes varies within their respective categories. The actual risks are determined by individual risk factors (e.g., dose, exposure duration, host susceptibility, cocarcinogens).

LUNG

Lung cancer was rare before the 20th century; later in the 1920s, epidemiological evidence of an association between lung cancer and smoking emerged.[3] In the United States and Europe, the age-adjusted lung cancer incidence increased substantially 1950s–1980s with ~237,000 new cases of lung cancer diagnosed yearly in the United States. Currently, tobacco smoking accounts for ~85% of lung cancers.[4,5] Given the 10- to 30-year latent period for lung cancer, increased lung cancer incidence during this time reflects changes occurring in the early 1940s–early 1960s.[6] Lung cancer rates vary dramatically by geographic and demographic characteristics (e.g., age, sex, ethnicity, location, socioeconomic status), resulting primarily from differences in smoking patterns.[7] Lung cancer incidence and mortality rates are similar because of low survival rates following diagnosis, particularly for advanced stages of lung cancer. Only ~15% of lung cancer cases are diagnosed in early stages when the prognosis is much better.[8] The long delay between smoking initiation and clinically apparent lung cancer results in rare presentations prior to 30 years of age; the peak rates at diagnosis develop at a median age of ~70 years. The incidence of smoking-induced lung cancer declines after the age of 80 years.[9]

CARCINOGENESIS

Lung cancer is a very heterogeneous disease consisting of many somatic mutations affecting multiple signaling pathways. Compared with 30–60 somatic mutations in most solid tumors, genome-wide gene sequencing analyses indicate a lung tumor contains ~150 somatic mutations along with chromosomal translocations/fusions and somatic copy number alterations (deletions, gains) producing subsequent disruption of signaling pathways.[10] Tobacco smoke strongly influences the development of lung cancer with a somatic mutation rate of ~10-fold higher in lung tumors from smokers than nonsmokers.[11] Although most of these changes revert to normal baseline in former smokers, some alterations are irreversible and persistent.[12] The variety of histopathological types of lung cancer also reflects the very large tumor heterogeneity and differences in molecular pathogenesis (driver genes) noted in the Cancer Genome Atlas (TCGA databases).[13]

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TABLE 53.1. International Agency for Research on Cancer (IARC) classification of respiratory tract cancer sites by sufficient and limited evidence of human carcinogenicity. (Adapted from Cogliano et al. and IARC).[1,2]

Anatomic Site	Carcinogens with *Sufficient* Human Evidence (Group 1)	Carcinogens with *Limited* Human Evidence (Group 2A or 2B)
Nasal cavity and paranasal sinuses	Isopropyl alcohol production, leather dust, nickel compounds, radium-226 and its decay products, radium-228 and its decay products, tobacco smoking, wood dust	Carpentry and joinery, hexavalent chromium compounds, formaldehyde, textile manufacturing
Larynx	Acetaldehyde associated with alcoholic beverage use, acid mists, strong inorganic, alcoholic beverages, asbestos (all forms), tobacco smoking	Human papillomavirus type 16, rubber production industry, sulfur mustard, tobacco smoke, secondhand
Lung	Acheson process, occupational exposures, aluminum production, arsenic and inorganic arsenic compounds, asbestos (all forms), beryllium and beryllium compounds, bis(chloromethyl)ether; chloromethyl methyl ether (technical grade), cadmium and cadmium compounds, chromium (6^+) compounds, coal, indoor (household emissions from combustion) coal gasification, coal-tar pitch, coke production, engine exhaust, diesel, hematite mining (underground), iron and steel founding, MOPP (vincristine-prednisone-nitrogen mustard procarbazine mixture), nickel compounds, outdoor air pollution, painting, particulate matter in outdoor air pollution, plutonium, radon-222 and its decay products, rubber production industry, silica dust, crystalline, soot, sulfur mustard, tobacco smoke, secondhand, tobacco smoking, welding fumes, X- and γ-radiation	Acid mists, strong inorganic art glass, glass containers, and pressed ware manufacturing, benzene, biomass fuel household combustion (indoor emissions from mostly wood), bitumens, occupational exposure (oxidized bitumens and emissions during roofing and mastic asphalt work), carbon electrode manufacture, α-chlorinated toluene and benzoyl chloride (combined exposures), cobalt metal with tungsten carbide, creosotes, diazinon, fibrous silicon carbide, frying (emissions from high-temperature), hydrazine, insecticides, non-arsenical (occupational exposures during spraying and application), printing processes, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin
Mesothelioma	Asbestos, painting, erionite, fluoro-edenite	Polyoma virus SV40 (simian virus 40)[a]

[a] cocarcinogen.

The most frequently mutated cancer driver gene in lung cancer is the tumor suppressor gene p53 (*TP53*) ranging from 50% in adenocarcinomas to 86% in small cell lung cancer based on the cBioPortal for Cancer Genomics database (http://www.cbioportal.org). For adenocarcinoma tumors, the next four most common driver genes are *LRP1B* (low-density lipoprotein receptor related protein 1B), *KRAS* (Kirsten rat sarcoma viral oncogene homolog), *EGFR* (epidermal growth factor receptor), and *KEAP1* (kelch-like ECH-associated protein 1). The next most common driver genes in squamous cell carcinoma lung tumors are *LRP1B*, *KMT2D* (lysine methyltransferase 2D, *KMTD2*), *PCLO* (piccolo presynaptic cytomatrix protein), and *KMT2C* (lysine methyltransferase 2C) compared with *RB1* (retinoblastoma transcriptional corepressor 1), *LRP1B*, *PCLO*, and the tumor suppressor *FAT4* (FAT atypical cadherin 4) in small cell carcinoma. Table 53.2 compares the percentage of the 10 most common mutations in profiled samples of adenocarcinoma, squamous cell carcinoma, and small cell lung cancer samples contained in the cBioPortal for Cancer Genomics database. Intratumor heterogeneity also occurs with a majority of mutations often not distributed uniformly across the tumor; mutational discordance also exists between primary tumors and their metastases.[14,15]

Adenocarcinoma

A prominent subset of adenocarcinomas develops from the progression of preinvasive atypical adenomatous hyperplasia followed by intermediate lesion of adenocarcinoma *in situ*, minimally invasive adenocarcinoma, and ultimately overt invasive adenocarcinoma with a lepidic pattern lining preexisting alveolar walls.[16] Atypical adenomatous hyperplasia is the presumed origin of lung adenocarcinoma; ~30–40% of these lesions contain mutations of *KRAS* (codon 12) genes.[17,18] This small (<0.5 cm), slow-growing, noninvasive lesion typically occurs in the peripheral lung near the pleura. Telomere shortening and DNA damage responses are early lung carcinogenesis events with the expression of these damage response proteins and mRNA

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TABLE 53.2. Comparison of the most frequent (percentage) somatic mutations in adenocarcinoma, squamous cell carcinoma, and small cell lung cancer samples within the cBioPortal for Cancer Genomics database (http://www.cbioportal.org). The number in parentheses represents the number of profiled samples for each histological type of lung cancer. These data reflect sampling in Western countries; the mutational status of populations depends on the distribution of ethnic groups within the database. Consequently, the frequency of mutations varies between databases.

Gene Mutations	Adenocarcinoma (2,322)[a]	Squamous Cell (841)[a]	Small Cell (210)[a]
TP53	50.3	83.0	86.2
RB1	5.0	6.5	65.7
LRP1B	30.1	36.6	42.4
PCLO	10.6	17.6	19.0
FAT4	7.8	14.0	17.6
FAT1	9.5	13.7	17.1
PTPRD	12.3	7.5	14.8
CPS1	6.3	12.7	14.3
NOTCH1	3.2	8.0	14.3
HGF	7.4	6.2	13.8
KMT2D	6.9	22.0	13.8
KRAS	29.1	1.3	—
EGFR	20.2	3.2	7.1
KEAP1	16.8	11.1	1.9
STK11	16.3	1.3	1.4
KMT2C	11.4	15.5	11.9
NF1	9.6	11.5	6.2
CDKN2A	4.8	15.3	1.9
NFE2L2	2.2	15.0	1.4
RELN	8.2	14.4	11.9
PDE4DIP	4.0	13.0	6.7

[a] Profiled samples.

encoding telomere-specific DNA-binding proteins (*TERF1* and *TERF2*) associated with the progression from atypical adenomatous hyperplasia to adenocarcinoma *in situ*. The latter lesion is a slightly larger (i.e., ≤3 cm), localized preinvasive lesion with densely packed atypical cells, greater cell–cell contact, and an abrupt transition to normal adjacent pneumocytes. Minimally invasive adenocarcinoma is a small adenocarcinoma (≤3 cm) with a predominately nonmucinous lepidic pattern; the invasive structure is <5 mm. Adenocarcinomas have distinct genomic alterations that separate these tumors from other lung cancers (e.g., squamous cell carcinoma, small cell carcinoma).[19] Major driver genes include *TP53*, *EGFR*, *KRAS*, *BRAF, NF1* (neurofibromin 1), *MET* (*MET* protooncogene, receptor tyrosine kinase), and *RIT* (Ras like without CAAX 1). Recurrent somatic copy number alterations include deletions of *CDKN2A*, *LP1B*, and *PTPRD* along with amplifications of *EGFR*, *ERBB2*, *KRAS*, *MDM2*, and *MET* involved with telomeric DNA, organogenesis (*NKX2-1*), and cell division (*MYC*). Signaling pathways affected by these genetic alterations include RTK/RAS/RAF, mTOR, JAK–STAT, cell cycle regulation, DNA repair, and epigenetic

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deregulation. The latter includes differential DNA methylation profiles, histone modification, and altered miRNA expression (oncogene upregulation, tumor suppressor gene silencing).[20] Highly expressed miRNAs in adenocarcinomas include miR-29b, miR-29c, miR-100, miR-125a-5p, and let-7e; miR-124a is specific to adenocarcinomas.[21,22]

The presence of chronic tobacco smoking impacts the pathogenesis of adenocarcinoma with the KRAS pathway (rat sarcoma viral oncogene) more prominent in smokers, whereas the EGFR (epidermal growth factor receptor) pathway is present in ~50% of adenocarcinoma tumors from nonsmokers.[23] KRAS mutations alone are insufficient to drive carcinogenesis. Inactivation of oncogene-induced senescence (e.g., *TP53*, *CDKN2A*) promotes tumor growth in KRAS-mutated adenocarcinomas by limiting senescence. The frequency of KRAS mutations progressively declines from 33% in atypical adenomatous hyperplasia to 0% in well-differentiated invasive adenocarcinomas and 17% in poorly differentiated invasive adenocarcinomas.[24] In contrast, the frequency of EGFR mutations remains similar during this progression.

Other molecular abnormalities in this premalignant lesion include loss of heterozygosity in chromosomes 3p, 9p (*CDKN2A*), 9q (*TSC1*, tuberous sclerosis complex 1), 17p (*TP53*), and 17q. Overexpression of survivin (apoptosis protein family inhibitor), CCND1 (cyclin D1), and ERBB2 oncoproteins occurs along with downregulation of serine/threonine kinase 11 (STK11, a tumor suppressor). Epigenetic alterations include DNA methylation of *CDKN2A* (p16) and *PTPRN2*. Progression of atypical adenomatous hyperplasia to adenocarcinoma in nonsmokers is associated with *EGFR* oncogene and TTF-1 amplification along with increasing frequency of TP53 mutations.[25] The BRAF mutation enhances tumor initiation and progression via activation of the ERK(MAPK1) pathway. *BRAF* gene is a member of the *RAF* gene family that encodes a serine/threonine protein kinase by activating RAS downstream. BRAF mutations occur primarily in early preinvasive adenocarcinoma lesions in nonsmokers.[26]

Squamous Cell Carcinoma

Early changes in the pathogenesis of squamous cell carcinomas include alteration of 3p chromosome sites and 9p21 (*CDKN2A*) in normally appearing bronchial epithelia along with increasing DNA methylation of *CDKN2A* as the premalignant lesion progresses.[27] Amplification of the *SOX2* oncogene (3q26.3) and overexpression of endothelial growth factor (*VEGF*) and *VEGF* receptors (*VEGFR*) support angiogenesis and promote tumor survival.

Small Cell Carcinoma

The pathogenesis of small cell lung cancer is not associated with phenotypically identifiable preneoplastic lesions; however, a very high incidence of alterations in epithelia occurs in histologically normal epithelium, suggesting the cells of origin may be normal or slightly abnormal bronchial epithelium.[23] In genetically engineered mouse models, small cell lung cancer is associated with *TP53* and *RB1* oncogene overexpression, resulting in hedgehog signaling pathway activation.[28] Integrative genome analyses in humans suggest key somatic drivers include TP53 and RB1 mutations as well as histone modifiers (*CREBBP*, *EP300*, *MLL*) and mutations of *FGFR1* oncogenes.[29]

EXPOSURE

Lung cancer incidence trends follow the pattern of tobacco consumption. However, the increased lung cancer incidence in nonsmokers suggests the possibility that other environmental or occupational factors will become more important etiological agents for lung cancer in the future, assuming the present decrease in overall tobacco consumption continues.[30] The contribution of outdoor and indoor pollutants (e.g., radon, formaldehyde, asbestos) is more difficult to assess, in part because of the strong confounding of smoking. Additionally, exposure to these potential carcinogens is typically much lower than the carcinogens in tobacco smoke.[31] At these exposure levels, ascertainment of true cases, accurate exposure measurement, and careful control of confounding variables are necessary to detect the attributable risk of pollutants. Host predisposition, the influence of microclimates on individual exposure, the interaction of carcinogens, and changes in exposure (e.g., job, residence) over the lifetime of an individual modify the ability of a study to detect an increased cancer incidence in the study population.[32]

Occupation

Attributable Risks

The average attributable risk of occupational exposure to lung cancer in men ranges from ~5–15%.[33,34] In 1981, Doll and Peto attributed 15% of the lung cancers among American men to occupational exposure.[35]

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A review of all case-control studies on lung cancer using age/smoking-adjusted estimates of relative risk reported that the attributable risk from occupational exposure depends on the prevalence of exposure within the population and the dose received by individual workers.[36] The attributable risk ranged from 1–40% in certain workers with high ionizing radiation exposure. A case-referent study of lung cancer in Swedish men estimated the attributable lung cancer risk from occupational exposure to combustion products including diesel exhaust and asbestos was ~9.5%.[37] In a case-control study of Italian lung cancer patients and local controls, the estimated percentage (population attributable fraction) of all occupationally related lung cancers in men was ~5% (range, 2.0–7.8%) based on self-reported exposure to known human lung carcinogens.[38] The risk of developing lung cancer in women following occupational exposures is relatively low compared with men.[39] In a case-control study of workers in Central and Eastern Europe, the attributable fraction of occupationally related lung cancer using Miettinen's formula was 7.9% in men and 1.4% in women.[40] The highest attributable fraction for men was squamous cell carcinoma (11.4%) and for women was small cell carcinoma (7.1%). Silica and metals accounted for most of the attributable fraction of occupationally related lung cancers.

Histological Types

There are limited data on the specific subtypes of lung cancer associated with known human lung carcinogens (e.g., some metals, benzene, asbestos).[41] Age is a confounding variable for studies correlating chemical exposures with histological lung cancer types because the distribution of lung cancers into histological types depends on age. Exposure to asbestos increases the incidence of all three histological lung cancer types,[42] whereas many other carcinogens demonstrate a predilection to a specific histological type. Each histological lung cancer type has a multifactorial etiology including smoking, occupation, and environmental exposures.[43] Smoking patterns account for only part of the difference in the prevalence of these different histological types.[44] Adenocarcinoma predominates in younger men, women nonsmokers, and arsenic-exposed copper smelter workers.[45]

Carcinogens

Occupational lung carcinogens include arsenic, asbestos, beryllium, cadmium, chloromethyl ethers, hexavalent chromium, nickel, radon, silica, and vinyl chloride. Of all occupational carcinogens, asbestos exposure accounts for the highest population attributable fraction of lung cancer.[46] Cancer registry-based, case-control studies suggest workers at increased lung cancer risk include wood-processing plant operators (OR 4.63; 95% CI: 1.05–20.29)[47] and meat/poultry workers from food animal oncogenic viruses (~30%);[48,49] however, the wide confidence intervals, imprecise estimates, and insufficient epidemiological data to exclude confounding prevent the establishment of a causal association for these workers. The Nordic Cohort Study on work-related cancers reported a reduced standardized incidence ratio (SIR) for lung cancer in wood workers (SIR = 93, 95% CI: 90–95) and a modestly elevated SIR in food manufacture workers (SIR = 117, 95% CI: 111–122) that included meat workers with other food preparers (e.g., dairy, bakers, grain millers).[5]

Asbestos accounts for substantial occupational cancer deaths in the United States. The estimated annual number of deaths attributed to asbestos exposure peaked in 1992 with a proportionate decline in the ratio of lung cancer/mesothelioma deaths since that time.[50,51] Occupations associated with increased lung cancer risk in the ICARE study included painters and welders, particularly gas welders.[52] Occasional welding was not associated with an increased lung cancer risk. A systematic review of lung cancer studies in refinery workers reported 27 studies with only 1 study demonstrating a statistically significant elevation of lung cancer rates in refinery workers.[53] The summary RR for lung cancer using the random effects model was 0.81 (95% CI: 0.76–0.86) with substantial heterogeneity (I^2 = 72%, $P > 0.001$).

Although some case reports associate vegetable dust exposure with lung cancer,[54] most observational studies of workers with high endotoxin exposure (agriculture, cotton textile) demonstrate reduced lung cancer risks and little association between hypersensitivity lung disease and lung cancer,[55] particularly active dairy (but not row crop/orchard) farmers[56] and cardroom sorters/weavers in the textile industry.[57] The lack of accurate endotoxin concentrations and substantial heterogeneity between studies limit conclusions regarding the role of endotoxin exposure; however, a systematic review and meta-analysis of cohort and case-control studies of agricultural and cotton textile workers exposed to high concentrations of endotoxin-contaminated organic dust generally support reduced lung cancer risks in these two industries. The summary lung cancer risks were 0.62 (95% CI: 0.52–0.75) and 0.72 (95% CI: 0.57–0.90), respectively.[58]

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Industries

The IARC lists aluminum production, coal gasification, and coke production as occupations associated with increased lung cancer risks.[2] A meta-analysis of 24 cohort studies involving 296,810 workers reported a statistically significant, modestly increased lung cancer risk in the coal/coke and related product industries (metaRR = 1.55, 95% CI: 1.01–2.37) and the iron/steel foundry industry (metaRR = 1.52, 95% CI: 1.05–2.20), but not in the iron/steel foundry (metaRR = 1.13, 95% CI: 0.88–1.33) or aluminum production industries (metaRR = 1.29, 95% CI: 0.96–1.33).[59] Wide variation in smoking habits and PAHs exposure occurred among the cohort studies with only 12 of the 24 studies reporting smoking status and 10 reporting smoking-adjusted data. In a meta-analysis of cohort studies using weighted average SMRs and random effects modeling, the overall SMR for lung cancer ranged from 1.05 for the iron/steel foundry industry (pooled RR = 1.31, 95% CI: 1.07–1.61, $n = 13$ studies, $P_{\text{heterogeneity}} = <0.0001$) to 1.12 for asphalt workers (pooled RR = 1.59, 95% CI: 0.68–3.76, $n = 3$ studies, $P_{\text{heterogeneity}} = <0.0001$) and 1.14 for aluminum production (pooled RR = 1.07, 95% CI: 0.93–1.23, $n = 10$ studies, $P_{\text{heterogeneity}} = <0.0001$).[60]

Chemicals

Exposure to organic solvents probably does not contribute significantly to occupational lung cancer risks. Although the presence of large numbers of substances in the work environment complicates the determination of the contributions of individual solvents to lung cancer risks, a French multicenter, population-based case-control (ICARE) study of 2,276 male lung cancer cases and age-matched 2,780 controls did not detect evidence of lung carcinogenicity from the solvents studied using stepwise logistic regressions with a Bayesian approach.[61] Exposure assessment involved questionnaires and job-exposure matrices separating solvent exposures into clusters including alcohol, benzene, carbon tetrachloride, chloroform, diethyl ether, ethylene glycol, gasoline, kerosene/diesel oil/fuel oils, ketones/esters, methylene chloride, mineral spirits and other light aromatic fractions (white spirits), special boiling point spirits and other aliphatic petroleum-based solvents, tetrachloroethylene, tetrahydrofuran, and trichloroethylene.

Using benzene soluble matter (BSM) as the surrogate for exposure to polycyclic aromatic hydrocarbons, some,[62,63,64] but not all,[65,66] epidemiological studies of exposed workers demonstrate modest, statistically significant, dose-dependent increases in the lung cancer risks above concentrations of 10 μg BSM/m^3/year. The lack of accurate historical data on the chemical concentrations and the difficulty identifying a truly nonexposed group limit the conclusions regarding quantification of the lung cancer risk.

The association between occupational formaldehyde exposure and lung cancer is weak and inconsistent with a comprehensive review of cancer in industry workers and professionals reporting no appreciable excess risk of lung cancer in these groups.[67] The overall pooled relative risks of lung cancer mortality were statistically nonsignificant in industry workers (RR = 1.06, 95% CI: 0.92–1.23, $n = 6$ cohort studies, $P_{\text{heterogeneity}} = 0.0019$) and inverse in professionals (RR = 0.63, 95% CI: 0.47–0.84, $n = 8$ cohort studies, $P_{\text{heterogeneity}} = <0.0001$). In a meta-analysis of 31 case-control, nested case-control, cohort, proportional mortality, and proportional incidence studies on occupational formaldehyde exposures using random effects models, the overall pooled risk estimate for lung cancer comparing exposed workers with unexposed controls was consistent with the null (pooled RR = 1.04, 95% CI: 0.97–1.12).[68] The risk estimate increased with study quality as evaluated by the Newcastle-Ottawa/scale (pooled RR = 1.13, 95% CI: 1.08–1.19, $I^2 = 40.2\%$, $P_{\text{heterogeneity}} = 0.066$); the risk estimates also increased with higher formaldehyde exposures but were statistically nonsignificant (pooled RR = 1.19, 95% CI: 0.96–1.46). Only 1/3 of the studies adjusted for smoking; however, a subanalysis comparing adjusted and non-adjusted studies did not detect a significant difference in the risk estimates. The lung cancer risks were higher in fiberglass industry workers compared with professionally exposed workers (pathologists, embalmers) and wood industry workers.

Sulfur Mustard (Mustard Gas) Mustard gas was one of the first chemical warfare agents introduced in World War I and the first chemotherapeutic agent used to treat cancer patients. The use of mustard gas produced a detectable increase in lung cancer in British veterans, although a small increased risk (i.e., ~1.5) appeared in American veterans. The results of these studies are inconclusive because of the poorly documented exposure and confounding of smoking.[69] A cohort of Japanese workers producing mustard gas during World War II experienced a 3-fold increase in lung cancer incidence compared with the local controls after considering smoking history.[70] A majority of these cases involved squamous cell carcinomas and undifferentiated carcinomas, whereas adenocarcinomas and small cell carcinomas were rare.[71] The latent period usually exceeds 20 years.[72] From 1929–1945, a prospective Japanese study evaluated lung cancer risks in a cohort of workers from a poisonous gas factory in Okuno-jima,

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Hiroshima Prefecture, Japan, exposed to mustard gas ($n = 480$), lewisite ($n = 55$), and/or diphenylcyanoarsine ($n = 178$).[73] The control group contained 969 manufacturing workers unexposed to these gases. A 1-year exposure to mustard gas in workers ≤18 years of age reduced the age at lung cancer diagnosis by 4.9 years (95% CI: 1.7–7.9 years) compared with controls. The effect declined with age. For workers of >18 years of age, the average age at diagnosis decreased by 3.2 years (1.2–5.5 years).

Chloromethyl Methyl Ether Chloromethyl methyl ether (CMME) and bis(chloromethyl)ether (BCME) are volatile colorless liquids recognized as established animal carcinogens. BCME is a contaminant of CMME and a much more potent animal carcinogen than CMME.[74] The relative risk of developing lung cancer increases with cumulative CMME exposure, reaching 10 in heavily exposed workers.[75] Maximal risk occurs ~15–20 years after exposure; however, heavy CMME exposure shortens the latent period.[76] The mean latent period from the onset of exposure to death for 59 moderately (10–<20 years) and heavily (>20 years) exposed workers was 21–25 years; the latent period was inversely related to cumulative exposure.[77] The exposure category was calculated by multiplying the estimated time-weighted average and the exposure time in years. In a French cohort study of a factory using technical-grade chloromethyl methyl ether in the manufacture of anion exchange resins, the mean time from first exposure to lung cancer diagnosis was 13 years (95% CI: 8–18 years), whereas cumulative dose was not correlated to induction time.[78] The rate ratio for lung cancer among potentially exposed workers was 5.0 (95% CI: 2.0–12.3) compared with nonexposed workers at the same plant; the incidence of lung cancer in the exposed workers was dose related. Small cell carcinoma accounts for ~80% of the lung cancers associated with CMME exposure.[77,79]

Diesel Exhaust

Although the IARC classified diesel exhaust as a human carcinogen in 2012 based primarily on the Diesel Exhaust in Miners Study and nested case-control studies of eight US nonmetal mines, the association between diesel exhaust and lung cancer remains controversial because of concerns regarding selection bias (low participation rates), exposure misclassification (insufficient latency based on job title), confounding (e.g., radon co-exposure), inconsistent exposure-response trends, and posteriori adjustment bias.[80,81,82] The cohort mortality study of 12,315 workers exposed to diesel exhaust at US nonmetal mining facilities reported a standardized mortality ratio for lung cancer of 1.26 (95% CI: 1.09–1.44).[83] The lung cancer mortality hazard ratios increased with increasing 15-year lagged cumulative estimates of respirable, elemental carbon exposure for ever-underground workers. The hazard ratio for lung cancer mortality was increased (HR = 5.01, 95% CI: 1.97–12.76) in ever-underground workers with ≥5 years of tenure to respirable elemental carbon ≤640–<1,280 μg/m^3/year compared with controls (0–<20 μg/m^3/year). However, the hazard ratio was not dose-dependent, as the HR for exposures ≥1,280 μg/m^3/year was not statistically significantly different than the control category (HR = 2.39, 95% CI: 0.82–6.94, $n = 14$ deaths, $P = 0.109$). The wide confidence interval suggests imprecise estimates.

Metals and Metalloids

The IARC lists types of five metals (arsenic, beryllium, cadmium, chromium, nickel) as human (Group 1) lung carcinogens. The classification of these metals is based primarily on the strength of the epidemiological data rather than an estimation of the carcinogenic potency of each metal.[84] For arsenic, beryllium, and cadmium, this classification applies to metallic compounds as a whole and not necessarily to individual species within the group of metallic compounds. There are very substantial differences in the physiochemical properties of individual species of the same metal that affect the carcinogenic potency of a specific species. Metallic chromium and metallic nickel are not included in the Group 1 classification. Some forms of arsenic (trivalent), chromium (hexavalent), and nickel (oxide, subsulfide) are well-established lung carcinogens.[85]

Arsenic Several epidemiological studies correlate exposure to arsenic trioxide in smelters[86] and arsenic-containing pesticides,[87] with a dose-related increase in lung cancer risks up to 10-fold in heavily exposed smelter workers[88] and 3-fold in arsenic-exposed pesticide workers. In a study of smelter workers exposed to arsenic, a relative excess of adenocarcinomas and a slight excess of small cell (previously named oat cell) carcinomas appeared.[89] The contribution of smoking to the appearance of lung cancer was almost multiplicative in a study of smelter workers;[90] however, the influence of smoking was less dramatic in another study.[91] Studies on the effect of air contamination with arsenic are inconsistent, and studies associating an increased lung cancer incidence with living near a smelter require further confirmation.[92,93,94] The carcinogenicity of arsenic compounds may result, at least in part, from the inhibition of DNA repair processes.[95]

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BERYLLIUM The epidemiological evidence for the carcinogenicity of beryllium is based on the US Beryllium Case Registry and studies of seven US manufacturing plants. Although criticized for lack of control over smoking, selection bias, poor dose-response relationships, and underestimation of expected lung cancer deaths,[96] several cohort studies of beryllium workers demonstrated excess mortality from lung cancer with a relative risk of 1.4–1.6.[97,98] However, the excess lung cancer risk was confined primarily to workers developing acute beryllium disease after short-term exposure (<1–5 years) rather than workers with a long-duration, high-intensity beryllium exposure. An analysis of the US Registry demonstrated an ~2-fold excess lung cancer risk in workers with acute beryllium disease and a 50% excess in workers with chronic disease;[99] however, the causal association between beryllium exposure and increased lung cancer risk remains controversial because of the lack of a clear dose-response and potential confounding from the relatively small increased cancer risk.[100,101]

CADMIUM The human data establishing a relationship between cadmium exposure and lung cancer are limited because of confounding variables (smoking, nickel and/or arsenic exposure) complicate the interpretation of positive studies. Some,[102] but not all,[103,104] studies of cadmium workers demonstrate a significant increase (average ~10–50%) in lung cancer mortality in cadmium-exposed workers. A retrospective cohort mortality study of 606 white, male workers at a cadmium smelter demonstrates marginal statistically significant excess lung cancer mortality (SMR = 149, 95% CI: 95–222) among workers exposed to cadmium based on a modified life-table analysis to estimate working lifetime risks (45 years).[105] This increase was dose-related. For workers in the highest cadmium exposure group, the SMR was 272 (95% CI: 123–513, $P < 0.05$).

CHROMIUM Hexavalent chromium (chromates, chromic acid) is a well-established lung carcinogen. Water-soluble hexavalent chromium compounds are particularly carcinogenic with zinc chromate being the most potent chromate carcinogen. Trivalent chromium does not penetrate cells; therefore, these compounds are not genotoxic. Depending on the study population, exposure duration/concentration, and study design, epidemiological studies of primary chromate production process and chromate pigment industry demonstrate highly variable excess lung cancer risks ranging slightly from >1–50-fold.[106,107] Chromium pigments are usually hexavalent typically containing zinc, strontium, and lead chromates. The most common histological type of lung cancer in chromate workers is squamous cell carcinoma followed by small cell carcinoma, usually located in the central bronchus.[108]

The risk of developing lung cancer is smaller in the chrome plating and stainless-steel welding industries. The Cr^{6+} concentration in stainless-steel welding fumes and ambient air of chromate industry workers developing lung tumors is similar. Some epidemiological studies detected a 30–40% increased lung cancer incidence among stainless-steel welders compared with unexposed controls;[109,110] however, a substantial portion of the increased lung cancer risk may be attributable to co-exposure to confounders (e.g., asbestos, smoking) or unidentified carcinogens.[111] Mild steel welders have negligible exposure to chromium and nickel; however, some European studies suggest an increased relative lung cancer risk among these welders. In a Finnish cohort study of welders born during 1906–1945, the relative risk of squamous cell lung cancer in the highest exposure category based on the Finnish job-exposure matrix as judged by 20 experts at the Finnish Institute of Occupational Health was 1.55 (95% CI: 1.08–2.24). The results were adjusted for a 20-year latency period for cumulative exposure and confounders (smoking, asbestos, silica dust, socioeconomic status).[112] There was no excess risk of small cell lung cancer in this cohort.

The standardized incidence ratio for lung cancer was higher in mild steel welders than in stainless-steel welders, despite relatively higher exposure to hexavalent chromium in the latter group. Chromium trioxide is a potential carcinogen in the chrome plating industry; a retrospective cohort study of 116 hard chrome platers and 62 bright chrome platers demonstrated an excess number of lung cancer deaths (observed = 3 deaths, expected = 0.6, latency period >10 years); however, the results were not adjusted for confounders.[113] The airborne chromium trioxide concentrations were substantially higher in hard chrome than bright chrome plating. In a prospective cohort study of 626 Japanese chromium platers, the standardized lung cancer mortality of the exposed group was borderline statistically significant (SMR = 1.46, 95% CI: 0.98–2.04, $n = 28$ cases) using nonexposed workers as referents.[114]

NICKEL Exposure to insoluble nickel compounds (e.g., subsulfide, oxide) produces an increased lung cancer risk in workers involved in the nickel refining industries, particularly with roasting, sintering, and calcining of ores.[115,116,117] The prior use of sulfuric acid contaminated with arsenic complicated the exposure assessment of older workers in these studies.[118] The risk of lung cancer in nickel mining and industries using nickel is less well defined. Excess mortality from respiratory tract cancers

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was not detected in studies of mortality in workers exposed to metallic nickel in nickel alloy plants[119] or gaseous diffusion plants.[120]

Fibers

Asbestos Asbestos exposures are well-known causes of malignant mesotheliomas, lung cancer, and pneumoconiosis.[121] In ancient times, asbestos use was very limited (e.g., weaving material for napkins, cooking, and storage pots); however, asbestos exposure dramatically increased during the early 20th century from the use of asbestos as a durable heat- and corrosion-resistant material in water and combustion pipes, car brakes/gaskets, house construction, and shipbuilding. Of an estimated 10,000–12,000 lung cancer cases/year attributed to occupational carcinogens, >½ of these cases were associated with asbestos exposure.[122] Risk factors for tumor induction in the respiratory tract include fiber origin and physical characteristics, cumulative exposure (i.e., duration, dose), latent period, smoking history, and confounding from other occupational and environmental carcinogens.[123] At low asbestos concentrations, the relationship between intensity and lung cancer risks is nonlinear. The validity of risk estimates depends on the appropriateness of the risk model, exposure measures, and control of confounding variables.[124] Individuals with radiological or pathological evidence of asbestosis have the greatest risk of developing lung cancer, with lung cancer developing primarily in patients with well-documented asbestosis.[125,126] The issue of whether asbestos-induced lung cancer develops in the absence of asbestosis remains controversial.[127,128] The presence of asbestosis indicates a relatively large cumulative asbestos dose because the threshold dose of 25–105 fibers/mL/year for asbestosis occurs almost exclusively in workers with heavy occupational exposures (asbestos insulators, miners, millers, textile workers).[129] About 30–40% of patients with well-documented asbestosis will die from lung cancer, whereas ~10% of this population will die from mesothelioma.[50,130]

Classification. Asbestos consists of two main forms of hydrated fibrous silicate minerals (i.e., serpentine, amphibole) that share common properties of flexibility, high tensile strength, and resistance to heat and chemicals. Table 53.3 outlines the common types of commercial asbestos, other silicate fibers, and man-made vitreous fibers.[131] Chrysotile is the principal variety of asbestos fiber, whereas other varieties (actinolite, amosite, anthophyllite, crocidolite, tremolite) account for <2% of commercial production.[132] Previously, these latter varieties accounted for ~10% of commercial asbestos production. Environmental asbestos exposure usually results from the presence of tremolite in local geological formations (French Corsica and New Caledonia, Cyprus, central and eastern Turkey).[133]

Dose-Response. For occupational asbestos exposures, the exposure-response relationships for lung cancer are linear and cumulative; however, these relationships also depend on the industrial process and type of asbestos fiber.[134] The relative risk is much smaller (i.e., 10–30 times) for workers in chrysotile mining and milling than other types of asbestos fibers.[135] Cohort studies of workers exposed to processed asbestos fibers in the insulation and textile industries demonstrate a steeper exposure-response curve compared with the risk (i.e., relative risk of 0.1%/year) associated with workers exposed to asbestos contained within a matrix, mining, or asbestos cement manufacturing.[121,136] Overall, relative lung cancer risks in studies of workers in asbestos cement production are not usually elevated.

Although the dose-response data in occupational cohorts appear linear at high asbestos concentrations,

TABLE 53.3. Major fiber categories include asbestos, other silicate fibers, and man-made vitreous fibers (synthetic or manufactured vitreous fibers). The main asbestos fibers are serpentine and amphiboles, whereas man-made vitreous fibers are divided into filaments and wools. The latter are noncrystalline fibers produced from inorganic fibrous material (e.g., inorganic oxides, glass, minerals, rock, slag).

Asbestos Groups	Asbestos Types	Other Silicate Fibers	Man-Made Vitreous Fibers	Vitreous Fiber Types
Serpentine	Chrysotile (white asbestos)	Attapulgite, erionite, sepiolite, talc, vermiculite, wollastonite	Filaments	Continuous glass filament
Amphiboles	Actinolite,[a] amosite (brown asbestos or cummingtonite-grunerite), anthophyllite,[a] crocidolite (blue asbestos or riebeckite), tremolite[a]		Wools	Glass wool, refractory ceramic fibers, rock (stone) wool, slag wool, other fibers (e.g., alkaline earth silicate wools, high-alumina, low-silica wools)

[a] Little commercial value, primarily found as contaminants.

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the extrapolation of a linear dose-response to environmental asbestos levels remains controversial.[137,138,139] Follow-up cohort studies in a British friction materials factory[140] and Australian crocidolite miners[141] did not detect an increased lung cancer relative risk in workers employed for <2 years. The odds ratio increased with employment duration after this time period to 2.2 (95% CI: 1.1–4.5) for employment ≥5 years. The major difficulty in determining the presence of a threshold results from the lack of accurate exposure data in occupational and community cohorts. In occupational exposures, duration of employment may be a much stronger component of cumulative exposure than dust concentrations, whereas fibers are typically short and poorly characterized in environmental settings. Cigarette smoking produces an almost multiplicative effect on the incidence of asbestos-related lung cancer. One cohort study of amosite workers followed from 1941–1977 demonstrated an 80-fold increase in lung cancer incidence among smoking workers.[142]

Histological Type. The histological types of lung cancer associated with asbestos and non-asbestos exposed cigarette smokers are similar; however, the frequency of histological types varies depending on the smoking history.[143] In a nested case-control study of 71 lung cancer cases among Australian crocidolite workers, the distribution of histological patterns was: 1) adenocarcinoma, 31%; 2) squamous cell carcinoma, 27%; 3) small cell carcinoma, 18%; 4) large cell carcinoma, 11%; and 5) unclassified, 13%.[144] The median cumulative exposure to crocidolite was 6 fibers/mL/year. After adjustment for smoking, commonly associated with squamous cell carcinoma, increasing crocidolite exposure produced a relatively greater increase in incidence of squamous cell carcinoma than adenocarcinoma. A Danish study of asbestos workers exposed primarily to chrysotile found a stronger relationship between asbestos exposure and adenocarcinoma than squamous cell carcinoma.[145] Lower lobe lung cancers predominate in asbestos workers, whereas upper lobe tumors dominate smoking-related lung cancers without asbestos exposure.[146] Pleural plaques are a marker of asbestos exposure rather than an independent marker for increased lung cancer risks.[129]

Silica and Other Silicates. The International Agency for Research on Cancer (IARC) concluded in 1987 that the evidence for the carcinogenicity of crystalline silica in experimental animals was sufficient but the evidence for cancer in humans was limited.[69] In 1997, the IARC changed the classification of crystalline silica to Group 1 (human carcinogen) based,[147] in part, on an increasing dose-response gradient in some studies with rate ratios up to 5.35 (95% CI: 2.23–12.8) for the highest crystalline silica exposure category (≥5.0 mg/m^3, 15-year latent period).[148] Other studies demonstrated no dose-response relationship,[149] particularly in studies of crystalline silica-exposed workers without silicosis.[150] Epidemiological studies of workers exposed to crystalline silica demonstrate variable findings with both positive and negative results on the association of silica exposure with lung cancer. The overall risk estimates from the positive studies are low (i.e., <2), and the risk of developing lung cancer appears concentrated in workers exposed to high silica concentrations that produce silicosis.[151] A meta-analysis of studies on silicosis indicates an ~2-fold increased lung cancer risk compared with the general population.[152] Frequently, exposure to other carcinogens (e.g., smoking, radon, asbestos, benzene) confounds the interpretation of these studies with inconsistent relationships between latent period, exposure duration, and quantitative exposure estimates. Smoking is a very strong confounding variable in studies on silica exposure; some positive studies are consistent with a multiplicative effect of smoking and dust exposure on the induction of lung cancer in silica-exposed workers.[153]

Epidemiological studies of exposures to other silicates are limited by difficulty identifying study populations with adequate size, latent period, and limited exposure to other carcinogens. Exposure of talc workers to tremolite and anthophyllite-contaminated talc as well as exposure of miners to tremolite-contaminated vermiculite produces increased lung cancer incidence; however, small studies of workers exposed only to trace contamination by asbestos demonstrate relatively small increased lung cancer risks.[123,154] Although data are limited, small studies of workers exposed to attapulgite, sepiolite, and wollastonite have not demonstrated a clear lung cancer excess.[123]

Man-Made Vitreous Fibers. A statistically significant elevation of standardized mortality ratios (SMRs) occurred in large epidemiological studies of rock/slag wool production workers in the United States (SMR = 134, n = 60 deaths)[155] and Europe (SMR = 124, n = 81 deaths).[156] These studies did not detect lung cancer excesses in glass wool or glass fiber (continuous filament) workers. In the European study, the excess lung cancer incidence was concentrated in the early technological phase of fiber production; this excess did not appear in workers employed in the later technological phase of fiber production following the introduction of dust-suppressing agents. Although there were insufficient data to estimate the qualitative lung cancer risk

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in the general population from exposure to man-made fiber, the World Health Organization concluded risks to the general population are several orders of magnitude below the risk of current occupational exposures.[157] Case-control studies of environmental and occupational exposure to man-made vitreous fibers do not support a consistently increased lung cancer risk.[158,159] In a systematic review and meta-analysis of lung cancer risks in man-made fiber workers, the summary relative risk (RR) was 1.21 (95% CI: 1.11–1.32, n = 1,662 cases).[160] The RR in studies of production workers was 1.26 (95% CI: 1.10–1.44), similar to the risks in rock and glass wool workers with statistically nonsignificant elevations of risks in end users [RR = 1.06 (95% CI: 0.77–1.48) and 1.18 (95% CI: 0.98–1.42)] in community-based studies.

Ionizing Radiation

Radon is a natural decay product of radium 226 and uranium 238, which exists as a ubiquitous gas in soil and rock with highly variable concentrations. This radionuclide has a half-life of 3.82 days with the radon decay products (radon daughters) including the α-emitting polonium 218 and polonium 214. The α-particles are highly damaging to respiratory epithelium. Epidemiology studies demonstrate a linear relationship between radon exposure and lung cancer risk in underground miners.[161] Underground uranium miners with >5 years of employment experience an ~10-fold increase in lung cancer incidence.[162] The actual lung cancer risk depends on cumulative radon exposure. Small cell undifferentiated carcinomas are the most common histological type of radiation-induced lung cancer.[163] Although an increased lung cancer risk occurs in nonsmoking Indian miners,[164] analysis of lung cancer mortality data in Colorado uranium miners suggests a multiplicative effect on the development of lung cancer between cumulative radon exposure and pack years of smoking.[165]

Environment

Environmental asbestos exposures are typically much lower than those in occupational settings; consequently, most lung cancer cases are related to occupational rather than environmental exposure. Lung cancer risks depend on the concentration and type of asbestos fibers. Epidemiological evidence associating passive asbestos exposure in buildings with lung cancer is weak with the exception of para-occupational exposure.[166] Mortality studies of populations surrounding point sources of asbestos have not demonstrated a statistically significant increase in mortality from lung cancer when occupationally exposed workers are excluded from the study population.[167] Epidemiological evidence suggests the balance between carcinogens and agents that stimulate defense mechanisms affects the risk of environmentally induced lung cancer.[168] Several epidemiological studies indicate workers exposed to dust containing bacterial endotoxins demonstrated a lower lung cancer incidence than controls.[169]

Outdoor Air

Outdoor pollution is a complex mixture of gases and particles, including soot, dust, metals, fibers, polycyclic aromatic hydrocarbons, aromatic amines, endotoxins, bacterial produces, and fungi. Associations between estimated air pollutant concentrations and lung cancer incidence/mortality typically involve exposure to nitrogen dioxide (NO_2), nitric oxide (NO), and/or PM_{10}/$PM_{2.5}$, whereas the associations between sulfur dioxide (SO_2) and these outcomes are usually weak and statistically nonsignificant.[170] An issue of concern is the presence of small particulate matter from vehicle exhaust, which is typically classified as fine particles with an aerodynamic diameter of ≤2.5 μm ($PM_{2.5}$) and inhalable particles with an aerodynamic diameter of ≤10 μm (PM_{10}). The mechanism of action involves genomic instability and alteration of DNA replication, DNA repair, cell-cycle progression, and chromosomal segregation.[171] The IARC designated particulate matter in air pollution as a human carcinogen (Group 1) based on the relationship of particulate matter to lung cancer risk.[172] The concentration of mutagens is typically higher in the $PM_{2.5}$ than PM_{10} fraction, whereas the PM_{10} fraction contains the $PM_{2.5}$ fraction plus relatively higher amounts of biological and mineral nanoparticles.[173] Consistent with analysis of data from the American Cancer Society Cancer Prevention II study using linked metropolitan air pollution data,[174] most positive studies associating air pollution with lung cancer demonstrate increased overall relative risks of <10% with each increment of 10 μg/m^3. In a systematic review and meta-analysis of incidence and mortality studies analyzing lung cancer relative risks associated with particulate matter exposure per 10 μg/m^3 increments, the overall summary relative risk meta-estimates were 1.09 (95% CI: 1.04–1.14, n = 14 studies, I^2 = 53.0%, P = 0.010) for $PM_{2.5}$ and 1.08 (95% CI: 1.00–1.17, n = 9 studies, I^2 = 74.6%, P = 0.000) for PM_{10}.[175] The funnel plot was asymmetric with substantial heterogeneity. The analysis demonstrated overall meta-estimate of adenocarcinoma for $PM_{2.5}$ of 1.40 (95% CI: 1.07–1.83, n = 3 studies); however, evidence for an association with squamous cell carcinoma was weak (1.11, 95% CI: 0.72–1.72, n = 2 studies).

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For meta-estimates involving smoking status and the lung cancer, relative risks associated with $PM_{2.5}$ were strongest for former smokers (1.44, 95% CI: 1.04–2.01) and weaker for never-smokers (1.18, 95% CI: 1.00–1.39) and current smokers (1.06, 95% CI: 0.97–1.15).

Indoor Air

Potential lung carcinogens in indoor air pollution include cooking fumes, radon, and environmental tobacco smoke. The strength of these associations with lung cancer is much weaker than that of mainstream tobacco smoke.

Environmental Tobacco Smoke

The lung cancer risk estimates from exposure to environmental tobacco smoke (ETS) are much smaller and more inconsistent than those from inhaling mainstream smoke, reflecting, in part, the difficulty in accurately measuring ETS (passive) smoke exposure. Overall, increased lung cancer risk for nonsmokers is relatively small (i.e., ~20%) compared with mainstream tobacco smoke. In a meta-analysis of 35 case-control and 5 cohort studies, the relative lung cancer risk in nonsmoking women ever-exposed to a smoking spouse was 1.20 (95% CI: 1.12–1.29).[176] The pooled relative risk was 1.19 (95% CI: 1.10–1.29) for case-control studies and 1.29 (95% CI: 1.04–1.62) for cohort studies, with increasing risk as ETS exposure increased. The prospective, multicenter US Women's Health Initiative Observational cohort study of 76,304 postmenopausal women (participation rate: 81%, age: 50–79 years) following a mean of 10.5 years identified 901 lung cancer cases.[177] Using Cox proportional hazards models and 152 never-smokers as referents, the lung cancer incidence was highest in current smokers ($HR_{multivariable\ adjusted}$ = 13.44, 95% CI: 10.80–16.75, n = 218 cases) and former smokers ($HR_{multivariable\ adjusted}$ = 4.20, 95% CI: 3.48–5.08, n = 531 cases). Among never-smokers, lung cancer incidence was not increased, comparing any passive smoking exposure with none ($HR_{multivariable\ adjusted}$ = 0.88, 95% CI: 0.52–1.49, n = 16 unexposed cases/136 ever-exposed cases); however, the lung cancer risk was marginally significant in women with ≥30 years of passive adult smoke exposure ($HR_{multivariable\ adjusted}$ = 1.61, 95% CI: 1.00–2.58, n = 32 cases).

Similar to mainstream tobacco smoke and lung cancer, the risks are highest for small cell lung cancers and lowest for adenocarcinomas. In an analysis of 18 case-control studies in the International Lung Cancer Consortium, the odds ratio for lung cancer in never-smokers comparing ever- and never-ETS exposure was 1.31 (95% CI: 1.17–1.45) for all histological subtypes combined.[178] The OR was 1.26 (95% CI: 1.10–1.44) for adenocarcinoma and 3.09 (95% CI: 1.62–5.89) for small cell lung cancer. The association was not statistically significant for squamous cell carcinoma (OR = 1.41, 95% CI: 0.99–1.99) or large cell lung cancer (OR = 1.48, 95% CI: 0.89–2.45); the association of ETS with lung cancer was greater for small than non-small cell lung cancer (OR = 2.11, 95% CI: 1.11–4.04).

In a Japanese systematic review and meta-analysis of four cohort and five case-control studies examining ETS exposure during adulthood and lung cancer, most populations studied demonstrated increased lung cancer risks from ETS exposure.[179] The pooled relative risk of lung cancer was 1.28 (95% CI: 1.10–1.48) comparing nonsmoking individuals (i.e., mostly women) with smoking and nonsmoking spouses. After adjustment, the funnel plot did not display significant publication bias. Examination of dose-response relationships suggested an increased lung cancer risk when comparing nonsmoking women living with current rather than former smokers; however, the frequency of ETS exposure or the number of household smokers did not clearly affect lung cancer risk. Long-term lung cancer risks following chronic exposure to inhaling hookah or e-cigarette smoke remain poorly defined.

Radon

Radon is a well-established lung carcinogen with highly variable exposures throughout the world. A meta-analysis of 13 European case-control studies involving 7,148 persons with lung cancer and 14,208 controls reported excess relative lung cancer risk per 100 Bq/m^3 increase in observed radon concentration of 8% (95% CI: 3–16%, $P = 0.0007$) after control for confounding.[180] Radon exposure was based on self-reported smoking history and long-term radon gas measurements of residential radon concentrations. After removing bias induced by random uncertainties related to radon exposure assessment, estimated risks at 0 Bq/m^3, 100 Bq/m^3, and 400 Bq/m^3 for lifelong nonsmokers compared with unexposed lifelong nonsmokers were 1.0, 1.2, and 1.6, respectively. The risks of radon and cigarette smoking were synergistic. A review of five North American studies on residential radon exposure demonstrated conflicting results on exposure-response relationships, statistical significance, and trends, with some studies reporting similar excess relative risks (ERRs) as the European meta-analysis (e.g., overall ERR = 0.24 (95% CI: −0.07–0.55 for nonsmokers with substantial heterogeneity).[181]

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Indoor Heating

The IARC classifies indoor coal emissions from combustion during heating and cooking as a human carcinogen (Group 1), whereas emissions from biomass combustion (wood, twigs, crop residues) are listed as probable human carcinogens (Group 2A). In a pooled analysis of 7 studies from the International Lung Cancer Consortium involving 5,105 lung cancer cases and 6,535 nonsolid-fuel using controls (oil, gas, electricity), the lung cancer risk was elevated in predominant coal users (OR = 1.64, 95% CI: 1.49–1.81) and predominant wood users in North American and European countries (OR = 1.21, 95% CI: 1.06–1.38).[182] The odds ratio for predominant coal users in Asia was higher and less precise than in other parts of the world (OR = 4.93, 95% CI: 3.73–6.52). A systematic review and meta-analysis of 8,221 lung cancer cases and 11,342 controls from 13 case-control studies on biomass cooking and/or heating reported an odds ratio of 1.17 (95% CI: 1.01–1.37) for lung cancer risk associated with biomass cooking and/or heating compared with controls.[183] Restricting data to studies with adequate adjustment and a clean reference category demonstrated an odds ratio of 1.21 (95% CI: 1.05–1.39) for men (two reports, compiling five studies) and 1.95 (95% CI: 1.16–3.27) for women (five reports, compiling data from eight studies). The exposure-response trends reflected the higher exposures of women from developing countries.

Ionizing Radiation

Data from Hiroshima and Nagasaki atomic bomb survivors indicate lung cancer incidence increases in a linear dose-response relationship to ionizing radiation.[184] Low-dose radiation effects from X-ray or computed tomography differ from the single, high-dose exposure received by the atomic bomb survivor, requiring extrapolation of the high-dose data below the range of observation.[185,186] Initiation processes dominate the risk of radiation exposure in younger individuals, whereas promotion of preexisting premalignant cells predominately influences cancer risks after radiation exposure in later years. Hence, cancer site-dependent balance between initiation and promotion determines the dependence of cancer risk on age at radiation exposure with radiation-induced cancer risks persisting into middle age.[187]

Lifestyle

Although alcohol consumption,[188] marijuana smoking, diet,[189] estrogen use, and some infections (human papillomavirus, HIV, Epstein–Barr virus) are suggested risk factors for lung cancer, current evidence is insufficient to establish a clear association between lung cancer and these potential risk factors.[190] A systematic review of lung cancer risks and alcohol consumption among the Japanese population identified seven cohort and two case-control studies with only five of these studies adjusting for smoking.[191] One cohort study reported a statistically significant increased lung cancer risk in daily-drinking women (RR = 2.53, 90% CI: 1.59–4.03, $P = 0.011$) compared with nondrinkers; however, the association became statistically nonsignificant after adjustment for smoking. Another two studies reported weak positive risks, whereas five studies reported no significantly increased lung cancer risk. Obesity is not strongly associated with lung cancer; some studies suggest an inverse association with BMI and a modestly increased risk for measures of central obesity (waist circumference, waist-to-hip ratio). A pooled analysis of 12 prospective cohort studies in the United States, Europe, and Asia identified 23,732 incidence lung cancer cases during an average 11.9 years of follow-up for 1,636,357 participants.[192] Using Cox proportional hazard regression and BMI of 23–24.99 kg/m^2 as referents, the BMI was modestly inverse and statistically significant for lung cancer risks in obese participants with BMI 30–34.99 kg/m^2 (adjusted HR = 0.81, 95% CI: 0.75–0.87, n = 1,100 cases) during 5–10 years of follow-up, but statistically nonsignificant for >10 years of follow-up. Similarly, for very obese participants (BMI = >35 kg/m^2), the adjusted HR was 0.81 (95% CI: 0.72–0.90, n = 382 cases) during 5–10 years of follow-up, but statistically nonsignificant for >10 years of follow-up (adjusted HR = 0.92, 95% CI: 0.77–1.09, n = 145 cases). In general, lung cancer risks were marginally increased for central measures of obesity (e.g., adjusted HR = 1.15, 95% CI: 1.00–1.33, n = 682 cases) for the highest category of waist-to-hip ratio during >10 years of follow-up. In the American Cancer Society Cancer Prevention Study-II Nutrition Cohort of 162,679 men and women, physical activity was not associated with lung cancer risk within any smoking strata, except for former smokers of 10 years since quitting (RR = 0.77, 95% CI: 0.67–0.90 for >17.5 MET-hours/week).[193] Waist circumference was not associated with lung cancer risk in any smoking category.

Tobacco Smoking

Approximately 15% of smokers develop lung cancer, whereas 10–15% of lung cancers occur in never-smokers.[194] Tobacco consumption accounts for 80–85% of US lung cancer deaths.[9,195] In 1964, the US Surgeon General's Report noted a 9–10-fold greater lung cancer

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risk comparing average male smokers with nonsmoking men.[196] The risk of developing lung cancer strongly correlates to cumulative smoking dose with an odds ratio of ~16 for male smokers with >40 pack-years smoking history.[66] Smoking declines with age; in the United States, current smokers account for ~5% of 75-year-olds compared with 21.5% of 18–44-year-olds.[197] The smoking rate continues to decline. The high lung cancer incidence in the general population attributable to smoking complicates the interpretation of studies examining causes unrelated to smoking. Because smoking is a very strong risk factor, cohorts must carefully categorize smoking history to avoid misclassification bias. Although cessation of smoking reduces lung cancer risks, the risk of cancer never returns to baseline levels.[198]

Although current tobacco smoking increases the risks of all four major histological lung cancer subtypes, the association is stronger for squamous cell carcinomas and small cell lung cancer than large cell lung cancer or adenocarcinomas.[199] Controls were hospital patients without a history of tobacco-related diseases. Most lung carcinomas including adenocarcinomas develop in the lungs of smokers with chronic obstructive pulmonary disease;[200] almost all (i.e., 98%) of the lung cancers in COPD patients are non-small cell lung tumors.[201] Although some case-control studies suggest an increased risk of large cell carcinomas in smokers,[202] poor exposure data, revisions of histological classifications, and wide confidence intervals indicate the potential for substantial misclassification and imprecise odds ratios. In a hospital-based case-control study of 851 male and 507 female lung cancer cases along with age/race-matched controls (888 men, 608 women), the adjusted odds ratio of lung cancer in current smokers of ≥30 cigarettes/day was highest for small cell carcinoma (OR = 5.5, 95% CI: 1.6–18.2, n = 40 cases), squamous cell carcinoma (OR = 2.3, 95% CI: 1.3–3.9, n = 100 cases), and adenocarcinoma (OR = 1.9, 95% CI: 1.1–3.2, n = 99 cases).[203] The results for large cell carcinoma were null (OR = 1.0, 95% CI: 0.5–2.3, n = 29 cases).

Marijuana Smoking

The results on chronic marijuana smoking and lung cancer are inconsistent. Although the possibility of potential adverse effect for heavy consumption was not excluded, pooled analyses from six case-control studies within the International Lung Cancer Consortium detected little evidence for an increased lung cancer risk among habitual or long-term cannabis smokers; the pooled OR for habitual versus non-habitual or never-users was 0.96 (95% CI: 0.66–1.38).[204] A meta-analysis of eight observational studies (five case-control, one cross-sectional, one prospective, one retrospective cohort) was unable to pool data for lung cancer because of inadequate adjustment, confounding by few marijuana-only smokers, and poor exposure assessment.[205]

Diet

Diet is not strongly associated with increased lung cancer risks. Previously, β-carotene was a prime candidate for lung cancer chemoprevention; however, subsequent studies demonstrated an increased lung cancer incidence following the administration of β-carotene alone or combined with vitamin E (α-tocopherol) or retinyl palmitate.[206] Although large-scale chemoprevention studies on vitamin supplementation were negative, most health professionals recommend a balanced diet of fruits and vegetables including β-carotene. After adjusted for smoking history and other covariates, the NIH-AARP study of 472,081 participants aged 50–71 years did not demonstrate a relationship between total fruit/vegetable consumption and reduced lung cancer incident in 6,035 lung cancer cases.[207] The study detected no evidence of a dose-response trend. The randomized, double-blind, placebo-controlled Beta-Carotene and Retinol Efficacy Trial (CARET) was terminated 21 months early when vitamin A and/or β-carotene supplementation produced a clear lack of efficacy and substantial evidence of harm.[208] The Physicians' Health Study of 22,071 male physicians followed over 12 years demonstrated no benefit (RR = 0.9, 95% CI: 0.7–1.2) or harm from β-carotene supplementation on lung cancer rates.[209]

Medications

Women are more likely to develop adenocarcinomas at a younger age of diagnosis compared with men, suggesting potential reproductive and hormonal risk factors; however, observational studies are conflicting and lack a clear consensus on the effect of female hormones on lung cancer risks. Most epidemiology studies do not support a clear association between lung cancer and hormone replacement therapy or oral contraceptives.[210,211] Although female hormones may influence lung carcinogenesis, the effect is probably modest varying by histological subtype and smoking status. The Italian Environment and Genetics in Lung Cancer Etiology is a population-based study consisting of 407 women lung cancer cases (91% participation rate) and 499 age/residence/smoking/education/BMI-matched controls (99% participation rate).[212] Using never-users

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as referents, the lung cancer risk in ever-users of hormone replacement therapy was inverse and statistically significant (adjusted OR = 0.61, 95% CI: 0.39–0.95, $n = 63$ cases/112 controls); however, the trend for duration of use was not significant ($P_{trend} = 0.11$). Similarly, lung cancer risk for ever-oral contraceptive users was inverse (adjusted OR = 0.60, 95% CI: 0.39–0.93, $n = 101$ cases/132 controls) with no significant dose-response relationship ($P_{trend} = 0.09$). The study suggested longer reproductive periods (i.e., prolonged endogenous estrogen production) are associated with reduced lung cancer risks (≥51 years: adjusted OR = 0.49, 95% CI: 0.31–0.79, $P_{trend} = 0.003$).

Diseases

Chronic Obstructive Pulmonary Disease

The prevalence of COPD in lung cancer patients ranges from ~28 to 51%.[213,214] Although chronic obstructive pulmonary disease (COPD) and lung cancer have a common risk factor (cigarette smoking), COPD is probably an independent risk factor for lung cancer in current, former, and never-smokers, depending on the type and severity of COPD.[215,216] Overall, increased lung cancer risk is ~1.25–2.5-fold higher in patients with COPD than in those without COPD.[217,218] In an analysis of pooled data from seven European and Canadian case-control studies involving 12,739 cases and 14,945 controls, a past history of chronic bronchitis and emphysema was positively associated with lung cancer independent of smoking history.[219] The odds ratio for lung cancer in men was 1.33 (95% CI: 1.20–1.48) for chronic bronchitis and 1.50 (95% CI: 1.21–1.87) for emphysema using subjects without a history of past respiratory disease as referents. The medical history was self-reported with potential for recall bias and misclassification. Pathways identified as potentially producing an association between COPD and lung cancer include oxidative stress, inflammation, and extracellular matrix proteolysis. The presence of COPD worsens lung cancer prognosis because of increased morbidity and mortality.[220]

Idiopathic pulmonary fibrosis is a chronic, nonmalignant disease with a grave prognosis from progressive fibrosis of pulmonary tissues. Although some studies do not confirm an association between lung cancer and idiopathic pulmonary fibrosis (IPF),[221,222] systematic reviews indicate the current evidence supports a positive association between IPF and lung cancer. The results from these studies demonstrate highly variable relative risks, wide confidence intervals, and substantial heterogeneity.[223,224] In an analysis of a UK longitudinal computerized primary care dataset (Health Improvement Network), the overall lung cancer incidence was elevated in patients with IPF (rate ratio = 4.95, 95% CI: 3.00–8.18) compared with the general UK population.[225] The results were adjusted for age, gender, and self-reported smoking history. Other studies reported higher rate ratios. In a population-based cohort study involving 890 subjects with cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis) and 5,884 control subjects from the United Kingdom General Practice Research Database, the RR was 8.25 (95% CI: 4.70–11.48, $P < 0.001$) after adjustment for smoking history.[226]

Infectious Agents

The role of infectious organisms as causal agents in the development of lung cancer remains unclear, with marginal evidence for a variety of these organisms (e.g., human papillomavirus, Epstein–Barr virus, *Chlamydia pneumonia*, HIV, pulmonary tuberculosis). In a Danish study of 1,747 cancers in 15,024 patients with active tuberculosis following a median of 8.5 years, the standardized incidence ratio (SIR) was 1.52 (95% CI: 1.45–1.59) for all cancers and 3.40 (95% CI: 3.09–3.74) for lung cancer.[227] Although tuberculosis was associated with an increased lung cancer incidence, the presence of tuberculosis was a marker of occult lung cancer and several nonpulmonary cancers. A prospective cohort study followed 1,607,710 Korean adults up to 16 years; the presence of tuberculosis was significantly associated with an elevated lung cancer incidence after controlling for cigarette smoking, age, and other covariates.[228] The hazard ratio was 1.37 (95% CI: 1.29–1.45) in men and 1.49 (95% CI: 1.28–1.74) in women. For mortality, the HR was 1.43 (95% CI: 1.34–1.52) in men and 1.53 (95% CI: 1.28–1.83) in women. In a meta-analysis of 37 case-control and 4 cohort studies using random effects models, the association with a history of tuberculosis was statistically significant after adjustment for smoking for adenocarcinoma (adjusted RR = 1.60, 95% CI: 1.24–2.05), but not for squamous cell carcinoma (meta RR = 1.30, 95% CI: 0.85–1.99) or small cell lung cancer (meta RR = 0.79, 95% CI: 0.25–2.55).[229] The overall meta RR for lung cancer and a history of tuberculosis across all global studies was 1.74 (95% CI: 1.48–2.03, $n = 11$ studies, $I^2 = 59.2\%$, $P_{heterogeneity} = 0.00\%$) with moderate heterogeneity.

HPV in lung tumors ranges widely between geographical regions, sex, and histological type, resulting in conflicting outcomes. In a meta-analysis of HPV16 and HPV18 presence in primary lung cancers from 2,435 subjects reported in 37 published studies, the

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overall HPV prevalence ranged from 0.0–78.3%, with large heterogeneity across geographical regions and histological tissue types.[230] An international pooled analysis of 27 cross-sectional studies containing tumors from 3,249 patients evaluated HPV DNA prevalence in these lung tumors.[231] The highest adjusted prevalence of HPV16/18 occurred in South and Central America (22%), followed by Asia (5%), North America (4%), and Europe (3%). The lung cancer risk in HIV-positive populations also varies with geographical region, with lung cancer being a common non-AIDS-defining malignancy among HIV-infected patients compared with the general population. In a review of 65 publications, the standardized incidence ratio (SIR) or incident rate ratio (IRR) for lung cancer in HIV-positive patients ranged from 0.7–6.9 in the United States, 1.5–3.4 in Europe, and 5.0 in Africa.[232]

HISTOLOGY

Classification

The major histological types of malignant epithelial and neuroendocrine lung tumors as defined by the World Health Organization (WHO) in 2015 include: 1) adenocarcinomas, 2) squamous cell carcinomas, and 3) neuroendocrine tumors (e.g., small cell carcinoma, large cell carcinoma, carcinoid), as listed in Table 53.4.[233] Squamous cell and small cell carcinomas are typically central lesions arising from epithelium in proximal bronchi, whereas adenocarcinomas frequently appear in the peripheral portions of the lung. Non-small cell lung carcinoma refers to the heterogeneous group of histological lung cancer types other than highly malignant small cell lung cancer that includes squamous cell carcinomas, adenocarcinomas, true large cell neuroendocrine carcinomas, and more poorly differentiated variants.[234] The variety of histopathological types reflects very large tumor heterogeneity from different cells of origin and differentiation pathways.[15]

Adenocarcinomas

The suspected cells of origin for lung adenocarcinomas are epithelial cells lining peripheral small bronchi, bronchioles, or alveoli (e.g., Clara cells);[235] however, some evidence suggests the surfactant protein C expressing AT2 (alveolar type II) cells are potential cells of origin in more central locations.[236] As noted in Table 53.4, premalignant lesions include benign atypical adenomatous hyperplasia and minimally invasive adenocarcinoma *in situ* (mucinous or nonmucinous). The latter typically consists of nonmucinous type II pneumocytes or Clara cells and rarely mucinous resembling goblet cells. Lepidic refers to the noninvasive component of an invasive adenocarcinoma. Pathologically, lepidic adenocarcinomas are tumor cells proliferating along the surface of intact alveolar walls without stromal or vascular invasion; these lesions do not metastasize when locally resected. Most studies indicate lepidic adenocarcinomas are low-grade, whereas acinar and

TABLE 53.4. Histological types and subtypes of epithelial and neuroendocrine lung tumors from the 2015 World Health Organization (WHO) classification of lung tumors. This classification also includes 12 mesenchymal tumor subtypes (e.g., pulmonary hamartoma, chondroma), six lymphohistiocytic tumor subtypes (e.g., extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue, MALT lymphoma), four tumors of ectopic origin (e.g., mature/immature teratoma), and metastatic tumors not listed in this table. (Adapted from Travis et al.).[233]

Histological Type	Subtypes	Malignant Potential
Adenocarcinoma	Lepidic, acinar, papillary, micropapillary, solid, invasive mucinous, colloid, fetal, enteric, minimally invasive (nonmucinous, mucinous).	Malignant
	Preinvasive lesions – atypical adenomatous hyperplasia and adenocarcinoma *in situ* (mucinous, nonmucinous).	Benign *In situ*
Squamous cell carcinoma	Keratinizing squamous cell carcinoma, nonkeratinizing squamous cell carcinoma, basaloid squamous cell carcinoma.	Malignant
	Preinvasive lesion – squamous cell carcinoma *in situ*.	*In situ*
Neuroendocrine tumors	Small cell carcinoma (combined), large cell neuroendocrine carcinoma (combined), carcinoid tumors (typical, atypical), large cell carcinoma, adenosquamous carcinoma, sarcomatoid carcinomas (pleomorphic, spindle cell, giant cell, carcinosarcoma, pulmonary blastoma), other/unclassified (lymphoepithelioma-like carcinoma, NT carcinoma), salivary gland-type (mucoepidermoid carcinoma, adenoid cystic carcinoma, epithelial-myoepithelial carcinoma).	Malignant
	Salivary gland-type pleomorphic adenoma, papillomas [squamous cell (exophytic/inverted), glandular, mixed squamous/glandular], adenomas (sclerosing pneumocytoma, alveolar, papillary, mucinous cystadenoma, mucous gland adenoma).	Benign

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papillary tumors are intermediate-grade and solid or micropapillary adenocarcinomas are high-grade.[237] Bronchioalveolar carcinoma and clear cell/signet ring adenocarcinomas are discontinued terms.[233] Former large cell carcinomas with pneumocyte marker expression (i.e., TTF-1 and/or Napsin A biomarkers) are now considered solid adenocarcinomas.

Squamous Cell Carcinoma

In Western, industrialized countries during the early 1990s, squamous cell carcinoma was the most common histological lung cancer type in smokers followed by adenocarcinoma and small cell carcinoma;[238,239] however, the predominance of squamous cell carcinoma declined in the last few decades while the prevalence of adenocarcinoma increased.[240] Smoking is typically more strongly associated with central lung tumors (squamous cell carcinoma, small cell carcinoma) than more peripheral lung cancer types (adenocarcinoma, large cell carcinoma). Pluripotent basal cells in the respiratory epithelia of the large airways of smokers are suspected cells of origin for metaplastic and dysplastic squamous cells.[241] The dose-response between smoking and squamous cell carcinoma was stronger in women than men.[203] In contrast to the previous 2004 WHO classification of squamous cell carcinomas, clear cell change is a cytological feature of both keratinizing and nonkeratinizing squamous cell carcinomas rather than a separate subtype. The diagnosis of surgically resected nonkeratinizing squamous cell requires positive squamous cell biomarkers (e.g., p40, p63) in the absence of unequivocal keratinization. As noted in Table 53.4, squamous cell carcinoma subtypes include keratinizing, nonkeratinizing, and basaloid, with the prognostic significance of these subtypes unclear.[242,243]

Neuroendocrine Tumors

Neuroendocrine tumors comprise a heterogeneous group of neoplasms ranging from well-differentiated bronchial carcinoids with a low mitotic rate to highly malignant, rapidly proliferating, poorly differentiated small cell lung cancer and large cell neuroendocrine carcinomas.[244] Carcinoids frequently occur in never-smokers, whereas small cell lung cancer and large cell neuroendocrine carcinomas usually develop in smokers.

Small Cell Carcinomas

Small cell carcinoma is the most common neuroendocrine lung tumor, particularly in younger patients, accounting for ~10–15% of invasive lung cancers; however, the US incidence decreased over the last several decades as smoking declined in the United States.[245] Histological features distinguishing small cell lung cancer from large cell neuroendocrine carcinomas include cell size and absent/inconspicuous nucleoli. Over 90% of small cell lung cancer tumors contain one of several neuroendocrine biomarkers (neural cell adhesion molecule, CD56; synaptophysin; chromogranin A). This tumor is the most malignant type of lung cancer, proliferating very rapidly (i.e., ~80-day doubling time)[246] and metastasizing early. The cell of origin is probably the pulmonary neuroendocrine cell (bronchial Kulchitsky-type cell) that is the first epithelial cells to form and differentiate during the earliest stages of lung development; however, the alveolar type II cell is also a potential cell of origin.[244]

Large Cell Carcinomas

This histological type is a rare tumor (i.e., <3% of invasive lung tumors). The 2015 WHO classification significantly revised the subtypes of large cell carcinomas using immunohistochemical biomarkers (the pneumocyte marker, TTF-1; p40). Several large cell carcinoma variants were reclassified into other categories, including basaloid carcinoma (squamous cell carcinoma subtype), lymphoepithelioma-like carcinoma (other and unclassified carcinoma), clear cell carcinoma/rhabdoid phenotype (cytological feature rather than specific histological subtype), and solid carcinomas (solid adenocarcinoma with TTF-1^+ or nonkeratinizing squamous cell carcinoma when p40 positive).[233] Significant histological, epidemiological, genetic, and clinical differences exist between typical/atypical carcinoid tumors and other neuroendocrine carcinomas (e.g., high-grade small cell lung carcinomas, large cell neuroendocrine carcinomas), including younger age, little association with smoking, fewer genetic abnormalities, and better prognosis.[247]

HOST SUSCEPTIBILITY

Nonsmoking individuals (i.e., <100 cigarettes/lifetime) account for about 15–20% of lung cancer patients. Risk factors include exposure to radon, asbestos, air pollution, and environmental tobacco smoke as well as a first-degree family member with lung cancer. The development of *ALK* gene rearrangements and EGFR mutations increase the lung cancer risks in these patients. Lung cancer incidence appears higher in nonsmoking women than in nonsmoking men. In a hospital-based, case-control study of 1,889 lung cancer patients and 2,070 controls, the portion of never-smoking patients with lung cancer was almost

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twice as high for women than men.[248] Potential factors contributing to an increased lung cancer risk include strong family history of lung cancer, chronic obstructive pulmonary disease, fibrotic disorders (asbestosis, idiopathic pulmonary fibrosis, silicosis), and tuberculosis. On a molecular level, more women than men have proportionally increased tobacco-related mutations (G → T transversion in the TP53 and KRAS) and EGFR gene mutations; the latter being a protype receptor tyrosine kinase epidermal growth factor receptor.[249] Substantial epidemiological evidence supports a ~2-fold increased lung cancer risk in smoking relatives with a family history of lung cancer using smoking relatives without a family lung cancer history as controls, particularly when lung cancer is diagnosed at a relatively young age (i.e., <60 years) and involves multiple family members.[250,251] The lung cancer risks increase (i.e., 2–4-fold) for first-degree relatives with lung cancer after adjusting for other risk factors (sex, age, occupation, COPD, smoking history).[194] Genetic susceptibility may result from rare, high penetrance genes in multiple locations (e.g., 6q23–25, 18p11.23, 2p22.2, 14q13.1, 16p13, 20q13.11)[252] or common, low penetrance genes (chromosomes 15q25, 6p21, 5p15). Although the lung cancer risk increases in individuals with a family history of lung cancer, irrespective of smoking status,[253] the addition of a smoking history to a family with genetic susceptibility substantially elevates lung cancer risks (e.g., 3-fold in persons with genetic susceptibility from 6q23–25).[254] Mechanisms of action for genetic susceptibility include polymorphisms in metabolic activation/detoxification of chemical carcinogens, chronic inflammation pathways, and alteration of DNA repair enzymes.[129]

CLINICAL FEATURES

Lung cancer commonly begins appearing clinically in the 6th and 7th decade of life; the mean age at diagnosis is ~71 years and the diagnosis of cancer in persons under 20 years is highly unusual.[129] The male/female lung cancer ratio was ~1.5 in the 1990s.[200] The trend for the last decade indicated lung cancer rates increased in women and never-smokers with adenocarcinomas representing a larger portion of the non-small cell lung cancers (NSCLCs).[255] In men, the diagnosis of NSCLC usually occurs at an advanced stage. The latent period for the clinical diagnosis of lung cancer following asbestos exposure typically ranges from 15–40 years.[256] The latent period decreases with increasing asbestos dose and younger age at exposure.

Lung parenchyma contains no pain sensory fibers. Consequently, many lung cancer patients present with an asymptomatic lung lesion discovered incidentally during radiological imaging. Clinical features of lung tumors include fatigue, dyspnea, pleuritic chest pain, cough, wheezing, and hemoptysis, depending on the presence of local/distant invasion, lung dysfunction, and tumor type/location/size. One-year mortality rates remain higher in men (56.6%) than women (50.9%). Small cell lung cancer is the most lethal lung cancer subtype with a 95% mortality rate; almost cases occur in heavily smoking patients (>30 pack-years) aged 60–80 years.[257] The 5-year survival rate for small cell lung cancer is substantially lower than for large cell neuroendocrine carcinomas (13–57%).[258] Current staging of NSCLC ranges from IA (≤3 cm, no regional metastasis) to IV (any tumor size with distant metastasis); the 5-year survival ranges from 50–2%, respectively.[259] Incidence-based NSCLC lung cancer mortality over the last few years has decreased over twice as fast as NSCLC incidence, reflecting the effectiveness of targeted therapies and immunotherapies (e.g., anaplastic lymphoma kinase, epidermal growth factor receptor).[260] During the same time period, small cell lung cancer incidence-based mortality has remained relatively flat until recently following advances in molecular profiling, immunotherapies, and targeted therapies. The 5-year overall survival rate in the US is 12–30% depending on whether (limited stage) or not (extensive stage) the disease can be treated within a radiation field confined to one hemithorax exclusive of contralateral mediastinal or supraclavicular nodes.[245]

MESOTHELIOMA

Although the association between asbestos exposure and lung cancer was reported in the early 1920s,[261] discovery of the relationship between asbestos and pleural mesothelioma did not occur until 1960, when J. C. Wagner et al. documented the high prevalence of mesotheliomas in residents and workers employed and/or living near South African crocidolite (amphibole) asbestos mines in Northwest Cape Province.[262] Eight case-control studies published from 1965–1975 on 657 mesothelioma cases from asbestos exposures in shipyards, factories, heating trades, and insulation manufacturing provided confirmation with relative mesothelioma risks ranging from 2.3–7.0.[263] Over the last several decades, the asbestos exposures of workers with malignant mesothelioma have shifted from asbestos workers handling raw asbestos material to end users typically installing or handling asbestos products.[264]

The importation and use of asbestos closely correlate with mesothelioma incidence.[265] Worldwide,

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estimated crude incidence mesothelioma rates range from 0.15 cases/1,000 person/year for cumulative exposure of <3,530 million particles/m^3/year (<100 million particles/ft^3/year) to 0.97 cases/1,000 person/year for cumulative exposure of >10,590 million particles/m^3/year.[135] Based on a mean latency of 40 years and historical asbestos use data, the projected peak mesothelioma incidence in the United States and Western Europe is near 2020.[266,267] The annual number of US mesothelioma cases is ~1,500–2,000 (~1/20,000,000 inhabitants) compared with ~30,000 cases worldwide.[268,269]

Observational studies on occupational asbestos exposures indicate that attributable risks for malignant pleural mesothelioma in developed countries vary by geographical location.[270] Male urban and rural mesothelioma rates increased in the 1980s and 1990s, followed by leveling and subsequently decreasing rates as declining asbestos production shifted occupational asbestos exposures from manufacturing to end uses, whereas female urban and rural mesothelioma rates remained relatively stable during this period.[271,272] Trend analyses indicate female urban and rural mesothelioma incidence rates remain ~5–6-fold lower than male urban and rural incidence rates, consistent with historical occupational asbestos exposures based on US SEER data. The lower mesothelioma rates in rural areas reflect the ~10-fold increased asbestos fiber concentrations in urban environments; the exact environmental asbestos concentrations are difficult to estimate given the differences in sensitivity and specificity of analytical techniques.

CARCINOGENESIS

Most mesotheliomas are associated with chronic asbestos exposure. Although chromosome 14q11 losses occur frequently in asbestos-related mesothelioma displaying macrophage-driven inflammation and reactive oxygen species-induced DNA damage,[273] no unique signature gene abnormality has been identified. Overall, the recurrent mutation load is limited compared with the high chromosomal aberration rate and subsequent gene copy number alterations, primarily chromosomal deletions (e.g., *BAP1*, 3p21.1; *CDKN2A*, 9p21.3; *NF2*, 22q12.2; *SETD2*, 3p21.31).[274] The composition and location of common genetic abnormalities vary substantially between and within tumors, resulting in both intra- and inter-tumor heterogeneity as well as the development of resistant clones.[275] Despite the wide heterogeneity between mesothelioma tumors, genetic alterations in mesotheliomas are limited compared with most other tumor types; the actual number of alterations depends on the sequencing technique used.

The most frequent driver gene mutations associated with mesotheliomas involve tumor suppressor genes, including *BAP1* (BRAC1-associated protein 1), *NF2* (neurofibromin type 2), and *CDKN2A* (cyclin-dependent kinase 2A).[276] In an examination of 42 mesotheliomas (55% pleural, 26% peritoneal, 5% pericardial, 14% unknown) referred to a clinical laboratory for analysis with next-generation sequencing, no two patients displayed identical molecular portfolios.[277] In this study, the most common aberrations occurred in the *BAP1* gene (47.6%), *NF2* gene (38.1%), *CDKN2A/B* loss (35.7%), and *TP53* aberrations (16.7%). Among 23 pleural mesothelioma patients in this study, *BAP1* was the most commonly altered gene (60.9%) followed by *CDKN2A/B* loss (52.2%), *NF2* loss (34.8%), and *TP53* (17.4%), whereas the most frequently altered genes in 11 peritoneal mesotheliomas were *NF2* (36.4%) and *BAP1* (27.3%).

Recurrent mutations of genes other than tumor suppressors involve the epigenetic regulators of histone methyl transferases (*SETD2*, *SETDB1*), ATP-dependent DEAD-box RNA helicases (*DDX3X*, *DDX51*), serine/threonine kinase-like (*ULK2*), and ryanodine receptor proteins (*RYR2*). The total number of protein-altering gene mutations in 216 mesotheliomas averaged 24 ± 11/tumor using exome sequencing.[278] In pleural mesotheliomas from this study, the most frequently altered signaling pathways involved Hippo, histone methylation, RNA helicases, mTOR, and p53. Mutation of *BAP1* (chromosome 3p21) is a tumor suppressor mutation present in 20–61% of mesotheliomas depending on the sequencing method. *CDKN2A* (chromosome 9p21) regulates the G_1 cell cycle progression by expressing $p16^{INK4A}$ and $p14^{ARF}$ proteins that suppress cyclin-dependent kinase 4/6 complexes (*CDK4*, *CDK6*). The loss of p14 protein is not unique to mesotheliomas. The *NF2* gene encodes the merlin protein that regulates multiple signaling pathways involved with cell proliferation (e.g., Hippo, hedgehog) and cell adhesion. Other less involved pathways include RAF/MEK-extracellular signal-regulated kinase and phosphoinositide-3 kinase (PI3K/AKT), mTOR, and Wnt.[279] *BAP1* gene encodes a nuclear deubiquitinase involved with chromatin remodeling, tumor suppression (*BARD1*, *BRCA1*-associated RING domain 1), and transcription regulation (*HCFC1*, host cell factor C1), which are important during cell proliferation, differentiation, and DNA damage repair. TP53 mutations are less frequent. Mutations in oncogenes (e.g., *BRAF*, *EGFR*, *KRAS*, *PIK3CA*) and mutations in the *TERT* promoter gene are infrequent, except for the latter in sarcomatoid mesothelioma.[280]

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EXPOSURE

Substances causally associated with mesotheliomas include asbestos, natural nonasbestos fibers, and probably ionizing radiation. The monkey polyoma virus (simian virus 40, SV40) is an animal carcinogen associated with pericardial rodent mesotheliomas; however, epidemiological data are insufficient to support causality in humans. Simian virus 40 (SV40) is a member of small, double-stranded DNA polyoma viruses that were widely disseminated in Salk polio vaccines during the 1950s–1960s. Although up to 60% of human mesotheliomas contain SV40 DNA, the presence of SV40 infections is not associated with increased mesothelioma incidence.[281] The IARC lists S40 viruses as potential risk factors for mesotheliomas (limited human epidemiology evidence); however, the role of SV40 in mesothelioma pathogenesis remains unproven.[282] Although SV40 is a carcinogenic virus in experimental and animal models, evidence for an association between mesothelioma and SV40 infection in humans is limited. From 1956–1962, ~1/3 of the UK population received SV40-contaminated polio vaccine. A pathological study evaluated tumor and background lung tissue microarrays from archival surgical specimens of 127 pleural mesothelioma cases collected during 1998–2005 using a highly sensitive and specific SV40 Tag RNA *in situ* hybridization detection method.[283] These samples represented birth cohorts overlapping the period 1950–1960 during the administration of the contaminated vaccines. None of these tumors had evidence of SV40 infection, whereas the positive and negative controls were appropriately positive and negative, respectively.

The potential role of high-aspect-ratio nanoparticles (HARN) in the formation of mesotheliomas remains undefined.[284] Currently, no synthetic mineral fibers are causally linked to mesotheliomas; however, carbon nanotubes demonstrate similar shape and cytotoxicity as asbestos and produce malignant mesothelioma in some rodent studies.[285,286] Mesotheliomas are not related to smoking, presumably because tobacco carcinogens do not diffuse into the pleural or peritoneal mesothelium.[287]

Asbestos

Asbestos exposure is the major risk factor for malignant pleural mesothelioma, with ~80% of mesothelioma cases having an asbestos exposure history, typically with a long latency period (i.e., 30–50 years);[288] however, mesothelioma develops in a small minority of asbestos-exposed persons. A population-based study on 437 incident mesothelioma cases and 874 unexposed controls suggests a dose-response relationship between pleural mesothelioma and occupational asbestos exposure based on a retrospective asbestos exposure analysis by two blinded expert hygienists.[289] For men with an estimated cumulative asbestos exposure of <0.1 fibers/mL/year, the odds ratio for pleural mesothelioma was 4.0 (99% CI: 1.9–8.3, $n = 54$ exposed cases/181 unexposed control cases) compared with an OR of 67 (99% CI: 25.6–175.1, $n = 97$ exposed cases/27 control cases) for men, with an estimated cumulative asbestos exposure of >10 fibers/mL/year. The population-attributable risk of mesothelioma for any asbestos exposure was 87.3% (99% CI: 78.9–95.7%) for men and 64.8% (99% CI: 45.4–84.3%) for women. The wide confidence intervals suggest imprecise estimates.

Approximately 5–20% of mesothelioma patients have no self-reported history of asbestos exposure.[285] Over 9 years, a hospital-based case-control study enrolled 38 mesothelioma cases and 134 controls (65 with nonasbestos-related cancers, 69 medical controls); the expected number of mesothelioma cases was 50 over 3–4 years.[290] The mesothelioma risk was borderline statistically significantly elevated for no known reason but likely occupational asbestos exposure (OR = 3.1, 95% CI: 1.0–9.6). Exposure was based on an interviewer-administered questionnaire covering 47 substances; however, no specific substance or group of substances had a statistically significant association with mesothelioma as coded by an expert industrial hygienist blinded to the respondent's diagnosis. The risk of developing mesothelioma depends more on the time since asbestos exposure began than the dose (i.e., increased dose does not shorten the latency period); smoking is not a significant risk factor for mesothelioma or asbestos-induced tumors.[291,292] These tumors may occur in the absence of asbestosis.[293]

In a UK study of 622 mesothelioma patients (512 men, 110 women) and 1,420 population-based controls using unconditional logistic regression, the estimated excess mesothelioma risk attributed to domestic (nonoccupational) asbestos exposure to a high-risk asbestos worker before age 30 years was doubled in Britons born in the 1940s for men (OR = 2.1, 95% CI: 1.0–4.5, $n = 13$ cases/98 controls) and women (OR = 1.9, 95% CI: 1.1–3.2, $n = 37$ cases/86 controls). This excess risk corresponded to a lifetime mesothelioma risk of ~1/1,000.[294] Approximately 14% of 512 male and 62% of 110 female mesothelioma cases were attributed to neither occupational nor domestic asbestos exposures; the authors opined that these cases presumably resulted from ambient or unreported asbestos exposures, natural causes,

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or unknown factors. The study reported no increased risk in men or women living within 1 mile of a potential asbestos environmental hazard (shipyard, asbestos factory, power plant, disposal site) before 30 years of age; however, the risk was positive, statistically nonsignificant, and imprecise for living near a potential source for ≥20 years (OR = 3.3, 95% CI: 0.7–14.8, n = 3 cases/6 controls). No historical environmental measurements were available. In an analysis of the Italian National Register of Mesotheliomas, domestic (living with occupationally exposed asbestos worker) and environmental asbestos exposures (residence near an asbestos pollution source) accounted for 4.9% and 4.4% of the total mesothelioma cases, respectively.[295] Nonoccupational sources were asbestos cement plants, shipbuilding/repair, and soil contamination (i.e., Biancavilla area in Sicily). The Italian standardized incidence rates for pleural mesothelioma are 3.84/100,000 in men and 1.45/100,000 in women; ~93% of these cases occur in men.[296]

Classification

Asbestos is a commercial name defining a family of six natural silicate mineral fibers. These fibers are <3 μm thick and >5 μm long, with an aspect (length/diameter) ratio of >3. Noncommercial, non-asbestiform amphiboles include richterite, winchite, and tremolite. Mesothelioma potency depends on biopersistence, diameter, and length, with fibers <0.1 μm thick and >5 μm long being the most potent.[297]

Amphibole Asbestos

Although all asbestos types can cause mesotheliomas, these tumors are primarily associated with amphibole-type asbestos (e.g., crocidolite, amosite), with serpentine-induced mesotheliomas (i.e., chrysotile) much less frequent.[123] The carcinogenic potency required to produce mesotheliomas is significantly greater (~2–10-fold) for crocidolite than amosite or mixtures of amosite and chrysotile when comparing amphibole mining in South Africa and Australia with chrysotile mines and mills in Canada and Italy.[263,298] Based on tremolite-contaminated Quebec and Libby Mine data on crocidolite, amosite, and tremolite exposures, these amphiboles account for most mesothelioma cases, with tremolite contamination (typically <1%) accounting for some of the cases associated with chrysotile.[263] Substantial uncertainty surrounds estimates comparing chrysotile, amosite, and crocidolite asbestos potency producing pleural/peritoneal mesotheliomas. The 2000 Hodgson-Darnton model predicts a ratio of 1:100:500, respectively, based on the percent of all expected deaths caused by mesothelioma per fiber/cc/year following initial exposure at age 30 per unit of cumulative exposure (e.g., fiber/cc/year).[137] The relative potency of chrysotile/amosite/crocidolite was similar (1:83:376) in a 2018 update of the 2000 Hodgson-Darnton model by Garabrant and Pastula.[299] The potency of Libby fibers for mesothelioma was ~23-fold higher than chrysotile and 3.5-fold smaller than amosite. Talc and gold mining non-asbestiform elongate mineral particles were not associated with mesothelioma. Environmental amphibole asbestos exposures associated with the development of mesothelioma include whitewashing Greek houses with soft tremolite[300] and tilling crocidolite-containing soil by Chinese farmers.[301]

Serpentine (Chrysotile) Asbestos

Occupational chrysotile exposure does not consistently increase mesothelioma risks, with chrysotile fibers commonly used in mining and milling producing a much lower mesothelioma incidence than amphibole asbestos material commonly present in manufacturing and insulation industries.[302,303] A hospital-based, South African study of 119 mesothelioma cases and 103 medical controls did not identify any chrysotile-induced mesothelioma cases from occupational or environmental chrysotile exposures.[304] Although recently manufactured asbestos contains primarily chrysotile, *potential* exposure to these mesothelioma-producing minerals continues because substantial quantities of amphiboles remain in building insulation.[123] Workers installing and/or repairing car and truck brakes have potential asbestos exposure, primarily chrysotile asbestos; however, epidemiology studies do not provide significant support for increased mesothelioma risks in automotive friction product (i.e., brake) workers.[305,306]

Nonasbestos Fibers

Natural, elongated nonasbestos mineral particles associated with the occurrence of mesothelioma include erionite, fluoro-edenite, richterite, and winchite; the IARC considers erionite and fluoro-edenite as human carcinogens (Group 1) based on sufficient evidence in humans.[307,308] The true risk of developing mesothelioma is less well defined for the latter natural fibers than asbestos because of the extreme rarity of these tumors and the limited power/precision of applicable epidemiology studies. Although silica is not associated with elevated malignant mesothelioma risks, the effect of simultaneous exposure to asbestos and silica remains unclear.[270] There is no significant epidemiological evidence of an association in these studies between

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mesothelioma and exposure to any man-made mineral fibers reflecting the relatively short biopersistence of these fibers compared with amphibole fibers.[309,310] Pure talc is not a recognized human carcinogen; however, some geological talc deposits may contain other silicates (e.g., tremolite, anthophyllite). Analysis of pooled data from four European cosmetic talc miner and miller cohorts totaling 113,344 person-years of observation did not support an association between cosmetic talc and pleural cancer/mesothelioma.[311] The study identified no incident cases of pleural cancer or mesothelioma (three cases expected) with a 79% power to detect a 3-fold increased incidence.

Erionite

Erionite is a fibrous form of the zeolite mineral group contaminated with tremolite asbestos that occurs in relatively high concentrations in volcanic rocks from certain Cappadocian villages in Turkey, central Mexico, and the western United States. The mesothelioma incidence in former villagers is elevated without occupational asbestos exposure.[285,312] In a prospective study of 891 residents of 2 exposed and 1 nearby control villages followed for 23 years, the standardized pleural mesothelioma mortality rate was 485 (95% CI: 395–590).[313] Mesotheliomas accounted for 119 of the 372 deaths (44.5%) in the exposed villages during the follow-up period compared with 2 deaths in the control village. Pleural and peritoneal mesotheliomas accounted for 86% and 14% of the mesothelioma-associated deaths, respectively.

Fluoro-edenite

Fluoro-edenite is a newly defined fibrous amphibole similar to actinolite-tremolite mineral species that exists in a volcanic area of the eastern Sicilian city of Biancavilla near Mt Etna;[314] exposure of the local population resulted from the use of material from stone quarries near Monte Calvario to pave roads and build houses. Examination of mortality data from this area demonstrated a geographical cluster of pleural mesothelioma cases.[315]

Ionizing Radiation

Occupational exposure to ionizing radiation occurs in aircrews, Chernobyl cleanup workforce, nuclear weapons test participants, nuclear industry workers, and underground hard-rock miners. The association between ionizing radiation and mesothelioma is strongest for exposures to α-particle emitting radiocontrast agents (i.e., Thorotrast exposure, 1930–1955) and local areas of skin irradiated by high doses of therapeutic radiation.[316]

Thorotrast

Thorotrast is an insoluble radionucleotide that is very poorly excreted after intravenous injection and diffusely distributed to most tissues including the pleural and peritoneal pleura. In the German Thorotrast study comprising 2,326 patients and 1,890 controls followed since 1968, mesotheliomas developed in 9 patients (5 pleural, 4 peritoneal) and no controls (RR not calculated).[317] In a Danish hospital-based study of 999 neurology patients administered Thorotrast for cerebral angiography in 1935–1947, the SMR for peritoneal mesothelioma was 11.54 (95% CI: 3.10–29.54, $n = 4$ cases/0 controls) and 4.05 (95% CI: 0.05–22.51, $n = 1$ case/1 controls) for pleural mesothelioma.[318] Subsequently, the authors reported two peritoneal and one pleural mesothelioma misclassified as other tumors.[319]

Therapeutic Radiation

Overall, epidemiological evidence is supportive of a causal link between therapeutic ionizing radiation and mesothelioma, including numerous case reports and comparisons with standardized incidence/mortality rates; however, poor statistical power from the low incidence of mesothelioma, potential misclassification from the nonuniform reporting of mesothelioma before the ICD-10 reclassified mesotheliomas into a separate category in 1999, long latency periods up to 40 years, and the confounding of asbestos limit firm conclusions, particularly for nuclear industry workers.[320] Although some studies show elevated peritoneal and pleural mesothelioma rates with wide confidence intervals following irradiation for Hodgkin lymphoma, non-Hodgkin lymphoma, and breast cancer,[321,322] several observational studies of therapeutically irradiated patients do not demonstrate statistically significant increases in these rates.[316,323] An analysis of data from the SEER database for mesothelioma incidence identified 21,881 patients with Hodgkin lymphoma (HL) and 101,001 patients with non-Hodgkin lymphoma (NHL). The SIR for mesothelioma in male HL patients with radiation exposure was statistically significant (SIR = 6.59, 95% CI: 1.79–16.87, $n = 4$ cases), but not in female HL patients with radiation exposure.[321] For male and female NHL survivors combined, the overall SIR was statistically significant (SIR = 2.24; 95% CI: 1.07–4.12, $n = 10$ cases); however, the SIR for mesothelioma was statistically nonsignificant in male (SIR = 1.91, 95% CI: 0.77–3.93, $n = 7$ cases) and female NHL patients

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(SIR = 3.75, 95% CI: 0.77–10.95, $n = 3$ cases). The mean follow-up period was ~11 years for Hodgkin lymphoma (HL) and ~5 years for NHL. In a Dutch study of 2,567 five-year survivors of Hodgkin lymphoma, 13 developed mesotheliomas during a median follow-up of 18.1 years (SIR = 25.7, 95% CI: 13.7–44.0, $n = 13$ cases).[322] Among HL patients receiving radiotherapy, the SIR was 29.4, (95% CI: 15.7–50.4, $n = 13$).

Nuclear Industry Workers

Observational studies of nuclear industry workers exposed to relatively low ionizing radiation doses report fewer statistically significant associations with mesothelioma than patients receiving Thorotrast or local, high-dose therapeutic ionizing radiation. In a review of 17 relevant epidemiology studies on pleural mesothelioma risks among mostly nuclear industry workers, 15 reported mostly modest positive results; however, of the 12 studies containing a dose-response analysis, only 1 study reported a statistically significant association between the radiation dose and pleural mesothelioma.[324] This follow-up UK cohort study of 19,454 radiation and non-radiation exposed workers ever-employed at the Springfields uranium production facility from 1968–1995 examined pleural cancer incidence and mortality. Although there was no excess of pleural cancers (presumably mostly mesotheliomas) at Springfields ($SMR_{\text{radiation workers}} = 67$, $SMR_{\text{nonradiation workers}} = 0$), pleural cancer registrations displayed significant trend statistics (simulated $P \leq 0.033$) when the dose was lagged by 0, 2, 10, 15, and 20 years, respectively. However, the result depended on only one registration. The mean follow-up was 24.6 years. The 15-country retrospective cohort study of 407,391 nuclear industry workers monitored individuals for external radiation.[325] The estimated ERR/Sv was high, but statistically nonsignificant and imprecise (ERR/Sv = 5.28, 90% CI: <0–39.9, $n = 39$ deaths), with no significant trend with ionizing radiation dose ($P_{\text{trend}} = 0.45$); the relative risk of pleural cancer at 100 Sv cumulative dose was 1.53 based on a linear excess relative risk model. None of these studies adequately evaluated asbestos exposures.[320]

The Rocketdyne (Atomics International) mortality study evaluated mortality data on 46,970 workers employed from 1948–1999, including 5,801 radiation-exposed workers (2,232 monitored for radionuclide intake) and 41,169 workers engaged in nonradiation-associated activities.[326] The mean external radiation dose was 13.5 mSv (maximum 1 Sv), whereas the total mean lung dose was 19.0 mSv (maximum 3.6 Sv). The mean follow-up was 33.9 years. Radiation exposure was not associated with increased mesothelioma (pleural/peritoneal cancer) risks based on two deaths (SMR = 0.63, 95% CI: 0.08–2.29, $n = 2$ obs/3.2 exp) with no evidence of a dose-response ($P_{\text{trend}} = 0.33$). The US Mallinckrodt Chemical Works (uranium processing facility) study consists of 2,514 white male workers employed from 1942–1966 and followed through 2012 ($\text{Mean}_{\text{followup}} = 43.3$ years, $\text{Mean}_{\text{duration employment}} = 5.2$ years).[327] Organ/tissue-specific dose reconstruction of external and internal sources provided radiation exposure estimates. Assuming a dose-weighting factor of 1 for absorbed internal radiation doses, the mean lung dose was 27.1 mGy (maximum 416 mGy). The SMR for pleural and peritoneal cancer (presumably, mesothelioma) was 0.95 (95% CI: 0.11–3.41, $n = 2$ deaths). Small case numbers preclude definitive conclusions regarding associations with occupational radiation and mesothelioma risks, particularly with potential asbestos confounding.

HISTOLOGY

Mesotheliomas are very rare pleural (~70–80%), less commonly peritoneal (10–20%), and rarely pericardial and scrotal/tunica vaginalis (<5%) tumors that arise from the neoplastic transformation of multipotential, self-renewing mesothelial cells.[328] The pleura is a 5-layer covering of the thoracic cavity with a single layer of mesothelial cells involved with inflammatory reactions and phagocytosis. Pleural mesotheliomas arise in the lining of the pleura from malignant transformation of mesothelial cells as a result of constant inflammation from asbestos fibers and the subsequent formation of reactive oxygen species, attraction of macrophages, and direct interference with mitotic spindles.[329] Inhaled fibers enter the parietal pleura retrogradely through the lymphatics or pass through the alveoli, visceral pleura, and pleural space to the parietal pleura.[330]

The 2015 World Health Organization classification of tumors did not change mesothelioma subtypes from the 2004 WHO classification. Epithelial mesothelioma consisting of cuboidal cells is the most common histological subtype of mesotheliomas (50–60%), whereas sarcomatous mesothelioma with spindle-like cells (10–20%) and biphasic (mixed) subtypes (25–35%) are less common.[331] Desmoplastic forms are rare (1–2%). Epithelial tumors contain large spherical cells that form solid masses and columns in local lymphatics and may resemble adenocarcinomas, whereas sarcomatoid tumors consist of ovoid-to-spindle-shaped cells resembling fibrosarcomas that arise in deep connective tissue. The main differential diagnosis for epithelioid mesothelioma

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is metastatic carcinoma, particularly adenocarcinoma. Although pleural plaques occur in parietal pleura and are strongly associated with asbestos exposure, the presence of pleural plaques as an independent risk factor for malignant mesothelioma remains controversial. A French 7-year follow-up study of 5,287 male participants with chest CT scan suggest an elevated mesothelioma risk in subjects with pleural plaques (adjusted HR = 6.8, 95% CI: 2.2–21.4, n = 17);[332] however, the large confidence interval indicates an imprecise measure of risk. Next-generation sequencing and cytogenic studies indicate mesotheliomas contain massive genomic damage with highly complex and variable chromosomal aberrations; no polymorphisms in a single gene or signature of genes reproducibly occurs in most mesotheliomas using current technology.[333]

HOST SUSCEPTIBILITY

Mesotheliomas develop in a minority of asbestos-exposed individuals. The relatively low occurrence (i.e., 5–10%) of mesothelioma following prolonged asbestos exposure and the linkage of certain families with elevated mesothelioma risks suggest the existence of some recessive genetic susceptibility; however, the specific proportion attributable to genetic susceptibility is difficult to estimate because of the strong confounding effects and ubiquity of asbestos exposure in familial cases.[334,335] Although germline BAP1 mutations commonly occur in familial mesotheliomas, germline BAP1 mutations in sporadic mesotheliomas are infrequent. In a study of germline BAP1 mutation status of 150 mesothelioma patients with a family history of cancer, 50 asbestos-exposed control individuals with a family history of cancers other than mesothelioma, and 153 asbestos-exposed individuals without familial cancer, 9 (6% of 150) mesothelioma cases with a family history of cancer had BAP1 alterations compared with none of the controls.[336] Five of the nine cases were peritoneal mesotheliomas. BAP1 mutation carriers developed mesothelioma at an earlier age, but long-term survival was higher in carriers than noncarriers.

Turkish pedigree and mineralogical studies indicate malignant mesothelioma occurs following erionite exposure in genetically predisposed individuals,[337] whereas a study of former workers and residents exposed to crocidolite at Wittenoom, Western Australia, demonstrated a modestly increased risk ratio for mesothelioma in blood relatives of 1.9 (95% CI: 1.3–2.9, P = 0.002).[338] However, a genome-wide association study for malignant mesothelioma risk did not demonstrate consistent genetic abnormalities between Australian cases (*SDK1*, *CRTAM*, *RAS-GRF2* genes, 2p12 chromosome) and Italian/Japanese studies (tumor suppressor gene *BAP1*, *BRCA1*-associated protein 1).[339] The *BAP1* gene (chromosome 3p21) expresses a nuclear protein (BAP1) involved in transcriptional and chromatin regulation along with multiple pathways that regulate cell cycle checkpoints, cell differentiation, and apoptosis.[340] Approximately 30–60% of mesotheliomas contain loss or deletion of regions in chromosome 3p21. Subsequent studies of families with malignant mesothelioma syndrome suggest the occurrence of this tumor involves genes other than *BAP1* (e.g., DNA repair genes).[341,342] Oncogene mutations are infrequent in malignant pleural mesotheliomas. A Turkish study of 142 consecutive cases of histopathologically confirmed malignant pleural mesothelioma associated with almost exclusively environmental asbestos exposure did not detect a relationship between asbestos fiber type and age or exposure period; 5 of 131 (3.8%) patients had a family history of mesothelioma.[343] The study did not separate erionite from asbestos exposure.

Children may be particularly susceptible to developing mesotheliomas. In a study of Western Australian adults exposed to crocidolite asbestos before the age of 15 years, the standardized incidence ratio of mesothelioma was very substantially elevated among men (SIR = 44.54, 95% CI: 29.83–63.98) and women (SIR = 70.05, 95% CI: 36.20–122.37) compared with the general population.[344]

CLINICAL FEATURES

Pleural mesotheliomas account for most mesothelioma cases, with peritoneal mesotheliomas occurring in most other mesothelioma cases.[345] In most epidemiological studies, mesothelioma develops more commonly in men than women, except in occupations dominated by women.[346] The mean latency period between the initial asbestos exposure and death typically averages ~35–45 years, with a range of 20–60 years. In a study of 557 Italian patients with the diagnosis of malignant mesothelioma, the latency period between first asbestos exposure and death ranged from 14–75 years with a mean of ~49 years.[347] Clinically apparent mesothelioma is rare before 45 years of age, with diagnosis of mesothelioma in this age group representing 2.4% of total cases in the Italian National Register of Mesotheliomas.[296] In a case series of 614 UK asbestos workers dying of mesothelioma between 1978 and 2005, the median latency defined as the time between first occupational asbestos exposure and mesothelioma-induced death was

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22.8 years (95% CI: 16.0–27.2 years).[348] The latency was ~30% longer for women than men in the fully adjusted generalized gamma accelerated failure-time model used to estimate latency. Greater asbestos exposure intensity was not associated with shorter mesothelioma latencies.

Pleura mesothelioma is an aggressive tumor typically presenting at an advanced stage with a unilateral pleural effusion and chest pain; weight loss, dyspnea, and fatigue frequently present later in the course of the disease.[282] Occasionally, mesothelioma patients present with no symptoms after routine chest radiographs reveal a pleural effusion. Peritoneal mesothelioma usually presents with abdominal distension, ascites, abdominal pain/tenderness, and occasionally bowel obstruction. These tumors may grow large enough to produce the superior venal caval syndrome. Common sites of metastasis include supraclavicular, mediastinal, hilar, and internal mammary lymph nodes; however, clinically related symptoms are uncommon.

Malignant mesothelioma is an incurable cancer. This tumor is a highly aggressive neoplasm that is relatively chemotherapy- and radiation-resistant, resulting in a very limited life expectancy after diagnosis (i.e., <1–1.5 years).[349] The median survival for advanced stages is shorter for malignant pleural mesothelioma (12–16 months)[350] than peritoneal mesothelioma (12.5–31 months).[351] In a study of 1,605 German patients with malignant mesothelioma, the estimated mean survival time after diagnosis was ~13–14 months, depending on the pathological type of mesothelioma.[352] Histological subtype is the most consistent predictor of mesothelioma survival. The prognosis for sarcomatoid and biphasic subtypes is substantially worse than that for epithelioid mesothelioma; however, histological subtype alone does not usually alter the management of mesotheliomas.[353]

SINONASAL

Malignant sinonasal cancer is a rare, clinically aggressive neoplasm with an annual incidence of $<1 \times 10^{-6}$ in most developed countries representing <1% of all neoplasms.[354] The overall male/female ratio from 1973–2006 was ~1.8;[355] however, the ratio decreased recently except for higher ratios in some adenocarcinoma subtypes (e.g., intestinal-type adenocarcinoma).[356,357] Although sinonasal cancers account for ~3–4% of head and neck tumors, sinonasal cancers display different epidemiology, etiology, and genetic profiles than histologically similar tumors in the pharynx, larynx, and oral cavity. Long-term sinonasal cancer incidence rates have been relatively stable over the last several decades.

CARCINOGENESIS

Sinonasal tumor genomes contain many, highly diverse chromosomal aberrations. The diversity of sinonasal tumors suggests the occurrence of various carcinogenic mechanisms for the many types and causes of this neoplasm; however, the limited number of genetic studies and rarity of these tumors significantly complicate the determination of driver genes, signaling pathway alterations, and epigenetic mechanisms causing these tumors. Organic dusts (wood, leather) are not directly mutagenic; however, chronic inflammation from continuous mucosal irritation and phagocytosis of organic dust releases cytokines (e.g., IL-1β, tumor necrosis factor), producing activation of transcription factor nuclear factor κB (NFκB) and downstream prostaglandin G/H synthase (also known as COX2).[358] Additionally, alveolar macrophages release mutagenic reactive oxygen (ROS) and nitrogen (oxides, peroxynitrites) species that generate mutagenic DNA adducts. Although chronic inflammation may be involved with the association of organic dusts and sinonasal cancers, inflammation from chronic rhinitis and nasal polyps are not associated with increased sinonasal cancer risks.

Specific data on sinonasal cancer subtypes are limited. Up to ~50% of intestinal-type adenocarcinomas contain aberrations of the canonical Wnt signaling pathway involved with the nuclear expression of β-catenin, particularly in the colonic and papillary subtypes.

TP53 mutations are common events in head and neck carcinomas, including sinonasal cancers with p53 overexpression ranging from 18–77% in different series of sinonasal cancer subtypes. Higher mutation rates typically develop in adenocarcinomas than in squamous cell carcinomas, particularly following prolonged exposure to high wood dust concentrations.[359] KRAS mutations and cyclooxygenase 2 (COX2) expression are usually rare in sinonasal squamous cell carcinomas. PCR amplification and sequencing identified only 7 of 58 (12%) intestinal-type adenocarcinomas with *KRAS* mutations in codons 12/13.[360] BRAF tumor suppressor mutations are usually absent in sinonasal tumors. DNA copy number alterations are common in sinonasal squamous cell carcinomas. Using multiplex ligation-dependent probe amplification and microarray comparative genomic hybridization on 27 sinonasal squamous cell carcinoma tissue samples, the most frequent copy number gains were 8q24, 11q13, 17q12, 19p13, and 20q11–q13.[361] The most common losses included 9q21, 13q14, 17p13, 17q12, and 18q11. Most recurrent gains occurred in *EMS1* and *BCL2L1* (37%), *RECQL4*, *RELA*, and *ERBB2* (25%), and *CCND1* (26%) genes, whereas the most common losses developed in *BRAC1* and *CDH2* (38%), *CRK*

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(33%), and *STCH* and *RB1* (29%) genes. Epigenetic hypermethylation and inactivation of tumor suppressor genes in sinonasal cancer include *CDH13* (cadherin 13, H-cadherin), *ESR1* (estrogen receptor 1), *RASSF1* (Ras association domain family member 1), and *TP73* (tumor protein p73).[362]

EXPOSURE

Similar to mesothelioma, sinonasal cancer is primarily an occupational cancer. In an analysis of data on 1,135 sinonasal cancer cases (878 men, 297 women) from the Italian National Surveillance System, 73% of male cases were attributed to occupational exposures compared with ~35% of the women based on in-person interviews (80% direct, 20% proxy) by trained interviewers.[363] Other studies report slightly smaller attributable risks for sinonasal cancer associated with occupational exposures (e.g., 43% in men and 20% in women).[364] The strongest occupational associations with sinonasal cancer involve adenocarcinomas in cabinetmakers/joiners exposed to wood dust and boot/shoe manufacturing/repair workers exposed to leather dust; less robust associations were reported for strong acid process of isopropyl alcohol production and nickel refining. The IARC lists all four processes as carcinogens with sufficient evidence in humans, whereas the evidence for sinonasal carcinogenicity in humans is limited for formaldehyde, hexavalent chromium, carpentry/joinery, and textile manufacturing. Data on the associations of environmental tobacco smoke, welding fumes, arsenic, textile industry, and human papilloma virus (HPV-16, HPV-18) with sinonasal cancer are conflicting.[365]

In contrast to laryngeal cancer, asbestos is not a recognized cause of sinonasal cancer. A retrospective cohort study of construction workers using Swedish Cancer Registry data did not detect an elevated sinonasal cancer risk after separating 280,222 participants into 4 asbestos exposure categories (very low, low, medium, high) and comparing the exposed group with the general population (i.e., standardized incidence ratio, SIR).[366] Exposure categories were based on job titles. The SIR for sinonasal cancer was 0.85 (95% CI: 0.68–1.03) with no apparent dose-response relationship. The lowest relative risk occurred in the highest asbestos exposure group (RR = 0.71, 95% CI: 0.33–1.53) using the very low asbestos category as referents and adjusting for smoking history. A Scandinavian study of 167 sinonasal cancer cases and age/sex-matched hospital controls reported no association between asbestos and sinonasal cancer based on self-reported asbestos exposures in telephone interviews with surviving cases.[367]

Occupation

The absolute sinonasal cancer risk is very low in the general population; consequently, studies associating sinonasal cancers with specific jobs and/or carcinogens typically involve small sample sizes, with low statistical power resulting in highly variable, imprecise risk estimates. The evidence of an association with sinonasal cancer is strongest for wood and leather dust, primarily hardwood, and suggestive for strong acid process of isopropyl alcohol production and nickel refining. In a mortality study of workers at the South Wales Clydach nickel refinery employed since 1930, the SMR for nasal cancer was 8.70, (95% CI: 1.05–31.41, $n = 2$ cases), with wide confidence intervals and imprecise estimates.[368] The risk of sinonasal cancer is substantially higher in nickel refinery workers employed before 1930 than after 1960, when exposure to soluble nickel compounds was significantly reduced from improvement in production processes using these compounds.[364,369] Other exposures inconsistently associated with sinonasal cancers include formaldehyde and hexavalent chromium. In an Italian study on 113 sinonasal cancer cases and 336 hospital-based controls using data from the Piedmont Region Sinonasal Cancer Registry, the odds ratios for epithelial sinonasal cancers were positive, but statistically nonsignificant (OR = 2.8, 95% CI: 0.55–4.06, $n = 3$ cases/3 controls). The OR for adenocarcinomas in this study was similarly positive, statistically nonsignificant, and imprecise (OR = 2.1, 95% CI: 0.22–21.1) based on one case.

Dusts

Wood

Fine particulate hardwood dust is strongly associated with increased sinonasal adenocarcinoma risks. In the latter 1960s, Acheson et al. identified a case series of 58 nasal adenocarcinomas in British furniture workers heavily exposed to hard wood dust at the Buckinghamshire woodworking industries in the UK.[370] Subsequently, the IARC classified cabinet and furniture manufacturing as Group 1 (human) carcinogen with wood dust being a recognized human carcinogen. The pooled adenocarcinoma relative risk in a meta-analysis of 17 case-control and 12 cohort studies involving workers exposed to wood dust was positive and statistically significant with high heterogeneity (pooled RR = 29.43, 95% CI: 16.46–52.61, $I^2 = 80.3\%$, $P_{\text{heterogeneity}} = <0.001$) using random effects models.[371] Wood dust concentration and cumulative exposure contributed independently to highly elevated risks; however, additional wood exposure other than hardwood did not

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increase the sinonasal adenocarcinoma risk. The risk of squamous cell carcinomas in workers exposed to wood dust is marginally significant (RR_{pooled} = 1.46, 95% CI: 1.01–2.1), with a possible exposure-response relationship based on duration of exposure of <15 years and ≥15 years. In a Scandinavian population-based, case-control study of 393 male cases of nasal adenocarcinoma, the hazard ratio for wood dust after adjustment for formaldehyde exposure in the highest cumulative exposure category (≥28.82 mg/m^3/year) was 16.5 (95% CI: 5.05–54.1) using healthy, age/country-matched controls as referents.[372] The wood exposure primarily involved softwood-contaminated mixed wood dusts. Cumulative wood dust exposure was not associated with other sinonasal cancer subtypes. A pooled analysis of 12 studies involving 930 (680 male/250 female) cases and 3,136 (2,349 male/787 female) controls used logistic regression to evaluate sinonasal cancer risks based on job-exposure matrixes.[373] Overall, for sinonasal cancer in male furniture workers, the odds ratio was 4.5 (95% CI: 3.2–6.4), whereas the adenocarcinoma sinonasal cancer risk in these workers was 41.1 (95% CI: 24.5–68.7). The risks for the few women in these studies were statistically nonsignificant.

The risks of sinonasal cancer are weaker for softwood than hardwood dust, particularly in North American studies.[374] In a French hospital-based, case-control study of 82 sinonasal adenocarcinomas, only 2 cases had no documented hardwood dust exposure or a combination of hardwood and other wood dusts based on expert assessment of self-reported exposures.[375] Using nonexposed workers as referents, the OR for adenocarcinomas in 80 workers exposed only to hardwood dust plus 2 workers exposed to hardwood and softwood dust for 16–35 years was 261 (95% CI: 57–1,190, n = 32 cases/2 controls). The odds ratio for squamous cell carcinoma did not demonstrate a statistically significant dose-response relationship for softwood workers based on duration of exposure and average estimated concentration or years since first exposure. In a meta-analysis of 12 primarily case-control studies, the summary odds ratio for sinonasal cancer in male wood workers was 2.6 (95% CI: 2.1–3.3), with risks substantially higher for adenocarcinomas than squamous cell carcinomas.[376] The authors opined that the differences may reflect variations in hardwood and softwood cancer risks or other exposure-related differences.

Leather

The IARC lists boot and shoe manufacturing and leather dust as carcinogenic based on sufficient evidence in humans. The pooled relative risk of adenocarcinomas in a meta-analysis of 17 case-control and 12 cohort studies involving workers exposed to leather dust was 35.26 (95% CI: 20.62–60.28, I^2 = 0%, $P_{heterogeneity}$ = 0.818) using random effects models.[371] In an Italian study based on data from the Piedmont Region Sinonasal Cancer Registry, occupational questionnaires were completed by 113 sinonasal cancer cases and 336 hospital-based controls with adjustment of the results for smoking, sex, age, and co-exposures while allowing a 10-year latency period and excluding cases appearing within 10 years of the initial exposure.[377] There were 53 adenocarcinomas and 37 squamous cell carcinomas. Using unconditional logistic models, the adjusted odds ratio (OR) for adenocarcinomas and leather dust was 26.6 (95% CI: 5.09–139.0, n = 7 cases), with a dose-response relationship based on questionnaires administered by unblinded interviewers and evaluated by a blinded occupational epidemiologist or physician. An analysis of pooled data from 8 European studies involving 555 (104 female/451 male) cases and 1,705 (241 female/1,464 male) controls demonstrated a statistically significant excess sinonasal cancer risk in men (pooled OR = 1.7, 95% CI: 1.10–3.35), but not among women (pooled OR = 2.71, 95% CI: 0.78–9.43, n = 7 cases/7 controls), primarily for adenocarcinoma (pooled OR = 2.99, 95% CI: 1.33–6.73, n = 15 cases/49 controls).[378] The pooled sinonasal cancer odds ratio was positive, but statistically nonsignificant for squamous cell carcinoma. A review of 14 studies including a meta-analysis of case-control studies reported 75–88% of the sinonasal cancers were adenocarcinomas in workers exposed to leather dust, with the relationship particularly strong for shoe shining, finishing, and repair work.[378,379]

Formaldehyde

Formaldehyde is an intermediary in industrial chemical manufacturing and production (e.g., melamine, phenolic compounds, polyacetal resins, urea) used in wood products and synthetic vitreous fiber industries. Overall, the association between occupational formaldehyde exposure and sinonasal cancer is inconsistent with positive data primarily involving adenocarcinomas.[380,381] In a pooled analysis of 12 case-control studies involving 195 adenocarcinomas, 432 squamous cell carcinomas, and 3,136 controls, the adenocarcinoma risk in the highest formaldehyde exposure group was increased and statistically significant in men (OR = 3.0, 95% CI: 1.5–5.7) and women (OR = 6.2, 95% CI: 2.0–19.7).[382] In an Italian study on 113 sinonasal cancer cases and 336 hospital-based controls using data from the Piedmont Region Sinonasal Cancer Registry, the odds ratio for sinonasal adenocarcinoma was 9.5 (95% CI: 2.62–34.2,

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n = 6 cases). This study identified no squamous cell sinonasal cancers. Although case-control studies of sinonasal cancer and formaldehyde exposure suggest elevated sinonasal cancer risks, cohort studies do not support the findings of the case-control studies.[383] In a meta-analysis of six case-control and two cohort studies of workers exposed to formaldehyde, the pooled relative risks for sinonasal cancers were 1.68 (95% CI: 1.37–2.06) for case-control studies and 1.09 (95% CI: 0.66–1.79) for cohort studies.[371] A British cohort study of 14,014 men employed in 6 factories using formaldehyde, the SMR for sinonasal cancer was 0.87 (95% CI: 0.11–3.14, 2 cases/2.3 expected 1941–2000).[384] No deaths were recorded in men with high estimated time-weighted average formaldehyde concentrations (i.e., >2 ppm). The IARC concluded the epidemiological evidence of a positive relationship was limited.

Lifestyle

Little epidemiological evidence associates lifestyle factors other than tobacco smoking with sinonasal cancers. Few data are available on diet, alcohol consumption, or obesity. The IARC associates cigarette smoking with an elevated sinonasal cancer risk based on case-control studies demonstrating dose-response relationships between squamous cell carcinomas and smoking, along with reduction in the relative risk with time since smoking cessation. However, the effect is relatively small compared with other body sites (e.g., lungs, larynx).[385] The association is particularly strong for keratinizing squamous cell carcinoma with TP53 mutations. In a pooled analysis of 8 European studies involving 555 (104 female/451 male) squamous cell carcinoma cases and 1,705 (241 female/1,464 male) controls, the odds ratio for sinonasal squamous cell carcinoma subtype (but not adenocarcinoma) in current smokers was elevated (OR = 1.72, 95% CI: 1.16–2.56, n = 103 cases/595 controls) compared with never-smokers.[378] Male ex-smokers had a modest excess overall sinonasal cancer risk (OR = 1.43, 95% CI: 1.03–1.97, n = 186 cases/514 controls); however, the difference in overall sinonasal cancer rates in female never-smokers and current smokers was not statistically different. The study reported no association between tobacco smoking and adenocarcinoma risks ($OR_{current\ smokers}$ = 0.65, 95% CI: 0.35–1.20, n = 39 cases/595 controls). An Italian case-control study on occupational risk factors for sinonasal cancer did not detect an association between epithelial sinonasal cancer and smoking history; however, the authors reported the information on smoking intensity and duration was incomplete for many participants.[377] The few data on environmental tobacco smoke and sinonasal cancer risks are conflicting.

Diseases

The epidemiological evidence for an association between HPV and sinonasal cancer is suggestive, but inconclusive. HPV DNA appears in ~20% of sinonasal carcinomas, with the high-risk type (HPV16/18) being the most common type, particularly squamous cell carcinoma subtypes;[365] however, HPV detection varies with geography and detection method.[386,387] Sinonasal nonkeratinizing squamous cell carcinoma subtypes and some squamous cell carcinoma variants (basaloid, papillomas) have a particularly high prevalence of HPV DNA and p16 overexpression.[388,389] Sinonasal cancer is not associated with non-irritant chronic inflammation (e.g., allergic rhinosinusitis).

HISTOLOGY

Most sinonasal tumors arise from epithelial cells in the nasal cavities or maxillary sinuses and less commonly the ethmoid sinuses; frontal and sphenoidal sinus tumors are very uncommon. Sinonasal tumors are one of the most diverse groups of neoplasms in the human body. These tumors represent ~3–5% of head and neck tumors, with a relatively small percentage of squamous cell tumors compared with other head and neck sites.[390] In a review of sinonasal tumors in the Italian Network of Cancer and US Surveillance, Epidemiology and End Results (SEER) Registries, the location of sinonasal tumors ranged from 45–58% in the nasal cavities compared with 20–30% in the maxillary sinuses and 8–13% in the ethmoid sinuses; the sphenoid and frontal sinuses together contained <3–5% of the tumors.[383]

Epithelial histological subtypes represent ~60–75% of sinonasal tumors with subtypes including squamous cell carcinomas, adenocarcinomas, esthesioneuroblastomas, and adenoid cystic carcinomas; the former two represent the majority of sinonasal tumors. Squamous cell carcinoma subtypes are further classified into keratinizing, nonkeratinizing, and variants (basaloid, papillary, spindle cell carcinoma, adenosquamous carcinoma).[388] Premalignant lesions associated with squamous cell carcinoma primarily involve inverted or oncocytic papillomas. Adenocarcinomas may arise from respiratory surface epithelium or underlying seromucinous glands, with tumors divided into rare multiple salivary subtypes (5–10%) and the rest into non-salivary subtypes; the latter surface epithelial adenocarcinomas are divided into intestinal and nonintestinal

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subtypes. The most common epithelial sinonasal tumors subtypes are squamous cell carcinoma arising in the maxillary sinuses or nasal cavity and intestinal-type adenocarcinomas developing in the ethmoid sinuses.[356] Undifferentiated and miscellaneous tumors account for ~10% of sinonasal tumors; these tumors represent a wide diversity of neoplasms (e.g., neuroectodermal, mesenchymal, and hematolymphoid tumors, undifferentiated carcinomas).[391] The subtypes include rare melanomas, mesenchymal (e.g., angiosarcoma, chondrosarcoma, fibrosarcoma), and hematological (e.g., lymphoma, plasmacytoma) neoplasms.[383]

The distribution of squamous cell carcinomas and adenocarcinomas varies with gender and location. In a US study based on Surveillance, Epidemiology and End Results (SEER) data 1973–2006, the approximate distribution of epithelial histological types included squamous cell (52%), adenocarcinoma (13%), melanoma (7%), esthesioneuroblastoma (6%), and adenoid cystic carcinoma (6%).[355] The Italian National Surveillance System reported squamous cell carcinoma (46%) was more common than adenocarcinoma (18%) in women, whereas adenocarcinoma (46%) was more common than squamous cell carcinoma (33%) in men.[363] Premalignant lesions (e.g., inverted papillomas in squamous cell carcinoma) are infrequently identified.

HOST SUSCEPTIBITY

Few data are available on familial syndromes associated with sinonasal cancer. Currently, no genetic predisposition to sinonasal cancer has been identified in specific familial syndromes.

CLINICAL FEATURES

The population-based incidence rates are age-related with median age at diagnosis in the 6th–7th decade, particularly in men with 20% of cases presenting before the age of 55 years and 38% after 70 years of age.[383] The clinical features of sinonasal cancer are nonspecific, including facial pain, nasal obstruction, epistaxis, and rhinorrhea. Diplopia, proptosis, or other neurological symptoms may occur in sinonasal cancer patients with advanced disease. Distant metastases are unusual (i.e., ~10%) in patients presenting with sinonasal cancers; most patients die of recurrences before metastases become clinically apparent, with possible exceptions of adenoid cystic carcinoma, malignant melanoma, and some sarcomas.[392] Metastasis of other tumors (e.g., kidney) to the paranasal sinuses is very rare.[393]

The prognosis of patients with sinonasal cancer is generally poor, with little change in overall survival during the last few decades; the overall 5-year survival rate is ~30–50% depending on primary tumor size, stage of disease at diagnosis, cervical lymph node involvement, and histological type.[394] In a study of 4,994 cases of sinonasal squamous cell carcinoma (64% men/36% women) in the US Surveillance, Epidemiology, and End Result (SEER) database, the overall 5-year survival was 53% compared with 45% for 10-year survival and 29% for 20-year survival.[356] Although prognosis is not strongly associated with histological subtypes, sinonasal cancer types varies with location within the nasal and paraspinal tissues; tumors are typically diagnosed earlier in nasal cavities than sinuses.

LARYNX

Laryngeal cancer incidence varies dramatically with location; incident rates are particularly high in Brazil, France, Italy, Spain, India, and some Southeast Asian countries.[395] Five of the 10 European regions with the highest laryngeal cancer incidence rates occur in Spain. Laryngeal cancers are much more common in men than women, particularly in Nordic, Eastern European, and Southern European countries. In Europe, during the 1990s and 2000s, laryngeal cancer accounted for ~52,000 new cases annually (~2% of the total cancer burden), with men representing 92% of the total.[396] By 2018, the age-standardized incidence rate for laryngeal cancer in Europe decreased to ~40,000 cases, with a male/female ratio of 7.65.[397] In the United States, the estimated annual laryngeal cancer incidence is ~12,400 with a male/female ratio of 3.9/1 and an estimated annual mortality of 3,800.[398] Although the incidence and mortality of laryngeal cancer has been decreasing, the overall case-fatality rate has increased as a result of the relative decrease in the incidence of localized compared with regional and distant disease. Worldwide, the estimated annual laryngeal cancer incidence is 177,000, with ~95,000 annual deaths.[269] Premalignant laryngeal dysplasia more commonly occurs in men (10/100,000) than women (2/100,000 women).[399]

CARCINOGENESIS

Early changes in the malignant process involve allelic chromosomal losses in regions 3p (possibly *FHIT* tumor suppressor; 57–68% frequency), 9p21 (*CDKN2A* tumor suppressor, p16 protein; 20–35% frequency),

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and 17p13 (*TP53*; 21% frequency).[400] The latter may not be associated with p53 tumor suppressor inactivation in early-stage laryngeal tumors because of the frequent absence of p53 expression during that stage of development. Other common (i.e., ≥20%) copy number alterations include chromosomal losses in 5q, 8p, 11q23–24, 13q, and 18q, whereas chromosomal amplifications or gains occur in 3q, 5p, 8q, 11q13, and 18p. Laryngeal tumors typically contain more chromosomal aberrations than other oropharyngeal cancers particularly chromosomal amplifications.[401] Chromosomal changes associated with these multiple focal, high-level amplifications involve overexpression of 7p12 (*EGF* receptor, transmembrane growth-regulating receptor glycoprotein), 9p24 (*AK3*, *MDS030*, *RNAC*), 11q22 (*BIRC2*, *BIRC3*, *YAP1*), 12q15 (*DYRK2*, *MDM1*, *MDM2*), and 17q23 (*APPBP2*, *PPM1D*).[402] EGFR overexpression dramatically increases during the progression of laryngeal dysplasia to squamous cell carcinoma;[403] however, early loss of *CDKN2A* ($p16^{INK4A}$, $p14^{ARF}$ protein expression, ↓ cell cyclin-dependent kinase inhibitor 2A) and *TP53* downregulation (↓cell cycle arrest, apoptosis) are less frequent in laryngeal than other head and neck cancers.

The protooncogene *BCL-2* is an antiapoptotic, membrane-associated molecule that modulates the interaction of apoptosis-activating factors (APAF-1) with caspase 9; overexpression of BCL-2 protein enhances tumor proliferation and progression by inhibiting tumor cell apoptosis.[404] Signaling pathways involved with the malignant transformation of premalignant lesions include the JAK–STAT, Hippo, and PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase) pathways.

Telomerase reactivation (*TERT* gene, telomerase reverse transcriptase) is a common event in all neoplasms, including in early events during the development of laryngeal carcinogenesis. The hTERT mRNA expression in laryngeal epithelium increases progressively as the degree of epithelial abnormalities increases. In an analysis of 140 frozen laryngeal tissues, hTERT mRNA expression was detectable in 7% of normal laryngeal epithelium compared with 20% of squamous hyperplasias, 75% of atypical hyperplasias, 89% of carcinomas *in situ*, and 85% of squamous cell carcinomas.[405] Innate and adaptive immune mediators enhance the progression of laryngeal tumors by releasing cytokines (IL-10, IL-6, vascular endothelial growth factor) and chemokines into the tumor microenvironment, resulting in suppression of immune responses to tumor evasion. These mediators include regulator T cells (Tregs, CD4+, CD25+ T cells with forkhead box P3), myeloid-derived suppressor cells, and tumor-associated macrophages.[406]

A single miRNA can regulate the expression of multiple mRNAs and several miRNAs can modulate the expression of a single miRNA. MicroRNAs (miRNAs) posttranscriptionally limit tumor growth by downregulating protooncogene activity or upregulating tumor suppressor gene activity. The complexity of these interactions complicates the determination of the effect of individual miRNAs on laryngeal squamous cell carcinoma oncogenes, tumor suppressors, and cancer stem cells. Both genetic (e.g., single-nucleotide polymorphisms) and epigenetic (e.g., aberrant DNA methylation/histone modification) can dysregulate miRNAs and downstream signaling pathways. Genetic targets and cellular effects of miRNAs dysregulation in laryngeal squamous cell carcinomas commonly include upregulation of miRNA-21 (*BTG2*, proliferation) and miRNA-196a (proliferation) along with downregulation of miRNA 26b (*ULK2*, autophagy/antiapoptosis) and miRNA-203 (*ASAP1*, proliferation, cell cycle control, apoptosis, invasion).[407] Autophagy is the process that maintains normal cell function by degrading intracellular macromolecular substances from aging organelles. Downregulation of *ULK2* (unc-51-like autophagy activating kinase 2) enhances laryngeal tumor survival by limiting miRNA-26b-induced cell proliferation and inactivating the PTEN/AKT (autophagy/antiapoptosis) pathway.[408]

EXPOSURE

The main risk factors for laryngeal cancer are tobacco use and, to a lesser extent, alcohol consumption, with some evidence of more than an additive interaction together. Asbestos and sulfuric acid exposures are the main occupational carcinogens associated with laryngeal cancer; however, a British review of occupational cancers estimated the attributable fraction of laryngeal cancers resulting from occupational exposures is relatively small (AF = 2.61%, 95% CI: 0.0083–0.0432).[409] Other studies suggest higher attributable fraction ranging from 1–20% (sulfuric acid, mineral oils) in the United States,[410] whereas a Finnish study reported an attributable fraction of 9.1% (9.3% men/0.5% women) based on combined factors (asbestos, welding fumes, metal dust, irritant gases, polycyclic aromatic hydrocarbons).[411] Asbestos exposure accounted for 8.3% of the attributable fraction among men compared with 0.3% in women. In contrast to sinonasal cancers, laryngeal cancer is strongly associated with lifestyle because of the synergistic interaction of smoking and alcohol consumption on laryngeal cancer risks.[412]

Diet is not a strong risk factor for laryngeal cancer based on limited observational data involving

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TABLE 53.5. Statistical data on various occupations in the ICARE (Introduce, Communicate, Acknowledge, Recommend, and Encourage) Study and the 5-Country Nordic Study. Substantial variation exists between studies of laryngeal cancer risks in specific occupations in part from multiple comparisons. The seven occupations in men that reached a statistically significant association in the ICARE study, with the risk of laryngeal cancer compared with standardized incidence ratios in similar occupations from the 15 million 5-Country Nordic Study.[415] The latter study reported statistically significant SIRs in 9 of 54 occupational categories, including mechanics, electrical workers, printers, food workers, public safety workers, building caretakers, hairdressers, and cooks/stewards. Only the latter category was statistically significant for the different measures of risk (i.e., OR, SIR) in the two studies. (Adapted from Paget-Bailly et al.).[414]

Occupation	Laryngeal Cancer Cases	Odds Ratio ICARE	SIR Nordic Countries	95% Confidence Interval ICARE	95% Confidence Interval Nordic Countries
Launderers, dry cleaning, pressing[a]	6	13.3	1.31	2.4–75.0	0.82–1.99
Agricultural, animal husbandry[a]	9	7.9	0.43 (farmers)	2.6–23.9	0.30–0.60
Fishing[a]	6	3.6	1.83	1.1–12.2	0.05–10.18
Plastering	10	3.3	—	1.3–8.2	—
Rubber, plastics production[a,b]	14	3.2	—	1.5–6.8	—
Welding, flame cutting	33	2.4	4.93 (welders)	1.5–4.0	0.60–17.81
Cooks[a]	25	2.4	1.59	1.4–4.2	1.09–2.24

Abbreviation: SIR = standardized incidence ratio.
[a] Although categories varied somewhat in a German meta-analysis of 21 case-control studies on laryngeal cancer, none of these categories were associated with statistically significant meta-effects using a fixed effects model.[416] The highest laryngeal cancer risks were associated with blue-collar jobs (miners, chemical processors, spinners, weavers, knitters, dyers, tailors, dressmakers, sewers, upholsterers, glass formers, potters, blacksmiths, toolmakers, machine tool operators, painters, maids, forestry workers). [b] Excludes tire makers and vulcanizers.

primarily pooled data from retrospective dietary analyses in case-control studies. Using self-reported or interview-administered food-frequency questionnaires, a study using pooled data from 2,452 cases and 5,013 controls in the International Head and Neck Cancer Epidemiology (INHANCE) consortium divided information on 24 nutrients into 3 major categories.[413] The adjusted laryngeal cancer risks were positively associated with animal products and cereals (aOR = 1.57, 95% CI: 1.15–2.15, n = 253 cases/983 control cases, $P_{\text{heterogeneity}}$ = 0.008) and fats (aOR 1.70, 95% CI: 1.23–2.36, n = 210 cases/981 control cases, $P_{\text{heterogeneity}}$ = <0.001) comparing the highest and lowest (referent) quintiles with unconditional logistic regression and fixed effects models on quintiles of factor scores. The highest quintile for antioxidant vitamins and fiber was inversely associated with laryngeal cancer risks (aOR = 0.52, 95% CI: 0.38–0.70, n = 85 cases/977 control cases, $P_{\text{heterogeneity}}$ = <0.001). Analysis indicated high heterogeneity; however, the results were similar using mixed effects models.

Occupation

A French population-based case-control study (ICARE) examined laryngeal cancer risks in men by comparing 33 occupations listed by 456 laryngeal cancer patients with local controls.[414] Table 53.5 lists the odds ratios for the seven occupations that reached statistical significance in an analysis of ICARE data. Determination of a causal association with these seven occupations and laryngeal cancer requires further confirmation.

A systematic review and meta-analysis of 30 case-control, 65 cohort, and 4 record-linkage studies suggested elevated laryngeal cancer risks following exposure to textile dust (metaRR = 1.41, 95% CI: 1.09–1.83), polycyclic aromatic hydrocarbons (metaRR = 1.29, 95% CI: 1.10–1.52), engine exhaust (metaRR = 1.17, 95% CI: 1.05–1.30), and work in the rubber industry (metaRR = 1.39, 95% CI: 1.13–1.71).[417] Egger testing and funnel plot analysis suggest some publication bias for the textile dust studies. The study detected no association between laryngeal cancer and cement dust, formaldehyde, or wood dust. In a meta-analysis of 13 mortality studies on laryngeal cancer in the synthetic rubber-producing industry, the pooled metaSMR was modestly elevated and statistically nonsignificant (metaSMR = 1.19, 95% CI: 0.88–1.60, $P_{\text{heterogeneity}}$ = 0.01).[418] The metaSIR for laryngeal cancer was similarly positive and statistically nonsignificant (metaSIR = 1.39, 95% CI: 0.75–2.59, $P_{\text{heterogeneity}}$ = 0.58). Limiting the meta-analysis to rubber-industry cohorts exclusively producing tires yielded null results (metaSMR = 1.01, 95% CI:

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0.70–1.48, $P_{heterogeneity}$ = 0.604). A French occupational study of 296 laryngeal cancers and 296 patients with other tumor sites did not detect an association between formaldehyde exposure and laryngeal cancer.[419] A systematic review and meta-analysis of 7 case-control and 16 cohort studies did not detect a statistically significant association between standardized incidence (pooled SIR = 1.50, 95% CI: 0.59–2.42) or mortality (pooled SMR = 1.38, 95% CI: 0.79–1.96) for laryngeal cancer and silica dust exposure.[420]

Asbestos

Although the IARC classifies asbestos as a human laryngeal carcinogen, the association between asbestos exposure and laryngeal cancer remains debatable, primarily because of potential recall bias and the lack in controlling the strongest risk factors (synergistic effects of tobacco smoking/alcohol consumption) in many studies, as noted in a systematic review in 2000.[421] Similarly, a subsequent systematic review of 10 cohort and 5 case-control studies published from 2000–2016 concluded the current medical literature on laryngeal cancer and asbestos exposure is conflicting and lacks support for a correlation between the two.[422] Among the three case-control studies controlling for smoking and alcohol use, the odds ratios ranged from 0.86 (95% CI: 0.51–1.0, n = 350 cases) to 1.0 (95% CI: 0.8–1.3, n = 150 cases). Only 2 of 10 cohort studies accounted for smoking with a relative risk of 1.8 (95% CI: 0.8–4.3, n = 18 ever-exposed cases) for one cohort study after controlling for smoking and mineral wool exposure. The study did not control for alcohol use or demonstrate a dose-response relationship between laryngeal cancer and asbestos exposure.[423] The hazard ratio for the other cohort study was 6.36 (95% CI: 2.18–18.53) using one job-exposure matrix and 1.49 (95% CI: 0.75–2.97) after adjustment for smoking and alcohol consumption using another job-exposure matrix.[424]

A case-control study of 100 men with laryngeal squamous cell carcinoma and 100 age-matched hospital controls reported a strong association between asbestos exposure and laryngeal cancer, with 31% of the cases and 3% of the controls having an "important exposure to asbestos" ($P_{difference}$ = <0.001).[425] The control group contained more nonsmokers than cases; no data were collected on alcohol consumption. Subsequent studies demonstrated a much weaker association based on better control of confounders (i.e., smoking, alcohol consumption).[421,426] In a meta-analysis of four cohort studies on laryngeal cancer mortality, the metaSMR was positive and statistically nonsignificant (metaSMR = 157, 95% CI: 95–245), with a latency of at least 10 years.[427] The data did not demonstrate a dose-response relationship or correlate laryngeal cancer to the percentage of mesothelioma deaths. The proportionate mortality from mesothelioma as a percentage of all deaths was a proxy marker for the semiquantitative estimation of asbestos doses. In the prospective Netherlands Cohort Study of 58,279 men followed for 17.3 years, the adjusted hazard ratio for laryngeal cancer was modestly positive and statistically nonsignificant (aHR = 1.20, 95% CI: 0.84–1.72, n = 52 cases/114 controls).[424] The association was stronger for supraglottic (aHR = 2.14, 95% CI: 1.13–4.04, n = 20 cases/24 controls) than glottic cancer (aHR = 0.94, 95% CI: 0.61–1.44, n = 32 cases/90 controls). Adjusted factors included age, current smoking, daily cigarette use, smoking duration, and alcohol consumption. The trends for almost all measures of cumulative intensity and duration of exposure were statistically nonsignificant.

In a German population-based study of 257 laryngeal cancer cases (236 men, 21 women) and 771 age/sex-matched controls, the odds ratio for laryngeal cancer in ever-asbestos exposed cases was 1.2 (95% CI: 0.83–1.7, n = 73 cases/18 controls) after adjusting for smoking and alcohol using nonexposed controls as referents. Asbestos exposure was determined from in-person interviews using job-specific questionnaires and substance check lists.[428] Although evaluation of crude odds ratios and cumulative asbestos exposures suggested the presence of positive dose responses, all the odds ratios were statistically nonsignificant after adjustment for smoking and alcohol.

Inorganic Acid Mists

Exposure to strong inorganic acid mists (sulfuric acid) is associated with laryngeal cancer in several industries, including the production of isopropanol/ethanol, battery manufacturing, sulfuric acid production, and steel pickling. A Canadian population-based study of 183 laryngeal cancer cases and 183 age/sex-matched controls used logistic regression to estimate odds ratios for laryngeal cancer exposures based on personal questionnaires and blinded, expert retrospective assessment.[429] Using the most sensitive, semiquantitative model, the odds ratio for laryngeal cancer in the high-sulfuric acid exposure group was 4.28 (95% CI: 2.13–8.58) compared with 1.91 (95% CI: 0.97–3.78) for the low-exposure group. Exposure-response gradients were strongly positive after adjustment for tobacco and alcohol consumption using a more specific semiquantitative model. The odds ratio for short-duration (≤10 years), low-level exposure was 1.97 (95% CI: 0.63–6.13) and 6.91 (95% CI: 2.20–21.74) for long-duration (>10 years) high-level exposure. In a retrospective cohort study of the metal pickling industry, Steenland et al. identified 9 incident

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laryngeal cancer cases in 879 workers (73% participation rate, 26% proxy interviews) exposed to sulfuric acid mists (40% additionally exposed to other acids).[430] The duration of exposure was 9.5 years with an estimated 8-hour TWA of 0.2 mg/m^3. After adjusting for tobacco smoking and alcohol consumption, the estimated standardized incidence ratio was 230 (95% CI: 105–436) using US population data. A review of 25 epidemiology studies on respiratory tract cancer reported a moderate association between sulfuric acid mists and laryngeal cancer with a suggestive dose-response relationship; however, the authors noted the study results were imprecise with inadequate control of confounding (tobacco smoking, alcohol consumption).[431] The authors identified three industries (sulfuric acid production, isopropanol production, metal pickling) with a high potential for sulfuric acid exposure (>1 mg/m^3 sulfuric acid as an 8-hour time-weighted-average typically occurring prior to 1970). Data were inadequate to evaluate laryngeal cancer risks in sulfuric acid and isopropanol production industries. The authors from the Steenland study opined the SIR did not vary with time since first exposure and evidence for a dose-response relationship was not persuasive; however, they noted residual confounding of smoking could not account for the excess laryngeal cancer SIR.

Lifestyle

Tobacco dominates the risk of glottic and vocal cord cancers, whereas alcohol is a stronger risk factor for supraglottic cancers. Overall, alcohol is a weaker risk factor than tobacco smoking. Most investigations indicate the synergistic effect of combined tobacco and alcohol consumption on laryngeal cancer risks is at least greater than additive and potentially multiplicative.[432,433] In the ICARE study, the interactions of asbestos exposure/alcohol consumption and asbestos exposure/smoking were additive, whereas the interaction of asbestos exposure/smoking/alcohol consumption was greater than additive.[434]

Tobacco Smoking

The relative risk of laryngeal cancer comparing ever- and never-smokers is ~10-fold, with a smaller risk in smokers exclusively using filtered cigarettes (RR = 0.5 compared with exclusively plain-cigarette smokers).[435] The laryngeal cancer risk in smokers decreases after smoking cessation (RR = 0.3 after 10 years). Smoking history accounts for an estimated 90–95% of laryngeal cancer cases.[436] The prospective Netherlands Cohort Study of 58,279 men aged 55–69 years identified 166 laryngeal cancers during 17.3 years of follow-up. The study did not detect a statistically significant interaction between smoking and asbestos exposure on laryngeal cancer risks based on self-reported questionnaires and job-exposure matrices.[424] The hazard ratio for asbestos exposure within the strata of cigarette smoking comparing 72 never asbestos-exposed versus 33 ever-asbestos exposed current smokers was 1.23 (95% CI: 0.78–1.94) without evidence of a multiplicative interaction ($P_{\text{multiplicative interaction}} = 0.85$).

Alcohol

The relative and absolute risks are small for moderate alcohol consumption in the absence of smoking (e.g., RR = ~2 for 4 drinks/day compared with nondrinkers).[437] In a Seattle, Washington, population-based, case-control study of 235 laryngeal cancer cases and 547 age- and gender-matched local residents, independent risk factors for laryngeal cancer were alcohol consumption (≥42 drinks/week compared with ≤7 drinks/week; OR = 3.1, 95% CI: 1.2–7.9), cigarette use (≥40 cigarettes/day compared with never-smoking; OR = 23.1, 95% CI: 9.4–52.6), and weighted positive responses to the Michigan Alcohol Screening Test (MAST score of ≥5 compared with 0; OR = 1.9, 95% CI: 1.1–3.4) using unconditional logistic regression.[438] A meta-analysis of 38 case-control studies and 2 cohort studies used random effects modeling to estimate laryngeal cancer risks in predefined consumption levels of light, moderate, and heavy alcohol consumption.[439] As displayed in Table 53.6, light alcohol consumption (≤1 drink daily) is not associated with increased laryngeal cancer risks, whereas the risk increases with increasing alcohol consumption using never/occasional drinkers as referents. Substantial heterogeneity limits definitive conclusions regarding causality following moderate to high alcohol consumption.

Diseases

Infections

The role of human papilloma virus (HPV) in the development of laryngeal cancer tumors remains controversial, in part because of the presence of HPV genotypes in normal pharyngeal tissue and the geographical variation in HPV laryngeal squamous cell carcinoma prevalence rates.[440] In eight studies with laryngeal sample sizes ranging from 86–110, the HPV prevalence ranged from 7–59%, most commonly high-risk HPV-16 and HPV-18.[441] In a meta-analysis of

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TABLE 53.6. In a meta-analysis of 40 studies using random effects modeling, adjusted meta-odds ratios, and 95% confidence intervals for estimated laryngeal cancer risks were estimated in four alcohol consumption categories (overall, light, moderate, high). The results are consistent with no association with light drinking, modest association with moderate drinking, and ~2.5-fold increase for drinking four or more drinks daily using never/occasional drinkers as referents. The results displayed substantial heterogeneity for overall, moderate, and high categories. The meta-odds ratios were adjusted for age, sex, and smoking by matched analysis, stratified analysis, or adjustments in multivariate models.[439]

Alcohol Category	Dose (Drinks/Day)	Studies (*n*)	Adjusted Meta Odds Ratio	95% Confidence Interval	I^2 Statistic (%)	$P_{heterogeneity}$
Overall	Any	20	1.84	1.50–2.26	81.5	<0.001
Light	>0–1	6	0.88	0.70–1.12	22.6	0.26
Moderate	>1–<4	20	1.50	1.23–1.83	64.2	<0.001
High	≥4	17	2.46	1.88–3.22	79.7	<0.001

55 studies involving 2,559 laryngeal cancer cases, 741 (28%) were HPV$^+$ (95% CI: 23.5–32.9, I^2 = 82.39%) with substantial heterogeneity; in this study 19.8% (95% CI: 15.7–24.6%, I^2 = 78.83%) were HPV-16$^+$ compared with 6.2% (95% CI: 4.0–9.5%, I^2 = 68.53%) for HPV-18$^+$ and 3.7% (95% CI: 2.4–5.7%, I^2 = 39.60%) for low-risk HPV genotypes overall.[442] The presence of HPV DNA alone does not indicate viral involvement in laryngeal squamous cell carcinoma.[443] Using more recent data, E6/E7 oncoproteins positivity of >70%, and high p16 protein positivity as documentation of integrated and transcriptionally active HPV linked to HPV-related carcinogenesis, the fraction of laryngeal cancers potentially associated with HPV infection was small (i.e., <5%).[444,445]

Gastrointestinal Reflux

Data on the association of gastrointestinal reflux disease (GERD) with laryngeal cancer are limited, with substantial potential for confounding (tobacco smoking, alcohol consumption) and misclassification from inaccuracies occurring in the diagnosis of reflux.[446] Gastrointestinal reflux disease, premalignant lesions, and laryngeal cancer commonly coexist; however, the role of GERD in the development of laryngeal cancer remains controversial. In a US study of 92 incident laryngeal cancer cases and 192 age/gender/ethnicity-matched, clinic-based controls, the increased laryngeal cancer risk was statistically significant (OR = 2.11, 95% CI: 1.16–3.85) for any criteria of GERD based on retrospective chart review (ICD-9 codes, symptoms of heartburn/acid regurgitation, multivariate conditional logistic regression).[447] Using univariate analysis, the association was much stronger based on symptomatic GERD (OR = 2.58, 95% CI: 1.11–6.10, n = 13 cases/11 control cases) than ICD-9 codes (OR = 0.52, 95% CI: 0.24–1.09, n = 12 cases/39 control cases). In a US study of 116 incident laryngeal cancer cases and 917 population-based controls, a history of often/extreme heartburn was not associated with an elevated adjusted laryngeal cancer risk (aOR = 0.84, 95% CI: 0.45–1.55) using subjects with no heartburn history as referents.[448] The odds ratio was adjusted for age, sex, race, smoking, alcohol consumption, HPV16 exposure, education, and BMI. A study of US Veterans Health Administration outpatient care files identified 14,449 incident laryngeal cancer cases 1:1 with frequency-matched controls based on the year of cancer diagnosis.[449] Controls were not matched to patient characteristics (e.g., age/sex). Using multivariate logistic regression analysis, GERD was not associated with laryngeal cancer (OR = 1.01, 95% CI: 0.92–1.12, P = 0.780), whereas the P value was positive for tobacco use, alcohol abuse, male gender, and age decile.

HISTOLOGY

Almost all laryngeal cancers (i.e., ~85–90%) are squamous cell carcinomas originating in the glottis, with supraglottic and subglottic tumors being much rarer.[395] Glottic tumors in the United States occur predominantly in the Anglo-Saxon population, whereas the number of glottic and supraglottic tumors is similar in France, India, and African-American populations. Most head and neck tumors including laryngeal cancer probably arise from common premalignant progenitor cells associated with the stepwise increase in genetic alterations during the progression from dysplasia to carcinoma *in situ* and invasive cancer.[450] The estimated progression of dysplastic epithelial lesions to malignant transformation is ~8–15%. In a meta-analysis of 9 observational studies involving 940 laryngeal cancer cases, the overall malignant transformation rate for laryngeal dysplasia was 14% (95% CI: 8–22%) with a mean time to malignant transformation of 5.8 years.[451] A review of 107 laryngeal dysplasia cases identified over 20 years at John Hopkins University reported ~8% of these cases progressed to laryngeal cancer.[452]

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The WHO classification separates precursor lesions into low- and high-grade dysplasia (squamous intraepithelial neoplasia, SIL) with the option of distinguishing carcinoma *in situ* from high-grade dysplasia for treatment purposes.[453] Laryngeal neuroendocrine carcinomas are divided into well- (carcinoid), moderate- (atypical carcinoid), and poorly differentiated neuroendocrine carcinomas; the latter subtypes of poorly differentiated neuroendocrine carcinomas include small cell and large cell neuroendocrine carcinomas.

HOST SUSCEPTIBILITY

Nucleotide excision repair system regulates the main pathway for repairing bulky DNA lesions common in tobacco smokers while maintaining genome stability. Polymorphisms in *ERCC1* and *ERCC5* increase susceptibility to laryngeal cancer, particularly in ever-smokers and alcohol drinkers.[454,455] Genetic polymorphisms of cytochrome P450 family (i.e., *CYP1A1*, *CYP2E1*) are not associated with increased susceptibility to laryngeal cancer.[456]

CLINICAL FEATURES

Laryngeal cancer typically presents in older patients. The diagnosis of laryngeal cancer is rare under 40 years of age, with the risk increasing rapidly with age. Survival varies with sex and tumor location. Approximately one-half of laryngeal cancers in men appear in the glottis, including the vocal cords. Advanced laryngeal cancer presents with pain, dysphagia, and airway obstruction, particularly with supraglottic tumors; however, an asymptomatic neck mass may be the first sign of a laryngeal tumor. The 5- and 10-year survival rates for men in England and Wales diagnosed with laryngeal cancer during the 1990s were 64% and 54%, respectively.[395] Overall survival rates have not improved dramatically in the last several decades, with 5-year survival rates ranging from ~40–60% in advanced stages depending on stage, treatment, location, and age.[457] Laryngeal cancers in the glottis typically have a relatively better prognosis in men from the early onset of hoarseness and diagnosis, smaller tumor size, and greater responsiveness to surgery and radiotherapy. The clinical presentation of supraglottic tumors occurs more often in women with a worse prognosis from delayed diagnosis and less responsiveness to surgery and radiotherapy.

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Chapter 54

GASTROINTESTINAL TRACT

Gastrointestinal tract cancers account for ~20–25% of the overall cancer incidence in the United States; these cancers include malignancies of the oropharynx (oral cavity, salivary glands, tonsils, pharynx), esophagus, stomach, colon/rectum, anus, liver/biliary tract, and gall bladder. The wide international variation in the incidence of each type of gastrointestinal cancer suggests the environment and genetics contribute significantly to cancer development in this part of the human body. Dietary and lifestyle factors are important determinants of gastrointestinal cancers; these factors may confound the interpretation of epidemiological studies on the effects of chemical exposures, particularly when the risks are relatively low. Table 54.1 lists the strength of the human evidence (sufficient, limited) for carcinogenic agents and processes associated with gastrointestinal tract cancers based on evaluations by the International Agency for Research on Cancer.[1,2] These evaluations indicate causal associations between gastrointestinal tract cancers and carcinogens primarily involve lifestyle and infectious processes rather than occupational exposures.

OROPHARYNGEAL

Head and neck cancers include tumors of the oral cavity, paranasal sinuses, oropharynx, and hypopharynx. These tumors arise from the lining or mucosa of the upper aerodigestive tract and almost all of these tumors are squamous cell carcinomas. Other than oropharyngeal cancer, head and neck cancers are covered in chapter 53. An estimated 85,000 oropharyngeal cancer cases occur worldwide annually, with enhanced risks for oropharyngeal cancers resulting primarily from lifestyle choices.[3] Most oropharyngeal cancers result from tobacco use; however, oropharyngeal cancer incidence has recently increased dramatically with the emergence of human papillomavirus (HPV)-associated squamous cell carcinomas. This increase occurred despite the reduced oropharyngeal cancer incidence rates since the late 1980s associated with reduced tobacco use since the mid-1960s. In men, the incidence of oropharyngeal cancer continues to increase in the United States, particularly in elderly men, whereas the increase is much less dramatic in women.

CARCINOGENESIS

Previously, tobacco use, including betel quid, snuff dipping (e.g., toombak),[4] and other smokeless tobacco, was the most important oropharyngeal cancer-related carcinogen along with alcohol.[5,6] In a New Zealand study of census and cancer registry data from 1981 and 1996, the standardized incidence rate ratio (SRR) of oropharyngeal cancer in current smokers versus never-smokers was 2.30 (95% CI: 1.94–2.72) after adjustment for age, sex, ethnicity, socioeconomic factors, confounding, and exposure misclassification.[7] Adjustment for residual confounding slightly reduced the SRR for oropharyngeal cancer. *N*-nitroso compounds (tobacco-specific *N*-nitrosamines, *N*′-nitrosonornicotine) in tobacco products are suspected carcinogens causing elevated

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TABLE 54.1. International Agency for Research on Cancer (IARC) classification of gastrointestinal tract cancer sites by sufficient and limited evidence of human carcinogenicity. (Adapted from Cogliano et al. and IARC).[1,2]

Anatomical Site	Carcinogens with *Sufficient* Human Evidence (Group 1)	Carcinogens with *Limited* Human Evidence (Groups 2A or 2B)
Oral cavity	Acetaldehyde associated with alcoholic beverage consumption, alcoholic beverages, betel quid with/without tobacco, human papillomavirus type 16, tobacco, smokeless, tobacco smoking	Bitumens occupational exposure during mastic asphalt work and roofing, human papillomavirus type 18
Salivary gland	Acetaldehyde associated with alcoholic beverage consumption, x- and γ-radiation	Iodine radionuclides including ^{131}I
Tonsil	Human papillomavirus type 16	
Pharynx, combined	Alcoholic beverages, betel quid with tobacco, human papillomavirus type 16, tobacco smoking	Asbestos (all forms), bitumens occupational exposure during mastic asphalt work and roofing, opium consumption, printing processes, secondhand tobacco smoke
Esophagus	Acetaldehyde with alcoholic beverage consumption, alcoholic beverages, betel quid with/without tobacco, smokeless tobacco smoking, x- and γ-radiation	Dry cleaning, opium consumption, pickled vegetables (traditional Asian), rubber production industry, very hot beverages (squamous cell carcinoma)
Stomach	*Helicobacter pylori*, rubber production industry, tobacco smoking, x- and γ-radiation	Art glass, glass containers and pressed ware manufacturing, asbestos (all forms), Epstein–Barr virus, inorganic lead compounds, nitrate or nitrite (ingested under conditions causing endogenous nitrosation), pickled vegetables (traditional Asian), salted fish, Chinese-style, processed meat consumption
Colon and rectum	Alcoholic beverages, processed meat consumption, tobacco smoking, x- and γ-radiation, processed meat consumption	Asbestos (all forms), firefighting, night shift work, *Schistosoma japonicum,* red meat consumption
Anus	Human immunodeficiency virus type 1, human papillomavirus type 16	Human papillomavirus types 18, 33.
Liver	Aflatoxins, alcoholic beverages, *Clonorchis sinensis*, 1,2-dichloropropane, Estrogen–progestogen contraceptives, hepatitis B virus chronic infection, hepatitis C virus chronic infection, *Opisthorchis viverrini,* plutonium, thorium-232 and its decay products, tobacco smoking (in smokers and smokers' children), vinyl chloride	Androgenic (anabolic) steroids, arsenic and inorganic arsenic compounds, betel quid without tobacco, DDT, dichloromethane (methylene chloride), human immunodeficiency virus type 1, *Schistosoma japonicum*, trichloroethylene, x- and γ-radiation
Bile duct	*Clonorchis sinensis* infection, 1,2-dichloropropane, *Opisthorchis viverrini*, plutonium, thorium-232 and its decay products, tobacco smokers	Androgenic (anabolic) steroids, arsenic and inorganic arsenic compounds, betel quid without tobacco, DDT, dichloromethane (methylene chloride), hepatitis B virus chronic infection, hepatitis C virus chronic infection, *Schistosoma japonicum*, trichloroethylene, x- and γ-radiation
Gallbladder	Thorium-232 and its decay products	
Pancreas	Smokeless tobacco, tobacco smoking	Alcoholic beverages, opium consumption, red meat consumption, thorium-232 and its decay products, x- and γ-radiation

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oropharyngeal cancer risks.[8] As tobacco use decreased since the mid-1960s, the incidence of oropharyngeal cancer also decreased along with reductions in some smokeless tobacco related carcinogen concentrations (e.g., *N*-nitrosodiethanolamine, *N*-nitrosomorpholine).[9]

Many of the newly diagnosed cases of oropharyngeal cancer do not have the traditional tobacco/alcohol risk factors for oropharyngeal cancer. In the US and Europe, human papillomavirus (HPV) accounts for 60–70% of oropharynx squamous cell carcinomas. Although there are over 100 HPV serotypes, almost 90% of HPV^+ oropharyngeal cancers develop from HPV16 infections.[10,11] These viruses infect basal keratinocytes in mucous membranes and skin, producing elevated risks of multiple cancers including anus, cervix, penis, vagina, and vulva. Other head and neck cancers (e.g., oral cavity, hypopharyngeal, nasopharyngeal, laryngeal) are usually HPV^-.[12]

HPV is a circular, double-stranded DNA virus encoding eight early genes (E1–E8) involved with host cell transformation and two late genes (L1, L2). HPV-associated carcinogenesis results from viral DNA integration, oncogene activation, cell proliferation, and neoplastic transformation. Integration of viral DNA into the human keratinocyte nuclear DNA and subsequent oncogenic protein E6/E7 mRNA expression promote the carcinogenic process. Integration of high-risk HPV (e.g., HPV16) causes insertional mutagenesis that produces chromosomal instability, double strand breaks, and precancerous lesions. The transcription of E6/E7 promotes cellular transformation by blocking inhibitory cell cycle regulators (p53, Rb1, Rb2). E6 binds tumor-suppressor protein p53 resulting in ubiquitination and proteasomal p53 degradation, whereas E7 binds pRb (retinoblastoma protein) allowing unrestrained cell proliferation and enhanced p16 expression.[13] The combined effects of E6/E7 oncoprotein production cause loss of cell cycle checkpoint control, genetic alterations, and abrogation of p53-dependent apoptosis.[14]

The immunohistochemical staining of p16 and p53 helps distinguish tobacco-induced from HPV-induced oropharyngeal cancers because tobacco-related cancers typically display high p53 and low p16 expression. Late capsid proteins (L1, L2) encapsidate viral genomes in the cornified skin layers followed by shedding of mature virions. The immune system clears most HPV infections with only ~1/2 of the cases developing antibodies to HPV.[10] HPV^- oropharyngeal squamous cell carcinomas are epidemiologically similar to the traditional squamous cell carcinoma of the oropharynx. In contrast to HPV-associated cervical cancer, no screening test reliably predicts neoplastic transformation after HPV exposure.[15]

EXPOSURE

Traditionally, tobacco smoking/chewing and, to a lesser extent, heavy alcohol consumption accounted for most oropharyngeal cancers;[16] residual confounding from inaccurate evaluation of lifetime alcohol exposures complicates the determination of the exact role of alcohol in the development of oropharyngeal cancer. In the INHANCE consortium study, most oropharyngeal cancer cases resulted from tobacco alone or the combined use of tobacco and alcohol with relatively few cases attributed to alcohol drinking alone.[16] The recent increased incidence of oropharyngeal cancer from human papillomavirus (HPV)-associated squamous cell carcinomas has unique epidemiological, molecular, and clinical characteristics, as displayed in Table 54.2. The incidence of HPV-associated oropharyngeal cancer has dramatically increased, particularly in elderly men. In 2005–2006, prior to the introduction of the 9 valent-HPV vaccines in 2014, seropositivity for any of the 9 HPV serotypes included in the Gardasil® vaccine (Merck & Co., Inc. West Point, PA) was ~40% for US females aged 14–59 years and ~20% for US males aged 14–59 years.[17] The highest seropositivity rate was 52.4 (95% CI: 46.5–58.3) for US women aged 30–39 years. The overall seropositive rate for HPV16/18 was 18.3%; however, HPV seropositivity does not necessarily reflect the HPV-related cancer status of an individual patient. Of over ¾ of individuals developing an HPV infection, only a fraction will seroconvert and many of these patients will subsequently lose their seropositivity.[18] Typically, HPV infections are sexually transmitted and asymptomatic with skin-to-skin transmission possible.

HISTOLOGY

Although pharynx commonly refers to nasopharyngeal, hypopharyngeal, and oropharyngeal locations, at least 80% of pharyngeal cancers occur in the oropharynx.[18] The oropharynx exists between the soft palate superiorly and the hyoid bone inferiorly, being continuous with the oral cavity anteriorly, the nasopharynx superiorly, and the supraglottic larynx and hypopharynx inferiorly. Most head and neck cancers are squamous cell carcinomas resulting from hyperplasia of squamous epithelium in the basal layer of the mucosal surfaces. Oral erythroplakia and leukoplakia represent red or white dysplastic, precancerous lesions, respectively, with ~20% of these lesions progressing to oral cancers, primarily tongue and buccal mucosa;[19] however, the absence of precancerous lesions among individuals with oropharyngeal cancer probably reflects the difficulty accessing deep tonsillar crypts.[20]

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TABLE 54.2. Tumor characteristics separating human papillomavirus poitive (HPV^+) and human papillomavirus negative (HPV^-) oropharyngeal cancers. (Adapted from Mallen-St Clair).[12]

Characteristic Tumor Signature	HPV^+	HPV^-
Molecular	Wild type p53, ↑p16, ↓Rb, ↓p53	Mutated p53, genomic instability, mutations ↑
Pathogenesis	E6/E7-induced cell transformation	Tobacco/alcohol use, poor oral hygiene with chronic inflammation/free radical formation causing DNA damage
Cell composition	B cells, NK cells, T cells (CD3+, CD4+, CD8+, CD34+), monocytes	Epidermal, dermal, endothelial cells, keratinocytes, fibroblasts
Epidemiological	Younger, white males with multiple oral/vaginal sexual partners, marijuana use, better treatment response	Older, African American population, ethanol/tobacco use, poor oral hygiene, poor treatment response
Clinical	Early T stage with extensive nodal involvement. Cystic, multilevel tumor phenotype	Late T stage with typically less nodal disease
Histological	Non-keratinized, lobular growth infiltrated by lymphocytes, well or undifferentiated histology with basaloid morphology	Keratinized, moderately differentiated
Metastasis	Distant metastasis post-chemotherapy with distinct pattern in liver, lung, bone, and other tissues requiring alternate surveillance strategies	Local and lung metastasis with relatively less distant metastasis pattern to bone, liver, and other sites

The epidermal growth factor receptor (EGFR) signaling pathway is highly upregulated in oral precancerous lesions; increased expression of this pathway strongly predicts the potential for malignant transformation.[21] Most oropharyngeal cancers associated with HPV occur in the lingual/palatine tonsils or base of the tongue; papillomaviruses typically infect basal epithelial cells of the reticulated epithelium lining the tonsillar crypts through localized wounds or abrasions.[11,22] Although HPV DNA exists in squamous cell carcinomas from other subsites of the upper aerodigestive tract (i.e., oral cavity, larynx, hypopharynx), HPV^- squamous cell carcinomas are most common in the oropharynx, whereas the role of HPV in the development of cancer at other aerodigestive subsites is unclear. Consequently, the presence of HPV DNA in a carcinoma does not necessarily imply causality.[10] Histologically, HPV^+ oropharyngeal cancers are usually basaloid, non-keratinizing, lymphoepithelial, or poorly differentiated.[23]

HOST SUSCEPTIBILITY

Genetic polymorphisms and variations in immune function may increase the risk of HPV^+ oropharyngeal squamous cell carcinomas;[24] however, the role of these potential risk factors is not well defined. Retrospective observational studies of diabetics suggest a slightly elevated risk of oropharyngeal cancer in diabetics. In a retrospective cohort study using the Taiwan Longitudinal Health Insurance Research Database containing 89,089 newly diagnosed diabetics and nondiabetic controls matched for comorbidities (coronary artery disease, hyperlipidemia, hypertension, obesity), sex, and age, the adjusted hazard ratio was 1.53 (95% CI: 1.01–2.31).[25] In general, the presence of the germline gene variants of DNA repair genes in Fanconi syndrome increases the risk of non-HPV head and neck cancers.

CLINICAL FEATURES

Overall, the incidence of head and neck cancers is about 2–4 times higher in men than women. The typical oropharyngeal, HPV^+ cancer patient is a middle-aged, nonsmoking Caucasian with higher socioeconomic status and a history of multiple orogenital sexual partners. Compared with tobacco-related oropharyngeal cancer, the diagnosis of HPV^+ oropharyngeal cancer usually occurs earlier (i.e., median age, 55–60 years) than HPV^- oropharyngeal cancer; however, the incidence of HPV^+

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oropharyngeal cancer in elderly patients (i.e., >65 years) is increasing. In an analysis of 40,264 cases of HPV^+ oropharyngeal cancer from the Surveillance, Epidemiology, and End Results (SEER) database (2000–2012), ~33% were aged ≥65 years and ~80% were male.[26] HPV^+ oropharyngeal cancer often presents as an asymptomatic neck mass. Potential symptoms include dysphagia, odynophagia, and earache.

The TNM staging system refers to the size and extent of the tumor (T), the number of positive local nodes (N), and the presence of metastasis (M). Patients with HPV^+ oropharyngeal cancer usually present with asymptomatic, small primary oropharyngeal tumors (T1, T2) and symptomatic cystic nodal disease (N1–N3). Cervical nodal metastasis without an obvious primary tumor is a classic presentation of HPV^+ oropharyngeal cancer; however, the anatomical distribution of positive cervical nodes is similar between HPV^+ and HPV^- oropharyngeal cancers.[27] Prognosis depends on tumor site, HPV status, age, and overall stage. Despite the presence of advanced nodal disease, survival rates are typically higher and recurrence rates lower in HPV^+ than HPV^- squamous cell cancers, in part, due to the increased chemo-radiosensitivity of HPV^+ tumors.[28,29] Recurrence that occurs in HPV^+ patients usually occurs at distant, nonpulmonary sites. The overall 3-year survival for HPV^+ patients with oropharyngeal squamous cell cancer is 93% for never-smokers or light smokers with a low N stage (ipsilateral disease) and 71% for nonsmokers with tumor stage T2 or T3 compared with 46% in high-risk patients.[29] Analysis of the SEER database indicates the estimated 3-year cause-specific survival is worse in elderly patients (60.8%, 95% CI: 59.6–61.9%) compared with 75.7% (95% CI: 75.1–76.4%, $P < 0.001$) in patients aged 45–64 years.[26] HPV vaccination is a conceptually safer preventative strategy than tonsillectomy based on current data.[30]

ESOPHAGUS

Worldwide in the 2010s, esophageal cancer was the eighth most commonly diagnosed cancer (~450,000 cases/year) and the sixth most common cause of cancer-related deaths (~400,000/year).[31] In the United States, the annual incidence of esophageal cancer is ~18,000 with ~16,000 annual esophageal cancer-related deaths; the lifetime risk of esophageal cancer in the United States is 1/125 men and 1/400 women.[32] The incidence of esophageal cancer modestly declined since 2004 compared with the squamous cell carcinoma subtype that plateaued in the middle 2010s. The geographical distribution of esophageal squamous cell carcinoma is highly uneven between and within countries, with the highest worldwide esophageal cancer incidence rates occurring in two geographical regions, including north central China, Golestan Province in Iran, Kenya, South Africa, Southern Brazil, and Uruguay.[33,34] The two main histological subtypes of esophageal cancer are squamous cell carcinoma and adenocarcinoma, with the prominent histological subtype depending on geography and smoking prevalence. Most esophageal cancers are squamous cell carcinomas, with cigarette smoking and heavy alcohol consumption being the major risk factors; the incidence varies 8–10-fold between countries.[35] Although esophageal squamous cell carcinoma represents ~90% of esophageal cancers worldwide, dramatic increases in esophageal adenocarcinoma cancer incidence in Western countries (e.g., Australia, New Zealand, the United Kingdom, Europe, Canada, the United States) resulted in this subtype becoming the predominant esophageal cancer histological subtype in these countries.[36] Figure 54.1 displays historical changes in the US incidence rates for esophageal adenocarcinoma and esophageal squamous cell carcinoma from 1973–2011. The dramatic increase in Western countries slowed after 2000. Recent data from the latter suggest overall declining esophageal cancer rates in US men and women.[37] The overall rate of increasing age-related, esophageal adenocarcinoma incidence declined from 8.4% 1975–1997 to 1.1% (95% CI: 0.2–2.1%) for the time interval 1997–2014 based on the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data.[33]

CARCINOGENESIS

Tobacco-specific nitrosamines [e.g., *N*′-nitrosonornicotine, NNN; 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, NNK] and polycyclic aromatic hydrocarbons are major carcinogens in tobacco. Urinary *N*′-nitrosonornicotine was strongly correlated with esophageal squamous cell carcinoma in the Shanghai Cohort Study of 77 esophageal cancer cases (subtype unreported) and 223 matched controls.[38] The odds ratio of esophageal cancer comparing the first and third tertiles of total NNN was 17.0 (95% CI: 3.99–72.8); however, the wide confidence limit suggests an imprecise OR. Esophageal squamous cell carcinomas contain numerous molecular alterations, particularly TP53 alterations. The diversity of TP53 mutations in esophageal squamous cell carcinomas reflects tumor heterogeneity; however,

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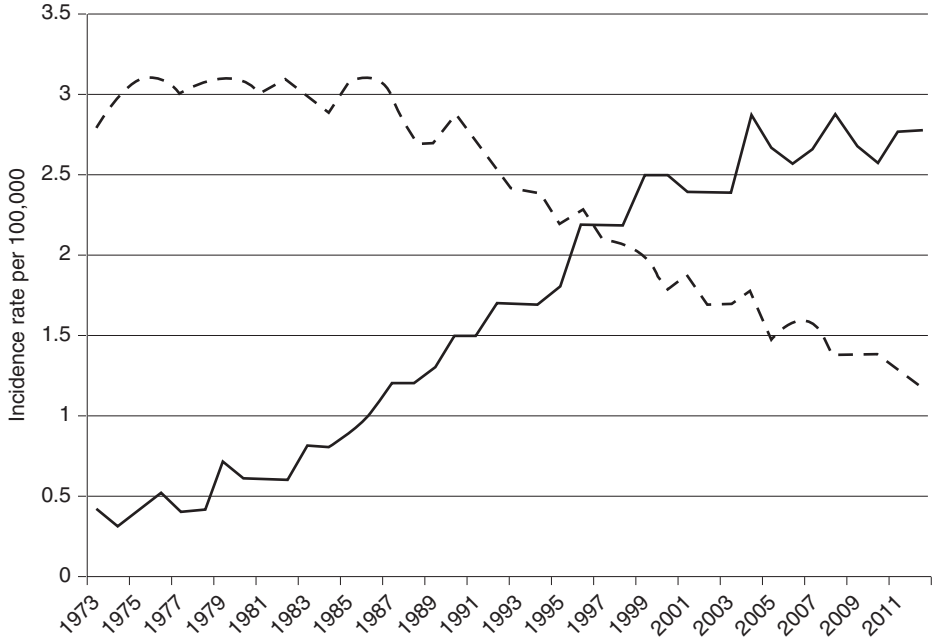


FIGURE 54.1. US historical change rates per 100,000 for declining esophageal squamous cell carcinoma incidence (dashed line) and increasing esophageal adenocarcinoma incidence (solid line) 1973–2011, based on US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data. (Adapted from Day).[33]

the proportion of TP53 mutation-containing tumors does not always predict differences in tumor incidence between various geographical regions.[39] In a study of 56 esophageal squamous cell carcinomas in north central China, at least one oncogenetic alteration occurred in 96% of the tumors, including 77% with mutations and 73% with allelic loss in the gene; 75% had ≥2 alterations.[40] Whole exome sequencing detected an average of 83 mutations/esophageal squamous cell carcinoma tumor ($n = 12$), with the most frequent mutations in *TP53* (92%), *NOTCH1* (33%) and *NOTCH3* (25%) genes.[41] Inactivating NOTCH1 mutations appeared in none of the 11 esophageal adenocarcinomas sequenced in this study.

A comparison of US and north central Chinese esophageal squamous cell tumors indicated the NOTCH1 mutation was much more frequent in the US than in Chinese tumors, suggesting environmental factors (e.g., polycyclic aromatic hydrocarbon exposure, thermal injuries, poor nutrition) rather than tobacco/alcohol use are major risk factors for Chinese tumors. Most mutations found in esophageal adenocarcinomas were previously present in patients with Barrett's esophagus, suggesting a clonal evolution promoted by chronic inflammation.[42] Tissues progressing to cancer acquire few alterations to genomic structure (e.g., cop-number alterations, heterozygous events).

EXPOSURE

The main risk factors for developing esophageal adenocarcinoma include gastroesophageal reflux disease, obesity, and cigarette smoking, which account for ~70% of esophageal adenocarcinoma cases in Western populations depending on the country and year. The primary risk factors for esophageal squamous cell carcinoma are cigarette smoking and heavy alcohol consumption, particularly in men. In an Australian population-based, case-control study of 305 esophageal squamous cell carcinoma cases and 1554 controls, the partial population-attributable fraction of these cancers in men attributed to the combination of heavy alcohol (>17 drinks/week) and cigarette smoking (>30 pack-years) was 77.7% (95% CI: 65.5–86.5%).[43] The main risk factors for these two esophageal cancer subtypes differ substantially as displayed in Table 54.3.

Occupation

Esophageal cancer subtypes are not strongly associated with occupational exposures. In a population-based, case-control study of 99 cases of esophageal cancer, logistic regression analyses of 35 occupational agents indicated sulfuric acid exposure (OR = 2.8, 95% CI:

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TABLE 54.3. Direction of major risk factors associated with esophageal adenocarcinoma and esophageal squamous cell carcinoma. (Adapted from Day).[33]

Risk Factor	Adenocarcinoma	Squamous Cell Carcinoma
Male sex	↑	↑
Cigarette smoking	↑	↑
Gastroesophageal reflux	↑	None
Barrett's esophagus	↑	None
Helicobacter pylori infection	↓	None
Obesity	↑	↓
Alcohol	None	↑
Nonsteroidal anti-inflammatory drugs	↓[a]	↓

[a] The direction of the effect of nonsteroidal anti-inflammatory drugs on the risk of adenocarcinoma in patients with Barrett's esophagus is conflicting, but probably small to clinically insignificant.

1.2–6.2) demonstrated the strongest association between chemical exposure and esophageal cancer based on retrospective analysis of job histories.[44] After adjusting for risk factors, the statistical significance of the association between carbon black and esophageal cancer was borderline, whereas the association of asbestos, mineral spirits, toluene, and other paints with esophageal cancer was equivocal. Other studies also indicate that the association between asbestos and cancer of the esophagus remains controversial. A large study of insulation workers revealed a small excess risk of esophageal cancer, as defined by a standardized mortality ratio of ~2.[45] Re-evaluation of the cohort data correcting the data for improper classification of lung cancers suggested an elevated risk for esophageal cancer of ~1.5.[46] Subsequent cohort studies have not confirmed the relationship between esophageal cancer and asbestos exposure; a review of these cohort studies did not find a consistent statistical association or a dose-response relationship between asbestos exposure and cancer of the esophagus.[47] In a 10-year follow-up study of 14,515 male subjects in an occupational asbestos exposure program (ARDCo Program), the hazard ratios for esophageal cancer (subtypes unreported) and cumulative asbestos exposure index were borderline (HR = 1.26, 95% CI: 1.00–1.58, $n = 33$) after adjusting for smoking.[48]

A meta-analysis of 92 studies covering 161 populations with results for 23 agents suggested that the following chemical exposures were most strongly associated with esophageal cancer: some chlorinated hydrocarbon solvents, nickel compounds, and hexavalent chromium.[49] Other chemicals potentially associated with esophageal cancer in exploratory studies include silica dust and detergents;[50] however, more data are necessary before a causal link can be established between *any* of these chemicals and esophageal cancer. A Swedish population-based, case-control study of 189 cases of esophageal adenocarcinoma and 820 age- and sex-matched general population controls indicated that airborne occupational exposures probably were not major risk factors for the development of this type of cancer, based on personal interviews.[51]

Lifestyle

In the United States, strong risk factors for the development of esophageal squamous cell carcinomas are smoking and heavy alcohol consumption; esophageal adenocarcinoma is associated with cigarette smoking but not heavy alcohol consumption, as displayed in Figure 54.1. Similarly, the use of betel quid and smokeless tobacco is associated with both esophageal cancer subtypes. Observational studies suggest nonsteroidal anti-inflammatory drug use is associated with a modest reduction in esophageal adenocarcinoma and squamous cell carcinoma,[52,53] whereas *Helicobacter pylori* infections are associated with reduced risk of esophageal adenocarcinoma but not esophageal squamous cell carcinoma.[54] Esophageal adenocarcinoma and probably squamous cell carcinoma are not associated with human papillomavirus (HPV) infection;[55,56] however, the frequency of HPV DNA in esophageal cancer is highly variable. Although some studies suggest a cohort of esophageal squamous cell carcinomas within certain geographical regions may be associated with HPV infections,[57] HPV detection rates are too low to confirm HPV as a definite esophageal squamous cell carcinoma risk factor.[58]

Other potential risk factors include reduced consumption of fruits and vegetables;[59,60] however, controlling bias and confounding, limiting measurement errors, and heterogeneity in nutritional or composite dietary pattern studies are complicated and challenging. Many cohort studies fail to associate individual foods or nutrients with reduced esophageal squamous cell carcinoma risks. Evaluation of dietary and nutritional

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studies by the World Cancer Research Fund International/American Institute for Cancer Research did not support strong evidence of reduced esophageal cancer risks from the ingestion of any food, nutrient, fiber, or dietary supplement.[61] Limited evidence suggests ingestion of fruits/vegetables reduces esophageal squamous cell carcinoma risks and vegetables reduce esophageal adenocarcinoma risks, whereas processed meats may increase esophageal squamous cell carcinoma risks. Evidence supported a probable association between regular consumption of hot maté and esophageal squamous cell carcinomas in the World Cancer Research Fund International/American Institute for Cancer Research evaluation.

Analysis of the strength of evidence by the World Cancer Research Fund International/American Institute for Cancer Research for vegetable intake and esophageal adenocarcinomas suggested an inverse relationship of $RR_{100\,g/day} = 0.89$ (95% CI: 0.80–0.99, $n = 3$). For esophageal squamous cell carcinoma, the risk for fruit consumption was inverse ($RR_{100\,g/day}$ of 0.84 (95% CI: 0.75–0.94, $n = 3$) and for processed meats increased ($RR_{50\,g/day}$ of 1.59, 95% CI: 1.11–2.28, $n = 3$).[62] Most of the evidence involved small numbers of case-control studies because of the rarity of esophageal adenocarcinoma. In a meta-analysis of 20 case-control and 5 cohort studies on fresh fruit and esophageal cancer risks using random effects models, fresh fruit reduced the relative risk of esophageal squamous cell carcinoma (RR = 0.59, 95% CI: 0.47–0.76, $I^2 = 60.7\%$, $P = 0.002$), whereas fruit intake was not associated with esophageal adenocarcinoma risks (RR = 0.86, 95% CI: 0.74–1.01, $I^2 = 0.0\%$, $P = 0.598$).[63] Of the 25 studies, 10 were from Europe, 6 from Asia, 6 from the United States, and 3 from South America. A meta-analysis of 12 observational Asian studies of green tea and esophageal cancer did not detect a significantly increased risk for green tea drinkers.[64] The pooled summary relative risk was 1.09 (95% CI: 0.76–1.55, $I^2 = 75.5$) comparing the greatest and non/least green tea drinkers; heterogeneity was substantial. The meta-analysis did not evaluate esophageal cancer subtypes.

Tobacco

Cigarette smoking is a major risk factor for esophageal adenocarcinoma and squamous cell carcinoma. In a pooled analysis of 10 population-based, case-control, and 2 cohort studies from the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON), the summary OR for esophageal adenocarcinoma in white non-Hispanic men and women was 1.96 (95% CI: 1.64–2.34) comparing ever- and never-cigarette smokers.[65] The dose-response relationship for esophageal adenocarcinoma and pack-years of cigarette smoking was statistically significant ($P_{trend} < 0.001$) using multivariable logistic regression models adjusted for age, sex, body mass index, education, and gastroesophageal reflux. The effect of cigarette smoking on esophageal adenocarcinoma rates may persist long-term (e.g., for 20 years).[66] In an Australian population-based, case-control study comprising 367 esophageal adenocarcinomas, 309 esophageal squamous cell carcinomas, and 1,580 age-matched general population controls, the OR for esophageal adenocarcinoma comparing ever- and never-cigarette smokers was 1.7 (95% CI: 1.3–2.3).[67]

Case-control studies suggest the relative risks of esophageal squamous cell cancer increase up to 9-fold when comparing current smokers and nonsmokers. The OR for esophageal squamous cell carcinoma in the Australian case-control study was elevated (OR = 2.8, 95% CI: 2.0–4.0) comparing ever- and never-smokers.[67] In the prospective NIH–AARP Diet and Health Study of 474,606 US participants using Cox models adjusted for potential confounders, the hazard ratio for esophageal squamous cell carcinoma was 9.27 (95% CI: 4.04–21.29); however, the wide confidence interval suggests an imprecise hazard ratio.[68] The attributable risks in economically developing countries appear lower (e.g., RR = ~1.5).[69]

Alcohol

Several issues complicate the establishment of alcohol consumption as a risk factor for esophageal cancer, including heterogeneity of consumption patterns, difficulty detecting potential nonlinear, dose-response associations, and misclassification of lifetime alcohol consumption. Most existing studies consistently demonstrate a dose-response relationship between esophageal squamous cell carcinomas and alcohol consumption in low- and high-incidence regions, particularly among heavy drinkers (e.g., 6–9 fold in Western countries with low incidences of this cancer).[70] Evidence for an association between heavy alcohol consumption and esophageal adenocarcinoma is weak and inconsistent, lacking a dose-response relationship, including the risk of developing Barrett's esophagus.[71,72] In an Australian study of self-reported consumption in 1,530 participants from the general population and 365 cases of esophageal squamous cell carcinoma, the overall OR comparing the highest estimated lifetime weekly alcohol consumption (≥420 g) with nondrinkers (<10 g) was 4.67 (95% CI: 2.28–9.55).[73] The dose-response

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curve was j-shaped with no increased risk below lifetime weekly alcohol consumption below 210 g. In a Spanish case-control study of self-reported alcohol consumption in hospital-based controls and esophageal squamous cell carcinoma cases, the odds ratio comparing never-drinkers and current drinkers was 4.48 (95% CI: 1.69–11.83, $n = 123$) after adjustment for age, sex, province, educational level, and tobacco smoking.[74] A large prospective cohort study (NIH–AARP Diet and Health Study) of 474,606 US participants using Cox models adjusted for potential confounders detected an elevated hazard ratio for esophageal squamous cell carcinoma of 4.93 (95% CI: 2.69–9.03) comparing daily alcohol consumption of >3 drinks and ≤1 drink.[68] However, the hazard ratio for nondrinkers relative to light drinkers (0–1 drink/day) was significantly elevated (HR = 2.06, 95% CI: 1.16–3.68), suggesting a lack of dose-response relationship and/or misclassification.

The Australian study did not demonstrate a similar increased risk for esophageal adenocarcinoma (OR = 0.89, 95% CI: 0.42–1.89) comparing lifetime heavy alcohol drinkers (≥420 g) with nondrinkers (<10 g).[73] Although the age and sex distributions were similar between participating and nonparticipating cases, Australian privacy laws prevented evaluation of the low participation rate because further details on the medical and social characteristics of nonparticipating cases were unavailable. The participation rate for eligible controls was 51%.

Obesity

Although the obesity epidemic in Western countries may account for some of the increased incidence of esophageal adenocarcinoma, the increasing incidence started before the beginning of the obesity epidemic. The association between obesity and esophageal reflux disease complicates the interpretation of studies associating obesity with esophageal adenocarcinoma because of the potential for residual confounding. Abdominal visceral obesity rather than BMI appears to be more closely associated with GERD and erosive gastritis.[75] Qualitative assessments using disease simulation modeling suggest the effect of obesity on esophageal adenocarcinoma rates is a relatively small portion (~6–7%) of the increased esophageal adenocarcinoma risk in the United States.[76] In an analysis of data from the BEACON consortium comprising 12 European, Australian, and North American studies, the OR for esophageal adenocarcinoma comparing cases with BMI of <25 and ≥40 was 4.76 (95% CI: 2.96–7.66), with evidence of a synergistic interaction between the presence of GERD and BMI.[77] In a pooled analysis of a European consortium of seven prospective studies (Metabolic Syndrome and Cancer cohort), BMI was associated with increased risk of esophageal adenocarcinomas (RR = 7.34, 95% CI: 2.88–18.7) comparing the highest (mean = 31.3 ± 3.3) and lowest (mean = 20.7 ± 1.5) BMI quintiles adjusted for sex, age at baseline (continuous), and smoking status.[78] The adjusted relative risk for esophageal adenocarcinoma comparing participants with BMIs of ≥ 30 and 18.5–25 (normal weight) was 3.29 (95% CI: 1.82–5.95).

Childhood and adolescent BMI may correlate more strongly with esophageal adenocarcinoma risks in later life than BMI.[79] Additionally, the effect of typical male obesity (abdominal circumference, ↑ waist circumference) and female obesity (gluteofemoral, ↑ hip and thigh subcutaneous fat) on esophageal adenocarcinoma risks may differ; however, the findings demonstrate inconsistent results and substantial heterogeneity depending on how obesity risk factors are measured. In a pooled analysis of data from the international BEACON consortium, waist circumference was significantly associated with Barrett's esophagus independent of BMI. Comparing the fourth and first quartiles of waist circumference, the OR was 1.87 (95% CI: 1.22–2.87),[80] whereas analysis of data from this consortium suggests an inverse association between gluteofemoral obesity and Barrett's esophagus in women and men.[81] Male predominance as a risk factor for esophageal adenocarcinoma persists at similar levels when comparing lean and overweight individuals.[82] Esophageal squamous cell carcinoma is not associated with GERD and inversely associated with obesity. Analysis of data from the Metabolic Syndrome and Cancer cohort (Me-Can project) demonstrated an adjusted RR for esophageal squamous cell carcinoma in participants with BMI of ≥ 30 of 0.47 (95% CI: 0.24–0.94, $n = 184$) compared with normal weight participants (BMI = 18.5–25).[78]

Diseases

Barrett's Esophagus

Barrett's esophagus is an acquired, dysplastic, precancerous lesion associated with an increased esophageal adenocarcinoma risk, but not squamous cell carcinoma. The lifetime risk of esophageal adenocarcinoma in an analysis of data from the Northern Ireland Barrett's esophagus Register was 5.8% for men and 3.0% for women.[83] About 6–12% of patients with GERD develop Barrett's esophagus, with 0.5–1% evolving into esophageal adenocarcinoma.[84] Although the presence

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of Barrett's esophagus increases esophageal adenocarcinoma risks at least 10-fold, small absolute risks limit the effectiveness of surveillance programs because of the rarity of esophageal adenocarcinoma. In a study of 11,028 patients with Barrett's esophagus from the Danish Pathology Registry and the Danish Cancer Registry followed for a median of 5.2 years, the relative risk of adenocarcinoma among patients with Barrett's esophagus was 11.3 (95% CI: 8.8–14.4) compared with the general population.[85] Barrett's esophagus is more frequently associated with factors that increase esophageal adenocarcinoma risks, including Caucasian men of >50 years of age, smokers, gastroesophageal reflux, and obesity.[86] Positive studies associating Barrett's esophagus with obesity more commonly involve central obesity (abdominal circumference, waist/hip ratio) than BMI or overall body fat content.[87] Potential chemopreventions for reducing increased esophageal adenocarcinoma risks from Barrett's esophagus include aspirin, nonsteroidal anti-inflammatory drugs, statins, and proton pump inhibitors;[88] however, none of these potential therapies have been validated in large-scale studies with long-term follow-up and tight control of confounding factors.

Genetic variants contribute relatively little to the increased risk of esophageal adenocarcinoma.[89] Approximately 7% of Barrett's esophagus occur in families with other familial cases; these esophageal adenocarcinomas usually develop at an earlier age than sporadic cases. Furthermore, typical risk factors for esophageal adenocarcinoma are less common in familial than sporadic cases. Candidate gene and genome-wide association studies suggest up to 1/3 of esophageal adenocarcinoma tumors may result from combinations of germline mutations; however, single nucleotide polymorphisms probably account for <20% of esophageal adenocarcinomas developing from Barrett's esophagus.[90]

Gastroesophageal Reflux Disease (GERD)

Gastrointestinal reflux disease is a major risk factor for esophageal adenocarcinoma. In a Swedish population-based, case-control study of 189 patients with esophageal adenocarcinoma and 820 controls, the odds ratio for esophageal adenocarcinoma was 7.7 (95% CI: 5.3–11.4) comparing participants with at least weekly self-reported symptoms and participants with less than weekly symptoms.[91] The esophageal adenocarcinoma risk was particularly high for participants with more severe reflux lasting for >20 years (OR = 43.5, 95% CI: 18.3–103.5). Classification was based on patient interviews; the large confidence interval suggests imprecise OR estimates.

The risk of esophageal squamous cell carcinoma was not associated with gastroesophageal reflux (OR = 1.1; 95% CI: 0.7–1.9) consistent with most studies.[33] In a pooled analysis of data from five population-based, case-control studies in the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) involving 1,128 esophageal adenocarcinoma cases and 4,057 controls from the general population, the summary odds ratios for at least weekly self-reported symptoms of GERD were 4.81 (95% CI: 3.39–6.82) and 7.96 (95% CI; 4.51–14.04) for daily symptoms.[92] The results demonstrated a dose-response relationship with duration of self-reported symptoms; for symptoms lasting for >20 years, the OR was 6.24. The results were not adjusted for cigarette smoking or alcohol use.

HISTOLOGY

The two primary histological types of esophageal cancer are squamous cell carcinoma and adenocarcinoma. Barrett's esophagus is a premalignant condition occurring in ~15% of patients with gastroesophageal reflux disease; this condition is a precursor lesion for the development of esophageal adenocarcinoma involving the replacement of the normal squamous cell lining of the distal esophagus with metaplastic columnar intestinal epithelium. Tumor development involves a progression from erosive esophagitis to nondysplastic Barrett's esophagus, low-grade dysplasia, high-grade dysplasia, adenocarcinoma *in situ*, and then invasive adenocarcinoma.[93]

Esophageal squamous dysplasia (ESD) is the primary histopathological precursor of esophageal squamous cell carcinoma, with increasing dysplasia grades predicting increased squamous cell carcinoma risk.[94] In a cohort study of 682 patients from a high-risk rural population in Linxian, China, undergoing endoscopy, 14.7% of 114 patients developed esophageal squamous cell carcinoma during the follow-up period of 13.5 years.[95] The relative risk of esophageal squamous cell carcinoma comparing grades of dysplasia with patients having a normal esophagus was statistically significant for moderate dysplasia (RR = 15.8, 95% CI: 5.9–42.2), severe dysplasia (RR = 72.6, 95% CI: 29.8–176.9), and carcinoma *in situ* (62.5, 95% CI: 24.1–161.9). The wide confidence limits indicate imprecise estimates. Approximately 8% of the endoscoped patients with a normal esophagus developed esophageal squamous cell carcinoma compared with 50% of patients with moderate dysplasia and 74% with severe dysplasia.

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HOST SUSCEPTIBILITY

Studies of family cancer histories suggest esophageal squamous cell carcinoma risk increases in families with histories of esophageal cancer. In a Chinese case-control study of 600 esophageal squamous cell carcinomas, the occurrence of esophageal cancer in a first-degree relative increases the odds ratio of developing esophageal squamous cell carcinoma (OR = 2.84, 95% CI: 2.09–3.86) compared with age-, gender-, and neighborhood-matched controls.[96] An Iranian study compared the risk of esophageal squamous cell carcinoma in 2,097 first-degree relatives of 167 esophageal squamous cell carcinoma cases and 2,783 first-degree relatives of the 200 Turkmen controls.[97] The hazard ratio of the risk to age 75 of esophageal squamous cell carcinoma in the first-degree relatives of Turkmen patients was 2.3 (i.e., reported as 34 vs. 14%).

Tylosis is a rare, autosomal-dominant syndrome characterized by non-epidermolytic palmoplantar keratoderma, oral precursor lesions (leukokeratosis), and a very high esophageal squamous cell carcinoma risk (i.e., up to 95% by age 65 years).[98] Genetic studies identified missense mutations in *RHBDF2* that encode the inactive rhomboid 5 homolog 2 protease (iRhom2) on chromosome 17q25 as the underlying cause of tylosis-associated esophageal squamous cell carcinomas. The subsequent dysregulation of the epidermal growth factor receptor EGFR signaling pathway causes cell proliferation and migration.

CLINICAL FEATURES

The clinical presentation of esophageal cancer results from direct effects of tumor growth on local and regional structures, with both main esophageal cancer subtypes demonstrating similar symptoms; the most common symptom is dysphagia following ingestion of solid foods. Esophageal adenocarcinoma incidence increases with age; however, diagnosis of this tumor in patients under 50 years of age is uncommon (i.e., <8%).[99] Multivariable logistic regression analysis of data from eight population-based, case-control studies (BEACON study) demonstrated a stronger association of younger patients (<50 years) with recurrent gastroesophageal reflux (OR = 8.06, 95% CI: 4.52–14.37) and BMI ($OR_{BMI \geq 30 \text{ vs. } <25} = 4.19$, 95% CI: 2.23–7.87) compared with older cases.[100] The epidemiology of esophageal adenocarcinoma demonstrates a marked male predominance in all populations that has changed little over the last three decades. In an analysis of the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) 9 data, the RR for esophageal adenocarcinoma comparing men with women was 7.49 (95% CI: 7.17–7.82).[101] Although the male/female ratio ranges up to 9/1, established risk factors do not explain the difference because the distribution of the major risk factors for this tumor is similar between men and women, with the possible exception of severe gastroesophageal reflux disease.[102] Consequently, the pathophysiology of this difference remains unclear. The prognosis for esophageal adenocarcinoma is generally poor, depending on the stage at diagnosis because of the late presentation and tumor aggressiveness. Approximate 5-year survival rates in the Northern Ireland Barrett's registry ranged from 80% for Stage I to 45% for Stage II, 17% for Stage III, and 2% for Stage IV.[89] Overall 5-year survivor rates are ~5–6%, with similar rates for men and women.[103]

Esophageal squamous cell carcinoma is more common in men than women (~2/1) overall, with the ratio varying from 4/1 in low-risk areas (e.g., the United States) to ~1/2 in high-risk areas (e.g., northern China).[104] Esophageal squamous carcinoma is a late complication (i.e., up to 40 years) of severe lye ingestions. The prognosis for esophageal adenocarcinoma is also poor, with an overall 5-year survival rate of ~20% and <3% for patients presenting with distant metastatic disease.[99]

STOMACH

From the 19th and first half of the 20th century to 1975, stomach cancer was the most common cause of cancer-related mortality in Western countries.[105] Worldwide, stomach cancer accounts for ~6% of all cancer diagnoses. Most stomach tumors are sporadic with familial susceptibility being much less common. About 10% of stomach cancers are familial gastric cancers as defined by two first- or second-degree relatives with gastric cancer before age 50 years or three first- or second-degree relatives with gastric cancer independent of age.[106] The most famous historical example of hereditary transmission of gastric carcinoma was Napoleon Bonaparte.[107] He had five first-degree relatives affected by gastric carcinoma in three consecutive generations. Although stomach cancer is now the fifth most commonly diagnosed cancer worldwide, it accounts for the third most common worldwide cause of cancer-related mortality.[108,109] During the last 50 years, the incidence of non-cardia (distal) gastric cancer

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has declined dramatically, whereas cardia gastric cancer (i.e., gastroesophageal junction adenocarcinoma) more closely follows the increasing incidence rates of esophageal adenocarcinoma as classified by recent stomach cancer subclassifications.[110,111] Potential reasons for the global decrease in non-cardia gastric cancer incidence include: 1) ↑ fresh fruit/vegetable availability with refrigeration; 2) ↓ reliance on preserved/salted foods; 3) ↓ smoking prevalence; and 4) ↓ *H. pylori* infections.

The initial decline of non-cardia gastric cancer corresponded to reduced nitrosamine consumption from preserved food sources and water contaminated by nitrates, particularly fresh fruits and vegetables followed by declines in the incidence of *H. pylori* infections. Stomach cancer incidence and mortality display substantial regional variation, with Japan, Korea, and China accounting for ~60% of newly diagnosed stomach cancers.[112] The distinct geographical differences in stomach cancer incidence strongly suggest that environment is a major determinant for developing stomach cancer, particularly geography, diet, and smoking. Compared with studies of Japan, China, Iceland, Chile, and Eastern Europe, stomach cancer incidence is relatively intermediate in Latin America and low in the United States and Western Europe.[113] Although stomach cancer incidence remains relatively high in East Asia, the implementation of advances in hygiene, sanitation, and food preservation/clean water supplies is rapidly reducing stomach cancer incidence in developing countries.[114]

CARCINOGENESIS

Gastric tumors display a complex and diverse array of genetic and epigenetic alterations. A variety of genes are upregulated in gastric tumors, including *HER2*, *PIK3CA*, *KRAS/NRAS*, *JAK2*, *RTK* (receptor tyrosine kinase), and *EGFR* (epidermal growth factor receptor).[115] These gene affect apoptosis, cell cycle progress, and inhibition of tumor suppressor gene expression/activity resulting in enhanced cell proliferation, invasion, and migration. The Cancer Genome Atlas Research Group (TCGA) molecular classification of gastric tumors includes microsatellite instable, EBV-positivity, chromosomal instable, and genomically stable categories based on next-generation sequencing data, as displayed in Figure 54.2.[116,117] The former two genetic profiles express programmed death-1 (*PD-1*) and programmed death ligand-1 (*PD-L1*) involving immune checkpoints, whereas chromosomal instable gastric cancers contain p53 mutations and receptor tyrosine kinase activating mutations (e.g., *HER2*, *EGFR* genes). Human epidermal growth factor receptor 2 (*HER2*) is a proto-oncogene located on chromosome 17q21 encoding a transmembrane protein with tyrosine kinase activity involving signal transduction pathways that enhance cell growth and differentiation. Overexpression of *HER2* occurs in ~18% of gastric tumors (range, ~4–53%).[118] *HER2*-positivity is a poor prognostic marker associated with decreased survival and tumor aggressiveness (serosal invasion, metastasis, higher disease stage).[119] Somatic mutations (e.g., indels) are also common in microsatellite instable gastric tumors, whereas global hypermethylation appears frequently in EBV-positive gastric cancers.[120]

EXPOSURE

Stomach cancer is a multifactorial disease involving epigenetic and, to a lesser extent, genetic factors; risk factors for stomach cancer vary with the two main subtypes (cardia, non-cardia). Cardia gastric and esophageal adenocarcinomas have similar risk factors, including gastroesophageal reflux, smoking, and obesity;[121] however, the association with the latter is relatively weak.[122] The association of cardia gastric cancer with alcohol consumption is conflicting with some positive[123] but more negative[124] mortality and incidence studies. Non-cardia gastric cancers of the distal stomach are associated with tobacco smoking, *H. pylori*, Epstein–Barr virus (EBV), and diet (primarily high dietary salt intake), but not with gastroesophageal reflux disease or obesity. *H. pylori* infections account for ~89% of non-cardia gastric cancers or more in high-risk areas. The actual risk depends on *H. pylori* virulence (viral genes CAGA, DUPA, ICEA1, NAPA, OIPA, VACA),[125] strain, host genetic diversity/inflammatory response (e.g., interleukin-1), and the presence of additional risk factors (e.g., smoking, high salt intake). In developing countries, ~1–3% of *H. pylori* infections progress to malignant tumors, whereas this rate may increase to 10% in high-risk locations.[108,126]

Environment

Helicobacter Pylori

Helicobacter pylori infections are the most consistent risk factor for non-cardia gastric cancer, with relative risks in the range of 3–6-fold for non-cardia gastric adenocarcinoma using ELISA testing and higher (i.e., up to 20-fold) using the more sensitive Western blot for assessing the prevalence of *H. pylori* infections.[127,128,129] In some high-risk Chinese regions, 50–85% of children

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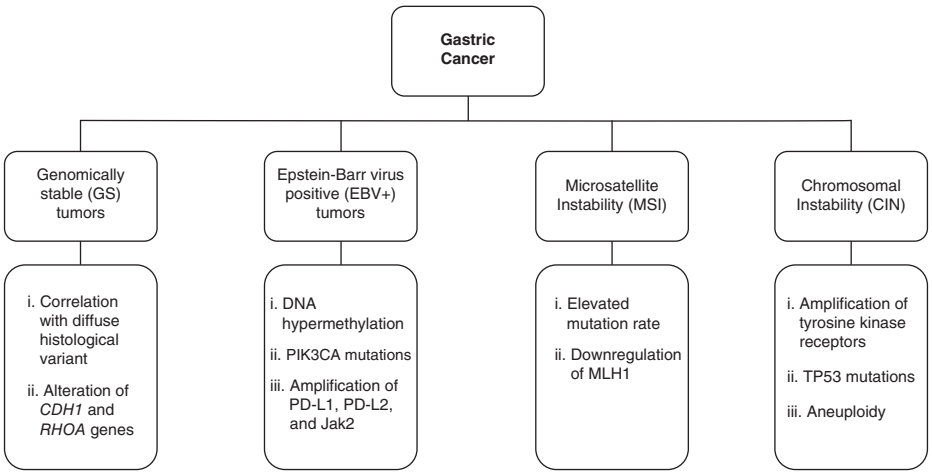


FIGURE 54.2. The Cancer Genome Atlas Research Group classification of gastric tumors with common molecular features. (Adapted from Carlomagno et al.).[116]

aged 3–10 years and 67% of adults with *H. pylori* infection are present in ~50% of the worldwide population and up to 92% in asymptomatic Bangladesh populations.[130,131] The incidence of gastric adenocarcinoma in Asia varies widely, with seropositive rates usually reflecting the incidence of non-cardia gastric adenocarcinoma; however, high seropositive prevalence rates in some Asian regions have relatively low incidence rates.[132] Enhanced risks of non-cardia gastric adenocarcinoma result from the complex interaction of host factors, environment, and *H. pylori* strain/virulence (e.g., CagA-positivity)[133] mediating cytokine-induced inflammatory response (e.g., tumor necrosis factor-α, IL-1β, IL-2, IL-8, IL-10).[134,135]

Epstein–Barr Virus (EBV)

Although ~9–10% of patients with gastric tumors are EBV-seropositive, much larger portions of the worldwide general population have asymptomatic chronic EBV infections.[136] Clinicopathological features of EBV-associated gastric tumors include proximal stomach location, lymphoepithelioma-like histology, male prominence, and relatively favorable prognosis. Gastric tumors contain multiple genetic and epigenetic alterations causing oncogene overexpression and inhibition of tumor suppressor genes, particularly DNA methylation and genetic alterations (e.g., PIK3CA and ARIDIA mutations, *JAK2* and PD-L1/L2 amplifications).[137,138] These abnormalities modify gene expression affecting cell proliferation, immune, migration, and apoptosis signaling pathways. Promoter DNA methylation is probably more frequent than DNA mutations. EBV infection promotes DNA methylation by upregulating DNA methyltransferase-3b (DNMT3b) resulting in transcriptional inactivation of tumor suppressor genes during early stomach carcinogenesis. Genome-wide studies indicate EBV-positive tumors demonstrate recurrent mutations of *PIK3CA* gene (p110α expression) along with *JAK2* (nonreceptor tyrosine kinase), *CD274* (immune inhibitory receptor ligand), and PDCD1LG2 (programmed cell death 1 ligand 2) amplification, among other genetic/epigenetic alterations.[139]

Occupation

The contribution of occupational exposures to the development of stomach cancer is relatively small and probably multifactorial; no single agent is a strong risk factor for stomach cancer. A Swedish population-based, case-control study of 189 cases of gastric cardia adenocarcinoma and 820 age- and sex-matched controls indicates airborne occupational exposures probably were not major risk factors based on personal interviews.[51] Hypothesis-generating studies suggest work in coal and tin mining, metal processing (steel, iron), and rubber manufacturing industries increases stomach cancer risks.[140] The IARC listed the latter as a human carcinogen (Group 1) in 1982. Several analyses of occupational incidence and mortality data demonstrate consistent elevations of stomach cancer rates in rubber workers, particularly in processing, tire building, and manual labor sections where dust, fumes, coal tar products, antioxidants, and carbon black are potential carcinogens;[141,142] however, co-exposure of these workers to other carcinogens (e.g., aromatic amines, asbestos,

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benzene) complicates interpretation of data from earlier studies, particularly for workers employed before the 1960s. A review of epidemiological studies of cancer risks in rubber industry workers including 12 cohort studies in 9 countries, 7 industry-based, nested case-control studies, 48 community-based, case-control studies in 16 countries, and 23 studies based on administrative data was inconsistent with stomach cancer risks below 1.6 in the 7 positive studies.[143] Standardized mortality and incidence studies of rubber workers employed since 1980 have not detected statistically significant elevations in stomach cancer rates. A cohort study of 8,933 German rubber industry workers hired after 1949 and followed from 1981–1991 reported national reference population mortality from stomach cancer of 117 (95% CI: 85–157, $n = 44$).[144] The SMR for stomach cancer (subtype unreported) in a cohort of 8,651 UK rubber factory workers was 86 (95% CI: 23–219, $n = 4$) based on national rates; the standardized registry rate for stomach cancer was also not statistically significant (SRR = 137, 95% CI: 66–252, $n = 10$).[145] In a cohort mortality study of 6,246 Italian rubber workers employed from 1954–2008, the standardized mortality rate (SMR) for stomach cancer (subtype unreported) was 99 (95% CI: 69–138, $n = 34$) without increasing with duration of employment.[146] Some older studies of coal miners revealed elevations for stomach cancer mortality (SMR = 140–275), particularly in the older age groups;[147,148] however, statistically negative case-control studies from the Netherlands (SIR = 1.15, 95% CI: 0.89–1.47)[149] and the United States (RR = 1.55, 95% CI: 0.72–3.30)[150] suggest the lifestyle of the coal mining community may be a more important stomach cancer determinant than occupational dust exposure.

A 1979 population-based, case-control study in Montreal suggested several substances as potential gastric carcinogens, including crystalline silica, leaded gasoline, grain dust, lead dust, zinc dust, hydraulic fluids, and glycol ethers;[151] however, this hypothesis-generating study did not establish a firm link between any of these substances and gastric cancer. A case-control analysis of mortality from gastric cardia/lower esophagus cancers reported no statistically significant excess of these stomach cancers in white men exposed to sulfuric acid mists based on an analysis of death certificates.[152] Dust alone is a potential risk factor for stomach cancer, particularly in occupations associated with woodworking, steel polishing, or abrasive working;[153] however, consistently elevated stomach cancer rates were not reported in studies of occupations with substantial dust exposure.[154] A retrospective cohort mortality study of 2,294 white male wood model makers with follow-up from 1940–1984 did not detect a statistically significant increase in mortality from stomach cancer (SMR = 1.6, 95% CI: 0.9–2.6) with no trend for increasing wood dust exposure.[155] A case-control study of an area in England where the prevalence of stomach cancer is high attributed only 23% of stomach cancer incidence to work in dusty industries (coal mining, iron and steel, ceramics, rubber).[156] Limited epidemiological evidence supports a modest association between asbestos exposure and stomach cancer. Mortality studies also suggest an association between asbestos exposure and stomach cancer;[157] however, outcomes between various studies have not demonstrated consistent, dose-related elevated stomach cancer rates in asbestos-exposed workers. The overall meta-SMR for stomach cancer in a meta-analysis of 40 mortality case-control and 14 cohort studies of asbestos workers was 1.15 (95% CI: 1.03–1.27), with moderately heterogeneous results across studies ($I^2 = 61.9\%$).[158] Statistically significant stomach cancer excess risks were reported in North American and Australian studies but not European studies.

Lifestyle

Historically, poor socioeconomic class (e.g., low income and education) has been a major determinate of stomach cancer risks that potentially confounds observational studies on the stomach cancer etiology.[159,160] Using the relative index of inequality (RII) as a measure of socioeconomic class, the overall combined pooled estimate of gastric cancer risk was 2.64 (95% CI: 1.05–6.63), comparing the lowest and highest socioeconomic categories.[161] These categories included income, occupation, and education.

Smoking

Smoking is a modest risk factor for non-cardia gastric cancers. A meta-analysis of nine studies on non-cardia gastric cancer reported an estimated summary relative risk of 1.60 (95% CI: 1.41–1.80; $I^2 = 18.9\%$) comparing current smokers and never-smokers.[162] The overall gastric cancer risk was greater in men than women. In the prospective NIH–AARP Diet and Health Study of 474,606 US participants using Cox models adjusted for potential confounders, the hazard ratio for non-cardia gastric cancer was 2.04 (95% CI: 1.32–3.16).[68] The population-attributable risk for ever smoking was 19% compared with 47% for cardia gastric cancer. The Netherlands study reported similar risks for non-cardia gastric cancer. The multivariable adjusted incidence rate ratio comparing current smokers and

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never-smokers was 1.86 (95% CI: 1.40–2.48, $n = 177$).[163] The P_{trend} for quartiles of pack-year smoking was statistically significant ($P_{trend} = 0.004$); in continuous 10 pack-years smoking, the RR was 1.08 (1.02–1.15). In a population-based, prospective cohort study (Hisayama study) of 1,071 Japanese men aged ≥40 years followed for 14 years (1998–2002), the multivariate-adjusted hazard ratio for non-cardia gastric cancer in participants currently smoking over 20 cigarettes daily was 1.88 (95% CI: 1.02–3.43) using current nonsmokers as controls.[164] The impact of smoking cessation is somewhat conflicting with some benefit from ≥20 years of abstinence.[165]

Diet

A modest association between diet and non-cardia gastric cancer remains controversial because of a lack of convincing evidence and the difficulty in measuring lifetime dietary intakes. Limited epidemiological evidence supports the association of high salted/smoked fish diets and low fruit and vegetable consumption with an increased stomach cancer incidence.[5] In the Hisayama study, the multivariate-adjusted hazard ratio of the highest quartile of daily dietary salt intake (≥16 g) was statistically significant (HR = 2.67, 95% CI: 1.36–5.24, $n = 30$) compared with the lowest quartile (<10 g).[166] Although the P_{trend} was 0.01, the comparison of the third and first quartiles was not statistically significant (HR = 1.88, 95% CI: 0.91–3.89, $n = 20$). A meta-analysis of 11 observational studies comparing highest and lowest categories of dietary salt intake reported a summary odds ratio of 1.22 with substantial heterogeneity (95% CI: 1.17–1.27, $I^2 = 92\%$); subanalysis of European studies did not demonstrate a statistically significant association between gastric cancer risk and dietary salt intake (OR = 1.15, 95% CI: 0.88–1.52, $I^2 = 41\%$, $n = 2$).[167] The presence of substantial heterogeneity weakens the positive association.

In a Portuguese population-based, case-control study of 305 non-cardia gastric tumors, the odds ratio comparing the highest versus lowest tertile of fruit consumption was 0.53 (95% CI: 0.35–0.80), whereas this comparison for vegetables was not statistically significant (HR = 0.85, 95% CI: 0.58–1.26).[168] In a meta-analysis of six prospective cohort studies (2,209 stomach cancer patients) and nine case-control studies (2,495 cases), the estimated summary relative risks of stomach cancer for an increase in processed meat consumption of 30 g/day (~1/2 an average serving) were 1.15 (95% CI: 1.04–1.27) for the cohort studies and 1.38 (95% CI: 1.19–1.60) for the case-control studies.[169] The effect size was relatively small, and confounding/bias could not be excluded, particularly when the effect size for qualitatively better cohort studies was lower than that for case-control studies.

Alcohol

The association between alcohol consumption and non-cardia gastric cancer is weak compared with diet and smoking. Several large prospective Asian and European cohort studies reported no significant association between alcohol and gastric cancer.[68,163] In the prospective Netherlands Cohort Study, the multivariable adjusted incidence rate ratio for non-cardia gastric cancer was 1.00 (95% CI: 0.68–1.47, $n = 59$), comparing daily consumption of ≥30 g ethanol/day with abstainers.[163] The P_{trend} for quartiles of alcohol consumption was 0.68. A meta-analysis by the World Cancer Research Fund suggested a weak, nonlinear association between heavy alcohol consumption (>45 g alcohol daily) and non-cardia gastric cancer.[61] The RR for men increased by 3%/10 g daily alcohol consumption (RR = 1.03, 95% CI: 1.01–1.05) after removal of a study using especially high alcohol consumption. However, the association for women was not statistically significant (RR = 1.02, 95% CI: 0.90–1.15).

HISTOLOGY

Several subsites separate the stomach anatomically into the cardia and more distal non-cardia sites (fundus, body, pylorus, antrum). Although previously stomach cancer was defined by anatomical location in the stomach, stomach cancer now usually refers to distal (non-cardia) cancer rather than the etiologically different proximal (gastroesophageal junction) stomach cancer. Gastric adenocarcinoma accounts for ~90–95% of stomach cancers, with the remainder being lymphomas, leiomyosarcomas, neuroendocrine tumors, and gastrointestinal stromal tumors.[108] Many more recent epidemiology studies subclassify gastric tumors into two main sites: cardia (proximal stomach involving gastroesophageal junction and proximal 5 cm) and the more distal non-cardia (body/fundus, pyloric antrum, or distal), with these subtypes having distinct epidemiological and clinical characteristics.[113] The latter subtype is further subclassified into intestinal and diffuse types, classically stratified by Lauren.[170] The World Health Organization (WHO) subclassified adenocarcinomas into tubular, papillary, mucinous, poorly cohesive including the signet ring cell variant, and mixed types. Gastric atrophy is strongly associated with atrophic gastritis produced by *H. pylori*. Chronic, progressive gastritis contributes significantly to the development

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of non-cardia gastric cancer with long-term mucosal inflammation, initially producing mucosal atrophy and metaplasia followed by intraepithelial neoplasia and finally a malignant tumor.[171]

HOST SUSCEPTIBILITY

Most gastric cancers are sporadic, whereas inherited cancer predisposition syndromes account for relatively few cases (~1–3%). The complex interactions of host factors (e.g., polymorphisms encoding pro- and anti-inflammatory cytokines, environment/socioeconomic influences) modulate gastric cancer risks following potentially oncogenic viral infections (i.e., *H. pylori*, EBV). The three recognized hereditary syndromes of gastric cancer are: 1) hereditary diffuse gastric cancer; 2) gastric adenocarcinoma and proximal polyposis of the stomach; and 3) familial intestinal gastric cancer. Compared with sporadic tumors, these hereditary cancers act more aggressively and occur at earlier ages.[172] Germline E-cadherin/CDH1 mutations occur in families with a rare autosomal dominant inherited predisposition to diffuse gastric cancer conferring a cumulative gastric cancer risk for CDH1 mutation carriers of 70% for men and 56% for women by age 80 years.[173] The diffuse type of non-cardia gastric cancer includes signet ring adenocarcinoma associated with hereditary gastric cancer, loss of E-cadherin expression, and relatively earlier onset.[174] The median age at diagnosis for this syndrome is 38 years.[175]

CLINICAL FEATURES

The incidence of gastric cancer increases with age; the median age at diagnosis is ~70 years with <1% presenting under 35 years of age.[176] Gastric cancer rates worldwide are 2–3-fold greater in men than women.[31] The diagnosis of gastric cancer typically occurs during advanced stages (i.e., with metastatic disease) because of the vague, nonspecific symptoms associated with this cancer, including weight loss, early satiety, anorexia, fatigue, epigastric discomfort, indigestion, and nausea/vomiting. None of these symptoms are unique to stomach cancer. The prognosis is usually poor (e.g., <20–30% 5-year survival and <1 year for the most advanced stages).[177] The case fatality rate (mortality rate/incidence rate for a specified time period) is ~75% compared with ~50% for colorectal cancer and ~97% for pancreatic cancer; however, the case fatality rate is better in high-income (~58%) than low-income (~82%) countries.[178]

COLORECTAL

Colorectal cancer is the second most common malignancy in the United States, with ~160,000 new cases annually, and the third leading cause of cancer-related deaths, with ~60,000 annual US fatalities and accounting for ~8% of cancer-related deaths worldwide.[32] The lifetime risk of developing colorectal cancer in the general population is ~2%, with higher risks in Western countries (i.e., ~3–4%).[31] The overall incidence of colorectal cancer increased by ~19% during 1950–1985; however, the mortality rate decreased by 20% during this period,[179] and subsequently, screening programs and lifestyle changes reduced colorectal cancer incidence by ~45%.[180] In contrast to the reduction in colorectal cancer among adults of ≥50 years of age, the incidence and mortality of colorectal cancer increased recently in the age group 20–49 years in the United States and Canada.[181,182] Significant geographical variation occurs in colorectal cancer incidence based on the common occurrence of colorectal cancer in industrialized Western countries (e.g., North America, Europe, Australia) and the less frequent occurrence of colorectal cancer in poorer countries in Africa, South America, and Asia.

CARCINOGENESIS

Most colorectal cancers develop from the adenoma–carcinoma sequence, beginning as a small, benign polyp that progresses to a large polyp (>1 cm), a dysplastic lesion, and then cancer typically over at least 10 years.[183] Gene mutations (aneuploidy, microsatellite instability), epigenetic factors (CpG island methylator phenotypes), and local inflammation involving many different signaling pathways drive this progression with the mutation of *APC* gene; an early event in the multistep process occurring in ~70% of colorectal adenomas.[184] These changes transform normal glandular epithelial cells into invasive adenocarcinomas.[185] Other mechanisms involve origins in right-sided, non-polyploid (flat) colonic lesions and morphologically normal areas of genetically altered epithelial cells.[186] Table 54.4 outlines the major genetic pathways involved in nonfamilial colorectal cancer, along with key genes. The main signaling pathways affected in hereditary colorectal cancers involve DNA repair and Wnt, PTEN/PI3K, Tgf-β/BMP, and RAS/MAPK signaling pathways.[187]

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TABLE 54.4. Major genetic pathways and genes involved with nonfamilial (sporadic) colorectal cancer cases. The adenomatous polyposis gene (*APC*) is the most common initially mutated gene in at least 70% of sporadic colorectal adenocarcinomas. Other frequently mutated genes include *TP53* and Kirsten Rat Sarcoma Viral Oncogene Homolog (*KRAS*). Approximately 15% of sporadic colorectal cancers develop from serrated precursor lesions in the proximal colon characterized by CpG island methylator phenotype and activating *BRAF* oncogene mutations. Most adenocarcinomas arising from sessile serrated adenomas in the proximal colon display high-level microsatellite instability phenotype from *MLH1* gene promoter methylation. (Adapted from Aran et al.).[188]

Genetic Pathway (% cases)	Description	Key Genes
Chromosomal instability (~70–85%)	Adenoma–carcinoma transformation sequence involving oncogene activation/tumor suppressor gene inactivation	*KRAS*, *c-Myc*, *c-Src*, *APC*, *TP53*, *PIK3CA*, tumor suppressor genes (*DCC*, *SMAD2/4*)
Microsatellite instability (~15–20%)	Clonal change in repeated DNA nucleotide units in microsatellites causing mismatch repair gene inactivation from insertion/deletion mutations often localized in the proximal colon	*APC*, *MLH1*, *MSH2/6*, *PMS2*
CpG island methylator phenotype	Global hypermethylation of promoter CpG islands inactivating tumor suppressor genes (e.g., p16)	*CACNA1G*, *CDKN2A*, *IGF2*, *NEUROG1*, *RUNX3*, *SOCS1*

EXPOSURE

Colorectal cancer is a multifactorial disease resulting from genetic, epigenetic, and lifestyle factors, with no single risk factor accounting for most colorectal cancer cases. This type of cancer is not typically associated with environmental exposures. A population-based study of cancer incidence in residents associated with increased tetrachlorethylene concentrations suggested the possibility of an association with colorectal cancer;[189] however, the small numbers, short latency period (7 years), low precision of odds ratios, and lack of statistical significance limit conclusions regarding causation.

Occupation

The role of occupational exposure in the etiology of colorectal cancer is probably relatively small.[190,191] Of all agents associated with the development of colorectal cancer, asbestos has been the most widely studied, with limited evidence of an association in humans. In 1964, Selikoff et al. reported a colorectal cancer relative risk of 3.7 in insulation workers exposed to asbestos for ≥20 years.[192] Subsequent studies of over 30 cohorts have not confirmed the magnitude of this risk in asbestos-exposed workers. Although early reviews supported the association between asbestos and colorectal cancer,[193] subsequent reviews have not supported a strong association.[47] A review of the medical literature from 21 cohorts of asbestos workers did not detect a dose-response relationship between latency period and colorectal cancer risk.[194] The summary SMR was 1.03 for 6 inception cohorts with observation periods beginning <20 years after the onset of exposure compared with a summary SMR of 0.86 (no 95% CI reported) for 7 inception cohorts of workers followed for ≥20 years after their initial exposure. All eight cross-sectional studies demonstrated no statistically significant increase in the summary SMR of 1.14. A meta-analysis of the medical literature revealed a small (SMR = 161) but statistically significant increase in the SMR for cohorts that had a SMR >200 for lung cancer.[46] The potential for misclassification (i.e., metastatic vs. primary colorectal cancer) and the dilution of the SMR by nonmalignant causes of death reduce the validity of the association between high lung SMR and colorectal cancer incidence. A case-control study of 261 cases of colon and rectal cancer did not demonstrate an increased odds ratio for asbestos exposure, as defined by employment in occupations with historically heavy asbestos exposures.[195] In a retrospective cohort study of 7,887 male and 576 female Danish cement workers exposed primarily to chrysotile asbestos, men employed from 1923–1950 had an SIR of 1.47 (95% CI: 1.05–2.01) with a 15-year lag; however, the overall SIR (1928–1984) was not statistically significant (1.22, 95% CI: 0.99–1.48, $n = 102$).[196] A retrospective study of 2,024 asbestos reprocessing plant workers reported a positive trend toward statistical significance ($P_{trend} = 0.02$) for average asbestos exposure level but not for exposure duration,

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asbestos fiber type, or cumulative exposure.[197] Information on potential confounding factors associated with lifestyle behavior was not available.

Cohort studies of rubber workers (SMR = 231, $n = 6$) suggest a potential association between the rubber industry and colorectal cancer.[198] In an analysis of standardized mortality ratios in styrene-butadiene rubber workers' cause-specific mortality (1943–1998) and the general US population for colorectal cancer, the slightly increased SMR was not statistically significant (SMR = 109, 95% CI: 94–125).[199] In a cohort of German workers in areas producing technical rubber goods, the elevated SMR was not statistically significant (SMR = 131, 95% CI: 86–191, $n = 27$).[200] Some cohort studies of chemists demonstrate excess colorectal cancer mortality;[201] however, the lack of a specific carcinogen limits conclusions about causation. A cluster of colorectal cancer occurred among employees of a polyolefin unit manufacturing polypropylene, particularly among mechanical (SIR = 10.6, 95% CI: 3.4–24.7) and process (SIR = 5.0, 95% CI: 0.6–17.8) workers.[202] However, a follow-up study of this cohort did not confirm the excess colorectal cancer risk among workers in the manufacture of polypropylene consistent with the lack of precision in the earlier SIR and the bias associated with including clusters in observational studies.[203] Other substances associated with potentially elevated colorectal cancer risks include wood dust,[204] solvents and fuel oil,[205] and methacrylate;[206] however, inadequate human evidence is available to confirm any association. A retrospective cohort mortality study of 2,294 male wood model workers did not confirm an increased risk of colon cancer in these workers.[155]

Lifestyle

Tobacco

Although the association between cigarette smoking and colorectal cancer is inconsistent between observational studies, some studies suggest a modest effect. A meta-analysis of 19 case-control and 6 cohort studies reported a pooled adjusted risk estimate of 1.18 (95% CI: 1.11–1.25) for colorectal cancer incidence comparing ever- and never-smokers.[207] A statistically significant dose-response relationship between colorectal cancer risks and increasing pack-years and intensity of cigarette smoking occurred only after 30 years of smoking. In the Nurses' Health Study, cigarette smoking was unrelated to colorectal cancer incidence until 35 years after smoking began, with a progressive stronger relationship suggesting a long latency period.[208] A modest increase (RR = 1.47, 95% CI: 1.07–2.01) in the risk of developing colorectal adenomas and cancers was reported in women smoking >10 cigarettes/day for >35 years. The association between cancer incidence and mortality was stronger for rectal than colon cancer. Some observational studies suggest smoking is not a strong colorectal cancer risk factor, even after long induction periods.[209] In an Italian case-control study of 955 colon cancers, 629 rectal cancers, and 2,879 hospital controls, the overall multivariate OR for colorectal cancer was 0.9 (95% CI: 0.8–1.1) in ex-smokers and 0.7 (95% CI: 0.6–0.8) in current smokers compared with never-smokers.[210] The results were adjusted for sex, age, diet, alcohol consumption, and family colorectal cancer history using multiple logistic regression analysis. Cox proportional hazard regression analysis of data from 465,879 participants in the European Prospective Investigation into Cancer and Nutrition study ($n = 2{,}741$ colorectal cancer cases; mean follow-up, 8.7 years) indicated a weak association between smoking and colorectal cancer.[211] Although colon cancer risk was increased among ever-smokers (HR = 1.18, 95% CI: 1.06–1.32) and former cigarette smokers (HR = 1.21, 95% CI: 1.08–1.36) compared with never-smokers, the colon cancer risk was not increased in current smokers (HR = 1.13, 95% CI: 0.98–1.31, $n = 285$). The results were adjusted for weight, height, physical activity, education, and diet. The study did not detect a dose-response relationship between colon cancer and duration or intensity of smoking. Twenty years after smoking cessation, the colon cancer risks of former-, ever-, and never-smokers were similar.

Alcohol

Heavy alcohol consumption is a recognized colorectal cancer risk. Although heavy alcohol consumption is probably an independent risk factor for colorectal cancer, the risks are not homogeneous across countries, chronic alcohol doses, intestinal tumor location, or possibly gender. In a meta-analysis of 16 cohort studies involving ~6,300 colorectal cancer patients comparing the highest and lowest alcohol consumption, the overall meta-RR for colorectal cancer was positive but not statistically significant (1.34, 95% CI: 0.92–1.96, $I^2 = 71\%$); however, the overall meta-RR was marginally significant for heavy alcohol consumption (>200 g/week) for men (RR = 1.73, 95% CI: 1.00–2.98, $I^2 = 74\%$), but not for women (RR = 0.88, 95% CI: 0.61–1.27, $I^2 = 0$).[212] Other meta-regression analyses indicate the relative risk of cancer was significantly increased for men in the colon and rectum, whereas the risks were marginally significant for the colon but not the rectum in women. In a pooled analysis of eight cohort studies from five

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North American and European countries, the pooled multivariate relative risk for colorectal cancer was statistically significant only for participants consuming >45 g/day (~3 drinks) when compared with nondrinkers (RR = 1.41, 95% CI: 1.16–1.72).[213] Significant heterogeneity was not detected by study location or sex. Colorectal cancer incidence in Japan is particularly high compared with the rest of the world, potentially because of the greater prevalence of the slow-metabolizing aldehyde dehydrogenase variant. Analysis of data from 5 Japanese studies involving 2,802 colorectal cancer cases reported a multivariate-adjusted, pooled hazard ratio of 2.96 (95% CI: 2.27–3.86) for daily alcohol intake of ≥92 g (~7 standard sake drinks) compared with nondrinkers.[214] The colorectal cancer risk was increased for women drinking >23 g/day (HR = 1.57, 95% CI: 1.11–2.21) compared with nondrinkers. The risk correlated with alcohol dose (P_{trend} ≤0.001) and was similar for colon and rectal cancer.

Diet

Low-fiber, high-fat diets, including the consumption of substantial amounts of red meat along with reduced physical activity in industrialized countries, may contribute to some of the excess colorectal cancer rates; the strongest evidence for increased colorectal cancer risk is the consumption of red and processed meat.[215,216] In a dose-response meta-analysis using random effects models, the estimated increased summary relative risk was 1.12 (95% CI: 1.04–1.21; $I^2 = 70\%$ $P_{heterogeneity} \leq 0.01$) for each 100 g/day increase in red and processed meat intake.[217] Foods containing fiber reduce colorectal cancer risk. Colorectal cancer risk decreased by ~17% (95% CI: 11–21%, $I^2 = 0\%$, $P_{heterogeneity} = 0.21$, $n = 6$) for each 90 g/day increase in whole grain consumption and by 13% (95% CI: 10–17%, $I^2 = 18\%$, $P_{heterogeneity} = 0.27$, $n = 10$) for each 400 g/day increase in dairy product intake. Evidence for a reduction in risk from vegetable and fish consumption was unconvincing. Cheese, coffee, fruit, legume, poultry, and tea consumption did not alter colorectal cancer risk. Random controlled trials do not support the use of low-fat, high-fiber diet to reduce the recurrence of colorectal adenomas.[218]

Physical Activity

Physically active occupations have been associated with a decrease in colorectal cancer risks;[219] however, confounding with lifestyle, diet, and social class limits the extrapolation of the studies demonstrating a negative association between physical activity and the development of colorectal cancer. Additionally, the potential for reporting bias from self-reports of activity/sedentary behavior and the lack of a universally accepted definition of insufficient physical activity complicate the evaluation of physical exercise as a colorectal cancer risk factor. Although objective and subjective physical activity measures give qualitatively similar results regarding gender and age patterns of physical activity, adherence to physical activity recommendations is substantially lower for accelerometer-measured than self-reported activity (e.g., <10% vs. 60%, respectively).[220]

In a systematic review and meta-analysis of leisure time physical activity, meeting WHO guidelines for leisure activity was associated with a reduction in colon cancer (RR = 0.81, 95% CI: 0.75–0.88, $I^2 = 4.2\%$) but not rectal cancer (RR = 1.07, 95% CI: 0.93–1.24, $I^2 = 0.0\%$) risks.[221] Dose-response analysis indicated the benefit of physical activity did not increase 2-fold above WHO recommendations. Systematic reviews and meta-analyses typically estimate that physical activity reduces colon cancer risk by ~20–25%, comparing the highest and lowest levels of assessed physical activity with a somewhat stronger risk reduction for case-control than cohort studies (i.e., 24% and 17%, respectively).[222] Clinically significant cancer incidence reduction may require 30–60 minutes of moderate to vigorous physical activity daily to lower colon cancer risks.[223]

Obesity

Excessive weight and adipose tissue induce tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor 1 (PAL-1), free fatty acid, leptin, and resistin along with decreasing adiponectin. These changes enhance insulin resistance and increase insulin-like growth factor-binding protein 1 (IGFBP1) and growth factor-binding protein 2 (IGFBP2), resulting in the inhibition of apoptosis and enhanced cell proliferation.[224] Direct measurement of visceral adipose tissue (VAT) using computed tomography indicates VAT is a better predictor of insulin resistance than waist circumference or BMI; however, most observational studies use BMI as the measure of obesity.[225] Cumulative lifetime excess weight may be a stronger risk factor than weight measured at a single point in time. In meta-analyses of colorectal cancer and obesity as measured by BMI, the increased relative risk of colorectal cancer with obesity was <1.5–2.0 in men and weaker in women (<1.2). Increasing BMI in a meta-analysis of 28 articles was associated with an increased overall risk ratio per 5 kg/m^3 of 1.24 (95% CI: 1.20–1.28, $I^2 = 20.7\%$, $P = 0.189$) in men and 1.09 (95% CI: 1.04–1.14, $I^2 = 39.1\%$, $P = 0.042$) in women.[226] The pooled relative risk of colorectal cancer per 5 kg/m^2

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increase in BMI using random effect models in a meta-analysis of 15 cohort studies was 1.37 (95% CI: 1.21–1.56) for overweight and obese men compared with 1.07 (95% CI: 0.97–1.18) for overweight and obese women.[227] Comparing the highest and lowest quantiles of waist-to-hip ratio, the pooled RR for colon cancer was 1.91 (95% CI: 1.46–2.49) for men and 1.49 (95% CI: 1.23–1.81) for women. Analysis of data from the prospective Nurses' Health Study II enrolling 85,256 female nurses aged 25–42 years at study enrollment detected 114 cases of early-onset colorectal cancer (median age at diagnosis, 45 years).[228] Based on biennially self-reported anthropomorphic measures and lifestyle information, the adjusted, multivariable relative risk of early-onset colorectal cancer was associated with obese women (BMI $\geq$ 30, RR = 1.93, 95% CI: 1.15–3.25) but not overweight women (BMI, 25.0–29.9, RR = 1.37, 95% CI: 0.81–2.30) when compared with women with a BMI of 18.5–22.9. Adjustments included height, history of diabetes, smoking, physical activity, alcohol intake, aspirin/nonsteroidal anti-inflammatory drug use, multivitamin use, menopausal status, hormone use, dietary intake (total calories, red meat, fiber, folate, calcium), and Alternate Healthy Eating Index 2010.

Diseases

Patients with inflammatory bowel disease have increased colorectal cancer risks, particularly the chronic colonic inflammation associated with ulcerative colitis; however, no significant colorectal cancer risk occurs in patients with Crohn's disease isolated to the small bowel.[229] The colorectal cancer risk is significantly higher in patients with longer disease duration, extensive disease, and the diagnosis of inflammatory bowel disease at a young age. Compared with the general population, colorectal cancer risk increases 2- to 5-fold, with the risk increasing throughout life after diagnosis (e.g., from 2% at 10 years to 18% at 30 years). In a meta-analysis of population-based, cohort studies of colorectal cancer and inflammatory bowel disease adjusting for isolated small bowel Crohn's disease, the pooled standardized incidence ratio (pSIR) for colorectal cancer was 1.7 (95% CI: 1.2–2.2).[230] High-risk groups were patients with extensive colitis (pSIR = 6.4, 95% CI: 2.4–17.5) and disease diagnosis before age 30 (pSIR = 7.2, 95% CI: 2.9–17.8). In a meta-analysis of eight population-based, cohort studies, the pooled SIR for colorectal cancer in ulcerative colitis patients was 2.4 (95% CI: 2.1–2.7) and 4.8 (95% CI: 3.9–5.9) in patients with extensive colitis involving >50% of the colon.[231]

Epidemiological studies have not consistently reported an association between pre-diagnosis, systemic inflammatory marker concentrations (e.g., tumor necrosis factor-α, interleukin-6, C-reactive protein), and colorectal cancer. However, the association of obesity with colorectal cancer risks suggests the presence of a low-grade inflammatory condition (e.g., obesity) may influence colorectal cancer risks. The empirical dietary inflammatory pattern (EDIP) score is a weighted sum of 18 food groups that assesses the inflammatory potential of a diet validated by comparing quintiles of the EDIP score with concentrations of systemic inflammatory markers (interleukin-6, C-reactive protein, tumor necrosis factor-α receptor 2) and adiponectin.[232] Pro-inflammatory foods included processed meat, red meat, organ meat, non-dark fish, tomatoes, vegetables other than green leafy and dark yellow vegetables, refined grains, and high-energy/low-energy beverages, whereas beer, wine, tea, coffee, dark yellow and leafy green vegetables, snacks, fruit juice, and pizza were considered anti-inflammatory. EDIP scores were calculated from food frequency questionnaires administered every 4 years in the Health Professionals Follow-up Study (46,804 men) and the Nurses' Health Study (74,246 women).[233] The hazard ratios for colorectal cancer comparing the highest and lowest quintile EDIP scores were modestly elevated for men (HR = 1.44, 95% CI: 1.19–1.74) and less for women (HR = 1.22, 95% CI: 1.02–1.45). Potential confounders in the analysis included higher BMI, increased rates of diabetes, and lower physical activity in the highest EDIP quintiles, limiting conclusions about causation.

Diabetes is probably an independent risk factor for colorectal cancer. In a systematic review and meta-analysis of 30 cohort studies using random effects models, diabetes was associated with an increased colorectal cancer risk with a summary relative risk of 1.27 (95% CI: 1.21–1.34); moderate heterogeneity appeared among the studies ($P = 0.002$, $I^2 = 48.4\%$).[234] Subgroup and meta-regression analysis with control of confounding demonstrated that the increased colorectal cancer incidence was independent of sex, smoking, physical activity, body mass index, geographic locations, and family colorectal cancer history.

Several meta-analyses suggest chronic *H. pylori*-induced gastritis is associated with an ~50% increased colorectal cancer incidence.[235,236] In an analysis of a database containing 156,000 surgical pathology reports, the odds ratio of colorectal adenocarcinoma in patients with chronic *H. pylori* gastritis compared with patients having normal gastric mucosa was 2.35 (95% CI: 1.98–2.80).[237] The risks of adenomatous polyps (OR = 1.52, 95% CI: 1.46–1.57) and villous adenomas or

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adenomas with high-grade dysplasia were also elevated (OR = 1.97, 95% CI: 1.82–2.14) in patients with chronic *H. pylori* infections.

HISTOLOGY

Most (i.e., 90–95%) colorectal cancers are adenocarcinomas arising from epithelial cells in the colonic crypts as polyps, with the sigmoid colon being the most common anatomical site.[238] Precancerous polyps include the following: 1) the common sessile, raised, or pedunculated tubular adenomas with conventional dysplasia; 2) sessile serrated adenomas without cytological dysplasia; and 3) relatively rare traditional serrated adenomas presenting as flat or villous, right-sided polyps with slit-like serrations and pink cytoplasm.[239] APC (adenomatous polyposis coli) gene mutations characterize tubular adenomas,[240] whereas CpG island methylation with epigenetic gene silencing characterizes traditional serrated adenomas.[241]

HOST SUSCEPTIBILITY

Although most colorectal cancers are not hereditary, genetic factors may contribute significantly to the occurrence of colorectal cancers. In the Nordic Twin Study of Cancer involving 39,990 monozygotic and 61,443 same-sex dizygotic twins, the familial risk ratio for colorectal cancer was 3.1 (95% CI: 2.4–3.8) relative to the cohort risk compared with 2.2 (95% CI: 1.7–2.7) for dizygotic twins of affected co-twins.[242] The authors suggested interindividual genetic differences could account for up to 35–40% of the variation in colorectal cancer susceptibility. A systematic review and meta-analysis of 27 case-control and cohort studies reported a relative risk of 2.25 (95% CI: 2.00–2.53) for individuals with a first-degree relative previously diagnosed with colorectal cancer and 2.26 (95% CI: 1.87–2.72) for a history of a parent with colorectal cancer when compared to controls without a family history of colorectal cancer.[243]

Approximately 5% of patients with colorectal cancer have an inherited predisposition.[188] The two well-defined inherited colorectal cancer syndromes accounting for the majority of colorectal inheritable syndromes are adenomatous polyposis coli (~1% of total colorectal cancer cases) and hereditary nonpolyposis colorectal cancer (Lynch syndrome, ~4–5% of total colorectal cancer cases). The lifetime risk of colorectal cancer in these hereditary diseases approaches 100% if untreated. These two diseases may reflect different susceptibilities to neoplastic transformation in proximal and distal tumors.[244,245] A family history of colon cancer is also a risk factor for the occurrence of sporadic colorectal cancer that does not demonstrate a family pedigree consistent with genetic transmission. Certain genetic abnormalities (e.g., allelic deletions on chromosomes 5, 17, 18; C-MYC amplification; *RAS* point mutations) may predispose patients to colorectal cancer by enhancing the progression from normal to malignant colonic mucosa.[246]

CLINICAL FEATURES

Older age is associated with increasing colorectal cancer risks, with an ~2-fold higher incidence in men than women.[247] The mean age of colorectal cancer diagnosis in sporadic cases is ~67 years compared with earlier onset in the 40s and 50s for hereditary colorectal cancer syndromes.[187] The classical symptoms of colorectal cancer (e.g., hematochezia, anemia, weight loss, abdominal pain) typically occur at relatively late stages of the disease. The diagnosis of 90% of colorectal cancer cases occur in patients over 50 years of age, with 40% of the cases involving localized disease.[37] However, the most rapidly increasing early-onset cancers (i.e., patients <50 years of age) are gastrointestinal cancers, particularly colorectal and gastric cancers. The 5-year survival rate ranges from 90% in patients with Stage I (localized, T1/T2N0M0) disease to ~10% in Stage IV (distant metastatic) disease. Although somewhat controversial, the survival rates are generally similar between the molecular subtypes noted in Table 54.4.[248,249] Approximately 1/2 of recently diagnosed patients with colorectal cancer will die from the disease; the 5-year survival rates decrease from 70% for regional disease to 10–13% for patients with distant metastasis.

ANUS

Anal cancer is a relatively uncommon malignancy; however, anal cancer incidence has increased since the late 1990s along with the increased prevalence of human papillomavirus (HPV) infections and improved survival of human immunodeficiency virus (HIV)-infected individuals treated with antiretroviral therapy, particularly among young men.[250] Anal cancers represent an estimated 2.7% of all US gastrointestinal malignancies and <0.5% of all US cancers, causing ~8,600 new cases and ~1,150 deaths per year.[32] In a study of 13 North American cohorts from 1996–2007, the unadjusted

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anal cancer incidence rate for HIV-infected homosexual men was 131/100,000 person-years compared with 46/100,000 person-years for other HIV-infected men and 2/100,000 person-years for men without HIV infections.[251] Approximately 80–90% of anal cancers are associated with HPV infections.[252] In a systematic review of studies on anal cancer incidence, the incidence of anal cancer among HIV-infected women ranged from 3.9–30/100,000.[253] Among women with a history of cervical cancer or high-grade cervical intraepithelial neoplasia 3, the anal cancer incidence rates ranged from 0.8–63.8/100,000 person-years compared with 0.55–2.4/100,000 person-years in the general population. Anal HPV infection is relatively common in the general population of women; however, healthy women clear HPV infections more easily from the anus than the cervix. Anal epithelial cells are less transformable than cervical cells, resulting in a substantially lower incidence of anal than cervical cancer in women.[254] The estimated age-adjusted incidence of invasive anal squamous cell carcinoma is higher in US women (~1.5/100,000) than US men (~1/100,000).[255] Most anal HPV infections in men are concentrated in high-risk groups (HIV-infected and homosexual men).

CARCINOGENESIS

The HPV genome is a double-stranded circular DNA with over 150 HPV types that infect the host genome of stratified epithelial cells with varying carcinogenic potency and preferential epithelial cell tropism; the highest carcinogenic risk occurs with HPV-16 and, to a lesser degree, HPV-18.[256] Biopsies from the vast majority of patients with anal cancer or precursor lesion contain DNA from human papillomavirus. In anal cancer specimens from 324 women and 93 men, HPV-16 was detected in 84% of the samples compared with none in the rectal cancer control group.[257] Detectable HPV DNA occurred in 94% of 72 participants in a study of patients with metastatic anal cancer; however, the prognostic value of HPV is unclear in contrast to the improved prognosis in HPV-associated head and neck cancer.[258]

HPV is a necessary but not sufficient factor for the development of anal cancer because only a small fraction of HPV-infected individuals develop squamous cell anal cancer from the infection. Over 90% of HPV infections in healthy individuals are undetectable within a few years after the initial infection; however, the infection may remain dormant for several decades.[259] HPV infects only epithelial cells spreading from one epithelial surface to another when the cells slough off or die.[260] The HPV genome encodes early structural genes (E1, E2, E4–E7) involved with viral replication and late structural genes (L1, L2) encoding major and minor capsid proteins, respectively. After entering the basal epithelial layer, the viral genome maintains a quiescent state with the E1 and E2 proteins coordinating viral replication with host cell division. The outcome of the infection depends on oncogenic potency of the HPV type, host immune response, host genetics, epithelial infection site, and other factors that modulate the HPV infection, including other sexually transmitted infections. Active viral replication produces low-grade squamous intraepithelial lesions important for HPV transmission, but not involved with cancer progression. An aborted infection results in the expression of oncogenic early region genes that progress to high-grade squamous intraepithelial lesions with greater risk of malignant transformation depending on the host immune response. Epigenetic factors (e.g., DNA methylation, histone deacetylation, cellular microRNAs, cellular transcription factors) may also enhance the malignant transformation of squamous intraepithelial lesions and oncogene expression produced by HPV infections.[260] Table 54.5 outlines the function and effect of HPV proteins on the malignant transformation of infected anal epithelial cells.

EXPOSURE

Lifestyle is the most important risk factor for anal cancer, particularly the presence of HPV. Major risk factors for the development of anal cancer correlate to sexual promiscuity (e.g., >10 sexual partners) and anoreceptive intercourse typically associated with HPV and HIV infections. No specific occupational exposures are associated with the development of anal cancers.

Human Papillomavirus (HPV)

Homosexual men with high-grade anal intraepithelial neoplasia grade 3 and HPV-16 infections are particularly vulnerable to developing anal cancer.[261] Recurrence of these high-grade lesions often occurs despite treatment (e.g., electrocautery). In a cohort of 100 HIV-infected homosexual men treated with electrocautery for high-grade anal intraepithelial neoplasia, the probability of recurrence at 24 months of follow-up was ~53% (95% CI: 34–73%).[262] Surviving patients with squamous cell carcinoma of the anus have an increased risk of developing HPV-related, second primary malignancies (e.g., oral cavity, pharyngeal, genital), particularly in never-married men.[263,264] In a cross-sectional observational study of 324 women with

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TABLE 54.5. Human papillomavirus (HPV) factors involved in the pathogenesis of anal cancer.

HPV Factor	Function	Effect
E1, E2	Insertion of viral DNA into host genome	Loss of E2 function and integration of the viral genome into the host genome increases the production of E6 and E7 oncogenes
E5	Accessory role in malignant transformation	Reduces epidermal growth factor receptor turnover resulting in increased susceptibility to mitogenic effects and inhibits cell-mediated immunity by decreasing cell surface major histocompatibility complex class 1 expression
E6	Binds and inactivates tumor suppressor protein p53	Formation of protein complex destroys p53 proteins and causes chromosomal instability from loss of p53 DNA repair and cellular apoptosis functions that normally removes DNA mutations. Also reduces immune surveillance by decreasing E-cadherin on keratinocyte surface
E7	Binds retinoblastoma (Rb) protein	Enhances cell proliferation by promoting progression past the mid-G1 restriction point into the S-phase along with accumulation of DNA mutations produced by HPV E6 protein
L1	Major capsid formation	Envelops HPV genome to form fully infectious viral particles when the infected epithelial cell sloughs or dies
L2	Minor capsid formation	Envelops HPV genome to form fully infectious viral particles when the infected epithelial cell sloughs or dies

anal cancer and age-matched controls (general population and patients with rectal adenocarcinoma) using telephone interviews, logistic regression indicted an increased anal cancer risk associated with anoreceptive intercourse, venereal infections in their partner, and sexual promiscuity, particularly for the first intercourse before age 30 years.[257] The adjusted odds ratio for ≥10 lifetime sexual partners was 4.5 (95% CI: 2.7–7.4) and 2.4 (95% CI: 1.3–4.5) for history of sexually transmitted diseases in their partner. The incidence of anal cancer is 10 times higher among HIV-seropositive homosexual men than among women with cervical cancer.[265] Examination of data from the Danish National Patient Register suggests an association between the presence of genital warts and an increased risk of anal cancer.[266] The standardized incidence ratio of anal cancer comparing individuals with genital warts and the general Danish population was 21.5 (95% CI: 14.4–30.9, $n = 29$) for men and 7.8 (95% CI: 5.4–11.0, $n = 33$) for women. Genital warts usually result from nononcogenic HPV types of infections (e.g., HPV6, HPV11).[267]

Tobacco/Alcohol Use

Case-control studies associate anal squamous cell carcinoma, but not anal adenocarcinoma with cigarette smoking in a dose-response relationship. In a meta-analysis of 45 observational studies, the overall summary prevalence estimate for anal cancer was ~2.5 times greater for current smokers (54%, 95% CI: 49–59%) than US adults in the general population (20–23%), with substantial heterogeneity (I^2 = 99%) in the studies.[268] Obesity and alcohol consumption were not associated with increased anal cancer risks. The population-based prospective study of 1.3 million women recruited via the UK National Health Service Breast Screening Program identified 517 anal squamous cell carcinoma cases; the relative risk of anal cancer in ever- versus never-smokers was 1.49 (95% CI: 1.24–1.83). The relative risk increased to 2.16 (95% CI: 1.65–2.83) in current smokers using >15 cigarettes/day. Alcohol use was not associated with an increased anal cancer risk. This study did not collect information on sexual behavior of the participants. A case-control study of 126 patients (67 women, 31 heterosexual men, 28 homosexual men) with anorectal squamous cell carcinoma and 372 randomly selected control subjects in the San Francisco Bay Area reported that the risk of anorectal cancer in homosexual men increased with self-reported pack-year history of cigarette smoking.[269] The relative risk for a 20-pack-year history was 1.9 (95% CI: 1.7–2.2) compared with 5.2 (95% CI: 4.2–6.5) for a 50 pack-year history, with higher risks for current smokers. In a study of 72 patients with metastatic anal

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cancer, a 30-pack-year history of smoking was relatively more common in HPV^- than HPV^+ tumors.[258]

HISTOLOGY

The anal canal is the last 3–5 cm of the gastrointestinal tract between the anorectal junction and the outer opening of the gastrointestinal tract (i.e., squamous-mucocutaneous junction with perianal skin termed the anal verge). The dentate line is the anatomical division of the rectum and the anal canal. The region proximal to the dentate line contains columnar glandular epithelia, whereas the distal region has stratified squamous epithelia. Anal cancer typically arises from mucosa-lined anal canal 1–2 cm proximal to the dentate line to the intersphincteric groove separating the anal canal and anal margin; this heterogeneous transitional zone contains un-keratinized squamous, transitional basal, columnar, and cuboidal cells. The specific cell of origin does not affect the outcome.[270] Approximately 80–85% of anal cancers are squamous cell carcinomas, with ~10% adenocarcinomas and the rest much rarer tumors (e.g., melanomas, small cell carcinomas). The anal canal is a very uncommon site for metastatic tumors.[271] The development of precancerous lesions (high-grade squamous intraepithelial lesions, HSIL) precedes the development of anal cancer. These lesions do not regress in most individuals with HSIL, despite antiretroviral therapy that increases CD4 concentrations and reduces viral loads;[272] however, the progression rates to anal cancer appear lower in anal than in cervical cancer.[273]

HOST SUSCEPTIBILITY

As mentioned above, the risk of developing anal malignancies is higher in immunocompromised and immunodeficient patients, particularly those with chronic active HIV infection and chronic immunosuppression in transplant patients.[274] The risk of anal cancer is ~12-fold greater in HIV patients who have been seropositive for 15 years compared with those with a 5-year history irrespective of highly active antiretroviral therapy (HAART).[275] Relatively rare forms of anogenital pre-malignancies associated with an increased risk of anal cancer include Bowen's disease, Bowenoid papulosis, and erythroplasia of Queyrat.

CLINICAL FEATURES

A substantial lag occurs between HPV infection and the diagnosis of anal cancer with the diagnosis uncommon before 40 years of age; anal cancer incidence increases with age, with occurrence more common in women than men.[276] The most common age at diagnosis of anal cancer in men is 40–49 years followed by men aged 50–64 years, whereas the most common age in women is ≥65 years followed by 50–64 years.[250] Anal squamous cell carcinoma develops up to two decades earlier in HIV-infected men than in non-infected men.[277] Analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data from 39 cancer registries for cases diagnosed from 1998–2003 indicated the overall mean age at diagnosis of invasive anal cancer was 62 years, with a majority of the cases staged as *in situ* or localized.[255] The most common clinical feature of anal cancer is rectal bleeding with or without pain, often attributed to hemorrhoids.[278] Less common symptoms include intense pruritis, altered bowel habits, and enlarged inguinal nodes. For localized disease, the 5-year survival rates for anal cancer range from 40 to 70% depending on the overall tumor/node/metastasis (TNM) stage.[279]

LIVER AND BILE DUCTS

Substantial variation in the occurrence of hepatocarcinoma exists worldwide. Liver cancer is the second most common cause of cancer-related deaths among men globally, with the highest incidence and mortality rates among both sexes in Eastern/Southeastern Asia and middle/western parts of Africa (e.g., southern Sahara).[280] Southern Europe has intermediate liver cancer incidence rates. Worldwide, liver cancer is the sixth most common human cancer. Liver cancer is the fourth leading cause of cancer deaths in the United States after lung, colorectal, and stomach cancers.[281] The age-adjusted mortality rates from 2000–2016 for liver cancer increased by 43% for US men (10.5 to 15.0/100,000) and 40% for US women (4.5 to 6.3/100,000).[282] Among men, global liver cancer incidence rates range from 1.9/100,000 (Algeria) to 41.3/100,000 (Korea) compared with 0.8/100,000 (Netherlands) to 13.9/100,000 (Zimbabwe) among women. Mongolia has the highest liver cancer rates (78/100,000) reflecting the high prevalence of HBV, HCV, and excessive alcohol consumption. Approximately 50% of liver cancer cases and deaths occur in China. However, these rates are decreasing in low-income countries as public health programs reduce HBV infections and aflatoxin exposures,

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while liver cancer mortality rates are increasing in high-income countries (e.g., North America, Oceania, Central/Northern Europe).[283] In the United States, increased prevalence of chronic HCV infections from contaminated blood and intravenous drug abuse during the 1960s and 1970s contributed to the increased rates, along with increasing rates of obesity and type 2 diabetes more recently.[284] The prevalence and incidence of liver cancer are similar because of very poor overall survival from late-stage presentations, aggressive tumors, and limited treatment options.

Primary liver tumors typically are classified based on their specific histology, including hepatocellular carcinoma (liver cell carcinoma), cholangiocarcinoma (intrahepatic duct carcinoma), angiosarcoma, and hepatoblastoma. Hepatocellular carcinomas account for most (75–90%) primary liver cancers, particularly in developing nations in Africa and Asia, where hepatitis B and C infections are common cocarcinogen. The biliary tract consists of the biliary ducts and the gall bladder; biliary duct cancers (intrahepatic and hilar/distal biliary duct cholangiocarcinomas) are rare cancers in the United States compared with primary liver cancer.

HEPATOCELLULAR CARCINOMA (HCC)

Although hepatic cancer commonly occurs in animal models in response to chemical carcinogens, these chemicals are an uncommon cause of liver cancer in the United States. US liver cancer-related death rates are the highest among all cancer sites in the United States.[285] HCC typically arises in patients with underlying cirrhosis in up to 90% of HCC cases.[286] Worldwide, liver cancer is the fifth most common cancer among men and ninth most common cancer among women; overall, liver cancer is the second most common cause of cancer death after lung cancer globally.[287] Although overall cancer rates declined by ~1.5% annually from 2003–2012, liver cancer-related death rates increased for most ethnic groups in the United States, with liver cancer incidence also increasing during this time.[288]

CARCINOGENESIS

Primary liver cancer is a common tumor in experimental animals exposed to a wide variety of chemicals. A number of factors modulate HCC incidence and yield in animal models including chronic exposure to peroxisome proliferators, pesticides, microsomal enzyme inducers, surgical alterations of blood supply, modification of dietary protein, and parasitic liver infections.[289] HCC is the prototypical inflammation-associated cancer commonly occurring in patients with advanced hepatic fibrosis and/or cirrhosis from chronic liver disease, particularly damage resulting from HBV/HCV infections and high alcohol consumption. This disease also develops in chronic, non-cirrhotic inflammatory conditions (e.g., non-alcoholic steatohepatitis, NASH; non-alcoholic fatty liver disease, NAFLD). Epigenetic changes (DNA methylation, histone modifications, and RNA-mediated alteration/silencing of gene expression) contribute to the promotion and progression of hepatocellular carcinoma by inducing genomic instability from global hypomethylation and tumor suppressor gene inactivation from hypermethylation of specific promoter genes.[290] Histone (chromatin) modifications involve covalent post-translational changes in histone proteins that affect cellular processes (e.g., DNA replication/repair, gene transcription). Alteration of non-coding RNA (microRNA, miR) deregulates several important cellular processes, including inhibition of apoptosis (miR-221), silencing of proliferation inhibition (miR23b), promotion of cell invasion (miR-9), and inhibition of tumor suppressor genes (miR-101, miR-122, miR-195, mir-338).

HBV is a DNA virus that causes insertional mutations in the setting of chronic inflammation; HCV is an RNA virus that also produces tumors after prolonged hepatic fibrosis and/or cirrhosis.[291] A hepatocellular carcinoma typically contains at least 40 genomic abnormalities; however, few of these mutations are drivers or necessary for the development of HCC tumors as defined as a statistically significantly mutated gene above background mutation rates. Common mutations involve Wnt pathway activation (e.g., β-catenin encoded by *CTNNB1*), p53 inactivation (*TP53*), and telomere maintenance (telomere reverse transcription mutations in *TERT* that evade the replicative senescence of cirrhotic hepatocytes), particularly in the late stages of HCC development.[292] A compilation of 1,340 multiethnic hepatocellular carcinomas confirmed a complex landscape of HCC driver genes, including the following three core drivers: 1) *TP53* (tumor suppression); 2) *CTNNBA* (Wnt signaling); and 3) *TERT* (immortalization, genomic instability).[293] The estimated latency period for HCC ranges from 10–40 years, with a typical latency of 20 years in patients with chronic HBV and/or HCV infections causing cirrhosis.[294,295] In Africa, aflatoxin consumption acts synergistically with HBV to produce a higher incidence and earlier onset of HCC compared with other parts of the world.[296]

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EXPOSURE

The main risk factors for hepatocellular carcinoma (HCC) in humans include cirrhosis (chronic liver inflammation and fibrosis), hepatitis B (HBV) and hepatitis C (HCV) virus infections, adeno-associated virus 2 (AAV2), alcohol abuse, and metabolic dysfunction-associated steatotic liver disease (e.g., diabetes, obesity).[292,297] Contributing factors include cigarette smoking, liver flukes in endemic areas, aflatoxin ingestion, and possibly excess body fat. Approximately one-quarter of HCC cases do not have known risk factors.[298] In humans, epigenetic mechanisms (DNA methylation, histone modulation, RNA interference) contribute to the development of hepatocellular carcinoma in response to the major risk factors.[299,300]

Almost all HCV-related HCCs occur among patients with cirrhosis. Other than HBV integration into the host genome targeting cellular genes involved in cell signaling,[301] there are no consistent genetic changes associated with liver cancer other than a few genes expressing axin (a negative regulator of Wnt/β-catenin signaling), β-catenin, and p53.[302] Aberrant DNA methylation is an epigenetic mechanism for gene silencing in human cancers, including hepatic cancer that promotes hepatocarcinogenesis by inactivating tumor suppressor and other cancer-associated genes. A study of hepatocellular carcinomas from France and Thailand found a high frequency of aberrant hypermethylation of specific genes (*CHRNA3*, *DOK1*, *GSTP1*, *RASSF1A*) in hepatocellular carcinoma tumors compared with cirrhotic and normal liver tissue.[303]

Occupation

There are no persuasively positive associations between occupational exposure to chemicals and the development of hepatocellular carcinoma, particularly for women.[304] A case-control study of 80 cases of hepatocellular carcinoma did not detect any statistically significant association between occupation and hepatocellular cancer.[305] This study suggested the possibility that pesticide exposure and road construction work with asphalt exposure may increase the risk of hepatocellular carcinoma, but to date, cohort and mortality studies have not validated this association.[306,307] A review of 15 studies demonstrated no consistent association between pesticide exposure and liver cancer using job exposure matrices, self-reported questionnaires, and geographical residence, with most case-control studies reporting no association.[308] Although weak, the strongest association involved exposure to organochloride pesticides (e.g., DDT).

Lifestyle

Tobacco

Tobacco smoking is a potential risk factor for HCC based on IARC evaluations;[309] however, the studies associating tobacco use and HCC remain somewhat inconsistent, even in the presence of HBV or HCV.[310] The interaction between HCC and viral infections appears more than additive for HBV and cigarette smoking and more than multiplicative for HCV and cigarette smoking.[311] The increased prevalence of high alcohol consumption and chronic viral hepatitis confounds the interpretation of studies on HCC risks and smoking. In a meta-analysis of 38 cohort and 58 case-control studies using never-smokers as controls, the estimated meta-RR for liver cancer (mostly HCC) in current smokers was 1.51 (95% CI: 1.37–1.67), whereas the estimated mRR for former smokers was not statistically significant (mRR = 1.12, 95% CI: 0.78–1.60) with substantial heterogeneity.[312] In a prospective cohort study of 17,363 London-based male government employees followed up to 38 years and the risk of liver cancer-related deaths using never-smokers as controls, the hazard ratio (HR) was not statistically significant for current smokers (HR = 1.43, 95% CI: 0.69–2.95) or former smokers (HR = 1.03, 95% CI: 0.49–2.16).[313] The Singapore Chinese Health Study reported an increased HCC risk in current smokers (HR = 1.63, 95% CI: 1.27–2.10) with a dose-response relationship.[314] Other studies suggest liver cancer risk and smoking are related in a dose-response relationship.[312]

Alcohol

The contribution of high alcohol intake to liver cancer risks is modest compared with HBV/HCV infections, with evidence associating HCC with high alcohol consumption weaker in cohort studies than case-control studies.[283,315] The primary difficulty in evaluating the effect of alcohol on HCC risks is a consistent definition of high alcohol consumption given the variability of alcohol use criteria in observational studies. In a systematic review and meta-analysis of 19 primarily Asian cohorts and nested case-control studies (4,445 liver cancer cases and 5,550 deaths), the pooled RR (pRR) for heavy drinking (≥3 drinks/day) was 1.16 (95% CI: 1.01–1.34) compared with nondrinkers.[316]

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The results for moderate drinkers (<3 drinks/day) were statistically nonsignificant (pRR = 0.91, 95% CI: 0.81–1.02). A meta-analysis compared adjusted relative risks of liver cancer in light (≤1 drink/day), moderate (≤4 drinks/day), and heavy (>4 drinks/day) alcohol drinkers compared with nondrinkers in 9 cohort and 27 case-control studies.[317] A standard drink had 12.5 g alcohol. The adjusted pooled RR was statistically different than nondrinkers only in heavy alcohol users with the pRR in cohort studies (pRR = 1.12, 95% CI: 1.02–1.23, I^2 = 0%, n = 7 studies) lower than in case-control studies (pRR = 2.79, 95% CI: 2.00–3.87, I^2 = 76%, n = 24 studies). The adjusted pRR for liver cancer in heavy drinkers was also significantly different than nondrinkers in men (pRR = 1.59, 95% CI: 1.21–2.09, I^2 = 69%, n = 11 studies), women (pRR = 3.89, 95% CI: 1.60–9.48, I^2 = 10%, n = 3), Asian studies (pRR = 1.59, 95% CI: 1.27, I^2 = 69%, n = 15), and North American studies (pRR = 3.40, 95% CI: 2.54–4.55, I^2 = 0%, n = 7).

Obesity

The presence of hepatic steatosis along with obesity and diabetes mellitus increases the risk of HCC, particularly in patients with chronic HCV. In a Japanese cohort study of 1,431 patients with chronic HCV followed for up to 10 years, obesity was an independent risk factor for HCC.[318] Compared with underweight patients (≤18.5 kg/m^2, n = 112), hazard ratio for HCC in overweight patients was 1.86 (95% CI: 1.09–3.16, P = 0.022, n = 265) and 3.10 (95% CI: 1.41–6.81, P = 0.005, n = 31) in obese patients. In a meta-analysis of 11 cohort studies (7 European, 2 United States, 2 Asian) using standard BMI measures, the summary RR for liver cancer compared with normal BMI participants was 1.17 for overweight individuals (95% CI: 1.02–1.34, I^2 = 52.5%) and 1.89 (95% CI: 1.51–2.36, I^2 = 86.4%) for obese individuals. The strong association of obesity with diabetes mellitus, fatty liver, and increased insulin resistance confounds these results.[319] Diabetes mellitus increases the risk of non-alcoholic fatty liver disease (NAFLD) and the more aggressive form, non-alcoholic steatohepatitis (NASH); NAFLD is independently associated with an increased risk of HCC.[320]

Diet

Contamination of foodstuffs (e.g., corn, peanuts) with aflatoxins occurs during the storage of foodstuffs in damp, warm conditions, particularly in eastern Asia and sub-Saharan Africa. Certain *Aspergillus* species produce these mycotoxins with aflatoxin B1 (AFB_1) being the most carcinogenic based on animal studies. Epidemiological studies indicate aflatoxins interact multiplicatively with chronic HBV infection to increase HCC risks. In a systemic review and meta-analysis of 1,680 HCC cases and 3,052 controls from Taiwan, China, and sub-Saharan Africa, the summarized OR of HCC from the combined effects of aflatoxin and HBV was 73.0 (95% CI: 36.0–148.3) compared with 11.3 (95% CI: 6.75–18.9) from HBV alone and 6.37 (95% CI: 3.74–10.86) from aflatoxin alone based on HBV biomarkers and urine aflatoxin concentrations, respectively.[321]

Other than aflatoxins, no other dietary factor consistently produces elevated HCC risks in epidemiological studies.[283] The results on meat intake and liver cancer risks are conflicting, with the Shanghai Women's and Men's Health Studies[322] and the EPIC cohort study[323] reporting no association between HCC risks and meat consumption, whereas the NIH-AARP cohort associated high red meat consumption with increased HCC risks.[324] In a Chinese systematic review and meta-analysis of 7 cohort and 10 case-control studies, the pooled relative risks of HCC for the highest versus lowest consumption levels were 1.10 (95% CI: 0.85–1.42) for red meat, 1.01 (95% CI: 0.79–1.28) for processed meat, and 0.97 (95% CI: 0.85–1.11) for total meat.[325]

Several epidemiological studies across multiple countries report an inverse relationship between liver cancer risk and coffee use, primarily high coffee consumption (i.e., >3–4 cups daily) when compared with non-coffee drinkers.[326] In a Finnish study of 27,037 male smokers with 194 liver cancer cases and light coffee drinkers (0–<1 cup/day) as controls, the RR of liver cancer in participants drinking >4 cups coffee/day was 0.53 (95% CI: 0.30–0.95) and 1.35 (95% CI: 0.65–2.82) for never-coffee drinkers.[327] The pooled analysis of two large, prospective Japanese cohorts compared never, occasional, and ≥1 cup daily coffee drinkers based on self-reported consumption.[328] After adjustment for potential confounders and using never-drinkers as a reference group, the pooled RR of occasional and ≥1 cup/day coffee drinkers were 0.71 (95% CI: 0.46–1.09) and 0.58 (95% CI: 0.36–0.96), respectively, with a P_{trend} of 0.024.

Infections

Hepatitis B virus infections are major etiological factor in the development of hepatocellular carcinoma particularly in regions where the prevalence of hepatocellular carcinoma (HCC) is high.[329] Of the six

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genotypes of HBV, HCC is usually associated with genotypes C, D, and possibly B. In the United States, HBV genotypes A and D occur more commonly in Afro-Americans and whites, whereas genotypes B and C are more common in people with Asian ancestry.[290] HCC risks in HBV-infected persons are ~15- to 20-fold greater than those in uninfected persons, with the HCC risk doubling in persons co-infected with HCV.[330] The risk of co-infection with HBV and HCV is probably sub-additive.[331] Hepatitis C virus also promotes tumor progress through cell proliferation and immune suppression rather than initiation because HCV is an RNA virus that does not insert into host DNA. Consequently, HCV is usually associated with cirrhosis in patients with HCC. HCC risks in HCV-infected patients vary with geography (10- to 20-fold) and HCV genotypes (↑↑ with 3 and 1b). HCV is more common in Mediterranean countries (e.g., Egypt from mass schistosomiasis treatment campaigns using non-sterile equipment in the 1950s), whereas HBV occurs more frequently in eastern Asia. The latter infection usually develops perinatally or in early childhood, resulting in the occurrence of HCC below the age of 40 in high-risk populations.

Diseases

Diseases associated with cirrhosis and increased incidence of HCC include non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), α1-antitrypsin deficiency, and hemochromatosis, whereas HCC is less commonly associated with cirrhosis produced by Wilson disease, cholestatic liver disorders, and autoimmune hepatitis.[332] HCC occurs in patients with NASH, NAFLD, or metabolic syndrome without advanced hepatic fibrosis and/or cirrhosis. In a cohort of 1,500 US veterans with verified HCC, the unadjusted odds ratio of HCC in patients with NAFLD and no cirrhosis was 5.4 (95% CI: 3.4–8.5) and 5.0 (95% CI: 3.1–7.8) for patients with metabolic syndrome in the absence of cirrhosis compared with patients with HCV-related HCC.[333] Diabetes mellitus is associated with a 2–3-fold increased HCC risks in case-control studies, even in the absence of major risk factors. In a population-based, case-control study of 2,061 HCC patients and 6,183 non-cancer controls, the adjusted odds ratio was 2.87 (95% CI: 2.49–3.30).[334] A meta-analysis of 21 cohort studies involving 2,528 HCC cases among 35,202 participants followed for a median of 6.4 years reported summary HCC relative risks for diabetic patients with chronic liver disease from various causes. For patients with type 2 diabetes mellitus, the overall OR for HCC was 1.86 (95% CI: 1.49–2.31) compared with 1.90 (95% CI: 1.37–2.63) for nondiabetic patients with hepatitis C virus infection, 1.93 (95% CI: 1.35–2.76) for patients with cirrhosis, and 1.69 (95% CI: 0.97–2.92) for nondiabetic patients with hepatitis B virus infection.[335]

HISTOLOGY

HCC is an epithelial solid tumor that originates from several cell types, including stem cells, progenitor cells, and mature hepatocytes.[336] The multistep process of HCC tumor formation typically begins as premalignant cirrhotic nodules with low-grade dysplasia that progress to high-grade dysplastic nodules and subsequently transform into early malignant lesions (stages 0 and A) as a result of the accumulation of multiple somatic genomic changes. Each tumor contains a unique combination of genetic mutations and epigenetic modifications contributing to the highly diverse pathology of HCC. Most individuals with HBV or HCV never develop cirrhosis or HCC.

HOST SUSCEPTIBILITY

Although some case series associate rare genetic syndromes (e.g., Wolf-Hirschhorn syndrome)[337] with hepatocellular carcinomas, some clinical data associate these tumors with specific genetic syndromes. Hereditary diseases associated with increased HCC risks include hemochromatosis, porphyria cutanea tarda, acute intermittent porphyria, and α_1-antitrypsin deficiency. Studies on genetic susceptibility based on enzyme deficiencies (e.g., glutathione-*S*-transferase, epoxide hydrolases, aldehyde dehydrogenase 2) are conflicting and inconclusive.[283] Familial clustering of HCC occurs in part from the transmission of HBV/HCV, lifestyle habits, and environmental factors including obesity, cigarette smoking, and high alcohol consumption; however, increased HCC risks develop in families in studies adjusting for hepatitis and other major risk factors.

In an Italian study of 229 hepatocellular carcinoma (HCC) cases and 431 hospital-based controls excluding diseases associated with HCC, the odds ratio for HCC in participants with ≥1 first-degree relative with HCC was 2.38 (95% CI: 1.01–5.58).[338] In the Shanghai Women's and Men's Health Studies, liver cancer risks increased with an adjusted hazard ratio of 2.60 (95% CI: 1.77–3.80) for any first degree relative with liver cancer when compared with controls without a family history of liver cancer.[339] Adjustments included age, sex, education, income, BMI, vegetable and fruit intake,

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history of chronic hepatitis, history of cirrhosis or other chronic liver disease, history of diabetes, and history of cholelithiasis or cholecystectomy. The authors also reported results of a meta-analysis of 21 case-control and 6 cohort studies on familial risks of liver cancer, with an overall pooled relative risk of 2.55 (95% CI: 2.05–3.16) and substantial heterogeneity ($I^2 = 78.4\%$). The liver cancer risks determined by case-control and cohort studies were similar.

CLINICAL FEATURES

The incidence of HCC is 2- to 4-fold higher in men than women, in part because of the higher prevalence of risk factors (e.g., alcohol abuse, smoking, viral hepatitis) in men.[286] In contrast to most neoplasms, the staging of liver tumors relies on the Barcelona Clinic Liver Cancer classification rather than the TNM system.[332] Most patients with HCC are ≥40–45 years of age, with the exception of relatively younger patients in sub-Saharan Africa exposed to aflatoxins and HBV.[340] The mean age at HCC diagnosis is 55–59 years in China compared with 63–65 years in North America and Europe.[290] Although cirrhosis is the major risk factor for developing HCC (i.e., 75–90% of cases), cirrhosis was previously undiagnosed in ~20% of patients presenting with HCC.[341] Five-year survival rates for primary liver cancer are generally poor (i.e., 5–15%) depending on the country.[283] Historic median survival rates are ~36 months; however, treatment of early stages (i.e., 0, A) with potentially curative therapies (resection, transplantation, local ablation) increases the median survival to 60 months and beyond.[292] The estimated median survival for intermediate stage B is 26 months compared with 11 months for advanced stage C.

CHOLANGIOCARCINOMA

After hepatocellular carcinoma, cholangiocarcinoma is the most common primary hepatic malignancy accounting for 10–20% of newly diagnosed liver cancers.[342] The incidence of cholangiocarcinomas in the United States is ~1/100,000 persons. Worldwide, cholangiocarcinomas account for ~15% of liver cancers; the incidence rates are particularly high in parts of Asia where infection with the liver fluke is common.[343,344] Cholangiocarcinomas are divided into intrahepatic (ICC) and extrahepatic (hilum and distal bile duct, ECC); the pathogenesis, morphology, risk factors, and prognosis of these two types differ with hepatocellular carcinoma features more similar to ICC than ECC. The worldwide incidence of intrahepatic cholangiocarcinoma ranges from 0.2/100,00 in Australian men to 96/100,000 in Thai men.[345] Previously, ICC was contained within the HCC staging system; most cancer registries combined cholangiocarcinomas with other hepatobiliary tumors (e.g., hepatocellular carcinoma, gallbladder cancer). Hence, earlier epidemiology studies on cholangiocarcinoma may not reflect current classifications.

CARCINOGENESIS

Malignant transformation of cholangiocytes in the biliary duct epithelium and the development of cholangiocarcinoma probably result from bile stasis and chronic inflammation followed by a multistep-process initiated by cytokines (e.g., IL-6) and growth-promoting factors (e.g., tumor growth factor-β, TGF-β). The resulting generation of reactive nitrogen and oxygen species induces a variety of oncogenic mutations in cell cycle control, cell signaling pathways, and chromatin dynamics including BRAF, KRAS, MLL3, PEG3, RNF43, ROBO2, SMAD4, and TP53 mutations along with epigenetic modulators of genes (e.g., *BAP1*, *PBRM1*).[346,347] Whole exome sequencing of eight cholangiocarcinoma tumors associated with Southeast Asian liver fluke (*Opisthorchis viverrini*)-related tumors identified 2,016 somatic mutations in 187 genes using Sanger sequencing.[348] Focusing on 15 genes for mutation prevalence screening in these and 46 additional cholangiocarcinoma samples, the most common mutations occurred in *TP53* (44%), *KRAS* (17%), and *SMAD4* (17%) along with genes associated with genomic stability, G protein signaling, and histone modification.

Cholangiocarcinomas are heterogenous tumors that demonstrate molecular differences between ICC and ECC types. Using next-generation sequencing and gene expression data in three ICC cases and eight ECC cases, mutations in *IDH1* (33%) and *NRAS* (33%) genes were the most common mutated genes in ICC tumors compared with *TP53* (75%), *KRAS* (50%), and *BRAF* (12.5%) in ECC tumors.[349] *KRAS* and *BRAF* genes produce mitogen-activated protein kinase/extracellular-signal-regulated kinases that mediate cellular responses to growth signals. Somatic mutation analysis also indicates molecular heterogeneity between ICC subtypes (mass-forming, periductal infiltrating, intraductal growth types).[350]

EXPOSURE

Risk factors are less well defined for ICC than HCC; frequently, detection of ICC occurs in patients without known risk factors or during screening processes for

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TABLE 54.6. Estimated summary odds ratios for suspected cholangiocarcinoma risk factors based on a meta-analysis of eleven case-control studies by Palmer. The studies demonstrated modest heterogeneity (cirrhosis, diabetes mellitus II) and high degrees of heterogeneity (alcohol, HBV, HCV, smoking) with relatively little heterogeneity in the obesity studies as determined by the I^2 statistic. Alcohol use was variously defined as >80 g/day (three studies), the presence of alcoholic liver disease (four studies), or alcohol use for ≥6 months. The odds ratio for smoking was not statistically significant. Tobacco use was based on ICD-9 coding (three studies) and history of use (five studies). (Based on Palmer and Patel).[352]

Risk Factor	Summary Odds Ratio	95% Confidence Limit	I^2 Statistic (%)	Number of Studies
Cirrhosis	22.92	18.24–28.79	62.4	7
Hepatitis B	5.10	2.91–8.95	86.3	8
Hepatitis C	4.84	2.41–9.71	83.6	8
Alcohol use	2.81	1.52–5.21	90.0	10
Diabetes mellitus type II	1.89	1.74–2.07	57.8	9
Obesity	1.56	1.26–1.94	0.0	3
Smoking	1.31	0.95–1.82	83.1	8

patients at risk for HCC.[351] Although several risk factors are associated with intrahepatic cholangiocarcinoma (e.g., HCV, HBV, heavy alcohol consumption, primary sclerosing cholangitis, and less strongly with diabetes and obesity), most patients with ICC in Western countries have no recognized risk factors. In a United States case series of 73 surgically treated intrahepatic cholangiocarcinomas, no identified risk factor accounted for 48 (66%), HCV for 13 (18%), HBV for 5 (7%), and primary sclerosing cholangitis for 3 (4%).[345] Cirrhosis appeared in 8 (11%) of the cases, whereas 3% had nonalcoholic steatohepatitis

Similar to hepatocellular carcinoma, the presence of cirrhosis increases the risk of intrahepatic cholangiocarcinoma (i.e., ~10- to 20-fold). A meta-analysis of 11 case-control studies from low and high prevalence regions of ICC identified several risk factors, including cirrhosis, diabetes, obesity, alcohol use, and chronic HBV/HCV infections, as displayed in Table 54.6.[352] Suspected extrahepatic cholangiocarcinoma (ECC) risk factors involve chronic biliary tract inflammation, including primary sclerosing cholangitis in Western countries, hepatolithiasis and liver fluke infections (*Clonorchis sinensis* in Southwest China, *Opisthorchis viverrini* in Laos/Thailand), various biliary malformations (choledochal cysts, congenital hepatic fibrosis, polycystic ovary syndrome), and thorium dioxide (Thorotrast) exposure.[353,354,355] In a case-control study of 246 cholangiocarcinoma cases (ICC, 83; ECC, 163) and 236 hospital-based controls from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data, the prevalence of anti-HCV antibodies, anti-HBc antibodies, and heavy alcohol consumption was statistically different than controls; however, the 95% CI were extremely wide, indicating poor precision in the estimates.[356] The prevalence of heavy alcohol consumption was the only ECC risk factor that was statistically different than controls (17.8 vs. 3.8%, $P = 0.003$); the prevalence of diabetes and smoking was also not statistically different in ICC patients and controls. The prevalence of cirrhosis was higher in ICC patients than ECC patients (24.1 vs. 4.9%, $P < 0.0001$).

Lifestyle

The association between smoking and ICC risks is relatively weak compared with HCC. In a meta-analysis of eight case-control studies from low and high prevalence regions of ICC, the summary relative risk for developing ICC tumors in smokers was statistically nonsignificant, with a high degree of heterogeneity based on administrative data and patient histories as demonstrated in Table 54.6.[352] The association of ICC with obesity is inconsistent. In a Danish population-based, case-control study using 764 histologically confirmed ICC cases from the Danish Cancer Registry and 3,056 age-/sex-matched hospital controls, the odds ratio for obesity persisting for >1 year and ICC risk was statistically nonsignificant (OR = 1.83, 95% CI: 0.54–6.14, $n = 4$).[357] The association between heavy alcohol consumption and ICC is somewhat inconsistent but strongest for patients with alcoholic liver disease.[352]

Diseases

In a meta-analysis of 10 case-control and 5 cohort studies, the summary relative risk of cholangiocarcinoma in diabetic patients was 1.60 (95% CI: 1.38–1.87;

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$P_{\text{heterogeneity}} = 0.992$).[358] In contrast to HCC, infection with HBV or HCV is a modest risk factor (i.e., ~2-fold) for intrahepatic cholangiocarcinomas; the association with ICC is weaker for HBV than HCV. In a Danish case-control study, chronic liver diseases associated with increased ICC risks included alcoholic liver disease (OR = 19.22, 95% CI: 5.55–66.54) and unspecified cirrhosis (OR = 75.9, 95% CI: 10.2–565.7).[357] Bile duct diseases were also associated with increased ICC risks, including cholangitis (OR = 6.3, 95% CI: 2.3–17.5), choledocholithiasis (OR = 23.97, 95% CI: 2.9–198.9), and cholecystolithiasis (OR = 4.0, 95% CI: 2.0–7.99); however, the wide confidence limits indicate imprecise odds ratios. The lifetime risk of cholangiocarcinoma in patients with primary sclerosing cholangitis ranges from 7–14%, with most tumors located in the hilum (i.e., ECC).[359] In a case series of 41 patients with primary sclerosing cholangitis, the estimated cumulative risk of cholangiocarcinoma (ICC + ECC) was 6% (95% CI: 2–15) after 10 years, 14% (95% CI: 4–25) after 20 years, and 20% (95% CI: 6–40) after 30 years.[360] The presence of primary sclerosing cholangitis in patients with inflammatory bowel disease (IBD) complicates the determination of an association between IBD and cholangiocarcinoma. A meta-analysis of seven case-control studies (four Asian, one pooled European, two American) on nonalcoholic fatty liver disease (NAFLD) suggested the presence of NAFLD modestly increased the risk of cholangiocarcinoma, with similar adjusted pooled risks for ICC and ECC.[361] The overall pooled adjusted odds ratios were 2.09 (95% CI: 1.49–2.91, $I^2 = 42\%$) for ICC and 2.05 (95% CI: 1.59–2.64, $I^2 = 0\%$) for ECC.

Medical

Cholangiocarcinoma is a common histological type of liver cancer along with hepatocellular carcinoma and angiosarcomas among patients receiving chronic α-particle radiation from thorium dioxide (Thorotrast) exposure. In a Danish study of 127 liver cancer patients diagnosed a median of 35 years (range, 18–48 years) after Thorotrast injection, 45 patients had hepatocellular carcinoma, 41 had cholangiocarcinoma, and 35 had angiosarcomas.[362] The increased ICC risks exceeding 300-fold suggest Thorotrast is more carcinogenic to bile duct epithelial cells and sinusoidal lining cells than hepatocytes. This imaging agent was banned over 50 years ago; consequently, the impact of this carcinogen is primarily of historical interest.[363] The latent period between exposure to Thorotrast and the diagnosis of cholangiocarcinoma is long (>20 years),[364,365] with a mean of 34.7 ± 6.6 years (range, 23–45 years) for a series of 44 cases.[366] In this series, cholangiocarcinoma represented ~43% of all histological types of liver cancer related to Thorotrast. Cholangiocarcinoma has been associated with the administration of some medications (isoniazid, methyldopa, oral contraceptives); however, the associations are relatively weak.

Occupation

The association between cholangiocarcinoma and chemical carcinogens (nitrosamines, dioxin, polychlorinated biphenyls) is relatively weak. Although the number of cases was small ($n = 15$), a hypothesis-generating, case-control study of patients with cholangiocarcinoma did not correlate exposure to organic solvents with the development of cholangiocarcinoma.[367] The International Agency for Research on Cancer lists 1,2-dichloropropane as a human carcinogen (Group 1). In 2014, Kubo et al. collected a cluster of 18 workers with cholangiocarcinomas (ICC, ECC) from a group of 111 offset proof-printing plant workers in Osaka, Japan.[368] Although these workers were exposed to several organic solvents (e.g., 1,1,1-trichloroethane, dichloromethane), all affected workers had long-term, high-dose exposure to 1,2-dichloropropane ranging from 6–16 years (median, 12.5 years) in estimated concentrations of 150–620 ppm during ink removal operations and shift TWA concentrations of 62–240 ppm.[369] Examination of these workers indicated that all had chronic bile duct injuries with dilated intrahepatic bile ducts.

HISTOLOGY

Cholangiocarcinomas (bile duct carcinomas) are usually adenocarcinomas in the biliary duct epithelium that originate from cholangiocytes in small intrahepatic biliary ductules (intrahepatic cholangiocarcinomas, ICC) or large hilar (Klatskin tumors)/extrahepatic bile ducts (extrahepatic cholangiocarcinoma, ECC). The cystic duct separates the hilum and distal ECC tumors. These two anatomical subtypes are divided into mass-forming, periductal infiltrating, and intraductal growth ICC histological types and polypoid, nodular, scirrhous constricting, and diffusely infiltrating ECC histological types. Cholangiocarcinomas usually are similarly distributed between ICC and ECC tumors. Other rarer histological types of cholangiocarcinomas include papillary carcinoma and mucinous carcinoma.[370] Classical ICC cancer is a moderately well-differentiated glandular, tubular, or nested type of large tumor (>5 cm)

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that develops in the absence of underlying liver disease (e.g., severe fibrosis), whereas nonclassical ICC cancer contains a trabecular pattern that has mixed features of extrahepatic carcinomas and intrahepatic carcinomas derived from hepatic progenitor cells.[345] Nonclassical cholangiocarcinomas are usually small tumors that develop in fibrotic livers infected with HCV. Less than 1% of liver tumors contain HCC and ICC areas (combined hepatocellular/cholangiocarcinomas) that are often associated with HBV/HCV infections and cirrhosis. Hepatocytes and cholangiocytes have the same progenitor cells. Since 2010, the American Joint Committee on Cancer Staging Manual has a specific TNM (tumor-node-metastasis) staging system for ICC.

In the workers developing cholangiocarcinomas after long-term 1,2-dichloropropane exposure, the tumors consist of mass-forming type with variously differentiated adenocarcinoma ICC, intraductal growth type ICC, or well-differentiated papillary type ECC.[371] Precancerous lesions precede the formation of these cholangiocarcinomas, including biliary intraepithelial neoplasia and intraductal papillary neoplasms of the large intrahepatic or hilar bile ducts.

HOST SUSCEPTIBILITY

In contrast to HCC, well-defined inheritable diseases are not prominent in patients with ICC. Biliary stasis and reflux of pancreatic secretions producing chronic inflammation probably predispose patients to developing ICC. Diseases potentially associated with chronic inflammation of the biliary duct include choledochal cysts (congenital dilation of the bile duct), primary sclerosing cholangitis, and hepatolithiasis.

CLINICAL FEATURES

Painless jaundice is the most common presentation (i.e., ~70–90%) for a tumor obstructing the biliary tree, with cholangiocarcinoma being the second most common cause after pancreatic cancer. Other clinical features include pruritus, abdominal pain, weight loss, and, less commonly, fever. Jaundice typically occurs earlier with ECC than ICC. Cholangiocarcinoma tumors rarely present before age 40 years; however, most workers develop cholangiocarcinoma following long-term 1,2-dichloropropane exposure at young ages (e.g., 25–45 years).[369] The overall average age of patients presenting with cholangiocarcinoma is ~60–65 years, with a male–female ratio of ~1.3:1 depending on age, with increasing male prominence >60 years of age.[355] ICC typically is diagnosed in the fifth or sixth decade, remaining asymptomatic longer than ECC. Consequently, ICC tumors are frequently not resectable; the median survival time from diagnosis in 51 cases of advanced intrahepatic cholangiocarcinoma was short (i.e., 2 months).[372] Hence, the long-term survival of patients with intrahepatic cholangiocarcinoma is very poor (median ≅ 6 months without surgery) in part because of the high propensity for regional/distant metastases and very limited systemic therapy options; the 5-year survival rate is 20–40% after resection producing clear margins. ECC usually presents early, with signs of biliary obstruction affecting men more than women, with a peak age in the sixth or seventh decade. Surgery is the only curative option for early-stage ICC and ECC patients because advanced tumors are very resistant to chemotherapy and radiotherapy.

ANGIOSARCOMA

Hepatic angiosarcomas are rare, aggressive tumors with an incidence of <0.25/1,000,000 (i.e., ~25 cases/year in the United States, 200 worldwide).[373,374] Although these tumors represent <1–2% of primary malignant hepatic lesions, hepatic angiosarcomas are the most common liver tumor of mesenchymal origin. Approximately one-half of thorium dioxide-associated tumors occur in the liver, involving all three major types of liver cancer.[375,376]

CARCINOGENESIS

Angiosarcomas are high-grade malignant tumors that develop in the endothelial cells of blood and lymph vessels in the liver and other organs. Primary hepatic angiosarcomas consist of pleomorphic or spindle cells that grow in the lumina of vascular spaces (e.g., sinusoids, terminal hepatic venules).

EXPOSURE

With the exception of a strong correlation between vinyl chloride monomer in the plastic industry and thorium dioxide exposure from previous radiological imaging, the etiology of over 3/4 of these cases is unclear.[377] The human evidence for an association between Fowler's solution (potassium arsenite) and angiosarcoma is limited, based on small series of German vintners in the 1940s and 1950s along with occasional case reports;[378,379] the human evidence for androgenic-anabolic steroid-induced hepatic angiosarcoma is also limited.[380,381] In contrast to hepatocellular

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carcinoma, hepatic angiosarcoma is not strongly associated with viral hepatitis.[382] Most angiosarcomas are now idiopathic.

Occupation

A summary of studies of workers exposed to vinyl chloride monomers indicated an ~5-fold increased risk of developing hepatic angiosarcomas compared with controls.[110] Like other solid tumors, the minimal latency period between initial vinyl chloride exposure and the diagnosis of cancer is at least ~9–10 years, with a mean often near 20 years. In a study of vinyl chloride workers, the average latent period for the development of hepatic angiosarcoma was 20 years with a range of 12–28 years.[383] In a case series of 20 British workers developing angiosarcomas after vinyl chloride monomer exposure, the mean latency period (from first exposure to diagnosis) of the angiosarcoma was 25 years (range, 9–35 years).[384] The mean duration of occupational exposure to vinyl chloride was 15 years (range, 3–29 years). In a case series of 64 cases of angiosarcomas in polymerization workers exposed to vinyl chloride monomer, the median latency period between initial exposure and the diagnosis of angiosarcoma was 21 years (range, 9–38 years).[385] A follow-up study of 25 highly exposed German vinyl chloride workers reported a mean latency period (from first exposure to diagnosis) of 22 years (range, 12–34 years).[386]

Chronic exposure to inorganic arsenicals is a possible risk factor for angiosarcomas based on autopsy reports from vineyard workers dying after chronic arsenic exposure[387] and case reports of short-term exposure to medicinal trivalent inorganic arsenic compounds (Fowler's solution).[388] However, a cohort study of patients exposed to Fowler's solution did not confirm an increased hepatic angiosarcoma incidence.[389]

Medical

Thorium dioxide (^{232}Th) is a radioactive powder used as an imaging agent (Thorotrast) beginning in 1928. Approximately 50,000–100,000 patients received Thorotrast as a contrast agent for radiographic procedures from 1928 to the mid-1950s.[390] The first reported case of angiosarcoma associated with Thorotrast appeared in 1947.[391] Thorotrast is primarily (i.e., 90%) an α-emitter that is retained by the hepatic reticuloendothelial system with a biological half-life of 200–400 years. Several histological types of liver cancer are associated with the infusion of thorium dioxide besides angiosarcoma, including cholangiocarcinomas and hepatocellular carcinomas.[392,393] Following exposure to Thorotrast, the risk of developing angiosarcoma is ~2 orders of magnitude above the risk of developing cholangiocarcinoma and ~10 times the risk of developing hepatocellular carcinoma; the latent period ranges from 16–40 years.[394]

HISTOLOGY

Angiosarcomas originate from mesenchymal tissues in intrahepatic blood vessels; on presentation, most of these hepatic tumors are bilobular and multicentric involving large portions of the liver. Tumor expansion typically follows preexisting sinusoids with invasion of the portal or hepatic veins common. Endothelial markers (CD31, CD34), ERG expression, and factor VIII-related antigen are frequently positive molecular markers along with mutations of *TP53* (vinyl chloride monomer) and *KRAS-2* (thorium dioxide, sporadic).[395]

HOST SUSCEPTIBILITY

No specific diseases are associated with the development of hepatic angiosarcomas.

CLINICAL FEATURES

The usual presentation for an angiosarcoma has a male predominance (3:1–4:1) in the sixth to seventh decade of life. Clinical features associated with angiosarcoma are vague and nonspecific, including weakness, fatigue, weight loss, jaundice, fever of unknown origin, hepatomegaly, and right upper quadrant pain; consequently, the stage of cancer is typically advanced resulting in a poor prognosis. Complications in advanced cases resulting in death include gastrointestinal hemorrhage, recurrent hemoperitoneum, and hepatic failure.[396] In a case series of 20 workers with angiosarcoma from high concentrations of vinyl chloride monomer, metastasis was uncommon (3/20 cases).[384] The median survival of five cases of hepatic angiosarcoma was 6 months;[397] only ~2% of patients diagnosed with hepatic angiosarcoma lived more than 2 years.[398]

HEPATOBLASTOMA

CARCINOGENESIS

Most hepatoblastoma cases are sporadic, with an estimated incidence of 1.2–1.5/1,000,000 population and little variance between countries.[399,400] The presence of

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some hepatoblastomas at birth and particularly in very low-weight, preterm infants (i.e., <1,500 g) suggests the possibility of developmental factors in pregnancy along with genetic and epigenetic interactions.[401] The most frequent genetic aberration in hepatoblastoma tumors involves the Wnt signaling pathway (e.g., *APC* and *AXIN* genes) that expresses cyclin D1, MYC, and survivin;[402] less frequently, alteration of telomerase activation and expression occurs from changes in expression of *TERT* (human telomerase reverse transcriptase) gene.[403]

EXPOSURE

The incidence of hepatoblastomas is too infrequent to reliably associate this very rare pediatric tumor with specific exposures. The highest incidence of hepatoblastoma at birth and the resemblance of hepatoblastoma cells to embryonal liver cells suggest initiation during gestation.[399] A case-control study compared the hepatoblastoma risk based on interviews with parents of 75 children from the Children's Cancer Study Group with hepatoblastoma and parents of 75 age-matched controls.[404] In this study, hepatitis infections, smoking, and alcohol consumption were not clearly associated with increased hepatoblastoma risk.

HISTOLOGY

Hepatoblastomas are embryonal tumors that probably originate from hepatocyte precursors (hepatoblast), most commonly containing epithelial components composed of embryonal and fetal patterns.[405]

HOST SUSCEPTIBILITY

The distinctive cytogenetic alteration in hepatoblastoma is the addition (e.g., chromosome 2, 8, or 20) or loss (chromosome 18, Trisomy 18) of whole chromosomes.[401] Although most hepatoblastoma cases occur in children without a family history of hepatoblastoma, ~15% of hepatoblastoma cases involve genetic syndromes, including familial adenomatous polyposis coli and overgrowth syndromes (Beckwith-Wiedemann, Simpson-Golabi-Behmel, Sotos). Adenomatous polyposis coli results from inherited mutation of the *APC* gene (adenomatous polyposis coli),[406] whereas Simpson-Golabi-Behmel patients have alteration of the *GPC3* gene (glypican 3) on chromosome Xq26.[407] A mutation or deletion of the *NSDA* gene characterizes Sotos syndrome.[408]

CLINICAL FEATURES

Hepatoblastomas are extremely rare, pediatric liver tumors that usually occur before 4–5 years of age, whereas hepatocellular carcinomas are the most common liver tumor in adolescents. In between these ages, pediatric liver tumors may contain pathological features of hepatoblastomas and hepatocellular carcinomas (i.e., transitional liver tumors of childhood). Although hepatoblastoma is the most common liver tumor in children of <2 years of age, the medical literature contains extremely rare case reports of adult hepatoblastomas.[409] Common presenting clinical features of hepatoblastoma include expanding abdominal mass, right upper quadrant discomfort, fatigue, weight loss, and less frequently fever and vomiting.[410] Children often do not report any physical abnormalities.[411] Advances in chemotherapy and complete surgical resection of hepatoblastoma have improved the overall survival from ~30 to >80% over the last several decades.[412] The median survival for hepatoblastoma patients is much lower for adults (e.g., ~6 months) than children.[413]

GALLBLADDER

Gallbladder cancer is the fifth most common gastrointestinal cancer in the United States (i.e., ~5,000/year), whereas this cancer is the most common biliary tract cancer worldwide, particularly in less developed countries.[414] Typically, the presentation is late in the course of the disease resulting in a poor prognosis; discovery of this cancer frequently occurs during cholecystectomy for cholelithiasis and biliary obstruction.[415] The estimated age-adjusted, worldwide incidence of gallbladder cancer is ~2.2/100,000 persons, with a female/male predominance of 2–3; there is marked geographical and ethnic variation.[287] The highest gallbladder cancer incidence occurs in the Andes (Bolivia, Chile, Ecuador), India (New Delhi), and China (Shanghai), whereas this cancer is rare in most Western countries, with the exception of certain ethnic groups (e.g., southwestern natives and Mexican Americans, Korean men in Los Angeles).[416,417]

CARCINOGENESIS

The two major pathological causes of gallbladder cancer are: 1) formation of gallstones, biliary stasis, and resultant cholecystitis affecting women more than men;

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and 2) congenital abnormality of the biliary tract (e.g., anomalous pancreaticobiliary duct junction) that allows reflux of pancreatic secretion into the gallbladder.[418] Anomalous pancreaticobiliary duct junction is a structural abnormality causing an abnormal connection between the bile and pancreatic duct outside the duodenal wall and unaffected by the sphincter of Oddi. This pathway occurs more commonly in Asia (Japan, Korea, China).

Gallbladder cancer develops from accumulation of multiple genetic alterations; however, genomic data on gallbladder cancers are limited. Available data indicate these tumors contain multiple mutations (oncogenes, tumor suppressor genes, DNA repair genes), microsatellite instability, and epigenetic changes (e.g., methylation of gene promoters). In a study of 57 Chinese gallbladder cancer samples, the most common driver genes were *TP53* (47%), *ERBB3* (~12%), and *KRAS* (~8%); the most extensively mutated pathway was ErbB signaling (*EGFR*, *ERBB2*, *ERBB3*, *ERBB4* genes).[293,419] The latter pathway involves the epidermal growth factor family of receptor tyrosine kinases (ErbBs) that help regulate cell proliferation, survival, differentiation, and migration; disruption of these processes results in cancer cell growth and immortality. Gallbladder tumors in patients with anomalous pancreaticobiliary duct junction (APDJ) commonly contain KRAS gene mutations that activate the mitogen-activated protein (MAP) kinase pathway and promote inappropriate growth signals (e.g., cell proliferation, differentiation, and death); whereas gallbladder cancer patients with cholelithiasis frequently have less KRAS mutations. The gallbladder tumors in the latter patients also commonly have early-onset TP53 mutations ranging from 35–92% in most studies.[420,421] This tumor suppressor gene helps regulate multiple cellular processes, including DNA repair, apoptosis, and gene expression.

EXPOSURE

The rarity of gallbladder cancer complicates the identification of specific risk factors. The primary risk factors for gallbladder cancer are gallstones, advanced age, and female gender.[422] Other potential risk factors for increased gallbladder cancer risks include obesity, gallbladder polyps, porcelain (calcified) gallbladder, and chronic infections (*Salmonella typhi*/*paratyphi*, *H. bilis*);[423,424] however, the association of the latter two factors with gallbladder cancer is less consistent than the former three factors, particularly with the strong association between gallbladder cancer and gallstones. Insufficient evidence exists to associate gallbladder cancer with parasites, viruses, fungi, or oral contraceptives.[425] Several case-control studies, but not cohort studies, suggest drinking coffee reduces gallbladder cancer risks. Analysis of data from a prospective cohort study of 72,680 Swedish adults (aged 45–83) identified gallbladder cancer in 74 adults.[426] Using Cox proportional hazards regression models and coffee data at baseline, the multivariable hazard ratio of gallbladder cancer was 0.41 (95% CI: 0.20–0.83) for ≥4 cups of coffee daily compared with 0.50 (95% CI: 0.24–1.06) for 3 cup/day and 0.76 (95% CI: 0.41–1.41) for ≤1 cup/day.

Cholelithiasis

Gallstones and subsequent chronic inflammation are the most significant risk factors associated with gallbladder cancer, being present in 60–90% of malignant gallbladder tumors.[427] Although most patients with cholelithiasis do not develop cancer, cholelithiasis is a common disease and most (i.e., 60–80%) patients with gallbladder cancer have cholelithiasis. The association with gallbladder cancer is stronger in case-control studies than cohort studies. Analysis of data from three cohort studies and seven case-control studies on gallbladder cancer risks in patients with a history of gallstones demonstrated a summary RR of 4.9 (95% CI: 3.3–7.4), with significant heterogeneity among all studies. The summary RR for cohort studies was 2.2 (95% CI: 1.2–4.2), whereas the summary RR for case-control studies was 7.1 (95% CI: 4.5–11.2). A prospective cohort study of 113,394 Japanese adults (42.0% males) aged 40–89 years followed for a mean of 11 years did not detect a statistically significant association between a history of gallstones and gallbladder cancer in men (age-adjusted RR = 1.2, 95% CI: 0.3–4.7) or women (age-adjusted RR = 1.1, 0.4–2.9).[428] Some studies suggest gallstone size, volume, and number may increase gallbladder cancer risks, particularly large stones (i.e., ≥3 cm); however, the association of age with these factors confounds the reported elevated gallbladder cancer risks.[415]

Obesity

The association of gallstones with obesity confounds the interpretation of studies on the risk of gallbladder cancer in obese patients. Several meta-analyses suggest the risk of gallbladder cancer increases in overweight women, but not for men, with the risk increasing for both obese men and women (BMI ≥ 30 kg/m^2); however, the pooled relative risks are all <2.[429,430] Analysis of age-adjusted cancer mortality and obesity in a prospectively studied cohort of >900,000 US adults

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using BMI 18.50–24.99 kg/m^2 as referents reported statistically significant increased relative risk of gallbladder cancer for mildly obese women (RR = 2.13, 95% CI: 1.56–2.90, n = 59, BMI, 30.0–34.9 kg/m^2), but not for overweight women (RR = 1.12, 95% CI: 0.86–1.47, n = 86, BMI, 25.0–29.9 kg/m^2).[431] Similarly, the relative risk for mildly obese US men was elevated (RR = 1.76, 95% CI: 1.06–2.94, n = 20), but not for overweight men (RR = 1.34, 95% CI: 0.97–1.84, n = 94). In a retrospective cohort study of 1,715 gallbladder cancer cases from 2 million Norwegian adults using Cox proportional hazards regression, overweight and obese women had a higher gallbladder cancer risk compared with referent women based on BMI.[432] Compared with the referent (BMI, 18.5–24 kg/m^2), the relative risk for overweight women (BMI, 25.0–29.9 kg/m^2) was 1.27 (95% CI: 1.10–1.47) and 1.88 (95% CI: 1.60–2.2 kg/m^2) for obese women (>30.0 kg/m^2). The risk of gallbladder cancer was slightly increased in obese men, with a relative risk of 1.38 (95% CI: 1.01–1.89), but not in overweight men (RR = 1.00, 95% CI: 0.84–1.17). The P_{trend} was <0.001. In a case-control study of 184 gallbladder cancer cases (26% men, 74% women) from a large UK primary care database using BMI of <25 kg/m^2 as the referents, the odds ratio for the risk of gallbladder cancer was not statistically significant for overweight (OR = 1.03, 95% CI: 0.62–1.72, n = 31) or obese cases (OR = 1.51, 95% CI: 0.83–2.75, n = 19).[433] Substantial data were unavailable for smoking (34% cases, 39% controls), alcohol consumption (46% cases, 49% controls), and BMI (45% cases, 48% controls).

Structural Abnormalities

Polypoid gallbladder lesions occur in ~5% of adults, with most polyps discovered in asymptomatic patients undergoing abdominal ultrasonography for unrelated conditions.[434] In a study of healthy Japanese adults, the prevalence of gallbladder polyps in men increased with a rise in the obesity index, particularly in middle-aged men (i.e., 40–50-year-olds).[435] Although the obesity index increased with age in women, the study detected no similar increase in the prevalence of gallbladder polyps.

Anomalous pancreaticobiliary duct junction (APDJ) produces chronic gallbladder inflammation and increases gallbladder cancer risk, particularly in Japan. Gallbladder cancer is strongly associated with bile stasis intermingled with refluxed pancreatic juice. In a Japanese study of 126 patients with gallbladder carcinoma, 23 (~18%) had APDJ.[436] Compared with non-APDJ cases, patients with this congenital abnormality were younger (mean = 54 ± 9.1 years of age vs. 65 ± 9.7 years of age) and had a lower incidence of gallstones (17 vs. 64%, P < 0.01). This congenital abnormality is also known as pancreaticobiliary maljunction (PBM). In a Japanese case series of 129 PBM patients, gallbladder cancer occurred in 15 (21 %) of 73 patients with congenital biliary dilatation and in 43 (77%) of 56 PBM patients without biliary dilatation.[437]

Chronic gallbladder inflammation is associated with punctate calcium deposition in the gallbladder mucosa, resulting in bluish discoloration of the gallbladder (porcelain gallbladder). Although some studies suggest selective mucosal calcification (but not complete intramural calcifications) is associated with gallbladder cancer risks,[438] other case series involving pathological reports of patients undergoing cholecystectomy have not supported an association between porcelain gallbladder and gallbladder cancer.[439,440]

Chronic Infections

Several case-control studies suggest chronic gallbladder infections from *S. typhi*/*paratyphi* or *H. bilis/pylori* may contribute to malignant transformation in the gallbladder mucosa;[441,442] however, most studies are small without well-matched controls (e.g., gallstones) or well-standardized testing for the presence of carrier states. In an Indian prospective case-control study of 54 gallbladder cancer cases and 54 age-, sex-, and location-matched controls, 1/3 of the cases had positive PCR tests for *S. typhi* compared with none for the controls.[443] Indirect measures of *S. typhi* infections were also more common in the cases (Widal test, 24 vs. 13; indirect hemagglutination assay, 12 vs. 5). Studies associating *Helicobacter* infections with gallbladder cancer are inconsistent, particularly in endemic areas.[444] In an Indian case-control study of 54 gallbladder cancer cases and 55 hospital controls with cholelithiasis using 16SrRNA PCR to identify *H. bilis*, the relative risk of gallbladder cancer in *H. bilis*-positive patients was 1.05 (95% CI: 0.49–2.24, n = 32).[445] The report included a meta-analysis of 3 previous case-control studies involving 108 cases and 152 controls with a pooled odds ratio of 1.24 (95% CI: 0.63–2.44). The authors concluded that their study failed to demonstrate an increased gallbladder cancer risk in the presence of *H. bilis*.

HISTOLOGY

Gallbladder cancer arises from the progression of metaplasia or, much less commonly, the malignant transformation of a preexisting adenoma into an adenocarcinoma.[427] The presence of intestinal metaplasia

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in ~60% and dysplasia in >90% of adjacent mucosa in gallbladder tumors supports a stepwise model of malignant biliary transformation beginning with intestinal metaplasia and progressing to dysplasia, carcinoma *in situ*, and finally, invasive carcinoma over ~15 years.[446,447] Over 80% of invasive gallbladder cancers contain foci of epithelial dysplasia or carcinoma *in situ*.[448] Anomalous pancreaticobiliary duct junction (i.e., pancreaticobiliary maljunction) is more frequently associated with papillary carcinoma rather than other gallbladder cancer types. Adenocarcinomas account for ~80–95% of gallbladder cancers, with ~2/3 being moderately to poorly differentiated; the most frequent histological subtypes are tubular and micropapillary.[427] Very rare histological subtypes include squamous, adenosquamous carcinomas, small cell carcinomas, carcinoids, and stromal tumors.

HOST SUSCEPTIBILITY

Several studies suggest a family history of gallbladder cancer is associated with an increased gallbladder cancer risk; however, the relative risks in some of these studies are imprecise and other studies do not support an increased risk in first-degree (parents, siblings, children) or second-degree (aunt/uncle, niece/nephew, grandparent/grandchild) relatives.[449] In an Italian study of 58 gallbladder cancer cases and 1,408 hospital controls, a family history of gallbladder cancer was associated with an increased relative risk of gallbladder cancer (RR = 13.9: 95% CI: 1.2–163.9).[450] Analysis of data from the Swedish Family-Cancer Database covering 10.2 million individuals from 1961–1998 identified 10 cases of gallbladder cancer in offspring from parents with a history of gallbladder cancer, resulting in an SIR of 5.05 (95% CI: 2.40–9.32).[451] The age at diagnosis of these 10 cases ranged from 45–63, with most familial cases involving females. Of the 18 offspring siblings, only 1 had another cancer (ovarian).

CLINICAL FEATURES

Gallbladder cancer occurs predominately in elderly women, with a peak incidence in the seventh decade of life.[415] Patients with gallbladder cancer typically present late in the course of the disease with few symptoms. Although early gallbladder cancer (pT1a) has 80–90% survival rate, the prognosis for advanced gallbladder cancer is poor (i.e., ~10% survival).

PANCREAS

Pancreatic cancer is a highly fatal disease with similar annual incidence and mortality resulting from a low 5-year survival rate; this cancer is the fourth leading cause of cancer mortality in well-developed countries, with a male/female ratio of ~1.3–2.[452] The highest incidences of pancreatic cancer occur in developed countries, particularly in North America (e.g., US incidence, 7.4/100,000), with trends varying widely between countries.[453] The US, European, Japanese, and Chinese pancreatic cancer incidence rates currently are increasing in both genders[454] with the incidence in the United States increasing by ~0.5–1.0%/year.[455] The main risk factors are lifestyle and genetic predisposition, whereas socioeconomic and occupational factors are probably not significant contributors to pancreatic cancer occurrence.[456]

CARCINOGENESIS

Most pancreatic tumors arise from microscopic, noninvasive epithelial proliferation in the pancreatic ducts (i.e., pancreatic intraepithelial neoplasia). In a global genetic analysis of tissue from 24 pancreatic cancers, the tumors contained an average of 63 mutations with a majority being point mutations involving a core set of 12 signaling pathways;[457] however, key mutations in each pathway varied between each tumor. The four major driver genes for pancreatic cancer are *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*, with mutations of *CDKN2A* and *KRAS* occurring early in the malignant process.[458] The *KRAS* oncogene encodes a small GTPase mediating downstream signaling from growth factor receptors, whereas the other three drivers are tumor suppressor genes. The KRAS mutation also occurs in chronic pancreatitis patients; however, not all chronic pancreatitis patients with this mutation develop pancreatic cancer because multiple mutations are necessary for malignant transformation in the pancreatic ducts.[459,460] *CDKN2A* encodes an important cell-cycle regulator, *TP53* expresses a protein (p53) necessary in the cellular stress response, and *SMAD4* mediates signaling downstream from transforming growth factor β (Tgf-β).[461] The latter two alterations occur relatively late (i.e., pancreatic intraepithelial neoplasia grade 3, invasive carcinoma). In a case-control study of 3,030 pancreatic cancer cases and 123,136 referent controls from the Genome Aggregation Database and 53,105 in the Exome Aggregation Consortium Database, 6 germline mutations were associated with pancreatic cancer in

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7.9% and 5.2% of patients with and without a family history of pancreatic cancer, respectively.[462] These germline mutations occurred in *CDKN2A*, *TP53*, and *BRCA2* genes as well as *BRCA1*, *ATM*, and *MLH1* genes.

In a study evaluating the clonal relationships among primary and metastatic cancers by sequencing the genomes of seven pancreatic cancer metastases, the estimated time between initial mutation until cancer death was ~20 years.[463] The estimated average time from initiation to the development of a parental clone was 11.7 years followed by another 6.8 years until metastatic subclones arose. Death occurred on average 2.7 years later.

EXPOSURE

Many pancreatic cancer cases are sporadic with no specific risk factors. The best-documented risk factors for pancreatic cancer are smoking, chronic pancreatitis, and type II diabetes mellitus, with weaker associations between pancreatic cancer and obesity, alcohol consumption, diet, and infections (HBV, HCV, *H. pylori*). Insufficient evidence currently associates sugar-sweetened carbonated soft drinks, tea, or coffee consumption with alterations in pancreatic cancer risks.[464,465] Although inadequate evidence associates pancreatic cancer risks with aspirin or statin use, some evidence supports a reduction in pancreatic cancer risks with the use of metformin. Using fixed- and random effects models to evaluate data from four studies (one case-control, three cohort), the summary RR for pancreatic cancer in metformin users was 0.38 (95% CI: 0.14–0.91, $P < 0.001$, $I^2 = 89\%$) with substantial heterogeneity.[466] A meta-analysis of nine observational studies (six cohort, three case-control) did not support an association between pancreatic cancer and metformin use. The adjusted OR was 0.76, 95% CI: 0.57–1.03, $I^2 = 86\%$) with substantial heterogeneity.[467] Some data suggest an inverse association between blood type O and pancreatic cancer. In a case-control study of 15,359 cancer patients from an Italian tumor registry, the pancreatic cancer risk was lower in cancer patients with blood type O (OR = 0.53, 95% CI: 0.33–0.83) compared with patients having other blood types.[468] A Chinese case-control study of 908 pancreatic cancer cases and 1,067 population controls reported that the only blood type with an elevated pancreatic cancer risk compared with blood type O was blood type A (OR = 1.60, 95% CI: 1.27–2.03).[469] Data on the protective effects of physical activity and pancreatic cancer risks are limited, with inadequate control of confounders to confirm a reduced risk.[464]

Occupation

Associations between occupational chemical exposures and pancreatic cancer are weak.[470,471] Based on mortality (hypothesis-generating) studies, potential associations between pancreatic cancer and occupational exposure to chemical carcinogens involve the metal, petroleum, and chemical industries; however, there are no confirmed occupational or environmental causes of pancreatic cancer. A meta-analysis of occupational exposure to chlorinated hydrocarbon solvents and pancreatic cancer demonstrated no strong causal association between chlorinated hydrocarbon solvents and pancreatic cancer.[472]

Lifestyle

Although the etiology of pancreatic cancer remains obscure, studies suggest heavy tobacco consumption significantly increases pancreatic cancer risks compared with never-smokers.[473] Other risk factors involve body mass index (BMI), family history of pancreatic cancer, and possibly heavy alcohol consumption and some dietary factors (e.g., increased fat intake associated with diabetes mellitus and obesity, low fruit and vegetable intake).[452,474] The evidence associating excessive alcohol consumption with pancreatic cancer is inconsistent;[475] however, heavy but not moderate or light alcohol consumption may increase pancreatic cancer risk. Poor nutrition, inflammation associated with chronic pancreatitis, and tobacco smoking confound the association between alcohol consumption and pancreatic cancer.[476] Most studies do not indicate coffee is a risk factor for the development of pancreatic cancer.[452]

Smoking

Tobacco smoking is the strongest risk factor for pancreatic cancer, with an attributable risk estimated at ~20–25% (range, 5–50%), depending on the population studied. In a meta-analysis of studies from four continents, smoking cigarettes increased pancreatic cancer risk by ~75% in smokers compared with non-smokers; the increased risk persisted 10–15 years after smoking cessation.[477,478] In an analysis of data from 465,910 participants in the European Prospective Investigation into Cancer and Nutrition (EPIC) study following a median of 8.9 years, 524 first incident pancreatic cancers were identified.[479] Using Cox proportional hazard models, the adjusted hazard ratio for pancreatic cancer in current smokers was 1.71 (95% CI: 1.36–2.15) compared with never-smokers; the

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risk increased with increasing smoking intensity and pack-years. Adjustment factors included weight, height, and history of diabetes mellitus. Pancreatic cancer risks in former smokers 5 years after smoking cessation and never-smokers were similar. Excess pancreatic cancer risks in smokers were similar to the EPIC study in a meta-analysis of 10 prospective, population-based cohort studies. The pooled RR comparing pancreatic cancer risks in current smokers and never-smokers was 1.66 (95% CI: 1.38–1.98, $I^2 = 70\%$), with moderate heterogeneity, whereas the pooled RR for pancreatic cancer comparing former and never-smokers was 1.40 (95% CI: 1.16–1.67, $I^2 = 63\%$), also with moderate heterogeneity.[480] Examination of three prospective, population-based cohort studies in this study did not detect a statistically significant interaction on pancreatic cancer risk by alcohol and smoking status. An Italian case-control study of 326 incident pancreatic cancer cases and 652 hospital patients without cancer matched for age reported additive effects of cigarette smoking and heavy alcohol consumption on pancreatic cancer risks.[481] Using multiple logistic regression, pancreatic cancer risk was elevated (OR = 4.29, 95% CI: 1.93–9.56) in heavy smokers (≥20 cigarettes/day) with heavy alcohol consumption (≥21 drinks/week) compared with never-smokers drinking <7 drinks/week.

Pooled analysis of data from the International Pancreatic Cancer Case-Control Consortium containing 6,056 cases and 11,338 controls supported an association between pancreatic cancer and cigar smoking, but not pipe smoking or smokeless tobacco use.[482] Using unconditional multiple logistic regression models adjusted for study center and covariates (age, sex, education, race, body mass index, diabetes history, total alcohol consumption), the odds ratio for pancreatic cancer in cigar-only smokers and cigarette smokers was similar, with a cigar-only pooled odds ratio of 1.6 (95% CI: 1.2–2.3, $n = 64$) when compared with never-smokers. The study did not support an association between pancreatic cancer and pipe smoking (pooled OR = 1.1 (95% CI: 0.69–1.6, $n = 38$).

Observational studies on the association of pancreatic cancer with secondhand smoke, and smokeless tobacco are inconsistent and the relative risks are weaker than studies on current or former cigarette smokers. A meta-analysis of 10 observational studies did not detect a statistically significant association between pancreatic cancer and childhood, adult residential, or occupational exposure to environmental tobacco smoke.[483] The summary RR for pancreatic cancer was 1.12 (95% CI: 0.89–1.43, $n = 5$ studies) for childhood environmental tobacco smoke (ETS) exposure, 1.23 (95% CI: 0.86–1.77, $n = 8$ studies) for adult ETS exposure, and 0.94 (95% CI: 0.67–1.33, $n = 3$ studies) for occupational ETS exposure. Most of the studies were North American or European. In a review of multiple cancer studies, the relative risk of pancreatic cancer in smokeless tobacco users was elevated (RR = 1.6; 95% CI: 1.1–2.2) compared with non-tobacco users;[484] however, a review of European and North American studies did not demonstrate a statistically significant increase in pancreatic cancer for smokeless tobacco users compared with nonusers.[485] Pooled analysis of data from the International Pancreatic Cancer Case-Control Consortium did not support an increased pancreatic cancer risk in smokeless tobacco-only users (pooled OR = 0.62, 95% CI: 0.37–1.04, $n = 23$).[482]

Alcohol

Alcohol consumption is a modest suspected pancreatic cancer risk factor (i.e., 20%); however, potential confounding from the association between alcohol and chronic pancreatitis complicates the quantitation of true risk. Evidence of an association primarily occurs in heavy alcohol consumers (i.e., >60 g ethanol/day, ≥21 drinks/week). Meta-analysis of two large, prospective, population-based cohort studies demonstrated a pooled RR for pancreatic cancer in heavy drinkers of 1.29 (95% CI: 1.20–1.38, $I^2 = 28\%$) compared with never-drinkers, whereas the pooled RR in light drinkers was similar to never-drinkers (RR = 0.96, 95% CI: 0.75–1.22, $I^2 = 91\%$) with significant heterogeneity.[480] In a hospital-based, case-control study involving 808 patients with pathologically confirmed pancreatic cancer and 808 healthy frequency-matched controls, only men consuming >60 g alcohol/day had an elevated pancreatic cancer risk ($OR_{adjusted} = 2$, 95% CI: 1.2–3.3, $P = 0.006$); the adjusted odds ratio in women was not statistically significant ($OR_{adjusted} = 1.2$ (95% CI: 0.5–3.5, $P = 0.5$) compared with nondrinkers.[486] A meta-analysis of 19 prospective studies (21 cohorts), including >4 million participants, reported little to no effect on pancreatic cancer rates for individuals consuming low to moderate alcohol doses. High alcohol consumption (>24 g alcohol/day) in men was associated with a marginally increased pancreatic cancer risk (RR = 1.18, 95 % CI: 1.00–1.39; $P = 0.045$, $I^2 = 12.9\%$) compared with the lowest level of alcohol consumption.[487] For women, no significant association was detected between pancreatic cancer risks and low, moderate, high, or total alcohol intake with no heterogeneity between studies.

Obesity

The associations between diet and pancreatic cancer, including obese and overweight patients, are

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modest (i.e., 10–20%) and somewhat inconsistent. In a case-control study of 841 patients with pancreatic adenocarcinoma and 754 healthy individuals, there was an increased pancreatic cancer risk in participants with obesity in early adulthood.[488] The odds ratio for obese individuals (BMI $\geq 30\,kg/m^2$) from ages 20–49 years was 2.58 (95% CI: 1.70–3.90). In an 8-year prospective study of pancreatic cancer in 77,255 men and 90,175 women in the Hawaii-Los Angeles Multiethnic Cohort Study, obesity (BMI $\geq 30\,kg/m^2$) was associated with an increased pancreatic cancer risk in men (RR = 1.51, 95% CI: 1.02–2.26, $n = 237$) and a reduced risk in women (RR = 0.65, 95% CI: 0.43–0.99, $n = 235$).[489] Physical activity did not affect pancreatic cancer risks. In a nested case-control study using pooled data on pre-diagnostic anthropometric measures from the National Cancer Institute Pancreatic Cancer Cohort Consortium (PanScan) involving 2,170 pancreatic cancer cases and 2,209 control subjects, the adjusted odds ratio for pancreatic cancer comparing the highest BMI quartile (severely obese, BMI $= \geq 35\,kg/m^2$) and normal-weight controls (18.5–24.9 kg/m^2) was 1.33 (95% CI: 1.12–1.58, $P_{trend} < 0.001$).[490] A meta-analysis of nine observational studies comparing pancreatic cancer cases with a BMI $> 25\,kg/m^2$ with normal BMI reported a statistically nonsignificant elevated pancreatic cancer risk (RR = 1.30, 95% CI: 0.90–1.87, $I^2 = 97\%$) with high heterogeneity.[491]

Using pre-diagnostic waist circumference and waist-to-hip ratio as measures of centralized fat distribution, the adjusted odds ratios comparing the same highest and lowest quartiles for pancreatic cancer risk were statistically nonsignificant for waist circumference (OR = 1.23, 95% CI: 0.94–1.62) but statistically significant for waist-to-hip ratio (OR = 1.71, 95% CI: 1.27–2.30). The odds ratios were adjusted for cohort, age (categorical), gender, BMI source (self-reported, measured), and smoking (never, former, current).

Diet

Limited data suggest a possible, albeit inconsistent, association between meat (e.g., grilled or barbequed, well-done red or chicken meat containing heterocyclic amines and/or benzo[a]pyrenes) and pancreatic cancer.[492,493] The association with pancreatic cancer involves high-temperature cooked meat and grill/barbequed meat consumption rather than pan-fried or microwaved meats.[494] In a hospital-based, case-control study of 626 pancreatic cases and 530 noncancer, hospital-based controls matched for race, sex, and age (±5 years), a statistically significant portion of cases than controls preferred well-done pork, bacon, grilled chicken, and pan-fried chicken, but not hamburger and steak.[495] Meat preparation and structured risk factors questionnaires collected during a personal interview provided the dietary information, whereas a self-administered food frequency questionnaire was returned by mail. In the prospective NIH-American Association of Retired Persons (NIH-AARP) Diet and Health Study cohort of 537,302 individuals aged 50–71 years, a complete baseline dietary data was ascertained from a food frequency questionnaire at baseline; ~62% completed a meat-cooking module 6 months later.[496] During 5 years of follow-up, 836 pancreatic cancer cases were identified, with 55% of these cases completing the meat-cooking module. Using Cox proportional hazard models, the calculated hazard ratio in men consuming red meat comparing the fifth and first quintiles was 1.42 (95% CI: 1.05–1.91, $P_{trend} = 0.01$) and 1.52 (95% CI: 1.12–2.06, $P_{trend} = 0.005$) for the same quintiles of high-temperature cooked meat intake. A similar association was not present in women. The EPIC study reported no association between red and processed meat intake and pancreatic cancer risk in the 865 nonendocrine pancreatic cancer cases identified in the cohort over 13 years of follow-up.[497] Using multivariable-adjusted Cox hazard regression models, the calculated relative risk of the highest quartile of red meat consumption compared with the lowest quartile (≥80 vs. <20 g/day) was 1.07 (95% CI: 0.83–1.38, $n = 183$) and 0.80 (95% CI: 0.63–1.02, $n = 260$) for the highest and lowest processed meat consumption quartiles (≥40 vs. <10 g/day). The diet was assessed by self-reported questionnaires on the average consumption of each food item over the previous 12 months. Little clear and consistent data supports an increased pancreatic cancer risk related to fruits, vegetables, chicken, or fish consumption, particularly in pooled analyses of cohort study data.[498]

Disease

Potential pancreatic cancer risk factors include chronic pancreatitis and diabetes mellitus with estimation of independent risks confounded by these diseases being both a result and cause of pancreatic cancer. The occurrence of chronic pancreatitis moderately increases the risk of pancreatic cancer.

Chronic Pancreatitis

Chronic pancreatitis is a relatively rare, progressive inflammatory disease that causes acinar cell destruction and fibrosis from several causes, including alcohol abuse, heredity, and idiopathic. The overall 20-year cumulative

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pancreatic cancer frequency for non-hereditary causes of chronic pancreatitis is ~4–5%.[499,500] The lag time between the diagnosis of chronic pancreatitis and pancreatic cancer is typically 1–2 decades. Development of chronic pancreatitis within 2 years of the cancer diagnosis may result from tumor-related ductal obstruction, as reflected in the reduction in pancreatic cancer risk as the lag time between the diagnosis of chronic pancreatitis and pancreatic cancer increases.[501] In a systematic review and meta-analysis of 13 observational (4 case-control, 9 cohort) studies on chronic pancreatitis and pancreatic cancer, the pooled overall effect estimates for pancreatic cancer in chronic pancreatitis patients with a 2-year lag period between the two diagnoses were 16.16 (95% CI: 12.59–20.73, $I^2 = 0\%$); however, the risk declined over time.[502] For a minimum 9-year lag time, the effect estimate was 3.53 (95% CI: 1.69–7.38, $n = 2$, $I^2 = 64.3\%$), with moderate heterogeneity and low precision for the estimates from these two studies. The authors opined some of the excess risk may result from confounding with other risk factors (e.g., smoking, heavy alcohol consumption), detection bias, small case number, and/or initial misclassification of cancer as pancreatitis. The risk of pancreatic cancer in patients with hereditary chronic pancreatitis is markedly elevated.

Diabetes

Diabetes type II is a risk factor for pancreatic cancer, particularly in patients with recent-onset weight loss.[503] In a nested, case-control study of 1,621 pancreatic adenocarcinoma cases and 1,719 matched controls from 12 cohorts, self-reported type II diabetes was associated with a 40% increased pancreatic cancer risk (OR = 1.40, 95% CI: 1.07–1.84) using unconditional logistic regression;[504] however, the risk was not related to the duration of the disease. The pancreatic adenocarcinoma risk was highest for patients with diabetes for 2–8 years (OR = 1.79, 95% CI: 1.25–2.55), whereas no risk was associated with a history of diabetes for ≥9 years (OR = 1.02, 95% CI: 0.68–1.52). The models were adjusted for age, gender, race, study, continuous BMI, alcohol use, smoking, and family history of pancreatic cancer. A meta-analysis of three case-control studies involving 827 pancreatic cancer cases and 2,407 controls reported a pooled adjusted odds ratio of 2.74 (95% CI: 1.63–4.62; $P < 0.01$; $I^2 = 60.4\%$) for history of diabetes with moderate heterogeneity.[505]

Limited studies on type I diabetics receiving routine insulin treatment have not consistently demonstrated an excess pancreatic cancer risk with an inconsistent duration–risk relationship.[506] In a pooled analysis of 3 large case-control studies involving 2,192 pancreatic cancer cases and 5,113 controls, multivariable analyses demonstrated an elevated pancreatic cancer risk for diabetics using insulin compared with no insulin use (OR = 2.2, 95% CI: 1.6–2.2, $n = 173$). However, 70% of the insulin users with pancreatic cancer began insulin use ≤2 years before diagnosis.[507] Compared with non-insulin users with pancreatic cancer, insulin use for >3 years was not associated with an elevated pancreatic cancer risk. For insulin-dependent diabetics using insulin for >10 years, the odds ratio compared with non-insulin users was reduced (OR = 0.5, 95% CI: 0.3–0.9, $n = 18$). The odds ratio was adjusted for age, sex, race, education, smoking, alcohol, BMI, and study site.

Helicobacter pylori

Evidence supporting an association between chronic *H. pylori* infection (gastric colonization) and elevated pancreatic cancer risks is relatively weak and inconclusive. Several studies suggest an independent association between pancreatic cancer and *H. pylori* infection, with some evidence of the association being strain-specific. A case-control study of 580 pancreatic cancer patients and 626 age-/sex-matched population controls did not detect an association between *H. pylori* positivity and pancreatic cancer ($OR_{adjusted} = 1.00$, 95% CI: 0.74–1.35) compared with seronegative patients.[508] Adjustment factors included age, sex, ever-smoking, education, and birthplace. A meta-analysis reported in this paper including the study and 10 observational studies (6 case-control, 3 nested case-control, 1 cohort) reported no statistically significant overall association between *H. pylori* seropositivity and pancreatic cancer risk ($OR_{adjusted} = 1.13$, 95% CI: 0.86–1.50); however, the adjusted odds ratio was elevated for cytotoxin-associated gene A (CAGA)-negative *H. pylori* strains ($OR_{adjusted} = 1.30$, 95% CI: 1.02–1.65). Other studies using overall *H. pylori* seropositivity have not supported a strong association between chronic *H. pylori* infections and pancreatic cancer. In a nested case-control study of 448 pancreatic cancer cases from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort and age-, sex-, and study center-matched controls, pancreatic cancer was not associated with *H. pylori* seropositivity (OR = 0.96, 95% CI: 0.70–1.31, $n = 196$ cases) or CAGA seropositivity (OR = 1.07, 95% CI: 0.77–1.48, $n = 140$ cases).[509] The study did not exclude an association between chronic corpus atrophic gastritis and pancreatic cancer among *H. pylori* seronegative cases. A meta-analysis of 6 nested case-control studies (4,577

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observations), 1 prospective cohort study (9,506 observations), and 1 case–cohort study (30,110 observations) did not confirm an association between pancreatic cancer and *H. pylori* seropositivity (OR = 1.09, 95% CI: 0.81–1.47) or atrophic gastritis (OR = 1.18, 95% CI: 0.80–1.72).[510] Subgroup analysis suggested the possibility of an association between CagA-negative *H. pylori* and pancreatic cancer (OR = 1.30, 95% CI: 1.05–1.62); however, sensitivity analysis (leave-one-out method) did not support the association (OR = 1.20, 95% CI: 0.93–1.56).

HISTOLOGY

Most pancreatic tumors (i.e., 85–90%) are highly heterogeneous ductal adenocarcinomas of the exocrine pancreas whereas approximately 5% comprised pancreatic neuroendocrine tumors; rare types of pancreatic cancer include adenosquamous carcinomas, squamous cell carcinomas, and giant cell carcinomas.[511,512] Invasive, gland- and mucin-forming tumors produce an intense stromal desmoplastic reaction (minimal cellular infiltrates in sclerotic collagen bundles) characterized by the degree of differentiation (poor, moderate, well). Most adenocarcinomas arise from microscopic (<0.5 cm), noninvasive epithelial proliferation in acinar cells of the pancreatic ducts (pancreatic intraepithelial neoplasias) that progress to more dysplastic lesions and then to invasive carcinoma.[513] Other less common precursors include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs).

HOST SUSCEPTIBILITY

Family history of pancreatic cancer in first-degree relatives (parents, siblings) approximately doubles the risk of developing a pancreatic tumor, with family history accounting for ~7–10% of pancreatic tumors.[514] Several genetic syndromes predispose patients to pancreatic tumors, including mutations of *BRCA2*, familial atypical mole melanoma (*CDKN2A* germline mutation, p16), Peutz-Jeghers (*STK11* germline alterations), hereditary pancreatitis (*PRSS1*, *SPINK1*, and *CFTR*) and Lynch syndrome (germline mutations of genes expressing DNA mismatch repair proteins). Hereditary pancreatitis is a rare autosomal dominant disease with an ~40–55% lifetime risk of developing pancreatic cancer. In a meta-analysis of three cohort studies on hereditary pancreatitis and pancreatic cancer, the pooled estimate of the summary relative risk for pancreatic cancer was 69.0 (95% CI: 56.4–84.4, $I^2 = 0$).[501] Carriers of the pathogenic *ATM* variant have cumulative increased risks of pancreatic cancer as they age.

CLINICAL FEATURES

Pancreatic adenocarcinoma affects primarily elderly patients (i.e., 60–80 years at presentation), with few pancreatic tumors developing in patients of <45 years of age. The median age at diagnosis is ~70 years. Typically, pancreatic cancer remains asymptomatic until late in the malignant process, depending on the tumor location (e.g., periampullary vs. body/tail); early symptoms are nonspecific with the most common being decreased appetite, indigestion, and change in bowel habits. However, no specific set of symptoms or signs characterize pancreatic cancer. Retrospective analysis of a large UK primary database suggests pancreatic cancer patients complained of back pain, shoulder pain, dysphagia, altered bowel habits, and lethargy in the 6 months prior to their cancer diagnosis.[515] Back pain, lethargy, and new-onset diabetes were particularly associated with pancreatic cancer. Diabetes and abdominal pain were frequently reported in patients with advanced stages of pancreatic cancer. Metastatic tumors to the pancreas result from renal cell cancer and less commonly from lung and colorectal cancers.[516] The survival rates from pancreatic cancer are among the lowest of all cancers, with a 5-year survival rate of ~5–7% as a result of high local infiltration and early distant metastasis rates. Primary squamous cell carcinoma represents 0.5–5% of pancreatic cancers; this aggressive subtype has a particularly poor prognosis (median overall survival ≅ 7 months).[517] Surgical resection is currently the only potentially curative treatment for pancreatic cancer; however, only ~20% of patients presenting with pancreatic cancer are eligible for surgery because of the advanced stage of most pancreatic tumors.

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Chapter 55

URINARY TRACT

Genitourinary tract tumors include cancers of the renal parenchyma, renal pelvis, ureters, and bladder. These tumors are relatively rare accounting for ~2–3% of all adult neoplasms;[1] however, in children, genitourinary tract tumors (e.g., nephroblastomas, Wilms tumors) represent 20% of all neoplasms. The ratio of renal parenchyma/renal pelvis tumors is ~5:1, with these two tumors displaying distinctly different etiologies. Most renal parenchyma neoplasms are clear cell adenocarcinomas (renal cell carcinomas, hypernephromas), whereas renal pelvis and bladder tumors usually involve transitional cell carcinomas. Additionally, renal pelvis tumors share similar etiological factors (e.g., aromatic amines) with bladder cancer that do not influence the development of renal parenchyma cancers.[2] Renal pelvis and ureteral tumors are usually multifocal with ~30–50% of upper urinary tract tumors metastasizing to the bladder, whereas only ~2–3% of bladder cancers metastasize to the upper urinary tract.[3] Table 55.1 lists the IARC classification of genitourinary tract carcinogens with sufficient and limited evidence in humans.

KIDNEY

Kidney cancers (i.e., renal cell carcinoma) are relatively rare malignancies (i.e., ~2–3% of the human cancer burden), with ~65,000 new cases and ~14,000 deaths in the United States annually.[4] Renal cell carcinoma (RCC) incidence rates vary between countries. Although these rates are typically higher in developed countries, the overall trend has begun to stabilize, particularly in higher socioeconomic groups in urban areas.[5,6] Despite the increased incidence of renal cell carcinomas that is partly attributable to improved diagnostic imaging, mortality rates have trended lower in developed countries (e.g., Europe, the United States, Australia) since the 1990s. Frequently, discovery of these tumors occurs incidentally when the tumors are smaller and at an earlier stage than tumors in symptomatic renal cell carcinoma patients.[7,8]

CARCINOGENESIS

A major driver for the development of 60–90% of renal clear cell carcinomas is a mutation of the tumor suppressor von Hippel-Lindau (*VHL*) gene that stabilizes the hypoxia response pathway involved in cell metabolism, angiogenesis, and cell migration.[9] The VHL protein is a component of the E3 ubiquitin-ligase complex that targets hypoxia-inducible factor (HIF) transcription factors and regulates vascular endothelial growth factor, platelet-derived growth factor, and glucose transporter 1.[10] Other gene mutations in renal clear cell carcinoma include alterations of chromatin remodeling genes (e.g., *ARID1a*, *PBRM1*, *SMARCA4*), DNA hypomethylation (*SETD2*), and other histone modifiers (*BAP1*, *KDM5a*, *UTX*).[11,12] DNA methylation near promoter regions silences tumor suppressor genes. Mutations of other genes associated with increased RCC risks include *FLCN*, *FH*, *MET*, *PTEN*, *SDHB*, *SDHC*, *SDHD*, *TSC1*, and *TSC2*.[13] MET alterations characterize papillary type I RCC tumors, whereas SETD2 mutations, CDKN2A silencing, and increased NRF2-antoxidant

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TABLE 55.1. International Agency for Research on Cancer (IARC) Classification of urinary tract and male reproductive tract cancer sites by sufficient and limited evidence of human carcinogenicity. (Adapted from Bray et al.).[4]

Anatomic Site	Carcinogens with *Sufficient* Human Evidence (Group 1)	Carcinogens with *Limited* Human Evidence (Groups 2A and 2B)
Kidney	Tobacco smoking, trichloroethylene, x- and γ-ray radiation	Arsenic and inorganic arsenic compounds, cadmium and cadmium compounds, perfluorooctanoic acid, welding fumes
Renal pelvis and ureter	Aristolochic acid containing plants, phenacetin and analgesic mixtures containing phenacetin, tobacco smoking	Aristolochic acid[a]
Urinary bladder	Aluminum production, 4-aminobiphenyl, arsenic and inorganic arsenic compounds, auramine production, benzidine, chlornaphazine, cyclophosphamide, firefighting, magenta production, 2-naphthylamine, opium consumption, painting, rubber production industry, *Schistosoma haematobium*, tobacco smoking, *ortho*-toluidine, x- and γ-radiation	4-Chloro-*ortho*-toluidine, coal-tar pitch, diesel engine exhaust, dry cleaning, hairdressers and barbers, 2-mercaptobenzothiazole, outdoor air pollution, pioglitazone, printing processes, soot from chimney sweeps, tetrachloroethylene, textile manufacturing
Prostate		Androgenic (anabolic) steroids, arsenic and inorganic arsenic compounds, cadmium and cadmium compounds, malathion, night shift work, red meat consumption, rubber production industry, thorium-232 and its decay products, x- and γ-radiation
Testis		DDT, diethylstilbestrol (*in utero* exposure), *N*,*N*-dimethylformamide, firefighting, perfluorooctanoic acid
Penis	Human papillomavirus type 16	Human immunodeficiency virus type 1, human papillomavirus type 18

[a] Although human evidence is limited, listed as a Group 1 carcinogen.

response element pathway expression characterize papillary type two RCC subtypes.[14] Chromophobe RCC have a relatively high incidence of Mutations of the *FLCN* gene along with loss of chromosomes 1, 2, 6, 10, 13, and 17. Mutations of *PTEN* and *TP53* genes are particularly common in metastatic chromophobe tumors.[15] Glutathione-*S*-transferase enzymes catalyze conjugation of electrophilic substrates with glutathione, primarily to detoxify reactive intermediates; however, mutations of the *GSTM1* and *GSTT1* genes are not typically associated with renal cell carcinomas.[16]

EXPOSURE

The primary risk factors for renal cell carcinomas are obesity, hypertension, and smoking;[17] however, most renal cell carcinoma patients do not have an established risk factor.[18] Limited data from case-control analyses have not detected renal cell carcinoma subtype differences for associations with smoking, hypertension, or family history of kidney cancer.[19] Although some studies associate specific dietary habits (vegetables, fruit, fat,[20] meat,[21] alcohol), diseases (diabetes type II, acquired cystic kidney disease, kidney stones),[22] and occupational exposures with increased renal cell carcinoma risks, the evidence is inconclusive with the exception of trichloroethylene.[23,24] In the Vitamins and Lifestyle (VITAL) study of 77,260 Washington state residents followed up to 9 years, multivariate analysis of 249 incident cases of renal cell carcinoma did not demonstrate an association between alcohol or fruit/vegetable intake and renal cell carcinoma.[25] The European Prospective Investigation into Cancer and Nutrition (EPIC) study enrolled ~500,000 participants and identified 691 renal cell carcinoma cases during a mean follow-up period of 6.2 years.[26] Country-specific dietary assessment instruments divided meat and fish consumption into quintiles at baseline. Using Cox proportional hazards regression to calculate multivariable-adjusted hazard ratios (HR), the HR for RCC in women within the highest meat consumption category (i.e., ≥80 g/day) was 2.03 (95% CI: 1.14–3.63) using women in the lowest category (<10 g/day) as the comparison. The RCC risk in men did not vary by meat consumption category. The RCC risk for poultry or fish consumption was not statistically significantly different in the consumption categories for men or women.

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Observational studies on the beneficial effects of physical exercise on RCC risk are inconsistent. A systematic review and meta-analysis of physical activity and renal cancer in 19 observational studies reported a reduced RCC risk, with a summary relative risk from random effects meta-analysis of 0.88 (95% CI: 0.79–0.97), particularly in the upper tertile of studies with high-quality scores (RR = 0.78, 95% CI: 0.66–0.92), I^2 = 33%).[27] Physical activity in these studies was not well defined, with large variations in physical activity definitions. Stratification of physical activity by assessment (qualitative, energy expenditure, duration, frequency), domain (total, occupational, recreational), or timing in life (recent, consistent, past) did not yield statistically significant reductions in RCC except for recent physical activity. The authors were unable to identify the specific type of physical activity (frequency, intensity, duration) necessary to reduce renal cell cancer risk. The use of Thorotrast® (thorium oxide) as a contrast agent to visualize the kidney and liver has been associated with the development of renal cell carcinoma.[28]

Occupation

Epidemiology studies yield no consistent patterns of elevated renal cell carcinoma risks from occupational exposures, in part because existing studies of this rare cancer have relatively low statistical power and poor exposure documentation. Although epidemiological and experimental animal studies suggest a possible association between renal cell carcinoma and metal salts (arsenic, cadmium),[29] organic solvents (tetrachloroethylene),[30] railroad workers (asbestos),[31,32] and hydrocarbons (tar, pitch, and petroleum products),[33] sufficient evidence of a cause-effect relationship exists only for trichloroethylene based primarily on case-control studies, mechanistic data, and experimental animal studies.[34,35] The IARC lists welding fumes and UV radiation from welding as human carcinogens (Group 1).[36] The IARC noted a statistically significant association between welders and kidney cancer in the range of 20–30% increase in relative risks in large census-based studies. Their analysis reported less precise risks ranging from 1.4–3.8 in cohorts of welders in diverse European and American industries; however, these studies did not adjust for lifestyle (e.g., smoking) or confounding (e.g., trichloroethylene exposure). Case-control studies were also supportive (RR = 1.2–~5.5), but the studies did not reasonably exclude bias, chance, or confounding with little evidence of exposure-response relationships. Overall, the evidence for a causal relationship between welding and kidney cancer was limited.

Case-control studies of patients with renal cell carcinoma suggest a weak, albeit inconsistent association with hydrocarbons,[37,38] gasoline,[39] inorganic lead compounds,[40] asbestos,[41] and organic solvents.[42] A case-control study of 165 women and 273 men with renal cell cancer detected a significantly elevated risk of renal cell carcinoma (OR = 2.3, 95% CI: 1.3–4.2) among women, but not among men, exposed to organic solvents.[43] Exposure to organic solvents was determined retrospectively based on job titles determined from mailed questionnaires and interviews on their usual occupation.

Renal cell carcinomas developed in male rats exposed chronically to unleaded gasoline,[44] but the nephropathy results from a unique sensitivity to a male-specific protein, α-2μ-microglobulin, in the rat that limits extrapolation of these animal studies to humans. To date, epidemiological studies of petroleum workers have not supported the association between gasoline vapor and renal cell carcinoma.[45,46] Standardized mortality studies of a refinery and petrochemical worker cohort reported a statistically nonsignificant excess of renal cancer (SMR = 143, 95% CI: 90–217, n = 22 cases) based on death certificates,[47] with the excess becoming statistically significant (SMR = 193, n = 21 cases) only in smokers in the 13-year follow-up using retrospective analysis of smoking history in medical records.[48] However, nested case-control studies[49] and reviews of cohort studies of petroleum workers[50] have not confirmed an increased kidney cancer risk or an exposure-response trend between nonaromatic, liquid gasoline distillate intensity/frequency, and renal cancer. Generally, these studies report relatively small case numbers with wide confidence intervals.

Lifestyle

Smoking

Cigarette smoking modestly increases the risk of developing renal cell carcinomas, with the risk somewhat stronger for upper urothelial carcinomas than renal cell carcinomas.[24] In a meta-analysis of 19 case-control and 5 cohort studies involving 9,358 RCC cases, the overall adjusted summary RR comparing ever-smokers to lifetime never-smokers was 1.38 (95% CI: 1.27–1.50), with significant heterogeneity in reported adjusted risks. The overall estimated RR for ever-smoking men before excluding any studies was 1.50 (95% CI: 1.37–1.65) compared with 1.27 (95% CI: 1.14–1.40) in women.[51] Analysis of dose-dependency in RCC risk indicated a

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strong increase in RCC with increasing cigarette consumption. Compared with lifetime never-smokers, the RR for RCC in ever-smoking men using >20 cigarettes daily was 2.03 (95% CI: 1.51–2.74) and 1.58 (95% CI: 1.14–2.20) in women with similar smoking habits. The RR for renal cell carcinoma in former smokers quitting >10 years previously was not statistically different from that of lifetime never-smokers; other case-control studies indicate the RCC risk in smokers persists for 20–30 years.[52] In a meta-analysis of 13 case-control and 10 cohort studies using maximum reported adjusted risk estimates for RCC, the overall pooled relative risk for all smokers compared with nonsmokers was 1.31 (95% CI: 1.22–1.40, I^2 = 60.8%) and 1.36 (1.19–1.56, I^2 = 73.7%) for current smokers.[53] All estimates had moderate heterogeneity. The overall RR for RCC in former smokers was lower than in current or all smokers (RR = 1.16, 95% CI: 1.08–1.25, I^2 = 17.6%) with little heterogeneity.

Obesity

Obesity is an established risk factor for renal cell carcinoma independent of smoking and hypertension, as measured by BMI (kg/m^2) with waist circumference (i.e., a measure of central obesity) also associated with modestly elevated RCC risks, particularly renal clear cell carcinomas; the positive association is stronger for women than men.[54] Obesity is a risk factor, particularly in older women overweight since adolescence; however, little increased RCC risk occurs in women for weight gained after midlife (<50 years).[55,56] In a meta-analysis of 21 cohort studies with 15,144 cases and 9,080,052 participants using random effects models and normal weight participants (BMI, 18.5–24.99) as controls, the pooled relative risks were 1.28 (95% CI: 1.24–1.33, I^2 = 35.6%) for BMI 25–29.99 (overweight) and 1.77 (95% CI: 1.68–1.87, I^2 = 44.2%) for BMI ≥ 30 (obese) with slight to moderate heterogeneity.[57] The pooled RR indicated a stronger risk for obese women (RR = 1.95, 95% CI: 1.81–2.10) than obese men (RR = 1.63, 95% CI: 1.50–1.77). Dose-response meta-analysis indicated a nonlinear relationship between BMI and RCC risk after adjustment for age, sex, smoking, and hypertension. The Egger's test suggested the possibility of publication bias (P = 0.001). In a meta-analysis of 17 studies primarily in North America and Europe, with a 5 kg/m^2 increase in BMI above normal weight, the rate ratio for RCC in men was 1.24 (95% CI: 1.15–1.34, I^2 = 37%, n = 11 studies) and 1.34 (95% CI: 1.25–1.42%, I^2 = 45%, n = 12 studies) in women.[58] The increased RCC risk was less in men (RR = 1.18, 95% CI: 1.08–1.29) and similar in women (RR = 1.35, 95% CI: 1.29–1.42) participating in the six studies examining data for both men and women. Analysis of data from the Women's Health Initiative after adjustment for age, smoking, and ethnicity demonstrated a consistently significant increased kidney cancer risk for obese women (BMI ≥ 30 kg/m^2) only with systolic blood pressure of >160 mmHg when compared with obese women with SBP of <120 mmHg (HR = 1.94, 95% CI: 1.07–3.50).[59] Limited data associates renal cell carcinoma subtypes with obesity, primarily renal clear cell cancer. Analysis of case-control data from a US population-based (933 cases, 1,235 controls) and a European hospital-based (905 cases, 1,476 controls) study associated morbid obesity (BMI, ≥35 vs. <25 kg/m^2) with an increased risk of clear cell RCC (OR = 2.0, 95% CI: 1.41–3.0, n = 196 cases, $P_{\text{trend}=}$ 0.001) and a statistically nonsignificant elevated chromophobe risk (OR = 2.0, 95% CI: 0.9–4.4, n = 12, P_{trend} = 0.007), but not papillary RCC risks (OR = 1.3, 95% CI: 0.8–2.2, n = 31, P_{trend} = 0.21).[19] Subtypes were not associated with smoking, hypertension, or family history of kidney cancer.

Diseases

Hypertension

Data from case-control studies suggest hypertension is an independent risk factor for renal cell carcinoma. In a case-control study of health maintenance organization members in western Washington State, the diagnosis of hypertension was associated with a statistically significant increased risk of renal cell carcinoma for women (OR = 2.5, 95% CI: 1.2–5.1), but not for men (OR = 1.3, 95% CI: 0.7–2.5).[60] The use of hypertensive medication was not associated with increased renal cell carcinoma risks when adjusted for hypertension. The European Prospective Investigation into Cancer and Nutrition (EPIC) study interviewed ~300,000 participants and identified 250 renal cell carcinoma cases during a mean follow-up period of 6.2 years.[61] Using <120 mmHg systolic and <80 mmHg diastolic as referents and adjusting for age, sex, body mass index, education, and smoking status/duration, the relative risk for renal cell carcinoma in the highest systolic blood pressure group (≥160 mmHg) was 2.48 (95% CI: 1.53–4.02, n = 57 cases) and 2.34 (95% CI: 1.54–3.55, n = 39 cases) for the highest diastolic group (≥100 mmHg). Difference in renal cell carcinoma rates in the middle two quartiles of systolic and diastolic blood pressure groups compared with the referents was not statistically significant in men or women. These studies indicated that antihypertensive medications are probably not a causal RCC risk factor.[62]

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Diabetes

The association between diabetes and kidney cancer remains inconsistent and relatively weak, particularly when controlled for obesity and hypertension.[63] Pooled data from Italian and Swiss case-control studies identifying 767 renal cell cancers and 1,534 controls did not demonstrate an elevated RCC risk in diabetics.[64] After adjustment for age, study center, interview year, education, alcohol consumption, tobacco smoking, and body mass index, the odds ratio in diabetics was 1.26 (95% CI: 0.91–1.75); however, RCC was weakly associated with BMI. The large, population-based Japanese cohort study did not detect a statistically significant increased incidence of RCC in diabetics (age-/sex-adjusted HR = 1.72, 95% CI: 0.51–5.79).[65]

HISTOLOGY

Renal clear cell and papillary cell carcinomas arise from the epithelium of the proximal convoluted renal tubules in various locations within the kidney parenchyma, whereas chromophobe subtypes develop from distal nephrons.[66] Collecting duct carcinomas, renal medullary carcinomas, and urothelial carcinomas are highly distinct diseases from renal cell carcinomas. Renal cell cancers are histologically and molecularly heterogeneous tumors. Classical histological subtypes of renal cell carcinomas (RCC) include ~65–70% clear cell (clear to yellowish or eosinophilic cytoplasm surrounded by a delicate, dense vascular network with necrosis and hemorrhage), ~15–20% papillary (parenchymal tumor with a papillary or tubulopapillary architecture, foamy histiocytes, basophilic cytoplasm, necrosis, and hemorrhage), and ~5–7% chromophobe (large, pale cells with prominent cell membranes and perinuclear clearing). Each subtypes has distinct genetic characteristics, with the latter having the lowest rate of metastasis.[67,68] In a study of 2,385 patients undergoing their first radical nephrectomy for unilateral RCC, the distribution of histological subtypes was as follows: 1,985 (83.2%) clear cell; 270 (11.3%) papillary; 102 (4.3%) chromophobe; 6 (0.3%) collecting duct; 5 (0.3%) purely sarcomatoid RCC with no underlying histological subtype; and 17 (0.7%) RCC not otherwise specified.[69] The 2016 WHO classification added seven new, relatively uncommon RCC subtypes, including clear cell papillary RCC associated with end-stage renal disease and von Hippel-Lindau (VHL) syndrome, representing up to 5% of renal tumors.[70]

HOST SUSCEPTIBILITY

Approximately 2–3% of RCC cases have familial, autosomal dominant syndromes predisposing them to renal cell carcinomas, with an increased risk of ~1.5–2-fold among first-degree relatives of RCC patients.[71] In a Central European case-control study of 1,097 kidney cancer cases and 1,555 controls, the odds ratio for RCC in participants with at least one first-degree relative with kidney cancer was 1.40 (95% CI: 0.71–2.76) adjusting for tobacco smoking, body mass index, and medical history of hypertension.[72] The association was strongest for participants with affected siblings (OR = 4.09; 95% CI: 1.09–15.4, n = 9 cases). The most common familial syndrome is a defect on the tumor suppressor *VHL* gene (von Hippel-Lindau syndrome) present in 1/36,000 births that predisposes affected patients to early onset, multifocal renal clear cell carcinomas, CNS hemangioblastomas, and pheochromocytomas.[73] Most sporadic (i.e., non-inherited) renal clear cell carcinomas acquire defects in both alleles of the *VHL* gene resulting in dysfunction of the tumor suppressor VHL protein causing unifocal neoplasms that present later than tumors with germline VHL mutations.

Familial syndromes producing papillary renal cell carcinoma include multifocal papillary type I involving the proto-oncogene *MET* and hereditary leiomyomatosis involving the *FH* (fumarate hydratase, familial type II papillary renal cell carcinoma) gene. The *c-MET* proto-oncogene encodes a growth-factor receptor that expresses a tyrosine kinase membrane receptor and promotes angiogenesis/tumor growth, whereas *FH* is a tumor suppressor gene encoding an enzyme for the tricarboxylic acid cycle (Krebs cycle conversion of fumarate to malate) leading to upregulation of hypoxia-inducible factor. The Birt–Hogg–Dube syndrome causes a germline mutation in the folliculin (*FLCN*) gene and the familial syndrome of chromophobe tumors.

CLINICAL FEATURES

Most renal cell tumor incidence increases with age and presents between the ages of 50 and 70 years, with a male/female ratio of ~2:1 reflecting, in part, the higher incidence of smoking in men.[74,75] In a case-control study of 706 US kidney cancers and 917 European kidney cancers reported papillary cases (n = 237) were older (OR = 1.2, 95% CI: 1.1–1.4/10-year increase), less likely to be female (OR = 0.5, 95% CI: 0.4–0.8), and more likely to be African-American (OR = 2.6, 95% CI: 1.8–3.9) compared with renal clear cell carcinoma (n = 1,524).[19] Renal clear cell carcinomas are the most

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common and aggressive renal cell carcinomas, with the highest incidence of local invasion, metastasis, and mortality rates among the RCC subtypes. These tumors are very vascular, resulting in frequent hemorrhage.[76] The prognosis is typically better for papillary than clear cell subtypes, with the prognosis being better for papillary type 1 than type 2; however, the prognosis is usually worse for metastatic papillary than clear cell renal carcinomas.[77] The tumor node metastasis (TNM) system correlates with RCC prognosis, with ~5-year survival rates of 80–95% for Stage I, 80% for Stage II, 60% for Stage III, and <10% for Stage IV (median survival ~2 years).[78,79] Overall, the 5-year survival rate is ~74% for men and ~78% for women.[80] Approximately 20–30% of renal cell carcinomas present with metastatic disease, and ~20–30% of patients undergoing nephrectomy will develop metastasis during follow-up.[81,82] Increased survival correlates to early diagnosis, small tumor size, and the absence of distant metastases.

RENAL PELVIS AND URETER

Upper-tract urothelial carcinomas are relatively uncommon tumors representing ~5–10% of all urothelial cancers with the incidence currently increasing; the estimated incidence ranges from 1–2 cases/100,000 population.[83] The incidence of these tumors is high in areas with endemic nephropathies (e.g., Balkan endemic nephropathy in Eastern Europe, Chinese herbal nephropathy in Taiwan, China), primarily as a result of contamination of food and medicines with aristolochic acid.[84] The association between upper-urinary tract urothelial carcinomas and Blackfoot disease from elevated drinking water arsenic levels remains unclear because of the presence of aristolochic acid exposure in Taiwanese residents.[85] Upper-tract urothelial carcinomas in Taiwan occur in areas without Blackfoot disease and in residents unaffected by the disease.[86] Although upper-tract urothelial carcinomas (UTUC) share some characteristics and risk factors with bladder cancer, the two cancers are distinct diseases, with UTUC displaying some unique etiologies (e.g., aristolochic acid, nonpolyposis colorectal cancer spectrum disease), prognosis, and pathology.[87]

CARCINOGENESIS

Aristolochic acid consumption causes a unique renal disease (aristolochic nephropathy, Balkan endemic nephropathy) frequently associated with upper-tract urothelial cancer. Aristolactam-DNA adducts formed by aristolochic acid in the renal cortex are unique biomarkers of aristolochic acid exposure. The presence of these adducts is a signature mutation associated with A:T-to-T:A transversions in the tumor suppressor *TP53* gene at codon 139.[88] In a Taiwanese study of 152 upper-tract urothelial carcinomas where aristolochic acid nephropathy is common, the presence of aristolactam-DNA adducts in the renal cortex of 93 patients indicated frequent aristolochic acid exposure in patients with these tumors.[89] Compared with patients without this biomarker, the patients were relatively younger, female, and nonsmokers with more severe renal disease. Chronic inflammation and irritation (e.g., urinary tract stones, chronic urinary tract infections) may slightly increase renal pelvic tumor formation;[90] however, data are limited. Although upper urinary tract and bladder urothelial carcinomas share similar pathology, their molecular pathways differ with hypermethylation and microsatellite instability more common in upper urinary tract urothelial tumors than bladder tumors.[91,92]

High-grade, upper-tract urothelial carcinomas and urothelial bladder carcinomas share a similar genetic landscape; however, upper-tract urothelial carcinomas are more often invasive at surgery than urothelial bladder carcinomas, suggesting the former has a more aggressive phenotype. Next-generation sequencing of 83 upper tract urothelial carcinomas and 102 urothelial bladder carcinomas detected similar genes that were mutated (e.g., *CDKN2A*, *FGFR3*, *KDM6A*, *KMT2D*, *TP53*), with differing frequencies in other genes (e.g., *HRAS*, *RB1*, *TP53*).[93] Compared with urothelial bladder cancer, upper-tract urothelial carcinomas had more frequent mutations of *CDKN2B*, *FGFR3*, and *HRAS* genes, and fewer in other genes (*ARID1A*, *TP53*). No RB1 mutations occurred in the latter cohort compared with 18.6% in the urothelial bladder carcinoma cohort. Whole-exome sequencing of 31 untreated, snap-frozen upper urinary tract urothelial cancers identified mutations in *FGFR3* (74%), chromatin modifier *KDM6A* gene (44%), *PIK3CA* (26%), and *TP53* (22%) genes, with C > T transitions at *APOBEC* and CpG islands being the most common mutational signatures.[94]

EXPOSURE

Most renal pelvic and ureteral tumors are urothelial (transitional) cell carcinomas that share more similar risk factors (e.g., aniline, benzidine dyes) with bladder cancer than renal cell carcinomas. Smoking is the

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major risk factor for developing upper-tract urothelial carcinomas; occupational exposure to aromatic amines (benzidine, 2-naphthylamine) and phenacetin abuse has dramatically decreased with improved industrial hygiene and the banning of phenacetin in pharmaceutical preparations for over 40 years. The incidence of upper urothelial carcinomas was high among patients using analgesic medication, primarily in abusers with renal disease. Case reports associate upper urinary tract urothelial carcinomas with the previous use of Thorotrast® (thorium oxide) as a contrast agent to visualize the kidney and liver.[95] In the Western Swedish Cancer Registry of 930 renal pelvic and ureteral tumors, 34 (8.7%) of 389 female patients had a history of gynecological malignancy and radiotherapy with a median of 21 years (range, 1–42 years) earlier.[96]

Occupation

Heavy occupational exposure to aromatic amines (e.g., benzidine, β-naphthalene) in the chemical, dye, rubber, and textile industries, prior to banning these substances in the 1960s and 1970s was associated with an increased incidence of upper-urinary tract urothelial carcinomas, particularly in a case series of dye workers (e.g., ~4–18%).[97,98] These studies suggested a mean latency period of 20–25 years for urothelial carcinomas; however, exposure categories were poorly defined, and reported odds ratios were highly imprecise, as reflected in 95% confidence limits ranging from 80–100 fold. In a multicenter, population-based, German case-control study involving 1,035 incident urothelial cancer cases and 4,298 controls matched for region, sex, and age, chemical exposure was evaluated retrospectively by self-reports and experts (2 job-exposure matrices, 1 job task-exposure matrix).[99] Using conditional logistic regression to calculate smoking adjusted odds ratios and control for age and study center, the adjusted OR for aromatic amine exposure was slightly elevated without reaching statistical significance for high aromatic amine exposure in men. The odds ratio using assessment by self-report was 0.6 (95% CI: 0.3–1.0, n = 14 cases) compared with 0.9 (95% CI: 0.7–1.2, n = 55) using the British job-exposure matrix. Although high PAH exposure in men assessed with the British job-exposure matrix demonstrated a marginally statistically significant elevation of urothelial carcinomas (OR = 1.3, 95% CI: 1.0–1.7, n = 123), other methods did not support statistically significant associations. The study reported >50 odds ratios for chemical exposures in men and women.

Lifestyle

Smoking is a major risk factor for renal pelvis and ureteral cancers, with case-control studies indicating a reduction in risks following smoking cessation, particularly after 10 years. In a population-based, case-control study involving 187 Los Angeles residents identified in a Cancer Surveillance Program with renal pelvis or ureteral cancers (60% response rate) and 187 age-, sex-, and race-matched controls, the relative risk of urinary tract urothelial cancer comparing current smokers and never-smokers was 5.2 (95% CI not reported, P_{trend} = <0.0001).[100] The P_{trend} comparing smoking duration (≥26 years vs. nonsmokers) and ≥1 pack/day and <1 pack/day current smokers was also P_{trend} = <0.0001 based on self-reported cigarette use. A larger, US population-based case-control study recruited 502 cases (58% of ascertained cases) including some cases from the previous study and 496 age- and sex-matched controls. The odds ratio comparing current and never-smokers was 4.4 (95% CI: 2.9–6.5) based on self-reported use determined by telephone interviews.[101] Comparisons of current smoking intensity (≥2 pack/day vs. <1 pack/day), smoking duration (<26 years vs. ≥ 46 years), and cumulative smoking history (≥60 vs. ≤20 pack-years) indicated a statistically significant difference (P_{trend} = < 0.001). Compared with current smokers, the reduction in the RR for renal pelvis and ureteral cancer in former smokers quitting ≥10 years previously was statistically significant (RR = 0.3, 95% CI: 0.2–0.5). In a German case-control study of 51 renal pelvic and 25 ureteral carcinomas, the odds ratio for renal pelvic and ureteral urothelial cancer in current smokers compared with age- and sex-matched never/non-daily smokers was 6.20 (95% CI: 2.04–18.81, n = 41).[102] The odds ratio for ex-smokers defined as not smoking for ≥2 years was 1.00 (95% CI: 0.31–3.21, n = 15) based on self-reported smoking history obtained at discharge from the hospital. The wide confidence limits reflect imprecise OR estimates.

Medications

Phenacetin

Case reports and small case series from large academic hospitals, along with limited case-control studies of renal pelvic carcinoma, suggest the presence of renal papillary necrosis and renal dysfunction following heavy phenacetin abuse increases renal pelvic urothelial carcinoma risk based on self-reported histories (i.e., personal interviews, questionnaires).[103,104] Analgesics without phenacetin are not causally related to renal

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pelvic carcinomas.[85] In a study of 170 patients with renal pelvic or ureteral tumors from a Berlin urology clinic diagnosed from 1948–1981, 18/83 (21.4%) of renal pelvic tumors and 4/35 (11.4%) of ureteral tumors were associated with phenacetin abuse defined by self-reported use of >1 kg total dose of phenacetin or >1 g/day for ≥1 year. [105] The average total phenacetin dose was 5.6 kg for renal pelvic cancer patients and 4.9 kg for ureteral tumors, with mean latency periods of 24 years and 26 years, respectively. The Swedish Cancer Registry identified 930 cases of renal pelvic and ureteral tumors diagnosed from 1971–1998 in Western Sweden.[96] This case series identified 41 cases (4.4%) with a history of phenacetin-containing analgesic abuse. The replacement of phenacetin with other analgesics (e.g., acetaminophen) dramatically reduced the development of analgesic-associated urothelial tumors.

Aristolochic Acid

This compound is an extract of *Aristolochia fangchi* and *Aristolochia clematis* that can be ingested as a traditional Chinese herbal medicine or bread contaminated with *Aristolochia* seeds. The IARC classifies plants containing aristolochic acid as human carcinogens (Group 1) based on increased urothelial tumors in patients with aristolochic acid-associated renal failure (Balkan endemic nephropathy, Chinese herb nephropathy).[4] These plants are associated with end-stage renal failure and increased risks of upper- and lower-tract urothelial carcinomas.[106] The incidence of urothelial cancer in Taiwan has been declining since aristolochic acid-containing herbal products were banned in the early 2000s.[107] A Taiwanese molecular epidemiology study examined tissues from 151 cases of upper urinary tract urothelial carcinomas and 25 patients with renal cell carcinomas. Using aristolactam adducts and the *TP53* tumor suppressor gene as mutational signatures, 60% of all cases and 84% of patients with A:T to T:A mutations in *TP53* contained the aristolactam-DNA adduct uniquely associated with aristolochic acid exposure.[89] This transversion was identical to the mutations associated with Balkan endemic nephropathy. The study design excluded residents of southwestern and northeastern Taiwan, where high arsenic concentrations occur in the drinking water.

Lithium

Chronic lithium therapy produces epithelial proliferation of the renal collecting ducts; however, there is no direct evidence that lithium therapy induces neoplastic changes in the urinary tract epithelium, including inhibition of the glycogen synthase kinase-3β (GSK-3β) pathway that promotes apoptosis and reduces cell proliferation. A Danish case-control study identified 829 cases of renal pelvic and ureteral cancer in the Danish Cancer Registry, along with 259,080 age- and sex-matched cancer-free controls.[108] Using conditional logistic regression, the fully adjusted odds ratio (i.e., medication use, diseases, education) for long-term lithium use (≥5 years) was 1.3 (95% CI: 0.8–2.2) compared with non-lithium users. Duration of lithium use was not associated with an increased risk of renal pelvic or ureteral cancer. The authors opined that lithium use was not associated with an increased upper urinary tract cancer risk.

HISTOLOGY

Urothelium is the epithelial lining of the upper (i.e., calyceal system to distal ureter) and lower (bladder to urethra) urinary tracts; urothelial neoplasms vary in location along the urinary tract, with distal ureter being the most common location for ureteral tumors.[96] About 90–95% of the urothelial carcinomas derive from urothelium; however, upper-tract urothelial carcinomas represent only ~5% of urothelial neoplasms, with the vast majority of these tumors occurring in the bladder.[109] Urothelial carcinomas in the renal pelvis are twice as common as more distal ureteral tumors.[110] Upper-tract urothelial carcinomas and urothelial bladder cancers are histologically similar. Typically, upper-tract urothelial carcinomas are more invasive at diagnosis than urothelial bladder carcinomas.[111]

Very rare renal pelvic tumors include squamous cell carcinomas and carcinosarcomas; squamous cell carcinomas of the upper urinary tract represent <10% of the calyceal urothelial tumors and a much smaller portion of upper urinary tract neoplasms.[112] The latter are highly malignant mesenchymal and epithelial tumors that grow rapidly, infiltrate widely, and usually arise from the bladder.[113] Squamous cell carcinomas of the renal pelvis and ureter derive from dysplastic squamous metaplastic epithelium and typically are associated with chronic inflammation from urolithiasis or hydronephrosis.[114] Retrospective review of medical records at a large Texas referral center from 1990–2004 identified 16 patients with primary nonurothelial tumors of the upper urinary tract; the tumors consisted of 12 squamous cell carcinomas, 2 adenocarcinomas, 1 sarcomatoid carcinoma, and 1 small cell carcinoma.[115] Squamous cell carcinomas frequently invade the renal parenchyma and retroperitoneal soft tissues, with >95% of the tumors displaying advanced stages when initially diagnosed.[116]

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HOST SUSCEPTIBILITY

Familial/hereditary forms of upper-tract urothelial carcinomas account for ~10–20% of all these tumors, with hereditary nonpolyposis colorectal carcinoma (Lynch syndrome type II) being the most common familial form. Upper-tract urothelial carcinoma is the third most frequent extra-colonic tumor site in patients with Lynch syndrome type II.[117]

CLINICAL FEATURES

Upper-tract urothelial carcinoma is a male-predominant disease (~2:1 ratio) that typically presents in the 7th–8th decade (mean ≅ 73 years), with presentation at <50 years of age being rare.[118,119] Many presentations (i.e., ~30%)[120] are incidental during imaging/endoscopic procedures. The presence of symptoms (e.g., palpable abdominal mass, flank pain, hematuria) usually indicates advanced disease and a poor prognosis, particularly when associated with systemic symptoms (fever, night sweats, fatigue, anorexia, weight loss).[121] In a Swedish case series of 930 renal pelvic and ureteral tumors, bloody urine was the presenting clinical feature of these tumors in 58% of cases, with 17% complaining of abdominal pain.[96] Symptoms other than hematuria suggest more advanced disease.[122] Hydronephrosis or hydroureter may develop from obstruction of the ureters by tumors. Known metastatic disease at presentation occurs in <10% of cases at diagnosis, with concurrent disease in the bladder present in ~10–30% at the initial diagnosis depending on the location of the primary urothelial tumor; however, ~50% of tumors at diagnosis are locally invasive.[123]

Systemic symptoms frequently represent paraneoplastic disease or metastases producing secretory proteins (e.g., parathyroid-hypercalcemia, renin-hypertension, erythropoietin-erythrocytosis) along with fever and wasting syndromes. Staging of urothelial cancers for prognosis usually involves the tumor, node, metastasis (TNM) classification system, with invasion of the muscle wall having a poor prognosis.[124] The survival rate for low-stage upper-tract urothelial carcinoma after radical nephroureterectomy is good (i.e., 90%), with the rate dropping to <30% with advanced stages; the 5-year survival for invasion of the renal pelvis or ureter is <50 and <10% for invasion of the kidney or adjacent organs.[125,126] In contrast to bladder cancer, gender does not affect survival from upper-tract urothelial carcinomas.[127] Typically, tumors associated with phenacetin abuse appear with a latent period of 10–20 years following heavy ingestion (>5 kg) that produces renal papillary necrosis.[128]

BLADDER

Bladder cancer is the second most common genitourinary system cancer after prostate cancer, with the age-standardized rate of bladder cancer much higher in industrialized and urban areas (16.9/10,000) than in less developed and rural areas (5.3/100,000).[4] Worldwide, bladder cancer is the ninth most common cancer, with the highest incidence rates in men from Southern (32–37/100,000) and Western Europe, North America, North Africa, and Western Asia.[129] In the United States, bladder cancer is the fourth most common cancer in men.[83] Although gender differences vary widely between countries, bladder cancer incidence rates are substantially higher in men than women; however, the age-standardized incidence of bladder cancer rates from 1990–2013 in *developed* countries decreased by 12.5% in men and 10.4% in women.[130] Bladder cancer incidence rates are significantly higher than mortality rates (9th vs. 13th most frequent worldwide) because of the slow progression of the disease.[131] In general, bladder cancer mortality rates have declined recently, except in regions undergoing rapid economic development, whereas bladder cancer incidence is decreasing in men while increasing in women *worldwide*. The latter probably reflects previous changes in smoking habits among men and women. Bladder cancers associated with schistosomiasis typically are squamous cell rather than urothelial carcinomas; the latter has increased reflecting smoking habits, whereas squamous cell bladder cancer is declining with reduced *Schistosoma* infections.[129,132]

CARCINOGENESIS

A potential mechanism of action for the association of smoking with bladder cancer is a multiplication effect with bladder carcinogens (e.g., aromatic amines).[133,134] Urothelial bladder carcinoma is a highly heterogeneous disease with a high somatic mutation frequency rate. Analysis of 131 urothelial bladder carcinomas by the Cancer Genome Atlas Research Network detected 32 recurrent gene mutations involving cell-cycle regulation, kinase signaling pathways, and chromatin regulation.[135] Genetic alterations of bladder tumor subtypes include oncogene fibroblast growth factor receptor 3 (*FGFR3*) activating mutations in papillary subtypes and inactivating mutations of tumor suppressor genes *TP53* and *RB1* in nonpapillary subtypes.[136] Mutations in genes encoding chromatin-modifying enzymes are frequent in both subtypes. Mutations of *KMT2D* (histone H3 lysine 4 methyltransferase) are more common in nonpapillary

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subtypes, whereas activating telomerase promoter mutations in *KDM6A* (histone H3 lysine 27 demethylase) and inactivating STAG2 mutations are more common in papillary subtypes.[137] Substantial evidence associates chronic inflammation (e.g., *Schistosoma haematobium* infection) with squamous cell carcinomas; however, the link between chronic inflammation and urothelial cell carcinomas is less clear.

EXPOSURE

The major bladder cancer risk factor is tobacco smoking worldwide, whereas infection with *S. haematobium* causes a relatively high burden of bladder cancer in northern and sub-Saharan Africa.[138] Additionally, a variety of occupational chemicals and industries are associated with bladder cancer with an estimated ~7% of bladder cancers in men and ~2% in women attributed to occupational exposures.[139] Implicated chemicals include 4-aminobiphenyl, inorganic arsenic, and aromatic amines (benzidine, 2-naphthylamine) along with painting and work in aluminum, auramine, magenta, and rubber production industries.[140] The carcinogenicity of magenta is difficult to separate from the production process because the latter often involves coexposure to aniline, auramine, benzidine, naphthylamine, and *o*- and/or *p*-toluidine. Radiotherapy of the genital tract (prostate, testis, ovary, cervix, uterus) along with radiation treatment of non-Hodgkin lymphoma are associated with subsequent development of bladder cancer, primarily after a 10-year lag. In a meta-analysis of four studies after multivariable adjustment, bladder cancer risk comparing ever- and never-treatment with radiotherapy was elevated (adjusted hazard ratio = 1.67, 95% CI: 1.55–1.80; $I^2 = 0\%$), whereas using a 10-year lag, the HR was 1.89 (95% CI: 1.65–2.16; $I^2 = 0\%$).[141] Examination of data from the extended Life Span Study of Japanese atomic bomb survivors reveals a dose-response relationship between bladder cancer and x-/γ-ray radiation (excess RR = 1.02/Sv).[142]

Occupation

In 1895, the German physician, Ludwig Rehn, first associated bladder cancer with work in the aniline dye industry theorizing that aniline (the simplest aromatic amine) was the carcinogen.[143] Later studies indicated other aromatic amines (benzidine, 1-naphthylamine, 2-naphthylamine, 4-aminobiphenyl) accounted for the elevated risk rather than aniline.[144] The percentage of bladder cancer cases attributable to occupational exposure in earlier studies ranged from 2–25%, depending on exposure intensity and the portion of the work force exposed to aromatic amines (2-naphthylamine).[145,146] Compared with men, the estimated attributable bladder cancer risk from these studies of occupational exposure in women was smaller (11%).[147] Later studies demonstrated reduced bladder cancer risks as a result of improved industrial hygiene conditions and better control of misclassification and confounders (e.g., tobacco smoking). However, definite conclusions regarding the current attribution of bladder cancer risk to occupational carcinogens remain limited by heterogeneity in accurately classifying exposures within specific groups of workers and controlling confounders (e.g., tobacco use).[148] A Spanish case-control study did not detect a statistically significant association between bladder cancer in women and a specific industry or occupation.[149] Table 55.2 lists chemicals that are known human bladder carcinogens.

TABLE 55.2. Recognized International Agency for Research on Cancer (IARC) human bladder Group 1 carcinogens.

Agent [CAS Number]
Chemicals
4-Aminobiphenyl [92-67-1]
Arsenic and inorganic arsenic compounds
Benzidine [92-87-5]
Chlornaphazine [494-03-1]
N,*N*-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine) [494-03-1]
Cyclophosphamide [50-18-0] [6055-19-2]
2-Naphthylamine [91-59-8]
Opium consumption
Painter occupation
Schistomsoma haematobium (chronic infection)
o-Toluidine [95-53-4]
Mixtures
Betel quid with tobacco
Tobacco smoking
Specific Exposures
Aluminum production
Auramine, manufacturing
Magenta production
Rubber manufacturing industry
X- and γ-ray radiation

Industries

Limitations to accurate estimation of bladder cancer risks from occupational exposures include retrospective exposure analysis (misclassification from using job titles instead of tasks), small case numbers, potential publication bias, and inadequate control of confounding (e.g., tobacco smoking). Exploratory case-control studies associate elevated bladder cancer risk with

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~40 occupations (e.g., painters, truck drivers, drill press operatives, textile workers, printers, auto mechanics and maintenance workers, dry cleaners, dyestuff producers, hairdressers, primary metal workers, petroleum refiners) based on relatively low odds ratios (i.e., <2).[150] In a systematic review and meta-analysis of bladder cancer and occupational carcinogen exposure, the highest bladder cancer risks resulted from exposure to aromatic amines (tobacco, dye, leather, and rubber workers, printers, hairdressers) and polycyclic aromatic hydrocarbons (chimney sweeps, aluminum workers, seamen, oil/petroleum workers, nurses, waiters).[151] A review of studies of coke oven workers, chimney sweeps, roofers, and blacksmiths suggests soot and gases from the combustion of coal may produce substances that increase urothelial cell carcinoma incidence in the bladder.[152]

Exposure in several industries is suspected bladder carcinogens (IARC Groups 2A and 2B), with limited or conflicting evidence of human carcinogenicity. A meta-analysis of observational studies on bladder cancer risks and diesel exhaust exposure suggests diesel exhaust exposure may increase bladder cancer occurrence.[153] The summary RR for studies using a job exposure matrix or a similar approach for diesel exhaust exposure was marginal (mRR = 1.13, 95% CI: 1.00–1.27, n = 10 studies), with a mRR for high diesel exposure of 1.44 (95% CI: 1.18–1.76). The authors opined on substantial heterogeneity, misclassification, publication bias, and confounding that limited definitive conclusions regarding risk estimates. A Canadian population-based case-control study identified 658 male bladder cancer cases and 1,360 age- and sex-matched controls with lifetime occupational histories supplemented by a job-exposure matrix for engine emissions exposure.[154] Using logistic regression, the odds ratio for men ever exposed to high concentrations of diesel emissions compared with unexposed controls was elevated but not statistically significant (OR = 1.64, 95% CI: 0.87–3.08, n = 28 cases, P = 0.12). The odds ratio comparing the highest cumulative diesel exposure tertile with unexposed controls was not elevated (OR = 0.93, 95% CI: 0.68–1.28, n = 111 cases, P_{trend} = 0.34). A hospital-based, case-control study of bladder cancer and diesel exhaust exposure did not support an excess bladder cancer risk based on job titles and self-reported diesel exhaust exposure.[155] The odds ratio for bladder cancer and any diesel exhaust exposure based on self-reports was not statistically significant (OR = 1.2, 95% CI: 0.8–2.0) after adjustment for smoking.

The IARC classified painting as an occupation with sufficient evidence of human carcinogenicity in 1989; however, the elevated bladder cancer risk is relatively small and dependent on individual techniques and materials. A meta-analysis of the pooled relative risk of bladder cancer combining four cohort studies on painters published from 1989–2004 was 1.10 (95% CI: 1.03–1.18, n = 893 cases), whereas the corresponding summary RR for four cohort mortality studies in painters was 1.23 (95% CI: 1.11–1.37, n = 370 deaths).[156] The pooled relative risk for 25 case-control studies was 1.35 (95% CI: 1.19–1.53, n = 465 cases), with an overall pooled RR of 1.17 (95% CI: 1.11–1.27, n = 1,728 cases, P = 0.10). Although significant heterogeneity occurred between study types (P < 0.001), the meta-analysis revealed no significant heterogeneity between studies. In a meta-analysis of bladder cancer morbidity/mortality and painting from 1950–2008, the summary risk estimates for bladder cancer were similarly elevated.[157] The summary risk estimate for case-control studies was 1.28 (95% CI: 1.17–1.41, n = 40 studies), whereas the summary risk estimate for cohort *morbidity* studies was 1.14 (95% CI: 1.06–1.22, n = 4 studies) and 1.27 (95% CI: 1.16–1.38, n = 9 studies) for cohort mortality studies. Although restricting meta-analysis to case-control studies adjusting for smoking did not significantly affect the summary odds ratios, adjustment for socioeconomic status reduced the odds ratio to a statistically nonsignificant value. The slight to moderate excess bladder cancer risk among painters appears greater in the distant past than more recent occupational exposures; social class and smoking remain potential confounding factors.

Chemicals

Aromatic Amines

Aromatic amines are chemicals with a nitrogen group attached to an aromatic hydrocarbon, with aniline (a noncarcinogen) being the simplest aromatic amine. Both benzidine and 2-naphthylamine are potent bladder carcinogens; workers exposed to these chemicals in the rubber, leather, and textile industries have elevated standardized mortality rates (SMR = ~2) from bladder cancer compared with the general population based on retrospective studies of death certificates.[158,159,160] The risk of bladder cancer exists primarily in the pre-synthesis stage of dye manufacture rather than in the processes involved with finished dyes.[161]

Many synthetic organic dyes contain benzidine or one of its congeners (*o*-toluidine, *o*-dianisidine). Although these dyes are benzidine analogs rather than parent compounds, animal studies suggest the possibility that intestinal flora or hepatic enzymes may convert the diazo linkage to the carcinogenic parent compound *in vivo*.[162] Dye stuff intermediate workers with low phenotype for *N*-acetyltransferase may be more susceptible

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to the development of bladder tumors when exposed to benzidine compounds and their analogs.[163]

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) are ubiquitous chemicals containing ≥2 benzene rings and formed from incomplete combustion of organic material (cooked meats, fossil fuels, rubber, plastic). The association of PAH exposure is substantially less consistent with bladder cancer than lung or skin cancers. A review of cohort studies on workers exposed to PAH reported significant excess risks in aluminum production (pooled RR = 1.29, 95% CI: 1.12–1.49), iron and steel foundries (pooled RR = 1.29, 95% CI: 1.06–1.57), and coal gasification (pooled RR = 2.39, 95% CI: 1.36–4.21).[164] An updated review of these estimates yielded borderline increased bladder cancer risk for aluminum production (pooled RR = 1.28, 95% CI: 0.98–1.68, n = 10 studies) and iron and steel foundries (pooled RR = 1.38, 95% CI: 1.00–1.91, n = 9 studies).[165] In a French hospital-based case-control study of 658 male bladder cancer patients and 658 male controls based on semi-quantitative questionnaires, the estimated overall odds ratio for PAH exposure was 1.3 (95% CI: 1.0–1.7, $P < 0.05$) after adjustment for smoking, coffee drinking, and occupational aromatic amine exposure.[166] The dose-response was slight but statistically significant (P_{trend} = <0.05) with an OR of 1.8 (95% CI: 0.8–3.9) comparing the highest PAH exposure category and unexposed controls.

Halogenated Hydrocarbons

Evidence associating halogenated hydrocarbons with bladder cancer primarily involves tetrachloroethylene (perchloroethylene), particularly in the dye cleaning industry; however, the human evidence is limited (IARC Group 2A). A critical review of epidemiological studies published in 2003 concluded that the evidence linking bladder cancer with occupational tetrachloroethylene exposure was inadequate. A more recent meta-analysis reported an increased bladder cancer risk in dry cleaners with some evidence of an exposure-response relationship.[167] The overall meta-RR for bladder cancer risk in dry cleaners was 1.47 (95% CI: 1.16–1.85, n = 7 studies and 139 exposed cases); however, the mRR for case-control studies adjusted for smoking was not statistically significant (mRR = 1.50, 95% CI: 0.80–2.84, n = 4 studies, I^2 = 0%). The mRR for tetrachloroethylene-exposed workers in this meta-analysis also was not statistically significant (mRR = 1.08, 95%% CI: 0.82–2.84, I^2 = 25.3%, n = 3 studies and 463 cases). Although tetrachloroethylene was a common potential carcinogen in the dry-cleaning industry during 1950–1990, mixed carcinogen exposures occurred in this industry.

Environmental

Chronic inorganic arsenic exposure is associated with several cancers, including lung, skin, and bladder cancers, following chronic exposure to high arsenic concentrations in drinking water.[168,169] Typically, arsenic exposure results from chronic ingestion of seriously contaminated groundwater exceeding several thousand ppb, with most positive studies conducted in areas with water containing >200 μg As/L (e.g., Taiwan, Chile, Gulf of Bengal), particularly >600 μg As/L for >40 years. Studies on bladder cancer incidence and chronic ingestion of <100–200 As μg/L are less consistent with wide confidence limits and imprecise exposure estimates (misclassification).[170,171] In the northern Chilean towns of Antofagasta and Mejillones, the arsenic concentration in drinking water averaged 870 μg/L (ppb) from 1958–1970 followed by a dramatic reduction after the installation of water treatment plants.[172] Compared with a Chilean region without arsenic contamination, bladder cancer mortality began increasing 10 years after drinking water became highly As-contaminated, followed by peak mortality in 1986–1987 based on death certificates. Peak bladder cancer relative risks (RR) for men were 6.10 (95% CI: 3.97–9.39) and 13.8 (95% CI: 7.74–24.5) for women.

Lifestyle

Tobacco use is the overwhelming lifestyle risk factor for bladder cancer, with little evidence of an association between bladder cancer and coffee, tea, fluid intake, moderate alcohol consumption, or micronutrient supplement consumption; potentially, diet, exercise, or weight may influence bladder cancer risks, but evidence is relatively weak and inconsistent.[173] There is no clear association between bladder cancer and personal use of hair dyes.[174,175] In a meta-analysis of 15 case-control and 2 cohort studies, the pooled RR for ever-compared with never-use of personal hair dyes was 0.93 (95% CI: 0.82–1.05, I^2 = 34.1%, P = 0.07), with slight to moderate heterogeneity among studies.[176] The results demonstrated a lack of exposure-response relationship between duration, frequency of use, or dye type (permanent, non-permanent) and bladder cancer risks when compared with no use. Artificial sweeteners (cyclamate, saccharine) are potent promoting agents in the rat model of carcinogenesis; however, observational studies indicate these substances are not significant human

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carcinogens.[177,178] Case series of patients with aristolochic acid nephropathy report urothelial carcinomas developing after kidney transplantations for end-stage kidney disease. In a case series of 38 women requiring kidney transplants followed by immunosuppression for end-stage aristolochic acid nephropathy, 17 patients developed upper-tract urothelial carcinomas, whereas only 3 of 21 patients developed urothelial bladder cancer without upper-tract urothelial carcinomas.[179] Of the 17 patients with upper-tract urothelial carcinomas, 15 developed urothelial bladder carcinomas 5½–14 years after transplant, suggesting the possibility of urothelial cancer metastasis to the bladder.

Tobacco Use

Smoking is the major risk factor (i.e., 2–4 fold elevation) for bladder cancer, displaying a strong dose-response between smoking intensity and bladder cancer; this risk factor accounts for up to 50% of the excess bladder cancer risk, despite reductions in smoking prevalence and cigarette composition.[53,180] Pooled analysis of 11 case-control studies indicates the proportion of bladder cancer cases attributable to ever-smoking was 0.66 (95% CI: 0.61–0.70) for all men and 0.73 (95% CI: 0.66–0.79) for men of <60 years of age, with a threshold limit for bladder cancer of ~15–20 cigarettes daily.[181] Cessation of smoking reduced the bladder cancer risk by >30% after 1–4 years (OR = 0.65, 95% CI: 0. 53–0.79) and >60% after 25 years (OR = 0.37, 95% CI: 0. 30–0.45); however, the bladder cancer risk of former and never-smokers was never similar. In a meta-analysis of 33 case-control and 12 cohort studies using maximum reported adjusted risk estimates for bladder cancer, the overall pooled relative risk for all smokers compared with never-smokers was 2.58 (95% CI: 2.37–2.80; I^2 = 88.8%, $P < 0.001$), 3.47 (95% CI: 3.07–3.91, I^2 = 81.9%, $P < 0.001$) for current smokers, and 2.04 (95% CI: 1.85–2.25; I^2 = 64.7%, $P < 0.001$) for former smokers.[53] All these comparisons had substantial heterogeneity in the types of smoking histories and cut-points used for stratifying smoking intensity and duration. The association was stronger for case-control (pooled RR = 2.76) than cohort (pooled RR = 2.17) studies. Visual inspection of the funnel plot could not exclude publication bias. The bladder cancer risk may be weaker in Japanese than in European or North American populations. In a meta-analysis of 3 cohort and 8 case-control studies of Japanese cigarette smokers, the summary relative risk for bladder cancer in ever-smokers was 2.14 (95% CI: 1.87–2.44) with no significant heterogeneity.[182]

Some observational studies suggest tobacco smoking is associated with a worse prognosis at the diagnosis of incident bladder cancers. A large hospital-based case-comparison study involving 1,544 cases examined the relationship of smoking to the clinical characteristics of bladder cancer at diagnosis. After adjustment for age and gender, current smokers had larger tumors (mean difference = 0.48 cm, 95% CI: 0.04–0.91), a higher T stage (mean difference = 0.25, 95% CI: 0.08–0.41), and a borderline higher grade (mean difference = 0.15, 95% CI: 0.00–0.30) compared with never-smokers.

Limited data on the risk of bladder cancer with cigar and pipe smoking suggest this form of smoking has lower bladder cancer risks than cigarette smoking; however, the actual risks are unclear. In a pooled data set of 2,279 cases and 5,268 controls from 6 studies of bladder cancer, 88 cases and 253 controls smoked only cigars or pipes.[183] Using never-smokers as controls, the odds ratio (OR) of bladder cancer for pure pipe smokers was 1.9 (95% CI: 1.2–3.1) and 2.3 (95% CI: 1.6–3.5) for pure cigar smokers compared with 3.5 (95% CI: 2.9–4.2) for pure cigarette smokers. The elevation of bladder cancer risk with duration of smoking was not significantly different between cigar and cigarette smokers. In a nested case-control study of 619 bladder cancer cases and 3,346 lifelong nonsmokers, age- and sex-adjusted incidence rate ratios for current cigar smokers were 2.88 (95% CI: 1.68–4.93) and 3.03 (95% CI: 1.67–5.50) for pipe smokers. These elevated bladder cancer risks disappeared after adjustments for cigarette smoking.[184]

The association between environmental tobacco smoke and bladder cancer is relatively weak and somewhat inconsistent.[184] A large population-based bladder cancer study in Los Angeles County, California, ascertained lifetime environmental tobacco smoke (ETS) exposure for 148 bladder cases and 292 controls (never-smokers). A statistically significant, dose-dependent increased in bladder cancer risk occurred in never-smoking women exposed to environmental tobacco smoke comparing the highest ETS category with controls (OR = 5.48, 95% CI: 1.06–28.36, P_{trend} = 0.03). The wide confidence intervals indicate imprecise risk estimates. ETS exposure was not associated with increased bladder cancer risks in men. A prospective cohort study established two cohorts from private censuses in Maryland to examine the effect of smoking on bladder cancer risks starting in 1963 (n = 45,749; 93 cases) and 1975 (n = 48,172; 172 cases).[185] Using Poisson regression models and never-smokers unexposed to environmental tobacco smoke as controls, bladder cancer risks among nonsmoking women were marginally elevated (RR = 2.3, 95% CL: 1.0–5.4) in the 1963 cohort and not elevated in the 1975 cohort (RR = 0.9, 95% CL: 0.4–2.3). In a meta-analysis of 83 studies, a random effects model detected no evidence

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associating environmental smoke with bladder cancer risk (RR = 0.99; 95% CI: 0.86–1.14, I^2 = 35.6%, P = 0.05) comparing nonsmokers with and without environmental smoke exposure.[186] The Q-statistic and I^2 statistic suggested some heterogeneity. Subanalysis of men and women did not reveal a statistically significant elevation of bladder cancer risks in either sex.

Alcohol

The association between alcohol consumption and bladder cancer is weak, with analysis of 594 incident bladder cancer cases and 3,170 subcohort Netherland members demonstrating no linear dose-response between alcohol consumption and bladder cancer risk (P_{trend} = 0.13).[187] The authors corrected for age and smoking in multivariable analyses. Although a case-control study using data from the nationwide Japanese clinical database and age-, sex-matched hospital-based controls suggested an elevated bladder cancer risk comparing ever- and never-drinkers (OR = 1.33, 95% CI: 1.06–1.66),[188] most larger studies have not reported a statistically significant increased bladder cancer risk or a dose-response relationship between alcohol consumption and bladder cancer. In the multicenter European Prospective Investigation into Cancer and Nutrition (EPIC) cohort of 476,160 individuals mostly aged 35–70 years followed for a mean of 13.9 years, men reporting alcohol intake of >96 g/day had an increased urothelial cancer risk (HR = 1.57; 95% CI: 1.03–2.40) compared with moderate intakes (<6 g/day). The data did not support a dose-response relationship between bladder cancer risks and quartiles of average lifetime alcohol consumption.[189] The study reported no association between alcohol consumption and urothelial bladder carcinomas in never-smoking women. A Japanese population-based cohort study identified 354 men and 110 women with newly diagnosed bladder cancer after following 95,915 participants (45,649 men and 50,266 women, aged 40–69 years) for a mean of 18.2 years.[190] Using multivariate Cox proportional hazard models, the hazard ratio (HR) comparing regular drinkers with non- and occasional (1–3 days/month) drinkers was 1.14 (95% CI: 0.91–1.41, P = 0.249, n = 259 cases). Analyzing alcohol consumption by separating regular drinkers into quartiles of alcohol use did not reveal a dose-response relationship between the amount of alcohol and bladder cancer risks ($P_{linear\ trend}$ = 0.412).

Diet

There is no consistent evidence for an increase in bladder cancer risk with tea, coffee,[191] fluid,[192] vitamin/antioxidants,[131] trihalomethanes in chlorinated water,[193] or nitrate[194] consumption.[148,195] Evidence of the reduction of bladder cancer risk by supplementation with common micronutrients is inadequate.[196] Although some studies suggest a protective effect of fresh fruits and vegetables,[131] the effect on urothelial bladder carcinoma risk in these studies is small and subject to recall bias/food misclassification, with little evidence in meta-analyses to support the reduction of bladder cancer risks using diets rich in fruits and vegetables.[197] A population-based case-control study of bladder cancer in New England region of the United States involving 1,171 cases and 1,418 controls detected no association between bladder cancer and fruits or vegetables based on comparing consumption quartiles using self-administered diet history questionnaires.[198] In the large EPIC cohort, the HR for urothelial bladder carcinoma risk comparing participants with high and low Mediterranean diet scores was not elevated (HR = 0.84, 95% CI: 0.69–1.03).[199] Although heterocyclic amines formed in meat and fish during cooking are carcinogenic in animal models, a Swedish population-based case-control study did not detect an increased bladder cancer risk (RR = 1.2; 95% CI: 0.7–2.1) between the highest and lowest quintiles of estimated heterocyclic amine consumption.[200] In a review of observational studies on dietary factors, high meat consumption was not associated with an increased bladder cancer risk (RR = 1.08, 95% CI: 0.82–1.42).[201] A meta-analysis of mostly European and American case-control studies suggests processed or red meat consumption may increase bladder cancer risk based on a linear association between bladder cancer risk and daily red meat consumption/100 g increment in case-control studies (pooled RR = 1.51, 95% CI: 1.13–2.02, n = 7 studies, P < 0.01) and daily processed meat consumption/50 g in case-control studies (pooled RR = 1.20, 95% CI: 1.06–1.37, n = 6, P = 0.02).[202] Prospective cohort studies in this meta-analysis did not support a statistically significant relationship between bladder cancer risks and red meat (pooled RR = 1.01, 95% CI: 0.97–1.05, n = 6 studies, P = 0.62) or processed meat (pooled RR = 1.10, 95% CI: 0.95–1.27, n = 5 studies, P = 0.83).

Obesity/Exercise

Data associating obesity and physical activity with bladder cancer are conflicting and generally weak. In a hospital-based case-control study in East and South China involving 438 incident bladder cancer cases and 427 controls, overall physical activity was not significantly associated with bladder cancer risks (P_{trend} = 0.61).[203] The P_{trend} was also not significant for

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vigorous physical activity (P_{trend} = 0.60) or moderate physical activity (P_{trend} = 0.21).

The use of various obesity measures, inadequate smoking control, and limited studies in women complicate the determination of the association between obesity and bladder cancer risks. In the EPIC cohort study, 1,391 incident bladder cancers (1,018 male; 373 female) occurred during a median follow-up of 11.3 years.[204] Never-smokers did not have an elevated bladder cancer risk, whereas overweight participants (BMI >28.96) had a slightly elevated bladder cancer risk (adjusted HR = 1.25, 95% CI: 1.04–1.50) suggesting confounding with tobacco use. In a meta-analysis of nine cohort studies on bladder cancer risks and obesity that adjusted for cigarette smoking, the pooled RR was 1.09 (95% CI: 1.01–1.17; $P_{heterogeneity}$ = 0.131, I^2 = 35.9%) with slight to moderate heterogeneity.[205] Obesity was self-reported or determined by BMI without specifically defining the BMI level associated with obesity. A meta-analysis of 14 prospective, primarily European and American cohort studies reported a weak positive association between BMI and bladder cancer risk, with the suggestion of a positive, nonlinear relationship between BMI and bladder cancer, primarily >30 kg/m^2.[206] The summary RR for the association of bladder cancer with obesity was 1.10 (95% CI: 1.03–1.17, I^2 = 58.5%, $P_{heterogeneity}$ = 0.003) with moderate heterogeneity.

Diseases

Chronic ingestion of drinking water contaminated by *S. haematobium* sporocysts released by a snail host results in adult parasites laying eggs in the veins surrounding the infected bladder. These eggs traverse the bladder wall, producing chronic inflammation, hematuria, and fibrosis. In Egypt, sub-Saharan Africa, and the Middle East, endemic schistosomiasis is associated with an increased squamous cell carcinoma risk in the bladder.[207] Assessing the bladder cancer risk from schistosomiasis is complicated by the presence of confounders, primarily tobacco smoking. Evidence for increased bladder cancer risks from other urinary tract infections or urinary tract stones is inconclusive. Historically, up to 8–10% of paraplegics using indwelling catheters developed squamous cell carcinomas;[208,209] however, safer methods of bladder emptying reduce the bladder cancer risks.[210]

Some studies suggest an association between diabetes and bladder cancer risks. A meta-analysis of 9 case-control and 27 cohort studies reported an increased bladder cancer risk in diabetics (pooled RR = 1.35, 95% CI: 1.17–1.56, I^2 = 94.7%, P < 0.001) with substantial heterogeneity in study design and adjustment for confounders.[211] The pooled RR for the eight cohort studies specifically on diabetics was not statistically significant (RR = 1.25, 95% CI: 0.86–1.81, I^2 = 97.4%, P < 0.001), also with significant heterogeneity. The data did not suggest a dose-response relationship between the duration of diabetes and bladder cancer risks.

Medications

The use of cyclophosphamide and ifosfamide without urothelial protection agents is associated with hemorrhagic cystitis and dose-related increase in urothelial cell carcinomas.[212] In a cohort of 6,171 2-year survivors of non-Hodgkin's lymphoma (NHL), 48 patients with secondary cancer of the urinary tract were matched to 136 NHL controls without a second malignancy.[213] The overall bladder cancer risk following cyclophosphamide therapy was 4.5 (95% CI: 1.5–13.6), with the risk increasing in a dose-response relationship. The wide confidence limits reflected small case numbers and imprecise estimates. Several meta-analyses suggest limited evidence for an association between pioglitazone, an oral antidiabetic agent, and elevated bladder cancer risk, particularly in doses above 28 g daily. In a meta-analysis of 14 case-control studies, the HR comparing ever- and never-use of pioglitazone was 1.16 (95% CI: 1.06–1.25, I^2 = 0.0%, P = 0.54), with no significant heterogeneity between studies.[214] However, a large cohort study of Kaiser Northern California patients did not confirm an increased bladder cancer risk in long-term pioglitazone users.[215] The adjusted hazard ratio for ever-compared with never-use of pioglitazone was 1.06, (95% CI: 0.89–1.26). The median duration of use was 2.8 years with a range of 0.2–13.2 years. Acetaminophen, non-steroidal anti-inflammatory drugs, metformin, sulfonylurea, and insulin are not associated with increased bladder cancer risks.

HISTOLOGY

Over 90% of bladder tumors are urothelial (transitional cell carcinomas), with squamous cell carcinomas and adenocarcinomas accounting for ~6–8% and 2%, respectively.[216] The percentages of squamous cell carcinomas are slightly higher in blacks and women. Approximately 70–75% of bladder tumors are non-muscle invasive at diagnosis, being confined to the mucosa and submucosa with the remainder

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muscle-invasive or metastatic; ~50% of patients without muscle-invasive bladder cancers have low-grade tumors in contrast to most high-grade tumors in almost all muscle-invasive or metastatic tumors.[137] Bladder tumors typically are papillary, solid, or mixed, with the papillary type predominant in non-muscle invasive bladder cancers.

HOST SUSCEPTIBILITY

Although urothelial cell carcinomas (UCC) are not well-known familial cancers, several case reports and population-based studies report some familial clustering of this cancer type. The incidence of urothelial cell carcinomas in the bladder is increased in Lynch syndrome, an autosomal dominant genetic disease; however, this increase may result from seeding by upstream upper urinary tract tumors rather than primary bladder tumors.[217] Population-based observational studies indicate the urothelial bladder carcinoma risk in patients' relatives is ~2-fold greater than the general population. Some of the increased risk may be attributed to shared environmental risk factors (e.g., smoking, occupational carcinogen exposures).[218] In a population-based, case-control study using the Utah Cancer Registry and matched 1:5 cancer-free controls, the hazard ratio for urothelial bladder cancer was elevated in first-degree (HR = 1.69, 95% CI: 1.47–1.95, $P < 0.001$) and second-degree (HR = 1.35, 95% CI: 1.2–1.5, $P < 0.001$) relatives.[219] A population-based, family case-control study enrolled 1,193 newly diagnosed UCC patients with bladder, ureter, renal pelvis, or urethra cancers and 853 partners with at least one relative diagnosed with UCC.[220] Using random effect proportional hazards regression analyses to compare disease occurrence among case-relatives and control-relatives, the adjusted hazard ratio was 1.8 (95% CI: 1.3–2.7). Analysis of nationwide family-cancer databases comparing native and immigrant residents indicate no single gene has a major influence on UCC incidence.[221] Segregation analysis of urothelial cell carcinoma in 1,193 families did not find evidence of strong Mendelian inheritance through a single major gene.[222] Consequently, combinations of genetic variants (i.e., "no major gene" or sporadic model) more likely account for the limited familial clustering of urothelial cell carcinomas.

Prominent polymorphisms include *N*-acetyl transferase 2 (*NAT2*) important for carcinogenic aromatic amine detoxification and glutathione *S*-transferase M1 (GSTM1) responsible for conjugating electrophilic substrates (e.g., polycyclic aromatic hydrocarbons). Genetic polymorphisms (i.e., *NAT2* slow acetylator, *GSTM1* null genotypes) may account for some interindividual susceptibility to bladder cancer, particularly for cigarette smokers;[223] however, case-control studies of patients genotyped for polymorphisms are inconsistent.[224] Potentially, slow acetylation of *N*-acetyltransferase 2 (NAT2) reduces the metabolism of aromatic amines and polycyclic aromatic hydrocarbons in tobacco smoke, thereby increasing contact with and risk from tobacco-related and occupational carcinogens. In a meta-analysis of 7 genome-wide association studies (GWAS) collaborating with the National Cancer Institute, analysis of 12 SNPs identified as potentially enhancing bladder cancer risks yielded only *NAT2* genes with a genetic variant that caused significant multiplicative gene-smoking interaction.[225] Analysis of data from >500,000 participants in the European Prospective Investigation into Cancer and Nutrition (EPIC) study did not confirm the influence of *NAT2* variants on smoking-related cancer or occupational bladder cancer risks.[226] Estimated occupational exposure to aromatic amines (OR = 1.37, 95% CI: 1.02–1.84) and PAH (OR = 1.50, 95% CI: 1.09–2.05) increased bladder cancer risk when comparing the highest exposure tercile with never-exposed controls. NAT2 slow acetylation did not modify these risk estimates or independently increase bladder cancer risk (OR = 1.02, 95% CI: 0.81–1.29). The risks were adjusted for age, gender, region, and smoking.

CLINICAL FEATURES

Gender is a strong predictive factor for developing bladder cancer. The male/female ratio of the total age-adjusted incidence of bladder cancer is ~3–4.[227] Bladder cancer incidence increases with age; few bladder cancers present before age 50. Peak bladder cancer incidence occurs in the 7th–8th decade of life; ~2/3 of bladder cancer cases present when patients are >65 years of age.[228] The average onset of bladder cancer is 15 years earlier in workers exposed to bladder carcinogens than in sporadic cases.[2] The latent period between first exposure and diagnosis of bladder cancer is relatively long compared with many other cancers. The estimated average latent period between exposure and development of bladder cancer is ~20 years with a range of 16–45 years.

Hematuria is the most commonly presenting clinical feature of bladder cancer, particularly gross hematuria; other symptoms include dysuria, urgency, incontinence, and urinary frequency. Patients without hematuria typically present with a longer onset of symptoms and signs (recurrent infections, urgency) prior to diagnosis.[229]

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Abdominal, pelvic, flank, or bone pain usually suggests advanced, metastatic disease. Although ~75% of bladder tumors are noninvasive at diagnosis, the recurrence rate is high despite local therapy, with ~25% of these patients progressing to muscle-invasive bladder cancer during the course of their disease;[230,231] the higher-stage tumors have poor outcomes despite systemic therapy (radical surgery, radiotherapy).[232]

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Chapter 56

MALE REPRODUCTIVE TRACT

PROSTATE

Prostate cancer is a leading cause of death in developed countries and the most common noncutaneous cancer in men worldwide. Although prostate cancer is an indolent disease with ~300,000 incident cases annually in the United States, prostate cancer is the second most common cause of US cancer-related mortality accounting for ~35,000 deaths/year.[1] Globally, prostate cancer mortality accounts for ~366,000 deaths with marked geographical variation reflecting the biological heterogeneity of this cancer.[2]

The estimated overall lifetime absolute prostate cancer risk in men without a familial history of prostate cancer is ~8%.[3] Worldwide, prostate cancer incidence varies 25-fold, with the rate increasing since the early 1990s following the introduction of prostate-specific antigen (PSA) screening;[4] the highest incidence of prostate cancer occurs in the most developed counties, including North America, Oceania, and western and northern Europe.[5] The odds of a 79-year-old man developing prostate cancer range from 1/47 in countries with a low-to-middle sociodemographic index (e.g., Caribbean, Middle-Southern Africa) to 1/6 in countries with a high sociodemographic index. African-Americans have the highest prostate cancer incidence in the world (223/100,000 men) along with a higher disease stage at presentation. The factors responsible for this highly elevated rate are unclear and potentially include genetic variation, socioeconomic status, access to early detection/treatment options, and environmental/lifestyle exposures. Table 55.1 lists substances and processes associated with increased risks of male reproductive tract cancers as determined by the International Agency for Research on Cancer (IARC).

CARCINOGENESIS

Prostate tumors display substantial mutational heterogeneity and a complex mutational landscape, with few recurrent gene abnormalities reflecting the highly variable clinical course. Common genetic and epigenetic abnormalities in prostate tumors involve cell cycle regulation, chromatin regulation (e.g., FOXA1 transcription network, Forkhead BoxA1), potential driver gene mutations in *TP53* and other genes, altered androgen response (e.g., *MLL2* in SET1 family of histone H3K4 methyltransferases), and disruption of several prominent pathways (e.g., tensin homolog/AKT, phosphoinositide 3-kinase) associated with tumor suppressor genes (*PTEN*, *PI3K*, *RB1*).[6,7] Many of the DNA mutations occur in the intron portion of the genome involving non-coding rather than protein-coding sections.[8] At least 10 androgen receptor gene mutations stimulate prostate tumor growth initially by upregulating and expressing androgen receptor activity.[9] A gene fusion between the androgen-regulating gene (*TMPRSS2*) and the *ETS* transcription factor gene family of oncogenic transcription factors (e.g., *ERG*) is the most frequent genetic alteration occurring in ~50% of prostate tumors.[10] Most prostate tumors respond to androgen-deprivation therapy until the establishment of an androgen-independent growth pathway. Pre-diagnostic circulating sex hormones (e.g., total/free testosterone, dihydrotestosterone,

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estradiol) are not associated with increased prostate-specific cancer mortality.[11]

Genome-wide association studies on prostate cancer tumors identified genes with high-risk mutations (e.g., *BRCA2*, *HOXB13* genes) and at least 77 low-risk, common alleles (e.g., *c-MYC* oncogene expression).[12] Although the latter have low penetrance, these mutations interact multiplicatively to substantially increase prostate cancer risk. The lack of linkage studies identifying multiple, high-risk genetic abnormalities in genes other than *BRCA2* and *HOXB13* suggests significant polygenic inheritance.[8] Loss or mutation of the tumor suppressor genes *PTEN* and *TP53* along with the abnormal substrate binding unit of a Cullin-based E3 ubiquitin ligase (*SPOP*), reactivation of androgen-receptor signaling in castration-resistant prostate tumors, and disruption of chromatin and histone modelers are frequent events in prostate cancer. Mutation of *BRCA2* is a rare germline event that is a DNA repair gene mutation present in families with high breast/ovarian cancer rates and confers substantially increased prostate cancer rates (i.e., 4–5-fold) in some but not all observational studies.[13] The relative prostate cancer risk in carriers of BRCA1 mutations remains controversial but suggests an increased, albeit much smaller risk than BRCA2 mutations in men of <65 years of age.[14] Compared with age-matched controls, the presence of *BRCA1/2* pathological variants increases the aggressiveness and early onset (<65 years of age) of prostate tumors.[15] Mutations in other DNA repair genes (e.g., *CHEK2*, *NBS1*) may also moderately increase prostate cancer risks in carriers. Dysregulation of *PTEN* is the most consistently identified lesion in prostate tumors and is associated with a poor prognosis. Figure 56.1 displays the ~35% of susceptibility variants associated with excess familial prostate cancer risks.

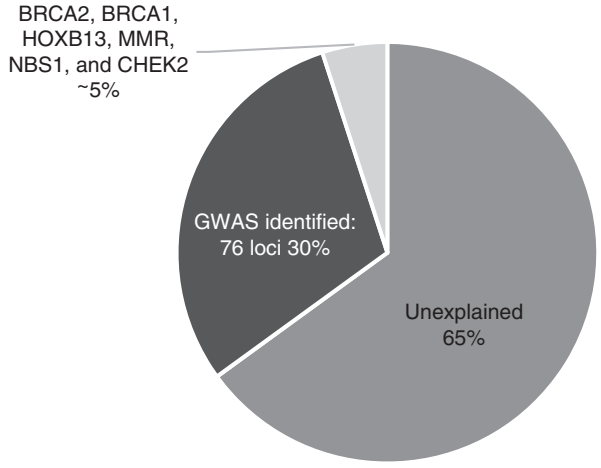


FIGURE 56.1. Low-penetrance and rare germline mutations associated with excess familial prostate cancer risks. (Adapted from Attard et al.).[16]
Abbreviation: GWAS = Genome-wide association study.

EXPOSURE

Prostate cancer is a complex, heterogeneous, hormonally driven disease with highly variable outcomes and different risk factors for indolent and progressive (aggressive, metastatic, fatal) prostate cancer as defined by grade, stage, and survival.[17] Similar to breast cancer, prostate cancer is one of the most common cancers without major lifestyle- or infectious agent-associated risk factors. The only established risk factors for developing prostate cancer (i.e., ↑incidence) are older age, African-American race, and positive family history;[16,18] Table 56.1 displays lifestyle and dietary risk factors associated with prostate cancer progression.[17] Genome-wide association studies also indicate genetic predisposition from over 180 genetic risk loci adds to prostate cancer risks.[2,19] Most meta-analyses do not

TABLE 56.1. Prostate cancer *progression* and *mortality* risk factors with direction and strength of the association. The strength and direction of the association with prostate cancer incidence and progression differ significantly. Few epidemiological data associate substantially *increased* prostate cancer risks with lifestyle and dietary factors. (Adapted from Peisch et al.).[17]

Risk Factor	Direction of Risk	Strength of Risk
BMI (obesity)	↑	Strong
Smoking	↑	Strong
Dairy/calcium	↑	Limited
Processed red meat	↑	Weak
Eggs/choline	↑	Weak
Poultry (unskinned)	↑	Weak
Animal fat/saturated fat	↑	Weak
Selenium supplementation	↑	Weak
Metabolic syndrome	↑	Weak
Physical activity	↓	Moderate
Fish	↓	Limited
Tomatoes/lycopene	↓	Limited
Vegetable fat	↓	Limited
Cruciferous vegetables	↓	Limited
Coffee	↓	Weak
Soy	↓	Weak
Tea	↓	Weak

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support an association between vasectomy and prostate cancer.[20,21,22]

Occupation

Few data associate increased prostate cancer incidence with occupational exposures, with no established occupational causes of prostate cancer. Hypothesis-generating studies suggest farmers, pesticide applicators, metal workers, rubber workers, repairmen, mechanics, and occupations with low physical activity have a slightly increased prostate cancer risk, but the actual risk factors are uncertain.[23,24] A large prospective cohort study of 58,279 men did not confirm previously investigated associations between occupation and prostate cancer risk, with the possible exception of policemen.[25] A meta-analysis of 22 case-control and cohort studies (1995–2001) demonstrated a small but statistically significant increase in the rate ratio for prostate cancer in pesticide applicators (overall pooled RR = 1.13, 95% CI: 1.04–1.22, $P_{\text{homogeneity}}$ = <0.001, n = 22 studies) with significant heterogeneity; the RR for prostate cancer in farmers was not elevated.[26] A prospective cohort study of 55,332 pesticide applicators with no prior history of prostate cancer detected a slightly increased standardized incidence ratio of prostate cancer (SIR = 1.14, 95% CI: 1.05–1.24).[27] Based on questionnaires regarding the use of 45 pesticides, subgroup analysis demonstrated a statistically significant increase in prostate cancer incidence only in workers with a history of methyl bromide use. A meta-analysis of 18 cohort studies on prostate cancer occurrence in pesticide manufacturing published from 1984–2004 using a fixed effect model compared ever- and never-exposed workers.[28] The overall estimated pooled RR demonstrated a modestly increased risk (pooled RR = 1.28, 95% CI: 1.05–1.58, $P_{\text{homogeneity}}$ = 0.973, n = 16 studies). Subgroup analysis did not identify any statistically significant increased prostate cancer risks in specific pesticide classes, except phenoxy herbicides containing dioxin and/or furan contamination (pooled RR = 1.50, 95% CI: 1.06–2.11, $P_{\text{homogeneity}}$ = 0.874, n = 5 studies). Some studies of pesticide applicators[29] and herbicide manufactures[30] have not demonstrated an increased prostate cancer incidence.

Lifestyle

Limited epidemiological data suggest lifestyle and diet may affect the risk of prostate cancer progression (biochemical recurrence, metastasis, hormone-refractory prostate cancer, prostate cancer-specific mortality); however, few data suggest these factors affect prostate cancer incidence.[17] The strongest associations with prostate cancer progression involve smoking, physical activity, and obesity (BMI). Evidence associating consumption of diets high in animal fat and/or red meat with increased prostate cancer risk is weak.

Diet

The complexity of multiple macro- and micronutrients in the diet contributes to the substantial heterogeneity in published dietary studies and complicates the determination of any contribution of dietary nutrients to prostate cancer.[31] Most observational studies do not report clear or consistent associations between prostate cancer incidence and diet including semi-vegetarian or vegetarian diets that exclude protein;[32] however, several risk factors are associated with the progression of prostate cancer. Results from the Health Professionals Follow-up Study suggested some reduction in overall mortality in 4,538 men with nonmetastatic prostate cancer adhering to the Mediterranean diet (HR = 0.78, 95% CI: 0.67–0.90, P_{trend} = 0.0007).[33] The risk of advanced or lethal prostate cancer was not associated with adherence to the Mediterranean diet. In the National Institutes of Health (NIH)-AARP Diet and Health Study containing 23,453 incident prostate cancer cases, reduced total prostate cancer risk occurred only in men reporting a recent history of prostate-specific antigen testing, when comparing the highest and lowest scores on the Healthy Eating Index-2005 (adjusted HR = 0.92, 95% CI: 0.86–0.98, P_{trend} = 0.01) and the Alternate Healthy Eating Index-2010 (adjusted HR = 0.93, 95% CI: 0.88–0.99, P_{trend} = 0.05). Adherence to the Mediterranean diet was not associated with a reduced prostate cancer risk (HR = 0.98, 95% CI: 0.86–1.11, P_{trend} = 0.51).[34] The P_{trend} and hazard ratios were not statistically significant in men with no PSA screening, advanced stages, or fatal prostate cancer. The prospective Melbourne Collaborative Cohort Study identified 1,018 incident prostate cancer cases during an average of 13.6 years for follow-up.[35] Using Cox proportional hazard models and data from a 121-item food frequency questionnaire, comparison of the highest and lowest quartiles of 4 dietary patterns demonstrated no association between overall prostate cancer risk and these dietary patterns, including the Mediterranean (HR = 0.93, 95% CI: 0.74–1.18, n = 193 cases, P = 0.9), meat/potatoes (HR = 0.87, 95% CI: 71–1.08, n = 231 cases, P = 0.2), and vegetable (HR = 1.12, 95% CI: 0.90–1.40, n = 307 cases, P = 0.5) diets.

The association between elevated risks of prostate cancer progression and processed red meat (bacon,

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bologna, hot dogs, salami, sausage), eggs/choline, or animal/saturated fats is weak and inconsistent. Some data support an association between prostate cancer progression and high dairy/calcium intake. A meta-analysis of 15 cohort studies suggests high consumption of total dairy products slightly increases prostate cancer incidence (summary RR = 1.07 per 400 g/day, 95% CI: 1.02–1.12, $I^2 = 43.9\%$) with slight to moderate heterogeneity, but not supplemental/nondairy calcium.[36] The multivariate analysis did not adjust for multiple risk factors. The meta-analysis did not support an association between prostate cancer progression and total dairy products or nondairy calcium. A cohort study in the Physicians' Health Study (n = 21,660) collected information on dairy product consumption at baseline with follow-up over 11 years.[37] Comparing high (>2.5 servings/day) and low total dairy product intake (<0.5 servings/day), high dairy intake was associated with a statistically nonsignificant elevation of prostate cancer incidence (multivariable adjusted HR = 1.12, 95% CI: 0.93–1.35, n = 2,806 cases, $P_{trend} = 0.06$). The association between prostate cancer mortality and whole milk consumption demonstrated a marginally statistically significant increase (multivariable adjusted HR = 1.49, 95% CI: 0.97–2.28, $P_{trend} = 0.01$) comparing intake of 1 serving/day with rarely consumed whole milk. In the Health Professionals Follow-Up Study cohort of 3,918 men diagnosed with localized prostate cancer in the pre- and post-PSA screening era (1986–2006), multivariate analysis demonstrates no increased lethal prostate risk after diagnosis and total milk/dairy intakes.[38] Comparing men with the highest and lowest intake quintiles, the prostate cancer progression risk was increased for whole milk (HR = 2.15, 95% CI: 1.28–3.60; $P_{trend} < 0.01$), whereas low-fat dairy intake did not statistically reduce the risk of progression (HR = 0.62, 95% CI: 0.40–0.95, $P_{trend} = 0.07$). Limited evidence supports a reduced risk of prostate cancer progression with the consumption of fish, tomatoes/lycopene, vegetable fats, or cruciferous vegetables (broccoli, Brussel sprouts, cabbage, cauliflower, kale, or mustard/chard greens).[39] Relatively little evidence conclusively associates reduced prostate cancer progression with coffee, soy, or tea. The epidemiological data associating red and processed meats with prostate cancer is relatively weak and inconsistent, in part because of confounding by family history, age, and PSA screening as well as recall bias (dietary history, diabetes).[40] In the large, prospective NIH-AARP Diet and Health Study of 175,343 US men aged 50–71 years followed for 9 years, the association between red and processed meat was marginal to small.[41] Comparing the fifth and first quintiles of total red meat consumption and overall prostate cancer incidence, multivariate modeling demonstrated a hazard ratio of 1.12 (95% CI: 1.04–1.21), whereas the HR for advanced prostate cancer was higher (HR = 1.31, 95% CI: 1.05–1.65). The hazard ratio of overall prostate cancer incidence comparing the highest and lowest quintiles of total processed meats was 1.07 (95% CI: 1.00–1.14) and higher for advanced prostate cancer incidence (HR = 1.32, 95% CI: 1.08–1.61). A meta-analysis of 19 cohort studies using random effects models to estimate summary relative risks for prostate cancer incidence in high versus low exposure categories did not support an association between red meat consumption and prostate cancer (RR = 1.02, 95% CI: 0.92–1.12), whereas the association with processed meats and total prostate cancer was weakly positive (RR = 1.05, 95% CI: 1.01–1.10).[42]

Physical Activity

Most population-based observational studies report no to little effect of overall total, vigorous, or non-vigorous activity on prostate cancer incidence; however, some studies associate a reduced risk of prostate cancer progression with high levels of physical activity. The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study identified 2,458 prostate cancer cases during 8.5 years of follow-up.[43] Prostate cancer incidence was not associated with any of the four leisure time activities (cycling, gardening, sports, walking), metabolic equivalent task (MET) hours/week of leisure time activity, participation in any of the four leisure activities, or a higher physical activity index score. Although comparing advanced-stage prostate cancer risks with low (sitting) and high (manual labor) occupational activity levels was not statistically different (RR = 0.75, 95% CI: 0.53–1.05), the overall trend of the three occupational activity levels together (sitting, standing, manual labor) with advanced-stage prostate cancer indicated a significant reduction ($P_{trend} = 0.024$) with increasing occupational activity levels. Using Cox regression in relation to multiple subcategories for prostate cancer in the Health Professionals Follow-Up Study, more frequent vigorous physical activity (↑ sweating, ↑ heart/respiratory rate) was associated with decreased advanced and fatal prostate cancer risks; multivariant analysis on data from men living at least 4 years after their postdiagnosis physical activity assessment yielded an overall reduction in prostate cancer mortality ($P_{trend} = 0.04$).[44] Men with ≥3 hours/week of vigorous activity had a 61% lower risk of death from prostate cancer (HR = 0.39, 95% CI: 0.18–0.84, $P = 0.03$) than men with <1 hour/week of vigorous activity. However,

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comparison of the highest and lowest quintiles of physical activity yielded a modest and statistically significant increase in non-advanced prostate cancer incidence (RR = 1.19, 95% CI: 1.03–1.37, $P_{trend} < 0.01$).[45] The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) study examined vigorous activity and brisk walking after prostate cancer diagnosis to reduce the potential for reverse causation (bias caused by men reducing physical activity due to disease recurrence).[46] Using Cox proportional hazards regression, the HR for prostate cancer progression in men walking briskly (≥3 hours/week) compared with men walking at an easy pace (<3 hours/week) was 0.43 (95% CI: 0.21–0.91, $P = 0.03$). Independent of pace, prostate cancer progression was not associated with walking duration; similarly, total non-vigorous activity was not associated with prostate cancer progression independent of vigorous activity.

Obesity

Most prospective studies do not support a statistically significant association between prostate cancer incidence and obesity,[47] particularly indolent prostate disease (local, low-grade) in North American studies during the post-PSA screening era.[45] Increasing epidemiological evidence from observational studies suggests obesity is associated with more aggressive prostate cancer (advanced stage, poor therapeutic response, ↑ mortality), particularly in men with the TMPRSS2:ERG gene fusion.[48,49] The Physicians' Health Study identified 2,546 men with prostate cancer and 281 prostate-related deaths during the 24-year study period; the median follow-up between diagnosis and death or termination of follow-up was 7 years, with baseline BMI reported in the pre-prostate screening era (1982–1990) and prostate screening era (1991–2007).[50] Compared with normal-weight men (BMI <25 kg/m^2), the proportional hazard ratio (HR) was 1.47 (95% CI: 1.16–1.88) for overweight men (BMI 25–29.9 kg/m^2) and 2.66 (95% CI: 1.62–4.39, $P_{trend} = <0.0001$) for obese men (≥30 kg/m^2). The trend remained significant after controlling for tumor severity (Gleason grade, clinical stage). In a cohort of 752 middle-aged men with prostate cancer under long-term follow-up for disease progression and mortality during a case-control study, the initial interview documented the BMI in the year before their prostate cancer diagnosis.[51] Using Cox proportional hazards models to estimate the adjusted hazard ratios, the HR for prostate cancer mortality was 2.64 (95% CI: 1.18–5.92, $n = 15$ deaths) in obese patients defined by BMI ≥30 kg/m^2 compared with normal-weight men (BMI <25 kg/m^2). Adjusted risk factors included age, race, diagnostic prostate-specific antigen level, smoking status, primary treatment, clinical stage at diagnosis, and Gleason score. For men with local or regional disease, the adjusted HR for developing metastasis in obese patients was 3.61 (95% CI: 1.73–7.51, $n = 73$ patients with 21 events) compared with normal-weight men. Using random effects meta-analysis to assess relative risks of prostate-specific mortality in six cohort studies, the pooled RR associated with a 5 kg/m^2 increase in weight above normal was 1.15 (95% CI: 1.06–1.25, $P < 0.001$, $I^2 = 59\%$, $n = 6{,}817$ cases) with moderate heterogeneity.[52]

Smoking

Although little epidemiological evidence associates smoking with increased prostate cancer incidence, the association between smoking and prostate cancer progression is relatively strong. In the prospective Health Professionals Follow-Up Study of 5,366 men diagnosed with prostate cancer (1986–2006), multivariable analysis demonstrated an increased prostate cancer mortality risk (HR = 1.61, 95% CI: 1.11–2.32) comparing current smokers with never-smokers.[53] The risk of biochemical recurrence was also elevated in current smokers (HR = 1.61, 95% CI: 1.16–2.22) when compared with never-smokers. Prostate cancer mortality risks were similar in never-smokers (HR = 0.61, 95% CI: 0.42–0.88) and former smokers quitting ≥10 years previously (HR = 0.60, 95% CI: 0.42–0.87) or quitting <10 years previously with a smoking history of <20 pack-years (HR = 0.64, 95% CI: 0.28–1.45) when compared with current smokers. A systematic review and meta-analysis reported a modest but statistically significant association between current- versus never-cigarette smokers and prostate cancer mortality (RR = 1.24, 95% CI: 1.18–1.31, $P_{heterogeneity} = 0.446$, $I^2 = 1\%$, $n = 21$ studies) with little evidence of heterogeneity or publication bias.[54] Other forms of tobacco use (smokeless, cigar, pipe) were not associated with increased prostate cancer mortality (RR = 1.16, 95% CI: 0.81–1.65, $P_{heterogeneity} = 0.017$, $I^2 = 70.6\%$) with significant heterogeneity. A meta-analysis of cohort studies confirmed the increased risk of fatal prostate cancer in current smokers versus never-smokers (summary RR = 1.14, 95% CI: 1.06–1.19, $n = 8$ studies) and no statistical difference in prostate cancer incidence between current smokers and never-smokers (RR = 1.04, 95% CI: 0.87–1.24, $n = 7$ studies).[55]

Alcohol

The association between alcohol consumption and prostate cancer is inconsistent and relatively weak. In a

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meta-analysis of 39 case-control and cohort studies comparing alcohol consumption with nonexposed controls, the effect of alcohol was modest and marginally to nonsignificant with little difference between consumption levels.[56] For light drinkers in cohort studies, the pooled RR was 1.04 (95% CI: 1.01–1.08, $I^2 = 0\%$, $n = 19$) compared with 1.06 (95% CI: 0.99–1.13, $I^2 = 24\%$, $n = 20$) for moderate drinkers and 1.04 (0.90–1.21, $I^2 = 45\%$, $n = 8$) for heavy drinkers with moderate heterogeneity. The pooled RR for case-control studies was similarly modest and statistically nonsignificant. A population-based Finnish cohort study with a median follow-up of 30 years suggests heavy drinking (>14 drinks/week) increases prostate cancer incidence based on lifestyle questionnaires on midlife drinking habits.[57] The adjusted hazard ratio was 1.46 (95% CI: 1.12–1.91, $n = 94$ cases) compared with light drinkers (0.01–3 drinks/week); however, the hazard ratio for prostate cancer-specific mortality was not statistically different than light drinkers (HR = 1.32, 95% CI: 0.66–2.62, $n = 15$ cases). Abstainers (adjusted HR = 1.90, 95% CI: 1.04–3.47, $n = 17$ cases) had a higher prostate cancer-specific risk than heavy or moderate drinkers. Adjustment variables included BMI, smoking, physical activity, education, and social class. An Australian case-control study using self-administered questionnaires examined the association between alcohol intake 2 years prior to enrollment and high-grade prostate cancer. Compared with no beer intake, heavy beer consumption (≥5 days/week) was associated with an increased risk of high-grade prostate cancer (OR = 1.66, 95% CI: 1.12–2.48, $P = 0.012$) after adjustment for intake of other alcoholic beverage types. Red and white wine consumption did not display a dose-response relationship with high-grade prostate cancer, similar to overall alcohol consumption.

HISTOLOGY

Almost all prostate tumors are adenocarcinomas. Human prostates contain pseudostratified epithelium composed of the three terminally differentiated epithelial cells (basal, luminal, neuroendocrine). Although the cellular origin of prostate cancer remains controversial, the most likely sources are stem/progenitor or differentiated cells with basal or luminal phenotypes.[58] The malignant transformation of prostate epithelial cells is a multistep process beginning with prostatic intraepithelial neoplasia followed by localized prostate cancer, advanced prostate adenocarcinoma with local invasion, and finally metastatic prostate cancer.[59] The Gleason grading system from 2–20 is the most widely used classification of prostate cancer aggressiveness with higher scores indicating increased risk of spreading. Hormone responsiveness is a common feature of prostate adenocarcinomas, particularly in untreated prostate cancer. Prostate cancer usually develops in the periphery of the gland, in areas outside those affected by benign hyperplasia.[60] Gleason scores above 7 indicate clinically significant disease.

HOST SUSCEPTIBILITY

Family History

A family history of prostate cancer increases the risk of prostate cancer ~2–4-fold depending on the number/closeness of affected relatives and the age of cancer onset in first-degree relatives;[61] a family history of prostate cancer in first-degree relatives almost doubles prostate cancer risk.[62] Analysis of data from the nationwide Swedish Family-Cancer Database demonstrated increasing hazard ratios of prostatic cancer diagnosis in 5,623 prostate cancer patients with a familial history of prostate cancer; the HR for developing prostate cancer increased with the number of affected relatives and decreased with the increasing age of the affected relative.[63] In a systematic review and meta-analysis using a weighted average model, the pooled RR estimates for prostate cancer in any affected family member were 1.93 (95% CI: 1.65–2.26, $n = 4$ case-control and 3 cohort studies) and 2.22 (95% CI: 2.06–2.40, $n = 11$ case-control and 5 cohort studies) in affected first-degree relatives.[64] Statistical comparison of pooled data demonstrated the relative risk of prostate cancer was significantly higher in brothers than fathers ($n = 8$ case-control and 4 cohort studies, $P < 0.03$). A measure of heterogeneity was not reported. Analysis of data on 635,443 men and 18,105 prostate cancer cases from a large population-based genealogy database supported the increased prostate cancer risk in families with affected members.[65] The prostate cancer risk in men with affected first-degree relatives ranged from 2.46 (95% CI: 2.39–2.53) for one first-degree relative to 7.65 (95% CI: 6.28–9.23) for four first-degree relatives. The study also suggested maternal family history and the presence of more distant affected family members (second-, third-degree relatives) also contributed to prostate cancer risks. The prostate cancer risk is higher, and the age at prostate cancer diagnosis is lower in monozygotic than dizygotic twins, consistent with genetic influence.[66] In an analysis of data from 44,788 pairs of twins listed in the Swedish, Danish, and Finnish twin registries, heritable factors accounted for 42% (95% CI: 29–50%) of incident prostate cancer cases.[67]

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Male Pattern Baldness

Male pattern baldness (androgenetic alopecia) is an age-related, androgen-independent genetic disorder caused by dihydrotestosterone-induced activation of androgen receptors in hair follicles; this disorder shares similar pathological mechanisms (e.g., aging, androgen influence) with prostate cancer suggesting the presence of male pattern baldness may be a high-risk factor important for prostate progression and screening.[68] Based primarily on case-control studies, the association between male pattern baldness and prostate cancer risks is inconclusive; however, the studies do not exclude a possible association between self-reported early-onset baldness and prostate cancer progression[69] or overall baldness (any pattern) and high-grade disease. Most epidemiological studies do not support an association between overall baldness (i.e., all patterns) and prostate cancer incidence using non-bald participants as controls; however, some,[70] but not all,[71] studies support an association between vertex male pattern baldness and high-grade disease. In a meta-analysis of seven case-control studies (4,078 cases/4,916 controls), the association between prostate cancer incidence and combined patterns of male baldness was not statistically significant (OR = 1.03, 95% CI: 0.93–1.13, $P_{\text{heterogeneity}} = 0.36$, $I^2 = 9\%$) with little heterogeneity.[72] The odds ratio for prostate cancer risk comparing vertex baldness with non-bald controls was statistically significant (OR = 1.25, 95% CI: 1.09–1.44, $P_{\text{heterogeneity}} = 0.35$, $I^2 = 10\%$). Similarly, a meta-analysis of nine case-control and two cohort studies did not detect a statistically significant difference in the prostate cancer rates between bald and non-bald participants. Subgroup analysis indicated the difference between aggressive prostate cancer rates in vertex baldness and non-bald participants was significant (OR = 1.60, 95% CI: 1.37–1.86, $P_{\text{heterogeneity}} = 0.65$, $I^2 = 0\%$, $n = 5$ case-control studies).[73] The age-varying rate of prostate cancer influences the association between male pattern baldness and prostate cancer risks. In a follow-up study of 9,448 participants in the Melbourne Collaborative Cohort (median follow-up, 11.33 years, $n = 476$ cases), the cumulative probability of prostate cancer comparing men with vertex baldness and non-bald controls was elevated at all ages up to 76 years; thereafter, the probability converged.[74] The age at diagnosis was greater in patients with vertex baldness at age 40 than in non-bald controls.

CLINICAL FEATURES

Prostate cancer is a slowly developing disease of aging with a long preclinical phase; the diagnosis often occurs incidentally in asymptomatic men or older, symptomatic men. The median at diagnosis is 67 years and the latent period for prostate cancer averages 20–30 years; there is no association between prostate hyperplasia and latent prostate cancer.[75] The vast majority of men presenting with prostate cancer have relatively low-risk, indolent tumors that are unlikely to progress or require treatment. Using logistic regression models with random effects, a systematic review of 29 observational studies (1948–2013), the prostate cancer prevalence increased with each decade of age in all populations (OR = 1.7, 95% CI: 1.6–1.8), particularly in studies using Gleason scores for severity. The mean prostate cancer prevalence was nonlinear increasing from 5% (95% CI: 3–8%) for patients aged <30 years to 59% (95% CI: 48–71%) for patients aged >79 years. Consequently, prostate cancer screening often detects nonprogressive cancers or nonmalignant diseases (e.g., prostatitis, benign prostatic hypertrophy), resulting in increased risks associated with overtreatment in men likely to die from other causes. In 2018 with moderate certainty, the US Preventive Services Task Force recommended that clinicians offer prostate-specific antigen (PSA) testing selectively to men aged 55 to 69 years old based on individual discussions of the potential benefits and harms of PSA testing. The Committee recommended against routine PSA testing in men 70 years and older with moderate certainty; however, the amount of evidence was limited. Currently, these recommendations are being reviewed, particularly for younger, high-risk men (e.g., African American men, strong family history of prostate cancer).[76] the ~20–30% of men with localized prostate cancer and some high-risk tumor features are the primary focus of PSA screening.

Approximately 92% of new prostate cancer cases have localized or regional disease with 5-year and 15-year survival rates approaching 100% and 94%, respectively; A PSA <1 ng/mL in a patient over 70 years of age indicates low-risk disease. The 5-year survival rate drops below 30% for patients with metastatic disease.[17] Metastatic prostate cancer is the most common cause of prostate-related deaths occurring primarily in men over 70 years of age. Adjacent lymph nodes are the initial sites of metastases, followed by metastases to bones, liver, and lungs; the osteoblastic lesions in bones cause severe pain, pathological fractures, and hypercalcemia. Treatment usually involves androgen deprivation therapy, and often is associated with erectile dysfunction and hot flashes. Approximately one-third

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of prostate cancer patients with localized disease may be managed with active surveillance including serial PSA measurements, magnetic resonance imaging, and prostate biopsies; initiation of treatment begins when the tumor stage or Gleason score increases. For patients with higher-risk disease, radical prostatectomy or radiation therapy are options. The treatment of metastatic prostate cancer typically involves androgen deprivation therapy (e.g., gonadotropin-releasing hormone agonists, medical castration). The addition of androgen receptor pathway inhibitors (abiraterone, darolutamide) improves survival for patients with recently diagnosed metastatic prostate disease.

TESTES

Although rare, testicular germ cell cancer is the most common cancer site among males aged 15–29 years; the incidence of this cancer ranks second among males aged 30–44 years (mean age of diagnosis, 33 years). Figure 56.2 displays the age-related incidence of total testicular germ cell tumors, seminomas, and nonseminomas. Testicular cancer incidence has increased over the last 50 years,[77] varying by ~6-fold worldwide depending on geographical, temporal, and ethnic factors. The highest incidences occur in Western countries, primarily in Caucasians from Western developed

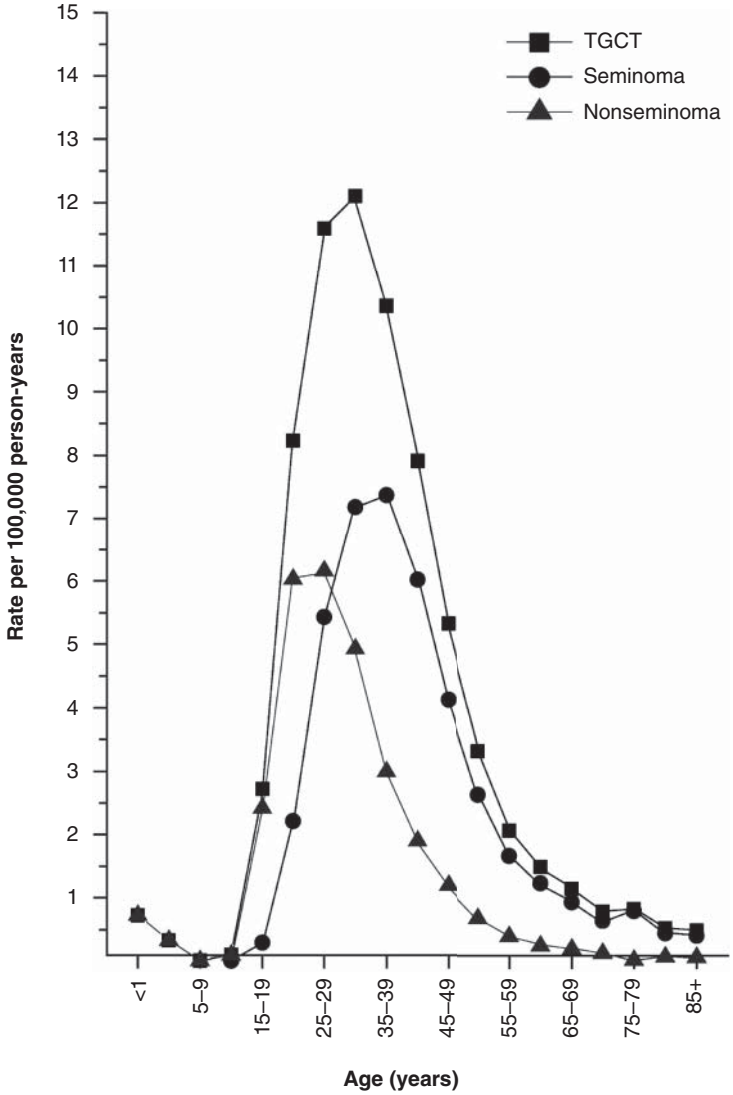


FIGURE 56.2. Age-related incidence of total testicular germ cell tumors (TGCT, square), seminomas (circle), and nonseminomas (triangle). (Adapted from McGlynn and Cook).[78]

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countries (e.g., northern Europe, Canada), and the lowest rates appear in Asia and Africa.[78,79] In the United States, testicular cancer incidence is highest among non-Hispanic white men (7.50/100,000, 95% CI: 7.27–7.74/100,000) based on SEER data, whereas the incidence is 2.16/100,000 (95% CI: 1.93–2.43) for Asian/Pacific Islanders and 1.35/100,000 (95% CI: 1.14–1.58) for African-Americans.[80] Approximately 500,000 new testicular cancers develop annually in the world, with most cases being germline tumors in young adult males.[81] In the United States, ~9,300 cases of testicular cancer occur annually, with ~400 testicular cancer-related deaths each year.[1]

CARCINOGENESIS

Seminomas display the features of pluripotent, primordial germ cells (gonocytes) that ultimately form spermatogonia, whereas nonseminomas are mixed germ cell tumors that may contain embryonal cell carcinoma, choriocarcinomas, teratomas, and yolk sac tumors. The development of testicular cancer involves at least 44 SNPs and candidate causal genes producing widespread disruption of developmental transcriptional regulators consistent with failed primordial germ cell differentiation as the initiating event.[82] Genome-wide association studies indicate these changes primarily involve noncoding regions of the genome that influence gene regulation and transcriptional initiation/enhancement through histone modifications and chromatin looping interactions. Two characteristic chromosomal abnormalities in testicular germ cell tumors are polyploidization (multiple double-paired, related chromosomes) and amplification of the short arm of chromosome 12 (i12p); the latter being present in 80% of testicular germ cell tumors and almost all invasive testicular germ cell tumors.[83] Compared with chromosomal abnormalities, specific gene mutations in testicular cancer are less frequent. Identified mutations in germ cell tumors often involve the *KIT* (proto-oncogene receptor tyrosine kinase) driver gene and RAS/MAPK (cell proliferation/migration, angiogenesis, stem cell maintenance) signaling pathways.[84] The most common single affected genes include *KIT*, *BRAF*, *DRAS*, *NRAS*, and *TP53*, depending on the tumor subtype. Mutation of the stem cell growth factor *KIT* gene occurs in ~19% of seminoma and 2% of nonseminoma tumors.[85] Single nucleotide polymorphisms (SNPs) typically affect genes involved in normal germ cell differentiation and apoptosis (e.g., *BAK1*, *KITLG*, *PDE11A*, *SPRY4*).[86] Mutations occur in ~25% of seminomas, whereas their presence in nonseminomas is uncommon.[87]

Most normal epigenetic signatures develop during differentiation with subsequent stabilization to allow multiple functions from the same genetic information. These epigenetic modifications are transmissible over cell generations including DNA methylation of cytosine bases, posttranslational histone protein alteration, and chromatin reorganization. Little CpG island methylation occurs in seminomas, whereas nonseminomas and other solid tumors display much higher levels of CpG island methylation, particularly in specific promoter regions (e.g., *RASSF1A*, a tumor suppressor gene).[88] DNA methylation is a critical epigenetic gene-silencing mechanism for cell-specific genes/transposons, cell differentiation and organ development, X chromosome inactivation, and maintenance of cellular pluripotency, whereas histone modifications involve the post-translational alteration of key proteins regulating gene expression by modification of chromatin conformation and stability. In testicular germ cell tumors, these two epigenetic processes display unique developmental rather than somatic epigenetic patterns. Demethylation occurs throughout the genome in germ cell neoplasia *in situ* and seminomas; however, demethylation involves only a few imprinted genes and *LINE1* (long interspersed nuclear element 1) in nonseminomas.[89] Promotor hypermethylation of piRNA along with corresponding genes (*PIWI1*, *PIWI2*, *PIWI4*, *TDRD1*) and resultant *LINE1* silencing enhances chromatin instability.[90] By altering RNAs and inserting the information back into the genome, Line1 proteins facilitate an epigenetic pathway from transcriptome (RNA) to genome (DNA) allowing the import of extracellular information. The miRNA profiles of germ cell tumors including germ cell neoplasia *in situ* closely resemble those of embryonic stem cells.[91] In contrast to normal testicular tissues, testicular germ cell tumors typically do not express genes in the PIWI/piRNA pathway critical to the normal development of male germ cells.[92]

EXPOSURE

Limited data exist regarding testicular cancer epidemiology or specific cancer subtypes; the lack of definite evidence of associations with occupation, lifestyle, or infection reflects the importance of *in utero* rather than postnatal exposures in the development of testicular cancer. Major risk factors for the development of testicular germ cell tumors are hypospadias (i.e., congenital displacement of urethral opening from tip to underside of penis), previous or family history of testicular cancer, and cryptorchidism (i.e., failure of testes to descend from abdomen to scrotum).[93,94]

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A hypothesis-generating study of 250 cases of testicular cancer found the following factors associated with an increased risk of developing testicular cancer: testis-related abnormalities including low sperm count (OR = 6.0), atrophic testis (OR = 20), cryptorchidism (OR = 5.17), and fertility problems (OR = 10).[95] Although the role of sex hormones, including prenatal exposure, in the formation of testicular cancer remains controversial, case-control studies of children exposed *in utero* to diethylstilbestrol have not demonstrated a definitive increase in testicular cancer risk in this population.[96] Most meta-analyses do not support an association between vasectomy and testicular cancer.[97] Higher socioeconomic status and especially professional occupations are associated with the development of testicular cancer in older studies.[98] More recent New Zealand cohort studies suggest testicular cancer rates are higher in men with low than high incomes (pooled rate ratio for lowest to highest income groups = 1.23; 95% CI: 1.05–1.44).[99] There is no strong evidence that disparities in testicular cancer incidence have varied by ethnicity or household income over time. Although testicular microlithiasis (i.e., seminiferous tubular calcifications) often occurs in the setting of testicular malignancy, prospective studies do not support microlithiasis as a risk factor for testicular cancer.[100]

Occupation

Occupational exposures are not strong risk factors for developing testicular cancer because of the probable prenatal and/or early life origin of this cancer and the difficulty of evaluating exposures retrospectively in case-control studies.[101] Little epidemiological evidence supports a strong association between specific chemical exposures in the work environment and the development of testicular cancer including endocrine disrupting chemicals.[102,103] Epidemiological data are particularly weak for occupational exposures and seminomas.[104] Although testicular germ cell cancer risk is often higher in studies of white-collar than blue-collar occupations,[105] socioeconomic status may contribute to this difference.[106] No single profession is conclusively associated with testicular germ cell tumors, including occupational exposure to ionizing radiation based on a systemic review (study heterogeneity prevented a pooled analysis)[107] and the relative insensitivity of the human testis to low levels of ionizing radiation in BEIR V data.[108] Evaluation of four cohort and five case-control studies suggests a possible association between occupational electromagnetic fields (EMF) and testicular cancer; however, most of the published evidence associating EMF with testicular cancer exists in the older medical literature with crude exposure estimations and often inconsistent findings. More recent, higher-quality studies have not demonstrated a statistical relationship between occupational EMF exposure (e.g., radar units, radiofrequency emitters, electrical machines, high-voltage lines or transmission installations) and testicular cancer incidence[107] or mortality.[109]

Job Classifications

Poor exposure data limit the ability of these studies to detect associations between specific chemicals and testicular cancer incidence. In the population-based Nordic study of 15 million residents followed up to 45 years, physicians had the highest seminoma risk (SIR = 1.48, 95% CI: 1.07–1.99), followed by artistic workers (SIR = 1.47, 95% CI: 1.06–1.99) and religious workers (SIR = 1.33, 95% CI: 1.14–1.56).[110] The lowest seminoma risks occurred in cooks and stewards (SIR = 0.56, 95% CI: 0.29–0.98) and forestry workers (SIR = 0.64, 95% CI: 0.47–0.86). The testicular cancer incidence was not increased in occupations involving pesticide exposures, including farmers (SIR = 0.97, 95% CI: 0.89–1.06) or gardeners (SIR = 1.03, 95% CI: 0.88–1.20). A Swedish register-based study reported a statistically nonsignificant increased SIR of 1.55 (95% CI: 0.92–2.45) for agricultural workers using pesticides;[111] a follow-up study including an additional 10 years of follow-up demonstrated a testicular cancer risk of (SIR = 1.09, 95% CI: 0.68–1.67, $n = 18$ cases).[112] A case-control study of 495 germ cell testicular cancers suggests the possibility of an association between nonseminomas and the following occupations: mining (OR = 12.39; CI: 2.22–69.27), food and beverage processing (OR = 3.2, 95% CI: 1.39–7.35), utilities (OR = 3.15, 95% CI: 1.15–8.61), and other service workers (OR = 1.05, 95% CI: 1.05–4.56).[113] The large confidence limits indicate imprecise estimates of the true odds ratios. A case-control study of leather workers initiated after the recognition of a cluster of three testicular cancer cases reported an elevated, age-adjusted odds ratio of 7.2 (95% CI: 1.89–27.2) for the development of testicular cancer in leather workers;[114] however, no specific carcinogen was identified, and the OR estimates were imprecise. In a cohort of 2,026 workers employed at least 1 year from 1900–1989 in 3 Swedish leather tanneries and followed from 1958–1989, the odd ratio using a 20-year latency period demonstrated no association between their work and testicular cancer (SIR = 0.97, 95% CI: 0.32–2.27, $n = 5$ cases).[115] Studies associating firefighters, military service, or aircraft maintenance with testicular cancer are inconsistent.[116]

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Chemical Exposures

Dimethylformamide

Limited human evidence associates the development of testicular cancer with dimethylformamide exposure, and the association remains controversial.[117] Studies associating dimethylformamide exposure with testicular cancer are older case-control studies with poor exposure data involving cancer cluster evaluations.[118] A cohort study of 3,859 workers followed from 1956–1984 for cancer incidence after dimethylformamide exposure during the manufacture of synthetic fibers did not detect an increased testicular cancer risk (1.7 cases expected/1 case observed).[119] No clear biological mechanism explains the association with testicular cancer; however, experimental studies suggest dimethylformamide is moderately genotoxic with experimental evidence that dimethylformamide increases oxidative stress and alters cell proliferation.[120] The IARC considers dimethylformamide a probable human carcinogen (Group 2A) based on limited human evidence and sufficient evidence in animals.

Endocrine Disrupters

Endocrine disrupting chemicals include the estrogenic dichlorodiphenyl-trichloroethane (DDT), polyvinyl chloride (PVC), bisphenol A, anti-androgenic DDT metabolite dichlorodiphenyl-dichloroethylene (DDE) phthalates, and 209 congeners of polychlorinated biphenyls (PCBs) with varying estrogenic and androgenic effects. Theoretically, these chemicals may impair androgen signaling during early development and potentially slightly increase testicular cancer risks; however, current organochlorine classification schemes do not separate or quantitate their estrogenic and anti-androgenic effects. The estrogenic/antiandrogenic effects of these chemicals are hundreds- to thousands-fold less potent than diethylstilbestrol, a chemical with limited evidence of human carcinogenicity. A meta-analysis of 6 case-control studies with 36 risk estimates did not detect a statistically significant association (OR = 1.20, 95% CI: 0.78–1.89) between testicular cancer and exposure to endocrine disrupting chemicals included in the European Commission's list of Category I endocrine disrupting chemicals.[121] This systemic review and meta-analysis did not detect exposure-response relationships.

In a review of organochlorine compounds and testicular cancer, the authors reported a weak association between DDE, *cis*-nonachlor, and *trans*-nonachlor and testicular germ cell cancer, whereas the review revealed no association between testicular germ cell cancer and DDT, PCBs, or other organochlorine compounds.[122] Although three of four case-control studies found a positive association between DDE exposure and testicular germ cell cancer,[123,124] only the STEED Study reported a statistically significant odds ratio (P_{trend} = 0.0002) that was limited to comparing the highest (>39 μg/g lipid) and lowest exposure quartiles (OR = 1.71, 95% CI: 1.23–2.38).[125] Additionally, the review did not demonstrate an association between organochlorines (DDT, DDE) or PCBs and congenital abnormalities (cryptorchism, hypospadias, fertility). A population-based, case-control study of 18–44-year-old male residents of three Washington State counties observed no clear association between testicular germ cell tumors and 11 serum organochlorine concentrations including comparison of high to low *p*,*p*′-DDE concentrations (adjusted OR = 0.61, 95% CI: 0.32–1.14, *n* = 21 cases).[126] Organochlorine atmospheric and biological concentrations are declining as a result of the elimination of more persistent organochlorine compounds (e.g., DDT, DDE, chlordane). Epidemiological data are insufficient to determine the association between other endocrine disrupting chemicals (e.g., bisphenol A, phthalates, PVC) and testicular germ cell cancer.[127,128]

Lifestyle

Lifestyle does not strongly affect testicular germ cell cancer risks including maternal smoking,[129] overall adult/adolescent BMI,[130] diet,[131] heat,[132] trauma, or physical activity (riding, recreational, occupational).[133,134] The development of testicular cancer is probably not significantly associated with residential electromagnetic field exposure. In a German population-based case-control study, the OR for testicular cancer in 145 Hamburg residents living within a 100-m corridor of high-voltage lines in Hamburg was 1.3 (95% CI: 0.56–2.80) compared with 313 controls (age-adjusted Hamburg residents with no excessive EMF exposure).[135] The risk was higher but statistically nonsignificant when comparing high EMF exposures to controls (OR = 1.7, 95% CI: 0.91–3.32).

The strongest epidemiological evidence associates taller heights with increased testicular germ cell cancer risk, particularly for seminomas.[136] A cohort of 557,032 adult Norwegian men registered 1,357 cases of testicular cancer.[137] Using proportional hazards regression, the RR comparing adults over 180 cm with adults measuring 170–179 cm in height was 1.09 (95% CI: 0.96–1.24, *n* = 1,004 cases, P_{trend} = 0.004). The same comparison for seminomas was borderline significant (RR = 1.17, 95% CI: 1.00–1.37, P_{trend} = 0.006, *n* = 693 cases). The difference in testicular cancer risk comparing obese

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men and referents (BMI = 18.5–24.9 kg/m^2) was not statistically significant (RR = 0.83, 95% CI: 0.58–1.17, n = 1,004 cases); however, the trend of <18.5–≥30 kg/m^2 was inversely related (P_{trend} = 0.02). A random effects meta-analysis of 12 case-control and 1 cohort study reported a relatively weak but statistically significant association between testicular germ cell cancer and height (per 5 cm) with an estimated OR of 1.13 (95% CI: 1.07–1.19, I^2 = 76.5%) and substantial heterogeneity.[138] The meta-analysis demonstrated no significant association between testicular germ cell cancer and BMI (OR per kg/m^2 = 0.99, 95% CI: 0.97–1.00, I^2 = 45.4%) with moderate heterogeneity.

Diseases

Cryptorchidism (undescended testes) is the antecedent medical condition most closely associated with testicular germ cell tumors accounting for ~5–10% of these tumors.[78,139] In a review of mostly retrospective studies, the relative risk of testicular cancer in cryptorchidism cases ranged from 2.75–8, with the RR dropping to 2–3 for patients undergoing prepubertal orchiopexy.[140] The relative risk of testicular cancer in a population-based, case-control study of 387 cases of cryptorchidism and 416 controls was 3.6 (95% CI: 1.8–6.9); the study detected no clear association of testicular cancer with inguinal hernias or testes that spontaneously descended after birth.[141] The relative risk of testicular cancer increased as the age at orchiopexy increased. The testicular germ cell cancer risk associated with perinatal risk factors (low birth weight, decreased gestational age, low maternal parity, low birth order, sibship size) is inconsistent and relatively weak.

Drugs

Diethylstilbestrol

Diethylstilbestrol (DES) is a synthetic nonsteroidal estrogen previously used to prevent miscarriages in the late 1940s–mid-1970s until withdrawn from the market because of the increased risk of clear cell vaginal and cervical adenocarcinoma in offspring following *in utero* exposure. Limited human data associate *in utero* DES exposure and testicular germ cell cancer. Although some,[94,142] but not all,[96,143] case-control studies suggest an association between *in utero* DES exposure and testicular cancer, a prospective cohort study of 3,613 men with prenatal DES exposure followed from 1978–1994 provided equivocal support for the association with testicular cancer. The relative risk of testicular cancer in exposed versus unexposed men was 3.05 (95% CI: 0.65–21.96, n = 6 cases) based on imprecise RR estimates and few cases. Using population-based rates, the SIR for testicular cancer in 1,787 exposed men was also not statistically significant (RR = 2.04, 95% CI: 0.82–4.29, n = 7 cases).

Cannabis

A systematic review and meta-analysis of studies regarding cannabis use and testicular cancer risk published from 1980–2015 yielded three case-control studies that used face-to-face interviews (two studies) or self-completed paper-based questionnaire (one study) to evaluate cannabis use.[144] All studies adjusted for cryptorchidism. The association between current cannabis use and testicular cancer was strongest for nonseminomas (pooled OR = 2.09, 95% CI: 1.29–3.37, I^2 = 0%) and total testicular germ cell tumors (pooled OR = 1.62, 95% CI: 1.13–2.31, I^2 = 0%) when compared with never users. Subanalyses indicated the pool OR was not statistically significant for seminomas (pooled OR = 1.25, 95% CI: 0.80–1.96, I^2 = 0%) when compared with never users. Similarly, the pooled OR for nonseminomas and total testicular cancers was statistically elevated for frequent (≥weekly) and chronic users (≥10 years), but not for ever users.[145] Some of these studies did not demonstrate simple dose-response patterns over categories defined by frequency or duration of cannabis use.[146] A Swedish cohort study of 49,343 military recruits followed up to 42 years did not demonstrate a statistically significant relationship between ever-cannabis users and testicular cancer (adjusted HR = 1.42, 95% CI: 0.83–2.45, n = 119 cases) based on non-anonymous questionnaire concerning drug use.[147] Heavy cannabis use defined by >50 lifetime cannabis usage at conscription was associated with an increased testicular cancer risk (adjusted HR = 2.57, 95% CI: 1.02–6.50, n = 119 cases).

HISTOLOGY

Testicular germ cell tumors arise from various locations in the testis and account for >95–98% of testicular malignancies; these tumors display substantial histological heterogeneity because of aberrant somatic differentiation and retained pluripotency. Stromal tumors of somatic origin (e.g., Leydig cells and Sertoli-cell tumors) along with rare, poorly defined histological types account for the remaining 2–5%. Testicular germ cell tumors and testicular cancer are terms often used interchangeably because the vast majority of testicular

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cancers are germ cell tumors. Testicular germ cell tumors initially arise from germinal cell neoplasia *in situ* (i.e., previously testicular intraepithelial neoplasia, intratubular germ cell neoplasia unclassified, carcinoma *in situ*) with the vast majority being malignant. These abnormal cells resemble fetal germ cells overexpressing the OCT4 protein encoded by the *POU5F1* gene critical to regeneration of undifferentiated embryonic stem cells. Noninvasive intermediate precursor lesions include intratubular seminoma and the much less common intratubular embryonal carcinoma; microinvasive germ cell tumors are a relatively frequent invasive intermediate precursor lesion in testicular germ cell tumors.[148]

Seminomas (i.e., ~55–60%) and nonseminomas (40–42%) are the most frequent histological types of testicular germ cell tumors, with spermatocytic tumors accounting for 1–5%.[149] Classically, seminomas are much more homogeneous than nonseminomatous germ cell tumors and spermatocystic seminomas; the former occurs in a younger age group (fourth to fifth decade) than the latter (sixth to seventh decade). Highly anaplastic and malignant embryonal cell carcinomas appear in ~30% of germ cell tumors, with the remaining 10–15% being more differentiated nonseminomas forms (yolk sac, teratoma, choriocarcinoma).[150] Rare nonseminoma tumors include adult teratomas and choriocarcinomas. The latter tumor is the most malignant testicular tumor, frequently appearing in combination with other histological testicular tumor subtypes. Spermatocytic tumors occur only in the testis. Epidemiological studies (e.g., age patterns, time trends) on seminoma and nonseminomas suggest different etiologies among newborns, infants, and elderly men, but not in the majority of patients with testicular tumors (i.e., adolescents, young men).[151] Table 56.2 displays the histological types of germ cell cancers based on the World Health Organization (WHO) classification of testicular and paratesticular tumors along with the typical onset of these tumors,[152] their origin, and immunohistochemical markers to help pathologists determine the tumor subtypes.[153]

These tumors contain all cell lineages, including somatic and extra-embryonic tumors. Seminomas are homogeneous tumors with characteristics of embryonic germ cells, whereas nonseminomas are highly heterogeneous tumors representative of specific characteristics of embryonic (germ) cells with multiple lineages (ectoderm, endoderm, mesoderm), particularly teratomas.[154] Nonseminoma germ cell tumors may present as pure or mixed (i.e., multiple histological subtypes), including elements of a seminoma. Approximately 5% of patients with unilateral testicular germ cell tumors have a contralateral testicle with neoplasia *in situ*.[127]

TABLE 56.2. Main testicular germ cell tumor histological categories based on the World Health Organization (WHO) classification of testicular and paratesticular tumors with associated onset, origin, and immunohistochemical markers. Nonseminomas include embryonal carcinomas, teratomas, yolk sac tumors, choriocarcinomas, and other trophoblastic tumors. (Adapted from Rajpert-De Meyts et al.).[128]

Tumor	Onset	Origin	Immuno-histochemistry
Seminoma	Median ≅ 35 years	Germ cell neoplasia *in situ* (malignant primordial germ cell/gonocyte)	OCT4+, CD117+, CD30−, SOX17+, SOX2−
Embryonal carcinoma[a]	≅25 years[b]	Germ cell neoplasia *in situ* (malignant primordial germ cell/gonocyte)	CD30+, CD117−, SOX17−, SOX2+
Teratoma[a]	≅25 years[b]	Germ cell neoplasia *in situ* (malignant primordial germ cell/gonocyte)	CD30−, OCT4−
Yolk sac tumor[a]	Postpubertal	Germ cell neoplasia *in situ* (malignant primordial germ cell/gonocyte)	CD30−, OCT4−
Choriocarcinoma/other trophoblastic tumor[a]	Postpubertal	Germ cell neoplasia *in situ* (malignant primordial germ cell/gonocyte)	CD30−, OCT4−
Childhood teratoma[a]	Prepubertal	Non-germ cell neoplasia *in situ* (embryonic germ cell)	CD117−, CD30−, OCT4−
Childhood yolk sac tumor[a]	Prepubertal	Non-germ cell neoplasia *in situ* (embryonic germ cell)	CD117−, CD30−, OCT4−
Spermatocytic tumor	Mid-life adult	Non-germ cell neoplasia *in situ* (spermatogonia/spermatocyte)	CD117−, CD30−

Abbreviations: OCT4+ = positive for octamer-binding transcription factor 4; CD117+ = positive for the proto-oncogene coding the stem cell factor for V-Hardy-Zuckerman feline sarcoma viral oncogene homolog KIT (KIT) ligand receptor; CD30+ = positive for a member of the tumor necrosis factor superfamily of receptors; SOX2/SOX17 = nuclear transcription factors important for cell differentiation into organs during embryonic development.

[a] Nonseminoma tumor. [b] Median age for nonseminomas.

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HOST SUSCEPTIBILITY

Familial risks associated with testicular germ cell cancer are relatively high (i.e., ~50%) compared with other cancer sites; however, the rarity of testicular cancer results in a relatively low attributable risk (i.e., ~5%) for hereditary causes.[155] In a joint European, population-based cohort study of 97,402 first-degree relatives of 21,254 testicular cancer patients diagnosed from 1955–2010, the lifetime cumulative risk of testicular cancer (any histology) in brothers of a testicular cancer patient was 2.3% with an SIR of 4.1 (95% CI: 3.6–4.6, $n = 270$ cases) compared with the general population.[156] The testicular cancer risk increased by ~2-fold (SIR = 2.0, 95% CI: 1.7–2.4, $n = 140$ cases) in sons of fathers with testicular cancer. The risk was dramatically increased (SIR = 20, 95% CI: 13–31, $n = 23$ cases) in a twin when the other twin developed testicular cancer.

Moderate- and low-risk single-nucleotide polymorphisms identify only ~1/3 father-to-son familial risk of germline testicular cancer. *CHEK2* gene encodes a protein kinase (CHEK2) that regulates >20 downstream effector proteins (e.g., BRCA1, BRCA2, p53, pRb) important in double-stranded DNA repair, cell cycle regulation, and apoptosis. Using gene-level enrichment analysis of germline pathogenic variants in a multistage, case-control study involving 884 men with testicular cancer, carriers of germline pathogenic variants of the *CHEK2* gene were four to six times more likely to develop testicular cancer than cancer-free controls.[157] The mean age at cancer diagnosis was ~6 years earlier in the variants than in carriers of the wild-type *CHEK2* alleles.

CLINICAL FEATURES

Unlike most adult cancers, testicular cancer incidence with the exception of spermatocytic seminomas does not increase with age; the peak occurrence of nonseminomas develops at 25–29 years of age compared with 35–39 years for seminomas.[158] Spermatocytic seminomas are less aggressive tumors that present in older men (e.g., 50–54 years of age). Germ cell neoplasia *in situ* is asymptomatic that is typically discovered during evaluations of fertility abnormalities or cryptorchidism, whereas patients with testicular germ cell tumors usually present with a unilateral painless testicular mass confirmed by ultrasound. Metastatic disease is often asymptomatic; symptoms may include cough, hemoptysis, dyspnea, flank pain, or gynecomastia. Clinical staging frequently involves the American Joint Committee on Cancer Staging Manual based on World Health Organization histological classifications.[159] Approximately 75% of testicular germ cell tumors (i.e., 80% seminomas, 60% nonseminomas) present with localized disease (Stage I, no regional or distant metastasis); spermatocytic tumors seldom metastasize, whereas choriocarcinomas metastasize early through the bloodstream to multiple locations (e.g., lungs, brain).[160] Teratomas usually invade locally. In a German case series of 422 patients with testicular germ cell tumors, the median age was 36 years (IQR, 31–45 years) compared with 41 years (IQR, 34–47 years) for seminomas and 31 years (IQR, 26–37.5 years) for nonseminomas.[161] The presenting clinical stage 1 represented ~67% of all tumor patients, ~79% of seminomas, and ~48% of nonseminomas, with higher clinical stage and metastasis more common in nonseminomas than seminomas.

Over 95% of intratesticular masses are malignant; however, the overall prognosis for testicular germ cell tumors is excellent with modern chemotherapy. Orchiectomy alone cures 80% of seminomas and 70% of nonseminomas; however, clinical stage I seminomas have 13–19% relapse rate compared with 30% for nonseminomas.[127] The 5-year survival rate for testicular cancer is excellent (i.e., ~97%) even when wide metastasis occurs (i.e., ~80%), particularly seminomas.[162]

PENIS

Penile cancer is a rare genital malignancy with an annual global incidence of ~26,000 cases that varies between countries depending on the prevalence of important risk factors (e.g., phimosis, HPV, chronic penile inflammation). The highest age-adjusted incidence occurs in developing countries of Asia, Africa (e.g., Uganda, 1.2–3.3 cases/100,000),[163] and South America (e.g., Brazil, 1.5–3.7 cases/100,000),[164] particularly in low-income, uncircumcised men.[165] The penile cancer incidence is much lower in developed countries, including North America (e.g., United States, 0.3–1.8 cases/100,000) and Western Europe (0.45–1.7 cases/100,000),[166] with higher socioeconomic status and religious practices that encourage circumcision (e.g., Israeli Jews, 0.1 cases/100,000).[167] About 1,000–1,500 new cases of penile cancer occur in the United States annually.[168,169]

CARCINOGENESIS

Penile cancer has distinct molecular pathways with diverse genetic and epigenetic alterations. The two major mechanisms responsible for the development of

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penile cancer are: 1) HPV-independent, chronic inflammation (phimosis, poor penile hygiene, lichen sclerosis); and 2) HPV-dependent oncogene formation.[170] Examination of archival tissues from penile tumors suggests gene alterations (i.e., somatic p53 mutations, gene promoter methylations including *CDKN2A*) are more common in HPV-independent than HPV-dependent tumors.[171,172,173] Although HPV-independent (negative) and HPV-dependent (positive) penile tumors have different molecular abnormalities, these tumors disrupt similar tumor suppressor gene pathways (e.g., p16INK4a/cyclinD/Rb, p14ARF/MDM2/p53). Genome-wide methylation and transcriptome analysis suggest CpG hypermethylation and underexpression of multiple genes (e.g., *TWIST1*, *RSOP2*, *SOX3*, *SOX17*, *PROM1*, *OTX2*, *HOXA3*, *MEIS1*) along with alteration of stem cell regulatory pathways may contribute to the development of penile cancer.[174]

In patients with phimosis, the inability to retract the foreskin over the glans allows smegma (urinary products, desquamated epidermal cells) to accumulate and prevents adequate penile hygiene. Lichen sclerosis is a chronic inflammatory skin condition that affects the anogenital area including the foreskin, glans, and coronal sulcus. The role of lichen sclerosis in penile cancer is unclear; however, some case series associate HPV-negative squamous cell carcinomas of the penis with lichen sclerosis. Analysis of 159 Italian cases of lichen sclerosis revealed 7 cases of penile squamous cell carcinoma and 7 cases of penile intraepithelial neoplasia.[175] In a Belgian study of 76 archived penile cancer specimens with ~71% positivity for HPV DNA, the presence of lichen sclerosis was similar in HPV+ and HPV− specimens ($P = 0.944$). The high prevalence of HPV in the population may have limited the power of the study to detect a statistically significant difference.[176]

Human papillomavirus is a DNA virus with >100 known genotypes. Viral infections are usually transient with most HPV infections failing to initiate premalignant lesions; however, morphologically low-grade lesions (e.g., mild dysplasia, condyloma) develop when the squamous epithelium maintains virion production. Precancerous lesions (e.g., penile intraepithelial neoplasia) result from the incorporation of the viral genome into the host genome producing overexpression of oncogenes (i.e., E5, E6, E7) that cause cell proliferation and malignant transformation. Most invasive hrHPV+ penile squamous cell carcinomas probably develop from undifferentiated hrHPV+ penile intraepithelial neoplasia that stains positive for p16INK4a.[177] In HPV-positive penile squamous cell carcinomas, the viral oncogenes E6 and E7 bind to tumor suppressor genes producing p53 and pRb (p107, p130), respectively; subsequent genetic changes enhance uncontrolled cell growth and impair DNA repair, resulting in genome instability, progression to invasive squamous cell carcinoma, and overexpression of cyclin-dependent kinase inhibitor p16INK4A. E5 enhances metastasis by upregulating epidermal growth factor receptor (EGFR) that reduces E-cadherin expression and increases matrix metalloproteinase with subsequent reduction in cell-to-cell adhesion.[178]

HPV DNA appears in up to 100% of the premalignant lesions, including penile intraepithelial neoplasia (carcinoma *in situ*) that contains Bowen's disease (keratinized cutaneous lesions of the shaft) and erythroplasia of Queyrat (lesions of the glans or inner prepuce).[179] Lichen sclerosis and lichen planus are penile dermatoses associated with erythroplasia of Queyrat. In a collection of 12 cases of condyloma, 30 cases of dysplasia, and 155 cases of penile squamous cell cancer from US and Paraguay medical institutions, the presence of HPV DNA as measured by the SPF10 HPV polymerase chain reaction assay was as follows: condyloma, 100%; dysplasia (penile intraepithelial neoplasia), 90%; and squamous cell carcinoma, 42%.[180] Table 56.3 displays the major HPV genotypes associated with HPV+ specimens.

HPV genotypes are classified as low-risk (lr) or high-risk (hr) based on their association with cervical malignancy. Benign penile lesions are related to the low-risk HPV genotypes (6, 11), whereas squamous cell carcinomas are associated with the high-risk genotypes (16, 18). Immunosuppressed patients have a higher risk of dysplasia and progression to carcinomas (i.e., 2–3 fold) compared with men in the general population as a result of higher viral loads and higher prevalence of coinfections in their benign lesions.[179] Most HPV infections clear within 12 months.

TABLE 56.3. Incidence of major human papillomavirus (HPV) genotypes reported in samples of 60 HPV-positive squamous cell carcinoma genotypes, 27 dysplasia cases (penile intraepithelial neoplasia), and 12 penile condyloma. (Adapted from Christodoulidou et al.).[166]

HPV$^+$ Tissue Type	Number of Cases	HPV6 (%)	HPV11 (%)	HPV16 (%)	HPV18 (%)
Condyloma	12	75	16.7	8.3	0
Dysplasia (penile intraepithelial neoplasia)	27	22.2	3.7	40.7	0
Squamous cell carcinoma	60	8.3	0	60.0	3.3

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EXPOSURE

The two most important risk factors for developing penile cancer are a history of phimosis (chronic penile inflammatory conditions) and human papilloma virus infection (HPV), with a substantially reduced risk associated with neonatal circumcision. The association of penile cancer with other risk factors is much weaker and less consistent, including smoking, socioeconomic status, and penile trauma.

Occupation

Although data are limited, no evidence causally associates specific occupations or chemicals with penile cancer.

Lifestyle

Phimosis/Circumcision

A history of phimosis is strongly associated with increased penile cancer risks, whereas neonatal circumcision is strongly associated with a reduced penile cancer risk. In a population-based case-control study of 62 men with invasive penile carcinoma, the penile cancer risk was significantly elevated in men with a history of phimosis (adjusted OR = 7.4, 95% CI: 3.7–15.0) compared with men without a history of phimosis.[181] The odds ratio was adjusted for age, cigarette smoking, lifetime sex partners. Penile cancer occurs predominantly in uncircumcised men, whereas these tumors rarely develop among groups practicing routine circumcision during the neonatal or childhood periods. Uncircumcised men also have a higher prevalence of high-risk, oncogenic HPV infection (HPV 16/18) in the glans/corona than circumcised men.[182] A retrospective case-ascertainment study reviewed clinical information on 89 patients with invasive penile carcinoma and 118 with penile intraepithelial neoplasia diagnosed from 1954–1997.[183] Only 2 (2.3%) of the 89 patients with penile carcinoma were circumcised at birth and 87 (97.7%) were uncircumcised, whereas 16 (15.7%) of the 118 cases with penile intraepithelial neoplasia had neonatal circumcisions. In a population-based, case-control study of 110 men with penile cancer and 355 age-matched controls in western Washington state and British Columbia, the age- and penile trauma-adjusted odds ratio for penile cancer in uncircumcised men was 3.2 (95% CI: 1.8–5.7, n = 69 cases) compared with men circumcised at birth.[184] Little evidence associates adult circumcision with reduced penile cancer risks.[185] In a meta-analysis of three case-control studies, the summary OR was significantly reduced for circumcised men (OR = 0.33, 95% CI: 0.13–0.83, I^2 = 55%, $P_{\text{heterogeneity}}$ = 0.11) compared with uncircumcised men; however, there was moderate homogeneity.[186] Adult circumcisions were not associated with a protective effect (summary OR = 2.71, 95% CI: 0.93–7.94).

Socioeconomic Status

Indicators of socioeconomic status include education, income, marital status, and the number of household individuals. Evaluation of the impact of socioeconomic status on penile cancer incidence is complicated by the confounding associated with social differences in lifestyle and health behavior. In general, the penile cancer risks comparing socioeconomic levels are relatively weak and inconsistent, despite the differences in penile cancer risks between developed and developing countries. In a Swedish population-based register study of 1,676 cases and 9,872 randomly chosen controls, the penile cancer risk in men with grade school education compared with men with some college education was not statistically different (adjusted OR = 1.05, 95% CI: 0.91–1.22).[187] Similarly, comparing penile cancer risks in the lower and upper 50% of incomes was not statistically different (adjusted OR = 1.04, 95% CI: 0.93–1.17). Smoking history was not available.

Smoking

Data associated with smoking and penile cancer primarily involve case-control studies with the usual issues of recall bias, imprecise risk estimates, and confounding. In a Los Angeles-based case-control study of 100 matched pairs, the adjusted OR for penile cancer in current smokers of >20 cigarettes/day was 4.0 (1.2–21, n = 26 cases/12 controls, P = 0.006) compared with never-smokers.[188] The adjusted odds ratios comparing ex-smokers and current smokers of <20 cigarettes/day with never-smokers were not statistically different. In a population-based case-control study of 62 invasive penile cancer patients and 671 controls, the adjusted odds ratio (age, number of sex partners) of penile cancer in current smokers was significantly elevated (OR = 4.5, 95% CI: 2.0–10.1, n = 28 cases/9 controls), but not in former smokers (OR = 1.8, 95% CI: 0.8–3.9, n = 25 cases/9 controls) compared with never-smokers.[181] The response rate for interviews was relatively low (55% for cancer registry patients, 66.4% for eligible controls).

Infection

The risk of HPV infection increases with several factors including concomitant sexually transmitted diseases, the

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number of sexual partners, and a history of genital warts. The estimated overall prevalence of HPV in penile cancer is 30–50%, with the most common subtypes being HPV 16 and, to a lesser extent, HPV 18 and HPV6, depending on the geographical location.[166,189] The association of these HPV genotypes with penile high-grade squamous cell intraepithelial neoplasia is relatively stronger than that of penile cancer. In a sample of 85 specimens of these lesions from 25 different countries, HPV DNA appeared in 87% (95% CI: 78.0–93.4%) of the samples.[190] The most common squamous cell carcinoma subtypes associated with HPV infections are warty and basaloid tumors. Penile intraepithelial neoplasia is associated with other HPV genotypes (e.g., 11, 31, 33, 35); however, the risk of malignant transformation with these HPV genotypes is low.[191]

HISTOLOGY

The vast majority of penile cancers are squamous cell carcinomas (i.e., 93–95%).[192] Table 56.4 lists penile cancer subtypes along with their approximate frequencies. Low-risk squamous cell carcinoma subtypes include condylomatous, papillary, verrucous, and warty tumors, whereas the intermediate risk group includes usual, some cases of mixed tumors, and pleomorphic condylomatous (warty) carcinoma.[193] Basaloid tumors, adenosquamous sarcomatoid tumors, and poorly differentiated solid squamous cell carcinomas are high-risk tumors. Basaloid and warty squamous cell carcinoma subtypes are closely associated with HPV with the former being the most common HPV-related penile carcinoma. These tumors typically present at relatively early ages (e.g., in the 50s).[189,194] Classification of premalignant penile intraepithelial neoplasia (PIN I–III) involves the site, appearance, and risk of progression to invasive penile cancer. The most likely PIN to progress to invasive cancer (i.e., ~30%), based on small, retrospective case series, is erythroplasia of Queyrat (PIN III, non-keratinizing carcinoma *in situ*), which presents as velvety red plaques on the glans penis or inner prepuce.[185] HPV-independent tumors arise from differentiated rather than undifferentiated penile intraepithelial neoplasia; the latter is associated with HPV+ penile squamous cell carcinomas.[172]

HOST SUSCEPTIBILITY

Family history or specific genetic anomalies are not recognized risk factors for penile cancer.

TABLE 56.4. Approximate relative frequency of histological subtypes of penile cancer. (Adapted from Arya et al.).[185]

Histological Subtype	Histological Type	Relative Frequency (%)
Usual type	Squamous cell carcinoma	60–70
Papillary	Squamous cell carcinoma	7
Condylomatous	Squamous cell carcinoma	7
Basaloid	Squamous cell carcinoma	4–10
Verrucous	Squamous cell carcinoma	7
Sarcomatoid	Squamous cell carcinoma	1–4
Malignant melanoma	Other	2
Basal cell carcinoma	Other	2
Extra-mammary Paget's disease	Other	<1
Sarcoma	Other	<1

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The incidence of penile cancer increases with age; the peak incidence occurs between 50 and 70 years, with <20% presenting at an age under 40 years and a median age at diagnosis of ~65–69 years depending on the histological subtype.[177] In a US study, the penile cancer rate increased with age among all ethnic groups; however, Puerto Rican men had a substantially higher penile cancer incidence (standardized rate ratio = 3.33, 95% CI: 2.80–3.95) compared with non-Hispanic whites and presented at an earlier age than other ethnic groups. Most men present with a penile lump or ulcer and less often with an erythematous lesion on the penis; penile bleeding and foreskin discharge are uncommon presentations.[195] Approximately ½ of these lesions appear on the glans and ¼ on the prepuce.

In an analysis of data from 12 European cancer registries (3,297 cases) and the US Surveillance, Epidemiology, and End Results (SEER) Program (1,820 cases), the 5-year relative survival of penile cancer patients from 1985–2007 increased from 65% to 70% in Europe and decreased from 72%–63% in the United States.[196] Trends in age-specific, 5-year relative survival were not statistically different for this time period in Europe or the United States. In a French study of long-term survival rates for penile cancer, the 5-year survival rate was 65% compared with 59% for 10-year survival; little change in the rates occurred over the previous several decades.[197] France has a relatively low rate of HPV infections.

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In general, 5-year survival is higher for HPV-positive than HPV-negative patients;[198] however, the 5-year survival rates for HPV+ penile cancer are the lowest among all HPV-related cancers (i.e., anal, rectal, vulvar, vaginal, cervical, oropharyngeal).[199] In multivariate analysis of specimens from 171 patients with penile carcinoma, HPV status was an independent predictor for disease-specific mortality ($P = 0.01$) with a hazard ratio of 0.14 (95% CI: 0.03–0.63).[200] Approximately 30% ($n = 50$) of the tumors had high-risk HPV DNA, primarily HPV16. Disease-specific 5-year survival was 78% in the high-risk HPV-negative group compared with 93% in the high-risk HPV-positive group. The presence of inguinal lymph node involvement is the most important prognostic factor reducing overall 5-year survival to ~50% with extension to pelvic nodes decreasing survival to ≪20%.[201] Approximately 20–25% of penile cancer patients initially diagnosed with node negative disease (cN0) will develop metastases.[202]

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Chapter 57

FEMALE REPRODUCTIVE TRACT

Globally, breast cancer is the most common cancer and the leading cause of cancer-related deaths in women. Other less common tumors of the female reproductive tract include those of the uterus and ovary. Table 57.1 lists the strength of the human evidence (i.e., sufficient, limited) for carcinogenic agents and processes associated with female reproductive tract cancers based on evaluations by the International Agency for Research on Cancer (IARC). The carcinogenic potential of these agents/processes varies within their respective categories. The risks for a person are determined by individual risk factors (e.g., dose, exposure duration, host susceptibility, cocarcinogens).

FEMALE BREAST

The incidence of female breast cancer increases with age; between 2007–2017, the estimated global breast cancer incident rates increased by 4.5% (95% CI: 0.7–7.5).[2] In the United States, ~64,000 new breast cancer cases occur annually in US women, resulting in 1 in 8 US women developing breast cancer in their lifetime.[3] Overall, breast cancer is the second leading cause of cancer-related death in US women, accounting for ~40,000 deaths annually. For US women between 29–59 years of age, breast cancer is the leading cancer-related cause of death. From 1989–2012, US breast cancer mortality rates decreased by 36%. Although the overall breast cancer incidence is slightly greater in Caucasian than African-American women in the United States, breast cancer incidence is greater in African-American than Caucasian women of <45 years of age.[3] The overall incidence of triple-negative breast cancer is almost twice as high in black, non-Hispanic women than in Caucasian women at all ages, regardless of their socioeconomic group, and particularly in young black women. The hazard ratio for triple-negative breast cancer in black women compared with Caucasian women of <35 years of age in the Breast Cancer Surveillance Consortium cohort was 3.05 (95% CI: 2.52–3.70).[4] Prognosis of this histological subtype is much worse than the more common estrogen-receptor-positive subtypes (luminal A/B).[5] The breast cancer incidence rates vary by ~4-fold between countries worldwide, ranging from the lowest incidence rates in women from lower-income countries in Eastern Asia and Middle Africa (~27/100,000) to the highest rates (>100/100,000) in US white women living in Los Angeles and San Francisco.[6,7] About 2,500 cases of male breast cancer occur in the United States annually.[3]

CARCINOGENESIS

Several signaling pathways (Wnt/β-catenin, PI3K/ALT/mTOR) along with estrogen receptors and human epidermal growth factor receptor 2 gene, *HER2* (now known as erb-b2 receptor tyrosine kinase 2 gene, *ERBB2*), control normal breast development including stem-cell proliferation, cell differentiation, cell motility/adhesion, and cell death. PI3K/ALT/mTOR pathway activates critical downstream mediators (Akt, mTOR) that promote cell growth, cell-cycle progression,

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TABLE 57.1. International Agency for Research on Cancer (IARC) classification of female reproductive tract cancer sites and associated carcinogens by sufficient and limited evidence of human carcinogenicity. (Adapted from International Agency for Research on Cancer, IARC).[1]

Anatomical Site	Carcinogens with *Sufficient* Human Evidence (Group 1)	Carcinogens with *Limited* Human Evidence (Groups 2A or 2B)
Breast	Alcoholic beverages, diethylstilbestrol, estrogen–progesterone contraceptives, estrogen–progesterone menopausal therapy, X- and γ-radiation	Dieldrin/aldrin metabolized to dieldrin, digoxin, estrogen postmenopausal therapy, ethylene oxide, night shiftwork (disruption in circadian rhythms), polychlorinated biphenyls, tobacco smoking
Vulva	Human papillomavirus type 16	Human immunodeficiency virus type 1 human papillomavirus types 18, 33
Vagina	Diethylstilbestrol (exposure *in utero*), human papillomavirus type 16	Human immunodeficiency virus type 1
Uterine cervix	Diethylstilbestrol (exposure *in utero*), estrogen–progestogen contraceptives, human immunodeficiency virus type 1, human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, tobacco smoking	Human papillomavirus types 26, 53, 66, 67, 68, 70, 73, 82
Endometrium	Estrogen menopausal therapy, estrogen–progestogen menopausal therapy, tamoxifen	Diethylstilbestrol
Ovary	Asbestos (all forms), estrogen menopausal therapy, tobacco smoking	Talc-based body powder (perineal use), X- and γ-ray radiation

anti-apoptosis, and translation. This signaling pathway is the most frequently enhanced oncogenic pathway in breast tumors, particularly in luminal type A and B breast tumors.[8] These oncogenic PI3K pathway mutations probably dedifferentiate luminal or basal mammary progenitor cells, resulting in multi-lineage potential.[9] Epigenetic regulators (e.g., DNA methylation) and noncoding RNA also promote estrogen signaling in luminal breast tumors, breast cancer proliferation, and metastasis, particularly in triple-negative (*BRCA1/2-*, *HER2-*) breast cancer.[10] BRCA1 promoter methylation downregulates the transcription of the *BRCA1* gene. About 25% of all triple-negative breast cancer patients have BRCA1 promoter methylation. In a genome-wide transcriptional survey of 995 breast tissue samples, breast tumors contained 215 aberrantly expressed long-noncoding RNA (lncRNAs).[11] Consistent with genomic instability present in triple-negative breast cancer tumors, the coding and noncoding mutation rates are higher in ER-negative/HER2-negative tumors than in other molecular breast cancer subtypes.[12]

Estrogen receptors (ERs) comprise membrane estrogen receptors (mostly G protein-coupled receptors) and nuclear estrogen receptors (ERα, ERβ). Approximately 70–75% of invasive breast tumor cells express ERα. The expression of this steroid hormone receptor and transcription factor activates oncogenic growth pathways in breast cancer cells. ERβ partially overlaps ERα in the tissue expression profile, declining as the tumor progresses.[13] *BRCA1* is a tumor suppressor gene that partially inhibits ERα signaling involved in complex biological and pathological processes (i.e., substantial cross-talk between multiple signaling pathways), including cell proliferation via activation of cyclin-dependent kinases (CDK4/6). Tamoxifen is an ERα antagonist. HER2 is a receptor tyrosine kinase affecting various pathways (e.g., mitogen-activated

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protein kinase, MAPK; phosphatidylinositol 4,5 bisphosphate 3-kinase, PI3K) involved with tumor-cell proliferation, cancer progression, and metastasis. The canonical Wnt/β-catenin signaling pathway produces proteins that affect embryonic induction, cell polarity, and cell differentiation. Downregulation of this pathway promotes triple-negative breast cancer and basal-like tumors targeting stem/progenitor cells and enhancing metastasis leading to poor prognoses.[14] Metastatic breast tumors are highly heterogeneous, with the most distant metastases acquiring driver mutations not seen in the primary breast tumor. In a meta-analysis of 48 mostly retrospective articles evaluating discordance in ER, PR, and HER2 status between primary and metastatic breast tumors, the discordance rates were 20% (95% CI: 16–35%, I^2 = 91%) for estrogen receptors, 33% (95% CI: 29–38%, I^2 = 79%) for progesterone receptors, and 8% (95% CI: 6–10%, I^2 = 77%) for human epidermal growth factor receptor 2.[15] The lack of similarity in discordance rates between these three tumor biomarkers suggests clonal genome evolution contributes to the differences as well as technical variation between studies.

EXPOSURE

Breast cancer is a biologically and molecularly heterogeneous disease involving many distinct histological types; multiple variables influence the occurrence of the tumor subtypes including lifestyle risk factors, reproductive cycle, breast density, family history, tissue origin (lobule, duct), and genetic predisposition (e.g., *BRCA1/BRCA2*, *TP53*).[16] Some risk factors are not amenable to modification, including family history, age, several reproductive factors, and breast density, whereas other risk factors of varying magnitude can be altered, including obesity in postmenopausal women, alcohol consumption, and combination menopausal hormone therapy. Some breast cancer risk factors reflect total lifetime exposure to bioavailable estrogens, including early menarche, late menopause, postmenopausal obesity, late conception of firstborn child, nulliparity, breastfeeding duration, and postmenopausal estrogen replacement therapy.[17] Age, menopausal status, and estrogen-receptor status interact to alter some strong risk factors (e.g., obesity, breast density).

Most information regarding risk factors is derived from self-reported questionnaires, usually obtained in retrospective case-control studies; consequently, recall and selection bias along with misclassification complicate the determination of precise risk estimates. The strength of these risk factors is relatively small including early menarche (<20%) and menarche ≥55 years (<12%), breastfeeding (<10%), and parity (<10–15%), depending on several factors including histological type and age. Lobular carcinomas are more variable and strongly associated with exposure to female hormones than ductal carcinomas; consequently, lobular carcinomas are more strongly associated with early menarche, later-stage first birth, and late menopause than ductal carcinomas.[18] In the 40–49-year-old age group, race and ethnicity are not risk factors for breast cancer using Caucasian women as the reference group.[19]

Using data from the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS), a cohort of 7,508 women was surveyed in the early 1970s and followed through 1987.[20] Well-established risk factors accounted for ~47% (95% CI: 17–77%) of breast cancer cases in the NHEFS cohort and ~41% (95% CI: 2–80%) in the US population. Population attributable risk (PAR) estimates suggest these risk factors included later age at first birth and nulliparity (PAR = 29.5%, 95% CI: 5.6–53.3%), higher income (PAR = 18.9%, 95% CI: −4.3 to 42.1%), and family history of breast cancer (PAR = 9.1%, 95% CI: 3.0–15.2%).

Environment/Workplace

Data confirming a causal link between chemical exposures in the environment or workplace and breast cancer are limited with no definitive occupational or environmental breast carcinogens.[21] In a large prospective study of US adults, 1,780 cases of fatal breast cancer occurred in the cohort after a 9-year follow-up.[22] Little variability in breast cancer mortality by 14 broad occupational and 16 more narrowly defined occupational titles occurred based on self-reports on current and former job titles, including women working ≥10 years in their occupation.

Chemicals

In *in vitro* and experimental animal studies, some organochlorine compounds act as estrogen agonists or androgen antagonists leading to concern that these chemicals potentially could be cumulative environmental endocrine disrupters that produce increased breast cancer risks, particularly for early, high-dose exposures. Potential chemical breast carcinogens include chlorinated solvents,[23] chlorinated hydrocarbon pesticides,[24] and polychlorinated biphenyls because of their potential binding to hormonal receptors in breast tissue. The Malmö Diet and Cancer Study collected baseline information on 16,084 postmenopausal Swedish women, including work history, lifestyle, and reproductive factors. The Scandinavian job-exposure matrices were

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used to estimate chemical exposures to 15 categories including organic solvents, aliphatic/alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, toluene, chlorinated hydrocarbon solvents, methylene chloride, 1,1,1-trichloroethane, other organic solvents, pesticides, fumes, polycyclic aromatic hydrocarbons, diesel exhaust, and oil mist.[25] The reported breast cancer risk was elevated in postmenopausal women with any chemical exposure (aHR = 1.26, 95% CI: 1.02–1.54) compared with no chemical exposure. The risk increased with duration of exposure ($P_{trend} = 0.01$); however, none of the breast cancer risks comparing the highest and lowest cumulative exposure groups in the 15 individual chemical categories reached statistical significance or demonstrated a significant trend between low and high cumulative exposure groups.

Organochlorines are a diverse group of synthetic chemicals that include polychlorinated biphenyls (PCBs), dioxins, and organochlorine pesticides (e.g., dichlorodiphenyl-trichloroethane, DDT, lindane, hexachlorobenzene). Although several cross-sectional[26] and nested case-control[27] studies reported statistically significant, albeit imprecise, associations between DDT, DDE, or chlordane concentrations and breast cancer incidence, most studies[28,29,30] found no clear causal association between these chemicals and breast cancer risks, including phenoxyl herbicides.[31,32]

A prospective case-control study of 148 women with breast cancer did not detect elevated DDE [1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethene] concentration, the main DDT metabolite, or polychlorinated biphenyls (PCBs) in blood samples drawn within 6 months of breast cancer diagnosis.[33] A case-control study of 120 Mexican women with breast cancer and 126 controls from Mexico City reported a statistically significant increased adjusted odds ratio for breast cancer comparing the highest and lowest quartiles of serum DDE concentrations (OR = 3.81, 95% CI: 1.14–12.80, $P_{trend} = 0.02$); however, the adjusted odds ratios were wide and most of the confidence intervals contained one.[34] The breast cancer risk did not correlate with serum DDT concentrations. In a case-control study of 304 Connecticut women with breast cancer and 186 controls aged 40–79, there was no statistically significant association between breast cancer and the concentrations of any PCB congeners tested.[35] A 2004 meta-analysis[36] and an updated 2013 meta-analysis[37] concluded that the existing information does not support the hypothesis that exposure to DDT/DDE increases human breast cancer risks. The summary odds ratios were slightly elevated but not statistically significant in the latter meta-analysis for both DDE (summary OR = 1.05; 95% CI: 0.93–1.18) and DDT (summary OR = 1.02; 95% CI: 0.92–1.13).

The IARC classifies the epidemiological data for an association between breast cancer and dieldrin, polychlorinated biphenyls, and ethylene oxide as limited. A population-based case-control study of 646 breast cancer cases and 429 controls conducted in Long Island, New York, did not detect a substantial elevation of breast cancer comparing the highest and lowest quintiles for several chemicals, including chlordane (OR = 0.98, 95% CI: 0.62–1.55), dieldrin (OR = 1.37, 95% CI: 0.69–2.72), or 4 PCBs (OR = 0.83, 95% CI: 0.54–1.29).[32] No dose-response relationships were apparent between the chemicals and breast cancer risks. In a cohort of 7,576 women employed for at least 1 year and exposed an average of 10.7 years while working in commercial sterilization facilities, the standardized incidence ratio for breast cancer in the top quintile of cumulative ethylene oxide exposure with a 15-year lag was 1.27 (95% CI: 0.94–1.69, $P_{trend} = 0.002$).[38] A weight-of-evidence evaluation by the US EPA including epidemiological, laboratory animal, and mechanistic studies concluded ethylene oxide is carcinogenic in humans with the strongest human evidence for female breast and lymphoid cancers.[39] Little data support an association between male breast cancer and chemical exposures. A hypothesis-generating case-control study of male breast cancer, based on job-exposure matrices, detected elevated odds ratios for individuals working with motor vehicle manufacturing, blast furnaces, steel manufacturing, and rolling mills;[40] however, excesses of breast cancer following exposure to specific chemicals, including pesticides, organic solvents, and polycyclic aromatic hydrocarbons, were not identified.

Radiation

Breast cancer is a well-recognized complication of ionizing radiation exposure that varies with dose, age at exposure, and gender. The IARC lists X-ray and γ-radiation as human breast carcinogens (Group 1) based primarily on the Life Span Study of Japanese survivors of the Nagasaki and Hiroshima bombings, as well as early studies on intensive therapeutic radiation (e.g., scoliosis, tuberculosis), particularly in teenagers or young women with developing breasts.[41] Data from the Life Span Study of the Japanese atomic bomb survivors indicate exposure to local ionizing radiation of >200 mGy increases breast cancer risks.[42,43] A Finnish study attributed 1.7% of female breast cancer cases to occupation[44] compared with 4.6% of female breast cancer deaths in a British study primarily related to shift work and radiation.[45] Neither

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cosmic radiation nor circadian rhythm disruption explain the elevated breast cancer risk in female flight attendants. Using self-reported questionnaires and dividing the exposed group into low, medium, and high occupational ionizing radiation exposure groups, a Western Australian population-based case-control study of 1,205 incidence breast cancer cases and 1,789 controls detected a weak, statistically nonsignificant association between breast cancer and occupational exposure to ionizing radiation.[46] Compared with unexposed controls, the OR for all categories of ionizing radiation exposure was 1.16 (95% CI: 0.86–1.57, $P_{trend} = 0.18$) without evidence of a dose-response relationship. The odds ratio was higher for the few premenopausal women with human epidermal growth factor receptor 2-positive breast cancer (OR = 2.57, 95% CI: 1.09–6.03, $n = 8$). Studies of women undergoing fluoroscopy for tuberculosis or radiation treatment for postpartum mastitis during the 1950s and 1960s indicate an ~2-fold increase in breast cancer risks.[47,48] Breast cancer was more common in women irradiated under the age of 40 years than in older women. An incidence survey among atomic bomb survivors identified a strongly linear radiation dose-response in 807 breast cancer cases.[41] The highest dose-specific excess relative risk (ERR) occurred among survivors that were <20 years of age at the time of the bombings.[49] Among this subset of young survivors at the time of the bombing, there was a 13-fold ERR at 1 Sv for breast cancer occurring before age 35 years compared with a 2-fold excess for breast cancer appearing after age 35 years.

Electromagnetic Fields

Exposure to electromagnetic fields occurs in occupational settings, residences, and electric blanket use (i.e., primarily on the body). The association of electromagnetic fields with breast cancer has been studied since the 1980s, following postulation of the theory that magnetic fields suppress melatonin production similar to night-shift work, resulting in the inhibition of the protective property of melatonin on breast cancer.[50] Some early experimental and epidemiological studies provided some support for this hypothesis; however, these studies had limited design and/or statistical power, with most of the positive results confined to subgroups, particularly premenopausal women with ER-positive tumors.[51,52] A population-based case-control study, which enrolled 6,213 breast cancer cases and 7,390 age-matched controls, with an industrial hygienist classifying electromagnetic field (EMF) exposure as background, low, medium, or high. Compared with referents with background EMF exposure, the breast cancer risk in the highly exposed group was slightly elevated but statistically nonsignificant (OR = 1.16, 95% CI: 0.90–1.50).[53] Large epidemiological studies with improved design and statistical power have not confirmed the earlier studies. A World Health Organization risk assessment concluded the evidence from experimental and epidemiological studies was sufficient to confirm that extremely low-frequency magnetic fields (50–60 Hz) do not cause breast cancer.[54] A meta-analysis of 15 case-control studies including 24,338 cases and 60,628 controls demonstrated no significant association between ELF magnetic fields and breast cancer (summary OR = 0.988, 95% CI: 0.898–1.088, $I^2 = 75.8\%$) with substantial heterogeneity.[55] Subgroup analyses detected no significant effect of menopausal status or estrogen-receptor status on the effect of ELF exposure on breast cancer rates. A Chinese nested case-control study of 1,687 incident breast cancer cases and 4,702 controls from a cohort of 267,400 female textile workers demonstrated no significant association between cumulative ELF magnetic fields and overall breast cancer risk comparing the highest and lowest quartiles of cumulative exposure (HR = 1.03, 95% CI: 0.87–1.21).[56]

Reproductive Cycle

Reproductive risks modestly associated with increased breast cancer risks include early menarche (<12 years), late menopause (>55 years), late conception of the firstborn child (i.e., >30 years), and nulliparity, whereas multiple pregnancies and prolonged breastfeeding duration (>1–2 years) are associated with slight reductions in breast cancer risks.[19] Epidemiological studies do not consistently associate alterations in breastfeeding and parity with the risk of specific histological subtypes.[18] In addition to lengthening the duration of estrogen effects (e.g., early menarche, late menopause), analysis of data from 85 epidemiological studies indicates breast cancer risks increase more with estrogen-receptor-positive than estrogen-receptor-negative disease and more for invasive lobular than invasive ductal histological subtypes.[57] Substantial heterogeneity complicates the determination of precise breast cancer risks among these risk factors. In a meta-analysis of 42 case-control and 5 cohort studies, the overall breast cancer risk decreased modestly with increasing parity and breastfeeding duration.[58] Compared with controls, women with breast cancer had fewer births (2.2 vs. 2.6) and shorter breastfeeding duration (9.8 vs. 15.6 months). The summary breast cancer relative risk decreased by 7.0% (99% CI: 5.0–9.0; $P < 0.0001$) for each birth and 4.3% (99% CI: 2.9–5.8; $P < 0.0001$) for every 12 months

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of breastfeeding. The effects of parity and breastfeeding on breast cancer risks differ between mutation carriers of *BRCA1* and *BRCA2* genes. Analysis of data from a large international cohort of *BRCA1/2* carriers indicated *overall* parity was associated with increased breast cancer risk for *BRCA2* mutation carriers (HR = 1.33, 95% CI: 1.05–1.69) but not for *BRCA1* carriers (HR = 0.99, 95% CI: 0.83–1.18) compared with nulliparous women.[59] Compared with uniparous *BRCA1* carriers, multiparous *BRCA1* carriers had lower breast cancer risks (HR = 0.50, 95% CI 0.40–0.63, $n = \geq 4$ pregnancies, $P_{trend} < 0.0001$). Duration of breastfeeding was associated with reduced breast cancer risks in *BRCA1* mutation carriers ($HR_{>24\ months} = 0.66$, 95% CI: 0.50–0.87, $P_{trend} = 0.0003$) but marginally in *BRCA2* mutation carriers ($HR_{>24\ months} = 0.74$, 95% CI: 0.55–1.00, $P_{trend} = 0.01$).

The median age at menarche for 946 US girls enrolled at 6–8 years of age in a longitudinal observational study was 12.25 years.[60] Body mass index had a greater effect on age at menarche than did race or ethnicity. In a meta-analysis of primarily case-control studies using menarche at 13 years as the reference group for 40–49-year-old women, the risk ratio for menarche of ≥15 years was 0.87 (95% CI: 0.78–0.97, $I^2 = 0\%$, $n = 9$ studies).[19] Although substantial heterogeneity existed in the studies, the reported breast cancer risk for parous women in this age group using nulliparous women as the reference group was 1.16 (95% CI: 1.04–1.26, $I^2 = 80.3\%$, $n = 14$ case-control/3 cohort studies). Multiple births modestly decreased the breast cancer risk, whereas the age at first birth of ≥30 years modestly increased the risk.

Lifestyle

Alcohol

The IARC classifies alcohol use as a breast carcinogen (Group 1) with the risk depending on the amount of chronic use. Alcohol consumption is the most consistent dietary risk factor for breast cancer;[61] heavy alcohol consumption (≥3 drinks/day) is probably a risk factor for breast cancer with an increased risk up to ~40–60% in heavy drinkers.[42,62] In a collaborative reanalysis of 53 epidemiological studies on breast cancer, the pooled RR for breast cancer in women consuming ≥45 g ethanol/day or ≥3 drinks/day was 1.46 (95% CI: 1.33–1.61) compared with nondrinking controls.[63] Controversy remains regarding the presence of a threshold for ethanol consumption and breast cancer risks; however, the breast cancer risk for drinking one alcoholic drink daily is small. A meta-analysis of 113 papers on light ethanol drinking (≤1 drink/day) and breast cancer suggested a modest effect of ethanol on breast cancer rates (random effect summary RR = 1.04, 95% CI: 1.02–1.07, $I^2 = 64\%$) with moderate heterogeneity among studies.[64] The adjusted relative risk of breast cancer in women consuming 3–6 drinks/week in the Nurses' Health Study was 1.15 (95% CI: 1.06–1.24) compared with nondrinking women with higher risks in binge drinking than more frequent drinking.[61] The consumption of <3 drinks (0.1–4.9 g)/week was not associated with a statistically significant increase in breast cancer risk (RR = 1.06, 95% CI: 0.99–1.12). In a meta-analysis of 3 studies comparing 40–49-year-old women consuming ≥2 alcohol drinks daily with nondrinkers, the breast cancer risk was not statistically different between the two groups (RR = 1.24, 95% CI: 0.87–1.78, $I^2 = 38.5\%$).[19] The mechanism of ethanol-mediated breast cancer is unclear; however, the mechanism probably involves more than increased estrogen concentrations associated with chronic ethanol consumption (e.g., acetaldehyde genotoxicity, oxidative stress/DNA damage, epigenetic alteration of DNA expression). Chronic ethanol consumption increases the risk of excessive breast density. In a meta-analysis of three studies on the effect of alcohol on breast cancer risks that quantitated breast density, the random effects summary RR was 1.81 (95% CI: 1.07–3.04, $I^2 = 80.13\%$) with very substantial heterogeneity between the studies.[65]

Tobacco Smoke

Although tobacco smoke is a well-established carcinogen, tobacco smoking has a weak association with breast cancer risks.[66] In a meta-analysis of 1 cohort and 11 case-control studies comparing ever- and never-smokers in the 40–49-year-old age group, the breast cancer risk for smokers was 1.05 (95% CI: 0.98–1.13, $I^2 = 31\%$) with mild heterogeneity.[19] This study did not detect statistically significant breast cancer risks in former or current smokers using never-smokers as the reference group. In a prospective cohort study of 3,920 *BRCA1* and *BRCA2* mutation carriers evaluated biannually with questionnaires, the adjusted RR for comparing ever- and never-smokers was elevated but not statistically significant (aRR = 1.16, 95% CI: 0.96–1.41).[67] The breast cancer risk was significantly elevated in the highest cumulative smoking group compared with never-smokers (adjusted RR = 1.33, 95% CI: 1.02–1.75); however, the trend for the three cumulative smoking groups did not display a statistically significant dose-response ($P_{trend} = 0.08$). The association between tobacco smoking and breast cancer did not differ by age at diagnosis or specific *BRCA* subtype. Environmental tobacco smoke exposure also

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adds little to breast cancer risks in nonsmoking women consistent with the minimal breast cancer risks from active tobacco smoking. In a meta-analysis of 47 mostly case-control studies comparing women with a spouse who is ever-smoking and a nonsmoking spouse, the estimated random-effects RR was weak but statistically significant (RR = 1.15, 95% CI: 1.07–1.23), with considerable evidence of heterogeneity.[68] However, the association between environmental tobacco smoke and breast cancer in prospective studies was statistically nonsignificant (RR = 1.003, 95% CI: 0.96–1.05) along with a lack of evidence of increased breast cancer risks for childhood or occupational environmental tobacco smoke exposures.

Obesity

The association between obesity and breast cancer risk is complex and inconsistent. Generally, breast cancer risk increases in overweight/obese postmenopausal women, whereas the risk is less in premenopausal overweight/obese women. Prior to menopause, the ovaries are the major estrogen source, whereas the fat tissues are the primary estrogen source postmenopause. Often, overweight premenopausal women have anovulatory cycles with reduced female hormone synthesis. Consequently, estrogen concentrations are higher in menopausal obese women and lower in premenopausal obese women than in less heavy women. Additionally, circulating metabolic and inflammatory factors (e.g., insulin, triglycerides, C-reactive protein, interleukin 6, leptin) are higher in obese postmenopausal women compared with normal-weight women.[69] In a meta-analysis of 9 case-control and 9 cohort studies using $<25\,kg/m^2$ ($\leq$ normal weight) as the reference group, the breast cancer risk decreased in overweight women aged 40–49 years (RR = 0.86, 95% CI: 0.82–0.90, $I^2 = 0.0\%$) and obese women (RR = 0.74, 95% CI: 0.68–0.81, $I^2 = 1.3\%$).[19] These values were consistent with their analysis of Breast Cancer Surveillance Consortium data with the exception that the latter data on breast cancer risk in obese women were not statistically significant (RR = 0.92, 95% CI: 0.84–1.01). BMI is positively associated with postmenopausal breast cancer with inconsistent results on the modification of this risk by using hormone replacement therapy. In the Women's Health Initiative, the hazard ratio of breast cancer for postmenopausal women with a BMI $\geq 35\,kg/m^2$ was 1.58 (95% CI: 1.40–1.79) compared with the reference group (BMI $< 25\,kg/m^2$).[70] The breast cancer risk for estrogen- and progesterone-receptor-positive tumors was higher (HR = 1.86, 95% CI: 1.60–2.17); however, the risk for estrogen-receptor-negative breast cancer was not statistically significant. Measures of central obesity (waist circumference, waist-to-hip ratio) did not modify the breast cancer risk factors. The inverse association between BMI and breast cancer risks in premenopausal women occurs primarily in hormone-receptor-positive rather than hormone-receptor-negative women; the greater magnitude of these effects appears in younger women.[71] The protective effect of higher BMI on premenopausal breast cancer occurs in the general population and *BRCA1/2* mutation carriers.[72]

Physical Activity

The association between breast cancer risk reduction and physical activity is relatively modest and inconsistent with negative and some positive studies, particularly in postmenopausal women;[73,74] however, the mechanism of action (e.g., altered sex hormones, insulin resistance, adipokines, inflammatory markers, body weight) is unclear. Recall bias, selection bias, and random errors are potential complications for determining the relationship between breast cancer risks and physical activity.[75] In a review of 10 studies using a variety of physical activity measures in women aged 40–49 years, none of the studies demonstrated a statistically significant difference in breast cancer risk among the physical activity groups; however, a meta-analysis was not possible because of the wide variation in techniques used to measure physical activity.[19] During 10 years of follow-up in the Nurses' Health Study II, 849 cases of premenopausal breast cancer occurred.[76] Comparing women in the self-reported high group ($\geq$27 metabolic equivalent (MET)-hours/week) with women reporting low physical activity (<3 MET-hours/week) as the reference group, the multivariate-adjusted breast cancer relative risk of the high-physical-activity group was 1.04 (95% CI: 0.82–1.33). In a review of 33 cohort and 40 case-control studies, null results were reported in 26%, 30% had borderline or statistically nonsignificant breast cancer risk reduction, 4% had an increased breast cancer risk, and 40% had a reduction in breast cancer risks.[77] The reduction in breast cancer risk was greater in case-control studies (30%) than cohort studies (20%), with the strongest reduction in postmenopausal women.

Diet

The effect of diet on breast cancer risks is very modest and somewhat inconsistent with the effect of dietary intake difficult to separate from the influence of body weight and other lifestyle and reproductive risk factors.[78] No conclusive evidence confirms an improved prognosis for early-stage breast cancer from changing dietary patterns after the diagnosis of breast cancer.[79]

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Study size, measurement error (intake, outcome), variable human genetics, diverse lifestyle factors, and lack of diverse dietary habits limit the ability to measure the relatively small changes in breast cancer risks associated with diet.[80] Some epidemiological evidence suggests adherence to the Mediterranean diet excluding alcohol reduces breast cancer risks in postmenopausal women. In a cohort of 335,062 European women, 9,009 postmenopausal and 1,216 premenopausal primary incident invasive breast cancer tumors occurred during an 11-year follow-up. Using the lowest of three categories as the reference group and Cox proportional hazards regression models to adjust for breast cancer risk factors, the adjusted hazard ratio for breast cancer in the highest tertile of adapted relative Mediterranean diet scores of postmenopausal women was 0.93 (95% CI: 0.87–0.99, P_{trend} = 0.037).[81] The multivariate hazard ratio was not statistically significant in the middle tertile scores in postmenopausal women (HR = 0.98, 95% CI: 0.93–1.04) or in either tertile scores in premenopausal women. In the Women's Health Initiative dietary modification trial of 48,835 healthy postmenopausal women, a modest, statistically significant reduction in dietary fat intake was not associated with a statistically significant reduction in breast cancer (HR = 0.91, 95% CI: 0.83–1.01).[82] Similarly, another primary prevention trial of women of 30–65 years of age with mammographic density of >50% achieved a modest 1.6 kg average reduction in body weight after a mean 10-year follow-up without a statistically significant reduction in breast cancer risks (HR = 1.19, 95% CI: 0.91–1.55).[83]

Most studies on the consumption of vegetables, fruits, vitamins, and/or supplements demonstrate minimal or no reduction in breast cancer risks.[84,85] Some data suggest some subgroups of breast cancer (e.g., estrogen-receptor-negative) may benefit from dietary changes. In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, comparison of the highest and lowest quintiles of vegetable intake demonstrated a reduced breast cancer risk (HR = 0.87, 95% CI: 0.80–0.94), mainly in total and hormone-receptor-negative breast cancer risk; however, overall intake of fruits and vegetables did not affect the overall breast cancer risk.[86] Pooled analysis of 993,466 women from 20 prospective, international cohort studies followed for >11–20 years reported a statistically significant reduction of breast cancer risks, comparing the highest and lowest quintiles of total vegetable consumption for ER− (multivariate RR = 0.82, 95% CI: 0.74–0.90, P_{trend} = <0.001, n = 917 cases), but not for estrogen-receptor positive cancer (multivariate RR = 1.04, 95% CI: 0.97–1.11, P_{trend} = 0.06, n = 4,217 cases) tumors.[87] The overall breast cancer risk comparing the highest and lowest quintiles of total fruit and vegetable consumption was not elevated (multivariate RR = 0.98, 95% CI: 0.93–1.02, P_{trend} 0.30, n = 6,981 cases). Total vegetable and fruit consumption also did not affect breast cancer risks. Although most prospective cohort studies on dietary fiber intake and breast cancer report statistically nonsignificant reductions in breast cancer, several meta-analyses suggest that increased self-reported dietary fiber intake modestly reduces breast cancer risk.[88] A meta-analysis of 20 cohort studies, mostly from developed countries, reported that increased dietary fiber content slightly reduced breast cancer risks.[89] The random-effects pooled risk estimate was 0.91 (95% CI: 0.87–0.95, I^2 = 19.6%, $P_{heterogeneity}$ = 0.210).

Medications

Cardiac glycosides are phytoestrogens that are associated with estrogen-sensitive cancers. A systematic review and meta-analysis of observational studies suggested an association between cardiac glycoside use and breast cancer (HR = 1.34, 95% CI: 1.25–1.44, I^2 = 16%, $P_{heterogeneity}$ = 0.30); however, the authors opined that confounding rather than a true causal effect may account for the association.[90] Multiple-subgroup analysis of cardiac glycoside use in a meta-analysis of 14 case-control studies and 15 cohort studies published between 1976 and 2016 indicated digoxin use was associated with an elevated risk in ER-positive breast cancer (RR = 1.332, 95% CI: 1.249–1.421) but not in ER-negative tumors (RR = 0.984, 95% CI: 0.611–1.584).[91] Experimental *in vitro* and *in vivo* studies suggest bisphosphonates can reduce tumor cell proliferation, adhesion, migration, invasion, and angiogenesis. A meta-analysis of four cohort and four case-control studies reported a reduced overall relative breast cancer risk for bisphosphonate use of 0.84 (95% CI: 0.77–0.90, I^2 = 52.1%, $P_{heterogeneity}$ = 0.041), with moderate heterogeneity between studies.[92] This reduction was greater for long-term use (>1 year) with an RR of 0.74 (95% CI: 0.66–0.83).

Menopausal Hormone Therapy

The IARC recognizes postmenopausal combined (estrogen–progesterone) hormone therapy as a human breast carcinogen (Group 1) based primarily on exogenous synthetic progestogen (progestin) use rather than endogenous progesterone. Limited studies on breast cancer risks and circulating progesterone concentrations among postmenopausal women are conflicting

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(null to slightly positive).[93,94] For postmenopausal hormone therapy, breast cancer risks begin ~2 years after medication use begins and continue until several years after cessation of use. A register-based cohort study of menopausal combination therapy in 449,717 Norwegian women, aged 50–65 years using combined estrogen and progesterone therapy for >1 year, demonstrated an elevated breast cancer risk (HR = 2.06, 95% CI: 1.90–2.24, n = 744 cases).[95] Short-term estrogen use alone does not increase breast cancer risks, with limited evidence of increased breast cancer risks with prolonged therapy. The hazard ratio for women using only systemic estrogens in the Norwegian study was 1.03 (95% CI: 0.85–11.25, n = 106 cases). A pooled analysis of 51 studies from 21 countries demonstrated a mean risk of 1.35 (95% CI: 1.21–1.49) for women using hormone replacement therapy for 5 years.[96] The risk of breast cancer varied little with dose; the risk decreased 5 years after cessation of therapy.

In 2 randomized, placebo-controlled studies involving 27,347 postmenopausal women aged 50–79 years from the Women's Health Initiative Trials followed over a median of 20 years, the findings for breast cancer incidence and mortality were mixed.[97] For 10,739 women with a prior hysterectomy, the treatment group receiving 0.625-mg conjugated equine estrogen daily with no medroxyprogesterone had a statistically significant reduction in breast cancer incidence (HR = 0.78, 95% CI: 0.65–0.93, n = 238 treatment cases/296 placebo cases, $P = 0.005$) compared with the placebo group (no treatment). Breast cancer mortality was also modestly lower in the treatment group (HR = 0.60, 95% CI: 0.37–0.97, n = 30 treatment deaths/46 placebo deaths, $P = 0.04$). In contrast, breast cancer incidence in postmenopausal women with an intact uterus was higher in the conjugated equine estrogen plus medroxyprogesterone group (HR = 1.28, 95% CI: 1.13–1.45, n = 584 treatment cases/447 placebo cases, $P < 0.001$) compared with the placebo group. There was no statistically significant difference in breast cancer mortality between the estrogen plus progesterone and placebo groups. Subgroup analysis of breast tumor subtypes suggested lower breast cancer risks in the conjugated equine estrogen alone group without an intact uterus for estrogen-receptor-positive, progesterone-receptor-positive, and *HER2* (*ERBB2*)-negative tumors. Limitations of the study included suboptimal adherence to treatment regimens (i.e., 54% discontinuing conjugated equine estrogen alone, 42% discontinuing conjugated equine estrogen plus medroxyprogesterone during the trials).

A meta-analysis of 13 case-control and 9 cohort studies reported a stronger association with combined menopausal hormones (estrogen/progestin) than estrogen therapy and invasive lobular carcinomas than invasive ductal carcinomas. Using never-menopausal hormone therapy users as the reference group, the overall reported relative risk of invasive ductal carcinoma in current combined menopausal hormone therapy users was 1.5 (95% CI: 1.5–1.6) compared with 2.0 (95% CI: 1.9–2.1) for invasive lobular carcinoma in current menopausal hormone therapy users.[18] The overall breast cancer risks for invasive ductal carcinoma in current estrogen-only hormone therapy users were marginal (RR = 1.1, 95% CI: 1.0–1.1) and statistically significant for invasive lobular carcinoma (RR = 1.4, 95% CI: 1.3–1.5). The relative risks were not statistically significant in seven case-control studies on invasive ductal carcinoma subtypes and two on invasive lobular carcinoma.

Diethylstilbestrol

The IARC classifies diethylstilbestrol (DES) as a Group 1 (human) breast carcinogen as a result of epidemiological evidence from women administered DES for the prevention of miscarriages during the 1940s–1970s. Follow-up studies demonstrated slight increases in breast cancer risks among the women and their daughters.

Contraceptives

Compared with women never using oral contraceptives, women using estrogen–progesterone contraceptives have a slightly elevated breast cancer risk; however, the risk decreases to baseline 5 years after cessation of use. Elevated breast cancer risks from oral contraceptives are not associated with specific histological subtypes.[18] In a meta-analysis of 2 cohort and 10 case-control studies among women in their 40s with never-oral contraceptive users as controls, none of the studies demonstrated a statistically significant difference between groups including former, recent (i.e., within 5 years), and postmenopausal estrogen-only hormone therapy users.[19]

Mammographic Breast Density

Breast density on mammography is a measure of the amount of radiopaque fibroglandular tissue in the breast because breast epithelium and stroma are lighter in appearance than the darker-appearing fat on mammography. Breast density changes over time increasing with combined estrogen plus progestin therapy and decreasing with age, increasing body mass index (BMI),

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and tamoxifen use; physical activity does not directly affect the breast cancer risks associated with breast density.[98] Substantial heterogeneity occurs for breast cancer risks between studies depending on several factors including the study outcome (incidence vs. prevalence), measure of breast density (qualitative vs. quantitative), and population characteristics (symptomatic vs. asymptomatic). The relative (percent) and absolute areas of breast density are relatively strong breast cancer risk factors with 4- to 6-fold differences between the highest and lowest breast density categories;[99] however, these studies frequently do not have sufficient size and statistical power to separate the effect of other breast cancer risk factors from mammographic density (e.g., parity, breastfeeding in premenopausal women).[100,101] Epidemiological evidence suggests the increased risks of invasive breast cancer continue in women aged 65 years and older. In a meta-analysis of nine well-designed studies using pre-diagnostic mammograms with <5% radiodense fibroglandular breast tissue as controls, the estimated pooled relative breast cancer incidence ranged from 1.79 (5–24% density) to 4.64 (≥75% density), as displayed in Table 57.2. Postmenopausal women with extremely dense breast tissue probably have an increased risk of breast cancer, particularly women using combined estrogen/progestin therapy.

Analysis of Breast Imaging Reporting and Data System (BIRADS) breast density data on 14,090 breast cancer cases among 587,369 women undergoing 1,349,027 screening mammography examinations demonstrated overall elevated relative risks (RRs) for breast cancer in women with extremely dense breasts (BI-RADS-4).[102] Compared with women with average breast density (scattered fibroglandular densities, BI-RADS-2), the overall RR for BIRADS-4 was 2.04 (95% CI: 1.84–2.26) and 1.62 (95% CI: 1.51–1.75) for women with heterogeneously dense breasts (BI-RADS-3). Women with low-density, almost entirely fatty breasts (BI-RADS-1) had reduced breast cancer risks (RR = 0.46, 95% CI: 0.37–0.58). The strength of the association of extremely dense breast tissues (e.g., BI-RADS-4) with ER-positive tumors declines with age, whereas ER-negative cancer risks in these women remain relatively constant. Comparing women aged 35 years and 70 years in the community-based, geographically diverse US cohort of women undergoing mammography, the strength of the hazard ratio for ER-positive breast cancer declined with age, whereas the risk of ER-negative breast cancer did not significantly change between ages 35 and 70 years, as displayed in Table 57.3.

TABLE 57.2. Meta-analysis of nine well-designed studies comparing the combined relative risks of breast cancer in quintiles of breast density percentage groups. (Adapted from Kelsey).[17]

Breast Density (%)	Combined Relative Risk	95% Confidence Limit	Heterogeneity
<5 (referents)	1.0	—	—
5–24	1.79	1.48–2.16	$I^2 = 27\%$, $P = 0.22$
25–49	2.11	1.70–2.63	$I^2 = 46\%$, $P = 0.09$
50–74	2.92	2.49–3.42	$I^2 = 0\%$, $P = 0.63$
≥75	4.64	3.64–5.91	$I^2 = 0\%$, $P = 0.50$

TABLE 57.3. Effect of age and estrogen-receptor status on breast cancer risk as measured by hazard ratio using partly conditional Cox proportional hazards regression to facilitate risk prediction in the Breast Cancer Surveillance Consortium cohort. (Adapted from Kerlikowske et al.).[102]

Statistical Value	Breast Cancer Hazard Ratio	95% Confidence Limit	$P_{interaction}$
Reference Group (BI-RADS 2)	1.0	—	—
ER+ 35 years (BI-RADS 4)	2.13	1.89–2.40	
ER+ 70 years (BI-RADS 4)	1.35	1.20–1.53	<0.001
ER− 35 years (BI-RADS 4)	1.68	1.34–2.11	
ER− 70 years (BI-RADS 4)	1.76	1.36–2.27	0.34

Abbreviations: BI-RADS = Breast Imaging Reporting and Data System category 2 = scattered fibroglandular densities; category 4 = extremely dense; ER+ = estrogen-receptor-positive; ER− = estrogen-receptor-negative; $P_{interaction}$ = significance of interaction of age and ER status.

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HISTOLOGY

Breast tumors are primarily carcinomas, whereas sarcomas (e.g., phyllodes tumors, angiosarcomas) account for <1% of mammary gland malignancies. Carcinomas develop in the epithelial cells that line the lobules and terminal ducts along with producing milk, whereas sarcomas are stromal breast components (blood vessels, myofibroblasts). Pathologically, breast cancers are divided into noninvasive (*in situ*), invasive, and metastatic breast tumors. Ductal carcinoma *in situ* (DCIS) develops inside preexisting normal ducts; however, these lesions often progress to invasive cancers. Infiltrating (invasive) breast cancer spreads outside the normal breast lobule or duct into stromal tissue. About 60–75% of women with breast cancer have invasive ductal carcinoma that includes several histological subtypes (cribriform, medullary, mucinous, papillary, tubular). Invasive lobular carcinomas are molecularly and genetically distinct from invasive ductal carcinomas, accounting for ~10–15% of breast cancers with a slightly later presentation (early 60s) than invasive ductal carcinomas (mid/late 50s). Compared with invasive ductal carcinomas, invasive lobular carcinomas are more strongly associated with prolonged estrogen/progesterone exposure (early menarche, delayed/low parity, late menopause).[18]

There are at least 20 histologically distinct female breast tumor types and 5 major molecular variations with each subtype differing in presentation and treatment response but not necessarily in a biologically significant way.[103] Beside substantial intertumor heterogeneity, intratumoral heterogeneity also occurs from the presence of multiple heterogeneous cell populations within the same (i.e., mixed) tumor. Heterogeneity involves molecular and clinical parameters (i.e., histological grade, tumor size, age, biomarker receptor status including HER2 (ERBB2 amplification), ER, and PR.[104,105] Gene expression profiling techniques allow classification of breast tumors into molecular subtypes, as listed in Table 57.4. Hormone-receptor-positive (HR+) and HER2-negative (HR+/HER2−) breast cancer occur in ~74% of US cases, whereas aggressive triple-negative breast cancer (ER−, PR−, HER2−) accounts for ~11% of cases.[106] Luminal A and B are estrogen-receptor-positive tumors. The prognosis for luminal A tumors is usually good, intermediate for luminal B, and worse for basal-like and triple-negative tumors. The vast majority of triple-negative tumors are high-grade, infiltrating basal-like ductal carcinomas exhibiting geographical necrosis.[107] The basal-like subtype is associated with inflammation, marked nuclear pleomorphism, necrosis, and high mitotic rates.[108] These tumors usually express genes present in normal breast myoepithelial cells (e.g., P-cadherin superfamily, *CK5*, *CD44*, *EGFR)* while often having triple-negative molecular biomarkers. Clinically, basal-like tumors present with large tumor sizes, high histological grades, and frequent lymph node invasion in young African-American women.[109]

The expression of genes activated by the estrogen-receptor positive (ER+) in the luminal epithelium lining

TABLE 57.4. Molecular breast cancer subtypes with biomarker receptor status characterized by molecular signatures, characteristic subtypes, common histology, and histological grade. Luminal A and B tumors are estrogen-receptor-positive (ER+) that may represent a continuum of the same subtype rather than a distinct subtype. Histological grade is a measure of differentiation (i.e., how similar are the tumor and normal breast tissue) evaluated as a summary score of epithelial tubule formation, nuclear pleomorphism, and proliferation (mitosis rate) with grade 1 being the most differentiated and grade 3 the least differentiated (i.e., most dysplastic). (Adapted from Eroles et al.).[104]

Subtype	Histology	Histological Grade	ER Status	HER2 Status	Ki67	Molecular Properties
Luminal A	Classical, lobular, tubular, cribriform	1–2	+	−	↓	Luminal CK+, E-cadherin +/−
Luminal B	Micropapillary	2–3	+/−	−/+	↑↑	Luminal CK+, p53 mutations
Basal-like	Medullary, metaplastic, adenoid cystic, secretory	3	−	−	↑↑	Basal CK+, p53 loss, *EGFR*+/− mutations
Molecular Apocrine	Apocrine, pleomorphic lobular	2–3	−	−/+	↑↑	Androgen gene receptor+
Claudin-low	Metaplastic	3	−	−	↑↑	Cancer-like stem cell, ↓E-cadherin

Abbreviations: CK = cytokeratins; *EGFR* = the epidermal growth factor receptor gene provides instructions for making a receptor protein called the epidermal growth factor receptor; ER = estrogen receptor; HER2 (human epithelial growth factor receptor 2), also known as ERBB2 or erb-b2 receptor tyrosine kinase 2, encodes a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases.

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the mammary ducts along with low expression of cell proliferation genes characterizes luminal A tumors. The ER+, human epidermal growth factor receptor 2 negative (HER2−), and/or progesterone-receptor positive (PR+/−) luminal A breast tumors are low-histological grade, slow-proliferating (↓Ki67 expression), hormone-responsive (e.g., aromatase inhibitors) neoplasms accounting for most breast tumors. All lobular carcinomas *in situ* and most infiltrating lobular carcinomas are luminal A tumors.[18] The luminal B tumors are similar to luminal A with the exception of high Ki67 and cyclin B1 levels, HER2+/−, slightly more rapid growth, resulting in a relatively higher histological grade, a more aggressive phenotype, an increased proliferative index, and a worse prognosis compared with luminal A tumors. Overexpression of the *HER2* gene increases cell proliferation with an increased histological grade and worse prognosis. Triple-negative (HER2−, ER−/PR−) breast tumors are typically aggressive infiltrating ductal carcinomas with a worse prognosis than other breast cancer subtypes. About 1/8 of breast cancers are triple (receptor) negative. The claudin-low tumor is an uncommon subtype (12–14%) characterized by low expression of genes involved with intercellular adhesion (E-cadherin), tight junctions (e.g., cingulin, claudin-3/4/7, occludin), and overexpression of tumor immune system cells, resulting in a poor prognosis.[110,111]

HOST SUSCEPTIBILITY

Although only 5–10% of women with breast cancer have cancer susceptibility genes, up to 20–30% have a family history of at least one relative with previously diagnosed breast cancer.[112] Approximately 15% of female breast cancer patients have a close family member with breast cancer. A first-degree relative (mother, sister, daughter) with breast cancer increases the breast cancer risk of >50%, particularly if the relative developed breast cancer before the age of 50 years.[113] Two 1st degree relatives with breast cancer increase the risk almost 3-fold.[16] In a meta-analysis of 44 case-control and 8 cohort studies using women with no first-degree relatives with breast cancer, the estimated overall breast cancer risk ratio for a woman with one first-degree relative with breast cancer was 1.80 (99% CI: 1.69–1.91).[114] For two 1st-degree relatives with breast cancer, the risk ratio was 2.93 (99% CI: 2.36–3.64) and 3.90 (99% CI: 2.03–7.49) for ≥3 1st-degree relatives with breast cancer. The risks were greatest at younger ages, particularly when the relative developed breast cancer at an early age (<40 years), whereas the risks were lower in women with relatives presenting with breast cancer at >60 years of age.

Breast cancer susceptibility involves >90 genes or genetic loci.[115] Mutations in *BRCA1* and *BRCA2* genes are highly penetrant gene mutations with a wide spectrum of variants that increase breast cancer rates in women and men when compared with the general population.[116] A 2018 report by the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) identified 1,650 unique BRCA1 mutations in 26,861 *BRCA1* mutation carriers from 18,435 families with BRCA1 mutations and 1,731 unique BRCA2 mutations in 16,954 *BRCA2* mutation carriers from 11,351 families with BRCA2 mutations.[117] Several other rare inherited germline mutations are associated with elevated breast cancer risks, including ataxia-telangiectasia, Li–Fraumeni syndrome (*TP53*), Cowden syndrome (*PTEN*), Peutz–Jeghers syndrome (*STK11/LKB1*), and hereditary diffuse gastric cancer (*CDH1*). High-risk genes with relative risks of 5 to >20 (e.g., *BRCA1*, *BRCA2*, *TP53*) confer a lifetime breast cancer risk of 40–85%, with higher risks in younger adults, whereas moderate-risk genes with relative risks of 1.5 to <5 including the DNA repair genes (*PALB1*, *BRIP1*, *ATM*, *CHEK2*) confer a lifetime breast cancer risk of 20–40% with relatively low frequency.[118] More recent studies that enroll breast cancer patients with family histories or early-onset breast cancer have more central estimates of penetrance (i.e., ~60% for *BRCA1*, ~50% for *BRCA2*).[119,120] These high- and moderate-risk gene variants explain only ~½ of the inherited breast cancer, with low-penetrance polymorphisms (RR = <1.5) accounting for the rest of the variance.[121] Although pathogenic mutations in *BRCA1* and *BRCA2* display high penetrance, the frequency of these mutated genes in the general population is rare (i.e., ~0.4–0.6%). In non-Ashkenazi Jewish populations, the frequencies of these two germline pathologic variants are ≈0.1–0.2% and ≈0.3–0.4%, respectively. Please make the font consistent with the first line and ≈ set on the baseline. These genes normally repair DNA damage including double-stranded DNA breaks through homologous recombination and nucleotide excision repair along with helping regulate cell-cycle progression.[122] Up to 20% of women (i.e., ~7–10% *BRCA1*, ~10% *BRCA2*) with a family history of breast cancer harbor the breast cancer susceptibility (tumor suppressor, cell checkpoint control) genes, *BRCA1* and/or *BRCA2*. Women with the *BRCA1* germline pathogenic variant have an increased risk of triple-negative breast cancer and high-grade serous ovarian cancer whereas ER+ breast cancer is more common in women with *BRCA2* germline variant. These gene mutations are particularly common among Eastern European Ashkenazi Jews.[123] The estimated prevalence of gene mutations other than BRCA1/2 is ~4–6%.[124] The frequency of TP53 germline

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mutations in the general population is less common than BRCA1/2 mutations;[125] however, the cumulative breast cancer risk increases up to 85% by age 60 years.[126] These tumors usually occur at a young age with a median age at presentation of ~34 years.

A meta-analysis of 22 studies identified 289 BRCA1 and 221 BRCA2 germline mutation carriers from 6,965 female breast cancer cases, 176 male breast cancer cases, and 998 ovarian cancer cases.[127] Using a modified segregation analysis based on breast cancer incidence in relatives of mutation-carrying index case patients, the estimated average cumulative breast cancer risk in BRCA1 mutation carriers by age 70 was 65% (95% CI: 44–78%) and 45% (95% CI: 31–56%) for BRCA2 mutation carriers. The estimated average cumulative breast cancer risks by age 70 years in the prospective UK EMBRACE cohort study for 978 BRCA1 mutation carriers were 60% (95% CI: 44–75%) and 55% (95% CI: 41–70%) for 909 BRCA2 mutation carriers, similar to the meta-analysis.[128] The presence of these mutations increases the risk of contralateral breast tumors and early-onset breast cancer. In a meta-analysis of 16 studies on female breast cancer recurrence rates, the cumulative invasive breast cancer recurrence rates for ipsilateral primary tumors ranged from 1.9–11.1% with a median of 6.2% (median follow-up, 10.5 years); in 9 studies, the cumulative recurrence rates for invasive contralateral primary tumors ranged from 1.1–8.3%, with a median of 3.6% (median follow-up, 7.5 years).[129]

The cancer susceptibility breast cancer genes vary with histological type. Mutations in the *CDH1* gene that alter epithelial cadherin (E-cadherin) and cell–cell adhesion in breast tumors are associated exclusively with invasive lobular carcinomas. This gene produces a protein, called epithelial cadherin (E-cadherin), which is important for cell adhesion and the formation of organized tissues.[18] The common breast cancer susceptibility genes (e.g., *BRCA1*, *BRCA2*, *TP53*) are less commonly associated with lobular breast carcinomas than ductal carcinomas. BRCA1 mutation-associated breast tumors are more often HER2-negative and progesterone-receptor-negative compared with controls, whereas BRCA2 mutation-associated tumors are more commonly estrogen-receptor-positive.[115] In women carrying germline TP53 mutations, the tumors are usually ER+, PR+, and HER2+.[130]

CLINICAL FEATURES

The development of breast cancer in premenopausal women of <40 years is rare and more genetically dependent than postmenopausal breast cancer;[42] most breast cancer cases develop after age 50–55 years, with the peak occurrence of breast tumors occurring in women aged 55–64 years. The minimum latency period for breast cancer is 10–12 years and usually ~20 years.[131] Typically, few signs or symptoms occur early in the disease with a painless breast lump as the most common physical sign; clinical features of advanced breast cancer include swollen, enlarged lymph nodes and erythema/swelling of the breast with or without bloody nipple discharge, skin thickening (peau d'orange), or skin retraction.

Approximately ½ of breast cancers in the United States are discovered during screening mammograms.[132] Only 6% of 90% of women presenting with breast cancer have identifiable metastatic disease at initial presentation; however, breast cancer patients have an increased risk for distant metastases during their remaining lifetime that occasionally develop >10–15 years after initial diagnosis. Approximately 10–15% of women initially diagnosed with breast cancer will develop distant metastases within 3 years;[133] the risk of metastasis increases with histological tumor size and the number of involved axillary lymph nodes.[134] Metastatic sites include axillary nodes, bones, lung, liver, and brain. In a review of organ-specific dissemination of breast cancer, the estimated occurrences of metastasis at specific sites were the following: bone, 47–60%; lung, 16–34%; liver, 19–20%; and brain, 10–16%.[16] Survival rates depend on the tumor stage and tumor type. Overall, US survival rates are 89% at 5 years, 83% at 10 years, and 78% at 15 years. The ~20–30% of breast cancer patients with metastatic breast disease have a median survival of 2–4 years depending on tumor subtype. Luminal A tumors have a distinct metastatic pattern with a relatively high bone metastasis rate (~20%) and metastasis to other tissue sites (i.e., brain, liver, lung) representing <10%, whereas luminal B tumors have a higher liver metastatic rate (~14%) and a high metastatic bone rate.[104] BRCA status alone does not predict the prognosis of a specific breast tumor.[16]

UTERUS

CERVIX

Cervical cancers represent the vast majority of cancers developing between the uterine cervix and the external vulva. Persistent infections by high-risk human papillomavirus (HPV) genotypes (HPV-16, HPV-18, HPV-31, HPV-33, HPV-45) are associated with increased risks

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of cervical, vaginal, and vulvar cancers; however, these infections are not sufficient to produce these cancers. Carcinomas of the vagina and vulva are rare, accounting for 2% and 4% of gynecological malignancies, respectively. The IARC lists *in utero* diethylstilbestrol exposure and HPV-16 as recognized and HIV-1 as suspected human vaginal carcinogens, whereas HPV-16 is recognized and HPV-18, HPV-33, and HIV-1 are suspected human vulvar cancers. In a Spanish study, analysis of tissue from 1,709 vulvar and 408 vaginal cancer cases detected HPV DNA prevalence rates of 84.9% and 28.6%, respectively.[135] HPV is also associated with carcinomas of the anus, penis, oropharynx, and skin. This section focuses on the most common HPV-related cancer, cervical cancer. The US Food and Drug Administration approved primary HPV screening for cervical cancer in 2014 with implementation guidelines by multiple professional organizations published in 2015.[136]

Worldwide, cervical cancer is the fourth most common female malignancy with an estimated ~570,000 incident cases and ~310,000 cervical cancer-related deaths annually.[7] Incidence and mortality vary widely between different geographical regions and countries. Over 90% of these deaths occur in low- and middle-income countries, primarily Sub-Saharan Africa and South-Eastern Asia, whereas the cervical-related death rates are 7–10 times lower in North America, Australia, New Zealand, and Western Asia (Saudi Arabia, Iraq).[137] In the United States, the estimated number of new cervical cancer cases is ~13,000, with ~4,250 cervical cancer-related deaths annually.[3] For the last decade, the incidence of cervical cancer has decreased with the exception of the 30–34-year-old group; however, the data are unclear if detection bias with a stable disease occurrence accounts for the modest decrease (i.e., ~0.3 annual percentage change). Recent data suggest the decline in the incidence of cervical cancer has moderated.

CARCINOGENESIS

The heterogeneous papillomavirus family consists of >150–200 HPVs; these non-enveloped, double-stranded circular DNA viruses infect cutaneous and mucosal squamous epithelia through defects in the skin, oral cavity, and anogenital tract exclusively targeting the nucleus; ~40 HPVs infect the genital tract. These viruses encode viral regulatory proteins (E1, E2, E4, E5, E6, E7) involved with replication and two structural viral capsid proteins (L1, L2). HPV oncogenes include E5 (viral assembly, growth stimulation), E6 (destabilizes p53 and reduces apoptosis), and E7 (promotes malignant transformation by degrading retinoblastoma protein pRb). The latter disrupts the Rb/E2F complex, producing nitric oxide, causing DNA damage, activating inflammatory pathways (cyclooxygenase2/prostaglandin/PG G receptor), and promoting tumorigenesis.[138] E1 and E2 initiate replication, integrate viral DNA into the human genome, and express E6 and E7 oncoproteins. After replication, L1 and L2 form the viral capsid, with E4 proteins helping release the mature virus to infect other cells. The virus may remain non-detectable in a dormant state before reactivating years later.[139] Figure 57.1 displays the structure and functions of viral proteins in the highly oncogenic HPV-16 genotype.

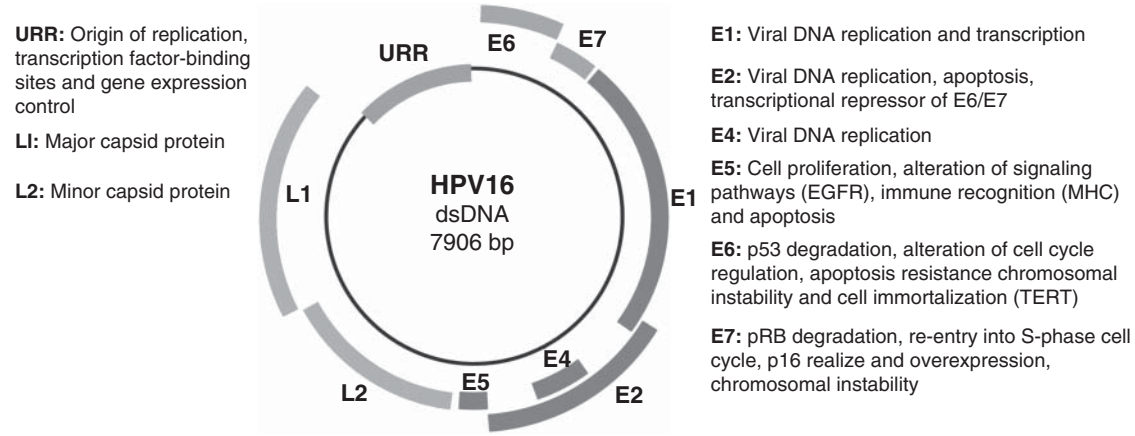


FIGURE 57.1. Human papillomavirus (HPV)-16 viral proteins, function, and structure. The early proteins (E) are necessary for initiating the viral life cycle and cell transformation. The late region (L) encodes the viral capsule and releases a mature virus capable of infecting another epithelial cell. E6 and E7 promote epithelial cell transformation by cell-cycle deregulation, telomerase activation, and enhancement of genomic instability. Over 60% of cervical cancers contain HPV-16 DNA. (Adapted from Eskander).[140]

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High-risk HPVs account for ~70% of invasive cervical cancers worldwide, with HPV-16 and HPV-18 being the most virulent.[141] Most HPV infections are subclinical with ~60–70% clearing within 1 year and 91% within 2 years.[142,143,144] Almost every cervical cancer specimen is positive for a high-risk HPV type (i.e., >95%).[145] In a histological study of 8,977 invasive cervical cancer specimens, the most common HPV types were HPV-16, HPV-18, HPV-45, HPV-31, and HPV-33, as displayed in Table 57.5 by histological type; these HPV genotypes account for ~80% of squamous cell carcinomas and ~94% of adenocarcinomas.[146] HPV-16 is the most common genotype associated with squamous cell carcinomas (62%), adenocarcinomas (50%), and adenosquamous cell carcinomas (39%), based on a retrospective cross-sectional worldwide study of 22,661 paraffin-embedded, cervical tumor samples.[147]

The quadrivalent human papillomavirus (types 6, 11, 16, 18) vaccine effectively prevents infections and precancerous lesions caused by these four HPV types (Gardasil®, Merck & Co., Whitehouse Station, NJ).[148] Since 2006, the US Advisory Committee on Immunization Practices recommended routine use of the quadrivalent HPV vaccine for girls 11–12 years old and catch-up vaccination for girls and women 13–26 years old. Within 6 years of introducing the quadrivalent HPV vaccine, the prevalence of vaccine-type HPV strains decreased from 11.5 to 4.3% among adolescents of 14–19 years old and from 18.5 to 12.1% among women of 20–24 years old.[149] In 2014, the US FDA approved Gardasil 9® (Merck & Co., Whitehouse Station, NJ), which covers the same four HPV types as the quadrivalent HPV vaccine plus an additional five HPV types (types 31, 33, 45, 52, 58). Gardasil 9® is approved for use in males and females aged 9–45 years of age. Table 57.6 lists the carcinogenic categories of specific HPV genotypes along with the associated diseases.

Common genes mutated in cervical tumors include *EGFR*, *KRAS*, *PIK3CA*, *PTEN*, *TP53*, and *STK11*, as well as *EP300* (cell growth/differentiation), *FBXW7* (cell-cycle control by targeting cyclin E for ubiquitin-mediated degradation), *NFE2L2* (antioxidant response elements), and *ERBB2* (regulates outgrowth and stabilization of peripheral microtubules).[151] High-throughput genotyping platform analysis of 80 tumors (48 tumors validated, OncoMap platform, Dana-Farber Cancer Institute, Boston, Massachusetts) for 1,250 known mutations in 139 cancer genes identified PIK3CA mutations in 31% of the tumors.[152] The next highest mutation rates were reported in *KRAS* (~9%) and *EGFR* (~4%) genes. At least 14 long noncoding RNAs (lnc/RNAs) affect the development of cervical tumors, along with miRNAs and several proteins that produce posttranscriptional modifications of important signaling pathways. The HOTAIR lncRNAs silence some tumor

TABLE 57.5. The five most common human papillomavirus (HPV) genotypes in HPV DNA-positive tumors by histological type. The total number of specimens was 8,977 with 100 unclassified. (Adapted from de Sanjose et al.).[147]

	Total Number (% Total)	Squamous Cell Carcinoma (% Total)	Adenocarcinoma (% Total)	Adenosquamous Cell Carcinoma (% Total)
All specimens	8,977 (100%)	8,252 (92%)	470 (5%)	155 (2%)
HPV-16	5,439 (61%)	5,090 (62%)	235 (50%)	61 (39%)
HPV-18	918 (10%)	687 (8%)	152 (32%)	49 (32%)
HPV-45	528 (6%)	446 (5%)	56 (12%)	18 (12%)
HPV-31	335 (4%)	328 (4%)	3 (<1%)	3 (2%)
HPV-33	345 (4%)	338 (4%)	2 (<1%)	4 (3%)

TABLE 57.6. General carcinogenicity risks associated with specific human papillomavirus (HPV) genotypes along with associated diseases. (Adapted from de Sanjosé et al.).[150]

Characteristic Carcinogenicity	HPV Genotypes	Associated Disease
High-risk	16, 18, 31, 33, 35, 39, 45, 51, 52 56, 58, 59, 68, 69, 73, 82	Precursor lesions; cervical, anal, vulvar, vaginal, penile, oropharyngeal cancers
Low-risk	6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 81	Genital warts, recurrent respiratory papillomatosis
Possible-risk	5, 8	Cutaneous squamous cell carcinoma in patients with epidermodysplasia verruciformis
Uncertain-risk	26, 30, 34, 53, 66, 67, 70, 73, 85, 97	

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suppressors (e.g., *HOXD10*, *PTEN*, *RBM38*) and activate some signaling pathways (PI3K/AKT, STAT3, Wnt/β-catenin) important in cervical tumor proliferation and progression.[153] DNA methylation and histone modifications are also epigenetic mechanisms that contribute to cervical tumor carcinogenesis. HPV-related promoter hypermethylation affects a variety of cellular processes including proliferation, differentiation, adhesion, and cell signaling. The principal targets of DNA promoter methylation and transcriptional repression include the tumor suppressor p16 protein along with cyclin A1 (cell-cycle control *CCNA1* gene), the antiapoptotic *DAPK1* gene, the tumor suppressor fragile histidine triad gene (*FHIT*), and *RAS*-associated domain family 1 isoform A (*RASSF1A* gene).[140]

EXPOSURE

Persistent HPV infection is a necessary but not sufficient factor for the progression of precancerous lesions to invasive cervical carcinomas.[154] In the National Health and Nutrition Examination Survey (NHANES), the overall HPV prevalence in US females aged 14–59 years was 26.8% (95% CI: 23.3–30.9%), with the highest HPV prevalence rate of 44.8% (95% CI: 36.3–55.3%) in women aged 20–24 years.[142] Chronic infection by high-risk human papillomavirus (HPV) genotypes accounts for almost all cervical cancers, with viral load and HPV genotype being the main determinants of progression from infection to cervical intraepithelial lesions and invasive cervical neoplasms. Therefore, the major risk factors for developing cervical cancer involve sexual behavior that increases the risk of HPV exposure and/or impairs immunity to HPV infection.[150] These cofactors include early age of initial sexual contact, multiple and/or high-risk sexual partners (e.g., prostitutes),[155] multiparity (≥5 pregnancies), tobacco smoking, lack of condom use, oral contraceptive use, immunosuppression (e.g., organ transplants), immunodeficiency disorders (e.g., HIV), sexually transmitted diseases, HPV-related vulvar or vaginal dysplasia, and inadequate HPV screening.[156,157] Oral contraceptive use for >5 years and hormone replacement therapy may upregulate HPV viral expression, whereas active tobacco smoking is a dependent cofactor for cervical cancer.

Diseases

HIV

The association between HIV and HPV-related cervical cancer results primarily from immunosuppression caused by active HIV infections rather than a direct effect of HIV; consequently, antiretroviral therapy probably significantly lowers HPV-related cancer risks in HIV+ patients.[150,158] Immunosuppression promotes persistent HPV infection with excess risk of cervical neoplasia occurring after human immunodeficiency virus (HIV) infection and subsequent immunosuppression, particularly with CD4 cell count <200 cells/μL. In a case-control study of 871 HIV-positive women and 439 HIV-negative women followed for a median of 2.5 years and 2.9 years, respectively, the relative risk of high-risk HPV infection comparing HIV+ and HIV− women was 1.8 (95% CI: 1.3–2.7), 2.1 (95% CI: 1.5–2.9) for intermediate-risk HPV, and 2.7 (95% CI: 2.0–3.6) for low-risk HPV genotype infections.[159]

Chlamydia trachomatis

Studies on the association between *C. trachomatis* and cervical cancer are inconsistent with both positive and negative studies. A nested case-control study using data from the Costa Rica HPV Natural History Study identified 182 women with prevalent and 132 women with incident cervical intraepithelial neoplasia grade 2(CIN2+) or higher including invasive cervical cancer; 995 women randomly selected from the cohort were controls.[160] *C. trachomatis* DNA-positive status at enrollment was associated with current and subsequent CIN+ status during follow-up (RR = 2.6, 95% CI: 1.6–4.2, n = 24 cases) compared with *C. trachomatis* DNA-negative controls. After restricting cases to *carcinogenic* HPV DNA-positive women, the association between *C. trachomatis* DNA (OR = 0.95, 95% CI: 0.44–2.04, n = 308) status and CIN2+ at follow-up was no longer statistically significant, indicating carcinogenic HPV status confounds the association between *C. trachomatis* status and high-grade intraepithelial neoplasia and invasive cervical cancer. The results using serum IgG as a surrogate for *C. trachomatis* were similar. In a meta-analysis of 22 studies (4,291 cases, 7,628 controls), the overall OR for cervical cancer comparing *C. trachomatis*-positive and *C. trachomatis*-negative patients was elevated in 3 prospective (OR = 2.21, 95% CI: 1.88–2.61, $I^2 = 46\%$, $P < 0.001$) and 22 retrospective (OR = 2.19, 95% CI: 1.74–2.74, $I^2 = 48\%$, $P < 0.001$) studies.[161] After multivariate logistic regression analysis adjusted for HPV and age in 11 studies, *C. trachomatis* was an independent risk factor in 11, but not all, studies (OR = 1.76, 95% CI: 1.03–3.01, $I^2 = 0\%$, $P = 0.04$).

Herpes Simplex

Studies on the association between *Herpes simplex type 2* (HSV2) and cervical cancer are more inconsistent

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and weaker than *C. trachomatis*-associated cervical carcinoma risks; the studies on the association with *Herpes simplex type 1* (HSV1) are mostly statistically nonsignificant. A study analyzing data from 8,184 women in the US NHANES database demonstrated seroprevalences of 60.73 ± 0.89 weighted percent for HSV1 and 25.02 ± 0.64 for HSV2.[162] The adjusted OR for cervical cancer associated with HSV2 seropositivity was elevated ($OR_{adjusted}$ = 1.72, 95% CI: 1.06–2.79). However, a meta-analysis of 20 studies (14 case-control and 6 longitudinal) involving 3,337 cases reported elevated pooled ORs for cervical cancer comparing HSV2-positive and HSV2-negative patients for case-control studies (OR = 1.37, 95% CI: 1.12–1.69) but not for prospective/nested case-control studies (pooled OR = 1.04, 95% CI: 0.82–1.31).[163] In the Nordic cohort of 550,000 women followed for an average of 5 years that identified 178 cervical carcinoma cases and 527 controls, HSV2 seropositivity did not significantly alter cervical cancer risks.[164] The adjusted relative risks of cervical cancer for this nested case-control study comparing HSV2-seropositive and -seronegative women were 1.0 (95% CI: 0.6–1.7) after adjusting for tobacco smoking and 0.7 (95% CI: 0.3–1.6) after adjusting for HPV-16, HPV-18, and HPV-33. A concurrent meta-analysis by the authors involving seven longitudinal studies (2,940,000 person-years of follow-up) reported an overall RR comparing HSV2-seropositive and HSV2-seronegative participants of 0.9 (95% CI: 0.6–1.3).

Occupation

Occupational exposures in women are not clearly associated with increased cervical cancer risks. The population-based Nordic study followed 15 million residents up to 45 years examining standardized cervical cancer incidence in 54 occupational categories. Beverage manufacturing workers had the highest cervical cancer risk (SIR = 2.01, 95% CI: 1.51–2.61), followed by "other construction workers" (SIR = 1.88, 95% CI: 1.30–2.63) and waiters (SIR = 1.64, 95% CI: 1.53–1.75).[165] The lowest cervical cancer risks occurred in dentists (SIR = 0.48, 95% CI: 0.30–0.74), physicians (SIR = 0.59, 95% CI: 0.41–0.83), and teachers (SIR = 0.59, 95% CI: 0.55–0.63). In a US mortality study of a cohort of 1,708 dry-cleaning workers with tetrachloroethylene exposure for >1 year based on retrospective analysis of union records, the national standardized mortality ratio for cervical cancer in tetrachloroethylene-exposed workers was marginally elevated (SMR = 195, 95% CI: 100–340, n = 12 cases). The study did not adjust for confounders or demonstrate sufficient dose-response data. In a pooled Northern European cohort study of 1,777 women with documented trichloroethylene exposure, the overall standardized incident ratio for cervical cancer was elevated (SIR = 2.31, 95% CI: 1.32–3.75, n = 16 cases); however, the SIR for cervical cancer in workers comparing the highest and lowest trichloroacetic acid ratios was not statistically significant ($HR_{adjusted}$ = 3.28, 95% CI: 0.73–14.91, P_{trend} = 0.08, n = 4 cases).[166] The estimated hazard ratios were imprecise due to small case numbers and limited statistical power; lifestyle factors potentially confounded the results. In a French case-control study of 67 cases (cervical dysplasia, cervical cancer) and 67 age-matched, clinic-based controls recruited by a local gynecologist, the adjusted OR for cervical dysplasia/cancer in ever-trichloroethylene-exposed workers was 1.51 (95% CI: 0.42–5.41, $n_{exposures}$ = 17 cases, 15 controls).[167] Cervical cancer rates did not correlate with cumulative dose, exposure time, or specific occupational sectors.

Lifestyle

Pregnancy

In the International Collaboration of Epidemiological Studies of Cervical Cancer on 11,161 women with invasive carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies, the number of full-term pregnancies was associated with invasive cervical carcinoma risk. After controlling for age at first full-term pregnancy, the RR for invasive cervical carcinoma comparing women with ≥7 and 1–2 births was 1.76 (95% CI: 1.53–2.02).[168] Comparing invasive cervical carcinoma rates in the first full-term pregnancy at <17 years of age and ≥25 years of age, the RR was also elevated at 1.77 (95% CI: 1.42–2.23) after controlling for the number of full-term pregnancies. These values did not change significantly when restricted to HPV-positive women. A pooled analysis of 10 case-control studies (8 invasive cervical carcinomas, 2 carcinomas *in situ*) suggested histological differences in cervical cancer rates.[169] Compared with nulliparous women, the ORs for squamous cell carcinoma risks in women with ≥7 full-term pregnancies were 3.8 (95% CI: 2.7–5.5) and 2.3 (95% CI: 1.6–3.2) for women with 1–2 full-term pregnancies. Adenocarcinoma and adenosquamous carcinoma risks were not significantly associated with the number of full-term pregnancies. All participants were HPV-positive. In a 10-year prospective study of 1,812 oncogenic HPV-DNA-positive individuals, parity was not associated with increased risks of high-grade cervical neoplasia or invasive cervical cancer.[170]

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Tobacco Smoking

Tobacco smoking is the most significant environmental risk for invasive cervical cancer. The IARC lists tobacco smoking as a cervical cancer risk factor with sufficient evidence of carcinogenicity in humans based primarily on retrospective case-control studies; most case-control and some prospective studies associate tobacco smoking with elevated invasive cervical cancer risks. The European Prospective Investigation into Cancer and Nutrition (EPIC) Study identified 261 invasive cervical cancers in a cohort of 308,036 women followed for a median of 9 years.[171] Using a nested case-control design with multivariate Cox regression models and never-smokers matched for HPV status as controls, the hazard ratio for invasive cervical carcinomas in self-reported current smokers was 1.9 (95% CI: 1.4–2.5, $n = 85$ cases) compared with 1.5 (95% CI: 1.1–2.1, $n = 66$ cases) for ever-smokers. Among ever-smokers, the trends for smoking duration ($P_{trend} = 0.08$), smoking intensity ($P_{trend} = 0.07$), and pack-years ($P_{trend} = 0.07$) were not statistically significant. Some evidence suggests cessation of tobacco smoking for ≥20 years reduced the invasive cervical carcinoma risks (HR = 0.4, 95% CI: 0.2–0.8, $P_{trend} = 0.02$, $n = 10$). The relative cervical cancer risk is probably higher in squamous cell cancers than in adenocarcinoma cervical cancers. Data from the 23 studies in the International Collaboration of Epidemiological Studies of Cervical Cancer suggest the risks associated with smoking and cervical cancer may be related to histological type. Using never-smokers as controls, the relative risk of cervical squamous cell carcinoma in current smokers was 1.60 (95% CI: 1.48–1.73, $P < 0.001$).[172] Although the relative risk was increased comparing former and never-smokers (RR = 1.12, 95% CI: 1.01–1.25), the trend for cervical squamous cell cancer and time since cessation was not statistically significant ($P_{trend} = 0.6$). The study reported no significant association between smoking and cervical adenocarcinoma in current or former smokers. In a pooled analysis of data from 10 case-control studies of HPV DNA-positive women, the excess cervical cancer risk for ever-smokers was 2.17 (95% CI: 1.46–3.22) using never-smokers as controls.[173] Analysis by histological type indicated an increased squamous cell carcinoma risk in current smokers (OR = 2.30, 95% CI: 1.31–4.04) and a statistically nonsignificant increase in ex-smokers (OR = 1.80, 95% CI: 0.95–3.44). The data did not demonstrate a clear association between adenocarcinomas and tobacco smoking.

The association of passive smoking with cervical cancer is difficult to separate from the effects of active smoking, with observational studies reporting inconsistent results. In a pooled analysis of 7 case-control studies enrolling 1,919 couples, invasive cervical cancer risks were elevated among couples with ever-smoking men and all women (OR = 1.57; 95% CI: 1.15–2.15), as well as couples with monogamous women (OR = 1.55; 95% CI: 1.07–2.23); however, the cervical cancer risk was not increased among lifetime nonsmoking monogamous women married to ever-smoking men.[174] The confounding of active smoking could not be separated from the effect of passive smoking on invasive cervical cancer risks. In a meta-analysis of 4 cohort and 10 case-control studies, the pooled OR for cervical cancer risk in participants exposed to passive smoke was 1.70 (95% CI: 1.40–2.07, $I^2 = 64.3\%$), with modest heterogeneity and evidence of publication bias (Egger's test, $P = 0.11$).[175] Subgroup analysis indicates substantially lower pooled odds ratios for cohort studies (OR = 1.37, 95% CI: 1.16–1.62, $I^2 = 0\%$) than case-control studies (OR = 2.09, 95% CI: 1.52–2.89, $I^2 = 76.6\%$).

Medications

Some studies suggest cervical cancer risks modestly increase with the duration of combined estrogen–progestogen oral contraceptive use, primarily ≥5 years;[176] however, the study results are conflicting. Rodent studies suggest progesterone and glucocorticoid response elements in HPV-16 and HPV-18 increase HPV E6 and E7 oncogene expression, providing a theoretical basis for an association between oral contraceptive use and invasive cervical cancer.[177] Analysis of pooled data from eight case-control studies and two studies of patients with carcinoma *in situ* suggested long-term oral contraceptive use increases cervical cancer risks. Compared with never-users, cervical cancer risks were not increased in women using oral contraceptives for <5 years (OR = 0.73, 95% CI: 0.52–1.03), whereas the odds ratio was increased for women using oral contraceptives for 5–9 years (OR = 2.82, 95% CI: 1.46–5.42) and >10 years (OR = 4.03, 95% CI: 2.09–8.02).[178] The imprecise OR suggests caution in interpreting the results. In the Nurses' Health Study cohort of 131,577 women followed for 36 years, ever-use of oral contraceptives did not increase cervical cancer-related mortality (HR = 1.04, 95% CI: 0.54–2.02, $n = 18$ deaths) using never-users as controls and adjusting for multiple risk factors.[179] In a systemic review of 5 cohort and 7 case-control studies, the overall pooled OR comparing ever-oral contraceptive users with never-users was 1.210 (95% CI: 0.911–1.607).[180] The quality ratings for these studies

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were 5 good, 4 fair, and 4 poor. The review detected no time-dependent relationship between oral contraceptive use and cervical cancer ($OR_{>5\ years\ use}$ = 1.47, 95% CI: 0.91–2.38, $P_{heterogeneity}$ = 0.0033, n = 6 studies) with substantial heterogeneity. The difficulty of controlling all confounding factors (sexual behavior, current HPV infection, reproductive history, smoking) limits conclusions regarding whether the use of oral contraceptives increases invasive cervical carcinoma risks.

Epidemiological studies do not support an increase in cervical cancer risks among hormone replacement users. In an Italian case-control study using hospital-based controls, the multivariate odds ratio for ever-hormone replacement therapy users was 0.5 (95% CI: 0.3–0.8, n = 40 cases).[181] Duration of use was not associated with increasing cervical cancer risks. The study did not control for cervical cancer screening or treatment of early intraepithelial lesions.

HISTOLOGY

The transition between squamous and columnar cells (squamocolumnar junction) is the area of greatest risk of viral neoplastic transformation; ectocervical tumors are most often squamous cell carcinomas, whereas endocervical tumors are usually adenocarcinomas. The most common histological subtypes of cervical cancers are squamous cell carcinomas (~70%) and adenocarcinomas (~25%).[137] Cervical cancer has a long preinvasive phase; the progression from normal tissue to low-grade squamous intraepithelial lesions (CIN1), high-grade squamous intraepithelial lesions (CIN3), and invasive cervical cancer is relatively slow (i.e., 10–30 years with an average of 5–14 years).[182,183] In a review of the natural history of cervical intraepithelial neoplasms (CIN), estimated regression of CIN1 dysplasia was 60% with 30% persistence; progression to CIN3 10%, and progression to invasion 1%; the likelihood of CIN3 regressing was 33% and progressing to invasion was >12%.[184] Invasive cervical cancers do not spontaneously regress. The time from transformation to invasive cancer ranges from ~1–10 years.

HOST SUSCEPTIBILITY

Epidemiological evidence indicates some genetic predisposition to cervical cancer with a family history of cervical tumors in first-degree relatives because of the similar cervical cancer risk in siblings sharing a mother or father, which means the vertical transmission of HPV from mother to child is unlikely. In an analysis of data from the population-based Swedish national registers of all individuals born after 1940, the relative risk for cervical tumor cases was similar for half-sisters having a father (RR = 1.41, 95% CI: 1.22–1.62) or mother (RR = 1.49, 95% CI: 1.29–1.73) in common.[185] The relative risk of cervical tumors in biological full sisters was elevated (RR = 1.93, 95% CI: 1.85–2.01), whereas the RR of cervical tumors in adoptive sisters was not statistically different from unity (RR = 1.15, 95% CI: 0.82–1.57).

The development of cervical tumors depends on the interplay between the tumorigenic properties of the HPV and host factors that affect HPV exposure and immunity to infection [e.g., human leukocyte antigen (HLA) molecules that present antigens to the immune system, major histocompatibility complex (MHC) region]. A genome-wide association study of 731,422 single nucleotide polymorphisms (SNPs) in 1,075 cervical cancer cases and 4,014 controls identified *MICA* (polymorphic major histocompatibility complex class I chain-related protein A), *HLA-DPB1*, and *HLA-DPB2* as potential host-susceptibility genes that may cause impaired immune activation and increased cervical tumor risks.[186]

CLINICAL FEATURES

The median age at diagnosis of cervical cancer in the United States is 47 years, with many cases presenting at <35 years.[187] In a study of data from the US National Cancer Database on 69,739 initial primary invasive cervical cancers, the average age was ~50 years. Advanced clinical stages of cervical cancer tumors (Stage III/IV) extend to the lower 1/3 of the uterus and/or the pelvic wall and other organs; these tumors occur more often in older women (~42% in 70-year-old women) than women aged 12–34 years (~17%).[188] Early-stage cervical cancers are often asymptomatic and detected on routine screening or pelvic examination.[189] Clinical features may include postcoital or abnormal vaginal bleeding, whereas lower limb edema, sciatica, and flank pain suggest pelvic sidewall invasion. Prognosis closely relates to clinical stage with a 5-year relative survival rate of ~91% for patients with localized disease compared with ~58% for regional disease and 17% for distant disease.

EPITHELIAL ENDOMETRIUM

Worldwide, epithelial endometrial carcinoma is the second most frequent histological type of female genital

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TABLE 57.7. World Health Organization (WHO) classification of uterine corpus tumors. This classification also includes another malignant tumor category for neoplasms that do not fit into the major categories (metastatic, unclassifiable).

Histological Category	Cell Origin	Subtypes
Epithelial	Epithelial	Endometrioid, serous, clear cell, mucinous, squamous cell, transitional cell, small cell, undifferentiated
Mixed	Epithelial/ mesenchymal	Carcinosarcomas (Müllerian tumors)
Mesenchymal	Mesenchymal	Sarcomas (smooth-muscle, endometrial stroma, supporting tissues)
Gestational trophoblastic diseases	Trophoblast cells	Hydatidiform mole, choriocarcinomas, placental-site trophoblastic tumors, epithelioid trophoblastic tumors

tract cancer after cervical cancer; however, epithelial endometrial cancer is the most common female genital tract cancer in developed countries, with the highest incidence occurring in North America and western Europe. The worldwide cumulative risk of developing endometrial cancer by age 75 in women is ~1%, compared with a cumulative risk of ~0.2% for women dying from endometrial cancer by age 75 years.[7] Over 90% of uterine cancers arise from glandular epithelium lining the uterine cavity (i.e., epithelial endometrial carcinomas). The remaining types of uterine corpus (body) cancers include uterine sarcomas (~5%, endometrial stroma sarcoma, leiomyosarcomas, sarcomas of other supporting uterine fundus tissues), mixed tumors (carcinosarcomas or Müllerian, adenosarcomas), and secondary tumors (e.g., metastatic, unclassifiable), as displayed in Table 57.7. This section focuses on epithelial endometrial cancer (i.e., the vast majority of non-cervical uterine tumors).

In the United States, uterine cancer is the fourth most common cancer and the seventh most common cause of cancer-related deaths among women.[190] US annual uterine cancer incidence (~54,000 in 2016) and mortality (~11,000 in 2016) are some of the few US cancer rates increasing over the last several decades, averaging an annual increase of 0.7% and 1.1%, respectively, since 1999.[191] This pattern parallels the increase in the prevalence of the strongest risk factors for uterine cancer and obesity. Uterine cancer incidence is higher in US non-Hispanic black and Caucasian women (27 cases/100,000) than in other racial/ethnic groups (19–23 cases/100,000).

CARCINOGENESIS

Estrogen promotes glandular proliferation producing endometrial hyperplasia, whereas progestin secretion following ovulation causes glandular luteinization and the cessation of estrogen-induced stimulation. Unopposed estrogen stimulation is associated with increased endometrial cancer risks, particularly in postmenopausal women. The Bokhman clinicopathological classification of epithelial endometrial tumors divides these tumors into type I (endometrioid) and type II (non-endometrioid) tumors, as explained in the Histology Section. Endometrioid cancers usually display a high mutational load distributed throughout the genome. The major affected signaling pathways are PI3K/AKT/mTOR (regulation of cell growth/survival) and Wnt/β-catenin (regulation of gene transcription/development).[192] The *PTEN* tumor suppressor gene inhibits the PI3K/AKT/mTOR signaling pathway with loss from mutation occurring in a majority of endometrioid cancers (i.e., 52–78%).[193,194] These mutations are associated with deregulation of apoptosis and enhanced tumor survival. Alteration of the Wnt/β-catenin signaling pathway with loss of E-cadherin develops in up to 50% of endometrioid tumors, with the nuclear accumulation of β-catenin indicating activation of the Wnt/β-catenin signaling.[195] Alteration of cell adhesion and communication from β-catenin gene (*CTNNB1*, catenin beta 1) mutations occur in 14–44% of endometrioid tumors independent of microsatellite instability and mutations of other genes (*PTEN*, *KRAS*).[196,197]

Microsatellite instability involves the alteration of short repetitive nucleotide DNA sequences primarily as a result of *MLH1* (mutL homolog 1) gene promoter hypermethylation and the subsequent loss of function of the mismatch-repair protein during cell replication.[198] This process occurs in up to 1/3 of endometrial tumors due to DNA hypermethylation.[199] Promoter hypermethylation also produces underex-

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TABLE 57.8. Comparison of estimated frequency of the six most common genetic alterations in Type I and II epithelial endometrial cancers. (Adapted from Murali et al.).[193]

Abnormality	Type I Tumors (%)	Type II Tumors (%)
PTEN mutation	52–78	1–11
PIK3CA mutation	36–52	24–42
Microsatellite instability	28–40	0–2
ARID1A mutation	25–48	6–11
PIK3R1 mutation	21–43	0–12
KRAS mutation	15–43	2–8
TP53 mutation	9–12	60–91
HER2 amplification	0	27–44
PPP2R1A mutation	5–7	15–43

Abbreviations: ARID1A = AT-rich interaction domain 1A that is part of the SWI/SNF complexes regulating chromatin remodeling; HER2 = a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases involved with cell surface receptor complexes and transcriptional regulation; KRAS = *KRAS* proto-oncogene that forms an oncogene via the action of GTPase on the RAS/MAPK pathway; PIK3R1 = phosphoinositide-3-kinase regulatory subunit 1 that affects signaling pathways for cell growth, division, migration, and survival; PPP2R1A = protein phosphatase 2 scaffold subunit A alpha of tumor suppressor PP2A complex; *PTEN* = phosphatase and tensin homolog tumor suppressor gene produces enzyme that affects cell division, adhesion, migration, and angiogenesis; TP53 = tumor suppressor protein p53 gene that helps control cell division.

pression of diverse genes involving PIK3 (*PIK3CA*, *PTEN*) and Wnt/β-catenin (*CTNNB1*, *APC*) signaling pathways in endometrioid tumors. Promoter hypermethylation is much less frequent in type II endometrial carcinomas.[200]

Mutation of the tumor suppressor gene *TP53* is the most common DNA abnormality in serous carcinomas present in ~90% of serous carcinomas compared with 30% of high-grade and 10% of low-grade endometrioid tumors.[193] In contrast to endometrioid tumors, type II (non-endometrioid) tumors also display frequent E-cadherin inactivation (80–90%), p16 tumor suppressor and cell-cycle regulator inactivation from CDKN2A (cyclin-dependent kinase inhibitor 2A) mutations (40%), c-erbB2 amplifications of epidermal growth factor receptor tyrosine kinases (30%), alterations of mitotic spindle checkpoint regulation genes (*STK15*), and chromosomal instability;[196,201] microsatellite instability is rare in serous tumors. Alterations of E-cadherin reduce cell adhesion and promote deep myometrial and vascular invasion as well as lymph node metastasis. Table 57.8 compares the percentages of the six most common genetic alterations in type I and II epithelial endometrial cancers.

EXPOSURE

The main risk factors for developing endometrial cancer include obesity, nulliparity, early menarche, late menopause, age ≥ 55 years, and tamoxifen use;[202] occupational and lifestyle factors contribute little to the overall endometrial cancer risk. Type I tumors (i.e., mainly endometrioid adenocarcinomas) are typically associated with unopposed estrogen stimulation, whereas less common and more clinically aggressive type II tumors (i.e., predominately serous carcinomas and mixed cell tumors) are estrogen independent. A large pooled analysis of 10 cohort and 14 case-control studies from the Epidemiology of Endometrial Cancer Consortium reported that endometrioid adenocarcinoma risk increases with BMI and diabetes, whereas the risk decreases with age at menarche, parity, oral contraceptive use, and cigarette smoking.[203] Endometrial cancer risk factors (i.e., ↑ parity, age at menarche, tobacco smoking) for heterogeneous, high-grade endometrioid tumors and type II tumors demonstrate similar reductions ($P_{trend} \leq 0.0006$), with the exception of clear-cell carcinomas. The latter tumors were not associated with age at menarche or parity. Although endometrial risk factors are similar between races, the prevalence of endometrial risk factors varies with race.[204]

Occupation

Increased endometrial cancer risks are not causally linked to any specific occupation. In the Nordic cohort study of 15 million people and 2.8 million incident cancer cases developing during follow-up in 1960–2005, analysis of the data demonstrated no clear pattern associating any of the 54 occupational categories with endometrial cancer risks.[165] A Chinese nested case-control study of textile workers suggested elevated age-adjusted hazard ratios for endometrial cancer in workers with ≥10 years in silk production (HR = 3.8, 95% CI: 1.2–11.8, $n = 4$ cases) and silica dust exposure (HR = 7.4, 95% CI: 1.4–39.7, $n = 2$ cases) using never-exposed textile workers as controls.[205] The imprecise hazard ratios, small number of incidence cases, and lack of a dose-response relationship indicate the results should be interpreted cautiously.

Lifestyle

Obesity

Obesity as measured by BMI and waist-to-hip ratio is the strongest risk factor for endometrial cancer, accounting

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for ~40% of endometrial cancers in the developed world .[206,207] The vast majority of epidemiological studies report a statistically significant positive association between obesity and endometrial cancer risks. Obesity is associated with endometrial hyperplasia from excess estrogen production because of peripheral conversion of androgens (e.g., androstenedione) secreted from the adrenal gland and ovaries into estrone by aromatase in adipose tissues (e.g., adipocytes, preadipocytes, mesenchymal stem cells). Aromatase concentrations and activity increase with age and degree of adiposity.[208] Anovulation in obese women also produces continuous, unopposed estrogen stimulation because of the lack of a corpus luteum to produce progesterone. Additional potential mechanisms include increasing insulin resistance (↑ insulin-like growth factor-1) and inflammation (↑ tumor necrosis factor-α, leptin, interleukin-6, adipokines, C-reactive protein) leading to increased cell proliferation and decreased apoptosis.

In an analysis of data comparing obese (BMI 30–<35 kg/m^2) with normal-weight (BMI < 25 kg/m^2) women, the overall pooled risk estimate for endometrial cancer was 2.32 (95% CI: 2.08–2.58) in 28 case-control studies and 2.49 (95% CI: 2.28–2.73) in 25 cohort studies.[209] A large pooled study from the Endometrial Cancer Consortium reported an overall pooled estimate for endometrial cancer risks in obese women of 2.65 (95% CI: 2.43–2.90) using normal-weight women as controls.[203] Increasing obesity was associated with increased endometrial cancer risks. The OR per 2 kg/m^2 per increase in BMI was weaker for type II tumors (OR = 1.12, 95% CI: 1.09–1.14) than for estrogen-dependent type I tumors (OR = 1.20, 95% CI: 1.19–1.21) with substantial heterogeneity ($P_{heterogeneity}$ = <0.0001). Measures of central obesity (waist circumference, waist-to-hip ratio > 0.85) were also associated with elevated endometrial cancer risks. Studies on the effect of menopausal status on obesity and endometrial cancer risks are inconsistent.

Physical Activity

Observational studies suggest physical activity may reduce endometrial cancer risks; however, the data are inconclusive, in part because of the difficulty accounting for the confounding of obesity, potential recall bias, and misclassification. Most studies adjusting for obesity use BMI, which is an imperfect measure of obesity, as a measure of body fat and lean body mass. In multivariate models using data from the Nurses' Health Study cohort (71,570 women assessed every 2–4 years during 1986–2008), the endometrial cancer risk was reduced in women engaged in recent moderate recreational activity defined by 9 to <18 MET-hour/week (RR = 0.61, 95% CI: 0.48–0.78) and high recent recreational activity defined by ≥18 MET-hour/week (RR = 0.73, 95% CI: 0.58–0.92) compared with women expending <3 MET-hour/week, P_{trend} = 0.001).[210] However, these estimates became statistically nonsignificant after adjustment for body mass index suggesting the reduced risks reflected confounding by adiposity. In a meta-analysis of eight prospective cohort studies comparing the highest and lowest levels of recreational physical activity after adjustment for BMI, the estimated RR for endometrial cancer was reduced (pooled RR = 0.78, 95% CI: 0.63–0.95).[211] Four out of seven cohort studies reported a significant dose-response relationship. The trend for increasing endometrial cancer risk with increased sedentary time was positive for inactive women (P_{trend} = 0.04) but not for active women engaging in vigorous physical activity defined by >20 minutes 3 times/week (P_{trend} = 0.08). In a meta-analysis of 18 cohort, 1 nested case-control, and 14 case-control studies using mostly self-administered questionnaires or job titles, the summary relative risk for endometrial cancer comparing high and low recreational physical activity was 0.84 (95% CI: 0.78–0.91).[212] Analysis of activity by MET-hour in nine studies yielded a nonlinear inverse dose-response relationship for endometrial cancer risk. The inverse relationship with endometrial cancer was smaller in cohort (RR = 0.84, 95% CI: 0.78–0.91) than case-control (RR = 0.72, 95% CI: 0.64–0.80, $P_{difference}$ = 0.03) studies. The meta-analysis did not detect difference in endometrial cancer risks with menopausal status ($P_{difference}$ = 0.07) or adjusting for BMI ($P_{difference}$ = 0.39).

Alcohol

Alcohol consumption is probably not a strong risk factor for endometrial cancer. Most studies report null or statistically nonsignificant results; however, the data do not exclude slight risks in subgroups of epithelial endometrial cancers. Analysis of data from the NIH-AARP Diet and Health Cohort Study (114,414 US women, 1,491 incident endometrial cancer cases) demonstrated no significant trend (P_{trend} = 0.90) for increasing alcohol consumption and endometrial cancer risks.[213] Using Cox proportional hazards regression and nondrinkers as controls, the adjusted multivariate RR for endometrial cancer was not significantly elevated for daily alcohol consumption of 12 to <24 g (RR = 1.06, 95% CI: 0.87–1.31) or ≥24 g (RR = 0.93, 95% CI: 0.71–1.20). Analysis of alcohol intake data and endometrial cancer risk from the Nurses' Health Study using nondrinkers as

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controls suggested a reduced endometrial cancer risk in women with light daily alcohol intake (<5 g, ~1/2 drink); the multivariable RR was 0.78 (95% CI: 0.66–0.94) with no increased risk for women consuming ≥2 drinks (multivariate RR = 0.78, 95% CI: 0.49–1.25).[214]

Tobacco Smoking

Cigarette smoking is associated with a reduced risk of endometrial cancer. Using never-smokers as controls in an analysis of pooled data from seven cohort and four case-control studies in the Epidemiology of Endometrial Cancer Consortium, endometrial cancer risks were decreased in current smokers in black (OR = 0.67, 95% CI: 0.47–0.95, $n = 58$ cases) and white (OR = 0.63, 95% CI: 0.56–0.72, $n = 406$ cases) women.[204] In the NIH-AARP Diet and Health Study of 110,304 US women (1,476 incident endometrial carcinomas) using never-smokers as controls, the endometrial carcinoma risk was marginally reduced in former smokers (RR = 0.89, 95% CI: 0.80–1.00) and reduced in current smokers (RR = 0.65, 95% CI: 0.55–0.78).[215] Smoking cessation within 1–4 years was associated with reduced risk (RR = 0.65, 95% CI: 0.48–0.89), but this reduction returned to baseline by 10 years post-cessation. Tumor characteristics did not substantially change the endometrial cancer risks.

Diet

Dietary factors are not clearly associated with endometrial cancer. Limited data suggest total fat and saturated fat are positively associated with endometrial cancer risk, but the epidemiology studies are inconclusive. In a meta-analysis of 5 cohort and 11 case-control studies, the pooled RR for endometrial cancer was reduced in the case-control studies comparing the highest and lowest categories of total dietary fat intake (pooled OR = 1.39, 95% CI: 1.10–1.76). However, the lower pooled RR in the cohort studies was not statistically significant (pooled RR = 0.91, 95% CI: 0.83–1.01).[216] The funnel plot and Egger test suggested significant publication bias ($P = 0.01$). Analysis of dietary saturated fat intake and endometrial cancer risk demonstrated similar risks. The pooled estimate of three cohort studies for monounsaturated fatty acids and endometrial cancer risks demonstrated an inverse association (pooled OR = 0.84, 95% CI: 0.73–0.98) but not case-control studies (pooled OR = 1.02, 95% CI: 0.85–1.22). The study reported no significant associations between monounsaturated fatty acids or linoleic acid and endometrial cancer risks.

Intrauterine Devices

Limited data suggest the use of nonhormonal intrauterine devices (IUDs) reduces endometrial cancer risks. A pooled analysis of data from 4 cohort and 14 case-control studies in the Epidemiology of Endometrial Cancer Consortium using multivariate logistic regression estimated a pooled OR of 0.81 (95% CI: 0.74–0.90) comparing endometrial cancer risks in ever- versus never-IUD users independent of known risk factors.[217] The estimates were significantly heterogeneous between studies (meta-OR = 0.83, 95% CI: 0.72–0.96, $I^2 = 68.6\%$, $P_{\text{heterogeneity}} \leq 0.0001$) and among case-control studies (meta-OR = 0.82, 95% CI: 0.69–0.98, $I^2 = 75.8\%$, $P_{\text{heterogeneity}} = <0.0001$) but not cohort studies (meta-OR = 0.86, 95% CI: 0.67–1.10, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.87$). The latter estimate was not statistically significant. The inverse association was strongest among inert IUDs and weaker among copper and hormone-releasing IUDs. Endometrioid (type I) tumors were inversely associated with ever-use of IUDs (pooled OR = 0.87, 95% CI: 0.79–0.95) but not non-endometrioid (type II) tumors (pooled OR = 1.05, 95% CI: 0.81–1.36). In a meta-analysis of 10 case-control studies, the pooled adjusted endometrial cancer risk for nonhormonal IUD users was 0.54 (95% CI: 0.47–0.63, $P_{\text{heterogeneity}} = 0.40$) with some evidence of a dose-response based on duration of use.[218] The biological mechanism for the inverse relationship between endometrial cancer risks and IUD use remains unclear.

Reproductive History

Parity is a strong risk factor for endometrial cancer. Approximately one-half of women of <45 years old diagnosed with endometrial carcinoma are nulliparous, frequently presenting with complex atypical hyperplasia.[219] Infertility related to anovulation and progesterone deficiencies rather than tubal factors increases endometrial cancer risks. Breastfeeding suppresses ovulation and maternal estrogen concentrations leading to reduced endometrial mitoses. A meta-analysis of 3 cohort and 14 case-control studies from the Epidemiology of Endometrial Cancer Consortium suggests breastfeeding modestly reduces endometrial cancer risks.[220] After excluding nulliparous women and using never-IUD users as controls, the pooled OR for endometrial cancer in self-reported ever-breastfeeding women was 0.89 (95% CI: 0.81–0.98, $I^2 = 45\%$, $P_{\text{heterogeneity}} = 0.02$) with moderate heterogeneity; however, the association with duration of IUD use was not clearly linear, particularly after 6–9 months. The

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inverse association did not vary substantially by recent BMI, parity, menopausal status, or tumor type (I vs. II).

Medications

Tamoxifen is associated with increased endometrial cancer in women treated for breast cancer, primarily low-grade endometrioid adenocarcinomas. Progestogens promote cellular differentiation, apoptosis, and cell-cycle arrest while inhibiting inflammation and invasion in endometrial tissue. Oral estrogen replacement therapy is associated with several-fold increased endometrial cancer risks, primarily low-grade endometrioid adenocarcinomas arising from complex atypical hyperplasia or endometrial intraepithelial neoplasia, whereas combined estrogen/progesterone therapy does not significantly increase endometrial cancer risks.[221] The use of oral contraceptives is associated with reduced endometrial cancer risks. In pooled data from seven cohort and four case-control studies from the Epidemiology of Endometrial Cancer Consortium using never-users as controls, the endometrial cancer risk was reduced in oral contraceptive users for ≥10 years in black (OR = 0.49, 95% CI: 0.27–0.88, $n = 29$ cases) and white (OR = 0.69, 95% CI: 0.58–0.83, $n = 389$ cases) women.[204] Observational studies on nonsteroidal anti-inflammatory drug (NSAID) and aspirin use on endometrial cancer are inconsistent. A systematic review and meta-analysis suggested a mild reduction in endometrial cancer risks; however, the pooled risk ratios were not statistically significant comparing regular use with nonusers.[222]

Diseases

Diabetes

The relationship between diabetes and endometrial cancer remains controversial. In a meta-analysis of mostly case-control studies (3 cohort, 13 case-control studies) including mostly type II diabetes, the summary relative risks for cohort studies were 1.62 (95% CI: 1.21–2.16, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = 0.60$, $n = 3$ studies) and 2.22 (95% CI: 1.80–2.74, $I^2 = 57.7\%$, $P_{\text{heterogeneity}} = 0.01$, $n = 13$ studies) respectively.[223] For the two studies controlling for physical inactivity and obesity, the summary RR was 2.47 (95% CI: 1.37–4.45, $I^2 = 48.8\%$, $P_{\text{heterogeneity}} = 0.16$, $n = 2$ studies) with moderate heterogeneity. For a meta-analysis of seven mostly prospective US and European cohorts involving mainly type II diabetics, the adjusted summary RR for endometrial cancer was 1.89 (95% CI: 1.46–2.45, $I^2 = 20.0\%$, $P_{\text{heterogeneity}} = 0.283$) using nondiabetics as controls.[224] Variation in study designs prohibited sensitivity and subgroup analyses; consequently, confounding by obesity and the effect of multiple comparisons were not excluded. In a review of four cohort studies adjusting for BMI, a Swedish study[225] reported a positive association between diabetes and endometrial cancer incidence and three US and Swedish studies did not.[226,227,228]

Polycystic Ovary Syndrome

Most observational studies indicate an increased risk of endometrial cancer in women with polycystic ovary syndrome (PCOS).[229] In a meta-analysis of five observational studies on women with PCOS, the risk of endometrial cancer was significantly increased when compared with controls without PCOS (OR = 2.79; 95% CI: 1.31–5.95, $P < 0.008$).[230] Exclusion of women >54 years of age increased endometrial cancer risks for PCOS (OR = 4.05, 95% CI: 2.42–6.76, $P < 0.00001$). The imprecise estimates of endometrial cancer risk suggest potential misclassification and selection bias. Analysis of data from the Danish National Patient Register identified 12,070 women with PCOS diagnosed between ages 9 and 49 years and followed during 1977–2012; the standardized incidence ratio (SIR) for endometrial cancer was 3.9 (95% CI: 2.2–6.3, $n = 16$ cases).[231]

HISTOLOGY

The vast majority (i.e., ~80%) of endometrial carcinomas are epithelial endometrial carcinomas, typically endometrial adenocarcinomas arising from glandular epithelium in areas of atypical hyperplasia.[232] Based on the clinical and epidemiological characteristics of Russian women in the former Soviet Union, Bokhman developed a dualistic clinicopathological classification that divides epithelial endometrial cancer into the following two major classifications: type I (low-grade, diploid, endometrioid, hormone-receptor-positive tumors with a good prognosis) and type II (high-grade, aneuploid, non-endometrioid, hormone-receptor-negative tumors with TP53 mutations, frequent metastatic lesions, and a poor prognosis).[233] Type I tumors are associated with obesity, excess estrogen stimulation, endometrial hyperplasia, and moderate-to-high differentiation; these tumors range widely from well-to-poorly differentiated (i.e., low- to high-grade) tumors. Low-grade endometrioid carcinomas usually occur in premenopausal women in association with endometrial hyperplasia. Type II epithelial endometrial tumors typically develop in

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nonobese women with absent metabolic/endocrine abnormalities, atrophic endometrium, and poorly differentiated tumors. Occasionally, these tumors arise from precancerous lesions in atrophic endometrium or endometrial polyps. Serous tumors usually develop in postmenopausal women with atrophic endometrium and aggressive features; however, overlap between types I and II tumors as well as heterogeneity within tumor subtypes occur. Some non-endometrioid carcinomas probably arise from preexisting endometrioid carcinomas by tumor progression.[196] Although the Bokhman model fits low-grade endometrioid and serous tumors well, many endometrioid tumors do not share all the characteristics of the type I classification, particularly molecular markers and prognosis.[193] Approximately 10–19% of endometrioid carcinomas are high grade, with characteristics being intermediate between types I–II or more similar to type II tumors (e.g., no endometrial hyperplasia, poor prognosis). Additionally, substantial overlap occurs between tumor subtypes and molecular markers, as displayed in Table 57.9. The depth of myometrial invasion correlates with lymph node spread.

The Cancer Genome Atlas (TCGA)/research network published a new molecular classification of epithelial endometrial tumors based on genomic analysis of endometrial tumors. This classification contains the following four subgroups: 1) POLE ultramutated tumors that can encode the central catalytic subunit of the polymerase epsilon involved with DNA repair; 2) hypermutated, microsatellite-unstable tumors with reduced *MLH1* gene expression from promoter DNA hypermethylation; 3) copy number-low, microsatellite-stable endometrioid tumors; and 4) copy number-high, serous-like tumors representing almost all serous carcinomas, some high-grade endometrioid carcinomas, a few low-grade endometrioid carcinomas, and most mixed histology tumors.[234,235]

HOST SUSCEPTIBILITY

Most endometrial cancers arise sporadically with only a small fraction attributable to inherited genetic susceptibility. Studies on the endometrial cancer risk in women with first-degree relatives with endometrial cancer are inconsistent. A systematic review and meta-analysis of four clinic-based case-control, six population-based case-control, and six cohort studies reported an ~2-fold increased endometrial cancer risk comparing women with and without self-reported first-degree relatives with endometrial cancer.[236] A majority of these studies adjusted for multiple endometrial risk factors. Using a fixed-effects model, the overall RR was 1.82 (95% CI: 1.65–1.98, I^2 = 29.6%, $P_{\text{heterogeneity}}$ = 0.402). Three studies estimated the relative risk of endometrial cancer by excluding Lynch syndrome families based on tumor microsatellite instability (OR = 1.3, 95% CI: 0.8–2.4),[237] mismatch-repair gene mutations ($HR_{\text{age 70 years for 1 first or second-degree relative}}$ = 3.40, 95% CI:

TABLE 57.9. Molecular and clinicopathological characteristics of type I (endometrioid) and type II (high-grade non-endometrioid) tumors. Serous and clear-cell tumors often present at advanced stages (International Federation of Gynecology and Obstetrics grade 3), whereas low-grade endometrioid tumors present at early stages. Prognosis is better at an early stage of presentation for clear cell than for serous tumors. (Adapted from Murali et al.).[193]

Characteristic	Endometrioid	Endometrioid	Serous	Clear Cell
Histological grade	Low	High	High	High
ER/PR expression	+	+/−	−/+	−
PTEN expression	−/+	−/+	+	+
DNA MMR loss	−/+	−/+	−	−/+
TP53 mutation	−	−/+	+	−/+
Ki67/*MIB-1*	Low	High	High	Low/High
Metastatic potential	Uncommon	Lymph nodes, distant organs	Lymph nodes, distant organs, peritoneal	Lymph nodes, −/+ peritoneal
Prognosis	Favorable	Poor	Poor	Poor

Abbreviations: + = present/high; −/+ = occasional; +/− = frequent; − = absent/low; ER = estrogen receptor; Ki67 = an antigen exclusively associated with cell proliferation; *MIB-1* = mindbomb E3 ubiquitin protein ligase 1 gene that promotes TNF-induced apoptosis; MMR = mismatch repair; PR = progesterone receptor; *PTEN* = phosphatase and tensin homolog tumor suppressor gene produces enzyme that affects cell division, adhesion, migration, and angiogenesis; *TP53* = tumor suppressor protein p53 gene that helps control cell division.

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2.32–4.66),[238] and clinical criteria (SIR ≅ 2).[239] These findings suggest familial endometrial cancer risks involve mutations other than mismatch DNA repair genes. *BRCA* gene carriers do not have an increased risk of endometrial cancer unless they receive tamoxifen.[206]

The most common genetic disease associated with endometrial cancer is hereditary nonpolyposis colon cancer (Lynch syndrome) that affects 2–3% of endometrial cancer patients; endometrial cancer is the second most common cancer occurring in patients with this syndrome.[240] This autosomal-dominant disorder results from DNA replication errors causing germline-inactivating DNA mismatch-repair mutations from several genes, including *MLH14* (mutL homolog 1), *MSH2* (mutShomolog 2), *MSH6* (mutShomolog 6), and *PMS2* (PMS1 homolog 2A). Approximately 75% of these patients with endometrial cancer have microsatellite instability. Most tumors in these patients display pure or mixed endometrioid features, with only ~15% demonstrating non-endometrioid histology.[241] In a study of 76 women with mutation-proven Lynch syndrome and pathology-confirmed endometrial cancer, 76% of these women had low-grade endometrioid carcinomas with the remaining being high-grade tumors (serous, clear-cell, mixed/other carcinomas, dedifferentiated carcinomas).[242] The approximate mix of common mutations involved *MSH2* (66%), *MLH1* (24%), and *MSH6* (10%) DNA repair genes. Rare causes of hereditary endometrial cancer include Cowden syndrome (PTEN mutations)[243] and Peutz–Jeghers syndrome (STK11 mutations).[244]

CLINICAL FEATURES

The vast majority of women with endometrial cancer present in the sixth and seventh decades of life with abnormal vaginal bleeding with or without vaginal discharge and pyometra; the bleeding involves postcoital or persistent inter-cyclic bleeding in premenopausal women or postmenopausal bleeding beginning 1 year after menopause.[245] Approximately 10% of women with postmenopausal bleeding have endometrial cancer.[206] Pelvic pain is a much less common feature of endometrial cancer; however, patients with advanced disease may complain of abdominal or pelvic pain and abdominal distension. Endometrial cancer is an age-related disease, with only ~14% developing in premenopausal women and ~5% in women of <40 years of age; the mean age for the most common endometrial cancer (i.e., endometrioid adenocarcinoma) is 61 years.[246,247] Endometrial cancer is usually primary with rare cases of metastatic disease from other organs (e.g., breast, ovary, lung, colorectal); the lungs are the most common site of distant metastasis.[206]

The annual mortality/incidence ratio for endometrial cancer is lower (0.24) than for breast (0.32), uterine cervical (0.55), or ovarian cancers (0.63).[248] Survival rates vary with clinical staging (International Federation of Gynecology and Obstetrics, FIGO) and histology as well as with age, comorbidities, and tumor size. Most endometrial cancers (i.e., ~75%) are diagnosed at an early stage (FIGO Stage I or II) with an overall survival rate of 74–91% in women without metastatic disease. The overall survival rate for FIGO Stage II is 57–66% with the rate decreasing to 20–26% for FIGO Stage IV.[3] The 5-year recurrence-free survival rates for endometrioid carcinomas range from 68–83%, with lower survival for high-grade endometrioid tumors.[249] Analysis of SEER data on 4,180 women with endometrial cancer, grade 3 endometrioid tumors, accounted for 15% of the endometrial tumors and 27% of endometrial cancer-related deaths, whereas grade 1/2 (low-grade) tumors represented 72% of the diagnoses and 26% of the endometrial cancer-related deaths.[250] Five-year survival rates for serous carcinomas range from 20–55% compared with ~40–50% for clear-cell carcinomas.[251]

OVARY

Ovarian cancer is the second most common gynecological cancer in the United States, with an annual incidence of ~22,000 cases and annual ovarian cancer-related deaths of ~14,000.[252] The average lifetime ovarian cancer risk in US women is ~1.3% (i.e., 1/78 women), with rates ~30% higher in non-Hispanic white women than African-American or Asian women and 12% higher than Hispanic women.[253] Ovarian cancer ranks first in overall mortality from gynecological cancers because the diagnosis of most ovarian cancers occurs in postmenopausal women of ≥50 years of age with advanced disease and widespread metastasis.[254] Worldwide, ovarian cancer is the eighth most common cancer and cancer-related cause of mortality among women.[7] The reported ovarian cancer incidence is highest in Northern, Central, and Eastern Europe; intermediate in Western Europe, North America, and Australia; and lowest in Asia and Africa.

The US ovarian cancer incidence decreased beginning in the mid-1980s, resulting in an overall reduction of 29% between 1985 (16.6/100,000) and 2014 (11.8/100,000).[252] Ovarian cancer-related deaths decreased by 33% between 1976 (10.0/100,000) and 2015 (6.7/100,000). Currently, there are no clearly

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effective ovarian cancer screening methods for the general population with benefits that outweigh potential risks.[255]

CARCINOGENESIS

Although several carcinogenic mechanisms have been proposed for ovarian cancer tumorigenesis, including hormonal (gonadotropin) stimulation, incessant ovulation, and chronic inflammation,[256] the etiology of ovarian cancer remains unclear. Ovarian cancer is a heterogeneous group of neoplasms of histological and clinicopathological subtypes that vary in risk factors, etiology, molecular biology, cellular origin, prognosis, and treatment. Low-grade serous, endometrioid, clear-cell, and mucinous epithelial tumors probably arise from inclusion cysts or extraovarian benign lesions that migrate to the ovary and undergo mutations of multiple genes (e.g., *BRAF*, *KRAS*, *PTEN*) to form a malignant neoplasm.[257] Extraovarian sources for ovarian tumors include benign deposits of fallopian tube epithelium (endosalpingiosis) for low-grade serous carcinomas, benign foci of endometrial tissue in the ovary (endometriosis) for endometrioid and clear-cell carcinomas, and benign foci of transitional epithelium from the tuboperitoneal junction for mucinous carcinomas.

EXPOSURE

Factors associated with an increased risk for invasive epithelial ovarian cancer include age, race, nulliparity, family history of breast or ovarian cancer, endometriosis, and prior history of breast or endometrial cancer.[258,259] Inherited genetic variants (e.g., BRCA1/2) account for up to about 25% of ovarian cancers. Higher androstenedione and dehydroepiandrosterone (DHEA) concentrations are associated with dose-related, increased ovarian cancer risks,[260] whereas multiparity, lactation, oral contraceptive use, and tubal ligation/hysterectomy are inversely related to ovarian cancer risks.[261,262] The cumulative risk of developing ovarian cancer by age 65 ranges from 0.3% for white women who had ≥3 pregnancies and ≥4 years of oral contraceptive use to 1.6% for nulliparous white women with no oral contraceptive use.[263] There is no clear, consistently strong association between ovarian cancer and smoking, coffee, alcohol consumption, or physical activity.[264,265] Dietary factors (e.g., fat, protein, calorie intake) are potential risk factors, but few data identify specific dietary factors with clinically significant increased ovarian cancer risks.[266]

The heterogeneity of ovarian tumors and differences in potency between histological subtypes complicate the evaluation of specific risk factors.[267] Most ovarian cancer risk data focus on invasive epithelial ovarian cancer.[268] Each subtype has a unique combination of risk factors, with the strongest associations with endometrioid and clear-cell tumors. The latter two subtypes share similar risk factors. Moderate-to-poorly differentiated serous cancers have distinctly different risk patterns, whereas well-differentiated serous carcinomas demonstrate risk patterns similar to endometrioid carcinomas. Most reproductive and hormonal risk factors are more strongly associated with endometrioid and clear-cell carcinomas than other subtypes. Serous and poorly differentiated carcinomas are the common aggressive subtypes, with the strongest association being with family history of ovarian cancer and modest associations with other common risk factors (e.g., menopausal hormone therapy, parity, oral contraceptive use). Table 57.10 summarizes the major risk factors associated with overall invasive epithelial ovarian cancer and, when sufficient data exist, with histological subtypes.

Occupation

Asbestos and asbestos-contaminated talc (hydrous magnesium silicates) are the two main industrial chemicals most often associated with ovarian cancer. No other single, non-asbestos-related occupation is an established ovarian carcinogen. Many occupational studies on ovarian cancer are ecological or lack adjustment for well-established risk factors and potential misclassification due to difficulty distinguishing peritoneal mesotheliomas from ovarian cancers.

Job Category

A hypothesis-generating case-control study of ovarian cancer suggests the following possible associations based on reported job titles: aromatic hydrocarbon solvents (SIR = 1.3, 95% CI: 1.0–1.7), leather dust (SIR = 1.4, 95% CI: 0.7–2.7), man-made vitreous fibers (SIR = 1.3, 95% CI: 0.9–1.8), high asbestos concentrations (SIR = 1.3, 95% CI: 0.9–1.8), and engine exhaust.[269] None of these associations reached statistical significance, although the trends for increasing exposure to chlorinated hydrocarbon solvents, man-made vitreous fibers, and chromium were statistically significant. The relatively low SIR suggests the possibility of confounding or misclassification. A population-based case-control study using self-administered questionnaires and adjusting for potential confounders suggests excess ovarian cancer risks for teachers, bookkeepers/accounting clerks, retail store employees, and

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TABLE 57.10. Summary of epithelial ovarian cancer risks and protective factors. Unless otherwise stated, the ovarian cancer risk refers to the overall epithelial ovarian cancer risk. (Adapted from Webb and Jordan).[253]

Association Strength	Increased Ovarian Cancer Risk	Primary Carcinoma Subtype	Reduced Ovarian Cancer Risk
Established	Ovarian cancer family history Tobacco smoking Obesity Endometriosis Estrogen-only hormone therapy	Mucinous Non-high-grade serous cancers Endometrioid, clear cell	Pregnancy (lasting >6 months) Oral contraceptives Tubal ligation
Probable	Delayed menopause		Breastfeeding
Possible	Early menarche Combined menopausal hormone therapy Pelvic inflammatory disease Diabetes mellitus Genital talc use Asbestos	Borderline tumors	Older first birth Aspirin Vitamin D
Unlikely or insufficient	Diet, physical activity, alcohol use, infertility treatment, hysterectomy without oophorectomy, polycystic ovarian syndrome, fibroids, ovarian cysts		

noninstitutional health services.[270] The lack of specific exposure information, low response rates for controls, failure to establish biological plausibility for increased risks in multiple job types, and multiple comparisons limit any conclusions about causality.

An Italian case-control, hospital-based study of women with definite exposure to triazine herbicides suggests the possibility of an increased ovarian cancer risk (OR = 2.8, 90% CI: 0.9–8.4, $n = 7$ cases) compared with 7 unexposed controls;[271,272] however, the results were not statistically significant with wide confidence intervals and no quantitation of triazine exposure. A population-based, case-control study of epithelial ovarian cancer in Central California did not detect a statistically significant increase in ovarian cancer risks between ever- and never-occupational triazine herbicide exposures (adjusted OR = 1.34, 95% CI: 0.77–2.33).[273] There was no dose-response relationship between triazine herbicide exposure and ovarian cancer ($P_{trend} = 0.22$).

Asbestos

The IARC lists asbestos as a human carcinogen causing ovarian cancer, with sufficient human evidence of carcinogenicity; however, this classification remains controversial because of methodological issues including failure to adjust for known risk factors, inappropriate comparison populations, and tumor misclassification. A meta-analysis of ovarian cancer and occupational exposure to asbestos, primarily from European studies, demonstrated an overall pooled standardized mortality ratio (SMR) of 1.77 (95% CI: 1.37–2.28, $I^2 = 35.3\%$, $P_{heterogeneity} = 0.061$) when compared with the general population SMR.[274] There was slight to moderate evidence of heterogeneity among the studies, with higher SMRs in European studies and cohorts compensated for asbestosis, whereas three US and Australian cohort studies of occupational asbestos exposure reported no increased ovarian cancer risks. Most of the positive studies used death certificates to validate the outcome of asbestos-related ovarian deaths. In a pooled Italian cohort of 5,741 female asbestos workers followed over 40 years, the SMR for ovarian cancer was borderline (SMR = 1.38, 95% CI: 1.00–1.87, $n = 43$ deaths).[275] A meta-analysis of 14 cohort and 2 case-control studies mostly in Europe reported an increased overall ovarian cancer effect size (SMR = 1.75, 95% CI: 1.45–2.10, $I^2 = 16.2\%$, $P_{heterogeneity} = 0.268$); however, sensitivity analysis indicated the effect size became statistically nonsignificant when analyzing only studies using pathologically confirmed ovarian cancers.[276] The analysis of four studies examining cancer incidence did not demonstrate a statistically significant effect. The authors recommended cautious interpretation of the data because of potential disease misclassification.

Reproductive History

Epidemiological studies indicate hormonal and reproductive factors influence ovarian cancer risks consistent

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with incessant ovulation and gonadotropin stimulation hypotheses; nulliparity is the strongest hormonal risk factor for ovarian cancer. Parous women have a dose-related reduction in ovarian cancer risk (i.e., 30–60%) compared with nulliparous women, particularly endometrioid and clear-cell carcinomas. Although age at first birth was not independently associated with ovarian cancer risk in the large prospective Nurses' Health Study of 121,700 female registered nurses aged 30–55 years, the age-adjusted, overall relative risk of epithelial ovarian cancer comparing parous (mean = 3.1 births) with nulliparous women was 0.55 (95% CI: 0.38–0.80).[277] The relative risk per birth was 0.84 (95% CI: 0.77–0.91, $P_{\text{trend for each birth}} = <0.001$). Analysis of data from the Ovarian Cancer Cohort Consortium indicates that the reduction in ovarian cancer with higher parity was most strongly associated with endometrioid (RR/birth = 0.78, 95% CI: 0.74–0.83) and clear-cell (RR/birth = 0.68, 95% CI: 0.61–0.76, $P_{\text{heterogeneity}} = <0.001$) histological subtypes.[268] The reduction in ovarian cancer with parity also occurs in carriers of the mutated *BRCA1* gene. In a matched case-control study of *BRCA* mutation carriers with (1,329 cases) and without (5,267 controls) ovarian cancer, increasing parity was associated with a significant inverse trend among *BRCA1* mutation carriers (age-adjusted OR = 0.87, 95% CI: 0.79–0.96; $P_{\text{trend}} = 0.005$) but not *BRCA2* mutation carriers (age-adjusted OR = 0.98, 95% CI: 0.81–1.19, $P_{\text{trend}} = 0.85$).[278] The association between ovarian cancer and older age at first or last birth is inconsistent based on limited evidence. Most studies indicate pregnancies of <6 months duration (e.g., abortions, ectopic pregnancies, miscarriages) do not significantly reduce the risk of ovarian cancer.[279] The influence of infertility is difficult to determine because of confounding associated with problems separating various causes of infertility that affect ovarian cancer risks; consequently, evidence from these studies is inconsistent.[265]

Menstruation

The quantitative associations between ovarian cancer and age at menarche or menopause remain uncertain, with stronger evidence for the latter. A meta-analysis of 22 case-control and 5 cohort studies using random-effects models comparing the oldest and youngest categories of age at menarche reported a summary relative risk of 0.85 (95% CI: 0.75–0.97, $P_{\text{effect}} = 0.016$, $I^2 = 42.2\%$) with slight to moderate heterogeneity and no indication of publication bias.[280] The summary relative risk for the five cohort studies was not statistically significant (RR = 0.89, 95% CI: 0.76–1.03, $I^2 = 0\%$). Analysis of data from the Ovarian Cancer Cohort Consortium did not confirm the reduced ovarian cancer risk with increasing age at menarche.[268] The overall invasive epithelial ovarian cancer risk per 1-year increase in menarche using the youngest age group (≤11 years) as referents was 0.99 (0.97–1.00), with no statistically significant difference between histological types except clear-cell tumors (RR = 0.92, 95% CI: 0.85–0.99). For age at menopause, a relatively small increase in overall ovarian cancer risks per 5-year increase in menopause using >50–55 years at menopause as referents (RR = 1.06, 95% CI: 1.02–1.10) was reported. The study reported marked heterogeneity ($P_{\text{heterogeneity}} = 0.009$) between histological subtypes and increased ovarian cancer risks per 5-year increase in age at menopause, particularly for clear-cell (RR = 1.37, 95% CI: 1.15–1.64) and endometrioid (RR = 1.19, 95% CI: 1.05–1.34) cancers.

In an analysis of data from the large prospective Nurses' Health Study categorizing menarche in 1-year groups <12–≥16 years, age at menarche did not significantly influence multivariate relative risks of ovarian cancer ($P_{\text{trend}} = 0.33$) using the <12-year group as referents.[277] Categorizing age at menopause in groups of <45, 45–49 (referents), 50–52, and ≥53 years, age at menopause also did not significantly influence multivariant relative risks of ovarian cancer ($P_{\text{trend}} = 0.43$).

Breastfeeding

Lactation suppresses pituitary gonadotropin secretion, resulting in anovulation, particularly in the initial postpartum period. Several meta-analyses and pooled analyses suggest breastfeeding reduces invasive and epithelial ovarian cancer risks by 25–30% comparing ever- with never-breastfeeding, consistent with lactation-induced anovulation from lower gonadotropin concentrations. However, the biological mechanism for a reduction in ovarian cancer risks with breastfeeding is not well defined. Overall, the evidence of an association is limited and inconsistent with the risks depending on lactation duration and histological subtype.[281] A metanalysis of 5 cohort and 35 case-control studies (12,765 parous, 4,374 nulliparous women) published through 2012 reported a pooled RR of 0.70 (95% CI: 0.64–0.76, $I^2 = 76.29\%$, $P_{\text{heterogeneity}} = 0$) comparing ever- versus never-breastfeeding using in-person interviews and questionnaires.[282] Subgroup analysis indicated the RR for case-control studies was statistically significant (RR = 0.67, 95% CI: 0.61–0.74, $I^2 = 77.4\%$, $P_{\text{heterogeneity}} = 0$), whereas the RR for cohort studies was

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weaker and marginally significant (RR = 0.89, 95% CI: 0.78–1.01, $I^2 = 0$, $P_{\text{heterogeneity}} = 0.96$). Meta-regression analysis indicated an increasing inverse linear trend for increased duration of breastfeeding and ovarian cancer. However, only analysis of North American studies demonstrated a statistically significant reduction in epithelial ovarian cancer with longer breastfeeding. In a pooled analysis of 13 case-control studies participating in the Ovarian Cancer Association Consortium of 7,991 parous women with invasive ovarian cancer and parous controls, the pooled odds ratio of invasive ovarian cancer was reduced in breastfeeding women (OR = 0.76, 95% CI: 0.71–0.80), particularly for high-grade serous subtype.[283] Compared with 4,426 never-breastfeeding parous women, the OR for invasive ovarian cancer in breastfeeding women ranged from 0.82 (95% CI: 0.76–0.88, $n = 1{,}879$) for reported breastfeeding for <3 months to 0.66 (95% CI: 0.58–0.75, $n = 400$) for breastfeeding for >12 months ($P_{\text{trend}} = 0.001$).

Longer durations of breastfeeding may account for some of the heterogeneity and inconsistency associated with studies on ovarian cancer risks comparing breastfeeding among parous women. An Australian population-based, case-control study of epithelial ovarian cancer (Australian Ovarian Cancer Study) reported an inverse association between breastfeeding duration (all episodes combined) and ovarian cancer incidence (OR = 0.986, 95% CI: 0.978–0.994) independent of parity;[284] however, extending breastfeeding beyond 12 months postpartum did not further reduce ovarian cancer incidence. Most benefits appear in the first 5–6 months of breastfeeding.

Analysis of data from the Ovarian Cancer Cohort Consortium demonstrated no statistically significant increase in overall invasive epithelial ovarian cancer risk (adjusted RR = 0.96, 95% CI: 0.89–1.03) per year of breastfeeding.[268] Similarly, no statistically significant differences appeared in the risk of developing any of the common histological subtypes ($P_{\text{heterogeneity between histological types}} = 0.64$). The rarity of most ovarian cancer histological subtypes limits the evaluation of the effect of breastfeeding on the risk of developing a specific ovarian cancer subtype. Although the Australian Ovarian Cancer Study did not detect statistically significant differences between ovarian cancer types (serous invasive, serous borderline, endometrioid, clear cell, mucinous) and duration of breastfeeding per month, the strongest association occurred with endometrioid (adjusted OR = 0.981, 95% CI: 0.962–1.001, $n = 102$ cases). The authors recommended caution when interpreting the importance of these values because of limited power in the study resulting from too few cases.

Lifestyle

Although vigorous physical activity potentially may reduce ovarian cancer risks by reducing inflammatory biomarkers and producing anovulation/amenorrhea, few data support a significant association between physical exercise and ovarian cancer. Leisure-time physical activity probably does not affect ovarian cancer risks,[285] whereas studies on increased ovarian cancer risk from sedentary lifestyles are limited and inconsistent.[286] The presence of selection and recall biases limits definite conclusions regarding a positive association between diet and ovarian cancer; however, current evidence provides little support for an association between ovarian cancer and overall dietary fat intake or consumption of micronutrients (vitamins A, C, E, folate), fruits, or vegetables, with the possible exception of vitamin D.

Tobacco Smoke

Most early studies of cigarette smoking and ovarian cancer reported null values; however, more recent studies suggest a positive association only between smoking and invasive mucinous ovarian cancer. In a meta-analysis of 51 observational studies using never-smokers as controls, the overall ovarian cancer risk was slightly increased but varied with study type and histological subtype ($P_{\text{heterogeneity}} = <0.0001$).[287] For 19 prospective studies, the overall adjusted RR for ovarian cancer in current smokers was 1.06 (95% CI: 1.01–1.11). The adjusted summary RR for ovarian cancer was elevated in current smokers (summary RR = 1.08, 95% CI: 1.03–1.14) in 21 population-based case-control studies (summary RR = 1.08, 95% CI: 1.03–1.14) and reduced in 11 hospital-based case-control studies (summary RR = 0.81, 95% CI: 0.75–0.89). The mucinous ovarian cancer risk was elevated in current smokers compared with never-smokers (RR = 1.79, 95% CI: 1.60–2.00), primarily from borderline malignant mucinous tumors, whereas current smokers had reduced risks of endometrioid (RR = 0.81, 95% CI: 0.72–0.92) and clear-cell (RR = 0.80, 95% CI: 0.65–0.97) epithelial ovarian cancers. Similarly, in a prospective study of 300,398 Norwegian women aged 19–67 years at enrollment in national registries and followed for a median of 19 years, the hazard ratio for invasive mucinous cancer in current smokers using never-smokers as controls was 1.78 (95% CI: 1.20–2.64, $P_{\text{heterogeneity}} = 0.34$) and 2.26 (95% CI: 1.71–2.97) for borderline mucinous ovarian cancer.[288] Smoking was not associated with serous or endometrioid ovarian cancers. In a prospective study of 100 incident ovarian cancer cases in *BRCA* mutation carriers followed for 15,720

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person-years, the adjusted hazard ratio was not statistically different when comparing ever- and never-smokers (RR = 1.45, 95% CI: 0.96–2.19, n = 51 ever-smokers/49 never-smokers) or current and never-smokers (adjusted HR = 1.25, 95% CI: 0.73–2.12).[67] Ovarian cancer risks did not differ by BRCA mutation type or age at cancer diagnosis.

Alcohol

Large-scale pooled analyses indicate alcohol consumption is not a significant risk factor for overall ovarian cancer risks, with most studies reporting null or decreased risks.[265] A large, US population-based case-control study reported no significant association of ovarian cancer with increasing alcohol consumption during ages 20–30 years (P_{trend} = 0.42) or the recent past (P_{trend} = 0.83).[289] The type of beverage did not affect ovarian cancer risks with the exception of beer consumption of ≥1 beer daily; a significant positive association was limited to serous tumors (OR = 1.52, 95% CI: 1.01–2.30) with relatively sparse data on other histological subtypes. A pooled analysis of 10 cohort studies comprising 529,638 women with 2,001 incident epithelial ovarian cases did not support an association between moderate alcohol intake and ovarian cancer risk.[290] Using random effects models, the pooled multivariate RR comparing daily consumption of ≥30 g alcohol with nondrinkers was 1.12 (95% CI: 0.86–1.44). The ovarian cancer risk did not vary significantly with the type of beverage (i.e., wine, beer, spirits).

Obesity

The association between obesity and ovarian cancer is inconsistent with high heterogeneity between studies, depending on the outcome measure (BMI, waist-to-hip ratio, waist circumference), menopausal status (pre- vs. postmenopausal), and ovarian cancer histological subtypes (serous vs. non-serous, low- vs. high-grade). In general, ovarian cancer risks are greater in premenopausal than postmenopausal women and strongest in non-serous and low-grade serous subtypes. Secondary analyses stratified by behavior/subtype on data from 39 studies in the Ovarian Cancer Association Consortium suggested the strongest ovarian cancer risks occurred in invasive low-grade/borderline serous cancers (OR = 1.93, 95% CI: 1.33–2.81, n = 1,411 cases) consistent with observational data.[291] A meta-analysis of 13 case-control and 13 cohort studies using normal weight (18.5–24.9 kg/m^2) as the reference group reported elevated ovarian cancer risks for overweight (pooled RR = 1.07, 95% CI: 1.02–1.12, I^2 = 11.2%, $P_{heterogeneity}$ = 0.302) and obese women (pooled RR = 1.28, 95% CI: 1.16–1.41, I^2 = 54.2%, $P_{heterogeneity}$ = 0.001).[292] However, subgroup analysis indicated no increased ovarian cancer risks in overweight (pooled RR = 0.97, 95% CI: 0.76–1.24, I^2 = 64.1%, $P_{heterogeneity}$ = 0.016, n = 6 studies) or obese (pooled RR = 0.93, 95% CI: 0.61–1.42, I^2 = 77.6%, $P_{heterogeneity}$ = 0, n = 6 studies) postmenopausal women with substantial heterogeneity between studies. A meta-analysis of 12 primarily US prospective studies reported increased ovarian cancer risks in obese premenopausal women (multivariate RR = 1.72, 95% CI: 1.02–2.89) but not in postmenopausal women (multivariate RR = 1.07, 95% CI: 0.87–1.33).[293] Analysis of data from the Ovarian Cancer Cohort Consortium did not detect a statistically significant increase in overall ovarian cancer risk or any subtype risk with increasing BMI using 20–<25 kg/m^2 as the reference group ($P_{heterogeneity\ between\ histological\ types}$ = 0.10).[268]

Talc

Talc is a magnesium silicate similar to asbestos, with a particular lamellar (sheet-like) structure. Although the IARC classified asbestos as a human ovarian cancer carcinogen, the association remains controversial because of limited studies, weak dose-response data (frequency/duration of talc use), potential recall bias of self-reports, and the common misclassification of peritoneal mesothelioma as an asbestos-related disease. Studies on the association between cosmetic talc use and ovarian cancer risks are conflicting. Although animal, pathological, and mechanistic studies generally do not support the carcinogenicity of talc on the ovarian epithelium with no clear evidence of genotoxicity or a dose-response relationship,[294] earlier studies suggested an ~20–35% (i.e., summary RR ≅ 1.2–1.5) increased ovarian cancer risk with talc use.[295] Some US and European baby powders manufactured in the 1970s contained small amounts of tremolite or quartz silica;[296,297] however, cosmetic talcum powder has reportedly not contained detectable asbestos concentrations for several decades.[298,299] Ovarian cancer subtypes most closely associated with talc include invasive serous and endometrioid tumors along with borderline serous and mucinous tumors. The potential risk factor associated with talc use is not a major contributor to the etiology of ovarian cancer because of the limited number (i.e., 14%) of women using talc in many of these studies.[300]

Several case-control studies reported increased ovarian cancer risks with relatively small effect sizes in talc users. A case-control study of 450 patients with ovarian

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cancer demonstrated a statistically significant association between the cosmetic use of talc and ovarian cancer risk (OR = 1.42, 95% CI: 1.08–1.86).[301] The relationship between increased ovarian cancer risk and duration of talc use was marginal, with no significant relationship to the frequency of talc use. A retrospective case-control study reported elevated ovarian cancer risks among talc users (OR = 1.33, 95% CI: 1.16–1.52), particularly for serous and endometrioid cancers in premenopausal and postmenopausal women using hormonal therapy.[302] A case-control study of 499 patients with epithelial ovarian cancer did not demonstrate an increased ovarian cancer risk with talc use when compared with a control population of 755 women after adjustment for known risk factors.[303] There was also no association with the duration of talc use for >20 years (OR = 0.9, 95% CI: 0.6–1.2).

Recent meta-analyses have not demonstrated consistent, statistically significant associations between talc powder use in the genital area and ovarian cancer risks, particularly in cohort studies. In a meta-analysis of 24 case-control studies (13,421 cases) and 3 cohort studies (890 cases totaling 181,860 person-years) using never-talc users as controls, any talc use was associated with a statistically significant risk of ovarian cancer in the 24 case-control studies (OR = 1.35, 95% CI: 1.27–1.43) but not in the 3 cohort studies (OR = 1.06, 95% CI: 0.90–1.25).[304] Subgroup analysis suggested an increased risk of serous ovarian cancer in the cohort studies (OR = 1.25, 95% CI: 1.01–1.55) but not clear-cell or mucinous subtypes. Most of the studies used self-reported talc use among ovarian cancer patients. In a pooled analysis of 4 large, US-based cohorts (252,745 women) followed for a median of 11.2 years, 38% reported ever-use of genital talc powder (10% long-term, 22% frequent use) and 2,168 women developed ovarian cancer. The pooled estimate of the adjusted hazard ratio for ovarian cancer in ever-users was 1.08 (95% CI: 0.99–1.17, $P_{\text{heterogeneity}} = 0.81$). Similarly, the estimate of the adjusted HR for ovarian cancer was statistically nonsignificant in long-term users (adjusted HR = 1.01, 95% CI: 0.82–1.25, $P_{\text{heterogeneity}} = 0.90$, $P_{\text{trend}} = 0.49$) and frequent users (adjusted $\text{HR}_{\geq 1/\text{week}} = 1.09$, 95% CI: 0.97–1.23, $P_{\text{heterogeneity}} = 0.65$, $P_{\text{trend}} = 0.20$). None of the hazard ratios for ovarian cancer histological subtypes reached statistical significance, including ever-use of talc in serous ovarian cancer cases (HR = 1.10, 95% CI: 0.97–1.25, n = 1,038 cases, $P_{\text{heterogeneity}} = 0.86$). Among 61,576 postmenopausal women in the Women's Health Initiative Observational Study cohort followed for a mean of 12.4 years, 52.6% reported ever-using perineal powder; the hazard ratio for ovarian cancer in ever-use was 1.06 (95% CI: 0.87–1.28) compared with never-use.[305] The ovarian cancer risks were not affected by the duration or location of talc use.

Medications

Several prospective and case-control studies suggest an inverse association between aspirin or nonsteroidal anti-inflammatory drugs and ovarian cancer incidence;[306] however, the relationship is inconsistent and not clearly dose-related, with no clinical trials to support efficacy.

Menopausal Hormone Therapy

Most initial studies on unopposed estrogen therapy in postmenopausal women did not demonstrate an association between duration of use and increased ovarian cancer risks.[307] More recent studies indicate increased ovarian cancer risks in ever-users of hormonal replacement therapy with increasing risk for longer use. In the prospective observational Nurses' Health Study of 82,905 postmenopausal women using never-users as the reference group, the ovarian cancer risks were elevated for current users with ≥5 years of use (RR = 1.41, 95% CI: 1.07–1.86) and former users with ≥5 years of use (RR = 1.52, 95% CI: 1.01–2.27).[308] However, hormonal therapy use for <5 years was not associated with increased ovarian cancer risks in current (RR = 1.01, 95% CI: 0.70–1.44) or former users (RR = 0.88, 95% CI: 0.64–1.19). Pooled data from 52 epidemiology studies comparing current users with <5 years of use with never-users demonstrated an RR of 1.43 (95% CI: 1.31–1.56, $P < 0{\cdot}0001$).[309] The addition of progestin to estrogen therapy mitigates the positive association between estrogen use and ovarian cancer. Most, but not all, observational studies report no or a weak positive association between estrogen plus progestin use and ovarian cancer risks.[265,310,311] The ovarian cancer risks are stronger for endometrial and serous subtypes and statistically nonsignificant for mucinous and clear-cell subtypes.[268,309]

Oral Contraceptives

Observational studies indicate oral contraceptive use reduces ovarian cancer risks regardless of the oral contraceptive formulation in gravid, but not nulligravid, women.[312] Although data are limited, similar reductions in ovarian cancer risks with other types of contraception including vasectomy suggest mechanisms other than hormonal or ovulation contribute to reduced ovarian

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cancer risks. The protection against ovarian cancer is similar for many subtypes (serous, endometrioid, clear cell) except for mucinous cancers in some studies.[265,268] In the large prospective Nurses' Health Study, oral contraceptive use reduced the relative risk of ovarian cancer by 30–60%, depending on the duration of use.[277] The relative risk decreased by ~11% per year of use, but there was little protective effect beyond 6 years of use. Analysis of pooled data for 23,257 women with ovarian cancer (cases) and 87,303 without ovarian cancer (controls) from 45 epidemiological studies in 21 countries indicated an ~30% reduction in overall ovarian cancer risk comparing ever-oral contraceptive users with never-users.[313] Longer use was associated with greater risk reduction ($P < 0.0001$) with effects persisting for >30 years; however, the effect attenuated over time.

Diseases

Most epidemiological studies on the inverse relationship between tubal ligation and ovarian cancer report reductions in the range of 20–30%, including *BRCA* mutation carriers with stronger effects for endometrioid and clear cell than invasive serous cancer risks.[253] The reductions persist at least 30 years after surgery, regardless of age when the procedure was performed.[314] Although the human papilloma virus occurs commonly in patients with ovarian cancer (i.e., 15–20%), evidence of a statistically significant positive association is inconclusive.[315]

Endometriosis

Endometriosis is a common estrogen-dependent inflammatory disease present in ~5–10% of reproductive-age women. Case-control[316] and cohort[268] studies suggest endometriosis substantially increases type I ovarian cancer (endometrioid, clear-cell carcinoma) risks. Analysis of pooled data from 13 ovarian cancer case-control studies in the Ovarian Cancer Association Consortium demonstrated elevated risks in self-reported endometriosis cases for clear-cell (OR = 3.05, 95% CI: 2.43–3.84, $P < 0{\cdot}0001$), low-grade serous (OR = 2.11, 95% CI: 1.39–3.20, $P < 0.0001$), and endometrioid (OR = 2.04, 95% CI: 1.67–2.48, $P < 0.0001$) invasive ovarian cancers when compared with controls (no reported endometriosis).[316] Endometriosis was not associated with statistically significant elevations in the risk of mucinous, high-grade serous, or borderline tumors of either subtype of invasive ovarian cancer.

Pelvic Inflammatory Disease

Although pelvic inflammatory disease (PID) is a potential risk factor for ovarian cancer because of the plausible biological mechanism of chronic inflammation (↑ cytokines, chemokines) and increased repair processes, studies on the overall association are inconsistent and relatively weak with limited statistical power and short follow-up periods and complicated by the heterogeneity of ovarian tumors. In an analysis of pooled data from 13 case-control studies involving 9,162 cases of ovarian cancer, 2,354 women with borderline tumors, and 14,736 controls from the Ovarian Cancer Association Consortium, the adjusted overall ovarian cancer risk was not associated with self-reported PID status (pooled OR = 0.99, 95% CI: 0.83–1.19, $I^2 = 36.8\%$, $P_{\text{heterogeneity}} = 0.09$) compared with controls (no history PID).[317] Subgroup analysis suggested a history of PID was associated with an increased risk of borderline ovarian tumors (adjusted OR = 1.32, 95% CI: 1.10–1.58, $I^2 = 0$, $P_{\text{heterogeneity}} = 0.85$, $n = 49$ cases), comparing participants with and without a history of PID, particularly serous and mucinous borderline tumors. However, the adjusted OR for these latter two borderline tumors did not reach statistical significance. In a meta-analysis of six cohort and seven case-control studies, the overall ovarian cancer risk comparing participants with and without a history of PID based on self-reporting (case-control studies) or hospital records (cohort studies) was elevated (summary RR = 1.24, 95% CI: 1.06–1.44, $I^2 = 58.8\%$, $P_{\text{heterogeneity}} = 0.003$) with moderate heterogeneity.[318] Subgroup analysis indicated significantly different results between Asian and Caucasian studies ($P_{\text{between-group heterogeneity}} = 0.054$), with the former studies demonstrating a statistically significant increased ovarian cancer risk. The authors recommended a cautious interpretation of the results.

Diabetes Mellitus

A meta-analysis of 14 cohorts suggested a modest increase in overall ovarian cancer risk in diabetic women (summary RR = 1.19; 95% CI: 1.06–1.34, $I^2 = 43.8\%$, $P_{\text{heterogeneity}} = 0.040$, $n = 5{,}534$ ovarian cancer cases) compared with nondiabetic women (diabetic type and metformin use not available).[319] A population-based cohort study of women with type 2 diabetes ($n = 319{,}310$) and age-matched, nondiabetic controls ($n = 319{,}308$) did not support an association between ovarian cancer and diabetes type II (covariate-adjusted HR = 1.06, 95% CI: 0.92–1.22).[320]

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HISTOLOGY

Epithelial ovarian cancers represent 90% of malignant ovarian cancer[321] comprising five major histotypes of invasive disease, including high- and low-grade serous (52%), endometrioid (10%), mucinous (6%), and clear cell (6%); two histotypes of borderline disease (serous, mucinous); and the remaining rare/unspecified.[322,323] Nonepithelial ovarian cancers are usually less aggressive tumors (e.g., germ cell tumors, 3%; sex cord–stromal tumors, 2–6%).[324] The rare ovarian germ cell tumors mostly affect children and young women consistent with their embryological origin.[325]

Clinicopathological classification of epithelial ovarian cancers involves low-grade type I neoplasms (unilateral, large, cystic tumors with indolent behavior) and genetically unstable, high-grade type II neoplasms (bilateral aggressive ovarian tumors with advanced stage and poor prognosis).[326] The latter tumors primarily consist of high-grade serous carcinomas and less often carcinosarcomas and undifferentiated carcinomas; high-grade serous carcinomas account for ~2/3 of epithelial ovarian cancer deaths.[327] Type I tumors include endometrioid, mucinous, clear-cell, and well-differentiated serous carcinomas that probably arise from ovarian epithelium or inclusions of germ cell layers from the Müllerian system;[257] type I tumors are typically associated with mutations in *KRAS*, *BRAF*, *PTEN*, *PIK3CA*, *CTNNB1*, *ARID1A*, and *PPP2R1A* genes, whereas TP53 mutations are rare.[328] Type II ovarian neoplasms probably arise from the fallopian tubular epithelium associated with TP53 mutations.

HOST SUSCEPTIBILITY

Heredity accounts for ~18–24% of ovarian carcinomas.[328] The strongest overall risk factor for ovarian cancer is a family history of ovarian or breast cancer with a family history of ≥3 first- or second-degree relatives, suggesting the presence of a significant genetic predisposition to ovarian cancer.[329] Twin studies indicate most of the familial ovarian cancer risk results from inherited genetic factors rather than environmental or lifestyle factors common to family members.[330] A woman with a first-degree relative diagnosed with ovarian cancer has an ~50% increased ovarian cancer risk, whereas a first-degree relative with breast cancer increases a woman's ovarian cancer risk by ~10%.[268] A past history of breast cancer was reported in 4.6% of 138 Italian women with ovarian cancer compared with 23.6% of women with ovarian cancer who had a history of familial ovarian cancer.[331] Approximately 2% of Ashkenazi (Eastern European) Jewish women have the BRCA1/2 mutations compared with <1% of women in the general population.[332]

Although the BRCA1/2 mutations are relatively rare in the non-Ashkenazi population, inherited mutations account for an estimated 14–18% of epithelial ovarian cancers, primarily high-grade serous carcinomas in patients with mutations in *BRCA1* and/or *BRCA2* genes.[327,333] These two mutations are high-penetrance mutations accounting for ~40% of ovarian cancer cases in women with a family history of ovarian cancer.[334,335] By age 80, an estimated 44% of women with BRCA1 mutations and 17% with BRCA2 mutations will develop ovarian cancer based on family studies; these risks are somewhat lower in population-based studies (e.g., 39% and 11%, respectively).[127,336] For women with BRCA1/2 mutations, bilateral salpingo-oophorectomy decreases ovarian cancer risks by ~80%.[337] Whole-exome sequencing indicates mutations in mismatch repair *MSH6* (genomic stability) as well as *RAD51C*, *TP53*, and *ATM* (cell-cycle regulation, serine/threonine kinase) genes contribute to ovarian cancer susceptibility.[338] Rare epithelial ovarian cancer mutations in genes with moderate penetrance include the homologous DNA recombination and repair genes *BRIP1* (BRCA1-interacting protein C-terminal helicase 1)[339] and the *RAD51C/D* recombinase genes.[340]

Lynch syndrome (hereditary nonpolyposis colon cancer) is a rare, autosomal-dominant hereditary condition associated with an ~11-fold increased cumulative ovarian cancer risk (i.e., 6–12%) by age 70 years compared with the general population; these tumors are primarily type I, non-serous epithelial tumors (endometrioid, clear-cell carcinomas) as well as cancers at other sites (e.g., colorectal, endometrial).[252] The main germline mutations involve DNA mismatch-repair genes, including *PMS1* (PMS homolog 1), *MLH1* (mutL homolog 1), *MSH2* (mutS homolog 2), and *MSH6* (mutS homolog 6).[341] In a systematic review of 747 patients with Lynch syndrome and ovarian cancer, the most frequent mutations were in *MSH2* (47%) and *MLH1* (38%) genes; 31% ($n = 136$) of these patients presented with mixed histological types (mucinous/endometrioid/clear-cell carcinomas).[342] The mean age at presentation was 45.3 years (range, 19–82 years). Other rare hereditary syndromes associated with increased ovarian cancer risks include Peutz–Jeghers and Li–Fraumeni syndromes.[327]

CLINICAL FEATURES

The median age for patients diagnosed with ovarian cancer is about 63 years. Ovarian cancer is rare before

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age 40, primarily involving germ cell tumors, whereas over the age of 40, the vast majority are epithelial ovarian cancers with the incidence increasing sharply until a peak at ~65–75 years of age. Serous tumors usually occur in women between 40 and 60 years of age, typically in an advanced stage at presentation. Patients with the BRCA1 and BRCA2 mutations usually present earlier (i.e., ~10 years) than other ovarian cancer patients.[128] In an analysis of data from an international registry containing 5,689 women with 195 incident cases of ovarian and fallopian tube cancer followed for a mean of 4.7 years (range, 0–22.6 years), the mean age at diagnosis was 51.3 years (range, 33–84 years) among *BRCA1* mutation carriers and 61.4 years (range, 44–80 years) among *BRCA2* mutation carriers.[343]

Early stages of ovarian cancer often do not display obvious symptoms. The most common feature of advanced disease is ascites; however, some women experience nonspecific symptoms during the months prior to diagnosis including abdominal distension, pain (back, abdomen, pelvis), anorexia, indigestion, early satiety, vomiting, altered bowel habits, and/or urinary frequency.[344]

The prognosis for ovarian tumors depends primarily on histological stage and tumor type. A majority of women present with advanced disease associated with many episodes of recurrent disease and progressively shorter disease-free intervals ultimately ending in bowel obstruction.[345] The overall median 10-year survival at major treatment centers is ~40–50%. The prognosis is progressively worse as the stage at diagnosis increases, as reflected by the following 10-year survival rates: Stage I, 73–92% (limited to ovary or fallopian tube); Stage II, 45–55% (spread to pelvis); Stage III, 21% (spread to lymph nodes and/or beyond pelvis); and Stage IV, <6% (spread to organs outside the abdomen). Most serous carcinomas are high-grade epithelial tumors that present in Stage III (~50%) or Stage IV (~30%), whereas most (i.e., 58–64%) endometrioid, clear-cell, and mucinous carcinomas present in Stage I.[252] The 5-year survival rate for Stage III serous carcinomas is ~42%, with the rate declining to 29% for Stage IV serous carcinomas. Analysis of US mortality data from the SEER*Stat database from the National Center for Health Statistics indicates the overall 5-year, cause-specific survival rate is 82% for endometrioid carcinomas compared with 66% for clear-cell carcinomas and 71% for mucinous carcinomas. The use of PARP inhibitors substantially improves 5-year survival (i.e., about 70%) in advanced-stage ovarian cancers with BRCA genetic variants.

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Chapter 58

CENTRAL NERVOUS SYSTEM

Central nervous system (CNS) tumors most commonly involve primary brain tumors, intracerebral metastases from primary extracranial tumors, extracerebral intracranial tumors (e.g., meningiomas), and meningeal carcinomatosis (invasions of meninges by a primary extracranial tumor, most commonly primary melanoma, breast, lung, or gastrointestinal cancer). Less frequent CNS tumors capable of compressing, invading, or spreading in the central or peripheral nervous systems include neoplasms in structures around the brain (e.g., dura, base of the skull, cavities in the skull) or tissue and skin around the skull or neck.[1] Brain tumors are a complex, heterogeneous group of rare pathological neoplasms that display different clinical, histological, and prognostic features. These tumors account for ~2% and 1.4% of all cancer mortality in men and women, respectively, with the incidence varying with sex, age, ethnic origin, location, and histological type. Based on cancer registry data, neuroepithelial tumors predominate in men, whereas meningiomas are more common in women.[2] The incidence of brain tumors ranges from 8.5/100,000 in Estonia to 21.4/100,000 in the United States.[3,4]

Brain tumors are the most common solid tumor in children of <14 years of age in the United States, with ~3,400 new cases annually; these tumors are also the leading cause of solid cancer-related deaths in this age group.[5] Before age 30 years, neuroepithelial tumor incidence is ~3/100,000 rising to 5/100,000 by age 50 years; the incidence peaks at 20/10,000 near age 70 years and decreases slightly thereafter. In most developing countries, epidemiological data suggest brain cancer incidence and mortality have increased slowly since the 1940s, particularly in elderly patients.[6,7] Overall, brain cancer incidence is relatively stable to decreasing in adults and stable to increasing in children.[8] Although improvements in diagnostic technology (e.g., CT, MRI), demographic variation, and classification changes account for part of the apparent changes in incidence, some histological types of brain tumors are probably increasing, including malignant astrocytomas in the elderly, intracranial lymphomas in HIV/AIDS patients, ependymomas in adults, nerve sheath tumors in males, and pituitary tumors in females.[9] Most intracranial tumors develop in older adults, particularly malignant astrocytomas in men of >60 years of age.[10,11] Although CNS tumors are rare, significant morbidity and mortality from brain tumors occur in children and young adults, with these tumors accounting for 30% and 20%, respectively, of cancer-related mortality in these age groups.[12] The incidence of nonmalignant brain tumors is more than twice as common as malignant tumors in adolescents and young adults (15–39 years of age).[13] Meningiomas are the most common brain tumors.

CRANIAL TUMORS

EXPOSURE

Most patients with brain tumors lack an identifiable risk factor. Aside from ionizing radiation and rare genetic causes,[14,15] there are no well-established environmental

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TABLE 58.1. International Agency for Research on Cancer (IARC) classification of brain and central nervous system cancer sites by strength of evidence categories. (Adapted from IARC).[17]

Anatomical Site	Carcinogens with *Sufficient* Human Evidence (Group 1)	Carcinogens with *Limited* Human Evidence (Groups 2A or 2B)
Eye	Human immunodeficiency virus type 1, ultraviolet-emitting tanning devices, ultraviolet emissions from welding	Solar radiation
Central nervous system	X-ray and γ-radiation	Radiofrequency electromagnetic fields (gliomas, acoustic neuromas, or vestibular schwannomas)

or lifestyle risk factors clearly associated with brain tumors including cell phone use.[16] The IARC lists only X-ray and γ-radiation as carcinogens with sufficient human evidence; radiofrequency electromagnetic fields including wireless phones are classified as carcinogens with limited human evidence (Group 2B) for gliomas and benign vestibular schwannomas (acoustic neuromas), as displayed in Table 58.1.[17] The latter remains particularly controversial because of the presence of multiple issues in case-control studies including recall bias, selection bias between studies, difficulty obtaining accurate cell phone long-term exposure data, and rapidly changing cell phone use and electromagnetic fields with continuing upgrades of cell phone transmission technology. Current data associating cell phone use with increased meningioma and glioma risks in adults are insufficient, whereas the data on vestibular schwannomas (acoustic neuromas) and gliomas are limited.[18,19]

Although some studies demonstrate a positive correlation between brain tumors and certain risk factors (nitrosamines, intracranial infections, radon, electromagnetic radiation, head trauma,[20,21] vinyl chloride,[22] pesticides[23]), overall the data are inconclusive, particularly with electromagnetic fields and childhood radon exposure.[24] Some reviews and meta-analyses suggest the presence of allergic conditions (e.g., asthma, eczema, hay fever, food allergies) has an inverse association with brain cancer incidence (e.g., meningioma, glioma, vestibular schwannoma);[25,26] however, the presence of substantial heterogeneity and limited exposure data produce inconsistent results regarding causation.[27] A death certificate-based case-control study associated socioeconomic status with increasing brain cancer risks, particularly for engineers.[28] The incidence of brain tumors after irradiation or chemotherapy for a previous malignancy is relatively small.

Occupation

Job Title

Although a number of occupations (agriculture, rubber and plastic manufacturing, electronics) have been associated with increased brain cancer risks, these associations are inconsistent and none of the associations are conclusive, including pesticides, herbicides, solvents, fertilizers, and infectious agents. Hypothesis-generating studies of patients with brain tumors suggest that white-collar workers (i.e., engineers, teachers, lawyers, physicians, accountants, judges) as well as foundry/smelter workers, petroleum/gas workers, and painters are at increased risk of developing brain tumors compared with the general population.[29,30] Among workers with potential exposure to carcinogens, mortality studies suggest an increased incidence of brain tumors in workers from the rubber industry, petroleum petrochemical and pharmaceutical production, farming, electrical industries, and polyvinyl chloride production.[6] However, the etiology of the increased risk is obscured by the small sample size, potential for misclassification of nonexposed workers, lack of confirmation of histological type of brain tumor, and inadequate exposure data. No consistent chemical exposure(s) accounts for the increased risk detected in these occupations. Using mailed questionnaires to assess occupational exposure history, a Canadian population-based case-control study of 1,009 brain cancer cases and 5,039 controls evaluated 18 chemicals and >100 occupations.[31] The results suggested potential associations between usual occupation and multivariate-adjusted brain cancer risks for protective services (OR = 1.67, 95% CI: 1.08–2.56, $n = 31$ cases), teaching (OR = 1.38, 95% CI: 1.02–1.87, $n = 57$ cases), knitting in textile processing (OR = 12.42, 95% CI: 2.00–77.1, $n = 3$ cases), construction trades (OR = 1.00–1.79, $n = 71$ cases), and transport equipment operation (OR = 1.43, 95% CI: 1.02–2.02, $n = 49$ cases). Brain cancer risks in the other over 100 occupations were statistically nonsignificant, including farmers (OR = 0.88, 95% CI: 0.56–1.38, $n = 24$ cases). Of the 18 chemicals evaluated, brain cancer risks were elevated only for asphalt (multivariant adjusted OR = 1.29, 95% CI: 1.02–1.62, $n = 120$ cases). Exposure duration also was not associated with brain cancer risks for any of the 18 chemicals, except asphalt ($P_{\text{trend}} = 0.033$, adjusted $\text{OR}_{\geq 10 \text{ years exposure}} = 1.39$, 95% CI: 0.97–1.99,

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$n = 43$ cases). The multiple comparisons and relatively weak results limit any causal conclusions regarding brain cancer risks and these occupations.

A retrospective cohort study from 1944–1952 of white male workers aged 25–64 years in four Ohio tire building and curing companies suggested a higher mortality rate due to tumors of the central nervous system in these workers compared with local residents (observed deaths = 77/expected deaths = 53.8).[32] A follow-up study of American rubber workers did not demonstrate an elevated risk of brain tumors after 1963; this study suggested that the excess of brain malignancies before 1963 resulted from high chemical exposure in earlier manufacturing processes.[33]

Extremely Low Electromagnetic Fields

Some, but not most, studies[34] of occupations with exposure to high levels of electric or magnetic fields suggest an increased risk of developing gliomas and benign vestibular schwannomas (acoustic neuromas); however, the studies are inconsistent and usually do not indicate elevated meningioma risks.[35,36,37] Based on mortality studies using job titles, the occupations at greatest risk of developing brain tumors are electrical engineers and technicians (OR = 2.7), telephone workers (OR = 1.6), electric power workers (OR = 1.7), and electrical workers in manufacturing industries (OR = 2.1).[38] Exposure to electromagnetic fields in these studies was based on job title rather than an estimation of actual exposure. A study of the Swedish Cancer-Environment Registry for the period 1961–1979 did not demonstrate an elevated incidence of gliomas in electrical occupations.[39] Similarly, a cohort of electric occupations followed for 18 years did not demonstrate an increased incidence of brain tumors overall, but an increased risk was detected for radio/TV assembly and repairmen.[40] In these jobs, the SMR for overall brain tumors was 290 (95% CI: 120–590), with particularly elevated risks for glioblastomas (SMR = 340, 95% CI: 110–800). Even though these studies suggest the need for further evaluation of the association between electromagnetic fields and brain cancer, especially in terms of documentation of exposure and histological type, the studies to date have not demonstrated a consistently strong relationship. The risk of developing brain cancer in a population-based study of eight Canadian provinces was not statistically different (OR = 1.33; 95% CI: 0.75–2.36) for men, with average magnetic field exposure of >0.6 μT compared with men exposed to <0.3 μT.[41] The more pronounced risk (OR = 5.36; 95% CI: 1.16–24.78) occurred in the subset of cases with more malignant gliomas (glioblastoma multiforme). Exposure to magnetic fields was not associated with an increased incidence of astrocytoma or other brain cancers. In a hospital-based case-control study of 489 glioma cases, 197 meningioma cases, and 799 controls using job-specific quantitative estimates of ELF–EMF, the study evaluated glioma, meningioma, and vesicular schwannoma risks associated with four exposure indices (maximum exposure, total exposure years of <1.5 mG, cumulative lifetime exposure, average lifetime exposure).[42] The age-, sex-, and location-adjusted odds ratios demonstrated no statistically significant elevations or trends across exposure categories for the four different exposure metrics and three tumor types. A case-control study of 1,346 gliomas investigated three categories of ELF–EMF exposure (cumulative, average, maximum) using a job-exposure matrix to compare the highest and lowest quintiles of exposure.[43] Generally, the odds ratios were weak and statistically nonsignificant, particularly for cumulative and maximum exposures except for astrocytoma grade IV (glioblastoma multiforme). For cumulative exposure of <15 years, the OR for the highest exposure category (2.75 μT-years) compared with the lowest (<0.91 μT-years) was 1.9 (95% CI: 1.4–2.6, $n = 89$ cases, $P_{\text{trend}} = <0.001$); however, the odds ratio for the highest cumulative exposure (≥15 μT-years) was not statistically significant ($P_{\text{trend}} = 0.44$), indicating the lack of a dose-response relationship.

Ionizing Radiation

Previously, human CNS tissue was considered relatively resistant to ionizing radiation-induced carcinogenesis; consequently, relatively high X-ray doses from diagnostic examinations and radiotherapy were relatively common. Ionizing radiation is now a well-established risk factor for cancer in previous cohorts receiving moderate- to high-dose radiation (atomic bomb survivors, prophylactic cranial irradiation, *Tinea capitis*, and adenoid hypertrophy radiation therapy).[12] Although a variety of rare CNS tumors (e.g., embryonal tumors, lymphomas, hemangioblastomas) developed in these cohorts, the most common radiation-induced CNS tumors were meningiomas, gliomas, and benign vestibular schwannomas.[44,45] The highest radiation-induced cancer risks occur in patients exposed as infants to particularly high radiation doses, with the risk decreasing as the time since radiation exposure increases. In a systematic review of eight cohorts receiving intracranial radiation with the average age at exposure ranging from 8 months (Pooled Skin Hemangioma cohorts) to 26 years (Japanese Life Span Study), mean brain radiation dose ranged from 0.07 Gy (Pooled Skin

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Hemangioma cohorts) to 10 Gy (US Childhood Cancer Survivor Study, British Childhood Cancer Survivor Study).[46] Phantom studies analyzing the irradiation for *Tinea capitis* treatment in Israeli children during the 1950s, using the most popular radiation protocol (Adamson–Keinbock technique), demonstrated a scalp surface radiation dose of 5–8 Gy and a brain surface radiation dose of 1.4–1.5 Gy.[47]

Generally, ionizing radiation-induced excess relative risks appeared higher for meningiomas than gliomas. The former displayed no effect modifications (i.e., sex, age at exposure, time since exposure, attained age), whereas glioma risks appeared stronger for younger than older age at exposure. Although all the studies reported elevated CNS cancer risks, substantial variation occurred across studies ($I^2 = 74.7\%$, $P_{\text{heterogeneity}} = 0.003$), and no summary excess relative risk was calculated.

Lifestyle

Conventional lifestyle factors (smoking, excessive alcohol consumption, diet) are not important risk factors for brain cancer risks.[48] Although a case-control study reported a weak association (RR = 1.44) between smoking and brain tumors,[49] other studies have not confirmed this link.[30,50,51]

Medications

Some case-control studies suggest self-reported hormone replacement therapy in postmenopausal women and oral contraceptive use reduce glioma risk, whereas delayed menarche or late menopause increase glioma risk; however, most studies do not demonstrate statistically significant alterations in risk or a dose-response relationship.[52] Generally, the results are heterogeneous, with limited power and relatively weak associations. There is no clear association between meningioma risks and oral contraceptives, pregnancy, parity, or breastfeeding. Some cohort studies on hormone replacement therapy and meningioma risks in postmenopausal women suggest an increased risk based on statistically significant increases in current users, primarily estrogen-only;[53,54] however, the studies are also conflicting and report no associations with past users or a dose-response relationship.

HISTOLOGY

Central nervous system (CNS) tumors are a heterogeneous group of tumors arising from cells within the CNS. The Central Brain Registry of the United States (CBRUS) lists over 100 histologically separate CNS tumors based on the World Health Organization (WHO) Classification of Tumors of the Central Nervous System using ICD-0-3 codes and the International Classification of Childhood Cancer (ICCC) grouping system for pediatric cancers with distinct clinical features and outcomes.[5] The incidence of CNS tumors varies with age and sex; the most common childhood brain tumor types are pilocytic astrocytomas, embryonal tumors, or malignant gliomas, whereas meningiomas, pituitary tumors, and malignant gliomas are the most frequent adult brain tumors.[5] About one-half of malignant brain tumors in adults are glioblastomas and 30% are diffusely infiltrating lower-grade gliomas. Most histological brain tumors are confirmed by microscopic techniques, with the exception of meningiomas and benign vestibular schwannomas (acoustic neuromas) that are established by radiography. Table 58.2 lists the frequency of CNS tumors based on a 5-year increment in age at diagnosis. The incidence rates for most CNS tumor histological types except for meningiomas are usually higher in men than women.

CNS tumors vary by location (Figure 58.1) and histology (Figure 58.2). Based on Central Brain Registry

TABLE 58.2. Common histological types of central nervous system tumors in the United States by age group. The age-adjusted incidence rates for adult CNS tumors increase from 10.55/100,000 (30% malignant, 70% nonmalignant) at age 20–34 years to 83.75/100,000 (24% malignant, 76% nonmalignant) at age 85 years and older. (Adapted from Ostrom et al.).[5]

Age (Years)	Most Common Tumor	Second Most Common Tumor	Third Most Common Tumor
0–4	Embryonal tumors	Pilocytic astrocytoma	Malignant glioma
5–9	Pilocytic astrocytoma	Malignant glioma	Embryonal tumors
10–14	Pilocytic astrocytoma	Pituitary tumors	Malignant glioma
15–19	Pituitary tumors	Pilocytic astrocytoma	Neuronal and mixed neuronal-glial tumors
20–34	Pituitary tumors	Meningioma	Nerve sheath tumors (e.g., vestibular schwannomas)
35–44	Meningioma	Pituitary tumors	Nerve sheath tumors (e.g., vestibular schwannomas)
45–54	Meningioma	Pituitary tumors	Glioblastoma
55–85+	Meningioma	Glioblastoma	Pituitary tumors

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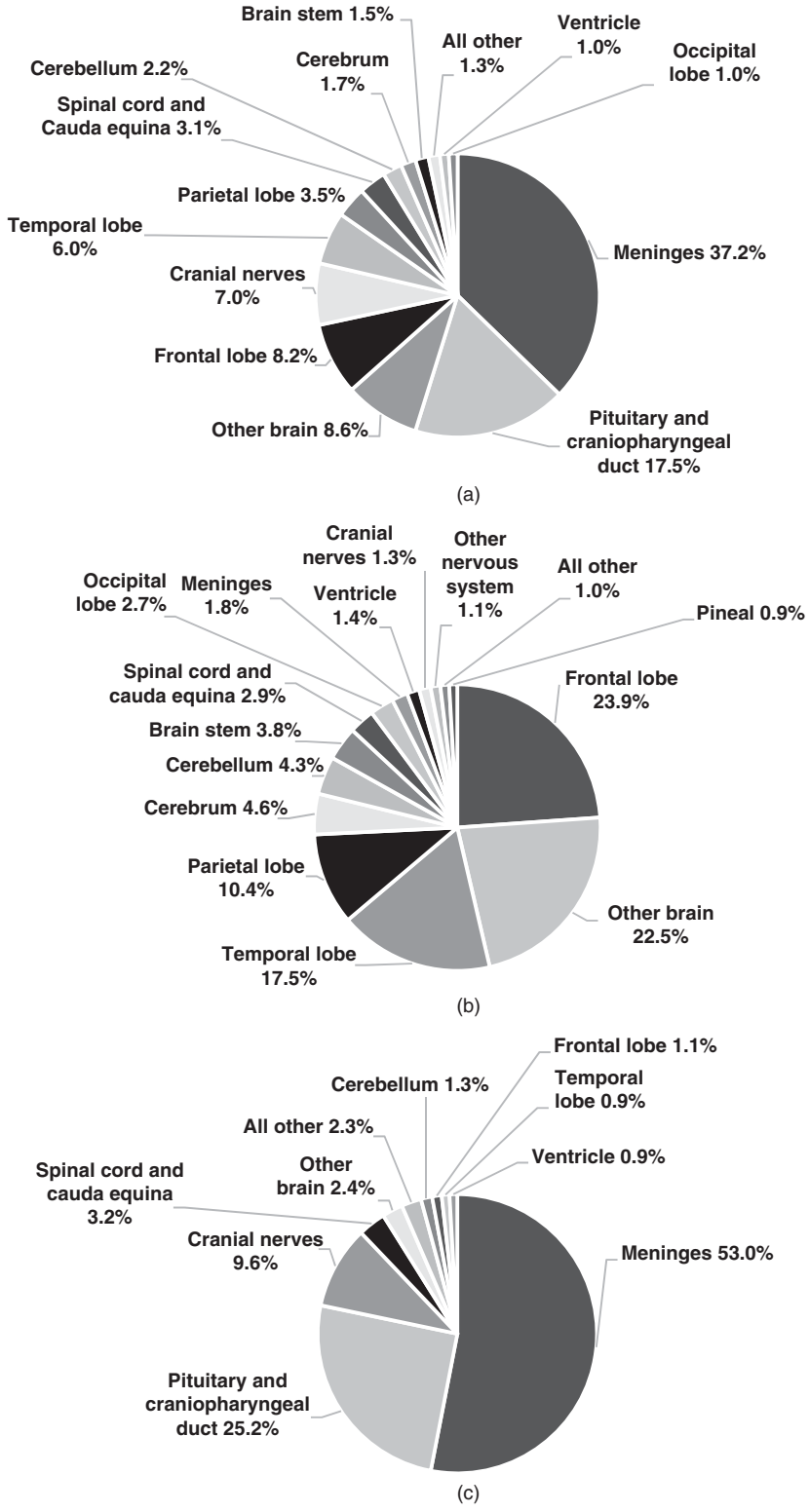


FIGURE 58.1. CNS tumors by location and malignant potential: (a) overall tumor site locations; (b) malignant tumor locations; and (c) nonmalignant tumor locations. The estimated percentage is an approximation of US figures based on the Central Brain Tumor Registry of the United States (CBTRUS) database. (Adapted from Ostrom et al.).[5]

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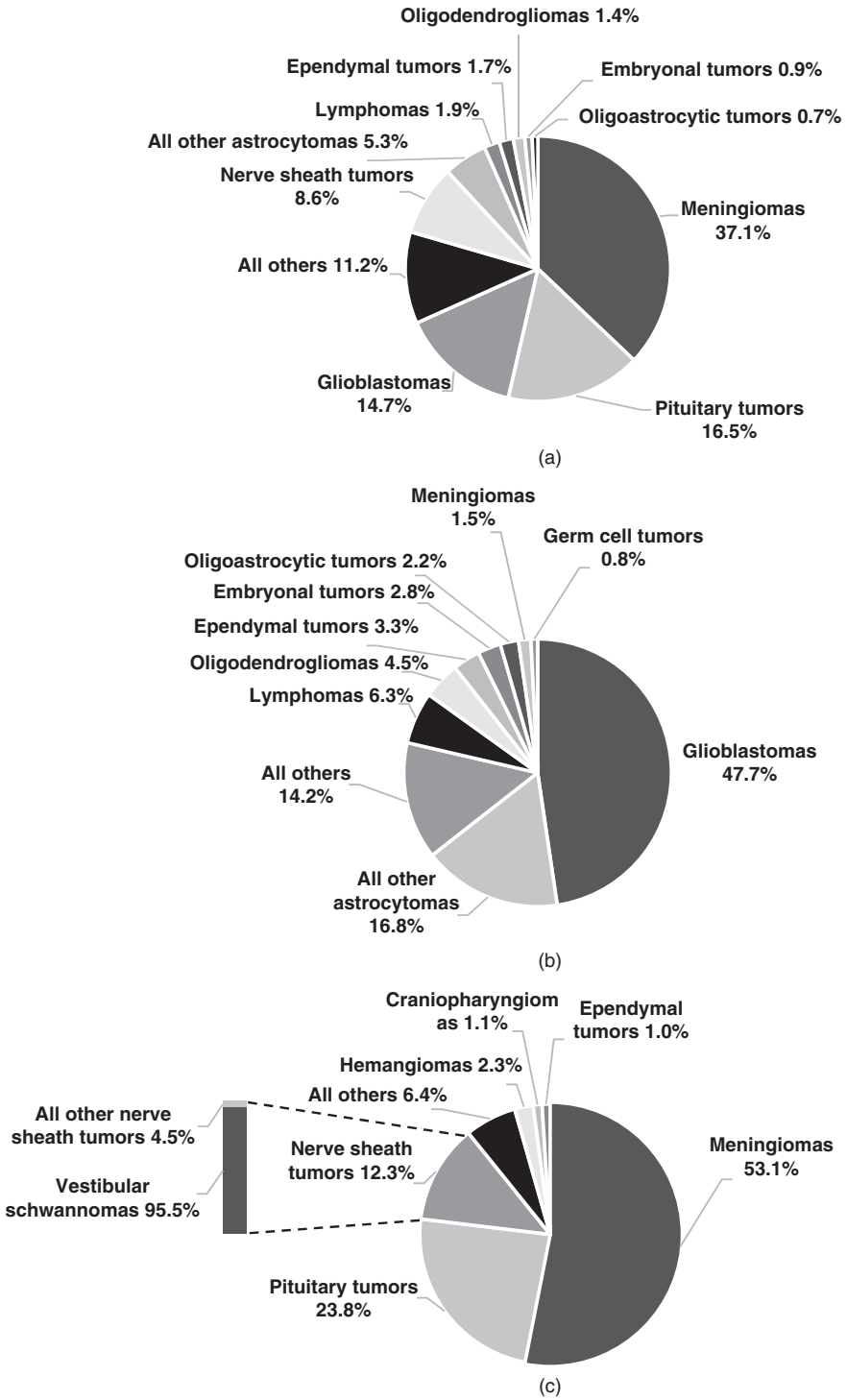


FIGURE 58.2. CNS tumors by histological type and malignant potential: (a) overall tumor sites; (b) malignant tumors; and (c) nonmalignant tumors. The estimated percentage is an approximation of US figures based on the Central Brain Tumor Registry of the United States (CBTRUS) database with a more detailed description of each histological category. (Based on Ostrom et al.).[5]

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of the United States (CBRUS) data, the estimated most frequent overall tumor sites were the meninges (36%), brain (frontal, 8%; temporal, 6%; parietal, 3.5%; occipital, 1%), and pituitary/craniopharyngeal duct (17.5%). The most common malignant tumor locations are frontal (24%), temporal (17.5%), parietal (10%), and occipital (3%), whereas the most common nonmalignant tumor sites involve the meninges (53%), pituitary (24%), and nerve sheaths (12%). The estimated most frequent overall histological tumor types were meningioma (37%), pituitary (16.5%), and glioblastoma (15%). The most common malignant tumor was glioblastoma (48%), whereas the most common nonmalignant tumor type was meningioma (53%). The vast majority of nerve sheath tumors are benign vestibular schwannomas (formerly acoustic neuromas).

Approximately one-half of brain tumors in infants and children are gliomas (e.g., pilocytic astrocytoma, other low-grade gliomas), whereas embryonal tumors (e.g., medulloblastomas, primitive neuroectodermal tumors) account for ~15%; the latter tumors are the most common childhood malignant brain tumors.[12] Medulloblastomas develop in the posterior fossa; primitive neuroectodermal neoplasms are supratentorial tumors.

HOST SUSCEPTIBILITY

Adults with malignant brain tumors rarely have a family history of brain tumors, and almost all brain tumors are sporadic; however, several familial syndromes are associated with increased brain cancer risks. Neurofibromatosis type I (NF1) is the most common familial syndrome associated with brain tumors occurring as an autosomal dominant inherited syndrome in ~1/3,000 live births.[55] In a British study of 448 NF1 patients (221 male and 227 female), followed for a median of 13.6 years, the cumulative malignancy risk by age 50 years was 20% (95% CI: 14–29%) with the incidence of brain and connective tissue tumors significantly increased.[56] The hallmark brain tumors were optic pathway, hemispheric, and brainstem gliomas. Neurofibromatosis type II (NF2) is a less frequent inherited syndrome (i.e., with an occurrence of ~1/40,000 live births). The most common brain tumors in patients with NF2 are vestibular schwannomas and multiple meningiomas.[57] Table 58.3 lists genetic syndromes commonly associated with CNS and other tumors.

CLINICAL FEATURES

The median age at diagnosis of CNS tumors varies with age, as outlined in Table 58.4. Pilocytic astrocytomas

TABLE 58.3. Association of the central nervous system and other tumors with most common genetic syndromes. (Adapted from Hottinger and Khakoo).[57]

Syndrome	CNS Tumor	Chromosome	Gene	Associated Tumors
Cowden disease	Dysplastic cerebellar gangliocytoma	10q23	*PTEN*	Colon polyps, breast and thyroid carcinomas
Li–Fraumeni syndrome	Gliomas, primitive neuroectodermal tumors/medulloblastoma, choroid plexus carcinoma	17p13.1	*TP53*	Breast carcinoma, sarcomas, leukemia, adrenocortical carcinoma
Neurofibromatosis type I (von Recklinghausen disease)	Optic pathway gliomas, astrocytomas, vestibular schwannoma, ependymomas, neurilemmomas, meningiomas, neurofibromas	17q11.2	*NF1*	Pheochromocytoma, gastrointestinal stromal tumors, juvenile chronic myelogenous leukemia, rhabdomyosarcoma
Neurofibromatosis type II (central neurofibromatosis)	Vestibular schwannoma, spinal ependymoma, astrocytomas, meningioma	22q12	*NF2*	None
Tuberous sclerosis	Giant cell astrocytoma	9q34.14, 16p13.3	*TSC1, TSC2*	Multisystem nonmalignant tumors
Von Hippel–Lindau	Cerebellar hemangioblastoma, retinal angiomatosis	3p25	*VHL*	Renal cell carcinomas, pheochromocytomas, endolymphatic sac tumors

Abbreviation: NF1 = neurofibromin 1; *NF2* = neurofibromin 2; *PTEN* = phosphatase and tensin homolog; *TP53* = tumor protein p53; *TSC* = TSC complex subunit 1; *VHL* = von Hippel–Lindau tumor suppressor.

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TABLE 58.4. Median age at diagnosis for specific histological type based on data from Central Brain Tumor Registry of the United States (CBTRUS). (Data adapted from Ostrom et al.).[5]

Histological Type	Origin	Median Age at Diagnosis (Years)
Astrocytoma, anaplastic	Neuroepithelial	53
Astrocytoma, diffuse	Neuroepithelial	48
Astrocytoma, pilocytic	Neuroepithelial	13
Ependymal tumors	Neuroepithelial	44
Glioblastoma	Neuroepithelial	64
Glioneuronal tumors, mixed	Neuroepithelial	27
Oligodendroglioma	Neuroepithelial	43
Oligodendroglioma, anaplastic	Neuroepithelial	49
Choroid plexus tumors	Non-neuroepithelial	19
Craniopharyngioma	Non-neuroepithelial	42
Embryonal tumors	Non-neuroepithelial	9
Germ cell tumors	Non-neuroepithelial	17
Lymphoma	Non-neuroepithelial	65
Meningioma	Non-neuroepithelial	65
Pineal tumors	Non-neuroepithelial	33
Pituitary tumors	Non-neuroepithelial	51

(grade I) occur primarily in children and young adults compared with the third to fourth decade for oligodendrogliomas (grade II) and the sixth to seventh decade for malignant gliomas.

Patients with primary brain tumors present with focal (i.e., related to specific location of tumor) or generalized symptoms (e.g., seizures) over days to years depending on the proliferation rate and tumor location.[58] About 50% of patients with malignant brain tumors present with headache and may have new neurological signs (e.g., seizures, neurocognitive impairment, focal neurological signs) depending on location. Frontal lobe tumors are associated with weakness or dysphasia, whereas parietal tumors cause hemineglect, spatial disorientation, and numbness. Visual field defects may result from occipital, parietal, or temporal neoplasms. Prefrontal lobe, temporal lobe, or carpus callosum lesions may produce cognitive impairment, memory loss, personality changes, and mood disorders. Infratentorial tumors are associated with cranial-nerve palsies, cerebellar dysfunction, and long-tract signs. Progressive headaches worse at night, early morning nausea and vomiting, drowsiness, blurred vision, diplopia, and seizures may indicate increased intracranial pressure.

The overall 1-year survival rate for nonmalignant CNS tumors in the United States is ~94–96% compared with 91–95% for 5-year survival, whereas the overall 1-year survival rate for malignant CNS tumors is ~57% and 32–34% for 5-year survival.[5,59] In Europe, the 5-year survival rate varies substantially between countries and histological types, with an overall average of 85% for benign and ~20% for malignant tumors.[60]

MENINGIOMAS

Meningiomas are the most common adult brain tumor accounting for ~50% of the total number based on data from the Central Brain Tumor Registry of the United States (CBTRUS), with ~24,000 new cases annually.[5] Figure 58.2 displays the distribution of the most common primary brain and other CNS tumors based on their histological type and malignant potential. The estimated incidence of meningiomas is 7.6 cases/100,000 with the incidence ~2- to 3-fold higher in women than men and ~20% higher in African-Americans than Caucasians;[61] however, the exact incidence is difficult to calculate because these neoplasms are often asymptomatic, benign, and discovered incidentally. Worldwide, the age-standardized cerebral meningioma incidence ranges from 1.28–7.80/100,000 inhabitants.[62]

CARCINOGENESIS

Meningiomas arise from arachnoid cap cells within the arachnoid layer of the arachnoid villi lining the skull vault, skull base, and spinal cord. Although most meningiomas (i.e., ~95%) are benign, encapsulated tumors with few genetic aberrations, serious, potentially lethal effects may result from the growth of

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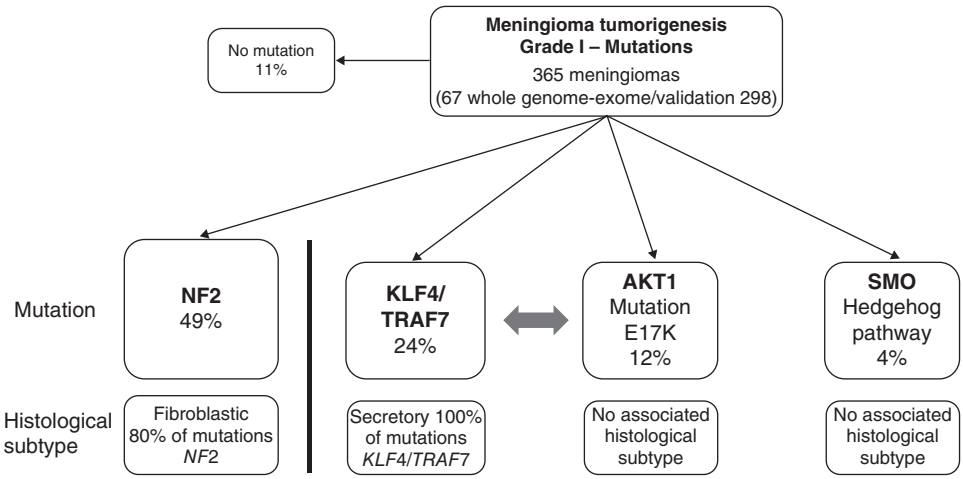


FIGURE 58.3. Benign meningioma molecular genetics and associated histological subtypes. Inactivation of *NF2* (neurofibromin 2) and chromosome 22 loss occur in ~50% of meningiomas. *NF2* expresses the merlin protein involved with cell shape, growth, adhesion, and tumor suppression. Among *NF2*-independent meningiomas, relatively frequent activation mutations include *AKT1* (AKT1 kinase) involved with cell proliferation, differentiation, apoptosis, *SMO* (G protein-coupled receptor for hedgehog proteins in Sonic Hedgehog pathway), and *KLF4/TRAF7*. The latter (Kruppel-like factor 4) modulates differentiation through transcriptional regulation of pluripotent stem cells, whereas tumor necrosis factor receptor-associated factor 7 is a proapoptotic protein and signal transducer for members of the TNF receptor superfamily. (Adapted from Peyre and Kalamarides).[65]

these tumors in certain intracranial locations. The long latency of meningiomas (i.e., 20–30 years post-ionizing radiation), difficult exposure ascertainment from recall bias, substantial subclinical disease in the general population, and detection bias complicate the determination of mechanisms and risk factors. The complexity of genetic aberrations increases with tumor grade. Sporadic meningiomas typically result from ≥1 focal chromosomal deletion commonly involving deletion and inactivation of *NF2* tumor suppressor gene on chromosomal locus 22q12 along with biallelic deletions.[63] Approximately 50% of meningiomas have an inactivation of *NF2*/chromosome 22 loss. *NF2* expresses the merlin protein; this tumor suppressor helps regulate cell adhesion, cell proliferation via induced senescence, and cell size.[64] Figure 58.3 displays the molecular genetics of benign meningiomas along with associated histological subtypes. This gene probably participates in tumor initiation rather than tumor promotion. Among NF2 mutation-negative meningiomas, relatively frequent activation mutations involve *AKT1* (AKT1 kinase) (involved with cell proliferation, differentiation, apoptosis), *SMO* (G protein-coupled receptor for hedgehog proteins in Sonic Hedgehog pathway), and *KLF4/TRAF7* genes. Kruppel-like factor 4 affects cell differentiation via transcriptional regulation of pluripotent stem cells, whereas tumor necrosis factor receptor-associated factor 7 is a proapoptotic protein and signal transducer for members of the TNF receptor superfamily.[65] Progression of benign meningiomas to grade II/III tumors results from activation of oncogenes, inactivation of tumor suppressor genes, and alteration of several molecular pathways (Hedgehog, Wnt, Notch, transforming growth factor β, and insulin receptor singling pathways).[66] Progression also involves: 1) altered DNA methylation of transcription-regulating genes; 2) epigenetic (posttranscriptional) changes including abnormal miRNA expression involving post-transcriptional regulation of gene expression, mRNA translation, and mRNA degradation; and 3) mutant epigenetic modifiers.[67]

EXPOSURE

Current weight of the evidence does not conclusively support increased meningioma risks from cell phone use, organic solvent exposure, or head trauma.[68] The association with the latter is inconsistent, probably from the influence of recall and detection bias. In a case-control study of 105 meningioma cases (mean age = 52 years) and age-matched neighborhood controls, self-reported serious head trauma (i.e., loss of consciousness, dizziness, medical consultation) was associated with meningiomas (OR = 1.9, $n = 39$ cases).[37] A population-based, case-control study of 200 meningiomas and 400 controls reported increased

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meningioma risks in cases with a self-reported history of head trauma (OR = 1.83, 95% CI: 1.28–2.62), particularly head trauma occurring 10–19 years prior to the reference date. The number, but not severity, of head traumas is correlated to meningioma risks. Other studies failed to detect increased meningioma risks in follow-up studies of head trauma patients. Analysis of data from 2,953 patients followed for 29,859 person-years demonstrated a relative meningioma risk of 1.6 (95% CI: 0.3–4.7, $n = 3$ meningiomas) using age-specific incidence rates for meningiomas.[69] Severity and location of head injuries were not related to tumor occurrence. In a Danish cohort of 228,055 residents hospitalized for head trauma (e.g., concussion, fractured skull) and followed up to 17 years (mean = 8 years), the standardized incidence ratio for meningioma after the first year was statistically nonsignificant (SIR = 1.2, 95% CI: 0.8–1.7).[70]

Ionizing Radiation

High-dose ionizing radiation is the established risk factor for meningiomas based on atomic bomb survivors and the 1950s *Tinea Capitis* cohort of Israeli children (~10-fold increase).[71] The follow-up cohort study of Israeli children irradiated for *Tinea capitis* indicated a stronger mean risk for the development of meningiomas (RR = 9.5) compared with gliomas (RR = 2.6).[72] The studies on dental X-rays are relatively weak and inconsistent. The ionizing radiation exposure for atomic bomb survivors in the Life Span Study was relatively low compared with the cohort of *Tinea capitis* radiotherapy. Over 50% of the Japanese cohort were ≥20 years of age at the time of the exposure, with the estimated brain radiation dose exceeding 1 Sv in only 3% of the cohort.[73] The distribution of brain tumor types in the Life Span Study cohort was similar to Japanese population data, with meningioma being the most common tumor type. Of the 88 meningiomas diagnosed from 1958–1995, three were malignant; however, the estimated dose did not correlate to malignancy (two of the three patients had no significant ionizing radiation from the atomic explosion). A Los Angeles-based retrospective case-control study of 101 cases in women and 101 neighbors matched for sex, age within 5 years, and race suggested an association between meningiomas and the frequency of full-mouth dental X-rays in early childhood based on self-reported questionnaires.[37] For the first full-mouth dental X-ray series before 20 years of age, the OR was 4.0 ($P = <0.01$) with no reported confidence limits. The odds ratio for a reported history of >10 full-mouth dental X-rays was 4.9 with $P_{trend} = 0.01$. The supratentorial and infratentorial locations of the meningiomas were similar between cases and controls. The study also reported positive associations for meningiomas with self-reported histories of head trauma (OR = 2.0, $P = 0.01$) and high-nitrite meats (OR = 2.8, $P = <0.01$). In a US population-based case-control study of 1,433 patients with intracranial meningiomas diagnosed at 20–79 years (mean = 57.3 years), neither the association between age at exposure nor the frequency of full-mouth X-rays was statistically significant.[74] However, the study reported elevated odds ratios for ever having a bitewing examination (OR = 2.0, 95% CI: 1.4–2.9) and for more frequent bitewing X-rays in adults, but not in children of <10 years of age. Cosmic radiation is not consistently associated with elevated CNS tumor risks including meningiomas using airline crew as surrogates for increased cosmic radiation exposures.[75,76] In a European and North American mortality study of ~94,000 airline crew members, the mortality rates were statistically similar to the general population for male cockpit crew (SMR = 1.14, 95% CI: 0.83–1.54, $n = 59$ cases), male cabin crew (SMR = 1.25, 95% CI: 0.64–2.18, $n = 16$), and female cabin crew (SMR = 0.95, 95% CI: 0.59–1.46, $n = 29$).[77] A US mortality study of ~6,000 former commercial airline cockpit crew members reported no statistically significant increased CNS tumor mortality (SMR = 1.39, 95% CI: 0.95–1.96, $n = 32$ cases) and a marginally increased standardized rate ratio comparing the highest (≥43.7 mSv) and lowest (<18.1 mSv) cumulative exposure categories (SRR = 3.84, 95% CI: 1.00–14.74, $n = 9$ cases) with a 10-year lag.[78] The CNS tumor risk was not associated with the duration of employment.

Occupation

No specific occupational substances are clearly associated with increased meningioma risks. The INTEROCC study of 1,906 meningioma cases and 5,565 population-based controls from European, Canadian, and New Zealand workers used job-exposure matrices based on interviews to evaluate three exposure indices (ever vs. never; lifetime cumulative exposure; total exposure duration) for 12 chemical substances.[79] This multinational case-control study reported little evidence of associations between meningioma and most of the 12 chemical exposures, including asbestos, animal dust, quartz, wood dust, benzo(a)pyrene, bitumen, diesel/gasoline engine exhaust, polycyclic aromatic hydrocarbons, and sulfur dioxide. The exception was oil mist; for ever-exposure to oil mists, the OR was elevated (OR = 1.57, 95% CI: 1.10–2.22, $n = 51$ exposed

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cases) with statistically significant exposure-response relationships for cumulative exposure ($P_{difference} = 0.01$) and duration of exposure ($P_{difference} = 0.04$). Among women in the highest exposure categories, the data suggested some indication of an exposure-response for asbestos and excess risks for formaldehyde-associated meningioma; however, the associations remain unconfirmed. Although several studies suggest an excess brain cancer incidence in farmers, the studies are inconsistent and primarily involve gliomas; the limited studies and lack of accurate exposure data among the many agricultural products limit conclusions. In a French population-based case-control study of 67 incident meningiomas and 77 matched, unexposed controls, the adjusted OR for the highest quartile of pesticide exposure was 0.65 (95% CI: 0.16–2.55, $n = 9$ cases).[80] Power analysis indicated the study design would identify a detectable meningioma risk of 2.6. The overall adjusted OR for ever- versus never-pesticide exposure was also statistically nonsignificant (adjusted OR = 1.26, 95% CI: 0.61–2.64, $n = 37$ exposed cases), with a detectable overall risk of 1.6 for all brain tumors.

Lifestyle

Although case-control studies on the association between cell phone use and gliomas are conflicting, the results on meningiomas are generally negative.[62] Interpretation of studies associating diet with meningiomas is complicated by the difficulty in obtaining accurate estimation of dietary components (e.g., *N*-nitroso compounds in smoked meats) and analysis of histological types. Currently, no evidence clearly supports an association between diet and meningiomas. The association between smoking and meningioma risks is weak and relatively small, with some studies suggesting a modestly increased risk in men but not women. In a meta-analysis of seven case-control and two cohort studies, the overall pooled estimated meningioma risk comparing ever- and never-smokers was not elevated (RR = 0.95, 95% CI: 0.87–1.05, $P_{difference} = 0.32$, $I^2 = 31.5\%$, $P_{heterogeneity} = 0.177$).[81] Pooled estimates comparing meningiomas in ever- and never-smokers were also statistically nonsignificant for case-control (pooled RR = 1.02, 95% CI: 0.85–1.21, $I^2 = 39.2\%$, $P_{heterogeneity} = 0.144$) and cohort (pooled RR = 0.93, 95% CI: 0.83–1.04, $I^2 = 18.2\%$, $P_{heterogeneity} = 0.269$) studies. Subgroup analyses suggested an increased meningioma risk in men (pooled RR = 1.49, 95% CI: 1.06–2.09, $P_{difference} = 0.02$, $I^2 = 33.6\%$, $P_{heterogeneity} = 0.210$) but not women (pooled RR = 0.86, 95% CI: 0.65–1.13, $I^2 = 66.2\%$, $P_{heterogeneity} = 0.019$). Current and past smoking did not correlate to meningioma risks with substantial heterogeneity.

Medications

The high incidence of meningiomas in women and the presence of hormone receptors (estrogen, progesterone, androgen) in some meningiomas suggest an etiological role for hormones. The most consistent results associate an increased meningioma risk with hormonal replacement treatment in postmenopausal women. There is little statistical evidence of an increased meningioma risk in women using oral contraceptives.[52] Additionally, limited evidence supports an association with parity, breastfeeding, or age at menarche. In a case-control study of 1,127 women of 29–79 years of age with intracranial meningioma and 1,092 age- and location-matched controls, the meningioma risk among premenopausal women was elevated with current use of oral contraceptives (OR = 1.8, 95% CI: 1.1–2.9).[82] Current use of hormone replacement therapy among postmenopausal women was not associated with a significantly increased meningioma risk (OR = 1.1, 95% CI: 0.74–1.67). In a nested case-control analysis using unconditional logistic regression, the study identified 741 meningioma cases aged 12–89 years from the Health Improvement Network UK primary care database along with 10,000 age- and sex-matched controls.[83] Compared with nonusers, meningioma risks were not elevated in women using oral contraceptives (OR = 1.15, 95% CI: 0.67–1.98) or hormone replacement therapy (OR = 0.99, 95% CI: 0.73–1.35). In a Finnish case-control study of 264 meningioma cases in women aged 20–69 years and 505 population-based controls, immunohistological analysis yielded 86.3% progesterone-receptor-positive results in successfully stained specimens and 50% for estrogen receptors.[84] Meningioma risks were not associated with postmenopausal hormonal treatment use (OR = 1.13, 95% CI: 0.76–1.67, $n = 50$ cases) or ever- versus never-contraceptive users (OR = 1.33, 95% CI: 0.94–1.89, $n = 182$ cases).

Diseases

In general, the effect of allergy on brain tumors remains controversial, with the evidence less consistent for meningiomas than gliomas. In a meta-analysis of three case-control and two cohort studies, the pooled RR for an association between self-reported atopy (allergy, asthma, eczema) and meningiomas was not statistically significant (pooled RR = 0.93, 95% CI:

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0.72–1.19, $n = 1{,}070$ cases, $P = 0.57$) with moderate heterogeneity.[85] A meta-analysis of 5 case-control and 2 cohort studies, including 54,391 participants and 2,656 meningiomas, reported a statistically nonsignificant odds ratio comparing meningioma patients with and without allergic conditions (summary OR = 0.91, 95% CI: 0.79–1.04, $P = 0.163$, $I^2 = 31.3\%$).[86] Subanalysis suggested an inverse association between eczema and self-reported allergy (summary OR = 0.75, 95% CI: 0.65–0.87, $P < 0.05$, $I^2 = 0.0\%$). A US population-based case-control consortium study of 1,065 surgically resected meningiomas reported an increased self-reported history of physician-diagnosed allergy (OR = 0.64, 95% CI: 0.51–0.80) compared with controls.[87] The serum IgE concentrations were also lower in cases than in controls. In a German population-based case-control study involving 381 meningioma cases and 1,494 controls, the odds ratio for self-reported allergies (asthma, eczema, hay fever) in meningioma patients was statistically nonsignificant (OR = 0.87, 95% CI: 0.66–1.14).[88]

HISTOLOGY

Approximately 95% of meningiomas are benign encapsulated tumors (grade I) with limited genetic aberrations; only ~1–3% progress to malignant (grade III) tumors.[12] Unlike most cancer histological types, brain tumors are not classically categorized by stages. Table 58.5 lists the central nervous system tumors of meningeal origin. Most meningiomas have mixed histology, with classification depending on the dominant part.

HOST SUSCEPTIBILITY

Genetic studies on factors associated with increased meningioma risk are limited. A meta-analysis of case-control studies using Mantel–Haenszel statistics reported statistical evidence for increased meningioma susceptibility for genetic variants of *MLLT10* (MLLT10 histone lysine methyltransferase DOT1L cofactor), *MTRR* (5-methyltetrahydrofolate-homocysteine methyltransferase reductase), and *MTHFR* (methylenetetrahydrofolate reductase) genes.[90]

Although most meningiomas are sporadic, having a first-degree relative with a meningioma increases the risk of developing this tumor. In a study of data from the Swedish Cancer Registry, the incidence of meningiomas was increased in patients with first-degree relatives with meningiomas (SIR = 2.17, 95% CI: 1.44–3.14, $n = 28$ cases), particularly in patients of <50 years of age at presentation.[91] Using data from the nationwide Swedish and Norwegian databases on familial cancer to calculate standardized incidence ratios, histology-specific population-based familial risks for meningioma were increased for offspring of affected parents (SIR = 1.6, 95% CI: 1.3–2.0).[92] People with certain mutations of the neurofibromatosis gene (*NF2* on chromosome 22) have a significantly increased risk for meningiomas; however, other genes are probably involved in other areas of the chromosomes, including 18q, 10q, 14q, 1p, and 6q.[93]

CLINICAL FEATURES

The most common symptoms associated with meningiomas include headache, sensorimotor impairment, and convulsions. Other symptoms include behavioral disorders and cognitive impairments with sensory changes, particularly common in patients of >70 years of age.[94] The incidence of meningiomas increases steadily with age, as noted in Table 58.4. As a result of their long latency time (i.e., 10–20 years) and subclinical presentation, these tumors are frequently discovered incidentally during imaging for other conditions.[95] The median interval between radiation and diagnosis ranged somewhat longer for meningiomas (17–23 years) than gliomas (9–18 years).[12] The mean latency period for the occurrence of meningiomas in Israeli children irradiated for *Tinea capitis* was ~36 years.[72,96] Table 58.6 displays average latency periods for meningioma patients receiving low, moderate, and high ionizing radiation doses based on a 1991 study by Harrison et al.[97] The latency period is significantly shorter in children irradiated at ≤5 years of age than in adults. Although the latency period tends to decrease with higher ionizing radiation doses, published studies have limited power to detect a statistically significant difference between high- and low-dose radiation and latency.

The clinical severity of these tumors depends primarily on their location.[98] The relatively rare malignant transformation of meningeal neoplasms (i.e., grade I to grade III) produces little mortality except for skull-based tumors. The overall 5-year survival rate of meningiomas is age-dependent, with an average of <70% decreasing with age.[99] Complete resection of meningiomas occurs in <50% of patients, with tumor recurrence developing in ~20% of benign meningiomas.[100] Malignant meningiomas are associated with significant morbidity and mortality because of their high recurrence rates and median disease-free interval of 2 years.

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TABLE 58.5. Central nervous tumors of meningeal origin. (Adapted from International Classification of Diseases for Oncology).[89]

Tumor Type	Classification	Morphology Code[a]
Meningothelial	Meningioma	9530/0
	Meningothelial	9531/0
	Fibrous (fibroblastic)	9532/0
	Transitional (mixed)	9537/0
	Psammomatous	9533/0
	Angiomatous	9534/0
	Microcystic	9530/0
	Secretory	9530/0
	Lymphoplasmacyte-rich	9530/0
	Metaplastic	9530/0
	Clear cell	9538/1
	Chordoid	9538/1
	Atypical	9539/1
	Papillary	9538/3
	Rhabdoid	9538/3
	Anaplastic meningioma	9530/3
Mesenchymal (non-meningothelial)	Lipoma	8850/0
	Angiolipoma	8861/0
	Hibernoma	8880/0
	Liposarcoma (intracranial)	8850/3
	Solitary fibrous tumor	8815/0
	Fibrosarcoma	8810/3
	Malignant fibrous histiocytoma	8830/3
	Leiomyoma	8890/0
	Leiomyosarcoma	8890/3
	Rhabdomyoma	8900/0
	Rhabdomyosarcoma	8900/3
	Chondroma	9220/0
	Chondrosarcoma	9220/3
	Osteoma	9180/0
	Osteosarcoma	9180/3
	Osteochondroma	9210/0
	Hemangioma	9120/0
	Epithelioid hemangioendothelioma	9133/1
	Hemangiopericytoma	9150/1
	Angiosarcoma	9120/3
	Kaposi sarcoma	9140/3
Primary melanocytic	Diffuse melanocytosis	8728/0
	Melanocytoma	8728/1
	Malignant melanoma	8720/3
	Meningeal melanomatosis	8728/3
Uncertain histology	Hemangioblastoma	9161/1

[a] Morphology code of the International Classification of Diseases for Oncology (ICD-0) and Systematized Nomenclature of Medicine: 0 = benign tumor, 1 = low or uncertain malignant potential, 2 = *in situ* lesions, 3 = malignant tumor.

TABLE 58.6. Summary of latency periods for meningioma based on a case series and published cases identified by a literature review by Harrison et al.[97]

Radiation Dose	Latency Average (Range in Years, Cases)	Patient Age at Exposure (Years, Cases)
Low (<10 Gy)	35.2 (12–58, $n = 120$)	44.5 (22–63, $n = 118$)
Moderate (10–20 Gy)	26.1 (2–63, $n = 11$)	32.3 (5–75, $n = 11$)
High (>20 Gy)	19.5 (4–50, $n = 31$)	34.2 (8–63, $n = 30$)

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GLIOMAS

Gliomas represent ~80% of malignant brain tumors, with glioblastomas and WHO grade IV astrocytomas accounting for >50% of malignant brain tumors. Figure 58.2 displays the distribution of the most common primary brain and other CNS tumors based on histological type and malignant potential. Overall, gliomas account for ~24% of adult brain tumors, with ~20,000 new cases annually in the United States. The overall glioma incidence rate is modestly lower in women than men, except for pilocytic astrocytomas (i.e., similar rates). Glioblastoma multiforme is the most frequent and lethal primary malignant CNS tumor in adults, with a US age-adjusted incidence rate of 3.97/100,000 in men and 2.53/10,000 in women.[5] The prevalence rate of glioblastomas is usually higher in whites than in other racial groups.[101] Overall, glioma incidence generally varies little between countries or various ethnic groups in the same country;[16] however, non-Hispanic whites have the highest glioma incidence rate in the United States.[99] The overall age-adjusted incidence of gliomas ranges from ~4.5–6/100,000, whereas the rate for glioblastoma is ~0.6–3.7/100,000.[102] Recent overall glioma rates are relatively stable.

CARCINOGENESIS

The vast majority of glioblastomas (>90%) arise *de novo* (i.e., ~90%), whereas ~5% are secondary glioblastomas progressing from lower-grade astrocytomas.[103] These tumors are molecularly heterogeneous and rapidly infiltrate local brain tissue; the overexpression and downregulation of a wide variety of miRNAs and lncRNAs contribute to tumor proliferation, cell migration, invasion, and neovascularization.[104] For glioblastomas, studies indicate recurrent alteration in several core pathways including: 1) retinoblastoma (RB) signaling involving RB mutation, CD4/CD6 amplification, and CDKN2A/CDKN2A deletion (cyclin-dependent kinase inhibitor 2A/2C); 2) TP53 protein signaling involving CDKN2A deletion, MDM1/MDM4 amplification; and 3) activation of the receptor tyrosine kinase signaling pathway and EGFR/PDGFRA amplification.[105] Molecular markers vary with histological subtypes. EGFR alterations and homozygous CDKN2A deletion characterize the classical glioblastoma subtype, whereas concomitant chromosomal loss of 1q/19q is associated with oligodendromas and improved survival.[106] Mutations of the *TP53* gene are often associated with WHO grade I–II astrocytomas that ultimately develop into secondary glioblastomas and primary glioblastomas *IDH1/2* wildtype.[107] Alteration of telomere maintenance mechanisms also occurs in some gliomas. Point mutations in the telomerase reverse transcriptase (*TERT*) gene promoter occur in ~75% of oligodendrogliomas and primary glioblastomas, resulting in increased telomerase activity. Alternately, ~75% of WHO grade II–III astrocytomas and secondary glioblastomas lengthen telomere by activating telomerase-independent telomere maintenance pathway (telomere binding protein ATRX mutations).[108] Epigenetic events (e.g., CpG island methylation) silence downstream genes. Glioblastomas frequently (i.e., ~40%) hyper-methylate the *MGMT* gene promoter (O^6-methylguanine-DNA methyltransferase) that codes the enzyme responsible for restoring guanine from *O*-6-methylguanine.[104]

At least 25 genomic variants are associated with increased glioma risk. Examination of nine gliomas arising 5–23 years after intracranial radiation indicates significant genetic deviation from spontaneous gliomas based on sequencing of *EGFR* (epidermal growth factor receptor), *K-RAS*, *MTAP*, p16 protein (*MTS1/CDKN2*), *TP53*, and *PTEN* genes.[109] Radiation-induced gliomas differ from spontaneous tumors in several features including higher grades, younger ages, and atypical sites (e.g., cerebellum, suprasellar region). Gene expression is more homogeneous in radiation-induced pediatric tumors than spontaneous glioblastomas, with greater overlap in pilocytic astrocytomas than glioblastomas.[110] Western blot analyses indicated much greater expression of ErbB3, SOX10, and platelet-derived growth factor receptor-alpha proteins in radiation-induced glioblastomas than pediatric glioblastomas.

EXPOSURE

Ionizing Radiation

Ionizing radiation is a well-established risk factor for gliomas in previous cohorts receiving high-dose radiation (atomic bomb survivors, prophylactic cranial irradiation, *Tinea capitis*, and scalp hemangioma radiotherapy). These studies indicate high therapeutic radiation doses are associated with increased CNS cancer risks, particularly gliomas, in children exposed at <5 years of age.[111] A retrospective analysis of 10,834 Israeli children treated with low-dose radiation (mean = 1.5 Gy, range, 0.98–6.0 Gy) reported 21 malignant gliomas in the irradiated group compared with 12 in the sibling/population control group after a 40-year follow-up with increased risk in younger children.[96] The excessive relative risk/Gy decreased

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from 3.56 in children of <5 years of age to 0.47 at the age of ≥10 years ($P_{trend} = 0.037$). The Swedish study of infants of <18 months of age treated with lower mean absorbed intracranial radiation doses (mean = 0.07 Gy, range, 0–11.5 Gy) for scalp hemangiomas also reported increased CNS tumor risks.[112] The standardized incidence ratio (SIR) was 1.42 (95% CI: 1.13–1.75) with an excess relative risk (ERR/Gy) of 2.7 (95% CI: 1.0–5.6). In the Life Span Study of atomic bomb survivors, glioblastomas accounted for 13 cases and anaplastic astrocytoma for 11 cases of the 44 total cases of neuroepithelial tumors;[73] 23% of these tumors were diagnosed postmortem. The age-adjusted incidence rate for gliomas in men was 3.5 compared with 2.0 in women. Several studies of survivors of childhood cancers treated with high-dose radiation reported increased glioma risks, particularly in children of <5 years of age at radiation exposure. In a retrospective cohort (Childhood Cancer Survivor Study) of 14,361 5-year survivors of childhood cancers, the odds ratio for glioma in irradiated children was markedly elevated (OR = 6.78, 95% CI: 1.54–29.7, $n = 40$ gliomas) compared with 160 age-, sex-, and time since original cancer diagnosis-matched controls.[113] The wide confidence limits suggest imprecise odds ratios. After adjustment for radiation dose, glioma risks were not associated with the original cancer diagnosis or chemotherapy. A national, population-based, UK cohort study (British Childhood Cancer Survivor Study) of 17,980 individuals surviving at least 5 years after diagnosis of childhood cancer also reported increased glioma risks.[114] The standardized incidence ratio for gliomas was 10.8 (95% CI: 8.5–13.6). Data associating gliomas with medical radiation exposure from diagnostic head CT scans remain inconclusive, with recent questionnaire-based case-control studies suggesting an inverse association, whereas most nested case-control and cohort studies report no association.[115]

Occupation

Detecting elevated glioma risks from occupational exposures is limited by the rarity of this cancer and methodological difficulties in estimating individual exposures retrospectively. Evidence for an association between occupational exposures and glioma incidence is generally weak and inconsistent.

Job Categories

Studies on glioma risks and job titles or specific chemical exposure have not demonstrated a clear association between glioma incidence and any occupational title or chemical. In the Upper Midwest Health Study using the longest employment duration for 780 cases and 1,156 controls, the engineer/architect group was the only occupational category with a statistically significant age/sex/education-adjusted odds ratio (OR = 2.5, 95% CI: 1.12–5.60, $n = 16$ cases, 10 controls).[116] The OR for food processing workers (e.g., butchers, meat cutters) was statistically marginally significant (adjusted OR = 1.78, 95% CI: 0.99–3.18, $n = 27$ cases, 21 controls), whereas the study did not support elevated glioma risks in farmers, electrical workers (polychlorinated biphenyls), or rubber workers (*N*-nitroso compounds). A subanalysis of 228 primary intracranial glioma cases (50% proxy respondents) in farm pesticide applicators and 417 population-based controls demonstrated no significant positive associations with cumulative years or estimated lifetime cumulative exposure to farm pesticides based on questionnaire responses evaluated by an industrial hygienist.[117] The odds ratio for nonfarm pesticide application was inversely related to glioma risk (adjusted OR = 0.79, 95% CI: 0.52–0.99, $n = 65$ cases, 48% proxy respondents). In the 15 million member Nordic cohort evaluating occupation and cancer, the highest glioma risks among male work categories were other health workers (SIR = 1.30, 95% CI: 1.02–1.64) and military personnel (SIR = 1.24, 1.06–1.44), whereas the SIR was below unity for forestry workers (SIR = 0.78, 95% CI: 0.70–0.88), fishermen (SIR = 0.81, 95% CI: 0.68–0.96), and seamen (SIR = 0.82, 95% CI: 0.71–0.96).[118] For women, the highest SIR was among physicians (SIR = 1.55, 95% CI: 1.02–2.25) with no SIR below unity.

Most studies on pesticide exposures and glioma risk have not observed a positive association, except for a population-based case-control study in southwestern France.[80] In this French study based on an expert review of job titles, the glioma risk in the highest quartile of cumulative pesticide exposure was elevated (OR = 3.21, 95% CI: 1.13–9.11, $n = 11$ cases) compared with unexposed controls, whereas the overall glioma risk was not significantly increased (OR = 1.47, 95% CI: 0.81–2.66, $n = 31$ cases). The Upper Midwest Health Study did not observe a positive association between cumulative pesticide use and glioma risk.[116] The INTEROCC study of 1,800 glioma cases and 5,160 population-based controls from European, Canadian, and New Zealand workers used job-exposure matrices based on interviews to evaluate three exposure indices (ever vs. never; lifetime cumulative exposure; total exposure duration).[119] None of the 10 agents displayed a statistically significant increase in OR or dose-response relationship between glioma risks and cumulative or exposure duration. The substances included asbestos, diesel/gasoline exhaust, formaldehyde, metals, and solvents. A mortality study of

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vinyl chloride polymerization workers reported a SMR of 329 for brain tumors, primarily glioblastomas multiforme.[120] A similar mortality study of workers exposed to vinyl chloride monomer in Great Britain did not detect an increased mortality from brain tumors compared with the general population.[121] Formaldehyde was implicated as a potential source of elevated brain tumor risks in pathologists[122] and embalmers[123] by mortality studies; however, the contribution of formaldehyde to the overall incidence of brain tumors remains unclear.

Electromagnetic Fields

A substantial number of studies explored the incidence of brain tumor/gliomas and a variety of extremely low-frequency magnetic fields (ELFs) exposure markers, including self-reported exposure, measured and modeled estimates, job-exposure matrices, and expert assessments with mixed results. The small study sizes, poor occupational history, and rarity/heterogeneity of glioma subtypes complicate the interpretation of these studies. A meta-analysis of 22 studies reported a small but statistically significant increase in glioma risk in workers exposed to ELFs (estimated pooled RR = 1.18, 95% CI: 1.1–1.26, $n = 22$ studies). The cumulative meta-plot demonstrated no clear exposure-response. In the INTEROCC study of 1,939 glioma cases and 5,404 population controls, glioma risk was not associated with average, maximum, or lifetime cumulative ELF exposure as measured by job-exposure matrix. The odds ratio for the highest cumulative ELF exposure group of ≥7.5 μT-years was 0.80 (95% CI: 0.63–1.00, $P_{\text{trend}} = 0.08$).[124] Although the glioma risk for the highest cumulative exposure group in the most recent duration category (1–4 years) was statistically significant (OR = 1.67, 95% CI: 1.36–2.07, $P_{\text{trend}} = <0.0001$), the longer ELF exposure groups did not demonstrate elevated glioma risks. In a retrospective US study of 489 glioma cases and 799 hospital-based controls using a job-exposure matrix supplemented with job-specific questionnaires, glioma risks were not associated with peak exposure ($P_{\text{trend}} = 0.19$), duration ($P_{\text{trend}} = 0.32$), lifetime average ($P_{\text{trend}} = 0.68$), or cumulative ($P_{\text{trend}} = 0.23$) exposures. None of the trends suggest a dose-response relationship.[42]

Lifestyle

Smoking

Most studies on brain cancer and smoking analyze glioma risks. In a meta-analysis of 6 cohort and 11 case-control studies using multivariate-adjusted risk estimates comparing ever- versus never-smokers, the overall odds ratio was 1.06 (95% CI: 0.97–1.15). For cohort studies, the OR was 1.10 (95% CI: 1.01–1.20) and 1.00 (95% CI: 0.88–1.15) for case-control studies.[125] The limited number of studies indicates no dose-response relationship between smoking and glioma risks. A meta-analysis of seven case-control studies demonstrated no significant association between smoking and glioma risks (OR = 0.96, 95% CI: 0.86–1.07, $P_{\text{difference}} > 0.05$, $I^2 = 48.0\%$, $P_{\text{heterogeneity}} = 0.073$).[126]

Mobile Phone Use

The IARC lists radiofrequency electromagnetic fields, including exposure from wireless phones as a suspected carcinogen with limited human evidence (Group 2B), primarily involving gliomas and, to a lesser extent, benign vestibular schwannomas (acoustic neuromas). Several,[19] but not all,[127] case-control studies, biological data, animal experiments, brain tumor incidence trends, and reviews suggest that 10–15 years of mobile phone use have not significantly increased glioma risks for regular cell phone users, particularly for fast-growing tumors (e.g., malignant glioma). A European study reported no clear trend indicating a change in the annual age-standardized glioma incidence rates from 1979–2008 in adults from Nordic countries.[128] In simulations, the observed time trends were incompatible with relative risks for all users of 2.0 for an induction of ≤15 years, 1.5 for <10 years, and 1.2 for <5 years. The trends were also incompatible with a relative risk of 2.0 among heavy cell phone users over <5 years. Another study estimated the projected glioma incidence rates using the combined relative risks reported in the 2010 Interphone study and the 2011 Hardell et al. Swedish study[129] with US incidence rates adjusted for age, registry, sex; mobile phone use; and latency periods.[130] The latter study was used by the IARC to reclassify mobile phone exposure. Similar to the previous study, the elevated glioma risks associated with mobile phone use reported by the Swedish study were 40% higher than the observed US incidence rates; however, US data could be consistent with the modest excess glioma risks reported in the Interphone study.

Current evidence has not supported a dose-response relationship between long-term cell phone use and gliomas, particularly when successive rollouts of cell phone technologies have reduced ELF and radiofrequency exposures. In a UK prospective cohort (Million Women Study) of cancer in 791,710 middle-aged women comparing long-term cell phone use (>10 years) with never-cell phone users as controls, the estimated glioma risk for the long-term users was not elevated

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(RR = 0.78, 95% CI: 0.55–1.10, $P_{\text{difference}} = 0.16$).[131] Furthermore, time trends in glioma incidence are not compatible with the estimated risks in positive case-control studies. An Israeli study of low-grade glioma incidence reported a statistically significant decrease in glioma risks during the 30 years after the introduction of cell phone technology in 1980.[132] The relative short observation period for slow-growing tumors (e.g., meningiomas, vestibular schwannomas) limits definitive conclusions regarding the causal connection between these tumors and long-term cell phone use including cell phone use in childhood. (See Mobile Phone section under Carcinogenesis in the Nonionizing Radiation – Radiofrequencies chapter for a detailed discussion.)

Reproductive Factors

Reproductive factors are not consistently associated with increased glioma risks. Although the NIH-AARP Diet and Health Study reported that older age at menarche (≥ 15 years) was associated with increased glioma risk (HR = 1.67, 95% CI: 1.03–2.69, $n = 23$ glioma cases), other reproductive factors demonstrated no association with glioma risks, including age at first live birth, parity, age at menopause, or ever-oral contraceptive use (adjusted HR = 0.74, 95% CI: 0.53–1.05, $n = 53$).[133] The European Prospective Investigation into Cancer and Nutrition (EPIC) study reported glioma risks were not associated with reproductive factors (age at menarche, parity, age at first birth, menopausal status, or age at menopause).[134] There were no exposure-response relationships for any of these risk factors.

Medications

Several studies suggest a reduced glioma risk with hormone replacement therapy and oral contraceptive use, along with an increased risk with later menarche and menopause;[52] however, the risk estimates from these studies usually do not reach statistical significance, particularly the higher-quality studies (nested case-control, cohort). Examination of data from the NIH-AARP Diet and Health Study on 225,355 women aged 50–71 years identified 174 cases of primary gliomas during a median follow-up of 7.5 years.[133] The reported hazard ratio comparing ever- versus never-use of menopausal hormone replacement therapy was 0.99 (95% CI: 0.63–1.56, $n = 61$ glioma cases) based on baseline questionnaires. Duration of use did not display an exposure-response relationship for oral contraceptives ($P_{\text{trend}} = 0.22$) or hormone replacement therapy ($P_{\text{trend}} = 0.22$). The European Prospective Investigation into Cancer and Nutrition (EPIC) study identified 193 glioma cases during a mean follow-up time of 8.4 years.[134] Current oral contraceptive use was not associated with increased glioma risks (adjusted HR = 0.76, 95% CI: 0.49–1.19, $n = 34$ glioma cases) using never-users as referents. Glioma risks in current postmenopausal hormone replacement therapy users were also not statistically different from those in never-use referents (adjusted HR = 1.23, 95% CI: 0.53–2.83, $n = 8$ glioma cases). There were no exposure-response relationships for these risk factors. In the San Francisco Bay Area Adult Glioma Study of 619 women with gliomas and 650 population-based controls using never-users as referents, glioma risks were inversely associated with self-reported ever-use of oral contraceptives (adjusted OR = 0.72, 95% CI: 0.53–0.99, $n = 405$ glioma cases) and postmenopausal hormone therapy (adjusted OR = 0.50, 95% CI: 0.25–0.98, $n = 47$ glioma cases).[135] A nested case-control study using data from population-based Danish registries on women aged 55–84 years identified 658 glioma cases and 4,350 controls.[136] Using never-users as referents, the glioma risk for ever-hormone replacement therapy was not elevated (adjusted OR = 0.9, 95% CI: 0.8–1.1, $n = 247$ cases). Glioma risks were also not statistically different than referents for overall long-term use (≥10 years), hormone replacement use (adjusted OR = 1.1, 95% CI: 0.7–1.7, $n = 26$ cases), estrogen-only use (adjusted OR = 1.6, 95% CI: 0.9–2.6, $n = 25$ cases), or progestogen use (adjusted OR = 2.2, 95% CI: 0.9–5.5, $n = 8$). None of the trends for cumulative exposure were statistically significant.

Diseases

Allergies

Although most studies suggest a modestly inverse glioma risk (i.e., ~40%) with self-reported allergies (asthma, eczema, food allergies, hay fever), these studies do not consistently report a dose-response relationship with duration, timing, antihistamine use, or allergy biomarkers.[102] Imprecise risk estimates, heterogenous allergy descriptions, self-reported histories, and varying outcome measures complicate the interpretation of positive studies. Several case-control studies report a modest inverse relationship between glioma risks and self-reported allergies, frequently with substantial proxy respondents. Using controls with no allergies, analysis of data from five INTERPHONE study countries (Australia, Canada, France, Israel, New Zealand) demonstrated an inverse association between any allergy and high-grade glioma risk (adjusted OR = 0.69, 95% CI: 0.55–0.87, $n = 123$

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cases, 17% proxy respondents). The inverse relationship with low-grade gliomas was not statistically significant (adjusted OR = 0.77, 95% CI: 0.57–1.04, $n = 72$ cases).[137] The exposure-response relationship for duration of allergy was stronger for hay fever than eczema or asthma. In a German population-based case-control study of 366 glioma cases and 1,494 nonallergic controls, the odds ratio between glioma risks and self-reported allergies was not statistically significant (OR = 0.92, 95% CI: 0.70–1.22, 3% proxy respondents).[88] Glioma risks were stronger, albeit statistically nonsignificant, for self-reported asthma (adjusted OR = 0.65, 95% CI: 0.36–1.1, $n = 15$ cases) than other allergic conditions. In a meta-analysis of eight observational (six case-control, two cohort) studies, the pooled glioma relative risk comparing an allergy history with nonallergic controls was inverse (adjusted RR = 0.61 (95% CI: 0.55–0.67, $P_{\text{difference}} < 0.001$, $P_{\text{heterogeneity}} = 0.51$).[85] The relationship between asthma and eczema was similarly inverse. The proxy response rate ranged from 2–34%.

Diabetes

The results of studies on the relationship between diabetes and glioma risks are highly variable, with risks including inverse, null, and positive results In a pooled analysis of US and Chinese data from 5 nested case-control and 2 case-control studies involving glioma cases and 2,195 controls, a self-reported diabetes history (type I/II) was inversely associated with glioma risk (adjusted OR = 0.58, 95% CI: 0.40–0.84) compared with nondiabetic controls.[138] The relationship was stronger for participants with BMI $< 25\,kg/m^2$. The relationship was no longer inverse in obese participants with BMI $\geq 30\,kg/m^2$ (OR = 1.16; 95% CI: 0.61–2.20). A cross-sectional case-control study of 1,144 glioblastoma cases and 969 age- and sex-matched controls assessed the association between diabetes type II, hyperlipidemia, and obesity with glioblastoma incidence.[139] Glioblastoma risks were not associated with diabetes type II (adjusted HR = 0.9, 95% CI: 0.7–1.2), hyperlipidemia, or obesity $\geq 30\,kg/m^2$ (adjusted OR = 0.7, 95% CI: 0.5–1.0, $P_{\text{difference}} = 0.72$).

HISTOLOGY

The origin of gliomas remains unclear. These tumors are highly heterogeneous, suggesting different molecular subtypes may arise from different cellular origins or develop distinct molecular alterations during carcinogenesis.[140] Some experimental evidence suggests adult neural stem and progenitor cells located in the subventricular zone, subcortical white matter, and dentate gyrus of the hippocampus are potential sites of origin for glioblastomas.[141] The most frequent locations for gliomas are the frontal (~26%), temporal (~20%), and parietal (~12%) lobes, whereas these tumors are rare in the spinal cord (~4%), brainstem (~4%), occipital lobe (~3%), and cerebellum (~3%).[142] The World Health Organization (WHO) restructured the classification of diffuse gliomas, medulloblastomas, and other embryonal tumors to incorporate new entities defined by histology and molecular features in 2016. Previously, histological classification depended on hematoxylin and eosin-stained microscopic features, ultrastructural characterization, and immunohistochemical expression of lineage-associated proteins.[143] The use of molecular markers improves the separation of biologically distinguishable groups with different clinical outcomes. In the case of discordant results, genotype has precedence over histological phenotype.[144] Table 58.7 displays the updated WHO classification of neuroepithelial CNS tumors (gliomas) with the morphology codes.

The most frequent histological types of adult gliomas are astrocytomas (grades I–IV), oligodendrocytic mixed, and oligoastrocytomas (grades II–III). Malignant gliomas arise from neuroepithelial tissue in the interstitium of the central nervous system. Tumors of neuroepithelial origin from glial or precursor cells include astrocytomas, glioblastoma multiforme, ependymoma, oligodendroglioma, astroblastoma, oligoastrocytoma, choroid plexus tumors, neuroblastomas, pineal tumors, and medulloblastomas (see Table 58.2).[145] The latest WHO histological classification combines phenotypic and genotypic categories by integrating the histopathological name followed by genetic features (e.g., glioblastoma, *IDH*-wildtype). Glioma histology ranges from benign and surgically curable pilocytic astrocytoma tumors (circumscribed gliomas, grade I) to highly aggressive diffusely infiltrating gliomas (glioblastomas, grade IV). Gliomas are separated into circumscribed gliomas (pilocytic astrocytomas, pleomorphic xanthoastrocytomas; WHO grade I) and diffusely infiltrating gliomas (astrocytic or oligodendroglial; WHO grades II–IV) based on growth patterns and IDH (isocitrate dehydrogenase) status. Diffuse gliomas range from low-grade astrocytomas (WHO grade II) to glioblastomas (WHO grade IV). Gliomas account for ~75 of malignant brain tumors with ~1/2 of these being glioblastomas.[5]

Glioblastoma multiforme (astrocytoma grades III and IV) accounts for the majority of malignant tumors in older age groups. The incidence of other gliomas decreases with age. Endothelial proliferation and necrosis characterize the histology of glioblastomas, resulting

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TABLE 58.7. Central nervous system (CNS) tumors of neuroepithelial origin based on the 2016 World Health Organization (WHO) CNS classification upgraded with 2021 WHO changes. This 5th edition of WHO CNS tumor classifications introduces major changes based on histology, immunohistochemistry, and some novel molecular diagnostic technologies (e.g., DNA methylome profiling). The three tumors with a superscripted "a" are provisional classifications requiring more evidence to be accepted as distinct disease entities. (Adapted from Louis et al.).[143]

Gliomas, glioneuronal tumors, and neuronal tumors
Adult-type diffuse gliomas
Astrocytoma, IDH-mutant
Glioblastoma, IDH-wildtype
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted
Pediatric-type diffuse low-grade gliomas
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered
Angiocentric glioma
Polymorphous low-grade neuroepithelial tumor of the young
Diffuse low-grade glioma, MAPK pathway-altered
Pediatric-type diffuse high-grade gliomas
Diffuse midline glioma, H3 K27-altered
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Diffuse hemispheric glioma, H3 G34-mutant
Infant-type hemispheric glioma
Circumscribed astrocytic gliomas
Pilocytic astrocytoma
High-grade astrocytoma with piloid features
Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma
Chordoid glioma
Astroblastoma, *MN1*-altered
Glioneuronal and neuronal tumors
Ganglioglioma
Desmoplastic infantile ganglioglioma / desmoplastic infantile astrocytoma
Dysembryoplastic neuroepithelial tumor
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters[a]
Papillary glioneuronal tumor
Rosette-forming glioneuronal tumor
Myxoid glioneuronal tumor
Diffuse leptomeningeal glioneuronal tumor
Gangliocytoma
Multinodular and vacuolating neuronal tumor
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
Central neurocytoma
Extraventricular neurocytoma
Cerebellar liponeurocytoma

(Continued)

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TABLE 58.7. (Continued)

Ependymal tumors
Supratentorial ependymoma
Supratentorial ependymoma, ZFTA fusion-positive
Supratentorial ependymoma, YAP1 fusion-positive
Posterior fossa ependymoma
Posterior fossa ependymoma, group PFA
Posterior fossa ependymoma, group PFB
Spinal ependymoma
Spinal ependymoma, *MYCN*-amplified
Myxopapillary ependymoma
Subependymoma
Choroid plexus tumors
Choroid plexus papilloma
Atypical choroid plexus papilloma
Choroid plexus carcinoma
Embryonal tumors
Medulloblastoma
Medulloblastomas, molecularly defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated and *TP53*-wildtype
Medulloblastoma, SHH-activated and *TP53*-mutant
Medulloblastoma, non-WNT/non-SHH
Medulloblastomas, histologically defined
Other CNS embryonal tumors
Atypical teratoid/rhabdoid tumor
Cribriform neuroepithelial tumor[a]
Embryonal tumor with multilayered rosettes
CNS neuroblastoma, *FOXR2*-activated
CNS tumor with *BCOR* internal tandem duplication
CNS embryonal tumor
Pineal tumors
Pineocytoma
Pineal parenchymal tumor of intermediate differentiation
Pineoblastoma
Papillary tumor of the pineal region
Desmoplastic myxoid tumor of the pineal region, *SMARCB1*-mutant
Cranial and paraspinal nerve tumors
Schwannoma
Neurofibroma
Perineurioma
Hybrid nerve sheath tumor
Malignant melanotic nerve sheath tumor
Malignant peripheral nerve sheath tumor
Paraganglioma

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TABLE 58.7. (Continued)

Meningiomas
Meningioma
Mesenchymal, non-meningothelial tumors
Soft tissue tumors
Fibroblastic and myofibroblastic tumors
Solitary fibrous tumor
Vascular tumors
Hemangiomas and vascular malformations
Hemangioblastoma
Skeletal muscle tumors
Rhabdomyosarcoma
Uncertain differentiation
Intracranial mesenchymal tumor, *FET-CREB* fusion-positive[a]
CIC-rearranged sarcoma
Primary intracranial sarcoma, *DICER1*-mutant
Ewing sarcoma
Chondro-osseous tumors
Chondrogenic tumors
Mesenchymal chondrosarcoma
Chondrosarcoma
Notochordal tumors
Chordoma (including poorly differentiated chordoma)
Melanocytic tumors
Diffuse meningeal melanocytic neoplasms
Meningeal melanocytosis and meningeal melanomatosis
Circumscribed meningeal melanocytic neoplasms
Meningeal melanocytoma and meningeal melanoma
Hematolymphoid tumors
Lymphomas
CNS lymphomas
Primary diffuse large B-cell lymphoma of the CNS
Immunodeficiency-associated CNS lymphoma
Lymphomatoid granulomatosis
Intravascular large B-cell lymphoma
Miscellaneous rare lymphomas in the CNS
MALT lymphoma of the dura
Other low-grade B-cell lymphomas of the CNS
Anaplastic large cell lymphoma (*ALK*+/*ALK*−)
T-cell and NK/T-cell lymphomas

(Continued)

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TABLE 58.7. (Continued)

Histiocytic tumors
Erdheim-Chester disease
Rosai-Dorfman disease
Juvenile xanthogranuloma
Langerhans cell histiocytosis
Histiocytic sarcoma
Germ cell tumors
Mature teratoma
Immature teratoma
Teratoma with somatic-type malignancy
Germinoma
Embryonal carcinoma
Yolk sac tumor
Choriocarcinoma
Mixed germ cell tumor
Tumors of the sellar region
Adamantinomatous craniopharyngioma
Papillary craniopharyngioma
Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocytoma
Pituitary adenoma/PitNET
Pituitary blastoma
Metastases to the CNS
Metastases to the brain and spinal cord parenchyma
Metastases to the meninges

Abbreviations: CNS, central nervous system; IDH, isocitrate dehydrogenase; NK, natural killer; PitNET, pituitary neuroendocrine tumor; SHH, sonic hedgehog.
[a] Provisional classification.

in grade IV classification. Glioblastomas typically infiltrate more than one lobe with both multifocal (multiple areas with a clear path of spread from one lesion to another, up to ~30%) and multicentric (multiple lesions with no clear path of spread, ~5%) lesions.[146]

HOST SUSCEPTIBILITY

Family history of brain cancer is not an important factor in the vast majority of brain tumors.[147] The incidence of glioma in patients with first-degree relatives is only slightly elevated, with glioma being sporadic as most gliomas occur in families without a known predisposing hereditary disease.[148] A Swedish population-based study of all astrocytomas occurring from 1985–1993, demonstrated an ~3-fold increased incidence in patients with first-degree relatives with astrocytomas, primarily in the younger cohort.[149] A Swedish population-based study using segregation analysis of 807 first-, second-, and third-degree relatives of glioma patients estimated familial gliomas occur in ~5% of glioma cases, with 1% possibly having an autosomal dominant inheritance.[150] Mendelian disorders include neurofibromatosis, Li–Fraumeni syndrome, and tuberous sclerosis.

Genome-wide association studies identify seven common heritable risk alleles associated with increased glioma risks. Four of these variant genes (*EGFR*, *TERT*, *RTEL1*, *TP53*) contribute to the development of all glioma grades and histological types, including oligodendroglial tumors, whereas other variant genes (*CCDC26*, *CDKN2B*, *PHLDB1*) affect specific grades, histology, and molecular subtypes.[151] Table 58.8 displays the seven common heritable gene variants associated with increased glioma risks.

CLINICAL FEATURES

The median interval between radiation exposure and diagnosis ranged from 9–18 years for gliomas in children

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TABLE 58.8. Common heritable gene variants associated with increased risks identified by genome-wide association studies. Some of these variants are also associated with other cancer sites including *TERT* (↑colon, lung, pancreas, and testis cancers) and *TP53* (↑ basal cell carcinoma, colorectal adenoma, prostate neoplasms). (Adapted from Ostrom et al.).[102]

Gene	Gene Function	Chromosome Location	Associated Glioma Subtype
CCDC26	Modulated cell differentiation/death	8q24.21	Oligodendromas, astrocytomas IDH-mutant
CDKN2B	Encodes cyclin-dependent kinase inhibitor	9q21.3	Astrocytomas WHO II-IV
EGFR	Produces transmembrane receptor	7p11.2	All
PHLDB1	Produces protein	11q23.3	IDH-mutant gliomas
RTEL1	Maintains stability/length telomeres	20q13.33	All
TERT	Maintains telomere ends	5p15.33	All
TP53	Encodes tumor suppressor protein	17p13.1	All

Abbreviations: CCDC26 = coiled-coil domain containing 26; *CDKN2B* = cyclin-dependent kinase inhibitor 2B; *EGFR* = epidermal growth factor receptor; IDH = isocitrate dehydrogenase; *PHLDB1* = Pleckstrin Homology Like Domain Family B Member 1; *RTEL1* = regulator of telomere elongation helicase; *TERT* = telomerase reverse transcriptase; *TP53* = tumor protein p53.

irradiated with relatively high ionizing radiation during radiotherapy.[12] The clinical course depends on tumor location and the extent of infiltration into brain tissue along with the amount of edema and tissue destruction. Seizures are a common feature of glioblastomas as a presenting symptom and during the disease course. Headaches occur in <1/3 of glioblastoma patients, typically occurring at night or early in the morning as a dull pain.[152] Increased intracranial pressure may cause nonspecific symptoms (e.g., nausea, vomiting, fatigue, dizziness, cognitive impairment). Painful nerve root compression and myelitis may result from leptomeningeal dissemination.[141] Most (i.e., 75–90%) recurrences of glioblastomas occur within 2–4 cm of the original border.[153] These tumors rarely metastasize, with the most common sites being the lung, pleura, lymph nodes, liver, and bone.

For prognostic purposes, gliomas frequently are divided into the following three categories based on median survival rates: 1) low-grade astrocytoma (5–8 years), 2) anaplastic astrocytoma (1.5–2.5 years), and 3) glioblastoma multiforme (1 year).[154,155] Survival depends on the histological type and grade ranging from 90%, 10-year survival for pilocytic astrocytomas to <5%, 5-year survival rate for glioblastomas; the latter tumor has one of the worst survival rates of all human cancers (i.e., 37% 1-year survival).[59] In a systematic review of 162 glioblastoma cases published from 1950–2014, the 10-year survival rate was 0.71% with a median age at diagnosis of 31.1 ± 11.1 years.[156] Several genetic and epigenetic markers affect survival, most commonly isocitrate dehydrogenase 1/2, 1p19q codeletion, *O*-6-methylguanine-DNA methyltransferase (*MGMT*) methylation, and glioma-CpG island methylator (G-CIMP) phenotype.[27] Substantial differences in glioblastoma patient survival and incidence exist between sexes. The survival is shorter and the incidence higher (male/female ≅ 1.6) in men than women. These differences occur across all age groups suggesting sex hormones alone are not entirely responsible for the difference. Glioblastoma transcriptome and outcome data suggest that these differences result at least in part from differences in tumor signaling pathway abnormalities (cell cycle in men vs. integrin signaling in women).[157]

PITUITARY TUMORS

Pituitary tumors account for ~15% of adult CNS tumors, with an estimated 11,000 new tumors annually (i.e., ~3.8/100,000); overall, pituitary tumors are more common in women than men.[5] Nonfunctioning pituitary adenomas account for 14–54% of pituitary adenomas, with a prevalence of 7–41/100,000 population.[158] The standardized annual incidence rate ranges from 0.6–2.3/100,000, with peak occurrence in the fourth to eighth decade. Many of these tumors are incidental with no obvious clinical impact. Pituitary incidentalomas represent mostly nonfunctioning pituitary adenomas discovered incidentally during radiological imaging or autopsy; the prevalence of these tumors ranges from 9–21% of nonfunctioning pituitary adenomas.[158] The relatively higher incidence of pituitary adenomas in autopsy series than in cancer registries suggests these tumors may be under-reported in the clinical literature.[159]

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CARCINOGENESIS

The anterior pituitary gland is the master endocrine gland that regulates multiple target glands by synthesizing and secreting multiple hormones into the blood, including prolactin, adrenocorticotropic (ACTH), growth (GH), thyroid-stimulating (TSH), follicle-stimulating (FSH), and luteinizing hormones. Pituitary tumors are monoclonal, mostly benign adenomas that arise from differentiated hormone-expressing cells and display features of premature proliferative arrest.[160] These tumors are often non-secreting benign neoplasms (nonfunctioning pituitary adenomas, NFPAs). However, adenomas may secrete one or more hormones (ACTH, GH, TSH, glycoprotein gonadotroph subunits) producing symptoms specific to the combination of one to three hypersecreted hormones.

Early events involve chromosome instability, multiple molecular alterations, epigenetic changes (p16 promoter methylation), and aneuploidy.[161] Gene mutations in sporadic pituitary tumors are not well defined. *PTTG* (pituitary tumor-transforming gene) overexpression occurs in a variety of tumors, including breast, colon, esophagus, ovary, prostate, and thyroid, as well as the central nervous system. *PTTG* gene inhibits sister chromatid separation as well as expression and secretion of angiogenic and metastatic factors, resulting in cell proliferation, chromosomal destabilization, and cell transformation.[162] Oncogene activation, tumor suppressor gene silencing, and epigenetic changes (hypermethylation-mediated DNA promoter silencing, miRNA-induced histone modification) produce a variety of changes in gene expression including: 1) alteration of cell-cycle gene expression (e.g., cyclin-dependent kinases, CDKs; retinoblastoma-associated protein, RB); 2) activation of specific pituitary oncoproteins; 3) loss of pituitary suppressor factors including CDK inhibitors *INK4a/ARG* (p15, p16, p18) and CIP/KIP inhibitors (p21, p27, p57); and 4) defective signaling transduction pathways (e.g., *GNAS* gene encoding G protein α subunit).[163,164] The rare mutations in cyclins and cyclin-dependent kinase inhibitors in human pituitary tumors suggest compromise of the cell-cycle regulatory protein expression and stability occurs upstream in signaling pathways.

Gene expression differs dramatically between pituitary adenomas and carcinomas. In a study of gene expression in an ACTH pituitary carcinoma metastatic to the liver and four pituitary adenomas using Affymetrix GeneChip HGU-133A-oligonucleotide arrays, the adenomas overexpressed 2,057 genes and underexpressed 2,241 genes compared with the carcinoma.[165] Common cancer-associated oncogene (*TP53*, *RB1*) and tumor suppressor (RAS-family) mutations are unusual during the unique indolent growth of pituitary adenomas. Mutations of the *HRAS* genes are reported rarely in invasive prolactinomas, whereas distant metastatic pituitary carcinomas typically overexpress p53 protein compared with adenomas.[166,167] Table 58.9 displays some of the genetic alterations present in pituitary tumors along with their function, type of action, and common tumor type. The most important oncogene in sporadic pituitary tumors is the GNAS (GNAS complex locus) gene mutation that normally encodes a stimulatory guanine-binding protein subunit (G protein$_{\alpha}$). The mutation dysregulates hypothalamic GH-releasing hormone in 40% of somatotrophinomas. Mechanisms associated with cessation of cell proliferation include G1 cell-cycle arrest with DNA damage and p53-induction of CDK inhibitor p21 that stops RB phosphorylation. Premature growth arrest (cell senescence) occurs in the early development of malignant tumors or slowly proliferating benign neoplasms but not in malignant or late-stage benign tumors.[168]

EXPOSURE

Few data are available linking environmental exposures with human pituitary adenomas. AIP (aryl hydrocarbon receptor-interacting protein) is a molecular chaperone to the dioxin receptor with multiple functions, including modulation of the transcriptional activity of the aryl hydrocarbon receptor that mediates the toxicological properties of dioxin. An ecological Italian study examined the incidence of pituitary tumors in the Seveso population exposed to 2,3,7,8-tetrachlorodibenzo-*para*-dioxin following an industrial accident in 1976.[169] The area was subdivided based on soil dioxin concentrations into the following three contamination zones: high (median = 447 ppt, $n = 804$ subjects, $n = 1$ prolactinoma), intermediate (median = 94 ppt, $n = 5{,}941$ subjects, $n = 2$ nonfunctioning pituitary tumors), and low (median = 48 ppt, $n = 38{,}624$ subjects, $n = 3$ prolactinomas and 2 nonfunctioning pituitary adenomas). The surrounding noncontaminated area contained the referents ($n = 232{,}745$ subjects, $n = 42$ pituitary adenomas). Based on the hospital discharge registration system of the Lombardy region and using the noncontaminated area for referents, the rate ratio for the high contamination area was 6.2 (95% CI: 0.9–45.5, $P_{\text{difference}} = 0.07$) and 1.9 (95% CI: 0.5–7.7, $P_{\text{difference}} = 0.39$) for the intermediate contamination area. None of these rate ratios were statistically significant, including the low contamination

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TABLE 58.9. Some of the complex genetic alterations occurring in pituitary adenomas. Transcriptional regulators (e.g., *HMGA2* gene, *PLADL1* expression of zinc finger protein) and miRNAs are also involved in pituitary adenoma proliferation; however, their roles are currently not well defined. (Adapted from Melmed).[160]

Gene	Function	Mode of Action	Tumor Type
GNAS	Oncogene	Activating, imprinting	Nonfamilial, syndromic, or sporadic
CREB	Transcription factor	Constitutive phosphorylation	Sporadic
AIP	Tumor suppressor	Inactivating	Familial, syndromic
MEN1	Tumor suppressor	Inactivating	Familial, syndromic
PRKAR1A	Tumor suppressor	Inactivating	Familial, syndromic
H-RAS	Oncogene	Activating	Invasive or malignant
CCNB2	Cyclin	Induced by HMGA	Sporadic
CCND1	Oncogene	Overexpression	Sporadic
CDKNIB	CDK inhibitor	Inactivating	Sporadic, syndromic
HMGA2	Oncogene	Overexpression	Sporadic
FGFR4	Oncogene	Alternative transcription	Sporadic
PTTG	Securin	Overexpression	Sporadic
RB	Tumor suppressor	Epigenetic silencing	Sporadic
CDKN2A	Cyclin-dependent kinase inhibitor	Epigenetic silencing	Sporadic
BRG1	Tumor suppressor	Glucocorticoid receptor function	Sporadic
GADD45G	Proliferation inhibitor	Epigenetic silencing	Sporadic
MEG3	Proliferation inhibitor	Epigenetic silencing	Sporadic

area (RR = 0.7; 95% CI: 0.3–1.8, $P_{\text{difference}} = 0.48$). The wide confidence limits for the more contaminated areas suggest imprecise risk estimates.

HISTOLOGY

Pituitary adenomas are heterogeneous tumors with a single tumor often containing multiple hyperplastic areas and numerous monoclonal tumors with different growth patterns, pathological features, and apoptotic rates. The most common pituitary adenomas are prolactinomas (~50%), followed by nonfunctioning pituitary adenomas (~30%), somatotrophinomas (~15–20%), corticotroph adenomas (~5–10%), and thyrotroph adenomas (<1%).[159,170] Metastatic tumors from other primary tumor sites account for ~1% of pituitary tumors. Pituitary carcinomas represent <0.2% of pituitary tumors. Typically, these tumors secrete ≥1 hormone, mostly ACTH and prolactin. Distant metastatic sites (e.g., brain, spinal cord, bones, lymph nodes, liver, lungs, ovary, heart) define these malignant pituitary tumors rather than immunohistological stains or specific genetic markers.

The 2017 WHO classification of pituitary tumors categorizes pituitary histological variants by hormone content, specific histological and immunohistochemical features (e.g., pituitary transcription factor 1, PIT-1), and proliferation potential (e.g., mitotic count, Ki67 index).[171] Table 58.10 displays the classification of pituitary adenomas, the most common pituitary tumor. Other much less common pituitary tumors include pituitary carcinomas, pituitary blastomas, and posterior pituitary tumors (pituicytoma, granular cell tumor of neurohypophysis, spindle cell oncocytoma, and sellar ependymoma).

Nonfunctioning pituitary adenomas represent a heterogenous group of pituitary tumors characterized by an absence of endocrine features associated with hypersecretion of adenohypophyseal hormones. About one-third of pituitary neuroendocrine tumors are nonfunctioning depending on the type of study (clinical registry vs. autopsy series).[172] These silent tumors typically present as macroadenomas invading the cavernous sinus or less often as incidentalomas. The histopathological types of nonfunctioning and functioning pituitary adenomas are similar based on the expression of adenohypophyseal hormones (e.g., gonadotroph, corticotroph) and pituitary-specific transcription factors (e.g., PIT-1, T-PIT).

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TABLE 58.10. 2017 World Health Organization (WHO) pathological classification of pituitary adenomas. These adenomas are also separated by transcription and other cofactors (e.g., PIT-1). The null cell adenoma is negative for pituitary transcription factors and hormones. Plurihormonal adenomas (formerly known as silent subtype III adenoma) contain various combinations of the three hormones and are PIT-1-positive. (Adapted from Mete and Lopes).[171]

Adenoma Type	Morphological Variant	Pituitary Hormones
Somatotroph	Densely granulated	Growth hormone, α-subunit
	Sparsely granulated	Growth hormone
	Mammosomatotroph	Growth hormone/prolactin ± α-subunit[a]
	Mixed somatotroph-lactotroph	Growth hormone/prolactin ± α-subunit[a]
Lactotroph	Densely granulated	Prolactin
	Sparsely granulated	Prolactin
	Acidophil stem cell	Growth hormone/prolactin
Thyrotroph		β-thyroid-stimulating hormone, α-subunit
Corticotroph	Densely granulated	Adrenocorticotropic hormone
	Sparsely granulated	Adrenocorticotropic hormone
	Crooke's cell	Adrenocorticotropic hormone
Gonadotroph		β-follicle-stimulating hormone, α-subunit,[a] β-luteinizing hormone, α-subunit[a]
Null cell		None
Plurihormonal		β-thyroid-stimulating hormone ± α-subunit,[a] growth hormone/prolactin ± α-subunit[a]

[a] The mammosomatotroph adenoma has the two hormones in the same cell, whereas the mixed somatotroph-lactotroph adenoma has this combination in different cells. Gonadotroph adenomas contain various combinations of their two hormones. The plurihormonal adenoma contains various combinations of the three hormones.

HOST SUSCEPTIBILITY

Although most pituitary tumors are sporadic, ~5% belong to 1 of the 4 most common familial tumor syndromes, including multiple endocrine neoplasia type 1 (MEN1), MEN1-like multiple endocrine neoplasia type 4 (MEN4), Carney complex syndrome (CNC), and familial isolated pituitary adenoma (PIPA).[173] MEN1 causes selective development of neuroendocrine tumors in the anterior pituitary (prolactinomas, GH/ACTH-secreting adenomas), pancreatic, and parathyroid glands. Angiofibromas, collagenomas, and lipomas are also common in this syndrome. The *MEN1* gene produces the transcriptional regulatory protein menin involved with transcription of endocrine gene promoters. About 2.7% of pituitary adenomas are autosomal dominant MEN type 1.[174] MEN4 is a rare syndrome involving acromegaly and Cushing disease as part of a multiple endocrine neoplasia type 4 syndrome unrelated to the *MEN1* gene. The primary gene mutation occurs in the *CDKN1B* (cyclin-dependent kinase inhibitor 1B) gene that encodes $p27^{kip1}$. Carney complex syndrome (CNC) results from mutation of the tumor suppressor *PRKAR1A* (protein kinase cAMP-dependent type I regulatory subunit α) gene. This syndrome is associated with myxomas, testicular, adrenal, and/or pituitary hyperplasia or adenomas. About 70% of CNC cases are familial with the syndrome occurring in all racial groups and demonstrating a slight female predominance.[175] FIPA is associated with several pituitary types including acromegaly/gigantism. The tumors in family members can be the same (homogeneous) or different (heterogeneous). Mutations of the *AIP* (aryl hydrocarbon receptor-interacting protein) gene occur commonly in somatotrophinomas and prolactinomas associated with this syndrome, particularly in young men diagnosed with acromegaly and gigantism.[176] The genes associated with the familial tumor syndromes are not usually mutated in sporadic pituitary tumors. In a prospective cohort study of 443 patients with *sporadic* pituitary adenomas of all histotypes, 16 of these patients (3.6%) had AIP mutations.[177] For 148 patients with acromegaly, 6 (4.1%) had the AIP mutation compared with 5 (4.5%) of 132 prolactinoma patients and 3 (6.8%) of 44 corticotropic adenoma patients. None of the thyrotropic adenoma patients and only 1 (0.9%) of the 113 patients with nonfunctioning pituitary adenomas had the AIP mutation.

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CLINICAL FEATURES

Most of these tumors are benign and often asymptomatic, with many pituitary tumors diagnosed incidentally (e.g., pituitary incidentalomas). The overall incidence of adult pituitary tumors increases with age peaking in the seventh decade, whereas pituitary tumors occur rarely in childhood or adolescence (i.e., 1–10% of brain tumors).[178] Incidence also varies with histological type. Prolactinomas most frequently develop during the second to fourth decades, while nonfunctioning pituitary adenomas are the most common pituitary tumor after 40 years of age.[179] The clinical features of hormone-secreting tumors reflect mass effects and the monoclonal cell of origin. Prolactinomas secrete prolactin, resulting in galactorrhea and hypogonadism, whereas GH-secreting somatotrophinomas cause acromegaly and gigantism, TSH-secreting thyrotroph tumors produce hyperthyroidism, and ACTH-secreting tumors cause Cushing disease. Symptoms associated with pituitary adenomas range widely from asymptomatic to manifestations of pituitary hormone hypersecretion or hypothalamic/pituitary dysfunction and/or local space-occupying effect (e.g., cranial nerve, visual field impairment). Headaches are common and present in up to 75% of patients with pituitary tumors. The acute onset of severe headache may occur with sudden vascular-induced expansion of tumor volume (apoplexy).[180] Visual field defects typically involve bitemporal hemianopia; however, the defects vary widely from asymmetric unilateral to whole central hemifield visual loss. Expansion of the tumor into the cavernous sinus produces highly variable clinical ocular abnormalities depending on the compromised nerve (e.g., ophthalmoplegia from pressure on the abducens or oculomotor nerves). Invasion of the dura and adjacent brain may produce temporal lobe epilepsy. Hypopituitarism often develops slowly with subtle signs of visual impairment. Pituitary microadenomas are typically <1 cm inside small intrasellar lesions, whereas macroadenomas are ≥1 cm localized within an enlarged sella turcica. Macroadenomas represent ~40% of pituitary tumors. Complications from these tumors result from pressure on the optic chiasm/pituitary stalk and local invasion of the suprasellar area, sphenoid sinus, and/or cavernous sinus. Very large macroadenomas may obstruct the foramen of Monro, resulting in hydrocephalus and intracranial hypertension.

Morbidity and mortality depend primarily on location, function, and progression. Mortality from pituitary adenomas can result from surgical complications, pituitary dysfunction, tumor recurrence, and tumor progression with local invasion. In a nationwide, population-based Swedish study of 2,795 patients with nonfunctioning pituitary adenomas followed for a mean of 7 years (range, 0–25 years), the SMR was significant for women (SMR = 1.29, 95% CI: 1.11–1.48, $n = 192$ deaths), but not for men (SMR = 1.00, 95% CI: 0.88–1.12, $n = 278$ deaths).[181] Some evidence suggested the diagnosis of a nonfunctioning pituitary adenoma at ≤40 years increased mortality (SMR = 2.68, 95% CI: 1.23–5.09, $n = 9$ deaths, $P_{\text{difference}} = 0.015$). A study using Swedish Cancer Registry data from the era before personalized chemotherapy (1958–1991) reported an elevated overall SMR of 2.0 (95% CI: 1.9–2.2) with a significantly higher SMR for women than men ($P_{\text{difference}} < 0.01$). However, the median survival was 25 years for women and 18 years for men. In a Danish study of 160 patients undergoing pituitary surgery for a nonfunctioning suprasellar pituitary adenoma, subsequent mortality was higher in women compared with the general population (SMR = 1.97, 95% CI: 1.20–3.21), but not in men (SMR = 0.83, 95% CI: 0.55–1.26).[182]

EYE

Ocular melanoma is a rare human malignancy accounting for <0.5% of human neoplasms.[183] After the skin, the eye is the most common location for primary melanomas. There are five types of primary ocular melanomas with the most common being uveal melanomas; choroid, ciliary body, iris, and conjunctival melanomas are much less common. The overall mean US age-adjusted annual incidence of uveal melanoma is ~5.1 cases/10^6,[184] whereas the standardized European incidence rates for uveal melanoma demonstrate a north-to-south decreasing incidence rate with a range of 1.3–8.6 cases/10^6.[185] Of all extracutaneous melanoma sites, ocular melanomas have the highest incidence and best survival rates with no recent statistically significant change in European incidence rates.[186] The epidemiological pattern of cutaneous and ocular melanomas differs. Conjunctival melanoma is almost exclusively a Caucasian disease. The incidence is increasing similar to cutaneous melanoma, whereas intraocular and mucosal melanoma incidence rates remain relatively stable.[187,188] The reported incidence rates of uveal melanoma are much lower in Africa and Asia (0.2–0.3 cases/10^6).

CARCINOGENESIS

Table 58.11 displays the most frequently known genetic mutations in uveal melanoma and their chromosome

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TABLE 58.11. Commonly recognized gene mutations in uveal melanoma with the approximate percentage of mutations in evaluated tumors. (Adapted from Kaur et al.).[192]

Gene	Chromosome	Uveal Melanoma (%)
HDM2 (MDM2)	12q15	97
GNAQ/GNA11	9p21	83
CCND1	11q13	65
NBS1	8q21	50
BRAF	3p21	48
BAP1	7q34	44
MYC	8q24	43

Abbreviations: BAP1 = BRCA1-associated protein 1. BAP1 protein is a deubiquitinase that helps to regulate the function of many proteins involved in diverse cellular processes; *BRAF* = *BRAF* proto-oncogene, serine/threonine kinase. The BRAF protein is involved in the RAS/MAPK pathway that helps regulate cell proliferation, differentiation, migration, and apoptosis. *CCND1* = cyclin D1. The encoded protein functions as a regulatory subunit of CDK4 or CDK6 and helps to regulate cell-cycle G_1/S transition; *GNAQ*/*GNA11* = G protein subunit alpha q/G protein subunit alpha 11. These encode G proteins that trigger a complex network of transduction signaling pathways that influence many cell functions. *HDM2* (*MDM2*) = *MDM2* proto-oncogene. These genes encode a nuclear-localized E3 ubiquitin ligase that promotes tumor formation by degrading tumor suppressor proteins (e.g., p53). *NBS1* = Nijmegen breakage syndrome (*NBN*) gene. The encoded protein (nibrin) recognizes broken strands of DNA and helps coordinate double-strand DNA break repair (RAD50 double-strand break repair protein).

locations. Somatic oncogenic GNAQ (heterotrimeric G protein α-subunit q) and GNA11 (G protein subunit alpha 11) mutations are much more frequent in uveal melanomas than in other melanomas. These mutations affect multiple downstream signaling pathways, including MEK, PI3K/AKT, protein kinase C, and YAP. The presence of GNAQ and GNA11 gene mutations in 80% of uveal melanomas suggests these mutations, rather than mutations of *BAF*, *NRS*, or *KIT* genes, initiate malignant transformation and activate these oncogenic pathways.[186,189] Cell-cycle deregulation by CCND1 mutations helps overcome the G1/S checkpoint, resulting in cell proliferation and cytogenetic instability (e.g., 1p, 6q, and 8p losses; monosomy 3; 6p and 8q gains). The *KIT* gene encodes a receptor tyrosine kinase involved with cell growth and survival, whereas the *NRAS* gene is a member of the *RAS* family that encodes GTPases involved with cell growth. Although mutations of *BAF*, *NRAS*, and *KIT* genes are associated with highly activated mitogen-activated protein/extracellular signal-regulated kinase/(MEK/MAPK) and mitogen-activated protein kinase (PI3K/AKT) pathways in some uveal melanoma tumors, these oncogenes are much less common in uveal than cutaneous melanomas.[190,191]

Conjunctival melanomas share more common mutations with cutaneous than uveal melanomas, particularly the mitogen-activated protein kinase (MAPK) signaling transduction pathway; ~50% of primary conjunctival melanoma tumors contain mutations of the *BRAF V600E* gene.[193] The *BRAF* gene encodes a protein that transmits chemical signals from the cytoplasm to the nucleus as part of the RAS/MAPK pathway. In contrast to uveal melanomas, fewer mutations of the *KIT* and *NRAS* genes occur in conjunctival melanoma mutations than uveal melanoma mutations. The role of oncogenic transformation of *NRS* and *KIT* genes in conjunctival melanomas remains unclear. Sporadic mutations of the tumor suppressor *RB1* (RB transcriptional corepressor 1) gene cause most retinoblastomas in children; however, germline mutations account for ~1/3 of these tumors. The *RB1* gene encodes the RB protein that prevents replication of damaged DNA by deacetylating chromatin and stopping the progression from G1 to the S phase. This protein inhibits transcription factors of the E2F family preventing entry of the cell into the S phase.[192]

EXPOSURE

Risk factors for ocular melanoma include light eye color, fair skin, propensity to sunburn, ocular or oculodermal melanocytosis, and atypical nevi (choroid, cutaneous skin, iris). In contrast to cutaneous melanoma risk factors (e.g., excessive sunlight exposure, hair/eye color, abundance of atypical skin nevi), intraocular melanomas have few strong environmental or occupational risk factors.[194] Most ocular cancers are uveal melanomas that preferentially affect the choroid of fair-skinned, light-eyed Europeans and their descendants. A systematic review of four meta-analyses suggests several *potential* risk factors for ocular melanoma (welding, occupational cooking, fair skin, light eye color, common

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cutaneous nevi count, sunburn propensity, iris nevi, cutaneous freckles) with odds ratios varying in order from atypical cutaneous neve (OR = 2.82, 95% CI: 1.10–7.26) to cutaneous freckles (OR = 1.27, 95% CI: 1.09–1.49).[195] All the studies were case-control designs of moderate quality, limited adjustment for potential cofounders, and wide confidence limits (e.g., atypical nevi). Factors without statistically significant positive associations with ocular melanomas include hair color, outdoor leisure activity, birth latitude, and occupational sunlight exposure. In a meta-analysis of 10 observational studies (1,732 cases) using random effects models, the uveal melanoma risk for blue-/gray-eyed cases was statistically different than brown-eyed cases (summary OR = 1.75, 95% CI: 1.31–2.34, $P_{\text{heterogeneity}} = 0.006$) with significant heterogeneity. For propensity to sunburn using a fixed model and an assessment of multiple previous sun exposures or general tanning ability, the summary uveal melanoma risk was 1.64 (95% CI: 1.29–2.09, $n = 1{,}021$ cases, $P_{\text{heterogeneity}} = 0.53$) compared with good tanning ability. The summary OR for uveal melanoma in fair-skinned cases was 1.80 (95% CI: 1.31–2.47, $n = 586$ cases, $P_{\text{heterogeneity}} = 0.50$) compared with dark-skinned cases, whereas the summary odds ratio was not statistically significant for the comparison of blond-/red-haired and dark-haired cases (OR = 1.02, 95% CI: 0.82–1.26, $n = 1{,}012$, $P_{\text{heterogeneity}} = 0.11$).

Atypical Nevi

The association between atypical (dysplastic) nevi and uveal melanoma is inconsistent. In a case-control study of patients with dysplastic nevi and volunteer controls, the relative risk for uveal melanoma was 4.36 (95% CI: 1.84–10.36). The wide confidence limit suggests imprecise RR estimates.[196] In a case-control study of 211 unselected ocular melanoma patients attending a UK oncology clinic and 416 hospital controls, the relative risk for ocular melanoma increased with the number of atypical nevi and common nevi; however, the two groups were not comparable.[197] Nine percent of cases and 1% of controls had the Atypical Mole Syndrome (AMS) phenotype, whereas six cases had concurrent primary cutaneous melanoma. A cross-sectional study of 65 consecutive patients diagnosed with posterior uveal melanoma and 218 consecutive controls referred for general retinal evaluation reported no association between posterior uveal melanoma and the presence of iris (4 cases, 6.2%; 9 controls, 4.1%; $P_{\text{difference}} = 0.955$) or choroidal (12 cases/18.5%; 38 controls, 17.4%; $P_{\text{difference}} = 0.815$) nevi.[198]

Choroidal nevi are the most common intraocular lesions; ~5% of the US Caucasian population has these nevi compared with 0.6% in blacks.[199] The annual malignant transformation rate for choroidal nevi is age-related, ranging from ~1/270,000 in 15–19-year-old adolescents to ~1/3,700 in 80–84-year-olds. Factors associated with increased transformation to melanoma include a thickness of >2 mm, symptoms, subretinal fluid, orange pigment, margin near disc, lack of halo, and ultrasonographic hollowness.[200] In a retrospective and comparative case series of 1,611 patients referred to an ocular oncology center with iris nevi, Kaplan–Meier estimates calculated the cumulative transformation to melanoma at <1% in 1 year, 3% in 5 years, 4% in 10 years, 8% in 15 years, and 11% in 20 years.[201]

UV Light

The evidence associating UV radiation with the development of intraocular melanoma is equivocal, without a strong correlation between high-UV occupational radiation exposure and intraocular melanomas. Little solar UVA and UVB radiation reach the pigmented layer of the uveal tract, including the ciliary body and choroidal melanocytes.[202] Dosimetry studies indicate <1–2% of UVB (280–315 nm) radiation at the exterior of the eye reaches the posterior portions of the eye.[203] Some case-control studies with retrospective analysis of UV exposure suggest the relative risk of ocular melanoma increases by ~1.5–3 with high sun exposure[204] or light complexion (blue, gray, hazel, or green eyes, red or blonde hair);[205,206,207] however, other studies report the absence of a significant relationship between chronic UV exposure and intraocular melanoma.[208,209] A meta-analysis of 10 case-control and 2 cohort studies reported inconsistent findings on the effect of ultraviolet light on uveal melanoma risks.[210] Comparing the highest and lowest scores for occupational sunlight exposure and fixed-effects models, the summary odds ratio for chronic ultraviolet exposure and uveal melanoma risk was nonsignificant (OR = 1.37, 95% CI: 0.96–1.96, $n = 4$ studies/572 cases) with substantial heterogeneity ($P_{\text{heterogeneity}} = 0.56$). A German case-control study compared 459 incident uveal melanoma cases and 3 control groups (827 population controls, 180 ophthalmologist controls, and 187 sibling controls).[211] The odds ratio for uveal melanoma in cases with >15 years of total lifetime occupational sun exposure was significant in ophthalmologist controls (OR = 2.8, 95% CI: 1.1–7.0), but not in population (OR = 1.1, 95% CI: 0.8–1.7) or sibling (OR = 1.6, 95% CI: 0.7–3.7) controls. The wide confidence limits suggest imprecise estimates.

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An analysis of UV exposure based on the job-exposure matrix demonstrated a significantly increased ocular melanoma risk in occupational groups exposed to artificial ultraviolet radiation but not in outdoor occupational groups exposed to sunlight. Based on geographical tumor mapping of 92 ocular melanomas, there was no significant correlation between tumor location in the choroid and the estimated UV radiation dose. Although choroidal melanomas are common ocular melanomas, significant doses of UVC (100–280 nm) and UVB radiation do not reach the choroid.[212] The cornea and lens filter UVA (315–400 nm) radiation.

Occupation

Using population controls, the relative risk of developing uveal melanoma after occupational exposure to sunlight was not statistically significant (RR = 1.24, 95% CI: 0.88–1.74). There was an excess risk of uveal melanoma in French welders but not in welders from eight other European countries. A French population-based case-control study of 50 incident cases of uveal melanoma diagnosed during 1995–1996 suggests an increased risk in male welders (odds ratio = 7.3, 95% CI: 2.6–20.1).[213] Although the study reported a dose-response relationship with job duration based on self-reported work history, the wide confidence limits indicate imprecise risk estimates. A European population-based, case-control study of uveal melanoma diagnosed during 1995–1997 did not detect an association between occupational sunlight exposure and the risk of uveal melanoma using a job-exposure matrix.[214] Using population controls and comparing ever with never occupationally exposed, occupational sunlight exposure was not associated with a statistically significant increased uveal melanoma risk (RR = 1.24, 95% CI = 0.88–1.74). A meta-analysis of 5 case-control studies involving 1,199 uveal melanoma cases and 6,927 controls suggests an increased uveal melanoma risk in occupational cooks (OR = 1.81, 95% CI: 1.33–2.46, $P_{\text{difference}} < 0.001$, $I^2 = 27.7\%$) with slight heterogeneity.[215]

HISTOLOGY

Melanomas arise from neural crest-derived dendritic melanocytes located in various anatomical locations, most commonly in skin, mucous membranes, or the eye. Conjunctival melanoma usually arises from primary acquired melanosis with atypia (~50–75%) and less frequently from conjunctival nevi (~5%) or sporadically (18–30%).[216] Analyses of the US National Cancer Database containing 84,836 melanoma cases diagnosed from 1985–1994 indicate cutaneous melanomas accounted for ~91% of the total compared with ~3–5% for the eye, ~2% for unknown primary melanomas, and ~1% for mucosal melanomas (nasal, oropharyngeal, pulmonary gastrointestinal, anorectal, vaginal, urinary tract).[217] The reported anatomical locations of ocular melanomas in this database primarily involve the uvea (~80–85%) and less commonly the conjunctiva (~1–5%) and other sites (~10%; eyelid, lacrimal gland, orbit, retina). Uveal melanomas are much more common in the posterior tract (choroid, ciliary body) than in the anterior tract (iris). A retrospective medical records review of 8,033 uveal melanoma cases indicates the vast majority of these tumors occurred in the choroid (90%), whereas the ciliary body accounted for 6% and the iris for 4%.

HOST SUSCEPTIBILITY

There is an absence of strong familial clustering in cases of uveal melanoma including choroidal melanomas. Mutations of the *BAP1* (BRCA1-associated protein 1) tumor suppressor gene are associated with increased uveal melanoma risks; the BAP1 hereditary cancer predisposition syndrome increases the risk of uveal melanoma as well as malignant mesothelioma, basal cell carcinoma, cutaneous melanomas, and renal cell carcinoma.[218] The BAP1 protein is a deubiquitinase that promotes the degradation of proteins tagged with ubiquitin; this protein is involved in numerous pathways ranging from DNA repair to cell differentiation. Mutations of the *BAP1* gene in uveal melanoma can be either germline (BAP1 hereditary cancer predisposition syndrome) or sporadic. In a retrospective cohort study of 507 patients at an academic ophthalmology referral center, analysis of blood samples indicated 5% (25 patients) had the BAP1 mutation with nine of the mutations being novel.[219]

Oculodermal melanocytosis is a congenital pigmentary abnormality involving slate-gray pigmentation at multiple sites in the head (sclera, uvea, periocular skin, orbit, palate, tympanic membrane, meninges), typically resulting in a unilateral reduction in pigmentation. In a retrospective chart review of 7,872 patients with uveal melanoma treated at a US eye institute, melanocytosis involved the sclera (92%), iris (17%), choroid (12%), eyelid (8%), and temporal fossa (1%) of the cases.[220] Approximately 1.4–3% of uveal melanoma cases have this pigmentation abnormality; the lifetime uveal melanoma risk in a Caucasian patient with ocular/oculodermal melanocytosis is 1/400.[221]

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CLINICAL FEATURES

Analysis of the US Surveillance Epidemiology and End Results (SEER) database revealed 7,069 ocular melanoma cases from 1988–2010, representing ~3% of all melanomas with a median age of 63 years (IQR = 52–73 years, male/female ratio = 1.1).[222] The incidence of this disease is much higher in white than black races (15–50:1).[223] The clinical course of ocular melanoma is difficult to predict because of the early hematogenous spread of micrometastases and the occurrence of metastatic disease after a prolonged disease-free interval. Clinical features of ocular melanoma associated with a poor prognosis include advanced age and stage (large size, diffuse configuration, extraocular invasion).[224,225] Metastasis and prognosis correlate to aberrations in 1, 3, 6, and 8 chromosomes, particularly monosomy 3. Conjunctival and cutaneous melanomas spread locally to lymph nodes via lymphatics and by hematogenous spread, whereas uveal melanoma usually metastasizes to the liver via hematological spread.[226] In the US SEER registry, the 5-year survival rate for ocular melanoma was 78.4% (95% CI: 76.9–79.8%) compared with 89.0% (95% CI: 88.7–89.2%) for cutaneous melanoma.[222] Metastatic melanoma to the eye is rare, with the orbit and retina being the most frequent metastatic sites.

Conjunctival

Conjunctival melanomas are typically present as asymptomatic light to dark brown macules or elevated pigmented plaques/tumors in the bulbar conjunctiva near the limbus.[227] Systemic disease in patients with conjunctival melanoma usually involves the lungs, liver, brain, bones, and gastrointestinal tract. The 5-year metastasis rate is ~16% (74–86% survival rate) and ~26% after 10 years (41–78% survival rate).[187]

Uvea

The uvea consists of three layers beneath the sclera including: 1) the iris, 2) the ciliary body that secretes the vitreous, and 3) the choroid that contains the connective tissue and vessels between the sclera and retina. Most cases of uveal melanoma occur after 50 years of age; the peak age is ~70 years, with a plateau after 75 years of age; children seldom develop uveal melanoma (e.g., <15% below 11 years of age).[223] The age-adjusted uveal melanoma incidence is higher in men (5.8 cases/10^6) than women (4.4 cases/10^6), primarily as a result of the increased uveal melanoma incidence in men of ≥65 years of age.[184]

A retrospective case series of 500 uveal melanoma cases reported monosomy 3 in 25%, partial monosomy 3 in 27%, and disomy 3 in 48%; the cumulative 3-year metastatic rates were 24% in monosomy 3 compared with 3% for disomy 3 and 5% for partial monosomy 3.[228] Univariate Cox analysis of whole-genome single-nucleotide polymorphism arrays from 320 uveal melanomas associated poor prognosis with chromosome losses in 3, 1p, 6q, and 8p and gain of function in 8q; sex, tumor basal height/diameter, and ciliary body involvement also affect the prognosis.[229] Using multivariate analysis of the joint effects of six chromosomal regional aberrations, the hazard ratios ranged from 7.90–37.25. Size of the uveal melanoma correlates to metastatic liver risks with metastasis 5 years after diagnosis being uncommon (i.e., <5%) when the tumor thickness and diameter are <3 mm and <10 mm, respectively, at the time of discovery.[230] The average survival after discovery of metastatic uveal melanoma is <6 months.[231]

Iris

The incidence of melanoma is much lower in the iris than in the uvea; iris melanoma is usually diagnosed 10–20 years earlier than ciliary body or choroidal melanomas.[223] The classic presentation of diffuse iris melanoma includes ipsilateral glaucoma, unilateral cataract, prominent episcleral (sentinel) vessels, anterior chamber inflammation, and acquired hyperchromic heterochromia iridis.[232] The prognosis is much better (5–10 times lower mortality rates) for iris than choroidal or ciliary body melanomas consistent with earlier presentation and smaller tumor size. In a case series of 317 iris melanoma patients, metastasis occurred in 4% with 2% dying during a mean follow-up of 4.5 years.[233]

Choroid/Ciliary Body

Choroidal melanomas usually present as a dome-shaped mass, whereas ciliary body melanomas are often diagnosed late because the lesion remains asymptomatic behind the iris. The most common clinical features include blurred vision, photopsia, and less often floaters, visual field loss, pain, and metamorphopsia.[234] About 30% of choroidal and ciliary body (posterior uveal) melanomas present without ocular symptoms. Posterior uveal melanoma has a relatively high metastatic rate. A Finnish cohort of 289 choroidal and ciliary body

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melanomas in the European Collaborative Ocular Melanoma Study was followed for a median of 28 years (50 survivors).[235] The Kaplan–Meier estimates of metastasis were 32% by 5 years, 50% by 15 years, 56% by 25 years, and 62% by 35 years. In the prospective, longitudinal follow-up study from the Collaborative Ocular Melanoma Study Group involving 739 choroidal melanoma cases with at least 1 metastatic site, the most common metastatic sites were liver (89%) followed by lung (29%), bone (17%), subcutaneous skin (12%), and lymph nodes (11%).[236] Ciliary body melanomas typically are more aggressive than choroid or iris melanomas, reflecting delayed detection, larger tumor size, and rich blood supply.[237]

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Chapter 59

LEUKEMIA

Leukemia is the common name for neoplasms presenting with increased abnormal or immature peripheral white blood cells derived from leukemogenic processes in the bone marrow; ultimately, this disease leads to bone marrow failure. Leukemias evolve from lymphoid and myeloid cells depending on the subtype, whereas lymphomas result from malignant transformation of B, T, or natural killer cells originating in the lymphoid stem cell lineage. The predominant leukemia cell typically consists of either mature cells (e.g., chronic lymphocytic leukemia, CLL), precursor cells of various lineages (e.g., acute myelocytic leukemia, AML; acute lymphoblastic leukemia, ALL), or both precursor and mature cells (e.g., chronic myelocytic leukemia, CML). Leukemias present at all ages, from newborns to the elderly; however, the distribution of major leukemia groups changes with age (e.g., ALL in children, CLL in the elderly), as displayed in Figure 59.1. Leukemia is the most common cancer in children, representing 20–30% of childhood cases.[1]

Overall, adult leukemia incidence declined after substantial increases during 1950–1985, with a slight male predominance, particularly in Caucasians.[3,4] Currently, ~62,000 new leukemia cases occur annually in the United States, with a male/female ratio of ~1.4/1.[5] Leukemias are the ninth most common cancer site accounting for ~4% of all cancers in men and the sixth most common cause of cancer-related deaths (~4% of all cancer deaths). In women, leukemias are the 10th most common cancer accounting for ~3% of new cancer cases and the 8th most common cause of cancer-related deaths (~3% of all cancer-related deaths). Worldwide, reported leukemia incidence rates trend lower in less socioeconomically developed countries than in more developed countries. Childhood leukemia increased by ~0.7% annually for the last several decades in higher socioeconomically developed countries, particularly for ALL (CD19/20+ B cell cALL) in 2–6-year-olds.[5,6] Similar peaks have not been reported in Africa and India, where overall incidence rates are lower. The incident rates also vary with race; higher childhood leukemia rates occur in Hispanics and whites with lower rates in blacks.[7,8]

CLASSIFICATION

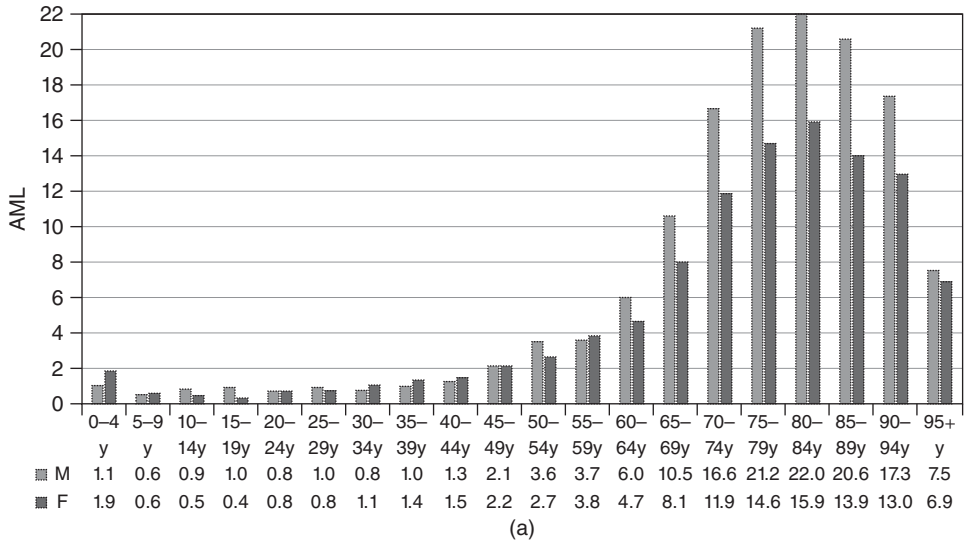
Historically, presumed cell lineage and clinical criteria separated leukemias into four major groups, including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and chronic lymphocytic leukemia (CLL). In 2008, the third edition of the International Classification of Disease for Oncology implemented the World Health Organization's recommendations for the classification of hematopoietic malignancies based on cytogenetic, morphological, and molecular criteria. Published in 2016, the fourth edition revised the 2008 classification by incorporating new clinical morphological, immunophenotypic, prognostic, and genetic data rather than creating a new classification scheme as listed in Table 59.1.[9]

Medical Toxicology of Occupational and Environmental Exposures, Volume 3, First Edition. Donald G. Barceloux, Edited by Robert B. Palmer.
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IMMUNITY

The basic organs of the immune system include: 1) bone marrow – repository of stem cells capable of forming all immune cells and blood types; 2) lymph system, including lymph nodes and spleen, that contains B and T cells, filter debris/antigens, and enhance contact between the immune system and foreign antigens; and 3) thymus gland – contains maturing T cells capable of remembering and recognizing host and foreign tissues.[10] The immune system responds to pathogenic foreign material by developing two types of responses (innate and adaptive immunity). Innate immunity is a rapid, nonspecific response without a prior memory of a similar exposure (e.g., macrophage engulfing a microbe); cells of innate immunity include neutrophils, eosinophils, basophils, natural killer cells, and mast cells. Adaptive immunity is a slower, more specific immune



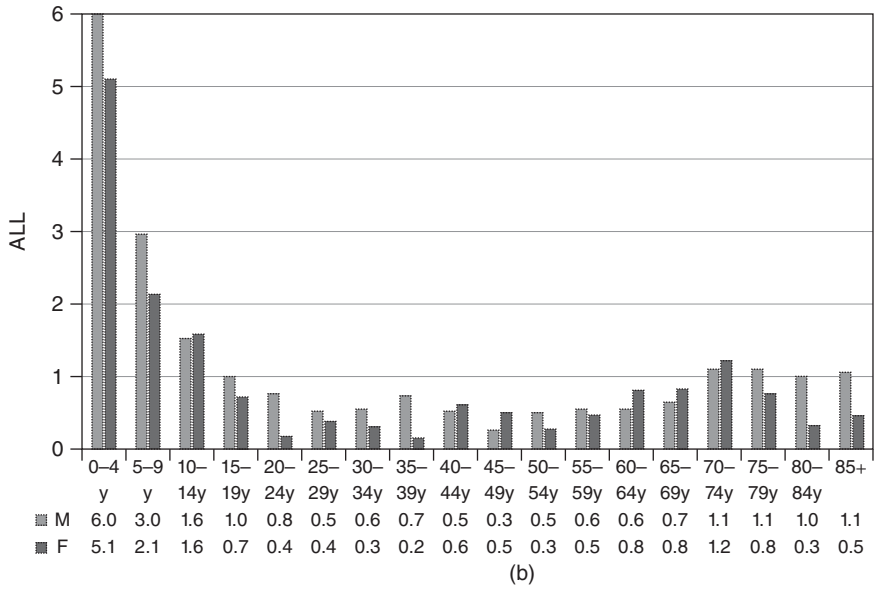


FIGURE 59.1. Age distribution of acute myelocytic leukemia (AML, a), acute lymphoblastic leukemia (ALL, b), and chronic myelocytic leukemia (CML, c) diagnosed in Sweden during 1997–2013 (AML), 2005–2014 (ALL), and 2005–2014 (CML) by 5-year increments (Adapted from Juliusson and Hough).[2] *Abbreviations:* F = annual incidence of leukemia type in females/100,000 Swedish inhabitants; M = annual incidence of leukemia type in males/100,000 Swedish inhabitants.

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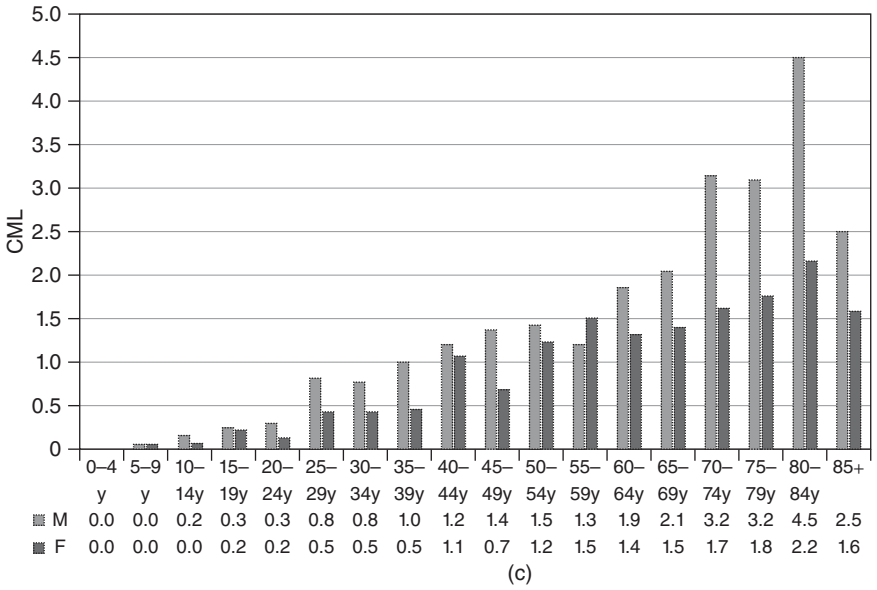


FIGURE 59.1. (*Continued*)

response with a past memory capable of distinguishing self from foreign antigens (e.g., response to measles virus in a vaccinated person); cells in the adaptive immune system include natural killer T cells, other T cells, and antibody-producing B cells. Figure 59.2 displays normal hematopoiesis that begins with a small population of multipotential hematopoietic stem cells in the bone marrow. These self-renewing stem cells produce self-renewing myeloid and lymphoid stem cells that subsequently produce committed progenitor cells. The latter cells begin the process of differentiation into mature leukocytes, erythrocytes, and platelets in the peripheral blood.

CARCINOGENESIS

Leukemia probably results from sequential accumulation of mutations in multiple oncogenes and tumor suppressor genes altering stem cell development. Many childhood leukemia subtypes develop from a series of genetic events within a previously initiated cell; the initiation may occur *in utero*. Myelodysplastic syndromes (MDSs) are a group of heterogeneous, premalignant bone marrow tumors characterized by ineffective hematopoiesis, peripheral cytopenias, and morphologically dysplastic hematopoietic cells. Analysis of MDS patients indicates the presence of multiple mutations of genes in 80–90% of these patients, with frequent mutations involving DNA repair (*ATM*, *BRCC3*, *DLRE1C*, *FANCL*), signal transduction/kinases (*FLT3*, *JAK2*), RAS pathway (*CBL*, *KRAS*, *NF1*, *NRAS*, *PTPN11*), cohesin complex (*CTCF*, *RAD21*, *SMC1A*, *STAG2*), RNA-splicing machinery (*SF3B1*, *SRSF2*, *U2AF1*, *U2AF2*, *ZRSR2*), transcription factors (*RUNX1*, *TP53*), DNA methylation (*DNMT3A*, *IDH1/2*, *TET2*), and chromatin modification (*ASXL1*, *EZH2*) genes.[11] Normal B cell maturation occurs in two phases: 1) "foreign antigen-independent" B cells existing primarily in fetal liver or bone marrow; and 2) "primarily foreign antigen-dependent" B cells developing in lymph nodes and spleen. Leukemias are a diverse group of malignancies that are clonal expansions of single cells at different stages of hematopoiesis. These transformed cells undergo uncontrolled proliferation, failing to differentiate into functionally mature cells.

Leukemia cells exhibit far fewer genetic aberrations compared with solid tumors, which require many genetic mutations to develop metastatic capabilities.[12] Common genetic mutations in childhood leukemia that form during the fetal period include t(12;21)TEL-AML1 and t(8:21)AML1-ETO; the former is the most frequent translocation in AML and the latter is the most common translocation in ALL. The inv(16)CBFB-MYH11 translocation in AML is also prenatal. The MLL (MLLT11 transcription factor 7 cofactor) translocation is prenatal in infants with ALL and postnatal in children of >2 years of age.[13] A significant portion (i.e., >1%) of normally born children have these translocations; however, the vast majority of these preleukemic clones are self-limiting and do not produce disease. Hence, mutations associated with leukemia are insufficient to produce disease without further gene mutations.[14] MLL

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TABLE 59.1. 2022 World Health Organization (WHO) classification of myeloid and histiocytic/dendritic neoplasms. The myelodysplastic/myeloproliferative neoplasm category was introduced in the 3rd edition to provide a classification for myeloid tumors that overlap myelodysplastic syndrome and myeloproliferative neoplasms. Classification is based on cell lineage from benign to malignant and divided into category, family, type (disease/tumor), and subtype. The arrangement of these tumors integrates cytology, histology, and immunophenotyping along with molecular and cytogenetic data. See reference 9 for details on complete diagnostic criteria.[9]

Myeloproliferative neoplasms
Chronic myeloid leukemia
Polycythemia vera
Essential thrombocythemia
Primary myelofibrosis
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia
Juvenile myelomonocytic leukemia
Myeloproliferative neoplasm, NOS
Cutaneous mastocytosis
Urticaria pigmentosa/Maculopapular cutaneous mastocytosis
Monomorphic
Polymorphic
Diffuse cutaneous mastocytosis
Cutaneous mastocytoma
Isolated mastocytoma
Multilocalized mastocytoma
Systemic mastocytosis
Bone marrow mastocytosis
Indolent systemic mastocytosis
Smoldering systemic mastocytosis
Aggressive systemic mastocytosis
Systemic mastocytosis with an associated hematologic neoplasm
Mast cell leukemia
Mast cell sarcoma
Mast cell sarcoma
Myelodysplastic neoplasms with defining genetic abnormalities
Myelodysplastic neoplasms with low blasts and isolated 5q deletion
Myelodysplastic neoplasms with low blasts and SF3B1mutation
Myelodysplastic neoplasms with biallelic *TP53* inactivation
Myelodysplastic neoplasms, morphologically defined
Myelodysplastic neoplasms with low blasts
Myelodysplastic neoplasms, hypoplastic
Myelodysplastic neoplasms with increased blasts
Myelodysplastic neoplasms-IB1
Myelodysplastic neoplasms-IB2
Myelodysplastic neoplasms with fibrosis
Childhood myelodysplastic neoplasms (MDS)
Childhood MDS with low blasts
Hypocellular
Not otherwise specified
Childhood MDS with increased blasts

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TABLE 59.1. (Continued)

Myelodysplastic/myeloproliferative neoplasms
Chronic myelomonocytic leukemia
Myelodysplastic/myeloproliferative neoplasm with neutrophilia
Myelodysplastic/myeloproliferative neoplasm with SF3B1 mutation and thrombocytosis
Myelodysplastic/myeloproliferative neoplasm, NOS
Acute myeloid leukemia
Acute myeloid leukemia with defining genetic abnormalities
Acute promyelocytic leukemia with *PML::RARA* fusion
Acute myeloid leukemia with *RUNX1::RUNX1T1* fusion
Acute myeloid leukemia with *CBFB::MYH11* fusion
Acute myeloid leukemia with *DEK::NUP214* fusion
Acute myeloid leukemia with *RBM15::MRTFA* fusion
Acute myeloid leukemia with *BCR::ABL1* fusion
Acute myeloid leukemia with *KMT2A* rearrangement
Acute myeloid leukemia with *MECOM* rearrangement
Acute myeloid leukemia with *NUP98* rearrangement
Acute myeloid leukemia with *NPM1* mutation
Acute myeloid leukemia with *CEBPA* mutation
Acute myeloid leukemia, myelodysplasia-related
Acute myeloid leukemia with other defined genetic alterations
Acute myeloid leukemia, defined by differentiation
Acute myeloid leukemia with minimal differentiation
Acute myeloid leukemia without maturation
Acute myeloid leukemia with maturation
Acute basophilic leukemia
Acute myelomonocytic leukemia
Acute monocytic leukemia
Acute erythroid leukemia
Acute megakaryoblastic leukemia
Myeloid neoplasms associated with germline predisposition
Myeloid neoplasms with germline predisposition without a preexisting platelet disorder or organ dysfunction
Germline CEBPA P/LP variant (CEBPA-associated familial AML)
Germline DDX41 P/LP variant[a]
Germline TP53 P/LP variant[a] (Li-Fraumeni syndrome)
Myeloid neoplasms with germline predisposition and pre-existing platelet disorder
Germline RUNX1 P/LP variant[a] (familial platelet disorder with associated myeloid malignancy, FPD-MM)
Germline ANKRD26 P/LP variant[a] (Thrombocytopenia 2)
Germline ETV6 P/LP variant[a] (Thrombocytopenia 5)
Myeloid neoplasms with germline predisposition and potential organ dysfunction
Germline GATA2 P/LP variant (GATA2-deficiency)
Bone marrow failure syndromes

(Continued)

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TABLE 59.1. (Continued)

Severe congenital neutropenia
Shwachman-Diamond syndrome
Fanconi anemia
Telomere biology disorders
RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders[a])
Down syndrome[a]
Germline SAMD9 P/LP variant (MIRAGE Syndrome)
Germline SAMD9L P/LP variant (SAMD9L-related Ataxia Pancytopenia Syndrome)
Biallelic germline BLM P/LP variant (Bloom syndrome)
Acute leukemias of ambiguous lineage
Acute leukemia of ambiguous lineage with defining genetic abnormalities
Mixed-phenotype acute leukemia with BCR::ABL1 fusion
Mixed-phenotype acute leukemia with KMT2A rearrangement
Acute leukemia of ambiguous lineage with other defined genetic alterations
Mixed-phenotype acute leukemia with ZNF384 rearrangement
Acute leukemia of ambiguous lineage with BCL11B rearrangement
Acute leukemia of ambiguous lineage, immunophenotypically defined
Mixed-phenotype acute leukemia, B/myeloid
Mixed-phenotype acute leukemia, T/myeloid
Mixed-phenotype acute leukemia, rare types
Acute leukemia of ambiguous lineage, NOS
Acute undifferentiated leukemia
Dendritic cell and histiocytic neoplasms
Plasmacytoid dendritic cell neoplasms
Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm
Blastic plasmacytoid dendritic cell neoplasm
Langerhans cell and other dendritic cell neoplasms
Langerhans cells neoplasms
Langerhans cell histiocytosis
Langerhans cell sarcoma
Other dendritic cell neoplasms
Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma
Histiocytic neoplasms
Juvenile xanthogranuloma
Erdheim-Chester disease
Rosai-Dorfman disease
ALK-positive histiocytosis
Histiocytic sarcoma

Abbreviations: CML = chronic myeloid leukemia; CMML = chronic myelomonocytic leukemia; CNL = chronic neutrophilic leukemia; NOS = not otherwise specified.

[a] Lymphoid neoplasms can also occur as well as the footnoted entities.

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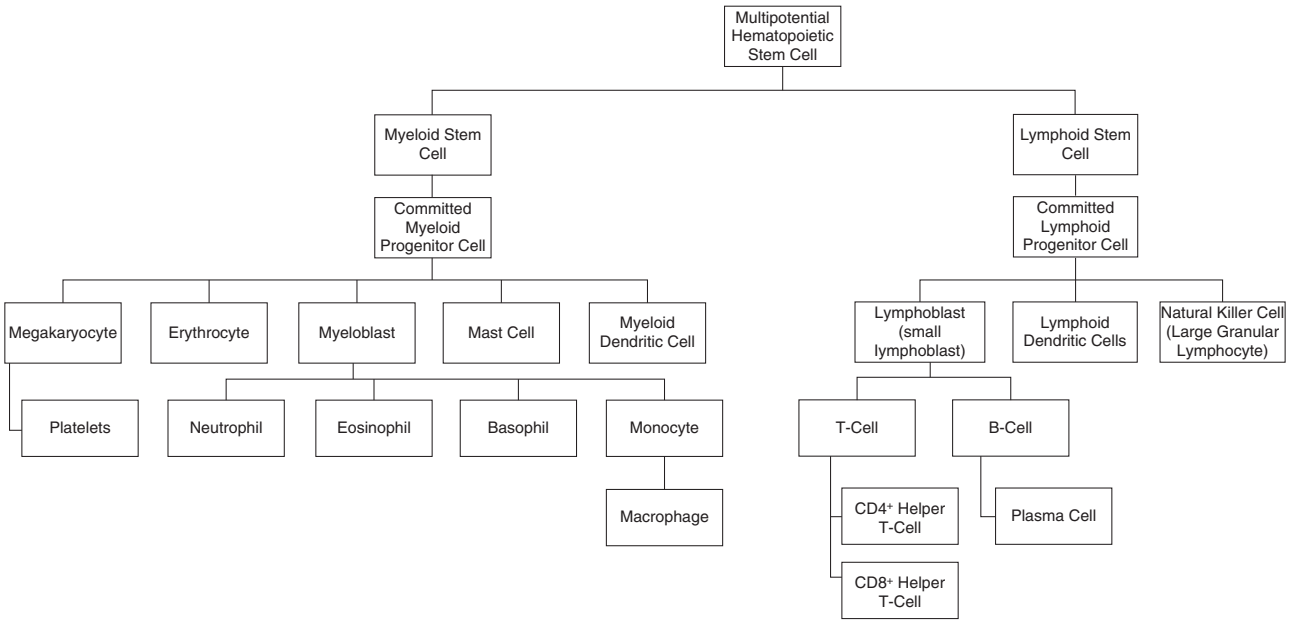


FIGURE 59.2. Normal hematopoiesis differentiation pathway. The multipotential hematopoietic stem cells produce self-renewing myeloid and lymphoid stem cells in bone marrow. Differentiation begins following the formation of committed myeloid and lymphoid progenitor cells from myeloid and lymphoid stem cells. These stem cells undergo self-renewal to maintain an adequate supply of stem cells for continued production of leukocytes. Ultimately, mature leukocytes (i.e., neutrophils, basophils, eosinophils, B cells, T cells, natural killer cells) appear in the peripheral blood along with erythrocytes and platelets. With an immature, B cell receptor, competent B cells migrate from the bone marrow to the spleen where they form a primary follicle with T cells and follicular dendritic cells with the B cell zone surrounding the T cell zone. Naïve follicular B cells that survive become fully mature B cells capable of participating in immune responses; these mature B cells subsequently circulate through all lymphoid tissues (spleen, lymph nodes, lymphoid-associated tissue) while being exposed to antigens. From the germinal center or the memory B cell population, antigen-specific B cells proliferate into plasma cells in the presence of the appropriate antigen. Plasma cells in the spleen or lymph nodes produce antibodies only for limited periods of time, whereas plasma cells that migrate to bone marrow are long-lived secreting antibodies into the blood for extended periods of time. T cells undergo further differentiation into CD4+ and CD8+ helper T cells in the thymus; these cells remain immunologically naïve until antigenic stimulation at sites of inflammation induces differentiation into effector cells capable of interacting with the antigens.

translocations are also complications of radiotherapy and chemotherapeutic drugs (e.g., topoisomerase II inhibitors, alkylating agents).[15] Figure 59.3 displays the probable cells of origin for AML, ALL, cALL (common acute lymphoblastic leukemia), and CML along with common translocations. Myeloid progenitor-derived leukemias are involved with innate rather than adaptive immunity that is important to monitoring native cellular processes. Alterations in immune surveillance may enhance the development of childhood leukemia. Immune stimulation from vaccinations and the normal course of childhood infections appears protective when some potentially childhood leukemia patients develop susceptibility to leukemia *in utero* from overactive immune responses.[12]

Adult leukemogenesis is a complex process involving multiple DNA mutations and structural changes; small, nonprotein-coding micro-RNAs (miRNAs) and long, nonprotein-coding RNAs (lncRNAs) also influence leukemogenesis by acting epigenetically to interact with signaling pathways that dysregulate gene expression in the nuclear compartment and cytoplasm. Numerous miRNAs and lncRNAs suppress or promote neoplasms by affecting tumor angiogenesis, growth, immune response, and metastasis.[16,17] These ncRNAs are potential biomarkers for determining the diagnosis and prognosis of leukemia subtypes (e.g., AML, CML, T-ALL).[18] Epigenetic functions include promoter-specific gene regulation, control of chromatin, structural maintenance of nuclear bodies, genomic imprinting/silencing, and X-chromosome inactivation.[19] Recent data suggest ~20,000 lncRNAs exist that potentially can interact with the human genome including a subset of lncRNAs capable of impeding miRNAs

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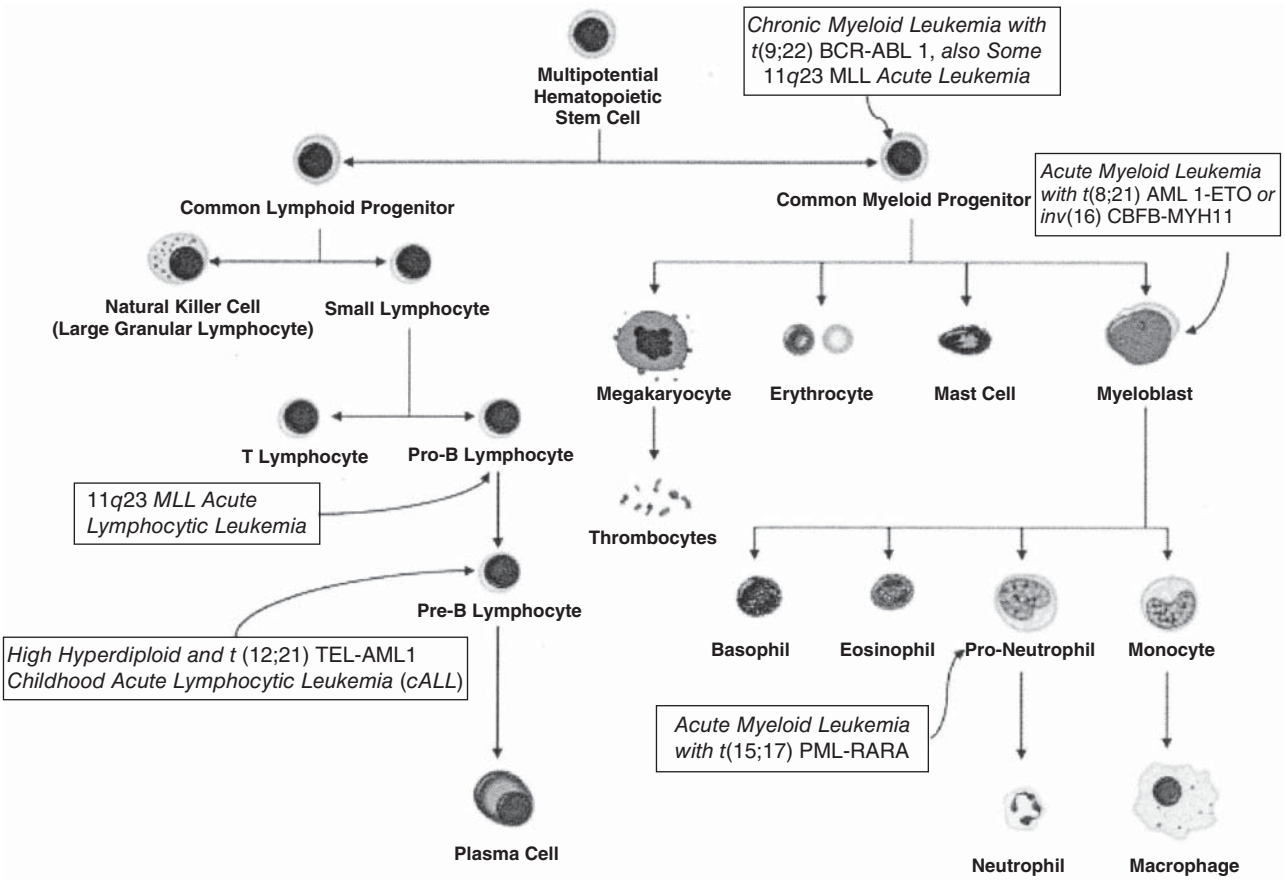


FIGURE 59.3. Cellular origin of common leukemias with the most frequent translocations. Most hematopoietic precursor cells have neoplastic counterparts that share similar morphological features with the original cell. (Adapted from Wiemels).[12]

and increasing mRNA expression.[20] Noncoding RNAs display significant tissue specificity functioning as transcriptional activators or cofactors as well as competing with endogenous RNAs, resulting in specific ncRNA expression patterns for leukemia subtypes. The *NOTCH1* gene has diverse functions (e.g., proliferation, differentiation, apoptosis) that allow the gene to function as an oncogene or a tumor suppressor. Aberrant expression of the oncogenic lncRNA, IGF1R activator RNA 1, enhances malignant T cell transformation during the development of *NOTCH1*-driven T cell acute lymphoblastic leukemia.[21]

EXPOSURE

Most leukemia cases are sporadic with no recognized risk factors; only an estimated 10% of childhood leukemias are associated with recognized risk factors (age, sex, race, ionizing radiation, certain congenital diseases).[22] Both childhood and adult leukemias are heterogeneous diseases with multiple subtypes and potentially different risk factors from variations in chromosomal translocations, fusion genes, and gene deletions/duplications. Hence, no single cause accounts for all leukemias or leukemia subtypes. Some leukemia subtypes (e.g., AML), but not all leukemia subgroups (e.g., CLL), have been causally linked with exposure to ionizing radiation, high-dose benzene exposures, some viruses, or chemotherapeutic agents.[23] Table 59.2 lists the strength of the human evidence (sufficient, limited) for carcinogenic agents and processes associated with hematopoietic cancers based on evaluations by the International Agency for Research on Cancer.[24,25] Some childhood leukemias are associated with congenital genetic syndromes (e.g., Down syndrome, neurofibromatosis, Fanconi's anemia); however, these disorders are uncommon (i.e., <5–10% of childhood cases). Pesticides are suspected agents associated with some adult lymphoproliferative cancers and childhood leukemias based almost

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TABLE 59.2. International Agency for Research on Cancer (IARC) classification of cancer sites by sufficient and limited evidence of human carcinogenicity in leukemias, lymphomas, and multiple myeloma. (Adapted from Cogliano et al.).[24]

Cancer Type	Carcinogens with *Sufficient* Human Evidence (Group 1)	Carcinogens with *Limited* Human Evidence (Groups 2A or 2B)
	Childhood leukemia	
Acute lymphocytic		Tobacco smoking (parents)
Acute myeloid		Benzene, teniposide, tobacco smoking (parents)
All childhood leukemias combined	Fission products including ^{90}Sr, ^{232}Th, x- and γ-radiation	Chloramphenicol, extremely low frequency magnetic fields, painter (mother), radioiodines including ^{131}I, tobacco smoking (parents)
	Adult leukemia	
Acute myeloid	Benzene, busulfan, chlorambucil, cyclophosphamide, etoposide with cisplatin and bleomycin, formaldehyde, melphalan, MOPP, and other combination chemotherapy including alkylating agents, ^{32}P as phosphorus, semustine, ^{232}Th and decay products, tobacco smoking, treosulfan, x- and γ-radiation	Bischloroethyl nitrosourea, etoposide, mitoxantrone, teniposide
Other acute non-lymphocytic	Benzene, formaldehyde, ^{32}P as phosphorus, ^{232}Th and decay products, tobacco smoking, x- and γ-radiation	Bischloroethyl nitrosourea
Chronic myeloid	Formaldehyde, ^{232}Th and decay products, tobacco smoking, x- and γ-ray radiation	Benzene
Acute lymphocytic	^{32}P as phosphorus, ^{232}Th and decay products, x- and γ-radiation	
Chronic lymphocytic		Benzene, ethylene oxide
Adult T cell leukemia/ lymphoma (ATLL)	Human T cell lymphotropic virus type 1, ^{232}Th and decay products, x- and γ-radiation	
All leukemias combined	1,3-Butaiene, fission products including ^{90}Sr, rubber manufacturing industry, thiotepa	Chloramphenicol, diazinon, nitrogen mustard, petroleum refining occupation, radioiodines including ^{131}I, ^{222}Ra and decay products, styrene
	Lymphoma	
Hodgkin	Epstein–Barr virus, human immunodeficiency virus type 1 infection	
Primary effusion	Kaposi sarcoma herpesvirus	
Non-Hodgkin: immunosuppression-related	Epstein–Barr virus	
Non-Hodgkin: Burkitt	Epstein–Barr virus	Malaria caused by endemic *Plasmodium falciparum* infection
Non-Hodgkin: NK/T cell (nasal type)	Epstein–Barr virus	
Non-Hodgkin: low-grade B cell mucosa associated lymphoid tissue (MALT gastric)	*Helicobacter pylori* infection	
Non-Hodgkin: combined	Azathioprine, cyclosporine, chronic hepatitis C virus infection, human immunodeficiency virus type 1 infection, lindane, pentachlorophenol	Benzene, chlorophenoxy herbicides, DDT, diazinon, dichloromethane (methylene chloride), ethylene oxide, firefighters (occupation), glyphosate, hepatitis B virus chronic infection, malathion, polychlorinated biphenyls, polychlorophenols, and sodium salts, 2,3,7,8-tetrachorodibenzo-*para*-dioxin, trichloroethylene, x- and γ-radiation
Multicentric Castleman disease		Kaposi sarcoma herpesvirus
Lymphoma: combined	1,3-Butadiene, rubber manufacturing industry	Styrene
	Multiple myeloma	
Multiple myeloma	1,3-Butadiene, pentachlorophenol	Benzene, ethylene oxide, styrene, 1,1,1-trichloroethane, x- and γ-ray radiation

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exclusively on unvalidated self-reports in case-control studies.[26,27] Inconsistent findings, imprecise exposure assessments (time/intensity), lack of exposure-response relationships, complex/changing lymphoma classifications/exposure misclassification, small sample sizes, long latency, and confounding factors limit definitive conclusions on causation.[28] The IARC lists diazinon as a carcinogen with limited human evidence. The prospective Agricultural Health Study of 23,106 eligible pesticide applicators (21.5% participation rate) identified 32 leukemia cases classified by ICD9 codes 204–208.[29] Using lifetime exposure days as a measure of cumulative diazinon exposure based on self-reported, take-home questionnaires, the adjusted relative risk of the highest tertile compared with no exposure was elevated, but imprecise (aRR = 3.36, 95% CI: 1.08–10.49, $n = 4$ cases, $P_{\text{trend}} = 0.026$). The aRR for leukemia in the highest tertile using intensity-weighted exposure days was statistically nonsignificant and imprecise (aRR = 2.88, 95% CI: 0.92–9.03, $n = 4$, $P_{\text{trend}} = 0.053$).

Other potential leukemogenic substances include some chemicals, electromagnetic fields, and lifestyle factors (e.g., smoking, alcohol consumption); however, none of these agents are proven risk factors for leukemia. Background ionizing radiation (e.g., radon) does not account for most leukemia cases based on case-control studies including childhood leukemias. In a German study of 82 childhood leukemia cases and 209 population-matched controls, indoor radon concentrations were not associated with childhood leukemia using a prespecified cutpoint of 70 Bq m^3 (OR = 1.30, 95% CI: 0.32–5.33).[30] The mean indoor radon concentration of 27 Bq m^3 was relatively low compared with other studies.

Ionizing Radiation

The IARC lists x-radiation, γ-radiation, and several isotopes as human carcinogens that increase leukemia risks, including ^{90}strontium and other fission products, ^{32}phosphorus, and ^{232}thorium and its decay products. Isotopes associated with limited human evidence for increasing leukemia risks include radioiodine (e.g., ^{131}iodine) and ^{222}radon and its decay products. Leukemia was the first cancer detected in atomic bomb survivors from Hiroshima and Nagasaki.[31] Significant dose-related elevated risks occurred for CML, AML, and ALL; however, no increased risk of CLL was observed. The incidence of CLL is much lower in Japan than in the United States or Europe. Although significant publication bias exists for the exclusion of CLL from outcome measures of radiation-induced epidemiology studies, most lymphoma/leukemia studies with >15 years of follow-up report odds ratios above 1, albeit without statistical significance, whereas results from occupational cohorts are more varied.[32] Significant excess relative risks (ERRs) of leukemia-associated mortality from non-CLL leukemias occurred in a cohort receiving radiotherapy for ankylosing spondylitis (ERR = 3.11, 95% CI: 2.37–4.07, $n = 53$, $P_{\text{trend decreasing with time}} = <0.001$).[33] In the Israeli *Tinea capitis* study using age- and sex-matched population controls, the relative risk of leukemia-related death was statistically marginally significant (RR = 2.3, 95% CI: 1.0–5.6, $n = 14$ cases).[34] The ERR/Gy was 2.22 (95% CI: 0.6–4.8/Gy).

The association between parental occupational sources and childhood leukemia is relatively weak and inconsistent. Most case-control studies do not report a statistically significant increase in leukemia risk. In a German study of 1,184 leukemia cases and 2,588 age-matched controls, preconception paternal occupation in the nuclear industry undergoing dosimetric surveillance was not associated with a statistically significant increase in childhood leukemia (OR = 1.80, 95% CI: 0.71–4.58). The radiation doses of these fathers were mostly below detection or unknown, with no radiation dose exceeding 30 mSv. A systematic review of nine case-control studies published from 1990–2006 did not detect an association between prenatal diagnostic X-rays and leukemia (pooled random effects OR = 0.99, 95% CI: 0.87–1.13, $n = 433$ cases/4,459 nonexposed controls, $I^2 = 0\%$).[35]

Electromagnetic Fields

Adults

The association between electromagnetic field exposure and adult leukemia is weak and inconsistent.[36] Occupations potentially at risk from electromagnetic fields include telephone and power linemen electrical and electronics technicians, radio operators, and radio and television repairmen.[37] In a California study of 2,355 men with leukemia working in occupations associated with electric field exposures and 65,792 controls with other non-CNS cancers, the OR for all leukemias comparing the highest (>20 V/m) and lowest (<10 V/m) estimated mean electrical field exposure was 1.15 (95% CI: 0.78–1.72, $n = 31$ cases/793 controls).[38] Calculation of electric fields was based on task-weighted exposure estimates for each job title reflecting exposure over the preceding 15–20 years. The results indicate no clear

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evidence of an exposure-response relationship between electric field estimates and leukemia. A case-control study of military personnel detected a borderline significant elevation (RR = 2.4, 95% CI: 1.0–5.0, $n = 7$ cases) of increased leukemia risks only in electrical mates exposed to 60 Hz electromagnetic fields.[39] Overall the standardized incidence ratio for leukemia in all US Navy occupations in the study was 0.9 (95% CI: 0.8–1.1, $n = 102$ cases) using Surveillance, Epidemiology, and End Results (SEER) data from the general US population. A population-based New Zealand study of 110 incident acute leukemia cases and 199 age-matched controls reported a marginally statistically significant increased acute leukemia risk comparing ever- and never-electrical workers (adjusted OR = 1.9, 95% CI: 1.0–3.8, $n = 26$ cases/27 controls) based on telephone interviews.[40] The strongest association occurred in telephone line workers and welders, with no statistically significant increased acute leukemia risks reported in occupations with the highest potential electric field exposures (e.g., electric vehicle operators, electricians, electrical power line/cable workers, electrical fitters).

Epidemiology studies suggest a weak positive association between occupational ELF-MF exposures and some leukemia subtypes, primarily myeloid types; however, the studies are inconsistent between the subtypes. In a UK study of 73,051 electrical workers employed for at least 6 months, overall leukemia risks were close to unity for all exposure categories without evidence of increased risks in the highest cumulative magnetic field exposure categories.[41] ALL risks demonstrated a significant positive trend based primarily on unusually low ALL risks in the lowest exposure category, whereas risks for AML, CML, and CLL showed no definite positive trend. In contrast, the prospective Netherlands Cohort Study reported an elevated AML risk for ever high-ELF-MF exposed category of the Dutch general population (HR = 2.15, 95% CI: 1.06–4.35), but no increased risks for ALL, CLL, or CML.[42] Analysis of data from the Nordic Occupational Cancer cohort on 5,409 adult AML cases and 27,045 age-, sex-, and country-matched controls did not demonstrate an association between high levels of ELF-MF exposure and AML (HR = 0.88, 95% CI: 0.77–1.01).[43] In the Swiss National Cohort, overall hemato-lymphopoietic cancer mortality was not associated with ELF-MR exposures, with the exception of increased myeloid leukemias (HR = 1.31, 95% CI: 1.02–1.97, $n = 70$ cases).[44] Their meta-analysis of occupational ELF-MF exposures and AML risks based on job-exposure matrices yielded a summary RR of 1.21 (95% CI: 1.08–1.37, $I^2 = 73.2\%$) with high heterogeneity.

The weaknesses of these studies include lack of control over confounding variables (benzene, ionizing radiation) and inadequate measurements of electromagnetic field exposures. Measuring residential fields is logistically difficult and expensive. Therefore, surrogates (e.g., wire-code classifications) are frequently used to estimate exposure. The wiring code correlates with factors other than residential magnetic fields, including age of house, housing density, and traffic density.[45]

Children

Childhood leukemia has been associated with electromagnetic field exposures in environmental settings in several different countries; however, no clear, plausible biological mechanism or experimental research supports a causal relationship.[46,47] The IARC considers ELF electromagnetic fields a possible childhood carcinogen (Group 2B) based on limited epidemiological evidence for an association with childhood leukemia, primarily in the top percentiles of extremely low frequency magnetic field exposure (>0.3–0.4 μT). The observational studies involve small case numbers and imprecise risk estimates.[48] This association was weaker in a pooled analysis of more recently conducted studies on childhood leukemia without a clear dose-response relationship.[49] Compared with the lowest tertile (≤0.1 μT), the childhood leukemia risk for the upper tertile (≥0.3 μT) was not statistically significant (OR = 1.44, 95% CI: 0.88–2.36).

Although some case-control studies suggest a positive correlation between exposure to electromagnetic waves and childhood leukemia, most cohort studies do not support a causal association between electromagnetic fields and leukemia. An approximate 1.5-fold excess of childhood leukemia is associated with living in a house belonging to the high wire-code category;[45] however, these studies have not demonstrated a dose-response relationship between exposure to electromagnetic fields and the risk of developing leukemia. Follow-up studies have not detected excess magnetic field exposures in children developing leukemia. A recently updated case-control study of 53,515 UK children from the National Registry of Childhood tumors reported a reduction in childhood leukemia risks for offspring of mothers residing within 199 m of overhead high-voltage powerlines (132–400 kV) at the time of birth when compared with controls (>1,000 m from powerlines).[50] For all voltages, the relative risks decreased from 4.50 (95% CI: 0.97–20.83) in the 1960s to 0.71 (95% CI: 0.49–1.03) in the 2000s. The aggregate over the entire

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time period was 1.12 (95% CI: 0.90–1.38). Positive values for childhood leukemia risks did not extend beyond 600 m.

Occupation

The IARC lists occupational exposures to several chemicals as human carcinogens that increase leukemia risks including 1,3-butadiene, formaldehyde, pentachlorophenol, and work in the rubber production industry. Agricultural and other occupational exposures associated with limited evidence of increasing leukemia risks include benzene, busulfan, chlorambucil, cyclophosphamide, diazinon, ethylene oxide, formaldehyde, melphalan, MOPP therapy, petroleum refining, ^{32}P as phosphorus, semustine, styrene, tobacco smoking, treosulfan, and x- and γ-radiation. In addition, the IARC classifies childhood leukemia from maternal exposure to painting occupations as limited human evidence of leukemia risks.

A New Zealand cancer registry study of 225 leukemia cases and 471 controls used unconditional regression to compare ever- versus never-employed workers in specific occupations based on information obtained from face-to-face interviews.[51] Statistically significant elevated leukemia risks occurred in the agricultural sector, including horticulture/fruit growing (OR = 2.62, 95% CI: 1.51–4.55, $n = 32$ cases/32 controls), plant nurseries (OR = 7.51, 95% CI: 1.85–30.38, $n = 8$ cases/3 controls), and vegetable growing (OR = 3.14, 95% CI: 1.18–8.41, $n = 10$ cases/8 controls); the elevated risks occurred in women only. Using semi-Bayes adjustment (gender, age, smoking history, occupational status) to compensate for multiple comparisons, statistically significant elevated leukemia risks appeared in physical science and engineering associated professionals (OR = 1.74, 95% CI: 1.03–2.94, $n = 29$ cases/27 controls). For industries, suggestive increased leukemia risks occurred in personal and household goods retailing (OR = 1.85, 95% CI: 1.25–2.75, $n = 63$ cases/94 controls). Poor participation rates (57% cases/48% controls), age differences (56.2 years cases/59.2 years controls), small numbers, imprecise exposure estimates, and potential misclassification limit conclusions regarding causation. An analysis of data from the Nordic Occupational Cancer Study estimated standardized incidence ratios for AML, CLL, and other leukemias in workers from over 300 occupational categories.[52] The study reported modestly elevated AML risks in drivers (SIR = 1.16, 95% CI: 1.07–1.26, $n = 555$ cases) and food workers (SIR = 1.13, 95% CI: 1.01–1.27, $n = 287$ cases), whereas CLL risks were modestly increased in clerical workers (SIR = 1.07, 95% CI: 1.01–1.14, $n = 1{,}086$ cases) and farmers (SIR = 1.09, 95% CI: 1.04–1.14, $n = 1{,}746$ cases). For other leukemias, the risks were increased in sales agents (SIR = 1.15, 95% CI: 1.06–1.25, $n = 562$ cases) and seamen (SIR = 1.24, 95% CI: 1.04–1.49, $n = 118$ cases). Five occupations had reduced SIRs including forestry workers and seamen for AML, seamen for CLL, and other health workers and fishermen for other leukemias. The study did not adjust for multiple comparisons.

Benzene and the Petroleum Industry

The association between high benzene exposures in industrial settings and acute myeloid leukemia is consistently strong and exposure-response related. The association with relatively low benzene concentrations (i.e., <1 ppm) or other lymphohematopoietic cancers is weaker, particularly with changes in refining processes and recent reductions in the benzene content in transportation fuels. A nested case-control study of 69 leukemia cases and 284 age-matched, unexposed company controls did not detect a clear association between work in refining division and leukemia based on job classifications and death certificates (OR = 0.85, 95% CI: 0.46–1.5, $n = 19$ deaths);[53] however, the study did suggest the possibility of an association between production and maintenance workers in oil and gas industries and myelogenous leukemia (adjusted OR = 3.2, 95% CI: 1.1–9.2, $n = 9$ deaths). In a pooled analysis of three nested case-control studies of Australian, Canadian, and UK petroleum distribution workers with 370 case subjects and 1,587 controls, data analysis suggests a dose-response relationship between myelodysplastic syndrome (MDS) and cumulative benzene exposure; the odds ratio of MDS comparing the highest (>2.93 ppm-years) and lowest tertile (≤0.348 ppm-years) of benzene exposure was 4.33 (95% CI: 1.31–14.3, 15 cases/39 controls, $P = 0.03$).[54] The study reported little evidence of exposure-response relationships between cumulative benzene exposure and AML, CLL, CML, or myeloproliferative disease. The large confidence intervals indicate imprecise OR estimates from small case numbers. A review of historical cohort studies of petroleum refinery and chemical manufacturing workers in Texas did not reveal any statistically significant increase in SMR for the 20 types of cancers studied including leukemia (SMR = 112, 95% CI: 94–130).[55] Some epidemiological evidence suggests benzene exposure increases leukemia risks other than AML, but the associations are relatively weak and varied based on mortality studies.[56,57] Most studies do not associate benzene exposure with non-Hodgkin lymphoma or multiple myeloma.[58,59]

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Smoking does not appear to increase the risk of developing leukemia following occupational benzene exposure,[60] despite cigarettes being a relatively high benzene source (30–73 μg benzene/*cigarette*).[61,62] In comparison to cigarette smoke, the benzene content of cigar and pipe smoke is higher (85–207 and 250–470 μg benzene/g tobacco, respectively).[63]

Gasoline

The presence of benzene in gasoline creates a potential leukemia risk, particularly for acute myelogenous leukemia; the epidemiological evidence for an association with other leukemia subtypes is weaker.[64,65] The mean benzene concentration averaged 0.8–3.18% from 1972–1991, with European gasoline typically containing <2%; however, the benzene concentration is significantly lower in gasoline vapor than liquid.[66,67] Control systems and refinery procedures have reduced benzene exposure from gasoline for most refinery and distribution workers to relatively low concentrations (e.g., <1 mg/m^3).[68] An evidence-based analysis ranked 54 epidemiology studies on occupational gasoline exposure and lymphatic/hematopoietic cancer risks; the 30 highest-ranked studies were divided into three tiers based on strength, specificity, consistency, temporality, dose-response trends, and coherence.[69] None of the meta-relative risks for total leukemias or leukemia subgroups in tier 1 (highest) or tier 2 (intermediate) studies were statistically significant, including the meta-RR for acute myelogenous leukemia (ICD 205.0) using fixed effects models (e.g., meta-$RR_{tier\,1} = 1.00$, 95% CI: 0.993–0.1007). The meta-RR for ALL in tier 3 (lowest category), but not tier 2 (intermediate), was statistically significant (meta-$RR_{tier\,3} = 1.92$, 95% CI: 1.05–2.79, $n = 3$ studies) using a fixed effects model. Subanalysis of the data reported elevated hematopoietic cancer risks in US refinery cohorts occurred primarily in workers hired before 1950, consistent with more recent studies.[70]

1,3-Butadiene and Styrene–Butadiene Rubber Industry

Epidemiological research on 1,3-butadiene focuses primarily on two cohorts: North American styrene–butadiene synthetic rubber production and the US butadiene monomer industry. The IARC considers 1,3-butadiene a human carcinogen associated with lymphohematopoietic cancers via a direct-acting genotoxic mechanism involving the formation of reactive epoxides and DNA damage. The epidemiological evidence for an association with hemolymphatic cancers is strongest for leukemias based on the styrene–butadiene synthetic rubber production cohort. The association with leukemia subtypes is weaker, in part, because of low case numbers and imprecise risk estimates. Furthermore, the evolving, multifaceted classifications and diagnostic criteria of hematopoietic and lymphatic tumors complicate the interpretation of results from these cohorts.

Mortality data from 17,924 men employed in the North American styrene–butadiene rubber cohort followed from 1943–1998 demonstrate elevated leukemia risks based on evaluations of work histories, standardized mortality ratios (SMRs), and procedures to determine the International Classification of Diseases (ICD) codes for decedents;[71] the monomer industry study was less conclusive. The SMR for overall leukemia in the whole cohort was positive, but not statistically significant (SMR = 116, 95% CI: 91–147, $n = 71$ cases). Subgroup analysis indicated statistically significant increased leukemia risks were concentrated in hourly employees employed for ≥10 years and 20–29 years since hire (SMR = 258, $n = 19$ cases), polymerization workers (SMR = 204, $n = 18$ cases), maintenance workers (SMR = 326, $n = 15$ cases), and laboratory operators (SMR = 326, $n = 14$ cases). For leukemia subgroups in the last 30 years of the cohort, data were difficult to interpret because the case numbers were small and the estimates imprecise. The authors opined that CML and CLL accounted for most of the overall increased leukemia SMR noted above in the hourly employees employed for ≥10 years and 20–29 years since hire. The data did not support an elevated risk of Hodgkin lymphoma, non-Hodgkin lymphoma, or multiple myeloma. Analysis of data on 4,863 female styrene–butadiene rubber plant workers did not support excess deaths for leukemia, Hodgkin lymphoma, multiple myeloma, or non-Hodgkin lymphoma.[72] Analysis of exposure-response relationships indicates average butadiene intensity and peaks (>100 ppm) were associated with leukemia mortality.[73] Some uncertainty about the strength of the results remained because the specific carcinogenic agent was not identified and cofounding was not excluded.

Leukemia mortality in the butadiene monomer industry is not clearly associated with butadiene exposure based on pre-2008 WHO leukemia classifications.[74] In a Texas study of 614 operations, shipping, laboratory, and maintenance workers at the Deer Park refinery with at least 5 years of employment while exposed to butadiene monomer, the SMR from 1948–1998 for these workers was 1.06 (95% CI: 0.22–3.11, $n = 3$ cases) based on death certificates.[75] There were no leukemia-related deaths. Random sampling indicates the mean 8-hour

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time-weighted average butadiene concentration was <1.75 ppm, except for shipping workers (i.e., ~10 ppm). The overall cancer standardized mortality rate was 0.55 (95% CI: 0.42–0.70, $n = 61$ deaths), whereas the 56-year mortality study of 10,621 male refinery workers at the Deer Park petroleum and chemical plant (mean = 34 years of follow-up) with ≥10 years of employment did not detect an elevated SMR for overall lymphatic and hemopoietic cancers.[76] The SMR was 1.04 (95% CI: 0.81–1.30, $n = 74$ deaths) with no increased SMR in any major lymphatic or hemopoietic subgroups (i.e., AML, ALL, CML, CLL). Although data analysis from 16,579 synthetic rubber industry workers followed from 1943–1998 suggests CML and, to a lesser extent, CLL mortality were elevated, the more commonly occurring, chemically induced leukemia subtype, AML, was not.[77] Exposure-response modeling of data from the styrene–butadiene synthetic rubber industry using cumulative 1,3-butadiene ppm-years as the predictor variable indicates the slope for lymphoid, but not myeloid (i.e., CML, AML), neoplasms is statistically significantly greater than zero.[78] *In vitro* studies indicate 1,3-butadiene can induce the pathological t(9:222) translocations (Philadelphia chromosome); however, the frequency of the translocations is much lower for butadiene than ionizing radiation.[79]

Formaldehyde

Although large positive cohort studies suggest an association between occupational formaldehyde exposure and lymphohematopoietic neoplasms, the ability of formaldehyde to cause leukemia or lymphomas remains controversial, particularly among specific leukemia and lymphoma subtypes including myeloid leukemia.[80] The IARC lists formaldehyde as a human (Group 1) carcinogen, with sufficient evidence of increased myeloid leukemia risks based on epidemiological studies of formaldehyde-exposed workers and moderate evidence of formaldehyde-induced cytotoxicity/genotoxicity in Chinese workers. However, a substantial minority of the working group considers the epidemiological evidence for formaldehyde-induced carcinogenicity limited.[81] After the IARC determined formaldehyde was a human carcinogen, the USEPA reviewed the carcinogenicity issue based on recommendations from a National Academy of Science Committee.[82] This review included several critical reviews and extended analyses of epidemiological studies, recent updates of earlier occupational cohort studies, mouse studies in a sensitive strain, and mechanistic studies on exogenous versus endogenous effects of formaldehyde on bone marrow. The review concluded, "with few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia."

Formaldehyde-exposed workers include anatomists, embalmers, and formaldehyde industrial workers; studies of these cohorts are inconsistent with the strongest evidence for combined myeloid leukemia.[83] Meta-analyses on formaldehyde exposure and leukemia risks demonstrated mixed results, with some analyses failing to support the association.[84] In a meta-analysis of four cohort studies of formaldehyde-exposed industrial workers, the meta-SMR for leukemia deaths was not elevated (meta-SMR = 0.90, 95% CI: 0.75–1.97, $n = 122$ deaths, $P_{\text{heterogeneity}} = 0.53$).[85] The meta-SMR for leukemia deaths in five cohorts of professionals (e.g., anatomists, embalmers) was increased (meta-SMR = 1.36, 95% CI: 1.03–1.79, $n = 51$ deaths, $P_{\text{heterogeneity}} = 0.84$). A meta-analysis of 15 studies focusing on the highest exposure groups in each study reported an elevated meta-relative risk for leukemia deaths (summary-RR = 1.54, 95% CI: 1.18–2.00, $P_{\text{heterogeneity}} = 0.11$) using fixed effects models with Shore adjustment.[86] The summary relative risk for myeloid leukemia was 1.90 (95% CI: 1.31–2.76, $n = 36$ deaths, $P_{\text{heterogeneity}} = 0.15$). A meta-analysis of cohort and case-control studies on formaldehyde and leukemia reported little support for a causal relationship between formaldehyde exposure and leukemia including leukemia subtypes.[87] For cohort studies, the summary relative risk was 1.05 (95% CI: 0.93–1.20) and 0.99 (95% CI: 0.71–1.37) for case-control studies. The analysis detected no evidence of serious heterogeneity or publication bias.

The association of formaldehyde with leukemia is weaker for industry than for professional workers. In the National Cancer Institute's (NCI) cohort of 25,619 workers in formaldehyde industries comparing the highest (≥4 ppm) and lowest (>0–<2 ppm) peak exposure categories, the relative risk of death was elevated for all lymphohematopoietic malignancies (RR = 1.37, 95% CI: 1.03–1.81, $n = 108$ deaths, $P_{\text{trend}} = 0.2$) and Hodgkin lymphoma (RR = 3.96, 95% CI: 1.31–12.02, $n = 11$ deaths, $P_{\text{trend}} = 0.01$) based on death certificates and ICD-8 codes.[88] The positive associations were reported as statistically nonsignificant for multiple myeloma (RR = 2.04, 95% CI: 1.01–4.12, $n = 21$ deaths, $P_{\text{trend}} = 0.08$) and myeloid leukemia (RR = 1.78, 95% CI: 0.87–3.64, $n = 19$ deaths, $P_{\text{trend}} = 0.13$). AML and CML were not separated despite genetically different mutations (e.g., Philadel-

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phia chromosome in CML) and substantially different risk factors. The study reported little evidence of associations between these neoplasms and cumulative or average intensity formaldehyde exposures. Analysis of mortality data from the US National Cancer Institute cohort did not support increased mortality from AML (SMR = 0.80, 95% CI: 0.56–1.14, $n = 30$ deaths) or CML (SMR = 0.97, 95% CI: 0.56–1.67, $n = 13$ deaths).[89]

The cohort mortality study of 11,043 formaldehyde garment workers provided limited evidence of an association between formaldehyde exposure and leukemia.[90] Compared with the US population, the SMR for myeloid leukemia was modestly elevated, but statistically nonsignificant (SMR = 1.28, 95% CI: 0.79–1.96, $n = 21$ deaths). Similarly, the SMR for AML, CML, Hodgkin/non-Hodgkin lymphoma, and multiple myeloma were elevated without statistical significance. In a US study of 168 deceased funeral directors and embalmers from lymphohematopoietic tumors and 265 unexposed deceased funeral industry controls, myeloid leukemia mortality significantly increased with duration of embalming compared with the lowest category of embalming (<500 lifetime); the odds ratio for the highest category of >34 years was 3.9 (95% CI: 1.2–12.5, $n = 14$ deaths, $P_{trend} = 0.020$).[91] The odds ratio for AML in this exposure category was not statistically significant (OR = 3.1, 95% CI: 0.7–13.7, $n = 8$ deaths, $P_{trend} = 0.63$) based on death certificates and ICD-8 codes; however, a considerable amount of missing data required the use of estimated exposures (i.e., imputation). The imprecise estimates reflect the use of next-of-kin interviews as the information source for formaldehyde exposure.

Most epidemiology studies have not reported significantly increased Hodgkin or non-Hodgkin lymphoma risks in formaldehyde-exposed workers. An Italian cohort study of 2,750 laminated plastic factory workers with at least 6 months of formaldehyde exposure reported a nonsignificant reduction in lymphohematopoietic cancer deaths (SMR = 68.6, 95% CI: 31.4–131.3, $n = 9$ deaths).[92] The SMR was unrelated to the likelihood of formaldehyde exposure with no increased deaths among blue-collar workers. No quantitative exposure measurements for formaldehyde were available. A nested case-control study from a cohort of 14,008 UK chemical workers reported no statistically significant elevation of overall myeloid leukemia deaths (SMR = 1.20, 95% CI: 0.84–1.66, $n = 36$ deaths) or deaths in the highest formaldehyde exposure category defined by >2 ppm for ≥1 year (SMR = 0.93, 95% CI: 0.40–1.82, $n = 8$ deaths).[93]

Ethylene Oxide

Ethylene oxide is a highly reactive epoxide that is a direct-acting alkylating agent and mutagen, producing ethylene oxide-derived hemoglobin and DNA adducts as well as chromosomal aberrations, sister chromatid exchanges, and micronucleus formation. The IARC upgraded this chemical to a human carcinogen based on genotoxic mechanistic data, sufficient evidence in animals, and limited evidence in humans.[94] Epidemiological data do not provide consistent and convincing evidence associating ethylene oxide exposure with increased leukemia or non-Hodgkin lymphoma risks.[95] A previous analysis of 10 studies on leukemia in workers exposed to ethylene oxide demonstrated a combined SMR of 1.06 (95% CI: 0.73–1.48).[96] Historical inconsistencies in the histopathological classification of leukemia and lymphomas complicate the interpretation of these studies. In a Swedish study of 733 ethylene oxide workers, the SMR was elevated (SMR = 9.21, 95% CI: 3.51–18.03, $n = 8$ leukemia cases); however, small sample size, imprecise SMR estimates, and poor control of confounding variables limit definitive conclusions on a causal association.[97] The estimated average airborne ethylene 8-hour time-weighted average for earlier workers was 5–8 ppm compared with 0.4–1.6 ppm for later workers.

The US NIOSH ethylene oxide cohort study of 18,254 ethylene oxide-exposed workers at 14 plants producing sterilized medical supplies and spices exposed them for an average of 4.9 years and followed them for 16 years.[98] The recent 8-hour time-weighted adjusted ethylene oxide exposure averaged 4.3 ppm for sterilizer operators and 2.0 ppm for other workers, with the authors opining that earlier ethylene oxide exposures were several times higher. Overall, the study demonstrated no significant increase in mortality from any cause, including an SMR of 0.97 for leukemia (95% CI: 0.52–1.67; $n = 13$ deaths) and 1.0 for non-Hodgkin lymphoma (95% CI: 0.57–2.37, $n = 8$ deaths). Although mortality was greatest in the highest cumulative ethylene oxide exposure category of >8,500 ppm-days (SMR = 1.24, 95% CI: 0.66–2.13, $n = 13$ deaths), the trend was weak ($P_{trend} = 0.32$) and statistically nonsignificant.[99] An additional follow-up period of 11 years revealed no overall excess of hematopoietic cancers combined or non-Hodgkin lymphoma.[100] In an internal analysis, log-cumulative ethylene oxide exposure was associated with lymphatic and hematopoietic cancers that lagged 15 years in men ($P_{trend} = 0.02$), but not in women. The combined lymphoid-cell cancer SMR (non-Hodgkin, myeloma, lymphocytic leukemia) for

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ethylene oxide workers was statistically significant but imprecise and lacked a dose-response relationship (SMR = 3.76, 95% CI: 1.03–13.64, $P_{trend} = 0.13$). Duration, average/cumulative exposure, and peak exposure were not correlated to lymphatic or hematopoietic cancer risks.

A study of 2,063 ethylene oxide-production workers in West Virginia exposed from 1940–1988 and followed through 2003 did not demonstrate any excess cancer deaths or dose-response relationships from lymphohematopoietic malignancies.[101] The hazard ratios comparing the highest (>65 ppm-year) and lowest (≤15 ppm-years) tertiles were 0.332 (95% CI: 0.044–2.496, $n = 11$ deaths) for leukemia mortality and 0.41 (95% CI: 0.128–2.276, $n = 17$ deaths) for lymphoid tumor mortality. In a meta-analysis of 10 cohort studies on ethylene oxide-exposed workers, the heterogeneity-adjusted meta-SMR for leukemia was 1.08 (95% CI: 0.61–1.93, $n = 35$ deaths), whereas the meta-SMR for non-Hodgkin lymphoma was 1.34 (95% CI: 0.96–1.89, $n = 33$ deaths).[102] There were no statistically significant positive trends in duration, intensity, or latency. In a Swedish study of 2,171 ethylene oxide sterilant workers employed for at least 1 year and followed up to 34 years, the median cumulative ethylene oxide exposure was 0.13 ppm-years.[103] The SIR for leukemia was 1.40 (95% CI: 0.45–3.26, $n = 5$ cases) and remained statistically nonsignificant with a 15-year lag (SIR = 1.15, 95% CI: 0.25–3.37, $n = 3$ cases). Using the bottom tertile as a referent, the SIR for lymphohematopoietic cancer in the top tertile (≥0.22 ppm-years) was 1.08 (95% CI: 0.35–2.54, $n = 5$ cases).

Lifestyle

Few lifestyle risk factors are causally associated with elevated adult or childhood leukemia risks. Although the IARC considers the evidence for environmental benzene exposure (e.g., parental smoking) and childhood leukemia stronger for AML than ALL, the reported risks are mostly statistically nonsignificant with bias, chance, and/or confounding potential alternate explanations of the results.[104]

Tobacco

The IARC lists tobacco smoking as a human carcinogen associated with at least nine cancers including acute myeloid leukemia, whereas limited human evidence associates childhood leukemia with maternal smoking and extremely low frequency magnetic fields.[105]

Adult Smoking

Epidemiology studies on overall leukemia incidence rates and tobacco smoking are mixed, with similar numbers of cohort and case-control studies reporting positive and null results.[106] The results are much stronger for myeloid than lymphoid leukemia, with most studies reporting positive results for myeloid leukemia in cigarette smokers,[107] particularly AML subtypes M2 and t(8:21) translocation,[108] whereas most,[109,110] but not all, studies on overall lymphoid leukemia incidence rates report null results.[111] Small case numbers and imprecise risk estimates complicate the interpretation of the rarer lymphoid leukemia subtypes in adults. In the Swedish prospective cohort study of 334,957 construction workers followed for 10 years, the AML incidence rate ratio adjusted for age and BMI in current smokers was 1.50 (95% CI: 1.06–2.11, $n = 92$ cases) and 0.94 (95% CI: 0.60–1.48, $n = 30$) in ex-smokers using never-tobacco users as referents.[112] The study reported no association between smoking and ALL ($n = 47$ cases). The Three Mile Island Cohort Study reported a marginally elevated adult AML risk in current smokers using never-smokers as referents (RR = 3.47, 95% CI: 1.002–11.99, $n = 9$ cases) after adjustment for age, gender, education level, race, and occupational/background radiation.[113] Examination of smoking intensity (daily cigarettes, smoking duration, pack-years) yielded no statistically significant trend using $P = 0.05$ as the cutoff. The overall leukemia risk in current smokers was not statistically different from that in referents (adjusted RR = 1.39, 95% CI: 0.69–2.82, $n = 17$ cases, $P_{trend} = 0.57$). In a population-based sample of 1,068 incident adult leukemia cases and 5,039 healthy controls with similar age and sex distribution, the association between the highest tertile of lifetime environmental tobacco smoke (ETS) exposure in never-smokers with overall leukemia (>123 smoker-years) was positive, but not statistically significant (adjusted OR = 1.46, 95% CI: 0.97–2.18, $n = 112$ cases, $P_{trend} = 0.001$) using healthy never-smokers as referents.[114] Analysis of leukemia subgroups yielded no association of lifetime ETS smoke with most leukemia subtypes, except CLL. The highest tertile of lifetime ETS exposure (>123 smoker-years) for CLL in nonsmoking adults was 2.31 (95% CI: 1.16–4.59, $n = 53$ cases, $P_{trend} = 0.001$). Smoker-years represent the lifetime sum of exposure to the number of smokers at work and home.

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Parental Smoking

The evidence for parental smoking causing substantially increased overall childhood leukemia risks is relatively weak, with varied results complicating the interpretation of contradictory conclusions.[115] Most studies on self-reported maternal smoking and childhood leukemia do not report a significant positive association either before or during pregnancy with some studies reporting an inverse association.[116,117] In contrast to maternal smoking, studies on paternal smoking and childhood leukemia report more positive studies, albeit less than a majority for smoking before, but not during pregnancy. The positive studies more often associated smoking with ALL than with AML.[118] Leukemia subtype risks may vary with exposure time (e.g., prenatal, postnatal, conception) and cytogenetic subtype reflecting the time of genetic mutations in fetal development [e.g., t(2/21)/ETV6-RUNX1)], postnatal (e.g., t(1;19)E2A-PBX1), or possibly both time periods (e.g., MLL fusion).[119] Small case numbers typically generate imprecise risk estimates. The Northern California Childhood Leukemia Study examined self-reported smoking information in 767 ALL/135 AML cases and 1,139 randomly selected controls matched to date of birth, sex, Hispanic ethnicity, and maternal race.[120] Multivariable regression analyses demonstrated no definite overall association between parental prenatal active smoking and the child's passive exposure. A history of paternal prenatal active smoking combined with the child's postnatal exposure to passive residential smoking increased ALL risks (OR = 1.5, 95% CI: 1.01–2.23, $n = 115$ cases/88 controls, $P_{\text{interaction}} = 0.02$). The magnitude of the association was strongest for B cell precursor ALL harboring t(12;21) translocation (OR = 2.08, 95% CI: 1.04–4.16, $n = 26$ cases, $P_{\text{interaction}} = 0.01$). Associations with other leukemia subtypes (e.g., AML) did not reach statistical significance. A meta-analysis of epidemiology studies on self-reported maternal smoking during pregnancy (any vs. none) involving 9,167 ALL and 1,925 AML incident childhood cases and 25,221 nonsmoking controls detected no significant deviation of AML/ALL risks from the null.[121] The pooled odds ratio estimate for AML was 0.99 (95% CI: 0.90–1.09, $n = 1$ cohort/14 case-control studies, $I^2 = 28.6\%$, random effects models) and 1.03 for ALL (95% CI: 0.95–1.12, $n = 1$ cohort/19 case-control studies, $I^2 = 49.21\%$, fixed effects models) with moderate heterogeneity.

A Canadian case-control study on self-reported smoking before and during pregnancy reported odd ratios mostly of >1 for maternal and paternal smoking; however, the odds ratios and exposure-response relationships (P_{trend}) were all statistically nonsignificant using nonsmokers as referents. Comparing the highest smoking tertile (≥20 cigarettes daily) with controls, the OR for maternal smoking during pregnancy was 0.98 (95% CI: 0.50–1.89, $n = 22$ cases/218 controls, $P_{\text{trend}} = 0.373$) for ALL and 0.40 (95% CI: 0.04–3.80, $n = 2$ cases/18 controls, $P_{\text{trend}} = 0.287$) for AML.[122] For paternal smoking before pregnancy, the odds ratio for ALL was 1.15 (95% CI: 0.79–1.67, $n = 95$ cases/179 controls, $P_{\text{trend}} = 0.399$) and 0.90 (95% CI: 0.34–2.38, $n = 11$ cases/19 controls, $P_{\text{trend}} = 0.736$) for AML. In the French ESTELLE study of 636 ALL cases (503 B cell precursors, 95 T cell precursors, 26 Burkitt's ALL, 12 unspecified/unable to complete study), 100 AML cases, and 1,421 population-based controls, preconception paternal smoking within 3 months of conception (ever vs. never) was associated marginally with ALL (OR = 1.2, 95% CI: 1.0–1.5, $n = 297$ cases/319 controls, $P_{\text{trend}} = 0.13$) and AML (OR = 1.5, 95% CI: 1.0–2.3, $n = 51$ cases/48 controls, $P_{\text{trend}} = 0.03$).[123] ALL and AML risks in children born to mothers who smoked before or during pregnancy did not deviate from the null.

Alcohol

The potential association between self-reported maternal alcohol consumption during pregnancy and ALL remains unclear with both positive and negative studies and studies demonstrating an inverse relationship; limited data on AML are also inconclusive. A Ukrainian nested case-control study of 137 leukemia cases and 873 controls in the male Chernobyl cleanup cohort reported no significant association between leukemia and alcohol consumption after adjustment for radiation doses; exposure was based on personal questionnaires and models of radiation dosage.[124] In the Canadian childhood leukemia study, consumption of >2 alcoholic drinks weekly was not associated with a statistically significant increased ALL risk (adjusted OR = 0.88, 95% CI: 0.46–1.67, $n = 21$ cases/220 nondrinking controls, $P_{\text{trend}} = 0.229$).[122] An Australian study of 388 ALL case families and 1,396 control families reported no evidence of maternal alcohol use before or during pregnancy and increased ALL risks.[125] Compared with nondrinkers, the adjusted odds ratio for ALL in children from mothers drinking >2 days weekly was reduced (adjusted OR = 0.56, 95% CI: 0.37–0.86, $n = 33$ cases/112 controls), with evidence of a dose-response relationship between wine consumption and reduced ALL risks.

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In a French study of 472 ALL cases and 567 population-based controls, consumption of >1 glass of alcohol daily during pregnancy was associated with a statistically significant increase in ALL risk (OR = 2.8, 95% CI: 1.3–5.9, $n = 23$ cases/344 controls).[126] The odds ratio was not calculated for AML because there was an insufficient number of smokers among the 62 AML cases. Using never-drinkers as controls, the French ESTELLE case-control study reported a positive, statistically significant AML risk for maternal alcohol consumption of >2 alcoholic drinks weekly during pregnancy (OR = 2.8, 95% CI: 1.2–6.7, $n = 7$ cases/69 nondrinking controls, $P_{trend} = 0.02$), but not for ALL (OR = 0.7, 95% CI: 0.4–1.5, $n = 10$ cases/495 nondrinking controls, $P_{trend} = 0.38$).[123] A meta-analysis of 21 case-control studies reported a much stronger association between maternal alcohol consumption during pregnancy and AML than ALL.[127] No cohort studies were available. Comparing yes versus no alcohol consumption during pregnancy, based mostly on interviews and self-administered questionnaires, the meta-OR for AML was statistically significant (OR = 1.56, 95% CI: 1.13–2.15, $n = 9$ studies/731 cases, $I^2 = 52.5\%$, $P_{heterogeneity} = 0.032$); for ALL, the meta-OR was statistically nonsignificant (OR = 1.10, 95% CI: 0.93–1.29, $n = 11$ studies/5,198 cases, $I^2 = 66\%$, $P_{heterogeneity} = 0.001$). Heterogeneity was moderate between studies.

Obesity

Recent epidemiology studies suggest a modestly positive association between leukemia risks and obesity, but not with subjects overweight in the several years before diagnosis based on self-reported height and weight. In general, leukemia risks are higher in men than women and stronger for AML than other leukemia subtypes. In a meta-analysis of 16 primarily American and European prospective studies (20,813 incidence leukemia cases) comparing obese (BMI $\geq 30\,kg/m^2$) participants with normal-weight controls (BMI: 18.5–24.9 kg/m^2), the overall maximumly adjusted RR for leukemia in obese men and women was 1.26 (95% CI: 1.17–1.37, $p < 0.001$, $I^2 = 43\%$).[128] The RR for overall leukemia was statistically significant in obese men (RR = 1.40, 95% CI: 1.24–1.57, $p < 0.001$, $I^2 = 33\%$) as well as the four common leukemia subtypes. For women, the adjusted RR was statistically significant for overall leukemia (RR = 1.20, 95% CI: 1.07–1.35, $P = 0.002$, $I^2 = 29\%$), marginally significant for AML and CML, and nonsignificant for CLL and ALL. Meta-regression revealed a significant association for leukemia incidence per kg/m^2 in obese men ($p = <0.001$), but not obese women ($p = 0.11$). The adjusted RR for overweight men and women was not statistically significant for overall leukemia or any subtype. Meta-analysis results were not adjusted for all potential confounders (e.g., smoking, alcohol intake, diet). The biological mechanism linking leukemias to obesity remains unclear.

Tea

Few studies analyze the effects of tea or coffee consumption on leukemia risks; many of the studies are population-based, case-control studies that report mixed results. A meta-analysis of 95 myeloid leukemias and 279 population-based controls suggests high-intensity tea consumption reduces the frequency of myeloid leukemias.[129] Compared with no tea consumption, the adjusted meta-OR for myeloid neoplasms in the highest category of tea consumption was significantly reduced statistically (adjusted meta-OR = 0.4, 95% CI: 0.2–0.9, $n = 10$ cases, $P_{trend} = 0.017$). None of the other adjusted meta-ORs for tea or coffee consumption indicate a statistically significant reduction or dose-response relationship. The authors opined that the reduced meta-OR for high tea consumption and myeloid leukemia should be interpreted cautiously because of the small case numbers. In a meta-analysis of six case-control and one cohort studies from the United States and China, the overall leukemia risk in the highest tertile using the lowest tertile/non-tea drinkers as referents was significantly reduced (meta-RR = 0.57, 95% CI: 0.41–0.78, $n = 700$ cases, $P_{heterogeneity} = 0.11$, $I^2 = 40.5\%$); statistical analysis indicated the presence of moderate heterogeneity and evidence of publication bias ($P_{Egger's\ test} = 0.01$).[130] In the French ESTELLE study, the acute leukemia risk (ALL/AML) for mothers drinking tea during their pregnancy did not deviate significantly from the null (OR = 0.9, 95% CI: 0.8–1.1), with no evidence of a dose-response relationship compared with nondrinkers.[123]

Coffee

A meta-analysis of 12 case-control studies involving 3,649 cases and 5,705 controls reported positive, but statistically nonsignificant, associations for ever-maternal coffee drinking during pregnancy and acute childhood leukemia (OR = 1.14, 95% CI: 0.95–1.37, $n = 7$ studies, $I^2 = 53.7\%$, $P_{heterogeneity} = 0.044$); the risk for ALL was also nonsignificant (OR = 1.10, 95% CI: 0.99–1.22, $n = 8$ studies, $I^2 = 0.0\%$, $P_{heterogeneity} = 0.434$).[131] The estimate for AML was statistically significant (OR = 1.44, 95% 1.01–2.04, $n = 6$ studies, $I^2 = 39.8\%$, $P_{heterogeneity} = 0.140$). The analysis associated high

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but not low-to-moderate maternal coffee consumption during pregnancy with childhood leukemia. Exploring exposure-response relationships by comparing high versus never/lowest coffee consumption, the risks were statistically significant for acute leukemia (OR = 1.57, 95% CI: 1.16–2.11, $n = 6$ studies, $I^2 = 55.2\%$, $P_{\text{heterogeneity}} = 0.048$) and ALL (OR = 1.43, 95% CI: 1.22–1.68, $n = 8$ studies, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = 0.464$), but statistically nonsignificant for AML (OR = 1.81, 95% CI: 0.93–3.53, $n = 6$ studies, $I^2 = 53.7\%$, $P_{\text{heterogeneity}} = 0.056$). Moderate heterogeneity occurred between studies suggesting limited control of confounding including the interaction of smoking and coffee.

In the French ESTELLE study, the association between ALL and maternal consumption of >2 cups of coffee daily during pregnancy was marginally significant (OR = 1.3, 95% CI: 1.0–1.8).[123] Similarly, analysis of pooled data from the Childhood Leukemia International Consortium suggested that high maternal coffee intake during pregnancy may increase childhood ALL risks.[132] The pooled OR for > 2 cups daily was 1.27 (95% CI: 1.09–1.43, $P_{\text{trend}} = 0.005$) using non-coffee drinkers as referents. Using multivariate unconditional logistic regression in an Italian study of 651 leukemia cases and 1,771 population-based controls, the lower leukemia risks in regular coffee users were not confirmed based on dietary questionnaires.[133] The odds ratio for myeloid leukemia in regular coffee consumers drinking >4 cups of coffee daily was 0.82 (95% CI: 0.50–1.3, $n = 28$ cases, $P_{\text{trend}} = 0.212$).

Medications

The IARC lists lindane and multiple chemotherapeutic and immunosuppressive agents as human carcinogens increasing leukemia risks, including busulfan, chlorambucil, chloramphenicol cyclophosphamide, cyclosporine, etoposide with cisplatin/bleomycin, melphalan, MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture), semustine (methyl-CCNU), thiotepa, and treosulfan. Therapeutic agents associated with limited human evidence of increased leukemia risks include chloramphenicol agents, including bischloroethyl nitrosourea (BCNU), etoposide, mitoxantrone, nitrogen mustard, and teniposide.

Diseases

The IARC lists multiple infectious agents as human carcinogens that increase leukemia risks, including Epstein–Barr virus, *Helicobacter pylori*, hepatitis C virus, human immunodeficiency virus type 1 (HIV1), human T cell lymphotropic virus type 1, and human herpesvirus-8 (HHV-8, Kaposi sarcoma herpes virus) but only one (human T cell lymphotropic virus type 1) as a cause of adult T cell leukemia/lymphoma.

HISTOLOGY

Adult leukemia accounts for 90% of all leukemias with the remainder being childhood leukemias. These two leukemia classifications differ in several respects. The most common adult leukemia is CLL, whereas CLL does not usually occur in childhood.[134] Adults display a wider range of leukemia subtypes with a much higher incidence of CML, AML, and myelodysplastic/myeloproliferative syndromes; the incidence of B and T cell ALL is lower in adults than children. For childhood leukemia, ALL accounts for ~80% of the cases in children of <16 years of age, with AML representing 15–17%, CML 2%, and rare subtypes (e.g., CLL) accounting for the remainder.[106]

HOST SUSCEPTIBILITY

Somatic and germline mutations drive the development of hematological malignancies. All human cells inherit germline mutations that are shared with multiple family members, whereas somatic mutations occur only in specific cells that drive malignant transformation and acquisition of subsequent mutations.[135] The absence of characteristic features or a positive family history does not exclude the presence of germline mutations. Phenotypic expression of germline mutations is highly variable among affected family members as a result of variable penetrance that silences or attenuates expression of the germline mutations. Consequently, cancer predisposition syndromes present a variety of clinical features including hemolymphatic malignancies, myelodysplastic syndrome, bone marrow failure, and systemic symptoms. In a case series of 71 pediatric and young adult patients diagnosed with idiopathic bone marrow failure or myelodysplastic syndrome after standard genetic testing based on a clinical evaluation, eight had serious germline mutations in multiple genes (i.e., *DKC1*, *GATA2*, *LIG4*, *RUNX1*).[136]

Few childhood leukemias have underlying hereditary genetic abnormalities. About 2–3% of children with leukemia have recognized genetic conditions that predispose them to developing leukemia, primarily Down syndrome, as demonstrated in Table 59.3.

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TABLE 59.3. Hemolymphatic neoplasms are commonly associated with cancer predisposition syndromes. Most of these syndromes have multiple gene mutations with only the predominate gene mutation listed when present. Formation of hematological neoplasm genes may occur somatically in hematopoietic cells or constitutionally in germline cells (e.g., *CEBPα*, *GATA2*, *RUNX1*, *TP53*, *RAS* genes). (Adapted from Furutani and Shimamura).[135]

Syndrome	Primary Gene Mutated	BMF	MDS	AML	ALL
Ataxia telangiectasia	*ATM*				X
Bloom syndrome	*BLM*		X	X	X
Constitutional mismatch repair deficiency syndrome (Lynch syndrome)			X	X	X
Diamond Blackfan anemia		Anemia	X	X	
Dyskeratosis congenita		X	X	X	
Familial acute myeloid leukemia	*CEBPA*			X	
Familial AML with mutated DDX41	*DDX41*		X	X	
Familial platelet disorder with propensity to myeloid malignancy	*RUNX1*		X	X	
Fanconi anemia		X	X	X	
GATA2 spectrum disorders	*GATA2*	X	X	X	
Li Fraumeni	*TP53*		X	X	X
Nijmegen breakage syndrome	*NBN*				X
Severe congenital neutropenia	*ELANE*	Neutropenia	X	X	
Shwachman diamond syndrome	*SBDS*	X	X	X	
Susceptibility to ALL 3	*PAX5*				X
Thrombocytopenia 5	*ETV6*		X	X	X
Wiskott Aldrich syndrome	*WAS*				X

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BMF = bone marrow failure; MDS = myelodysplastic syndrome.

CLINICAL FEATURES

Acquired genetic defects in early hematopoietic progenitors produce a much more rapid progression (i.e., 2–4 weeks) to bone marrow failure in untreated acute than chronic leukemias, with bone marrow failure in the former occurring in weeks to months. Clinical features result from bone marrow failure (lethargy/anemia, anorexia, bruising, bleeding, infection, fever related to leukemia) and organ infiltration (bone pain, pathological fractures, limping, hepatomegaly, splenomegaly, lymphadenopathy, headache, seizures). Hyperviscosity (dyspnea, confusion, impaired hearing/vision) or superior vena caval syndrome (stridor, cough, orthopnea) may complicate the course of leukemia. The differential diagnosis of leukemia includes bone marrow infiltration from other tumors (e.g., neuroblastoma) and aplastic anemia.

The occurrence of leukemia increases steadily with age in the major leukemia subgroups, with the exception of ALL; this leukemia peaks in early childhood before declining with age. Among atomic bomb survivors in the Life Span Study, the risk and dose-response of the major leukemia subgroups vary with age at exposure, temporal risk pattern, and gender. CML risk declines over time with a relationship to time of exposure, whereas adult AML risk rises with increasing attained age. As the incidence of leukemia increases with age, excess leukemia risks generally decline with attained age or time since exposure.[137] Excess incidence of radiation-induced leukemias begins ~2 years after radiation exposure, with peak excess in ~7–8 years. Radiation-associated excess non-CLL leukemia risks persisted in the Life Span Study cohort throughout the 55-year follow-up after the bombings, particularly for acute myeloid leukemia; however, the increased leukemia risk very significantly decreased after 20 years.[138] The benzene-induced leukemia risk also decreases with time since exposure ceased; leukemia risk is small 10–15 years after exposure ceases.[139] The AML dose-response relationship is nonlinear; other subgroups also do not display a linear dose response. Figure 59.1 compares the age-related incidences of AML, ALL, and CML based on Swedish

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data; CLL is a lymphoid disease primarily of the elderly.

The cure rates for childhood leukemia have improved dramatically because of improved chemotherapy, better risk stratification, and improved supportive care. Prognosis depends on multiple factors including age, leukocyte count, circulating blasts, molecular mutations, cytogenetic abnormalities, metastatic (i.e., extramedullary) disease, stage, initial therapeutic response, and presence of secondary leukemia. While >80% of childhood ALL resolves with chemotherapy, successful responses to chemotherapy for adult ALL remain below 30%. The prognosis for childhood AML also remains poor and variable depending on multiple factors.[140]

ACUTE MYELOGENOUS LEUKEMIA (AML)

Although AML is the most common adult leukemia in Western countries representing ~25% of all leukemias, it is a relatively rare disease accounting for ~1.3% of annual US cancer cases.[141] The adult incidence varies slightly between races and genders.[4,106] Geographically, reported AML incidence is higher in Western countries (United States, Australia, Western Europe) than Asian countries and Asian/Pacific Islanders, typically with a slight male predominance. AML incidence is increasing, in part, due to the occurrence of more common risk factors including complications of previous hematological malignancy (e.g., myelodysplastic syndromes/myeloproliferative neoplasms) and previous cancer-related therapy from medications associated with AML (e.g., alkylating agents, topoisomerase II inhibitors, radiotherapy).

The two peaks in AML incidence occur in early childhood and later in adulthood; AML incidence peaks occur during the first two years of life and decreases afterward until slowly increasing in adolescence. In childhood, AML incidence is much less common (i.e., 5-fold) than ALL. The variation in childhood AML between racial/ethnic groups is relatively small. The possible exception is the slightly increased risk of the AML subtype, acute promyelocytic leukemia in Asian/Pacific Islanders and Hispanics compared with Caucasians and African Americans.[6] Substantial geographical differences in childhood AML rates exist between Western and less developed countries, at least partly due to differences in ascertainment methods between registries. Juvenile myelomonocytic leukemia is a myelodysplastic/myeloproliferative disorder subtype unique to children.

CARCINOGENESIS

AML is a genetically and molecularly complex disease with at least 11 distinct subgroups containing many recurrent mutations in many genes (e.g., core-binding factor, *BCR-ABL1*, *CEBPA*, *FLT3*, *KIT*, *KMT2A*, *NPM1*, *RUNX1*); consequently, no singular pathogenic model accounts for all AML tumors.[142] The most favored pathogenetic model involves a group of mutations in genes that activate signal transduction pathways (e.g., *FLT3*, *KIT*, *PTPN11*, *RAS*) resulting in proliferation and enhanced survival of hematopoietic cells and a second group of mutations in genes that later alter transcription factors inhibiting cell differentiation and apoptosis (e.g., *CEBPA*, *RUNX1*). Compared with most cancers, the number of recurrent mutations is relatively small. The vast majority of AML tumors contain at least two driver gene mutations (median = 3, range 2–9).[143,144] Additionally, individual tumors usually contain subclones with substantial mutational diversity resulting in a genetically unique neoplasm. Table 59.4 displays the diverse mutation spectrum of adult AML.[145] The most frequent mutations occur in signaling pathway components, tumor suppressors, epigenetic (histone) modifiers, and cohesin complex members.

Genetic

The critical initial pathogenic event in most AML tumors involves translocation or inversion events that produce chimeric fusion genes in hematopoietic stem and progenitor cells. The gain in stem cell-like self-renewal properties is sufficient to maintain malignant transformation and clonal expansion.[146] The Philadelphia chromosome occurs in <1% of *de novo* adult AML patients. In elderly patients, the genetic landscape of AML resembles secondary AML associated with myelodysplastic syndrome rather than AML in adult patients of <60 years of age.[147] Approximately 50–60% of AML patients have chromosomal abnormalities; these changes help predict prognosis and relapse.[148] Different AML subtypes express diverse miRNAs. A novel chimeric fusion gene involving the core-binding factor complex results from t(8;21) and inv (16) chromosomal aberrations; this abnormality disrupts normal hematopoiesis leading to core-binding factor acute myeloid leukemia (CBF-AML).

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TABLE 59.4. Frequent mutations in adult (<60 years of age) acute myeloid leukemia (AML) based on analysis of cytogenetic and molecular features in large patient cohorts. These mutations reflect the genetic heterogeneity of AML involving multiple functional categories including signaling pathway components, tumor suppressors, cohesion complex members, transcription factors, epigenetic modifiers (DNA methylation, chromatin regulators, spliceosome complex components). The mutations in *FLT3* tyrosine kinase receptor gene increase cell proliferation through activation of signaling pathways (JAK-STAT, P13K-AKT, RAS-RAF), whereas myeloid transcription factor mutations (*RUNX* gene) impair hematopoietic differentiation. Mutations in the nucleophosmin gene (*NPM1*) disrupt multifunctional chemical signaling that controls the shuttling of proteins between the nucleus and cytoplasm, whereas mutations in the tumor suppressor gene (*TP53*) deregulate transcription and inhibit apoptosis. Deregulation of RNA processing results from mutations in the spliceosome-complex genes (*SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*), whereas mutations in the genes affecting epigenetic cell homeostasis include chromatin modification deregulation (ASXL1, EZH2) and impairment of DNA methylation (DNMT3A, IDH1/2, KMT2A-MLLT3 gene fusion, TET2). (Adapted from Grimwade et al.).[145]

Function	Genes Mutated	Expressed Protein	Frequency (%)
Activate signaling	*FLT3-ITD*	FMS-related tyrosine kinase 3-internal tandem duplication	27
	FLT3-TKD	FMS-related tyrosine 3-kinase domain	11
	NRAS	*NRAS* proto-oncogene, GTPase	11
	KRAS	*KRAS* proto-oncogene, GTPase	5
	PTPN11	Protein tyrosine phosphatase, non-receptor type 11	5
	KIT	*KIT* proto-oncogene receptor tyrosine kinase	4
Tumor suppression	*TP53*	Tumor protein p53	8
	NPM1	Nucleophosmin 1	33
Cohesin	*RAD21*	RAD21 cohesin complex component	6–9
	STAG1 and 2	Stromal antigens 1 and 2	
	SMC1A/3	Structural maintenance of chromosomes 1A and 3	
Myeloid transcription factor	*RUNX1*	Runt-related transcription factor 1	5
	CEBPA	CCAAT enhancer-binding protein α	4
DNA methylation	*DNMT3A*	DNA methyltransferase 3 α	20
	TET2	Tet methylcytosine dioxygenase 2	8
	IDH1	Cytosolic NADP+-dependent isocitrate dehydrogenase 1	7
	IDH2	Cytosolic NADP+-dependent isocitrate dehydrogenase 2	9
	WT1	Wilms tumor 1	9
Chromatin regulation	*ASXL1*	ASXL transcriptional regulator 1	5
	ASXL2	ASXL transcriptional regulator 2	2
	MLL-PTD	MLLT11 transcription factor 7 cofactor-partial tandem duplications	5
	KMT2A	Lysine methyltransferase 2A	5
	PHF6	PHD finger protein 6	3
	BCOR	BCL6 corepressor	1
	EZH2	Enhancer of zeste 2 polycomb repressive complex 2 subunit	1
Splicing factors	*SF3B1*	Splicing factor 3b subunit 1	3
	SRSF2	Serine and arginine-rich splicing factor 2	2
	U2AF1	U2 small nuclear RNA auxiliary factor 1	2

In AML, the genes most commonly involved in signaling pathway mutations include *FLT3-ITD*/*TKD*, *NRAS*/*KRAS*, *PTPN11*, and *KIT*; however, ~40% of AML tumors lack gene mutations encoding classical signaling pathway components.[149] The FLT3 protein is a receptor tyrosine kinase that transmits signals from the cell surface into the cell (signal transduction). Subsequently, this protein activates a series of intracellular processes involved with cell proliferation and survival, particularly in hematopoietic progenitor cells.[150] *NRAS* and *KRAS* genes belong to the *Ras* family of proto-oncogenes. The *NRAS* proto-oncogene

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expresses the GTPase protein, N-RAS, primarily involved with cell division, whereas the K-RAS protein is a GTPase that is part of the RAS/MAPK signaling pathway involved with cell division, differentiation, and apoptosis. Activation of proto-oncogenes enhances cell proliferation and tumor formation. The *PTPN11* (protein tyrosine phosphatase, non-receptor type 11) gene encodes the SHP-2 protein. This protein helps regulate the RAS/MAPK pathway and several other important cellular processes (e.g., cell differentiation, migration, apoptosis) during the embryonic development of blood cells and bones. The *KIT* (*KIT* proto-oncogene receptor tyrosine kinase) gene expresses a receptor tyrosine kinase protein involved with transduction of extracellular signals; stem cell factor activates this proto-oncogene resulting in the phosphorylation and activation of multiple intracellular signaling pathways regulating cell proliferation, survival, and migration in germ cells and hematopoietic stem cells.

The most common tumor suppressor mutations in AML tumors involve *NPM1* and *TP53* genes. The *NPM1* gene encodes the intranucleolar protein, nucleophosmin, which protects the tumor suppressor *ARF* gene from degradation.[151] Nucleophosmin travels between the nucleolus and cytoplasm while participating in multiple cellular processes (e.g., cell-cycle progression, DNA replication, protein formation). The tumor protein p53 is a tumor suppressor (i.e., guardian of the genome) essential for regulation of cell division and prevention of tumor formation; this protein plays a critical role in determining whether damaged DNA will undergo repair or will self-destruct (apoptosis).

Common mutated myeloid transcription factor mutations that involve AML include *RUNX1* and *CEBPA* genes.[152] The RUNX1 protein is a transcription factor that interacts with core-binding factor β to form a core-binding factor complex. The complex helps control the proliferation and differentiation of hematopoietic stem cells.[153] The *CEBPA* (CCAAT enhancer-binding protein alpha) gene encodes the transcription factor and tumor suppressor CCAAT enhancer-binding protein α that binds DNA regions controlling the expression of specific genes involved with blood cell differentiation.

The chromosome cohesion complex, cohesin, forms a large proteinaceous ring that traps sister chromatids during prophase and prometaphase. In anaphase, the complex dissociates from chromatin, resulting in segregation of sister chromatids. *STAG1/2* (stromal antigen 1/2) gene expresses intranuclear members of the SCC3 family of proteins that form a component of the cohesin complex. SMC1 and SMC3 proteins produced by these genes also help regulate chromosomal structure and organization as components of the cohesin complex.[154] The latter proteins stabilize the chromosomes by repairing damaged DNA and activating genes essential for normal development. The protein expressed by the *RAD21* gene is also part of the cohesin complex that holds the sister chromatids together during early cell division. Mutations of these genes disrupt chromosomal DNA causing translocations and deletions.

Epigenetic

Some AML tumors contain hematopoietic stem and progenitor cells with epigenetic-modifying gene mutations and normal multipotent differentiation characteristics. Clonal evolution studies suggest this epigenetic dysregulation in preleukemic hematopoietic stem cells occurs early in AML tumorigenesis prior to malignant transformation. Epigenetic modifiers in AML primarily involve DNA methylation with gene silencing (e.g., *DNMT3A*, *IDH1/2*, *TET2*, *WTI*) and chromatin regulation (e.g., *ASX1*); mutations of these genes are not unique to AML.[155,156] Mutations in *DNMT3A*, *NPM1*, and *FLT3-ITD* often co-segregate, suggesting interaction in developing AML. Although these mutations precede overt leukemia, some preleukemic mutations in genes (e.g., *DNMT3A*, *TET2*, *ASXL1*) are biomarkers of a poor prognosis.[145] DNA methyltransferase 3α promotes differentiation of stem cells into mature blood cell types. The role of *TET2* gene is not well defined; however, the enzyme produced by *TET2* probably helps regulate the initial step in DNA demethylation.[145] Hypothesized effects include tumor suppression and differentiation of hematopoietic cells into mature blood cells. *IDH1* and *IDH2* genes encode the enzymes, isocitrate dehydrogenase 1 and 2; these enzymes catalyze the cellular process that produces energy from fat-forming NADPH and protect the cell from reactive oxygen species. The WT1 protein is a transcription factor that helps regulate differentiation and apoptosis.

In AML neoplasms, the most frequent mutations involved with chromatin regulation include *ASXL12*, *MLL-PTD*, *KMT2A*, *PHF6*, *BCOR*, and *EZH2* genes.[157] The *ASXL1* (ASXL transcriptional regulator 1) gene encodes a transcriptional regulator involved with chromatin remodeling and probably gene silencing via DNA methylation. The *MLL-PTD* (mixed lineage leukemia-partial tandem duplications) gene helps regulate development in all leukemic cell lines. Also known as the *KMT2A* (lysine methyltransferase 2A) gene,

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this gene encodes a transcriptional coactivator (histone methyltransferase) essential in regulating gene expression during early development and hematopoiesis. The *BCOR* (BCL6 corepressor) gene encodes the BCL6 corepressor protein that interacts with the DNA-binding protein produced from the *BCL6* gene. The *BCL6* gene enhances the function and survival of certain immune system cells. The *EZH2* (enhancer of zeste 2 polycomb repressive complex 2 subunit) gene produces a histone methyltransferase that binds to DNA and modifies chromosome shape; the resulting changes can suppress gene activity during normal development.

Spliceosomes are relatively large RNA–protein complexes that remove noncoding segments (introns) from premessenger RNAs; this process is critical to the accurate reproduction of mRNA and subsequent protein translation by the ribosome. Mutations of several genes occur in AML tumors that change the spliceosomes including *SF3B1*, *SRSF2*, and *U2AF1* genes. These mutations alter the spliceosomes by modifying subunit 1 of the splicing factor 3b protein complex (SF3B1) or pre-mRNA splicing factors (SRSF2); mutations of *U2AF1* (U2 small nuclear RNA auxiliary factor 1) gene disrupt the interaction between *U2AF2* and the enhancer complex. SF3B1 mutations correlate to the presence of ring sideroblasts, whereas SRSF2 mutations are also prominent in chronic myelomonocytic leukemia. These splicing factor gene mutations are part of a hallmark panel of mutations pathognomonic of AML arising from myelodysplasia syndrome.[147]

MiRNAs control the expression of numerous genes involved in normal cell processes, including proliferation, differentiation, and apoptosis. In AML, the failure of hematopoietic stem cells and myeloid precursor cells to undergo terminal differentiation causes tumorigenesis. These small, noncoding RNAs interact with multiple genes rather than a single gene target to determine their effect on gene expression; multiple miRNAs may be upregulated or downregulated depending on the specific genomics of the AML subtype.[158] MiRNA-expression profiling can distinguish myeloid leukemia from lymphoid leukemia as well as various AML subtypes using the upregulation and downregulation of specific miRNAs.[159] Specific miRNAs involved with the progression of AML include miRNA-29, miRNA-125, miRNA-142, miRNA-146, and miRNA-155, with the presence of miRNA-20a, miRNA-25, miRNA-191, miRNA-199a, and miRNA-199b adversely affecting overall survival.[160]

EXPOSURE

Recognized risk factors for adult AML include age, gender, ionizing radiation exposure, certain prior hematological disorders, some chemotherapy drugs, germline genetic abnormalities, benzene, and cigarette smoking; however, these risk factors are relatively modest accounting for a small portion of AML cases.[161] Most AML cases are sporadic (i.e., *de novo*). In a large, population-based study of 3,363 AML patients in the Swedish Acute Leukemia Registry, 12% had previous myelodysplasia, 8% had therapy-related disease (chemotherapy, radiotherapy), and 6% had previous myeloproliferative disease.[162]

Few risk factors have been identified for childhood AML as a result of small sample sizes and the frequent inclusion of childhood AML with the more common ALL. *In utero* ionizing radiation is the only well-established *de novo* childhood AML risk factor other than advanced maternal age. In a US case-control study using pooled population-based data, AML risks increased slightly with advancing maternal age (OR = 1.08, 95% CI: 1.01–1.16, $n = 804$ cases).[163] Although paternal age is not typically associated with AML risks, the estimated odds ratio for AML became statistically nonsignificant after adjustment for paternal age (OR = 1.06, 95% CI: 0.96–1.17, $n = 722$ cases).

Ionizing Radiation

Adults

AML is a heterogeneous disease with multiple subtypes and variations in risk factors. Increased AML incidence occurred in groups receiving high-ionizing radiation doses (e.g., Japanese atomic bomb survivors,[164] medical radiation for ankylosing spondylitis, and Hodgkin disease[33]). Dose-related excess AML developed in these cohorts with the relative AML risk decreasing with increased time since radiation exposure. A California study of 412 matched case-control pairs reported no statistically significant association between *diagnostic* X-rays and AML or AML subtypes based on interviews and medical records using the older French–American–British classification of AML subtypes.[165] In a risk analysis of total estimated bone marrow dose of >2,000 mGy from diagnostic imaging procedures in the 2–10 years preceding diagnosis, the AML odds ratio was 1.6 (95% CI: 0.8–3.2, $n = 23$ cases/13 controls, $P_{trend} = 0.28$) using medical records and 2.5 (95% CI: 1.0–6.0, $n = 18$ cases/8 controls, $P_{trend} = 0.70$) using interviews.

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Children

In utero ionizing radiation is a recognized cause of childhood AML based on older studies of mothers receiving relatively high radiation doses from diagnostic abdominal X-rays during pregnancy. Case-control studies of these offspring suggest relative risks in the range of 1.3–1.5 for studies published before 1980.[166] The Oxford Survey of Childhood Cancers identified 866 childhood deaths during 1953–1967 from myeloid leukemia (AML/CML) in children of ≤14 years of age receiving *in utero* exposure. Compared with healthy age/sex/residence-matched controls, the RR was 1.47 (95% CI: 1.20–1.81, $n = 120$ cases/80 controls).[167] In a US study of 116 AML cases aged ≤14 years diagnosed from 1995–2008 and age/sex/race-matched controls, *in utero* diagnostic X-rays were not associated with increased childhood AML risks (OR = 0.85, 95% CI: 0.26–2.78, $n = 111$ cases).[168]

A pooled analysis of nine historical cohort studies supported increased AML risks in children receiving postnatal cumulative bone marrow doses of ≤100 mSv; the dose responses remained significant for doses of ≤50 mSv.[169] The fitted RR for acute myeloid leukemia at a cumulative bone marrow dose of 100 mSv was 2.56 (95% CI: 1.09–5.06, $n = 79$ cases, $P_{\text{trend}} = 0.033$). Relative risks for CML at 100 mSv were not elevated (RR = 0.36, 95% CI: 0.00–2.36, $n = 36$ cases, $P_{\text{trend}} = 0.394$). In general, little epidemiological evidence supports increased childhood AML risks from preconception maternal X-rays. Additionally, several case-control studies have not reported elevated AML risks for children receiving postnatal diagnostic X-rays. A Chinese population/interview-based case-control study did not report a statistically significant increased ANLL (primarily AML) incidence in children receiving 1–5 postnatal X-rays (OR = 0.9, 95% CI: 0.5–1.5, $n = 25$ cases/68 controls, $P_{\text{trend}} = 0.81$).[170] A US case-control study of 116 AML cases aged ≤14 years also did not detect an association between self-reported child X-rays and AML risks (OR = 1.05, 95% CI: 0.90–1.22).[168]

Extremely Low Frequency Electromagnetic Fields

Analysis of data from the Los Angeles County Cancer Surveillance Program on 412 adult AML cases using interview information and age/race/gender-matched population controls did not support an association between AML risks and exposure to electric blankets, electrically heated waterbeds, or occupations associated with high potential exposures to electromagnetic fields.[171] The study reported no association for work near high-voltage equipment (OR = 1.0, 95% CI: 0.6–1.6, $n = 42$ cases/42 controls) or large electrical motors (OR = 1.1, 95% CI: 0.7–1.7, $n = 50$ cases/46 controls). The study also reported similar results for the highest categories of electric waterbed (6–23 years, $n = 79$ cases/83 controls) and electric blanket (10–45 years, $n = 14$ cases/21 controls) use when compared with nonusers. Even though electric blankets emit relatively large electromagnetic fields, a population-based case-control study did not detect an increased AML risk in adults aged 20–69 years regularly using electric blankets when compared with nonusers (OR = 0.9, 95% CI: 0.5–1.6, $n = 40$ cases/43 controls).[172]

Chemicals

Benzene

There is general scientific agreement that exposure to high benzene concentrations causes AML and related diseases; however, controversy remains regarding the association of low benzene exposures (<30–40 ppm-years) and leukemias, particularly with other hematological neoplasms (lymphomas, multiple myeloma). AML includes most leukemias previously classified as acute nonlymphocytic leukemia (ANLL). Both case-control[173] and retrospective cohort[174] studies of petroleum and rubber workers demonstrate a 5–10-fold increase in AML risks following exposure to high benzene concentrations (usually >100–400 ppm-years). Most studies of workers exposed to low benzene concentrations report null findings or slightly elevated rates of ANLL or all leukemias.[175,176,177,178] In a meta-analysis of 1 case-control and 8 cohort studies using fixed effects models, the summary-effect estimate for AML in benzene-exposed workers was significantly elevated at 1.38 (95% CI: 1.15–1.64, $I^2 = 51.4\%$, $P_{\text{heterogeneity}} = 0.036$) with moderate heterogeneity.[179] Dose-response analysis of cumulative benzene exposure indicates the summary-effect estimate for high dose exposure (≥100 ppm-years) was positive and statistically significant at 3.20 (95% CI: 1.09–9.45, $n = 12$ cases, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.624$). The estimate for low cumulative benzene exposure (>0–<40 ppm-years) was not statistically significant (summary-effect estimate = 1.94, 95% CI: 0.95–3.95, $n = 18$ cases, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.737$).

Several large studies of petrochemical workers exposed to low benzene concentrations did not detect an elevated leukemia risk;[173,180] however, the lack of quantitative exposure data raises methodological

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questions regarding potential misclassification of the exposed cohort.

A large study of Chinese workers exposed to relatively low benzene concentrations (<10 ppm benzene) reported no statistically significant increase in AML with increasing exposure to benzene.[181]

Non-benzene Solvents

Few studies investigate the association between solvents other than benzene and AML risks; existing data are inconsistent. A Texas study enrolled 638 *de novo* adult AML cases (87% participation rate) and 636 controls from random digit dialing.[182] Occupational solvent exposure was estimated using a job-exposure matrix developed by the National Cancer Institute for each job held for at least 1 year using information from patient interviews (11% proxy interviews). The solvent category contained benzene (a known carcinogen) as well as gasoline and other organic solvents as measures of solvent exposure because of the low prevalence of workers with AML and individual chemical exposures. Compared with no solvent exposure, medium/high solvent exposure was associated with statistically significant positive odds ratios for women (OR = 4.18, 95% CI: 2.28–7.64, $n = 50$ cases, $P_{trend} = 0.013$) and men (OR = 4.26, 95% CI: 3.00–6.04, $n = 168$, $P_{trend} = <0.0001$). The inclusion of benzene confounds the estimated odds ratios. A nested case-control design using data from the Nordic Occupational Cancer Study identified 15,332 incident AML cases and 76,660 age/sex/country-matched controls.[183] Cases and controls could have a previous history of any cancer other than AML. Individual solvent exposures were estimated by a job-exposure matrix designed for the study; the solvents included aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, chlorinated hydrocarbon solvents, methylene chloride, perchloroethylene, toluene, 1,1,1-trichloroethane, trichloroethylene, and other organic solvents. All of the hazard ratios for individual solvents were statistically nonsignificant with P_{trend} ranging from 0.13–0.58 consistent with the lack of evidence associating trichloroethylene with myeloid leukemias.[184]

Pesticides and Other Agricultural Exposures

Adults

Few data associate pesticide use with adult AML. A Minnesota population-based study investigated chemical exposures and AML risks using data from the Minnesota Cancer Surveillance System with controls identified through driver licenses (participation rate = 64%).[185] The study reported no association between pesticide classes and AML. Comparing any versus no occupational pesticide exposure, the adjusted OR for AML was inverse, but statistically nonsignificant (aOR = 0.89, 95% CI: 0.64–1.24, $n = 63$ cases); for the comparison of >10 years of occupational pesticide exposure with no pesticide exposure, the adjusted OR was also inverse, but statistically nonsignificant (aOR = 0.87, 95% CI: 0.51–1.47, $n = 20$ cases, $P_{trend} = 0.78$). An Italian study with limited power reported a statistically significant AML risk in female farmers (OR = 3.4, 95% CI: 1.3–8.9) and women exposed to pesticides (OR = 4.4, 95% CI: 1.7–11.5); however, the study detected no elevated AML risks in male farmers.[186]

Children

Several meta-analyses suggest an association between maternal, but not paternal occupational pesticide exposure and childhood AML risks in offspring;[187,188] however, low-to-moderate quality epidemiological evidence, the lack of accurate exposure and dose-response data, heterogeneity in structure/mechanisms of action (e.g., fungicide, insecticide, herbicide), small case numbers, potential recall/selection biases, and misclassification limit definitive conclusions about causation. In a meta-analysis of five case-control studies from the Childhood Leukemia International Consortium on AML risks in offspring of mothers with occupational pesticide exposures during pregnancy, the summary OR for childhood AML was 2.69 (95% CI: 1.49–4.86, $I^2 = 0\%$, $n = 895$ cases/5,428 controls).[189] Only studies containing at least some cases with high likelihood of pesticide exposures (category 1) during pregnancy were included in the meta-analysis. Using unconditional logistic regression to estimate pooled odds ratios from data in 10 case-control studies, the adjusted pooled OR for childhood AML comparing category 1 with category 4 (no or minimal likelihood of pesticide exposure during pregnancy) as the control was 1.94 (95% CI: 1.19–3.18, $n = 1{,}329$ cases/12,141 controls). When exposure assessment was based only on coded job titles, the adjusted summary OR for childhood AML was positive, but no longer statistically significant (OR = 1.63, 95% CI: 0.90–2.98, $n = 760$ cases/10,212 controls). Paternal occupational pesticide exposure around the time of conception was not associated with childhood AML.

As reported in the previous meta-analysis, the results of a meta-analysis of 22 case-control studies after stratification were consistent with the lack of an association between paternal pesticide exposure and childhood AML.[26] The meta-rate ratio for childhood acute nonlymphocytic leukemia (ANLL, primarily AML) in fathers with occupational pesticide exposure was 0.73 (95% CI: 0.19–2.76, $n = 2$ studies, $I^2 = 0\%$).

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The meta-rate ratio for ANLL in offspring of women with occupational pesticide exposure was statistically significant (mRR = 2.68, 95% CI: 1.06–6.78, $n = 2$, $I^2 = 0\%$). The limited statistical power of these two studies resulted in imprecise estimates. The job title of farming/agriculture for men or women was not associated with elevated leukemia risks.

The relationship between residential pesticide use during pregnancy and childhood AML is inconsistent, based almost exclusively on unvalidated self-reports in case-control study designs with very limited data on the timing, intensity, type, class, or specific pesticide involved. A systematic review and meta-analysis of case-control studies examining residential pesticide exposures during pregnancy and childhood leukemia identified three case-control studies that reported data on AML incidence with and without unspecified residential pesticide exposure.[27] The summary OR was positive, but statistically nonsignificant (OR = 1.44, 95% CI: 0.81–2.59, $I^2 = 80\%$) with substantial heterogeneity. Limiting pesticide exposures to insecticides only, the summary OR was statistically significant (OR = 1.85, 95% CI: 1.29–2.64, $n = 2$ studies, $I^2 = 0$).

Lifestyle

Smoking

Adults

Although tobacco smoking is the strongest lifestyle factor associated with adult AML consistent with tobacco smoke containing multiple genotoxic constituents including benzene,[105] the association with smoking is relatively modest and mixed. In a prospective cohort study of 330,000 Swedish construction workers, the incidence rate ratio of AML in current smokers was 1.5 (95% CI: 1.06–2.11) compared with nonsmokers.[112] The smoking status was established by self-administered questionnaire and face-to-face interviews with a nurse. In a California population-based study of 412 AML cases (57% participation rate) and 412 age/gender-matched matched controls, the odds ratio for AML comparing ever-smokers with never-smokers was not statistically significant (OR = 1.2, 95% CI: 0.9–1.6, $n = 250$ cases/232 controls).[190] For cases aged 60–75 years, the OR was marginally significant (OR = 1.6; 95% CI: 1.0–2.6, $n = 120$ cases). AML is a heterogeneous disease with distinct histological subtypes that have undergone several reclassifications since publication of this study; however, this study suggests some differences in the effect of smoking on AML subtypes based on older French-American-British AML classifications. A Canadian population-based study of 307 AML cases and 5,039 controls (63% participation rate) reported a statistically significant positive association comparing AML risks in never- and current-smokers (adjusted OR = 1.4, 95% CI: 1.1–1.8, $n = 83$ cases/1130 controls, $P_{trend} = 0.03$); the results suggest a dose-response relationship in heavy smokers with >20 pack/year smoking history (adjusted OR = 1.5, 95% CI: 1.1–2.0, $n = 88$ cases/1,178 controls, $P_{trend} = 0.003$).[114] Odds ratios were adjusted for occupational benzene/ionizing radiation exposures and 10-year age groups.

In the US NIH-AARP Diet and Health Study using multivariate Cox models and never-smokers as controls, the hazard ratios were significantly elevated for former smokers of >1 pack/day (HR = 1.79, 95% CI: 1.32–2.42, $n = 97$ cases), current smokers of ≤1 pack daily (HR = 2.42, 95% CI: 1.63–3.57, $n = 37$ cases), and current smokers using >1 pack daily (HR = 2.29, 95% CI: 1.38–3.79, $n = 19$ cases) based on questionnaires. The P_{trend} was 0.09. The OR for AML comparing never- and ever-smokers in a Chinese hospital-based case-control study was marginally elevated (OR = 1.28, 95% CI: 1.00–1.63, $n = 227$ cases/508 controls); the OR for men was statistically significant (OR = 1.36, 95% CI: 1.04–1.77).[191] Smoking duration in years was marginally positive ($P_{trend} = 0.05$), but not smoking intensity in pack-years ($P_{trend} = 0.08$). The results for passive smoking were statistically nonsignificant (OR = 1.08, 95% CI: 0.83–1.41, $n = 19$ cases/209 controls).

Children

Epidemiological evidence associating childhood AML with tobacco smoke is weaker for passive than active smoking. Overall, most studies report no association between childhood AML risks and maternal smoking during pregnancy, whereas the results for paternal smoking are mixed. In a meta-analysis of 14 case-control and 1 cohort study comparing any and no maternal smoking during pregnancy using fixed effects models, the summary AML OR was null (summary OR = 0.99, 95% CI: 0.90–1.09, $I^2 = 28.6\%$, $P_{heterogeneity} = 0.14$) with mild heterogeneity.[192] All studies were North American or European. The only cohort study enrolled 1,440,542 Swedish children and identified 48 incident AML cases.[193] Comparing any smoking with no smoking during pregnancy based on a standardized questionnaire collected by a nurse-midwife, the adjusted hazard ratio was positive, but statistically nonsignificant (aHR = 1.41, 95% CI: 0.74–2.67, $n = 15$ cases). The aHR was 0.91 (95% CI: 0.38–2.21) for women smoking 1–9 cigarettes daily during early pregnancy and 2.28 (95% CI: 1.05–4.94) for women smoking ≥10 cigarettes daily, with a statistically nonsignificant trend ($P_{trend} = 0.084$).

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TABLE 59.5. Acute myeloid leukemia (AML) risks associated with intensity and the time of paternal and maternal smoking surrounding the child's birth using nonsmokers as referents and pooled data from the Childhood Leukemia International Consortium. Moderate smokers were defined by 1–15 cigarettes daily, whereas ≥16 cigarettes daily defined heavy smoking. The odds ratios were adjusted for age, sex, ethnicity, parental education, and study center. (Adapted from Metayer et al.).[194]

Time Period	Smoking Status	Odds Ratio	95% CI	Cases	Controls	Studies
			Paternal			
Prenatal	Nonsmoker	1.00	Referent	375	5,296	7
	Moderate	1.18	0.96–1.45	141	1,726	7
	Heavy	1.31	1.08–1.60	174	1,949	7
Preconception	Nonsmoker	1.00	Referent	254	3,252	5
	Moderate	1.04	0.79–1.35	85	1,113	5
	Heavy	1.37	1.07–1.37	117	1,217	5
Pregnancy	Nonsmoker	1.00	Referent	149	2,283	3
	Moderate	1.03	0.74–1.44	58	884	3
	Heavy	1.41	1.06–1.89	89	997	3
Postnatal	Nonsmoker	1.00	Referent	139	2,546	3
	Moderate	0.93	0.65–1.33	43	779	3
	Heavy	1.27	0.93–1.73	68	937	3
			Maternal			
Prenatal	Nonsmoker	1.00	Referent	512	6,037	11
	Moderate	0.82	0.66–1.00	130	2,074	11
	Heavy	0.74	0.50–1.11	404	4,321	11
Preconception	Nonsmoker	1.00	Referent	461	5,569	6
	Moderate	0.82	0.65–1.04	99	1,576	6
	Heavy	0.83	0.61–1.13	54	854	6
Pregnancy	Nonsmoker	1.00	Referent	723	8,448	9
	Moderate	0.96	0.79–1.17	139	1,812	9
	Heavy	0.68	0.44–1.07	23	383	9
Postnatal	Nonsmoker	1.00	Referent	301	3,544	4
	Moderate	0.87	0.61–1.23	41	570	4
	Heavy	0.54	0.28–1.04	10	206	4

Abbreviation: CI = confidence interval.

Paternal smoking was not associated with an increased childhood AML risk in this meta-analysis; however, a pooled analysis of data from the Childhood Leukemia International Consortium supported a statistically significant and modest association between heavy (≥16 cigarettes daily), but not moderate (1–15 cigarettes daily) paternal smoking and childhood AML using nonsmoking fathers as referents.[194] The vulnerable exposure time period was difficult to determine; the adjusted OR was positive and statistically significant for heavy smoking fathers during the prenatal, preconception, pregnancy time periods, but not during the postnatal time period, as displayed in Table 59.5. Overall, pooled results indicated maternal smoking was not associated with increased childhood AML risks. The meta-analysis of nine case-control studies in this study using random and fixed effects models demonstrated no significant association with childhood AML comparing self-reported, ever-smoking, and nonsmoking mothers (meta-OR = 1.02, 95% CI: 0.88–1.18, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.468$).

The French nationwide, population-based (ESTELLE) study of 100 childhood AML cases and age/sex-matched controls reported no association between self-reported maternal smoking during pregnancy and childhood AML comparing ever-smokers with never-smokers with no evidence of a dose-response relationship (summary OR = 0.9, 95% CI: 0.5–1.5, $n = 51$ ever-smokers/48 never-smokers, $P_{\text{trend}} = 0.83$).[123] The

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association between self-reported paternal smoking during preconception and childhood AML comparing ever-smokers with nonsmokers was marginally significant (summary OR = 1.5, 95% CI: 1.0–2.3, $n = 585$ ever-smokers/806 never-smokers) with a positive dose-response ($P_{trend} = 0.03$).

Alcohol

Adults

Little epidemiological evidence supports an association between alcohol consumption and adult AML risks. The California case-control study on lifetime alcohol consumption in 164 pairs matched for smoking, sex, age, and ethnicity did not detect an elevated adult AML risk for lifetime consumption of >1 alcoholic drink/day (OR = 0.8, 95% CI: 0.4–1.6, $n = 6$ cases/4 controls, $P_{linear\ trend} = 0.20$).[195] A Chinese hospital-based study of 722 confirmed AML cases and 1,444 age/gender-matched patient controls suggests an association between any alcohol consumption and adult AML risks (OR = 1.53, 95% CI: 1.17–2.01) based on interviews, particularly for wine.[191] Multiple comparisons, potential for recall bias, and comparability of patients to the general population limit definitive conclusions regarding causation.

Children

Most case-control studies suggest a positive association between maternal alcohol consumption during pregnancy and childhood AML; in a meta-analysis of 39 case-control studies, the summary OR was elevated significantly for AML risks in offspring of women consuming moderate (OR = 1.64, 95% CI: 1.23–2.17) and high (OR = 2.36, 95% CI: 1.60–3.49) alcohol doses during pregnancy.[196] In a meta-analysis of eight case-control studies comparing women ever consuming alcohol during pregnancy with abstinent women, the childhood AML risk was elevated with moderately high heterogeneity (summary OR = 1.56, 95% CI: 1.13–2.15, $P_{random\ effects\ model} = 0.007$, $I^2 = 52.5\%$, $P_{heterogeneity} = 0.032$).[127] The AML risk was substantially higher in children aged 0–4 years (summary OR = 2.68, 95% CI: 1.85–3.89, $n = 5$ studies, $P_{random\ effects\ model} = 0.001$, $I^2 = 0.1\%$, $P_{heterogeneity} = 0.761$). Wine, but not spirits or beer, was associated with increased childhood AML risk (summary OR = 1.67, 95% CI: 1.21–2.32, $n = 4$ studies, $P_{heterogeneity} = 0.870$). Insufficient published data were available to calculate dose-response relationships.

The nationwide French ESTELLE study identified 100 childhood AML cases, 348 ever-maternal alcohol use during pregnancy, and 1,069 population-based controls.[123] Comparing ever-drinkers during pregnancy with never-drinkers, the summary odds ratio was positive, but statistically nonsignificant (OR = 1.3, 95% CI: 0.8–2.0). Dividing alcohol consumption during pregnancy into low (<1 drink/week), moderate (1–2 drinks/week), and high (>2 drinks/week) categories, the estimated childhood AML risk for the highest tertile was statistically elevated (OR = 2.8, 95% CI: 1.2–6.7, $n = 7$ cases, $P_{trend} = 0.02$) compared with controls; however, the estimate was imprecise from small case numbers, and alcohol consumption categories were lower than most studies. The study did not report statistically significant differences between childhood AML risks and beverage classes (wine, beer, beverages). Paternal alcohol consumption during preconception is not associated with elevated childhood AML risks in offspring.[196]

Caffeinated Beverages

Data are limited on any association between caffeinated beverages and AML risks. Some case-control studies report modestly positive, but mostly statistically nonsignificant childhood AML risks in offspring of mothers who consumed high amounts of coffee during pregnancy. An exception was high coffee use (>2 cups/day) based on self-reported questionnaires by mothers recruited in the French ESCALE population-based case-control study (adjusted OR = 1.5, 95% CI: 1.1–2.0, $P_{trend} = 0.0027$).[197] In another French population-based case-control study, self-reported maternal coffee consumption during pregnancy exceeding three cups daily was associated with a positive, but statistically nonsignificant adjusted odds ratio for childhood AML in offspring (aOR = 1.4, 95% CI: 0.5–4.4, $n = 5$ cases) compared with nondrinkers.[126] The French ESTELLE population-based case-control study reported a statistically nonsignificant AML risk *reduction* in offspring (aOR = 0.5, 95% CI: 0.2–1.1, $n = 8$ cases) of mothers drinking >2 cups of coffee during pregnancy using mothers classified as never/occasional coffee users.[123] In a meta-analysis of seven case-control studies comparing the highest-level with non/lowest maternal coffee drinkers during pregnancy, the estimated childhood AML risk in offspring was significantly elevated (summary OR = 1.58, 95% CI: 1.20–2.08, $n = 4$ studies, $I^2 = 0\%$).[198] Dose-response analysis estimated the OR for childhood AML risks in offspring of mothers drinking coffee during pregnancy ranged from 1.15 (95% CI: 0.98–1.34) for 1–2 cups daily to 1.65 (95% CI: 1.26–2.16) for 10 cups daily.

In a meta-analysis of six case-control studies comparing childhood AML risks in offspring, the

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summary odds ratio was statistically significant for mothers ever drinking coffee during pregnancy using never-drinkers as referents (summary OR = 1.44, 95% CI: 1.01–2.04, $I^2 = 39.8\%$, $P_{\text{heterogeneity}} = 0.14$) with some heterogeneity.[131] Comparing high versus never/lowest coffee consumption categories, the summary OR was positive, but statistically nonsignificant (OR = 1.81, 95% CI: 0.93–3.53, $I^2 = 53.7\%$, $P_{\text{heterogeneity}} = 0.056$) with moderate heterogeneity. The association between maternal consumption of other caffeinated beverages during pregnancy and childhood AML is much weaker. Maternal tea consumption during pregnancy was not associated with increased childhood AML risks in the latter meta-analysis.

The Japan Public Health/Center-based Prospective Study identified 85 AML and 70 myelodysplastic syndrome cases among 95,807 Japanese participants followed for a mean of 18.3 years.[199] No statistically significant difference was detected by comparing the lowest and highest consumption categories using Cox proportional hazard models with adjustment for potential confounders. For the highest coffee consumption category (≥1 cup daily), the adjusted HR for AML was 0.95 (95% CI: 0.34–1.66, $n = 27$ cases, $P_{\text{trend}} = 0.796$) and 1.20 (95% CI: 0.62–2.32, $n = 28$, $P_{\text{trend}} = 0.449$) for the highest green tea consumption category (≥5 cups daily). The study reported a statistically significant inverse association between coffee and myelodysplastic syndrome (MDS) risks for men consuming ≥1 cup daily (aHR = 0.47, 95% CI: 0.22–0.99, $n = 13$, $P_{\text{trend}} = 0.049$), but not for women; green tea consumption did not alter MDS risks.

Diet

Limited data on maternal diet and childhood leukemia suggest diet is not an important risk factor for childhood AML; however, AML is a heterogeneous disease with multiple subtypes that may differ in risk factors. Approximately 75% of infants with leukemia have a rearrangement of the *MLL* gene at chromosome 11q23, particularly in children treated for secondary leukemias following therapy with the DNA topoisomerase II inhibitor, epipodophyllotoxin.[200] Dietary sources of DNA topoisomerase II inhibitors include beans, flavonoids (e.g., quercetin), some fruits and vegetables, soy (e.g., genistein), and catechins (coffee, green/black tea, cocoa, wine). In a case-control study of 240 incident acute leukemia cases in infants of ≤1-year-old and 255 random controls, mothers of these children completed a food frequency questionnaire. Comparison of the highest and lowest (reference) quartiles of the DNA topoisomerase II inhibitor index demonstrated no overall elevated risk of acute leukemia, or for AML-MLL$^+$ or AML-MLL− subtypes, whereas the adjusted AML-MLL+ subgroup risk was increased, but statistically nonsignificant and imprecise (aOR = 3.2, 95% CI: 0.9–11.9, $n = 9$ cases, $P_{\text{trend}} = 0.10$).[201]

Obesity

Some recent studies suggest adult obesity increases AML risk more than other common leukemia subtypes; however, the findings are mixed. In a meta-analysis of 16 primarily North American and European prospective studies, the maximumly adjusted RR for overall leukemia in obese participants was positive for AML (RR = 1.53, 95% CI: 1.26–1.85, $p = <0.001$, $I^2 = 50\%$) with moderate heterogeneity.[128] The RR was also statistically significant for obese men (RR = 1.30–2.07, $p = <0.001$, $I^2 = 55\%$), but marginally significant in obese women (RR = 1.48, 95% CI: 1.00–2.20, $p = 0.05$, $I^2 = 0\%$). There was little support for an association between overweight participants and increased AML risks. In a Minnesota study of 420 AML cases, 265 myelodysplastic syndromes (MDS), and 1,388 age-matched controls (64% participation rate) using self-reported height and weight, the increased AML risk for obese participants (BMI = 30–34.9 kg/m^2) compared with normal weight participants (BMI = 18.5–24.9 kg/m^2) 2 years before diagnosis was statistically significant for men (OR = 2.24, 95% CI: 1.40–3.59, $P = 0.001$, $n = 75$ cases/181 controls) and women (OR = 1.85, 95% CI: 1.08–3.15, $P = 0.02$, $n = 32$ cases/113 controls). Limited data support an association between MDS and obesity in women, but not in men, whereas the results for AML in overweight participants were null consistent with most epidemiological studies. Weight change during adulthood was not associated with AML or MDS risks.

The US NIH-AARP Diet and Health Study identified 338 *de novo* AML cases. Using multivariate Cox models to estimate hazard ratios, the HR comparing overall AML risks in obese (≥30 kg/m^2) and normal weight participants (BMI = 25 to <30 kg/m^2) was positive, but not statistically significant (HR = 1.24, 95% CI: 0.92–1.66, $P_{\text{trend}} = 0.52$, $n = 80$ cases) based on baseline questionnaires.[202] A Chinese hospital-based study of 722 confirmed AML cases and 1,444 gender/age-matched controls reported a statistically significant reduction in AML risks (OR = 0.67, 95% CI: 0.46–0.97, $P_{\text{trend}} = 0.03$, $n = 43$ cases/120 controls) comparing obese (BMI = >28 kg/m^2) with normal weight participants (18.5–23.9 kg/m^2).[191] Height was negatively associated with AML risks ($P_{\text{trend}} = 0.01$).

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Medications

In general, maternal infections (viral, urinary tract, lower genital tract) and use of antibiotics are not associated with increased childhood AML risks, except for chloramphenicol- or phenylbutazone-induced aplastic anemia.[203,204,205] Chemotherapeutic agents associated with AML include alkylating agents (melphalan, chlorambucil, busulfan, cyclophosphamide, combined chemotherapy with alkylating agents, MOPP for treatment of Hodgkin disease, and epipodophyllotoxins).[206]

HISTOLOGY

AML is a genetically complex, clonal stem cell cancer that causes maturation arrest and proliferation of immature myeloid cells. Prior to the 1980s, early pathological studies considered leukemia a single diagnostic category. Subsequently, pathologists divided leukemias into four categories (AML, CML, ALL, CLL); however, by 2001, the World Health Organization began subdividing these categories into multiple subcategories based on cytogenetic, morphological, and molecular criteria with further revisions in 2008 and 2016. The latter classifications are displayed in Table 59.1. AML results in the clonal expansion of myeloid blast cells with accumulation of immature progenitor cells and impairment of normal hematopoiesis. Most AML tumors display clonal heterogeneity that involves the presence of at least one founding clone and one subclone.[149] The recent WHO classifies acute myeloid leukemia into subcategories, as displayed in Table 59.1.

HOST SUSCEPTIBILITY

Several observational studies including reports of familial AML clusters suggest an association between family history of hematological malignancies in first- and second-degree relatives and increased AML risks;[207] however, small sample sizes, few studies, and imprecise risk estimates limit definitive conclusions. In a French population-based study of 472 *de novo* acute leukemia cases and 567 age/gender/region-matched controls, a family history of hematological cancer in first- or second-degree relatives was associated with elevated AML risks (OR = 4.3, 95% CI: 1.4–13, $n = 5$ cases) compared with controls without a positive family history of AML.[208] AML risks were similarly imprecise in a French hospital-based study of 279 *de novo* childhood acute leukemia cases and 285 age/gender/region-matched controls.[209] A family history of hematological cancer in first- or second-degree relatives was associated with an elevated, albeit imprecise, estimated AML risk (OR = 13.3, 95% CI: 2.5–70.9, $n = 4$ cases).

In children, genetic disorders and constitutional genetic defects are associated with increased AML risks, particularly the AML subtype acute megakaryocytic leukemia. A case series suggests a 10–20-fold increase in acute leukemia incidence occurs in patients with Down syndrome, including elevated AML risks.[210] The most common genetic factor associated with AML is trisomy 21. Approximately 10% of Down's syndrome infants have transient abnormal myelopoiesis with mutations of the *GATA1* gene that progresses to myeloid leukemia in ~20% within the first 5 years of life. Additional mutations beside the *GATA1* gene are necessary to develop this AML subtype. Myeloid leukemia is a specific AML subtype characterized by megakaryoblastic cells. Other congenital disorders associated with aneuploidy demonstrate an increased AML incidence including ataxia telangiectasia, Bloom syndrome, familial monosomy 7, Klinefelter syndrome, Li–Fraumeni syndrome, Fanconi anemia, Shwachman–Diamond syndrome, and von Recklinghausen's neurofibromatosis.[203,211]

Only ~5% of childhood leukemias involve high-penetrance germline mutations, more commonly in AML than ALL. Common germline mutations of genes associated with familial myeloid neoplasms include ANKRD26, CEBPA, DDX41, ETV6, GATA2, RUNX1, SRP72, TERC, TERT, and TP53.[212,213] Somatic mutations of genes involved in epigenetic regulation (e.g., *ASXL1*, *DNMT3A*, *TET2*) increase with age, resulting in an increased AML risk with increasing age in adults.[214] Clinical testing is available for *CEBPA*-associated familial acute myeloid leukemia, inherited bone marrow failure syndromes (dysregulated telomere maintenance associated with dyskeratosis congenita), familial platelet disorder with AML susceptibility (*RUNX1*), and *GATA2*-associated familial myelodysplastic syndrome/acute myeloid leukemia.

CLINICAL FEATURES

The clinical features of AML reflect bone marrow failure and organ infiltration include fatigue, dyspnea, severe sepsis, bruising, and epistaxis. Extramedullary involvement may occur, including CNS involvement. Life-threatening coagulopathy (i.e., acute promyelocytic leukemia) or rapidly fatal tumor lysis syndrome may occur. In childhood, AML usually occurs in the first year of life with similar incidence rates in boys and girls.[115] Myelodysplastic syndrome (MDS) frequently precedes AML development in the elderly. The median age of diagnosis for adult AML patients is ~66–70 years with almost 70% being >55 years.

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Secondary AML peaks ~5–10-years after chemotherapy, whereas the peak AML incidence in the Life Span Study of Japanese atomic bomb survivors was 5–7 years.[215] The data from Hiroshima and Nagasaki are limited by a lack of prospective data from the first 5 years after the atomic bomb explosions; subsequent data suggest that the latency period is <5 years.[31] European studies suggest the occurrence of space-time and/or spatial clustering of childhood leukemias related to time/place of birth and time/place of diagnosis, suggesting environmental factors (e.g., viruses).[216]

AML is a rapidly fatal disease if untreated; even with treatment, adult AML has the lowest survival rates of all leukemias. Specific chromosomal abnormalities affect AML prognosis. Favorable subtypes include acute promyelocytic leukemia (t(15;17) translocation, PML-RARA rearrangement)) and core-binding factor-associated AML leukemia subtypes (8:21 translocation, chromosome 16 inversion), whereas adverse AML risk groups include monosomal and complex karyotypes (e.g., aberrations of chromosomes 5 and 7).[217] Approximately 50–60% of adult AML patients have chromosomal abnormalities detectable on cytogenetic testing that are significantly associated with survival. The remaining AML patients with cytogenetically normal testing have variable clinical outcomes depending on acquired gene mutations, miRNA/gene-expression profiles, age, coexisting diseases, and other risk factors.[148] The 5-year survival rate ranges from ~5–15% in AML patients of >60 years of age compared with 35–40% for adult AML patients presenting at age ≤60 years.[212,218] The recent development of more targeted AML therapy may improve these survival rates. For childhood AML, survival rates increased over the last several decades with improvements in chemotherapy, stem cell transplants, and supportive care. The overall survival rate now is ~65–70% with event-free survival of 50–60%; however, the cumulative relapse rate remains high (35–40%), depending in part on the specific AML subtype.[219,220]

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

ALL is the predominant childhood leukemia (<15 years of age), with ~60% of cases occurring before 20 years of age.[221] The annual childhood ALL incidence is five times higher for ALL than AML, with ALL incidence decreasing with age relative to AML. Childhood ALL accounts for the most cancer-related deaths in patients of <20 years of age. The incidence rates vary between countries; ~6,000 ALL cases occur annually in the United States, with 75–80% of the disease in children/adolescents.[5,222] The annual ALL incidence is ~4/100,000 population in the United Kingdom. The highest reported incidence exists in Europe, Oceania (Australia, New Zealand), and North America, whereas lower reported rates are reported in Africa, Asia, and South America. Time trends in developing countries demonstrate a modest increase in childhood ALL rates in the last three decades of the 20th century followed by a flattening of the curve in the early 2000s; however, the temporal trend may also represent improvements in diagnosis, reporting, and healthcare access.[223] Immigrants to developed countries acquire incidence rates similar to those of the host nation.[224] The presentation of childhood ALL peaks during ages 2–5 years, with ALL incidence higher in boys than girls after the first year of life (i.e., 1.2:1), particularly for T cell ALL. Peak adult ALL incidence occurs at ~50 years old after a trough between 30 and 40 years of age.[225]

The overall age-adjusted annual incidence of ALL in the United States is 1.7/100,00 men and women. Although age patterns are consistent across racial/ethnic groups, some variation occurs with race/ethnicity (e.g., white/black ratio = ~1.6) reflecting genetic variation as well as socioeconomic factors.[106,226] African Americans have the lowest ALL incidence rate compared with European Americans and Asians, while Hispanics and probably Native Americans have higher rates.[227] Several ALL subtypes occur differentially in racial/ethnic groups (e.g., *CCRLF2*-rearranged ALL, Hispanics; *TCF3-PBX1* ALL, blacks).[228]

CARCINOGENESIS

ALL is a lymphoid malignancy affecting B (75–80%) or T (20–25%) cell lineages. Both B cell and T cell ALL comprise multiple subtypes containing distinct somatic structural DNA rearrangements and sequence mutations that disrupt lymphoid development (*ETV6*, *RUNX1*), Janus kinase and RAS signaling pathways, cytokine receptors, tumor suppression, DNA methylation, and chromatin modification along with oncogene activation (e.g., *MYC* gene).[229] Typically, childhood ALL genomes contain 10–20 non-silent coding mutations at presentation with the number doubling at relapse.[230]

Epigenetic alterations contribute significantly to leukemogenesis including ALL development,

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particularly DNA methylation. Methylation of cytosine residues in CpG dinucleotides establishes cellular identity by influencing gene expression. Recurrent ALL subtypes have subtype-specific signatures consisting of methylated CpG sites. Common genes associated with epigenetic dysregulation include *ASXL1*, *ATRX*, *CREBBP*, *EP300*, *KMT2A* (MLL rearrangements), *KMT2D*, *NSD2*, *PRC2* (polycomb repressive complex 2), and *SETD2*.[231] The KMT2A fusion protein is an important driver gene in the ALL landscape affecting histone methyltransferase involved with epigenetic regulation of blood–cell development.[232] Over 2/3 of B cell ALL tumors contain mutations involved with transcriptional regulation of B cell development (e.g., *EBF1*, *IKZF1*, *PAX5* genes), whereas >80% of T cell ALL tumors contain alterations of INK4/ARF tumor suppressors.[221]

The molecular phenotypes of childhood and adulthood ALL differ. The most common structural cytogenetic abnormality in adult ALL is the Philadelphia chromosome involving translocation t(9;22)(q34;q11), resulting in the BCR-ABL fusion gene and activation of tyrosine kinase, whereas TEL-AML1 t(12;21) translocation is the most frequent (i.e., ~20%) in childhood ALL. The mutations of the *TEL-AML1* gene and hyperdiploid childhood ALL subtypes account for half of childhood leukemias, while adult leukemias are dominated by more complex chromosome aberrations, including the Philadelphia chromosome (*BCR-ABL1* gene). The former two subtypes rarely occur in adult leukemia.[233] For infant *MLL*-positive ALL, prenatal initiation of a malignant clone appears sufficient to develop ALL; however, most childhood ALL requires further genetic changes. The TEL-AML1 fusion protein alone is insufficient to transform hematopoietic cell lines into leukemic cells.

Delayed, dysregulated immune responses to common infectious agents may contribute substantially to the conversion of preleukemic clones to overt precursor B cell ALL.[115] In the United Kingdom Childhood Cancer Study of 425 ALL cases aged 2–5 years and 1,031 sex/age/region-matched population controls from UK primary-care registers, the number of clinically diagnosed infectious episodes in infancy was greater in leukemia cases (3.6 infections, 95% CI: 3.3–3.9) than controls (3.1 infections, 95% CI: 2.9–3.2), particularly in the neonatal period (24% of cases vs. 18% of controls).[234] The onset of leukemia was ~7 months earlier in leukemia cases with >1 neonatal infection than in cases with ≤1 neonatal infection. The relative expression of various miRNAs helps diagnose and classify B and T cell ALL subtypes including miRNA 126, 128, 146b, 148, 151, 191, 424, 425-5p, and 629.

EXPOSURE

In contrast to AML, few environmental risk factors are causally associated with increased childhood or adult ALL, as displayed in Table 59.6.[235] The risk of acquiring ALL increases with ionizing radiation exposure similar to AML.[164] Increased ALL risks associated with overhead power lines, electromagnetic fields, and air pollution remain unsubstantiated.[2]

Ionizing Radiation

High- and medium-ionizing radiation doses are an established cause of adult and childhood ALL based on studies of Japanese atomic bomb survivors and the slightly increased ALL incidence in offspring of mothers receiving X-ray pelvimetry during pregnancy. Epidemiology studies on diagnostic X-rays and high-dose CT scans are inconsistent with a relatively weak association at radiation doses of <100 mSv. A retrospective UK cohort study of 176,587 patients from the NHS Central Registry identified 26 ALL cases among patients receiving CT scans (64% head CT). The excess relative risk (ERR) for ALL using controls with <5 mGy exposure was 1.719 (95% CI: >0–17.73, $P_{\text{dose-response}} = 0.0053$) with some estimate instability. Follow-up for leukemia began 2 years after the scans.

Although most ecological studies on leukemia and radon exposure report statistically significant positive results, case-control studies demonstrate mixed, generally weak results with few reporting statistically significant associations with leukemia reflecting difficulties with estimating radon exposures.[236] The retrospective, census-based cohort study of over 2 million Swiss children of <16 years of age suggests estimated dose rates of ≥0.2 mSv/hour increased childhood ALL risks (HR = 2.12, 95% CI: 1.09–4.16, $n = 9$ cases) based on a few cases and referents with exposure to <0.1 mSv/hour.[237] Using 10,843 direct indoor radon measurements and a co-kriging model, the French Geocap study of 7,434 ALL cases found little evidence of increased ALL risks with increased estimated radon doses (SIR by 0.01 mSv γ-radiation/hour = 1.01, 95% CI: 1.00–1.02).[238]

Adults

Significant dose-related elevated ALL risks occurred in the Life Span Study cohort of Japanese atomic bomb survivors, with ALL excess relative risks significantly decreasing with increasing time since exposure and increasing age at exposure.[215] Pooled data from 9 historical cohort studies involving 262,573 participants

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TABLE 59.6. Current strength of epidemiological evidence for an association of specific risk factors and childhood leukemia (mostly acute lymphoblastic leukemias) along with estimation of the overall contribution of that factor to childhood leukemia incidence *if* causal. Many studies lack sufficient size to separate preconception, prenatal, and postnatal time periods. The overall contribution categories based on the estimated attributable fraction include small (<5%), modest (5–15%), and marked (>15%). (Adapted from Schüz and Erdmann).[235]

Risk Factor	Convincing	Limited	Little	Overall Contribution
		Environmental		
Postnatal pesticides			X	
Parental pesticides			X	
Air pollution			X	
		Ionizing radiation		
Therapeutic (high dose)	X			Small
Diagnostic		X		Modest
Radon		X		Modest
Nuclear power plant operation			X	
Parental occupational exposure			X	
		Electromagnetic fields		
Radiofrequency			X	
Extremely low frequency[a]		X		Small
Parental occupational exposure			X	
		Lifestyle		
Maternal smoking			X	
Paternal smoking		X		Modest
Maternal alcohol consumption			X	
Paternal alcohol consumption			X	
Maternal diet			X	
Obesity		X		Small
Maternal folate use		X (inverse)		Modest
		Infection		
Day-care attendance		X (inverse)		Modest
Pattern/timing infections	X			Marked
Lack of immune stimulation		X		Modest
Specific infections				
Breastfeeding		X (inverse)		Modest
		Personal		
Genetic syndromes (e.g., Down's syndrome)	X			Small
Birth weight	X			Small
Sex/age	X			Marked
Parental age			X	
Allergies/atopic disease		X (inverse)		Small

[a] Extremely low frequency electromagnetic fields.

receiving mean cumulative active bone marrow doses of 19.6 ± 22.7 mSv prior to age 21 identified 40 ALL cases. The odds ratio for ALL was positive and statistically significant, but unstable (OR = 5.66, 95% CI: 1.35–19.71, $P_{trend} = 0.023$).[169] The estimated dose-response curve for ALL remained positive below 50 mSv.

Children

For current radiation doses, little evidence supports an association of childhood ALL with preconception maternal abdominal/pelvic X-rays with conflicting results for preconception paternal and postnatal diagnostic radiation exposures. In an Australian study of 389 incident ALL cases and 876 frequency-matched controls (no diagnostic X-rays), little evidence supported an increased ALL risk in offspring with any maternal abdominal X-rays during pregnancy (OR = 0.46, 95% CI: 0.15–1.40) or any paternal preconception abdominal X-rays (OR = 1.17, 95% CI: 0.88–1.55).[239] The ALL risk increased for >1 paternal preconception X-ray (OR = 1.47, 95% CI: 0.98–2.21) or an intravenous pyelogram (OR = 3.56, 95% CI: 1.59–7.98). Little evidence supported an increased ALL risk

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with any childhood X-rays 6 months before diagnosis (OR = 1.15, 95% CI: 0.88–1.51). In a US study of 652 ALL cases aged ≤14 years diagnosed from 1995–2008 and age/sex/race-matched controls, *in utero* diagnostic X-rays were associated with a positive, but statistically nonsignificant childhood ALL risk (OR = 1.20, 95% CI: 0.71–2.04, $n = 652$ cases) based on in-home maternal interviews.[168]

Extremely Low Frequency Electromagnetic Fields

Although a meta-analysis suggests relatively high electromagnetic field (ELF) radiation (i.e., magnetic flux densities of >0.3–0.4 μT) may slightly increase childhood ALL,[46] the findings are inconclusive and relatively weak given the lack of a confirmed biological mechanism, credible models, difficulty assessing/comparing ELF exposures accurately, and the potential presence of bias and confounding.[240,241] Results from case-control studies on childhood ALL risks from ELF fields are mixed with both positive[242,243] and negative[244,245] findings. More recent pooled analyses from case-control studies using more direct methods comparing estimated high (≥0.3–0.4 μT) and low (<0.1 μT) ELF exposures suggest weaker, nonsignificant associations (RR = 1.44, 95% CI: 0.88–2.36, $n = 6$ studies)[49] than older epidemiological studies (RR = 2.00, 95% CI: 1.27–3.13, $n = 9$ studies).[246]

Chemicals

Benzene

Although benzene is a recognized cause of ALL in adults, the association between benzene exposure and childhood ALL is less clear.[247] Parental benzene exposure is a plausible ALL risk factor for offspring; however, epidemiological evidence for an association of ALL with benzene and other chemicals is limited. The available studies use less accurate indirect measures of benzene exposure (self-reported benzene/related product use, job titles/matrices, surrogates) than direct measurements (e.g., personal, prospective). The epidemiological evidence for increased ALL risks is stronger for maternal benzene exposure during pregnancy than paternal preconception exposure. A Danish population-based, case-control study used data from the Danish Cancer Registry to identify children born between 1968 and 1974 prior to banning workplace benzene and the nationwide pension fund records to match unexposed controls and parental occupational benzene exposure using a job-exposure matrix.[248] The adjusted ALL relative risk in offspring was statistically significant for any maternal benzene exposure during pregnancy (aRR = 2.28, 95% CI: 1.17–4.41, $n = 11$ cases), but not for any paternal benzene exposure within 3 months of conception (aRR = 1.40, 95% CI: 0.88–2.22, $n = 22$ cases).

A meta-analysis of 14 case-control studies on ALL and any occupational or household benzene exposure reported a summary relative risk of 1.57 (95% CI: 1.21–2.08) with significant heterogeneity ($P_{\text{heterogeneity}} = 0.03$) using a fixed effects model adjusted for between-study heterogeneity; the referents were nonexposed controls.[249] The use of multiple exposure types (occupational, residential), times (preconception, periconception, gestational, postnatal, overall), and persons (maternal, paternal) limits extrapolation of the results to any particular benzene exposure. All of the included ALL occupational case-control results were statistically nonsignificant, with the exception of a highly imprecise Columbian study that combined any benzene exposure in either parent with nonexposed controls (OR = 11.65, 95% CI: 2.98–45.59). Consistent with other studies, the associated risk was higher for AML than for ALL. A census-based cohort study on over 2 million Swiss children of <16 years of age identified 19 ALL cases.[250] Based on parental occupations reported at census and job-exposure matrix to assess benzene exposure, maternal occupations with any benzene exposure were associated with increased ALL risks in offspring (HR = 1.88, 95% CI: 1.16–3.04). Paternal benzene exposure at work was not associated with an elevated hazard ratio for ALL in their offspring. No information was available for prenatal exposures, smoking, or alcohol consumption. In a case-control study of 33 paternal occupations and 12,288 lymphoid leukemia cases identified in the UK National Registry of Childhood Tumors, no paternal occupation was associated with a statistically significant increased risk in offspring.[251]

Pesticides and Other Agricultural Exposures

Some epidemiological evidence suggests an association between parental occupational pesticide exposure and ALL, whereas the association of ALL with postnatal pesticide exposure is much weaker. Most of this evidence involves case-control designs with inability to identify specific pesticides, heterogeneity across studies, and potential design issues (recall/selection bias, confounding). A US study of 41 incident childhood ALL cases and mothers compared maternal questionnaire data with measured urine concentrations in the children. The results demonstrated little statistical correlation between the questionnaire and measurement data on

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high and low pesticide exposures.[252] A meta-analysis of 12 case-control studies in the Childhood Leukemia International Consortium suggests maternal pesticide exposure during pregnancy does not increase ALL risks in offspring (summary OR = 1.03, 95% CI: 0.77–1.38, n = 8,236 cases/14,850 controls, I^2 = 11.2%), whereas paternal pesticide exposure around preconception may slightly increase ALL risks (summary OR = 1.22, 95% CI: 0.94–1.58, n = 8,157 cases/14,201 controls, I^2 = 68.7%).[189] The latter result demonstrated moderate heterogeneity. A meta-analysis of ALL risks in offspring and unspecified residential pesticide exposure during pregnancy reported an elevated ALL risk (summary OR = 2.04, 95% CI: 1.54–2.68, n = 3 studies, I^2 = 19%).[27] All pesticide exposures were based on self-reports without validation.

Lifestyle

Smoking

Although case-control studies of paternal smoking during the immediate preconception period suggest a modest association with childhood ALL in offspring in most, but not all studies,[253] epidemiological studies on ALL risk from maternal smoking during pregnancy report null results.[193] In the French ESTELLE study of 636 childhood ALL cases and 1,421 age/gender-matched population controls using self-reported smoking and never-smokers as referents, maternal smoking during pregnancy was not associated with childhood ALL risks.[123] For cigarette consumption in the highest maternal exposure group (≥11 cigarettes daily), the OR was 1.0 (95% CI: 0.5–2.0, n = 13 exposed cases/15 exposed controls, P_{trend} = 0.95). The odds ratio for childhood ALL in offspring of fathers who smoked during pregnancy was marginally elevated (OR = 1.3, 95% CI: 1.0–1.7, n = 115 exposed cases/213 exposed controls, P_{trend} = 0.09). In an Australian population-based study of 388 childhood ALL cases of 15-year-old and 868 nonsmoking controls, maternal smoking was not associated with increased childhood ALL risks, including the highest cigarette use category of ≥15 cigarettes/day during pregnancy (OR = 0.98, 95% CI: 0.67–1.44, n = 49 exposed cases/107 exposed controls, P_{trend} = 0.98).[254] The same category for paternal smoking was associated with an OR of 1.28 (95% CI: 0.97–1.70) with a significant trend (P_{trend} = 0.03).

Alcohol

Although alcohol is a potential ALL leukemogen, little epidemiological evidence supports an association between maternal or paternal alcohol consumption and increased childhood ALL risks based primarily on interviews using self-administered questionnaires. A meta-analysis of 21 case-control and no cohort studies reported no association between any maternal alcohol consumption during pregnancy and ALL risks in offspring ≤4 years old using nondrinkers as referents.[127] The summary OR for ALL was statistically nonsignificant using random effects models (sOR = 1.17, 95% CI: 0.83–1.65, n = 3 studies, I^2 = 31.7%, $P_{heterogeneity}$ = 0.231) with slight to moderate heterogeneity. Dose-response analysis was inconclusive due to inadequate study numbers. In the French ESTELLE study of 636 ALL cases (503 B cell precursors, 95 T cell precursors) and 1,421 population-based controls, maternal alcohol consumption (ever vs. never) during pregnancy was not associated with increased childhood ALL risks.[123] The odds ratio was 1.0 (95% CI: 0.8–1.2, n = 136 cases) with no dose-response relationship (P_{trend} = 0.38). An Australian study of 388 ALL cases and 1,396 family controls reported no evidence supporting an increased childhood ALL risk from maternal alcohol consumption before or during pregnancy; the odds ratio comparing any and no wine during pregnancy suggests an inverse ALL relationship (OR = 0.66, 95% CI: 0.49–0.89, n = 356 cases).[125] Although any versus no paternal alcohol consumption was not associated with childhood ALL (OR = 0.72, 95% CI: 0.48–1.08, n = 281 cases), the OR for high beer consumption (≥28 beers/week) was positive but statistically non-significant (OR = 1.23, 95% CI: 0.73–2.05, n = 36 cases) with a quadratic term P value of 0.03.

In the French population-based study of 407 childhood ALL cases and 567 age/gender/region-matched, nondrinking controls, maternal alcohol consumption of >1 glass/day was associated with increased childhood ALL risks (OR = 2.8, 95% CI: 1.3–5.9, n = 23 cases).[126] An exploratory pooled study of 152 ALL cases and 23,096 controls using data from 16 case-control studies suggests ALL risks from alcohol consumption may be stronger for B cell than T cell ALL.[255] Although overall ALL risks comparing any history of alcohol consumption (≥1 drink/month) with nondrinking referents were null (OR = 1.01, 95% CI: 0.63–1.61, n = 64 cases), B cell ALL risks were increased (OR = 2.87, 95% CI: 1.18–6.95), whereas T cell ALL risks were not (OR = 0.46, 95% CI: 0.18–1.19, n = 15 cases).

Diet

Limited observational studies suggest maternal diet is not an important risk factor for childhood ALL in

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offspring. Some studies suggest food groups in the traditional Mediterranean diet (fruit, legumes, vegetables), as well as folate and vitamin supplementation during pregnancy, have a modest inverse association with childhood ALL risks.[256] In a Greek hospital-based study of 131 ALL cases aged <5 years and age/gender-matched controls hospitalized for minor conditions, the ALL risks in offspring were lower with increasing maternal quintiles of fruit, vegetable, and fish/seafood groups based on in-person interviews.[257] The increasing risks were associated with the maternal sugar/syrup group and marginally increased with quintiles of the meat/meat products group. A population-based study of 282 ALL cases (86% participation rate) from the Northern California Childhood Leukemia Study and age/sex/racially matched controls (56% participation rate) reported ALL risk reductions for maternal consumption of similar food groups using conditional logistic regression models.[258] Adjusted odds ratios for offspring ALL risks were reduced for maternal consumption (median times/day) of vegetables (aOR = 0.65, 95% CI: 0.50–0.84), legumes (aOR = 0.75, 95% CI: 0.59–0.95), protein sources (aOR = 0.55, 95% CI: 0.32–0.96), and marginally for fruit (aOR = 0.81, 95% CI: 0.65–1.00) food groups. The participation rate of controls was modest with higher incomes, more education, and older maternal ages than cases.

An analysis examined prenatal folic acid and vitamin supplementation from 12 case-control studies participating in the Childhood Leukemia International Consortium (6,963 ALL cases, 11,635 controls).[259] Any maternal supplementation before conception or during pregnancy was associated with reduced childhood ALL risk for vitamin (OR = 0.85, 95% CI: 0.78–0.92) and folic acid (OR = 0.80, 95% CI: 0.71–0.89) use. Neither ALL-MLL+ nor ALL-MLL− risks or linear trends were significantly associated with total maternal consumption of dietary DNA topoisomerase II inhibitors based on food frequency questionnaire and a calculated DNA topoisomerase II inhibitor food index.[201] The overall P_{trend} was 0.19 for ALL-MLL+ and 0.83 for ALL-MLL−.

Although caffeine is a topoisomerase II inhibitor, observational studies on caffeinated products and ALL risks are inconsistent with some evidence of a positive effect. In a meta-analysis of five case-control studies comparing the highest and never/lowest coffee drinkers during pregnancy, the odds ratio was statistically significant (OR = 1.65, 95% CI: 1.28–2.12, $I^2 = 47\%$) with moderate heterogeneity and a linear dose-response ($P_{\text{nonlinearity}} = 0.67$).[198] In a meta-analysis of eight case-control studies on maternal coffee consumption during pregnancy, the OR was not statistically significant (OR = 1.10, 95% CI: 0.99–1.22, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.434$) comparing ever- versus never-coffee drinkers; however, the odds ratio was statistically significant comparing the highest and never/lowest categories (OR = 1.43, 95% CI: 1.22–1.68, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.464$).[131] The French ESCALE study identified 648 ALL cases of <15 years of age; mothers were interviewed during their pregnancy using a standardized questionnaire. Comparing regular maternal coffee consumption of ≥1 cup/week during pregnancy with never/occasional use, the adjusted OR was marginally significant (aOR = 1.6, 95% CI: 1.0–2.6, $n = 71$ cases); however, the trend was significant ($P_{\text{trend}} = 0.002$) with an elevated childhood ALL risk for regular maternal coffee consumption of >2 cups daily (aOR = 2.4, 95% CI: 1.3–4.3 $n = 25$ cases).[197] Observational studies typically do not associate tea consumption with childhood ALL risks.

Obesity

Limited data from cohort studies suggest obesity defined by a BMI of ≥30 kg/m^2 and based on self-reported height and weight increases adult ALL risks relative to normal weight participants. In a meta-analysis of five cohort studies comparing obese and nonobese (BMI <25 kg/m^2) participants, the summary relative risk for adult ALL was 1.65 (95% CI: 1.16–2.35, $n = 588$ cases, $I^2 = 6.8\%$).[260] A meta-analysis of four cohort studies reported statistically significant summary rate ratios for adult ALL using normal weight referents (18.5–24.9 kg/m^2) in obese men (sRR = 1.69, 95% CI: 1.04–2.73, $P = 0.03$, $I^2 = 29\%$), but not for obese women (sRR = 1.09, 95% CI: 0.38–3.07, $P = 0.88$, $I^2 = 32\%$).[128] The data also indicated an increased ALL risks in overweight participants (sRR = 1.36, 95% CI: 1.06–1.76, $P = 0.02$, $I^2 = 0\%$). Meta-regression analyses did not demonstrate a linear relationship between BMI and ALL risks in men or women. The mechanism for an association between ALL and obesity remains unclear.

Medications

An international population-based study examined data from the Children's Oncology Group, which enrolled 1,843 ALL cases of ≤14 years of age and 1,986 individually matched controls with information based on telephone interviews. For maternal exposure during pregnancy, use of vitamins (OR = 0.7, 95% CI: 0.5–1.0), $n = 1{,}287$ exposed cases/1,465 exposed controls, $P_{\text{difference}} = 0.01$) and iron supplements (OR = 0.8, 95%

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CI: 0.7–1.0, $n = 490$ exposed cases/616 exposed controls, $P_{\text{difference}} = 0.01$) were borderline statistically significant.[261] Although some associations for 18 drug classes were positive, none were statistically significant, including antibiotics, anti-inflammatory drugs, hormones, and mind-altering drugs. An exploratory case-control study enrolled 157 mothers of infants <18 months of age with ALL and 255 control mothers identified by random digital dialing.[203] Although some medications had positive odds ratios, none of the specific antibiotics examined were associated with elevated infant ALL risk with the exception of trimethoprim/sulfamethoxazole (5 exposed cases/0 exposed controls). Antibiotic use in the peri-pregnancy period was not associated with ALL risks in offspring (OR = 0.96, 95% CI: 0.62–1.50, $n = 48$ exposed cases/65 control cases) in the population-based, case-control Northern California Childhood Leukemia Study.[262]

Diseases

Infectious diseases are suspected causes of childhood ALL because of dysregulated immune responses to common infections (e.g., influenza viruses/bacteria) in susceptible individuals. Although some animal models support a single transforming virus, this event has not been identified in human leukemia cells and no specific infection is causally linked to ALL with the exception of adult T cell leukemia/lymphoma and human T cell lymphotropic virus type1.[263,264] Case-control studies on the association between ALL in offspring and maternal infections during and immediately before pregnancy based on self-reports are varied. The population-based, case-control Northern California Childhood Leukemia Study reported a statistically significant elevation of self-reported influenza/pneumonia in mothers of ALL cases during the time period between 3 months prior to conception and the end of pregnancy (OR = 2.02, 95% CI: 1.28–3.18, $n = 64$ exposed cases/44 control cases).[262] Antibiotic use was correlated to influenza/pneumonia ($r = 0.14$, $P < 0.001$) and urinary tract infection ($r = 0.12$, $P < 0.001$).

HISTOLOGY

ALL arises from hematopoietic cells representing B cell precursors (BCP-ALL) or T cell lineage (T-ALL), with both immunophenotypes comprising multiple subtypes based on the initial transforming chromosomal alterations, as displayed in Table 59.1. Childhood ALL usually results from B cell lineage (i.e., ~80% typically CD19+/CD10+) and less often from T cell lineage (~20%), whereas adult ALL tumors are ~75% B cell and 25% T cell. Approximately 25–30% of B cell childhood ALL cells display high hyperdiploidy (>50 chromosomes) from nonrandom chromosome gains, whereas hypodiploidy (<44 chromosomes) occurs in 2–3% of children with B cell ALL. Low hypoploidy (30–39 chromosomes) suggests Li–Fraumeni syndrome.[265]

The predominant childhood leukemia involves the pre-B lymphocytic phenotype, primarily the cALL (common acute lymphoblastic leukemia) subtype that exhibits normal pre-B cell surface markers; these cells manifest characteristics of clonal expansion of normal pre-B cells that fail to mature. Teenagers typically trend toward increasing myeloid-type adult leukemias with disappearance of cALL as age increases. Circulating blast cells in peripheral blood indicate the presence of acute leukemia; characteristics of these blast cells include open chromatin, prominent nucleoli, and scant, basophilic cytoplasm. Myeloid blasts usually have large cytoplasmic granules (Auer rods), whereas lymphoid blasts are agranular. Immunotyping helps distinguish AML from ALL.

HOST SUSCEPTIBILITY

Overall, inheritance of several low-risk variants (e.g., *ARID5B*, *CDKN2A*, *CEBPE*, *IKZF1* genes) can increase childhood ALL risks;[266] however, little evidence supports the existence of highly penetrant ALL mutations in children or adults. ALL potentially can arise in monozygotic twins after *in utero* mutation and clonal expansion of one cell in one fetus reflecting the prenatal initiation of ALL by a chromosome translocation; however, some childhood leukemias require secondary transformation from acquired genetic mutations. Family clustering of ALL is limited. Examination of data from the Swedish Family-Cancer Database suggests a family history of leukemia increases ALL risks; however, the effect is very small. Of the 1,925 childhood ALL cases, 19 had a first-degree relatively diagnosed with ALL. Twins had a markedly increased standardized incidence ratio (SIR) for childhood ALL based on six cases. Siblings with a positive family history excluding twins had a positive, but statistically nonsignificant and imprecise estimated ALL SIR of 2.22 (95% CI: 0.51–7.32, $n = 5$ cases).[267] The addition of Finnish data yielded 3,994 cases.[268] The SIR for ALL in twins remained dramatically elevated, whereas the SIR for childhood ALL in singleton siblings was statistically significant (SIR = 3.2, 95% CI: 1.5–5.9, $n = 10$). An exploratory pooled study of 152 ALL cases and 23,096 controls from 16 case-control studies used referents with

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no familial hematological malignancies.[255] For families with any hematological malignancy in first-degree relatives, the risks were higher for B cell (OR = 3.30, 95% CI: 1.10–9.91, $n = 4$ cases/236 controls) than T cell ALL (OR = 3.33, 95% CI: 0.73–15.11, $n = 2$ cases/200 controls); however, the estimates were highly imprecise from a few cases. Rare germline mutations associated with familial ALL include *ETV6* [269] and *PAX5* genes.[270] The presence of Down syndrome substantially increases ALL risks.

CLINICAL FEATURES

Clinical features of ALL result from bone marrow failure and leukemic infiltration of the spleen, lymph nodes, and mediastinal masses. Bone marrow failure may produce infections from neutropenia, fatigue, and pallor from anemia, and/or easy bruising/hemorrhage from thrombocytopenia, whereas T cell ALL tumors may obstruct venous flow resulting in the superior vena caval syndrome. Coagulopathy is uncommon in ALL. Other nonspecific symptoms include fever, night sweats, and weight loss. Central nervous system involvement at presentation occurs in <10% of ALL cases manifested by meningismus and cranial nerve abnormalities.

With current therapy, >95% of children (age <12 years) achieve complete remission and ~80% have long-term event-free survival with ~90% overall survival compared with 10% in the 1960s.[219] Cure rates for older adult (age >59 years) ALL increased to the 40–50% range; the prognosis for infants (<1 year of age) is also worse than that for older children.[271] The main basis for ALL diagnosis, risk stratification, and prognosis includes structural chromosomal rearrangements (e.g., fusion genes), white blood cell count at diagnosis, and minimal residual disease status.[229] The higher prevalence of high-risk leukemia subtypes (e.g., BCR-ABL1 fusion gene, MLL rearrangement) along with a lower incidence of favorable subtypes (ETV6-RUNX1 fusion gene, hyperdiploidy) and poor tolerance of treatment in adolescents and adults reduce the prognosis compared with preadolescents.[272]

CHRONIC MYELOGENOUS LEUKEMIA (CML)

CML is a relatively rare, heterogeneous disease (0.6–2.0/100,000) accounting for ~15% of new leukemia cases in the Western hemisphere, with a male/female ratio ranging from 1.3–1.8.[273,274] In the United States, the age-adjusted CML incidence is 1.6/100,000, with a male/female ratio of ~1.75.[275] Some epidemiological data suggest ethnic differences (e.g., lower in Asians than Caucasians) and differences in incidence between European countries; however, the differences are relatively modest.[276] Although CML prevalence has increased as a result of the effectiveness of tyrosine kinase inhibitor therapy, CML incidence has been relatively stable over time. Estimates suggest the CML prevalence will increase from 70,000 in 2010 to a plateau of 181,000 in 2050 due to dramatic improvements in treatment.[277]

CARCINOGENESIS

CML is a clonal myeloproliferative disorder that results from a reciprocal translocation between the long arms of chromosomes 9 and 22 (Philadelphia chromosome).[278] In 1960, Nowell and Hungerford described the first malignancy (CML) associated with a recurrent cytogenetic abnormality, the Philadelphia chromosome (t(9;22)(q34;q11));[279] the latter was identified in 1973 by Janet Rowley.[280,281] This translocation occurs between the Abelson murine proto-oncogene (*ABL1*, chromosome 9) and the breakpoint cluster region (*BCR* gene, chromosome 22). Both genes are active tyrosine kinases. The oncogenic BCR-ABL1 fusion gene encodes a chimeric oncoprotein that markedly enhances tyrosine kinase activity producing unregulated cell proliferation, reduced stromal adhesion, and resistance to apoptosis via downstream pathways (JUN kinase, MYC, RAC, RAS, STAT).[282] This oncogene is a biomarker of CML and a drug target. The most frequently downregulated miRNAs include miRNA 10a, 17/92, 150, 203, and 328.[283] Progression to CML blast crisis involves downregulation of miRNA 328.

EXPOSURE

The only established causative agent for CML is high-dose ionizing radiation (e.g., Japanese atomic bomb survivors,[284] ankylosing spondylitis/pulmonary tuberculosis radiotherapy).[285] In the US National Institutes of Health-AARP Diet and Health study of 493,188 participants, 178 incident CML cases appeared during a median of 10.5 years of follow-up.[286] Using Cox proportional hazards models and data from self-reported baseline questionnaires, vigorous physical activity 3 times/weekly was inversely associated with CML (HR = 0.70, 95% CI: 0.49–0.99) compared with <1 time/week. Exclusion of the 41 CML cases

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identified in the first 2 years of follow-up resulted in a statistically nonsignificant hazard ratio (HR = 0.75, 95% CI: 0.50–1.12, $P_{trend} = 0.15$). Little data associate CML with dietary factors; this study reported no association between CML and a variety of dietary factors (e.g., red/white meat, processed meat, fish, fruit, vegetables, grains, total fat/fiber, alcohol consumption, coffee/tea intake) consistent with previous studies.[112,287]

Occupation

A Swedish exploratory study of 255 CML-Ph+ cases and age/sex/county-matched controls reported limited evidence of an association between CML and moderate/high organic solvent exposure (OR = 3.4, 95% CI: 1.1–11, $n = 12$ cases) based on a Finnish job-exposure matrix using data primarily from next of kin (proxy = 81%).[288] The study reported no association between CML and gasoline, diesel, or agricultural exposures. Poor exposure data and the absence of exposure-response data limit extrapolation of the results. In a study of data on North American workers in the styrene–butadiene rubber industry, Cox proportional hazard models examined exposure-response curves based on cumulative 1,3-butadiene exposure data as predictors of CML risks.[78] The slope of the model was not statistically greater than zero for CML, indicating no relationship. The IARC lists benzene, formaldehyde, ^{32}P as phosphorus, ^{232}Th and decay products, and X- and γ-ray radiation as carcinogenic agents with sufficient evidence in humans.

Benzene

Most observational studies of CML and benzene exposures do not report a strong association. Although several studies in the UK petroleum industry and French gas/electric utility workers report statistically nonsignificant increases in CML risks, other studies show no association including two with quantitative benzene exposure estimates and no dose-response relationships.[104] In a nested case-control study of Canadian, Australian, and UK petroleum refinery workers exposed to low benzene concentrations using the lowest benzene exposure tertile (≤0.348 ppm-years, 4 cases/44 controls) as referents, the CML odds ratio for cumulative exposure in the 2nd tertile (>0.34–2.93 ppm-years) was 5.04 (95% CI: 1.45–17.50, $n = 16$ cases/38 controls) and 2.20 (95% CI: 0.63–7.68, $n = 8$ cases/40 controls) in the highest tertile (>2.93 ppm, $P_{trend} = 0.02$).[54] Conditional logistic regression models did not demonstrate a monotonic dose-response relationship between cumulative benzene exposure and CML incidence ($P_{spline} = 0.12$). Using never-exposed workers as referents, a nested case-control study of French gas/electric utility workers reported an increased overall leukemia risk in workers with ≥16.8 ppm-years benzene exposure (OR = 4.6, 95% CI: 1.2–17.4, $n = 6$ cases, $P_{trend} = 0.05$); however, no dose-response relationship was detected in CML incidence with only one case and imprecise exposure estimates ($OR_{\geq 5.5\,ppm\text{-}years} = 1.2$, 95% CI: 0.1–11.4, $n = 1$ case/4 controls, $P_{trend} = 0.85$).[289] Confounding could not be excluded as a cause of the positive CML odds ratio.

A meta-analysis of six studies on CML reported no evidence of an association between benzene exposure and CML.[179] The summary-effect estimate for CML was 1.05 (95% CI: 0.83–1.34) with no studies on cumulative exposure and no evidence of publication bias ($P = 0.57$). In a meta-analysis using stratification of the data, the overall CML meta-relative risk using data from 17 cohort studies was positive, but statistically nonsignificant (mRR = 1.23, 95% CI: 0.93–1.63, $n = 76$ exposed cases); however, stratification provided some evidence of a significant association.[290] Although loss of statistical power limited conclusions about the true association, restricting the start of follow-up to 1970 or later resulted in the m-RR becoming statistically significant (mRR = 1.67, 95% CI: 1.02–2.74, $n = 32$ exposed/8 studies). Stratifying for exposure assessment quality increased the mRR, but the mRR remained statistically nonsignificant with a wider confidence limit. Another meta-analysis of 6 case-control studies with a total of 410 CML cases (range, 6–255) reported a combined OR of 1.003 (95% CI: 0.941–1.07, $P = 0.918$), indicating no significant difference in CML risks between exposed and nonexposed groups using fixed and random models.[291] Over 95% of the cases were CML-Ph+.

Magnetic Fields

A Swedish exploratory study of 255 CML-Ph+ cases and age/sex/county-matched controls reported limited evidence of an association between extremely low frequency magnetic fields and CML based on a Finnish job-exposure matrix using data primarily from next of kin (proxy = 81%).[288] The odds ratio was marginally significant statistically for low exposure to extremely low frequency electromagnetic fields (OR = 2.0, 95% CI: 1.0–4.1, $n = 25$ cases), but not for more intense exposures. The poor exposure data, imprecise estimates, and lack of exposure-response data limit definitive conclusions

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regarding causation. A population-based, case-control study reported null results for CML in adults aged 20–69 years regularly using electric blankets when compared with nonusers (OR = 0.8, 95% CI: 0.4–1.6, $n = 38$ cases/42 controls) based on self-reported electric blanket use during interviews.[172] The participation rates were low with 61% of eligible cases responding; 26% of the participating cases were not asked about electric blanket use.

Lifestyle

Tobacco Smoking

The association between CML and smoking is relatively weak, with most,[287,292] but not all,[293] case-control studies reporting negative results. A Canadian population-based case-control study using never-smokers as referents reported no association between CML and current smokers (adjusted OR = 0.7, 95% CI: 0.4–1.1, $n = 28$ cases among smokers) or >20 pack-years of smoking (adjusted OR = 0.9, 95% CI: 0.4–1.6, $n = 35$ cases among smokers, $P_{trend} = 0.72$).[287] A US population-based study of 185 CML cases and 692 adult controls used unconditional logistic regression and cubic spline modeling to examine CML risks in smokers based on self-administered questionnaires.[294] Compared with controls, the age/BMI adjusted OR for current heavy smokers (≥1 pack/daily) was positive, but statistically nonsignificant (aOR = 1.58, 95% CI: 0.84–2.98, $n = 16$ cases among smokers). Similarly, the adjusted OR for CML in smokers with >30 pack-year histories of smoking was positive, but statistically nonsignificant (aOR = 1.59, 95% CI: 0.97–2.60, $n = 61$ cases among smokers).

Obesity

Obesity is a postulated risk factor for CML with a modest effect. The US National Institutes of Health-AARP Diet and Health Study suggests a positive association between CML and obesity;[286] however, the results were inconclusive and statistically nonsignificant. The multivariable-adjusted HR for CML in participants with BMI ≥ 30 kg/m^2 was 1.46 (95% CI: 0.95–2.23, $n = 46$ cases, $P_{trend} = 0.08$) when compared with referents (<25 kg/m^2). Exclusion of the 41 CML cases identified in the first 2 years of follow-up resulted in a statistically significant hazard ratio (HR = 2.06, 95% CI: 1.25–3.39, $P_{trend} = 0.005$). In a meta-analysis of five US and European prospective studies comparing obese (BMI ≥ 30 kg/m^2) participants with normal weight controls (BMI = 18.5–24.9 kg/m^2), the overall maximumly adjusted RR for CML in obese men and women was statistically significant, but small in size (aRR = 1.16, 95% CI: 1.04–1.30; $I^2 = 0\%$, $P = 0.007$).[128] Separate analysis of men and women yielded similar results that were marginally significant statistically. Some studies used measured markers of obesity, whereas others used self-reported height and weights. A meta-analysis of four cohort studies comparing obese and nonobese (BMI <25 kg/m^2) participants reported a summary CML relative risk of 1.26 (95% CI: 1.09–1.46, $I^2 = 0\%$, $P_{heterogeneity} = 0.51$).[260] A Norwegian study measured the height and weight of 2 million men and women aged 20–74 years during 1963–2001 with normal weight (18.5–24.9 kg/m^2) as referents. For obese men (≥30 kg/m^2), the RR for CML was 1.65 (95% CI: 1.18–2.31, $n = 40$ obese cases, $P_{trend} = 0.009$), whereas the RR for obese women (30–34.9 kg/m^2) was 1.06 (95% CI: 0.76–1.48, $n = 47$ obese cases, $P_{trend} = 0.02$). A Texas study conducted at the M.D. Anderson Cancer Center on 253 CML cases (86% participation rate) and 270 age/gender/ethnicity-matched controls (40% friends, 36% spouses, 24% other family members) used self-reported weight and height to examine obesity and CML risks with a BMI of <25 kg/m^2 as referents.[295] At the time of diagnosis, moderate/severe obesity (≥35 kg/m^2) was associated with an odds ratio of 3.09 (95% CI: 1.56–6.13, $n = 35$ obese cases, $P_{trend} = <0.001$). An overweight BMI is not usually associated with increased CML risks in these studies.

Diseases

An exploratory study examined the association between 16 self-reported medical conditions, 701 population-based controls, and 186 CML cases using logistic regression.[296] Cases reported more tobacco smoking, obesity, and benzene exposures. CML was associated with peptic ulcers (OR = 2.0, 95% CI: 1.1–3.8, $n = 16$ cases), but not with other diseases including autoimmune conditions, diabetes mellitus, mononucleosis, or chronic fatigue syndrome. A personal history of cancer increased CML risks (adjusted OR = 3.6, 95% CI: 1.9–7.0, $n = 32$ cases). Controlling for therapy, personal history of cancer remained an independent risk factor.

HISTOLOGY

CML is a clonal myeloproliferative disorder involving unregulated bone marrow myeloid hyperplasia and increased peripheral blood myeloid cells with variable progression to pancytopenia and bone marrow failure;

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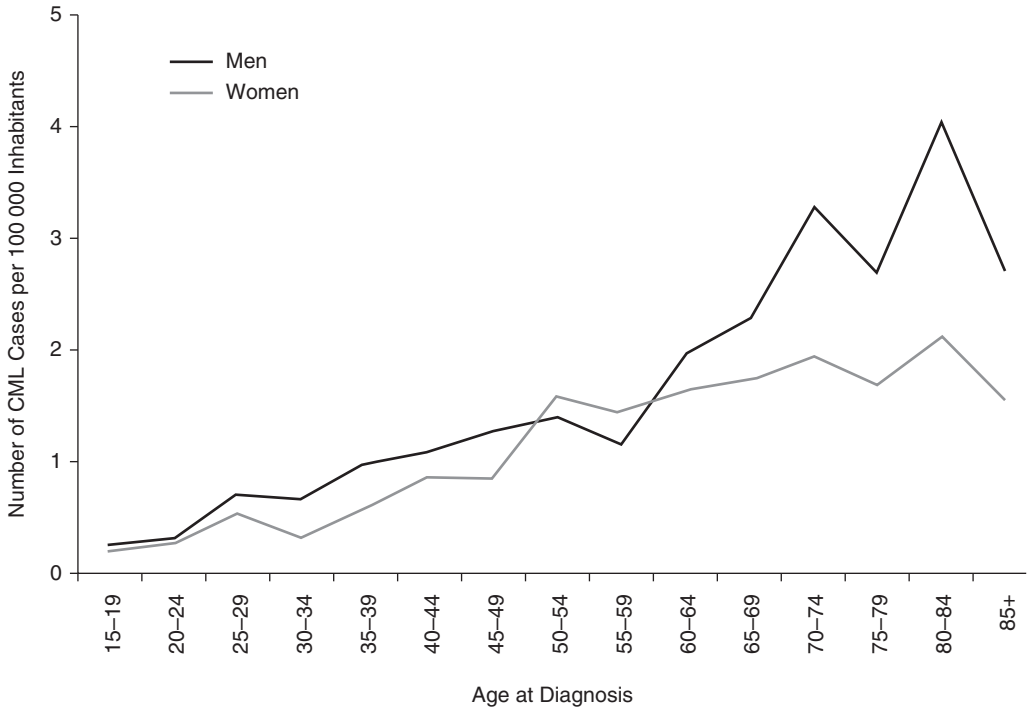


FIGURE 59.4. Annual chronic myeloid leukemia (CML) incidence by age and gender at diagnosis during 2002–2012 adjusted to the World Standard Population based on Swedish Cancer Registry (SCR) data. CML incidence is usually higher in men than women after 50–60 years of age. (Redrawn from Höglund et al.).[275]

the origin is probably a primitive progenitor cell or a stem cell. The bone marrow is typically hypercellular with grossly elevated myeloid/erythroid ratios along with elevated immature granulocytes (neutrophils, basophils, eosinophils) in peripheral blood. Nucleated erythrocytes may appear.

HOST SUSCEPTIBILITY

Few epidemiological data demonstrate familial aggregation of CML.[297] In a population-based study of 4,287 cases from the Swedish CML Registry diagnosed by the Philadelphia chromosome and 20,930 age/sex/residence-matched controls, no cases had first-degree relatives with CML, whereas 4 CML cases appeared in first-degree relatives of controls.[298]

CLINICAL FEATURES

Most patients with AML present with the Philadelphia chromosome and an indolent chronic phase (<10% blasts, no extramedullary involvement). The classic natural history of CML is a chronic phase (CML-CP, median: 4–5 years) followed by an accelerated phase (CML-AP) manifested by increasing peripheral immature leukocytes that progresses to a blast phase (AML, ALL) or blast crisis.[299] In 5 CML patients receiving a median radiotherapy dose of 2,080 (range: 1,750–2,450), the median latency period between radiation exposure and CML diagnosis was 15 years with a range of 2–34 years.[300] The CML incidence increases with age up to at least 75 years and a median age at diagnosis of 57–60 years, as displayed in Figure 59.4.

The most frequent clinical features at diagnosis include nonspecific symptoms (fatigue, night sweats, malaise, weight loss) and symptoms related to splenomegaly (abdominal fullness/pain, early satiety); one-half are asymptomatic at presentation with only leukocytosis and splenomegaly.[278] Headaches, dyspnea, visual disturbances, or priapism may occur associated with leukostasis, whereas bone pain, lymphadenopathy, and extramedullary masses suggest advanced-phase disease.[273] About 85% of CML patients in the chronic phase present with leukocytosis and splenomegaly.

The introduction of tyrosine kinase inhibitors (bosutinib, dasatinib, imatinib, nilotinib, ponatinib) dramatically improved CML prognosis from a fatal leukemia to a chronic disorder responsive to oral medications.[301] The 5-year relative survival rate for newly

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diagnosed chronic myeloid leukemia increased from 22% in the mid-1970s to 69% in 2014 with most patients treated with tyrosine kinase inhibitors experiencing nearly normal life expectancy (92–95%).[5,302] The treatment and prognosis are distictly different for CML-AP than CML-CP. Most patients presenting in the chronic phase have a good prognosis, whereas patients in the more advanced phases still have a poor prognosis due to resistance. About 2–4% of patients in the chronic phase and a significant portion of advanced phase patients are refractory to tyrosine kinase inhibitor treatment initially or acquire resistance later as a result of mutations to the *BCR-ABL* kinase domain genes.[303,304]

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Chapter 60

LYMPHOMAS

Lymphomas are a heterogenous group of clinically and biologically distinct tumors originating in lymph tissues; historically, Hodgkin and non-Hodgkin lymphomas were the two major classic types. Leukemias evolve from lymphoid and myeloid cells depending on tumor subtype, whereas lymphomas develop from malignant transformation of B, T, or natural killer (NK) cells that originate from the lymphoid lineage. Lymphomas are usually clonal expansions of B cells (i.e., 85%), less often T cells (i.e., 15%), and rarely natural killer cells. Chronic lymphocytic leukemia/small lymphocytic lymphoma derives from mature B cells; therefore, this neoplasm is considered part of the lymphoma group. Non-Hodgkin lymphomas (NHL) represent a very large subset of lymphoid neoplasms, as noted in Table 60.1.

The incidence of malignant lymphoma subtypes varies with demographics and geography. Marginal zone B cell lymphomas occur more commonly in Asia than in Western countries, whereas Hodgkin lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphomas are much rarer in Asia than in Western countries. The decreasing incidence of NOS (not otherwise specified) subtypes supports enhanced diagnostic specificity; however, the changing classification of lymphomas complicates the interpretation of incidence trends among lymphoma subtypes. Worldwide, lymphomas account for ~3–4% of all cancers.[1] Lymphomas are the third most frequent childhood malignancy (i.e., ~12–15%) behind acute leukemia and central nervous system tumors.[2] For adolescents and young adults (15–24 years), Hodgkin lymphoma represents 16% of all cancers, whereas NHL accounts for 6%, primarily mature B cell NHL.[3] The latter includes primarily high-grade lymphomas (Burkitt lymphoma, diffuse large B cell lymphoma, ALK+ anaplastic large cell lymphoma, lymphoblastic lymphoma).[4] Most lymphoma subtypes have a strong male predominance and a sharply increasing incidence with age.[5]

LYMPHOGENESIS

Acquired immunity to foreign agents/antigens requires the formation and interaction of thymus-derived lymphocytes (T cells) and bone-marrow-derived lymphocytes (B cells). Although lymphocytes circulate in lymph and blood, these cells concentrate in lymphoid organs including the thymus, bone marrow, lymph nodes, spleen, and upper respiratory/intestinal structures (e.g., adenoids, tonsils, Peyer's patches, appendix). Cellular immunity (e.g., graft-rejection, viral protection) depends on T cells, whereas humoral immunity depends on B cells and their antibody secretion. T cells help B cells produce antibodies; however, T cells do not produce antibodies themselves. Additionally, T cells interact with a variety of tissue processes, including disruption of tissue flora, metabolism, repair mechanisms, and pregnancy.

Figure 60.1 displays the development of high-affinity B cells (memory and plasma cells) in the germinal centers of the spleen and lymph nodes. Maturation of B cells in the bone marrow is independent of antigen stimulation; the B cell receptor becomes a monomeric IgM molecule before leaving the bone marrow. Immune activation of these cells occurs outside the marrow following antigen stimulation with or without helper

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TABLE 60.1. 2022 World Health Organization (WHO) classification of lymphoid neoplasms, 5th edition. This edition represents a revision of the 2016 classification rather than a significant alteration of the categories. Tumors are organized based on increasing levels of specification by category, entity/type, and subtype. The order of classification follows cell lineage beginning with precursor cell neoplasms and progressing to mature malignancies. Provisional entities are not included in this edition compared with the 4th edition. See reference[12]. For details on specific diagnostic criteria, see Alaggio R, et al.[13]

Tumor-like lesions with B-cell predominance
Reactive B-cell-rich lymphoid proliferations that can mimic lymphoma
IgG4-related disease
Unicentric Castleman disease
Idiopathic multicentric Castleman disease
KSHV/HHV8-associated multicentric Castleman disease
Precursor B-Cell neoplasms
B-cell lymphoblastic leukemias/lymphomas
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with high hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with iAMP21
B-lymphoblastic leukemia/lymphoma with *BCR::ABL1* fusion
B-lymphoblastic leukemia/lymphoma with BCR::ABL1-like features
B-lymphoblastic leukemia/lymphoma with KMT2A rearrangement
B-lymphoblastic leukemia/lymphoma with *ETV6::RUNX1* fusion
B-lymphoblastic leukemia/lymphoma with ETV6::RUNX1-like features
B-lymphoblastic leukemia/lymphoma with *TCF3::PBX1* fusion
B-lymphoblastic leukemia/lymphoma with IGH::IL3 fusion
B-lymphoblastic leukemia/lymphoma with TCF3::HLF fusion
B-lymphoblastic leukemia/lymphoma with other defined genetic abnormalities
Mature B-cell neoplasms
Pre-neoplastic and neoplastic small lymphocytic proliferations
Monoclonal B-cell lymphocytosis
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Splenic B-cell lymphomas and leukemias
Hairy cell leukemia
Splenic marginal zone lymphoma
Splenic diffuse red pulp small B-cell lymphoma
Splenic B-cell lymphoma/leukemia with prominent nucleoli
Lymphoplasmacytic lymphoma
Lymphoplasmacytic lymphoma
Marginal zone lymphoma
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
Primary cutaneous marginal zone lymphoma
Nodal marginal zone lymphoma
Pediatric marginal zone lymphoma

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TABLE 60.1. (Continued)

Follicular lymphoma
In situ follicular B-cell neoplasm
Follicular lymphoma
Pediatric-type follicular lymphoma
Duodenal-type follicular lymphoma
Cutaneous follicle center lymphoma
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasm
Mantle cell lymphoma
Leukemic non-nodal mantle cell lymphoma
Transformations of indolent B-cell lymphomas
Transformations of indolent B-cell lymphomas
Large B-cell lymphomas
Diffuse large B-cell lymphoma, NOS
T-cell/histiocyte-rich large B-cell lymphoma
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
ALK-positive large B-cell lymphoma
Large B-cell lymphoma with *IRF4* rearrangement
Lymphomatoid granulomatosis
EBV-positive diffuse large B-cell lymphoma
Diffuse large B-cell lymphoma associated with chronic inflammation
Fibrin-associated large B-cell lymphoma
Fluid overload-associated large B-cell lymphoma
Plasmablastic lymphoma
Primary large B-cell lymphoma of immune-privileged sites
Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma
Primary mediastinal large B-cell lymphoma
Mediastinal grey zone lymphoma
High-grade B-cell lymphoma, NOS
Burkitt lymphoma
Burkitt lymphoma
KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas
Primary effusion lymphoma
KSHV/HHV8-positive diffuse large B-cell lymphoma
KSHV/HHV8-positive germinotropic lymphoproliferative disorder
Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation
Hyperplasias arising in immune deficiency/dysregulation
Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation
EBV-positive mucocutaneous ulcer
Lymphomas arising in immune deficiency / dysregulation
Inborn error of immunity-associated lymphoid proliferations and lymphomas

(Continued)

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TABLE 60.1. (Continued)

Hodgkin lymphoma
Classic Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Plasma cell neoplasms and other diseases with paraproteins
Monoclonal gammopathies
Cold agglutinin disease
IgM monoclonal gammopathy of undetermined significance
Non-IgM monoclonal gammopathy of undetermined significance
Monoclonal gammopathy of renal significance
Diseases with monoclonal immunoglobulin deposition
Immunoglobulin-related (AL) amyloidosis
Monoclonal immunoglobulin deposition disease
Heavy chain diseases
Mu heavy chain disease
Gamma heavy chain disease
Alpha heavy chain disease
Plasma cell neoplasms
Plasmacytoma
Plasma cell myeloma
Plasma cell neoplasms with associated paraneoplastic syndrome
POEMS syndrome
TEMPI syndrome
AESOP syndrome
Tumor-like lesions with T-cell predominance
Kikuchi-Fujimoto disease
Indolent T-lymphoblastic proliferation
Autoimmune lymphoproliferative syndrome
Precursor T-cell neoplasms
T-lymphoblastic leukemia/lymphoma
T-lymphoblastic leukemia/lymphoma, NOS
Early T-precursor lymphoblastic leukemia/lymphoma
Mature T-cell and NK-cell neoplasms
T-prolymphocytic leukemia
T-large granular lymphocytic leukemia
NK-large granular lymphocytic leukemia
Adult T-cell leukemia/lymphoma
Sezary syndrome
Aggressive NK-cell leukemia
Primary cutaneous T-cell lymphomas
Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder
Primary cutaneous acral CD8-positive lymphoproliferative disorder
Mycosis fungoides

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TABLE 60.1. (Continued)

Primary cutaneous CD30-positive T-cell lymphoproliferative disorder:Lymphomatoid papulosis
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Primary cutaneous anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous gamma/delta T-cell lymphoma
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous peripheral T-cell lymphoma, NOS
Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas
Indolent T-cell lymphoma of the gastrointestinal tract
Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma
Intestinal T-cell lymphoma, NOS
Hepatosplenic T-cell lymphoma
Hepatosplenic T-cell lymphoma
Anaplastic large cell lymphoma
ALK-positive anaplastic large cell lymphoma
ALK-negative anaplastic large cell lymphoma
Breast implant-associated anaplastic large cell lymphoma
Nodal T-follicular helper (TFH) cell lymphoma
Nodal TFH cell lymphoma, angioimmunoblastic-type
Nodal TFH cell lymphoma, follicular-type
Nodal TFH cell lymphoma, NOS
Other peripheral T-cell lymphomas
Peripheral T-cell lymphoma, NOS
EBV-positive NK/T-cell lymphomas
EBV-positive nodal T- and NK-cell lymphoma
Extranodal NK/T-cell lymphoma
EBV-positive T- and NK-cell lymphoid proliferations and lymphomas of childhood
Severe mosquito bite allergy
Hydroa vacciniforme lymphoproliferative disorder
Systemic chronic active EBV disease
Systemic EBV-positive T-cell lymphoma of childhood
Mesenchymal dendritic cell neoplasms
Follicular dendritic cell sarcoma
EBV-positive inflammatory follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Myofibroblastic tumor
Intranodal palisaded myofibroblastoma
Splenic vascular-stromal tumors
Littoral cell angioma
Splenic hamartoma
Sclerosing angiomatoid nodular transformation of spleen

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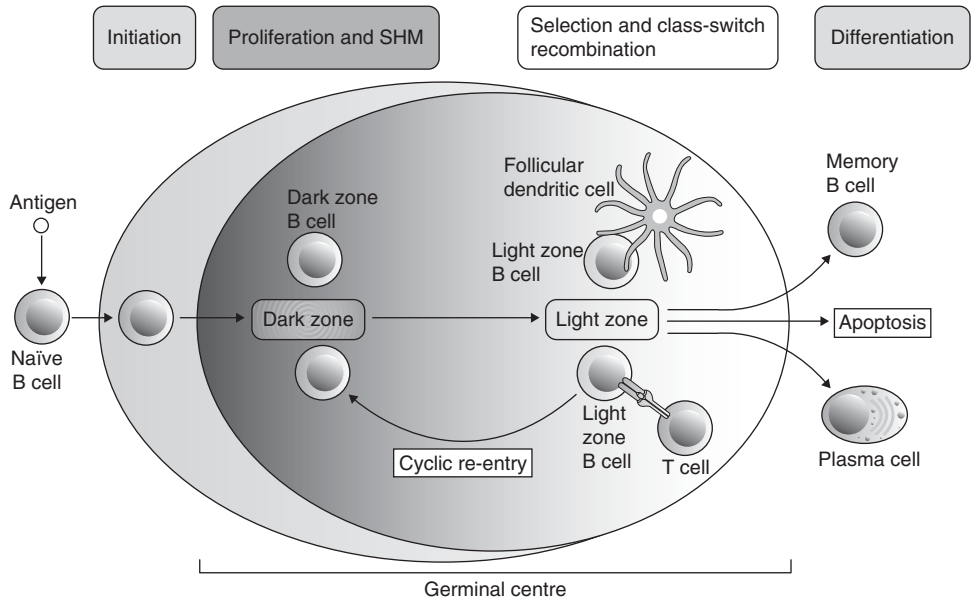


FIGURE 60.1. B cell development and germinal centers. Following V(D)J recombination in the bone marrow, naïve B cells with functional B cell receptors migrate to secondary lymphoid organs, where these cells interact with $CD4^+$ cells in T cell-rich areas; these cells aggregate into primary follicles to form germinal centers. Immunoglobulin gene remodeling processes (somatic hypermutation, SHM; class-switch recombination) generate various classes of high-affinity antibodies within the B cells that subsequently differentiate into plasma and memory B cells. The dark zone contains highly proliferating B cells, whereas B cell activation occurs in the light zone after interaction with follicular dendritic cells. Low-antigen B cells that fail to develop into high-antigen immune cells ultimately undergo apoptosis in the light zone. (Adapted from Basso and Dalla-Favera).[7]

T cells. Lymphocytes are the carriers of humoral immunity that arises from a common pluripotent stem cell in the bone marrow, where cleavage and rejoining of the variable (V), diversity (D), and joining (J) segments of the immunoglobulin heavy-chain gene (IgH locus) followed by rearrangement of the immunoglobulin light-chain gene segments (IgL) kappa and lambda occurs. The V(D)J recombination process assembles immunoglobulin heavy-chain and light-chain antibody foci in precursor B cells. Immunological B cells are divided into B1 and B2 cells. B2 cells are involved with classical antibody responses that generate specific antibodies against foreign antigens in secondary lymphoid organs. After an encounter with a foreign antigen, these mature, low-antigen affinity (naïve) B cells migrate to germinal centers in the spleen, mucosa-associated lymphoid tissue, and lymph nodes, where the B2 cell undergoes further maturation in a highly specialized microenvironment formed with help from antigen-presenting and CD4+ T cells.[6] Within the germinal centers, centroblasts rapidly proliferate and modify the variable region of Ig genes (*IgV*) in maturing B2 cells via a process called somatic hypermutation. These centroblasts express elevated levels of the transcriptional repressor, BCL6, that negatively regulates a variety of cellular processes including adaptive immune responses (CD40+ and B cell receptor (BCR) signaling, T cell-mediated B cell activation, cytokine/chemokine signaling), cellular processes (apoptosis, DNA damage sensing/repair), and plasma cell differentiation.[7] The centroblasts differentiate into centrocytes in the light zone of the germinal centers, where they select high-antigen affinity B2 cells for survival and terminally differentiate into memory B cells or plasma cells.[8] The former participates in secondary immune responses, whereas the latter secretes antibodies. B1 cells perform innate immune functions by expressing evolutionarily selected BCRs (BCR, RhoGEF, and GTPase activating protein) with limited somatic mutations; these immune cells occur primarily in the pleural and peritoneal cavities as an initial response to common bacterial pathogens. B2 cells have B1 cell differentiation potential in addition to their classical capacity to differentiate into memory and plasma cells.[9] Most B cell non-Hodgkin lymphomas with the exception of mantle cell lymphoma arise from germinal-center-experienced B cells during aberrant somatic hypermutation processes that alter *IgV* sequences via chromosomal translocation.[10] The tumor phenotype depends on the affected stage of differentiation. Arrested development in the early

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lymphocyte progenitor stage results in ALL or lymphoblastic lymphoma, whereas intermediate-stage involvement produces mature lymphomas and terminal stages involving plasma cells and myelomas.

T cell development begins with the migration of committed lymphoid progenitor cells from the bone marrow to the thymus gland as T cell progenitor or double-negative 1-thymocytes without T cell receptors (TCR) or CD4/CD8 expression. These cells undergo rearrangement at the *TCRβ* locus to acquire pre-TCR expression along with further differentiation into double-positive cells (CD4+/CD8+) with a complete surface T cell receptor. After a selection process in the thymus to eliminate autoreactive clones, these cells exit into a pool of mature T cells. Most mature T cell non-Hodgkin lymphomas probably arise from post-thymic T cells in the lymphoid organs; however, some evidence suggests immature hematopoietic cells may also be involved in some of these tumors.[11] Natural killer (NK) cells are cytotoxic lymphocytes that lack T cell receptors and primarily eliminate malignant and infected cells.

CLASSIFICATION

Table 60.1 lists the major WHO 5th edition lymphoid neoplasms along with subgroups and new classifications based on updated genetic and molecular data.[2] The latest revision provides substantial data on the diagnosis and prognosis of the multiple subgroups of lymphoid neoplasms.[1]

CARCINOGENESIS

During differentiation, normal naïve lymphocytes undergo immense clonal expansion and mutations requiring DNA double-strand breaks and point mutations mediated by alterations of gene expression. The subsequent genetic instability predisposes lymphocytes to chromosomal translocations and oncogenic mutations conducive to malignant transformation when these processes become dysregulated. B cell development begins with proliferation of progenitor cells in the bone marrow, resulting in immunoglobulin production; surviving mature B cells migrate to germinal centers in secondary lymphoid tissues (lymph nodes, spleen), where interactions with antigen result in immunoglobulin gene modification and increased affinity for the antigen. These processes (somatic hypermutation, class switch recombination) produce small deletions, point mutations, insertions, and the potential to form chromosomal translocations and oncogenic mutations. Figure 60.2 displays the origins of B cell lymphomas in germinal centers from extra-marrow lymph tissues. Naïve B cells migrate to dark zones of secondary lymph tissues where these cells differentiate into centroblasts; point mutations in the variable region of Ig heavy- and light-chain sequences develop during somatic hypermutation in the dark zone generating variant B cell receptors. Centroblasts differentiate into centrocytes and migrate to the light zone. After moving to the light zone, variant B cells with advantageous mutations interact with follicular dendritic cells to receive T cell survival signals required to avoid apoptosis. These variant cells undergo multiple cycling back to the dark zone while proliferating, mutating, and forming translocations via class switch recombination until exiting the germinal center as memory B cells or plasma cells. This process changes the B cell isotype from IgM to IgA, IgE, or IgG. B cell lymphoma subtypes correspond to a normal cellular phenotype in the differentiation process, whereas determination of T cell NHL subtypes is often difficult.

EXPOSURE

In contrast to leukemias, the association of ionizing radiation with increased lymphoid cancer risks is relatively modest. The Life Span study did not report excess radiation-associated risks for T cell leukemia, Hodgkin lymphoma, or multiple myeloma. Epidemiology studies of diagnostic ionizing radiation exposure during early childhood do not report consistently elevated lymphoma risks; however, some of these studies have limited power to detect small increases in cancer risks.[15]

Occupation

The etiology of most lymphomas remains unknown. Recognized risk factors involve immune dysregulation and infectious processes; however, these risk factors account for a small portion of lymphoma cases. Epidemiology studies on occupational groups and lymphoma risks based on job-exposure matrices and self-reported occupations are exploratory with multiple comparisons lacking exposure data and confirmatory exposure-response data. These studies are subject to misclassification and recall bias, particularly for rare conditions (i.e., lymphomas). A meta-analysis of studies on TCE-exposed workers suggested a positive association with NHL (summary RR = 1.32, 95% CI: 1.14–1.54, n = 19 studies, I^2 = 25.20%, $P_{\text{heterogeneity}}$ = 0.12). The summary estimates did not indicate an association between occupational TCE exposure and Hodgkin

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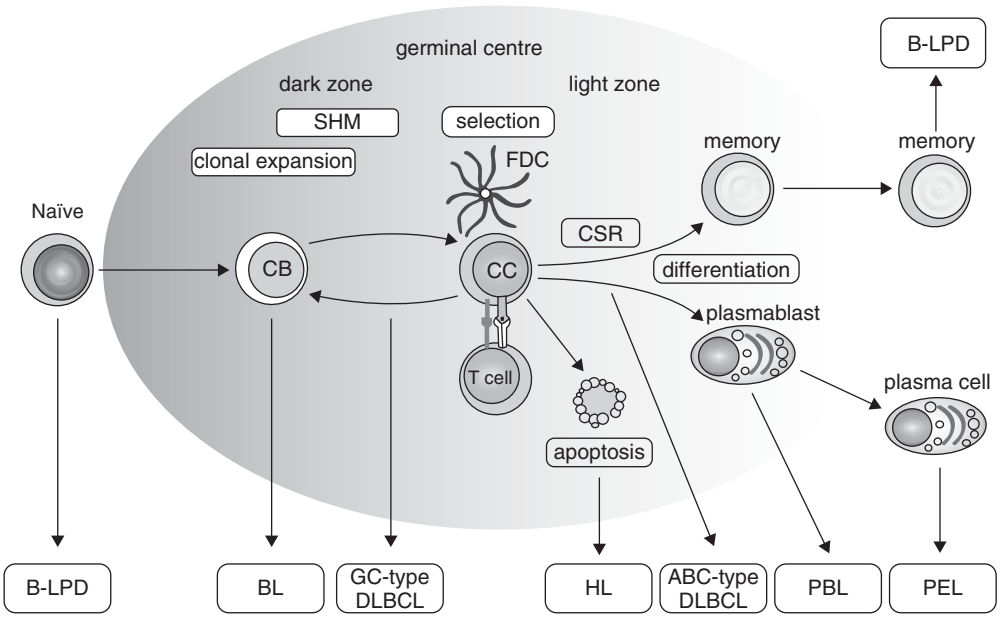


FIGURE 60.2. B cell lymphoma origins. Morphologically different B cell tumors develop from the processing of naïve B cells in the germinal centers depending on where in the differentiation process the initial clone develops, as noted in the text. (Adapted from Shannon-Lowe et al.).[14] *Abbreviations:* ABC-type DLBCL = activated B cell-like diffuse large B cell lymphoma; BL = Burkitt lymphoma; B-LPD = B-lymphoproliferative disease; CB = centroblast; CC = centrocyte; CSR = class switch recombination; FDC = follicular dendritic cells; HL = Hodgkin lymphoma; PBL = plasmablastic lymphoma; PEL = primary effusion lymphoma; SHM = somatic hypermutation.

lymphoma, multiple myeloma, or chronic lymphoblastic leukemia.[16] The summary RR for case-control studies was positive, but statistically nonsignificant (summary RR = 1.09, 95% CI: 0.94–1.25, $n = 12$ studies, $I^2 = 11.63\%$, $P_{\text{heterogeneity}} = 0.39$) with evidence of publication bias in five studies ($P_{\text{Egger}} = 0.003$).

Job Descriptions

Case-control studies suggest a variety of occupational exposures may increase risks for Hodgkin lymphomas (carpenters, chemical/solvent production workers, farmers, painters, paper industry workers, teachers, welders, woodworkers) and non-Hodgkin lymphomas (chemical workers, cobblers, cowmen, dairy workers, farmers, female physicians, furniture makers, leather manufacturing, workers machine fitters, metal workers, painters, porcelain industry workers, shoe printers, makers, woodworkers). These associations are relatively modest and inconsistent. A German case-control study of 710 adult lymphomas and sex/age/region-matched, population-based controls used unconditional logistic regression analysis to calculate odds ratios adjusted for smoking and alcohol consumption.[17] The adjusted OR for all lymphomas in this exploratory study was statistically significant for >1-year employment in food products, beverages, tobacco workers (OR = 1.7, 95% CI: 1.1–2.5, $n = 71$ cases/45 controls) and marginally significant in pulp paper, paper products, publishing, and print workers (OR = 1.7, 95% CI: 1.0–2.8, $n_{\text{NHL}} = 43$ cases/26 controls). The multicenter, prospective cohort study, European Prospective Investigation into Cancer and Nutrition (EPIC), identified 866 NHL and 48 HL cases during a mean of 9 ± 2 years of follow-up.[18] Compared with all other workers using Cox proportional hazards models and self-reported job status among a list of 52 occupations, the elevated adjusted hazard ratio for NHL, excluding multiple myeloma, was statistically significant in car repair workers (aHR = 1.51, 95% CI: 1.01–2.31, $n_{\text{NHL}} = 23$ cases) and marginally significant in butchers (aHR = 1.30, 95% CI: 1.00–2.66, $n_{\text{NHL}} = 11$ cases), but statistically nonsignificant in gasoline station workers. For HL, the adjusted OR was statistically significant for gasoline station workers (aHR = 4.59, 95% CI: 1.08–19.6, $n_{\text{HL}} = 2$ cases), but not for car repair workers or butchers. The cohort study did not confirm elevated lymphoma risks in other occupations noted in case-control studies. Analysis of data from 15 million Nordic residents enrolled in the nationwide registration of 2.8 million incident cancer cases reported the highest SIR for NHL among 54 occupational categories in male physicians (SIR = 1.22,

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95% CI: = 1.08–1.39, n_{NHL} = 234 cases) with no confirmation of increased NHL risks in hairdressers, food or tobacco workers, shoe and leather workers, or farmers.[19] For Hodgkin lymphoma, bricklayers had the highest risk (SIR = 1.33, 95% CI: 1.04–1.68) with marginally increased risks in female farmers (SIR = 1.21, 95% CI: 1.00–1.45, n_{HL} = 114 cases), but not male farmers (SIR = 1.03, 95% CI: 0.96–1.11, n_{HL} = 733 cases).

Dioxin

The association between lymphomas (i.e., HL, NHL, MM) and dioxin exposure remains controversial.[20] Dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, TCDD) is an IARC human carcinogen (Group 1) based on limited evidence for all cancers in humans, sufficient evidence in animals, and a plausible genotoxic mechanism (altered gene expression, cell proliferation, and apoptosis from binding to the aryl hydrocarbon receptor).[21] TCDD is a weak initiator and a strong promoter. Seven polychlorinated dibenzo-*p*-dioxins can activate the aryl hydrocarbon receptor, with TCDD being the standard to compare with the six other dioxins. Exposure to dioxins occurs in military (Agent Orange defoliant), industrial trichlorophenol/pentachlorophenol production facilities, and environmental contamination (Seveso, waste-burning plants, widespread background dietary exposure). TCDD is a synthetic by-product of chlorophenol or chlorophenoxy herbicide manufacturing rather than a commercially produced chemical. Dioxins accumulate in food chains similar to other chlorinated compounds, with these chemicals being recognized as contaminants in the environment and diets.

Industrial cohort studies suggest a statistically positive association with NHL mortality; however, positive results are not consistent across nonindustrial cohorts or display a clear exposure-response relationship.[22] The US Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides study reviewed the scientific and medical evidence for Agent Orange and other herbicides used by the military in the Vietnam War. The Committee concluded the evidence was sufficient for a (statistically) positive relationship between herbicides and NHL with reasonable confidence that chance, bias, and confounding could be ruled out; however, the Committee noted the data did not establish the relationship as causal or specific to Agent Orange.[23]

The relative risks of NHL, Hodgkin lymphoma (HL), and multiple myeloma (MM) in most studies range from 0.3–3.0 based on <5 cases, with the exception of the IARC/NIOSH international cohort that reported more consistently positive risks with higher exposures.[24] In this historical cohort study of 21,863 male and female workers in 36 cohorts exposed to phenoxy and/or chlorophenol herbicides potentially contaminated with TCDD, the SMR for non-Hodgkin lymphoma was slightly elevated, but not statistically significant (SMR = 1.39, 95% CI: 0.89–2.06, n_{NHL} = 24 deaths);[25] however, NHL mortality did not increase with longer duration of exposure. Additionally, the NHL SMR was not substantially higher in production workers than sprayers, despite higher serum TCDD concentrations in the former group. Although many of the industrial and Seveso cohort studies demonstrate positive, statistically nonsignificant associations with NHL,[26,27] these studies did not exclude the lack of an association and other studies demonstrated no association resulting in inconsistent results.

A retrospective cohort study of 2,192 trichlorophenol and pentachlorophenol production workers reported no statistically significant increased mortality from NHL (SMR = 1.92, 95% CI: 0.83–3.79, n_{NHL} = 8 deaths) or Hodgkin lymphoma (SMR = 1.17, 95% CI: 0.14–4.22, n_{HL} = 2 deaths).[28] The dioxin concentrations were well above background with the highest estimated historical TCDD concentration of 8.848 ppb. Most studies of HL mortality were statistically null,[29,30] whereas limited studies of estimated Agent Orange/TCDD exposure and MM were positive in Seveso studies,[27] but not in Vietnam veterans[31] or industrial cohorts.[25] The industrial and Seveso cohorts do not demonstrate consistent trends between increased TCDD exposure and NHL mortality or HL incidence/mortality; however, MM incidence and mortality were increased in some cohorts with dioxin exposures.[27,32]

Lifestyle

Existing epidemiological evidence indicates lifestyle factors do not strongly influence lymphoma risks; however, limited data and the heterogeneity of lymphoma origins and etiologies complicate the determination of lifestyle factors for lymphoma subtypes.

Tobacco Smoking

Case-control and cohort studies suggest tobacco smoking modestly increases Hodgkin lymphoma risks, particularly nodular sclerosis and mixed cellularity subtypes.[33] The risks for lymphoma subtypes are mixed with weak evidence for a dose response reflecting small study sizes and inconsistent results/exposure classifications. The adjusted pooled estimated OR for HL using

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data from 12 case-control studies in the InterLymph Consortium and random effects models was 1.10 (95% CI: 1.01–1.21) comparing ever- with never-smokers, whereas the association with mixed cellularity HL subtype was higher (adjusted OR = 1.60, 95% CI: 1.29–1.99).[34] In the prospective National Institutes of Health-former American Association of Retired Persons (NIH-AARP) Diet and Health Study using never-smokers as controls, Hodgkin lymphoma risks were elevated in current smokers (adjusted RR = 2.25, 95% CI: 1.04–4.88, n_{HL} = 11 cases) and recent former smokers quitting ≤4 years earlier (aRR = 4.20, 95% CI: 1.94–9.09).[35] Current cigarette smokers using >2 ppd did not have a statistically significant elevated RR for overall HL risk (RR = 1.00, 95% CI: 0.28–3.41, n_{HL} = 3 cases, P_{trend} = 0.52) or NHL (RR = 0.83, 95% CI: 0.65–1.06, n_{NHL} = 76 cases, P_{trend} = 0.16). The study reported a marginally significant reduced trend of follicular lymphoma risks in current smokers (RR = 0.66, 95% CI: 0.42–1.02, n_{FL} = 24 cases, P_{trend} = 0.005). Comparing current cigarette smokers with never-smokers in the UK Million Women Study, overall risks were significantly increased for Hodgkin lymphoma (RR = 1.57, 95% CI: 1.29–1.90, n_{HL} = 152 cases, P_{trend} < 0.001) and NHL (RR = 1.12, 95% CI: 1.05–1.18, n_{NHL} = 2,227 cases, P_{trend} = <0.001), but not for myeloma (RR = 0.92, 95% CI: 0.83–1.02, n_{MM} = 856 cases, P_{trend} = 0.1).[36] Additionally, the risks of mature T cell but not mature B cell lymphomas in current cigarette smokers were significantly increased.

The European Prospective Investigation into Cancer and Nutrition (EPIC) study reported similar results.[37] The overall HL risk comparing current with never-smokers was increased (HR = 2.14, 95% CI: 1.18–3.87), but not for NHL (HR = 1.06, 95% CI: 0.94–1.19), chronic lymphocytic lymphoma (HR = 0.77, 95% CI: 0.52–1.12, n_{CLL} = 40 cases), plasma cell neoplasms (HR = 0.88, 95% CI: 0.63–1.23), or mature B cell NHL lymphomas. In an Italian hospital-based case-control study, an analysis of NHL histological subtypes in heavy smokers revealed a statistically significant increased risk only for follicular NHL (OR = 2.43, 95% CI: 1.31–4.51).[38] Compared with never-smokers, the overall risks for current smokers were statistically nonsignificant for NHL (OR = 1.18, 95% CI: 0.91–1.54, n_{NHL} = 186 cases/326 controls) and HL (OR = 1.50, 95% CI: 0.93–2.44, n_{HL} = 80 cases/66 controls).

Alcohol

Epidemiological evidence from some cohort studies and pooled analyses of case-control studies suggests alcohol consumption decreases the risk of some lymphoma types, primarily non-Hodgkin lymphomas (NHL). Most studies on the association of multiple myeloma or chronic lymphocytic leukemia/small lymphocytic lymphoma with alcohol consumption report null results.[39] In general, the association between specific types of alcohol consumption and NHL subtypes is null to weakly inverse.[40] In a sex/smoking/age-matched, hospital-based Japanese study of 782 malignant lymphoma cases, frequent, heavy alcohol consumption (≥50 g daily) was inversely associated with all malignant lymphomas (OR = 0.40, 95% CI: 0.23–0.68, n = 20 cases/162 controls, P_{trend} = <0.001).[41]

The prospective National Institutes of Health-former American Association of Retired Persons Diet and Health Study identified 58 Hodgkin lymphoma and 1,381 non-Hodgkin lymphoma cases via linkage to cancer registries during a mean follow-up of 4.3 years.[35] Using baseline questionnaires on self-reported alcohol consumption with nondrinkers as controls, alcohol consumption decreased NHL risks including the most common NHL subtypes, but not Hodgkin lymphomas. For consuming 2–4 alcohol drinks daily, the overall NHL relative risk was 0.76 (95% CI: 0.59–0.97, n_{NHL} = 35 cases, $P_{trend\ among\ drinkers}$ = 0.008), whereas the HL risk was null ($P_{trend\ among\ drinkers}$ = 0.97). The inverse alcohol-lymphoma association persisted for common B cell subtypes (e.g., diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma). The UK Million Women Study identified 7,047 lymphoid cancers in 1.3 million middle-aged, mostly moderate drinking women followed for a mean of 10.3 years with similar results.[42] Using self-reported alcohol consumption on baseline questionnaires and occasional drinkers (0.5–<3 drinks weekly) as referents, ≥7 drinks weekly was associated with a reduction in NHL risks (RR = 0.84, 95% CI: 0.77–0.92, n_{NHL} = 3,084 cases, P_{trend} = <0.001) and multiple myeloma (RR = 0.85, 95% CI: 0.74–0.98, n_{MM} = 1,262, P_{trend} = 0.02), but not HL (RR = 1.06, 95% CI: 0.76–1.49, n_{HL} = 173, P_{trend} = 0.6). The reduced risks of mature B cell NHL subtypes (diffuse large B cell lymphoma, follicular lymphoma, plasma cell neoplasms) were similar to overall NHL risks.

A meta-analysis of cohort studies reported that alcohol consumption reduced the risks of hematological malignancies, primarily NHL.[43] Moderate alcohol consumption (12.5–50 g daily) reduced NHL risks (pooled RR = 0.85, 95% CI: 0.80–0.90, n = 13 studies, I^2 = 1.6%, $P_{heterogeneity}$ = 0.430) consistent with heavy alcohol consumption (pooled RR = 0.88, 95% CI: 0.81–0.96, n = 5 studies, I^2 = 8%, $P_{heterogeneity}$ = 0.361). Similar pooled estimates supported reduced risks of diffuse

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large B cell lymphoma and follicular lymphoma. Alcohol consumption did not affect pooled estimates of Hodgkin lymphoma risks.

Obesity

Epidemiological studies on the association of obesity with malignant lymphomas (NHL, HL, CLL, multiple myeloma) are mixed with the association stronger for early adulthood obesity than baseline BMI, particularly for diffuse large B cell lymphoma.[44] Pooled data from 18 case-control studies in the International Lymphoma Epidemiology Consortium did not support an increased lymphoma risk in obese participants.[45] Using logistic regression and random effects models, severe obesity ($BMI \geq 40\,kg/m^2$) was not associated with overall NHL risks (pooled OR = 1.00, 95% CI: 0.70–1.41) or most NHL subtypes with the exception of diffuse large B cell lymphoma (pooled OR = 1.80, 95% CI: 1.24–2.62). The large Multiethnic Cohort (African Americans, Caucasians, Japanese, Latinos, Native Hawaiians) of 87,079 men and 105,972 women identified 461 male and 378 female NHL cases.[46] Using Cox regression to model NHL risk and adjusting for age at baseline, alcohol intake, education, ethnicity, and age at first live birth, BMI at age 21 was a stronger predictor of NHL risk than anthropometric characteristics at baseline. The increased overall NHL risk was statistically significant, but not dose-related for obese men at age 21 (HR = 1.86, 95% CI: 1.02–3.40, n_{NHL} = 11 cases/338 controls, P_{trend} = 0.27); in obese women, the overall NHL hazard ratio was not statistically significant (HR = 1.07, 95% CI: 0.47–2.41, n_{NHL} = 6 cases/267 controls, P_{trend} = 0.03). Height was associated with overall NHL risks in men (P_{trend} = 0.02), but not in women (P_{trend} = 0.14), suggesting height is a potential confounder of BMI-associated NHL risks in men. The evidence for an association with NHL subtypes was modest.

Several meta-analyses support a relatively small, but statistically significant increased association between lymphoma risk and obesity. In a meta-analysis of 16 prospective studies on NHL and 5 studies on HL incidence, the overall summary relative risk for NHL/5 kg/m^2 BMI increments was 1.07 (95% CI: 1.04–1.10, I^2 = 9.6%, $P_{heterogeneity}$ = 0.33).[47] BMI was positively associated with diffuse large B cell lymphoma (summary RR/5 kg/m^2 = 1.13, 95% CI: 1.02–1.26, n = 8 studies, I^2 = 37%, $P_{heterogeneity}$ = 0.13), but not for follicular lymphoma or CLL. Obesity ($\geq 30\,kg/m^2$) was also associated with increased HL risks (summary RR = 1.41, 95% CI: 1.14–1.75, n = 4 studies, I^2 = 21.6%, $P_{heterogeneity}$ = 0.30). Most weights/heights were self-reported. In a meta-analysis of 44 cohort studies, the summary relative risks were modestly positive and statistically significant in men and women for NHL, HL, and MM.[48] The DLBCL risks were also statistically significant in women, but not in men, as displayed in Table 60.2. Waist circumferences and waist-to-hip ratios in women were not associated with any hematological malignancies.

A meta-analysis of 62 prospective cohort studies, 1 case–cohort study, and 2 pooled analyses was consistent with modestly elevated risks of hematological lymphomas in studies of adult obesity using mostly self-reported BMI.[49] The summary RR/5 kg/m^2 increments in BMI were statistically significant for NHL (RR = 1.05, 95% CI: 1.03–1.08, n = 20 studies, I^2 = 45%, $P_{heterogeneity}$ = 0.02), HL (RR = 1.12, 95% CI: 1.05–1.20, n = 5 studies, I^2 = 1.6%, $P_{heterogeneity}$ = 0.40), DLBCL (RR = 1.11, 95% CI: 1.05–1.16, n = 19 studies, I^2 = 16%, $P_{heterogeneity}$ = 0.29), MM (RR = 1.06, 95% CI: 1.03–1.10, n = 23 studies, I^2 = 13%, $P_{heterogeneity}$ = 0.31), and

TABLE 60.2. Summary of relative risks for hematological malignancies in obese participants based on 44 studies using mostly self-reported baseline body mass index (BMI). Substantial heterogeneity exists in the estimated summary risks for NHL, MM, and CLL/SLL. (Adapted from Psaltopoulou et al).[48]

Hematological Malignancy	Studies Men/Women	Men Summary Relative Risk (95% CI)	Heterogeneity Men (I^2 %)	Women Summary Relative Risk (95% CI)	Heterogeneity Women (I^2 %)
NHL	15/20	1.17 (1.06–1.28)[a]	52.4	1.14 (1.05–1.24)[a]	58.7
DLBCL	3/8	1.07 (0.64–1.78)	41.3	1.33 (1.18–1.50)[a]	0.0
FL	3/8	1.35 (0.83–2.20)	0.0	1.17 (0.97–1.42)	33.5
CLL/SLL	6/12	1.13 (0.91–1.40)	66.0	0.98 (0.82–1.17)	50.7
HL	7/5	1.36 (1.09–1.69)[a]	33.7	1.61 (1.34–1.93)[a]	0.0
MM	12/11	1.17 (1.01–1.34)[a]	45.6	1.27 (1.15–1.40)[a]	24.7

Abbreviations: 95% CI = 95% confidence limit, I^2 = I^2 statistic; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL = diffuse large B cell lymphoma; FL = follicular lymphoma; HL = classic Hodgkin lymphoma; MM = multiple myeloma; NHL = non-Hodgkin lymphoma.

[a] Statistically significant summary relative risks ($P < 0.05$).

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marginal for CLL (RR = 1.04, 95% CI: 1.00–1.09, $n = 7$ studies, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.65$). The data provided little support for an association between obesity and follicular lymphoma or between waist circumference/waist-to-hip ratio and hematological malignancies.

Diet

The results of studies on the effect of diet on lymphoma risks are conflicting, with mostly positive and statistically nonsignificant associations; most results were from case-control studies subject to selection and recall biases, particularly among NHL subtypes. The European Prospective Investigation into Cancer and Nutrition (EPIC) study examined the effects of consuming foods of animal origin by dietary questionnaires assessing dietary choices in the preceding 12 months using Cox proportional hazard regression.[50] Overall, the consumption of foods of animal origin (red/processed meats, poultry, milk/dairy products) was not associated with increased lymphoma risks; however, some increased risks were reported in NHL subgroups (↑B cell chronic lymphocytic leukemia and meat, ↓follicular lymphoma and meat, ↑B cell lymphomas and poultry). In contrast to other cohort studies,[51] high poultry consumption was associated with increased risks of B cell CLL, follicular lymphoma, and B cell lymphomas, whereas milk and dairy products were not associated with elevated risks of B cell, T cell, or Hodgkin lymphomas.

A meta-analysis of 23 case-control and 10 cohort studies using random effects models reported a statistically significant, positive association between red meat consumption and NHL (summary RR = 1.22, 95% CI: 1.03–1.44, $n = 14$ studies, $I^2 = 35\%$), whereas the consumption of fish and seafood was inversely associated with multiple myeloma (summary RR = 0.71, 95% CI: 0.51–1.00, $n = 11$ studies, $I^2 = 82\%$) with very substantial heterogeneity between studies and marginal statistical significance.[52] Dairy consumption was associated with NHL (summary RR = 1.26, 95% CI: 0.99–1.60, $n = 6$ studies, $I^2 = 49\%$), also with moderate heterogeneity and marginal statistical significance. The risks of NHL, CLL, and multiple myeloma from processed and white meat consumption were similar to the null. A Sardinian study of 322 incident lymphoma cases and 446 randomly selected population controls compared the highest and lowest quintiles of food consumption based on food frequency questionnaires covering 112 food items using unconditional and polytomous logistic regression analysis and adjusting for age, education, and gender.[53] The association was positive, but statistically nonsignificant between overall lymphoma risks and well-done red meat (OR = 1.3, 95% CI: 0.8–2.0, 74 cases/81 controls) and processed meat (OR = 1.1, 95% CI: 0.7–1.8, 84 cases/89 controls), whereas the results for consumption of fresh seafood (OR = 0.8, 95% CI: 0.4–1.3, 49 cases/84 controls) and overall Mediterranean diet score (OR = 0.9, 95% CI: 0.6–1.5, 57 cases/99 controls) were not different than the null. Subgroup analysis of lymphoma subtypes suggests a positive association with B cell lymphoma for well-done/roasted chicken ($P_{\text{trend}} = 0.01$) and pizza ($P_{\text{trend}} = 0.047$); the analysis included >130 comparisons with few statistically significant results consistent with chance.

Physical Activity

Epidemiological evidence does not support a significant effect of physical activity on lymphoma risks. In a meta-analysis of seven case-control and five cohort studies, the pooled OR was 0.90 (95% CI: 0.79–1.02, $P_{\text{effect}} = 0.10$, $I^2 = 59\%$).[54] Although case-control studies suggest an inverse effect with physical activity (pooled OR = 0.81, 95% CI: 0.68–0.96, $P_{\text{effect}} = 0.02$, $I^2 = 49\%$), cohort studies confirmed the lack of an association with lymphoma and physical activity (pooled OR = 1.02, 95% CI: 0.88–1.19, $I^2 = 52\%$, $P_{\text{effect}} = 0.76$). The study did not detect statistically significant differences between results for HL and NHL or between recreation and occupational physical activities. The meta-analysis reported moderate heterogeneity between case-control and cohort studies.

Medication

Immunosuppressive drugs (e.g., azathioprine, cyclosporine) used to treat cancers, autoimmune diseases, and organ transplants confound risk assessments of hematological neoplasms including lymphomas. In a cohort of 12,656 incident rheumatoid arthritis cases from the Swedish Cancer Register, treatment with methotrexate or tumor necrosis factor inhibitors was not associated with increased leukemia risks (HR = 0.9, 95% CI: 0.4–1.9).[55]

Diseases

Diseases associated with increased lymphoma risks include infections, immune-deficient states/organ transplantation, and autoimmune conditions.

Infections

Using electron microscopy in 1964, Anthony Epstein and Yvonne Barr discovered the first known human

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oncovirus when they identified the Epstein–Barr virus (EBV) in Burkitt lymphoma cells from a Ugandan patient.[56] Almost all endemic (African) Burkitt lymphomas contain latent EBV with clear evidence that EBV infection precedes B cell clonal expansion.[57] Viruses associated with lymphoproliferative cancers include Kaposi sarcoma herpesvirus-8 (primary effusion lymphoma), HIV-1 (non-Hodgkin/Hodgkin lymphoma), Epstein–Barr virus (non-Hodgkin/Hodgkin lymphoma, Burkitt lymphoma), hepatitis C virus (non-Hodgkin lymphoma), and human T cell lymphotropic virus type 1 (adult CD4+ CD25+ T cell leukemia/lymphoma).[58] Human T-lymphotropic virus 1 (HTLV-1) is an RNA retrovirus that develops most commonly in adults of African, Caribbean, Japanese, and South American descent 20–60 years after infection.[59] The herpesvirus-8 (HHV-8) is a DNA virus infecting primarily immunocompromised patients, with Kaposi sarcoma being the most frequent cutaneous manifestation. Latent HHV-8 proteins activate various cytokine-mediated proliferation and oncogenic pathways, while lytic replication disseminates the reactivated virus in immunocompromised patients.[60]

EBV is a B cell lymphotropic, human gamma-1 DNA herpesvirus that infects >90% of the population, primarily during childhood and usually resulting in a latent asymptomatic infection. Under certain circumstances, EBV eventually produces latent membrane protein 1 (LMP1); this oncoprotein activates CD40 receptors using host cell replication machinery and transforms B lymphocytes into proliferating lymphoblastoid cells.[61] A wide range of B, T, and NK cell malignant lymphomas and lymphoproliferative lesions are causally linked to EBV, primarily involving the B cell malignancies, including Burkitt lymphoma, Hodgkin lymphoma, diffuse large B cell lymphoma, and other rare B cell tumors (e.g., primary effusion lymphoma, plasmablastic lymphoma).[14] EBV does not typically infect T or NK cell lineages; on rare occasions, T and/or NK cell infections cause chronic active EBV infection or highly aggressive monoclonal malignancies (e.g., aggressive NK leukemia, extranodal NK/T cell lymphoma). T cell-mediated immune surveillance probably controls EBV infections during primary inoculation and throughout life.[62]

Autoimmune Diseases

Dysregulation of the adaptive immune system (e.g., loss of T cell regulatory mechanisms) and chronic inflammation from autoimmune conditions (e.g., systemic lupus erythematosus, rheumatoid arthritis, psoriasis, Sjögren syndrome, Hashimoto thyroiditis) are associated with elevated lymphoma risks, including Hodgkin lymphomas and non-Hodgkin lymphomas, particularly diffuse large B cell lymphoma, based on observational studies. The risk estimates in these studies vary substantially with relatively wide confidence intervals.[63] Germline and somatic mutations of normal regulatory signaling pathways probably contribute to dysregulation of lymphoid cell proliferation in these patients. In a population-based case-control study of ~25,000 non-CLL NHL cases and 55,000 controls using linkages to central Swedish and Danish Cancer Registries, the overall NHL odds ratio for patients with systemic autoimmune diseases was 2.6 (95% CI: 1.7–4.1).[64] The NHL odds ratios for specific autoimmune diseases ranged from 1.6–5.4.

A family history of systemic autoimmune disease in first-degree relatives was not associated with statistically significant NHL risks (OR = 1.3, 95% CI: 0.85–2.0). The overall Hodgkin and non-Hodgkin lymphoma risks in systemic autoimmune disease patients are similar, whereas associations with CLL and multiple myeloma in these patients are weaker and mostly statistically nonsignificant.

Using Cox regression to analyze lymphoma risks in a cohort of 12,656 incident rheumatoid arthritis cases from the Swedish Cancer Register, the overall hazard ratio for lymphomas was 1.6 (95% CI: 1.2–2.1, n = 62 cases); each case had 10 population-matched controls.[55] The risk of Hodgkin lymphoma was elevated (HR = 4.1, 95% CI: 1.9–9.1, n_{HL} = 9 cases). Inflammatory activity did not correlate to future lymphoma risks. In a Taiwanese study of 23,644 rheumatoid arthritis patients, the highest reported risk among hematological malignancies was for NHL (SIR = 3.54, 95% CI: 3.45–3.63, n_{NHL} = 59 cases); however, this subgroup included many other lymphomas, including multiple myeloma, lymphosarcoma, and reticulosarcoma.[65] The reported SIR for Hodgkin lymphoma was also positive (SIR = 1.76, 95% CI: 1.45–1.56, n_{HL} = 1 case); however, the results were statistically nonsignificant and limited by inadequate sample size. In a pooled analysis of a multisite international systemic lupus erythematosus (SLE) cohort containing 16,409 patients, the standardized incidence ratio was elevated for non-Hodgkin lymphoma (SIR = 4.39, 95% CI: 3.46–5.49, n_{NHL} = 76 cases).[66] The SIR was positive, but statistically nonsignificant for Hodgkin lymphoma (SIR = 2.28, 95% CI: 0.92–4.70, n_{HL} = 7 cases) and multiple myeloma (SIR = 1.88, 95% CI: 0.90–3.46, n_{MM} = 10 cases).

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HISTOLOGY

Lymphomas are malignancies of hematological cells that may occur throughout the body where lymph tissue exists. The two main histological types of lymphomas are Hodgkin (HL) and non-Hodgkin (NHL) lymphomas distinguished by the presence of Reed–Sternberg cells in Hodgkin tumors; NHL is 10-fold more common than Hodgkin lymphoma.[67] All Hodgkin and most non-Hodgkin tumors arise from B cells; NHL has >35 subtypes with some NHL subtypes originating from T cells or natural killer cells. Lymphoma subtypes vary in aggressiveness, geographic/demographic distribution, and nongenetic risk factors (e.g., diseases, pharmaceuticals, radiation, immune suppression).

HOST SUSCEPTIBILITY

Most lymphomas are sporadic, with no known familial history; however, a small fraction have germline genetic abnormalities that predispose to lymphomas and other cancers including rare family clusters of ≥2 lymphomas.[68] These inherited syndromes include ataxia-telangiectasia, Bloom syndrome, Li–Fraumeni syndrome, Lynch syndrome (constitutional mismatch repair deficiency syndrome), Nijmegen breakage syndrome, and Wiskott–Aldrich syndrome. Few genes associated with familial lymphoid cancer have been identified. Biological mechanisms involving increased lymphoma susceptibility include genomic instability, disruption of lymphoproliferative homeostasis, immune deficiencies (genetic, immunosuppressive drugs), and chronic antigen stimulation from autoimmune-related diseases, including celiac disease, rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus.[67] Dysregulation of the cell cycle (e.g., mutations in *ATM* gene in ataxia-telangiectasia) or interruption of DNA repair processes (mutations in *TP53*/*CHEK2* genes in Li–Fraumeni syndrome) produce a general predisposition to several cancers. Enhanced production of lymphoid cells from an imbalance between proliferation and apoptosis (e.g., mutations in *FAS* gene in autoimmune lymphoproliferative syndrome) increases lymphoid malignancy risk. Inappropriate lymphoid proliferation also occurs in immunodeficient patients with persistent oncogenic viral infections (e.g., EBV, Kaposi sarcoma-HHV-8), resulting in insufficient cancer surveillance and the formation of premalignant and/or malignant cells (e.g., PASL1 disease, AIDS-related cancers).

Although the relative risks are not well defined, a family history of hematopoietic malignancy increases NHL and HL risks, with lymphoma subtypes sharing some inherited genetic susceptibility while displaying substantial heterogeneity. Generally, a family history of a specific lymphoma subtype is most strongly associated with the risk of a specific lymphoma reflecting the unique genetic landscape for each lymphoma; for HL, the risk of HL is stronger for a personal history of HL in siblings than parents.[69] Approximate increased lymphoma risks among relatives of family members with lymphomas range from 20–50% for HL, 20–60% for CLL, 15% for multiple myeloma, and 9–16% for diffuse large B cell lymphoma (NHL subtype). Lymphoma susceptibility varies significantly between NHL subtypes with particularly high risks for first-degree relatives of family members with diffuse large B cell lymphoma, follicular lymphoma, and Hodgkin lymphoma.[70,71] In a population-based study of 1,506 lymphoma cases (85% participation rate) and 1,229 controls (75% participation rate) linked to the Swedish Multi-Generation and Cancer registries, the occurrence of a first-degree relative with a hematopoietic malignancy increased NHL, HL, and some B cell NHL subtype risks.[72] Using multiple logistic regression to estimate odds ratios, a first-degree relative (parent, sibling) with a hematopoietic malignancy increased NHL risk (OR = 1.8, 95% CI: 1.2–2.5); the NHL risk was stronger for a history of hematopoietic cancer in a sibling (OR = 3.2; 95% CI: 1.3–7.6) than a parent (OR = 1.6, 95% CI: 1.1–2.3). A family history of NHL increased NHL risks (OR = 2.2, 95% CI: 1.4–3.5, n_{NHL} = 62 cases/26 controls), whereas a family history of HL did not significantly increase HL risks (OR = 3.3; 95% CI: 0.5–21.5, n_{HL} = 2 cases) based on a few cases. For NHL subtypes, a history of paternal hematopoietic cancer was statistically significant only for diffuse large B cell lymphoma (OR = 2.2; 95% CI: 1.1–4.2, n_{DLBCL} = 321 cases), whereas a maternal hematopoietic cancer history was associated only with chronic lymphocytic leukemia (OR = 2.4, 95% CI: 1.2–5.0, n_{CLL} = 272 cases). Estimated risks for T cell lymphoma were unstable because of the few cases and inadequate statistical power. The study did not detect any difference in environmental risk factors between familial and nonfamilial NHL.

CLINICAL FEATURES

No presenting clinical features distinguish lymphomas from other diseases except for tumor expansion; the clinical presentations of Hodgkin and non-Hodgkin lymphomas are also similar. Lymphadenopathy in a well-appearing child frequently is a self-limited, transient process that resolves without medical interventions. Physical signs associated with lymphadenopathy

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and increased lymphoma risk include duration >6 weeks; size >2.5 cm with matted, painless, nonmobile appearance; and >1 noncontiguous lymph node area.[2] Complications from tumor growth include superior vena cava syndrome (chest discomfort, tachypnea, orthopnea), abdominal masses (abdominal discomfort, musculoskeletal pain), and CNS involvement (headache, seizures, focal paresthesias/weakness). Nonspecific symptoms from inflammatory cytokine release from advanced tumors may involve fatigue, anorexia, fever (bone marrow infiltration), night sweats, and weight loss.

Patients with lymphomas secondary to inherited cancer predisposition syndromes typically present earlier (i.e., 6–9 years) compared with sporadic cases;[70] Hodgkin lymphoma has a bimodal age distribution peaking in childhood and later adulthood. In an analysis of the Surveillance, Epidemiology, and End Results (SEER) database, the median age at diagnosis for CLL was 71 years compared with 66 years for NHL, 39 years for HL, and 69 years for multiple myeloma.[73] An analysis of data from the Swedish Family-Cancer database indicates the overall mean age at diagnosis was 57 ± 6.9 years for chronic lymphocytic leukemia, 57 ± 7.8 years for multiple myeloma, and 51 ± 13.8 years for NHL.[74] For NHL subtypes, the mean age at diagnosis for diffuse large B cell lymphoma was 51 ± 13.0 years compared with 49 ± 15.0 years for T cell lymphoma and 51 ± 13.0 years for follicular lymphoma, similar to overall NHL rates.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

The World Health Organization classifies chronic lymphoid leukemias (CLL) with small lymphocytic lymphoma (SLL) based on a common immunophenotype and a similar clinical course. These tumors are mature B cell neoplasms derived from clonal expansion and accumulation of these malignant cells in bone marrow, spleen, lymph nodes, and peripheral blood. The difference between these two tumors is greater tumor involvement in bone marrow (CLL) than solid lymphoid tissue (SLL).[75] CLL is the most common adult leukemia in Western countries, accounting for ~30% of all leukemia cases; the US age-adjusted CLL incidence is ~4–6/100,000 population, with an estimated ~21,000 new cases, ~4,000 deaths annually, and fairly stable rates.[76] CLL incidence varies with race; a lower incidence occurs in African Americans than Caucasians, with a particularly low incidence in Asian countries (China, Japan, Korea). The difference remains for Asian Americans migrating to the United States.[77] CLL incidence in African American men is 4.6/100,000 compared with 6.2/100,00 for Caucasian men; however, age-adjusted 5-year CLL/SLL survival is higher in Caucasian men (76%) than African American men (63%).[78] The latter is frequently present at later clinical stages with significantly shorter subsequent event-free survival periods.

CARCINOGENESIS

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a highly proliferative disorder of multipotent, self-renewing hematopoietic stem-like cells with a high apoptotic rate. Slow expansion of a B cell clone of antigen-experienced cells occurs in lymphoid tissues, peripheral blood, and bone marrow with the accumulation of incompetent B cell (CD19+/CD23+) and T cell (CD5+) surface antigen-positive lymphocytes despite the high apoptotic rate.[79,80] Additionally, this leukemia is associated with low concentrations of surface immunoglobulins/B cell receptors (IgM, IgD), CD20, CD22, and CD79b; the B cell receptor (BCR) functions as a component of the B lymphocyte antigen-actuated signal transduction pathway.[81] The current diagnostic criteria for CLL require an absolute peripheral B cell count of ≥5,000 cells/μL. Small lymphocytic lymphoma require an absolute peripheral B cell count of ≥5,000 cells/μL, clonal B cell-induced lymphadenopathy with CLL phenotype, and the absence of cytopenias from marrow infiltrates.

Chromosomal Aberrations

CLL/SLL is a very complex, heterogeneous disease with strong familial risks but no CLL-specific genomic aberrations; individual CLL tumors contain wide intra-clonal heterogeneity with different CLL subpopulations and diverse genomic aberrations that evolve in response to the microenvironment and chemotherapeutic pressures.[82] The most common chromosomal abnormality is the 13q14.3 deletion (downregulation of miRNA-15a.16-1 expression) present in ~50–60% of CLL cases.[83,84] This deletion also occurs in other hematopoietic malignancies (diffuse large B cell lymphoma, mantle cell lymphoma, mature T cell lymphoma, multiple myeloma) and some solid tumors.[85] Other common CLL aberrations involve other chromosomal

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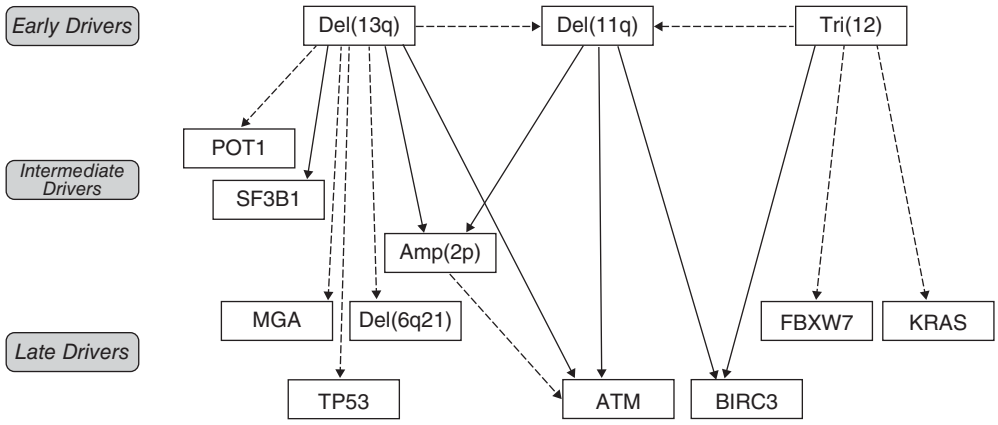


FIGURE 60.3. Chronic lymphocytic leukemia (CLL) deletions and drivers of tumor initiation and progression. Although cancers result from somatically acquired DNA changes in the tumor cells, all mutations do not contribute to cancer development. Malignant neoplasms contain driver and passenger mutations. Driver mutations are selected by the tumor microenvironment to confer a growth advantage and enhance oncogenesis. Passenger mutations are not selected by the microenvironment because they do not confer a growth advantage or contribute to cancer development. (Adapted from Hallek et al.).[87] *Abbreviations:* ATM = Ataxia-telangiectasia mutated serine/threonine kinase; BIRC3 = baculoviral IAP repeat containing 3 (apoptosis inhibitor); FBXW7 = F-box and WD repeat domain containing 7 (tumor suppressor); *KRAS* = *KRAS* proto-oncogene, GTPase; MGA = MAX dimerization protein MGA (3-methylglutaconic acid); POT1 = protection of telomeres 1; SF3B1 = splicing factor 3b subunit 1; *TP53* = tumor suppressor gene expressing p53 protein.

material loss/gain including deletions (11q, 17p, 6q) and gains (trisomy 12, chromosome 19), as well as mutations of tumor suppressors (*TP53*, *ATM*), immunoglobulin heavy-chain variable region (IGHV)-containing genes, and oncogenes (*MYCN, MYCN* proto-oncogene, basic helix-loop-helix transcription factor).[86] Comprehensive genomic analyses indicate the malignant CLL transformation begins with the loss or gain of chromosomal material (e.g., trisomy 12, deletion of chromosomes 13q), as displayed in Figure 60.3.[87] Later, frequent deletions in chromosome 13q (tumor suppressor inhibition) enhance proliferation by dysregulating cell-cycle control and apoptosis; chromosome 11p deletion (DNA damage response kinase, *ATM* gene) and 17 p deletion (*TP53* gene) help drive tumor progression, relapse, and treatment resistance.[88,89]

Mutations

CLL typically has a low mutation rate; these tumors contain large numbers of relatively infrequent mutations rather than a few common mutations. The most common somatic mutations beginning with the most frequent occur in the following genes: *NOTCH1*, *ATM*, *SF3B1*, *BIRC3*, *CHD2*, *TP53*, and *MYD88*; none of these mutations are specific to CLL.[90] These genetic aberrations affect genes in multiple critical cellular pathways including DNA damage/cell-cycle control (*ATM*, *BIRC3*, *TP53*), messenger RNA processing (*SF3B1*), and inflammatory pathways (*MYD88*), NOTCH signaling (*NOTCH1*), as well as BCR signaling, NF-κB signaling, and chromatin remodeling.[91] The latter pathway encodes a class 1 transmembrane protein that acts as ligand-activated transcription factor important for cell proliferation, differentiation, and apoptosis. The *SF3B1* gene encodes a component of the spliceosome that impairs protein binding. The *BIRC3* gene inhibits apoptosis and regulates NF-κB nuclear factor/proinflammatory signaling pathway for cytokines, chemokines, and adhesion molecules (e.g., interleukin 1, tumor necrosis factor α) necessary for inflammatory responses to infection and tissue injury. The mutations in the *TP53* (DNA repair) genes are low at diagnosis but increase with disease progression.

Monoclonal B Cell Lymphocytosis

Monoclonal B cell lymphocytosis (MBL) is defined by the presence of <5,000 B cells/μL in the absence of other lymphoid symptoms and features (i.e., B symptoms, cytopenia, hepatomegaly, lymphadenopathy, splenomegaly). This disorder shares the morphology and immunophenotype of CLL without the leukemic characteristics. This entity is subdivided into low-count (LC-MBL) and high-count (HC-MBL) monoclonal B cell lymphocytosis. The former has <500 CLL-like immunophenotype B cells/μL, whereas the latter has ≥500–<5,000 B cells/μL. LC-MBL is usually an

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incidental finding identified by highly sensitive flow cytometry techniques.[92] MBL often precedes CLL with a conversion rate to CLL of ~1–2%/year;[93,94] up to 5–12% of healthy individuals have monoclonal B cell lymphocytosis without obvious evidence of CLL, depending on the population studied, age, and cytometry sensitivity.[95]

EXPOSURE

Currently, no acquired risk factors are causally associated with increased CLL/SLL risks reflecting, in part, the difficulty establishing causation for risk factors in rare diseases.[91] A pooled analysis of 2,440 CLL/SLL cases and 15,186 age/sex/race/ethnicity/social/economic status-matched controls from 13 North American, European, and Australian case-control studies used multivariate logistic regression analysis to estimate odds ratios based on telephone or in-person interviews.[96] Positive results suggested potential associations with infection (hepatitis C virus seropositivity), family history, and self-reported height; the results also suggested inverse association with immune function (any atopic condition, recreational sun exposure) and smoking. CLL/SLL risk was not associated with body mass index, weight, specific autoimmune disease, or reproductive history/hormone replacement therapy. The Spanish population-based MCC-Spain study of 560 CLL/SLL cases (87% participation rate) and 1,845 controls (53% participation rate) reported statistically significant increased CLL/SLL risks for central obesity as measured by waist-to-hip ratios ($P_{\text{interaction}} = 0.03$) based on face-to-face interviews.[97] The interaction was statistically significant in women (OR = 1.67, 95% CI: 1.14–2.01, $n_{\text{CLL}} = 175$ cases), but not in men (OR = 1.22, 95% CI: 0.81–1.83, $n_{\text{CLL}} = 299$ cases) or with current BMI. Alcohol consumption was inversely associated with CLL/SLL risks comparing the third and first tertiles of alcohol consumption (OR = 0.65, 95% CI: 0.46–0.92, $P_{\text{trend}} = 0.02$).

Occupation

Although animal data and limited epidemiological data suggest the possibility of an association between leukemia and some chemicals (atrazine, dichlorvos, dioxins, formaldehyde, butadiene, ethylene oxide),[98] there is little definitive evidence linking CLL to specific chemical toxins.[99,100] Observational studies report excess CLL/SLL risks in some industries (agriculture, mining, petroleum, rubber–styrene, wood processing, hairdressers/hair dye) and high occupational exposures (butadiene, ethylene oxide, solvents, styrene);[101] however, study results are generally relatively modest and inconsistent, with some studies reporting no elevated CLL/SLL risks.[98,102] Analysis of human data on CLL is limited by inconsistent classification schemes of lymphohematopoietic malignancies, imprecise exposure data, multiple chemical exposures, long latency/morbidity periods, and small sample size.[103,104]

Benzene

Although occupational benzene exposure is associated with myeloid leukemia, the association with CLL and other non-Hodgkin lymphomas is not conclusive.[105] In a review of benzene exposure and leukemia subtypes, nested case-control studies demonstrated some increased CLL risks with suggestive dose-response relationships, but cohort studies and most population-based case-control studies demonstrated no elevated CLL risks.[106] There is no clear relationship between CLL and chemical exposures including work in the petrochemical industry; most mortality studies of petrochemical workers do not demonstrate a statistically significant increased risk of CLL-induced mortality.[107,108] Although a cohort study of male workers at a Louisiana refinery and chemical plant detected a statistically significant increase in CLL-related deaths (SMR ≈ 3.5, 95% CI: 1.68–6.45), there was no association between CLL and any job or work area.[109] A cross-sectional cohort study of 81,746 former and current male petrochemical workers found a non-statistically significant increase in CLL-related mortality (SMR = 1.60, 95% CI: 0.85–2.73), primarily among white, office-based workers.[110] There were 13 cases of CLL-related deaths with no increased risk by job type. Eleven of the decedents began work from 1934–1955; the latency period was >35 years. A meta-analysis of leukemia subtypes among ~208,000 US and UK petroleum worker cohorts reported a meta-SMR for CLL mortality of 0.84 (95% CI: 0.67–1.04, n = 98.89 deaths expected/83 deaths observed).[111] Thirteen of the 17 US cohorts reported lower than expected CLL mortality rates. CLL incidence was not increased in a cohort of 8,942 Louisiana petrochemical workers with 4 cases of CLL identified among 7,773 workers employed before 1950 compared with 3.27 cases expected.[112] A nested case-control study of petroleum distribution workers in the UK detected 31 incident CLL cases.[113] Analysis of these 31 cases and matched controls from the same company associated CLL with duration of employment; however, the highest risk occurred in white-collar workers with long service and low chemical exposure. There was no definite evidence of an association between benzene exposure and CLL. The mean cumulative benzene exposure for

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cases and controls was 2.6 ppm-years and 3.6 ppm-years, respectively. Examination of shoe workers exposed to very high benzene concentrations did not detect any CLL cases in a case series of 26 Turkish workers.[114,115]

Pesticides

Some case-control studies suggest a slightly elevated CLL risk for ever-working as a farmer (e.g., range, 1.4–1.7) based on mortality studies, death certificates, and interviews;[97] however, the results are inconsistent and generally lack an exposure-response relationship between any particular pesticide and CLL risks. In a population-based study of 578 Minnesotan and Iowan Caucasian farmers (40% deceased) and 1,245 controls (34% deceased), the CLL risk in ever-farmers was elevated (OR = 1.4, 95% CI: 1.1–1.9, n_{CLL} = 156 cases) using never-farmers as referents.[116] No common leukemia subtype was positively associated with farming duration; the odds ratio for CLL risk for >45 years of farming was 1.1 (95% CI: 0.7–1.8, n_{CLL} = 28 cases). The CLL risk was statistically marginal for using insecticides (OR = 1.3, 95% CI: 1.0–1.8, n_{CLL} = 122 cases) and herbicides (OR = 1.4, 95% CI: 1.0–2.0, n_{CLL} = 74 cases). No specific pesticide was associated with increased CLL risks. In a pooled analysis of 13 mostly Caucasian North American, European, and Australian studies, ever-living or ever-working on a farm was associated with modestly increased CLL/SLL risks (OR = 1.21, 95% CI: 1.07–1.36, n_{CLL} = 835 cases, $P > 0.002$) using nonfarm residents as referents. Individually, CLL/SLL risks for ever-working on a farm were marginally significant (OR = 1.16, 95% CI: 1.00–1.35, n_{CLL} = 290, $P = 0.051$); however, the CLL/SLL risk for ever-living on a farm was statistically nonsignificant (OR = 1.12, 95% CI: 0.97–1.30, n_{CLL} = 487 cases, $P = 0.130$) compared with never-living on a farm.

Ionizing Radiation

In contrast to other major leukemia subtypes, CLL is not typically associated with elevated risks following ionizing radiation exposure. CLL does not share the same risk factors as CML or AML, including no statistically significant increased CLL incidence or a definite dose-response relationship in cohorts exposed to high ionizing radiation doses. However, the potential for a positive, albeit lower, risk than other leukemia subtypes remains because of study limitations including long latency, low morbidity, and small sample size.[117,118] Analysis of cohorts (e.g., X-ray therapy for ankylosing spondylitis, Japanese atomic-bomb survivors) receiving high ionizing radiation doses has not detected statistically significant increased CLL risks.[119,120] Newly identified CLL cases in the Japanese Life Span Study suggest CLL risk might increase at higher ionizing radiation doses (P = <0.05) with longer follow-up based on linear age/gender-adjusted baseline model; however, the statistical significance was marginal.[121] In predominately European populations, CLL risks were marginally elevated following ionizing radiation exposure in Czech uranium miners and Chernobyl cleanup workers,[122] but not significantly elevated in Russian radioactive waste Techa River workers, Canadian uranium miners, or medical radiation treatment including radiation-treated primary cancers.[123]

Lifestyle

Lifestyle is not a strong CLL risk factor. In a pooled analysis of 13 mostly Caucasian North American, European, and Australian studies, total (OR = 0.75, 95% CI: 0.59–0.96, n_{CLL} = 173 cases, $P = 0.005$) and recreational (OR = 0.80, 95% 0.69–0.94, n_{CLL} = 428 cases, $P = 0.029$) sun exposures were inversely associated with CLL/SLL risks comparing the highest and lowest exposure quartiles. The study results did not support an association between CLL/SLL risks and alcohol consumption or physical activity. Overall, CLL risks are not associated with alcohol consumption. In a meta-analysis of four case-control and one cohort study using random effects models to estimate relative risks and nondrinkers as referents, the overall pooled RR for any alcohol drinkers was 0.94 (95% CI: 0.77–1.15, n = 5 studies, $I^2 = 0.0\%$, $P_{heterogeneity} = 0.639$).[124] The results demonstrated no dose-response relationship between CLL risks and light (RR = 0.89, 95% CI: 0.62–1.29, n = 5 studies, $I^2 = 32.4\%$, $P_{heterogeneity} = 0.218$) or moderate-heavy (RR = 0.99, 95% CI: 0.78–1.24, n = 5 studies, $I^2 = 0.0\%$, $P_{heterogeneity} = 0.240$) alcohol consumption.

Tobacco Smoking

Some epidemiological data support an inverse association between CLL risks and cigarette smoking. In a pooled analysis of 13 mostly Caucasian North American, European, and Australian studies, a history of cigarette smoking was inversely related modestly to CLL/SLL risks (OR = 0.90, 95% CI: 0.81–0.99, n_{CLL} = 1,246 cases, $P = 0.38$) compared with never-smokers.[96] The frequency ($P = 0.68$) and duration of smoking ($P = 0.165$) were positive, but not statistically different than CLL/SLL in nonsmokers. The Spanish population-based MCC-Spain study of 560 CLL/SLL cases (87% participation rate) and 1,845 controls (53% participation

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rate) reported no increased CLL/SLL risks for cigarette smokers based on data from face-to-face interviews.[97] The age/sex/region-adjusted odds ratio for CLL/SLL in ever-smokers was 0.95 (95% CI: 0.61–1.46, n_{CLL} = 64 cases) using never-cigarette smokers as referents.

Obesity

The association between obesity as measured by BMI and CLL/SLL risks is weak. In a meta-analysis of six prospective studies using random effects modeling, the relative risk/5-kg/m^2 increased BMI was marginally significant and small (RR = 1.04, 95% CI: 1.00–1.09, I^2 = 0.0%, $P_{heterogeneity}$ = 0.648).[125] Another meta-analysis using random effects modeling and normal weight participants as referents reported no significant relationship between BMI and CLL/SLL risks.[48] The pooled RR for overweight participants was 1.10 (95% CI: 0.98–1.22, n = 10 studies, I^2 = 54.8%, $P_{heterogeneity}$ = 0.217) and 0.98 (95% CI: 0.82–1.17, n = 12 studies, I^2 = 50.7%, $P_{heterogeneity}$ = 0.022) for obese participants. CLL/SLL risks were not associated with abdominal fatness (waist circumference, waist-to-hip ratio) comparing the highest and lowest categories (RR = 0.82, 95% CI: 0.56–1.19, n = 6 studies, I^2 = 60.0%, $P_{heterogeneity}$ = 0.028).

Diet

The Iowa Women's Health Study on 35,221 women aged 55–69 years followed for 14 years reported little evidence of an association between dietary factors and leukemogenesis based on baseline food frequency data.[126] Examining 17 food groups in 58 CLL cases, none of the food groups were associated with statistically significant elevated CLL risks; the P_{trend} ranged from 0.08–0.99. The European Prospective Investigation into Cancer and Nutrition (EPIC) study involving 476,160 participants from 10 European countries examined the effect of the Mediterranean diet on lymphoma risks using an adapted relative Mediterranean diet score.[127] After adjusting for potential confounders using multivariate Cox proportional hazards regression models stratified for age, sex, education, BMI, height, physical activity, smoking, and alcohol consumption, analysis of lymphoma subtypes did not display any statistically significant associations. Comparing the highest and lowest diet scores, the hazard ratio for CLL/SLL was not positive or statistically significant (HR = 0.92, 95% CI: 0.68–1.25, P_{trend} = 0.45).

Diseases

The Spanish population-based MCC-Spain study of 560 CLL/SLL cases (87% participation rate) and 1,845 controls (53% participation rate) reported an inverse association between diabetes type II and CLL/SLL risks (OR = 0.72, 95% CI: 0.54–0.97, n_{CLL} = 69 cases).[97] In a pooled analysis of 13 North American, European, and Australian studies, hepatitis C virus seropositivity was strongly associated with increased CLL/SLL risks (OR = 2.08, 95% CI: 1.23–3.49, n_{CLL} = 95 cases) compared with seronegative referents.[96] A family history of any atopic disorder was inversely associated with CLL/SLL risks (OR = 0.86, 95% CI: 0.78–0.95, n_{CLL} = 705 cases) and allergies (OR = 0.87, 95% CI: 0.77–0.98, n_{CLL} = 462), but not specifically with food allergies, asthma, hay fever, or eczema.

HISTOLOGY

Chronic lymphocytic leukemia and small lymphocytic lymphoma are lymphoid neoplasms classified together by the World Health Organization as a non-Hodgkin lymphoma subtype; these tumors originate from the expansion of a clone of mature CD5+ B cells. Peripheral blood smears demonstrate many small lymphocytes with scanty cytoplasm, dense nucleus without nucleoli, and clumped chromatin. A histological hallmark of CLL/SLL is the presence of smudge cells (Gumprecht nuclear shadows); these leukemic cells rupture during peripheral blood smear preparation due to increased cell membrane fragility.[128] Lymphoid infiltration of the bone marrow typically represents >30% of the cellularity in CLL. Peripheral blood immunophenotyping usually demonstrates high expression of CD5, CD19, CD23, and CD200, whereas CD20 and surface immunoglobulins (IgM/IgD) expression is typically low (dim) with light-chain restriction to either kappa or lambda.[91] B cell clones in CLL develop predominately in the bone marrow and blood, whereas small lymphocytic lymphoma localizes primarily in the lymph nodes. Small B cell clones with CLL phenotype characterize monoclonal B cell lymphocytosis (MBL) in the *absence* of clinical features of a lymphoproliferative disorder (e.g., cytopenia, B symptoms, lymphadenopathy, organomegaly).

HOST SUSCEPTIBILITY

The inherited susceptibility to chronic lymphocytic leukemia is one of the strongest of all hematological malignancies. A family history of CLL or non-Hodgkin lymphoma is a strong risk factor for CLL, with ~10% of incident CLL cases having at least two close family members with CLL.[69,129] In a case-control study of 14,336 first-degree relatives of 5,918 CLL cases from

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the Swedish Family-Cancer Database using 28,876 first-degree relatives of 11,778 controls in the database, the CLL relative risk in first-degree relatives of CLL patients was 7.52 (95% CI: 3.63–15.56).[130] The large confidence interval suggests imprecise risk estimates. Excess non-Hodgkin subtypes include lymphoplasmacytic lymphoma/Waldenström macroglobulinemia and hairy cell leukemia.[131] In a pooled analysis of 13 North American, European, and Australian studies, a family history of any hematological malignancy was strongly associated with increased CLL/SLL risks (OR = 2.17, 95% CI: 1.77–2.65, n_{CLL} = 153 cases, P = <0.001) including non-Hodgkin lymphoma (OR = 1.92, 95% CI: 1.41–2.61, n_{NHL} = 62 cases, P = <0.001).[96]

CLL/SLL tumors have >30 identified susceptibility loci. Meta-analyses of genome-wide association studies indicate established loci explain ~20–30% of familial CLL risks; these hereditary analyses confirm the importance of apoptosis and/or immune function in CLL susceptibility.[132,133] The histological features of familial and sporadic CLL are similar, with the exception of a higher frequency of somatic immunoglobulin heavy-chain variable region (IGHV) gene hypermutation.[134]

The major histocompatibility complex (HLA) plays an important part in immune surveillance by identifying malignant cells for T cell-mediated destruction. HLA class I proteins present peptides from endogenous proteins to cytotoxic CD8+ T cells, whereas HLA class II proteins detect exogenous proteins and present their peptides to CD4+ helper T cells. Downregulation of HLA class I/II and dysregulated immune surveillance occur in CLL/SLL cells. A German Caucasian case-control study suggests an increased CLL/SLL risk associated with HLA class II ($RR_{HLA\text{-}DRB4*0103}$ = 2.74, P < 0.0025).[135] In a HLA genotyping study of 3,491 US whites, 397 African Americans, and 90 Hispanic CLL patients requiring stem cell transplants for survival with 50,000 population-based controls, predisposing HLA alleles differed between races.[136] Two HLA class II predisposing HLA genotypes (HLA-A*02:01, HLA-DRB4*01:01) were overrepresented in whites, whereas several other predisposing haplotypes (DRB4*01:01~DRB1*07:01~DQB1*03:03) occurred across all three racial populations.

CLINICAL FEATURES

CLL is typically a slowly progressive disease associated with an increased incidence with age. Chronic lymphocytic leukemia is a disease primarily of the elderly with >70% presenting over the age of 65 years and a median age at diagnosis of 72–73 years. CLL occurs more often in men than women (male/female range, 0.5–2.1). Although frequently asymptomatic and discovered as an incidental finding of sustained lymphocytosis or lymphadenopathy, some CLL patients develop a more fulminant course depending on tumor genetics (e.g., miRNA-15a/16.1, miRNA-29b).

Patients may complain of nonspecific symptoms (fatigue, fever, night sweats, weight loss) from marrow infiltration (anemia, thrombocytopenia, neutropenia), splenomegaly (abdominal pain, bloating), lymphadenopathy, or immune dysfunction (recurrent infections). B symptoms include fever of unknown origin (>100.5°F for ≥2 weeks), ≥10% weight loss within 6 months, and night sweats >1 month without infection; occurrence of these symptoms with CLL is uncommon. Autoimmune hemolytic anemia and less commonly immune thrombocytopenia are the most frequent autoimmune manifestations. Opportunistic infections and secondary malignancies may complicate the clinical course of monoclonal B cell lymphocytosis and CLL/SLL. Reduced humoral and cell-mediated immunity predisposes the CLL patient to infections (e.g., upper/lower respiratory and urinary tracts, reactivated herpes zoster).

CLL is an incurable disease; however, treatment with kinase inhibitors (ibrutinib, idelalisib), BCL-2 antagonists (venetoclax), and anti-CD20 monoclonal antibodies (rituximab) significantly improves the lifespan of these patients. Survival after CLL diagnosis is highly variable, ranging from a normal lifespan for age/sex-matched healthy individuals to death shortly after diagnosis.[137] Unmutated immunoglobulin heavy-chain variable (*IGHV*) genes, CD38 overexpression, 11q deletion, SF3B1 mutation, and the presence of *TP53* deletion and/or mutation worsen CLL prognosis, whereas the presence of *IGHV* gene hypermutation and deletion of the long arm of chromosome 13 improves survival.[138] The overall 5-year survival rate is 66% in the United States with a median survival of ~10 years depending on the initial clinical stage.[139]

HODGKIN LYMPHOMA

Hodgkin lymphoma (HL) is a unique tumor characterized by malignant Hodgkin–Reed–Sternberg cells surrounded by a large inflammatory microenvironment. In the United States, the annual incidence of HL is ~8,000 cases with an estimated 1,000 HL-related deaths. Hodgkin lymphoma accounts for ~10–12% of lymphomas, whereas non-Hodgkin lymphoma incidence

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is ~9-fold higher.[76] The estimated worldwide annual incidence of Hodgkin lymphoma is ~80,000 (i.e., 27th most common cancer) with ~26,000 annual attributable deaths.[1] These rates have been relatively stable in the recent past, while mortality rates have steadily declined by ~75% over the last 40 years in economically developed countries. Little racial differences in HL incidence exist between whites and blacks; Asian/Pacific Islanders and American Indians/Alaskan Natives have ~½ the HL incidence of blacks/whites. Hodgkin lymphoma incidence has a bimodal peak (young adults 15–24 years, elderly) in economically developed countries, with a median age of ~39 years depending somewhat on the distribution of subtypes.[140,141] For adolescents aged 15–19 years, lymphomas are the most common cancer accounting for 21% of newly diagnosed (incident) cases with ~2/3 being Hodgkin lymphoma.

CARCINOGENESIS

Hodgkin lymphoma arises from germinal center B cells that proliferate and overcome apoptotic signals from activation of NF-κB and JAK/STAT pathways as well as expression of latent membrane protein (LMP1) in tumors with Epstein–Barr virus (EBV)-infected cells. EBV+ Hodgkin–Reed–Sternberg cells express three viral proteins (LMP1, LMP2, EBNA1). LMP1 activates JAK/STAT, NF-κB, and PI3K cell signaling pathways along with inducing transcriptional changes in germinal center B cells.[142] NF-κB complexes regulate a variety of proinflammatory cytokines and antiapoptotic factors, whereas the JAK/STAT pathway mediates cytokine stimulation to enhance the inflammatory microenvironment. In addition to inhibiting apoptosis, LMP1 also suppresses the virus lytic cycle. EBV nuclear antigen 1 (EBNA1) contributes to malignant transformation by downregulating protein-tyrosine phosphatase-κ (tumor suppressor); this viral protein also helps maintain the HL microenvironment by attracting regulatory T cells through upregulation of chemokine CCL20 (macrophage inflammatory protein 3 alpha). PD-1 (program death receptor-1) and CTLA-4 (cytotoxic T cell-associated protein 4) are immune checkpoint receptors in activated T cells that recognize host tissue and prevent autoimmune disease.[143] PD-1 mutations exhaust activated T cells, reduce tumor surveillance, and provide a favorable environment for tumor growth.

EXPOSURE

There are few established risk factors for Hodgkin lymphoma. Classic Hodgkin and non-Hodgkin lymphomas share some risk factors including EBV, certain autoimmune disorders, family hematopoietic malignancies, and severe congenital/acquired immune deficiencies.

Occupation

Several studies investigated the association of Hodgkin lymphoma with multiple occupational categories including pesticide exposures (insecticides, fungicides, herbicides, fumigants), farming, woodworking, and ionizing radiation; however, inconsistent results, multiple comparisons, overly broad, heterogeneous exposure categories, and small sample size limit definitive conclusions regarding causation and specific exposures. Although these studies suggest several potential occupational HL carcinogens, particularly multiple carcinogens, no single occupation, chemical exposure, or pesticide has been causally linked to HL.[144] A review of the Silver Platter Occupational and Environmental Medicine CD-ROM database on articles published on Hodgkin lymphoma through 5/1997 noted no particular occupation or chemical exposure was a confirmed increased HL risk with the possible exception of woodworkers.[145] In that database, 5 of 12 observational studies reported statistically significant increases in HL risks ranging from 1.8–7.2; however, no specific chemical carcinogen was identified and subsequent studies have not confirmed an elevated HL risk in these workers. In a meta-analysis of glyphosate and Hodgkin lymphoma, the meta-relative risk was statistically null (metaRR = 1.1, 95% CI: 0.7–1.6, $n = 2$ studies).[146]

Solvents are a very broad chemical class. An Italian study identified 304 HL cases and 1,530 population controls (no solvent exposure); they investigated age/sex/education/region-adjusted HL risks for six solvent classes (aromatic, chlorinated, technical, aliphatic, and derivative oxygenate hydrocarbons) using in-person interviews and expert ratings of exposure intensity/duration.[147] For medium/high exposure to any solvent, the HL risk was not statistically significant (adjusted OR = 1.4, 95% CI: 0.9–2.1, $n_{HL} = 49$ cases/208 controls, $P_{trend} = 0.09$). None of the six solvent classes demonstrated statistically significant trends in HL risks for exposure intensity (P_{trend} range, 0.28–0.78) or duration (P_{trend} range, 0.13–0.90). The trend comparing exposure duration ≤15-year and >15-year exposures to any solvent was statistically significant ($P_{trend} = 0.01$), along with the HL risks for >15-year exposure to technical and aliphatic hydrocarbons. A systematic review and meta-analysis of 41 cohort studies of polycyclic aromatic hydrocarbon (PAH) exposure workers did not detect any statistically significant excess HL risks

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in jobs or industries with high PAH exposure.[148] The highest reported positive HL risk occurring in iron and steel foundry workers was statistically nonsignificant (metaRR = 1.38, 95% CI: 0.95–2.01, n = 6 studies/27 cases, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.53$).

Job Title

A Canadian study on 316 HL cases and ~5 age-matched male adult controls (no exposure) for each case investigated HL risks for 7 broad classes and 49 individual occupational exposure categories based on self-reported mail questionnaires.[149] Ionizing radiation was the only broad class associated with a statistically significant increase in HL risks based primarily on uranium exposure (adjusted OR = 2.42, 95% CI: 1.12–5.24). None of the 49 individual exposure categories were associated with a statistically significant increased HL risk, whereas 1 class (nonionizing radiation, primarily sunlight) and 3 categories (grain dust, sour gas, ultraviolet light) had an inverse association between HL risks and occupational exposures. The study reported no association between HL risks and long-held jobs (>1 year) or specific classical HL subtypes.

Pesticides

Although some studies associate chlorophenol and pesticide exposure with elevated Hodgkin lymphoma risks, large case-control studies report no consistently elevated Hodgkin lymphoma risks in these workers.[150] A meta-analysis of 30 observational studies on farmers and Hodgkin lymphoma suggests male, but not female, farmers have a slightly elevated Hodgkin lymphoma risk; however, the specific cause (e.g., pesticides or infections) was not identified.[151] The combined RR for HL risk was statistically significant (metaRR = 1.25, 95% CI: 1.11–1.42) with significant heterogeneity, whereas the metaRR for women was not statistically significant (metaRR = 1.08, 95% CI: 0.91–1.29). Only one cohort study reported a statistically significant increased RR with the combined estimate HL risk for cohort studies of 1.08 (95% CI: 0.97–1.20). HL risks decreased in more recent studies. Limited observational data do not support an exposure-response relationship between farming and HL risks.[152]

A French study identified 87 HL cases and 265 hospital controls (no exposure).[153] Based on self-reported use in face-to-face interviews, HL risks were statistically significant for domestic insecticide use (OR = 2.9, 95% CI: 1.6–5.4, n_{HL} = 38 cases/74 controls), but not herbicide use (OR = 1.5, 95% CI: 0.6–4.1, n_{HL} = 7 cases/22 controls) or occupational pesticide use (OR = 2.1, 95% CI: 0.8–5.2, n_{HL} = 9 cases/24 controls). Dramatically elevated HL risks were reported for triazole fungicides (OR = 8.4, 95% CI: 2.2–32.4, n_{HL} = 6 cases/6 controls) and urea herbicides (OR = 10.8, 95% CI: 2.4–48.1, n_{HL} = 5 cases/4 controls). The large confidence intervals reflect small sample size and imprecise estimates. In a Canadian case-control study of 316 HL cases and 1,506 population-based controls (no herbicide exposure), the HL risk for any phenoxy herbicide exposure was null (OR = 0.99, 95% CI: 0.70–1.38, n_{HL} = 65 cases).[154]

Lifestyle

Few risk factors are associated with Hodgkin lymphoma (HL) including childhood HL. In a US study of 17,672 childhood cancer cases (390 Hodgkin lymphomas) and 57,966 controls using pooled population data, maternal age was not associated with childhood HL (OR = 0.97, 95% CI: 0.83–1.12) after adjustment for paternal age and multiple potential risk factors (sex, birthweight, birth order, birthyear, region, gestational age, and maternal race).[155] The association between tobacco smoking and HL is suggestive, but not conclusive.

Tobacco Smoking

Although tobacco smoking is the best-studied potential HL risk factor, results are inconsistent with statistically inverse (OR = 0.7, 95% CI: 0.5–0.9, n_{HL} = 134 cases/289 controls, P = 0.02),[156] null (OR = 0.8, 95% CI: 0.6–1.3, n_{HL} = 88 cases/261 controls),[157] and positive (OR_{men} = 2.83, 95% CI: 1.37–5.84, n_{HL} = 47 cases/259 controls)[158] associations comparing ever- and never-tobacco smokers. In a population-based case-control study, current male smokers aged 32–60 years had a significantly increased Hodgkin lymphoma risk (OR = 1.8, 95% CI: 1.4–2.5, n_{HL} = 155 cases) using never-smokers as referents.[159] The trend for tertiles of smoking duration in years (P_{trend} = <0.001) and cumulative smoking in pack-years (P_{trend} = <0.001) was statistically significant. The OR for the tertile of smokers with ≥40 pack-years was 2.7 (95% CI: 1.8–4.3, n_{HL} = 51 cases). The odds ratio for the most common HL subtypes (nodular sclerosis, mixed cellularity) was also significantly increased. Specific smoking information was available for only a portion of the 308 HL cases (155 cases for current smokers, 51 cases for ≥40 pack-year smokers).

A pooled analysis of data from the European International Lymphoma Epidemiology Consortium

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(InterLymph) containing 12 case-control studies reported marginally increased adjusted HL risks comparing ever- and never-smokers (OR = 1.10, 95% CI: 1.01–1.21).[34] Stratified analyses demonstrated increased risks for mixed cellularity and EBV+ classical HL subtypes, whereas the risks for nodular sclerosis and EBV− classical HL subtypes were not statistically significant. The study did not find supportive evidence for monotonic dose-response associations between classical HL risks and smoking. In a Danish-Swedish Scandinavian Lymphoma etiology (SCALE) study of 586 classical HL cases and 3,187 population controls using never-smokers as referents, the odds ratios were statistically significant for ever-smokers with EBV+ classic HL and HL overall in current smokers, but not in ever-smokers with overall HL risks or EBV− classic HL, as displayed in Table 60.3.[160] The smoking information was based on standardized telephone interviews. The authors opined that the limited evidence of a dose-response pattern suggests the association between tobacco smoking and classical Hodgkin lymphoma is causally weak.

A meta-analysis of 14 case-control and 3 cohort studies reported a modestly elevated adjusted meta-OR for Hodgkin lymphoma in ever-smokers of 1.13 (95% CI: 1.01–1.27, I^2 = 49.7%, P = 0.01) and 1.35 (95% CI: 1.17–1.56, I^2 = 48.9%, P = <0.001) in current smokers using never-smokers as referents.[161] The results for former smokers were null (meta-OR = 0.95, 95% CI: 0.81–1.10, I^2 = 43.1%, P = 0.48), with slight to moderate heterogeneity similar to current and ever smokers. The HL risk for current smokers of ≥10 cigarettes daily was not statistically different than the null.

Alcohol

A French study of 824 lymphoma cases and age/sex/center-matched controls reported an inverse association between ever- and never-alcohol consumption (OR = 0.5, 95% CI: 0.3–0.8, n_{HL} = 104 cases/337 controls, P = <0.01), including a statistically significant trend comparing the highest quartile (>21 drinks/week) and <3.8 drinks/week as referents (OR 0.3, 95% CI: 0.1–0.6, n_{HL} = 12 cases/80 controls, P_{trend} = <0.05).[157] A German case-control study also supported an inverse association between alcohol consumption and HL risks, with no specific association with beverage type. The HL risk was statistically marginal for men (OR = 0.51, 95% CI: 0.26–1.01, n_{HL} = 38 cases/329 controls) and significant for women (OR = 0.42, 95% CI: 0.20–0.89, n_{HL} = 30 cases/255 controls).[158]

Diseases

Epstein–Barr Virus

A substantial portion of Hodgkin lymphoma (HL) tumors contain evidence of Epstein–Barr virus (EBV) infection, with serologically confirmed infectious mononucleosis associated with persistently increased Hodgkin lymphoma risks. In a Danish cohort study of Hodgkin lymphoma incidence rates in 17,045 participants with serological evidence of a prior acute EBV infection and 24,614 controls without evidence of an EBV infection, the EBV+ Hodgkin lymphoma risk was significantly increased (RR = 4.0, 95% CI: 3.4–4.5) with an estimated median incubation time from mononucleosis to EBV-positive Hodgkin lymphoma of 4.1 years (95% CI: 1.8–8.3).[162] Although early EBV exposure has protective effects against Hodgkin lymphoma in children, EBV is associated with childhood classical HL (cHL) depending on subtype; for the most common histological cHL subtype in early childhood, EBV positivity occurs in 70–80% of mixed-cellularity cHL. The hallmark malignant cell of Hodgkin lymphoma (Hodgkin–Reed–Sternberg cell) contains genetic fragments produced by this virus.[163] EBV infection is not associated with the other major cHL type (nodular lymphocyte-predominant).[162]

TABLE 60.3. Multivariate odds ratios for association between classic Hodgkin lymphoma risk and categories of cigarette smoking, including Epstein–Barr virus (EBV) status, based on a Danish-Swedish case-control study. (Adapted from Hjalgrim et al.).[160]

Smoking Category	HL Overall Cases/Controls	HL Overall OR (95% CI)	EBV+ Classic HL OR (95% CI)	EBV− Classic HL OR (95% CI)
Never	299/1,460	Referent	Referent	Referent
Ever	275/1,665	1.18 (0.94–1.48)	1.62 (1.08–2.43)	1.13 (0.86–1.49)
Current	182/712	1.57 (1.22–2.03)	2.36 (1.51–3.71)	1.43 (1.05–1.97)

Abbreviations: CI = confidence interval; EBV+ = Epstein–Barr seropositive; EBV− = Epstein–Barr seronegative; HL = Hodgkin lymphoma; OR = odds ratio.

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Immunodeficiency

Immunosuppression from a variety of medical conditions increases HL risks, including human immunodeficiency virus (HIV), organ transplants with immunosuppressive therapy, and primary immunodeficiency disorders (ataxia-telangiectasia, autoimmune lymphoproliferative syndrome). In the Surveillance, Epidemiology, and End Results (SEER) program of 13 US population-based, central cancer registries using data from 54,780 HIV-infected persons in the Adult and Adolescent Spectrum of HIV Disease Project (47,832 patients) and 6,948 patients in the HIV Outpatient Study, the standardized rate ratio for Hodgkin lymphoma in HIV+ participants was 14.7 (95% CI: 11.6–18.2, n_{HL} = 150 cases).[164] HL is a late complication of solid organ transplantation. A retrospective cohort study of US solid organ transplant recipients (1997–2007) reported an elevated HL risk (SIR = 2.2, 95% CI: 1.7–2.7, n_{HL} = 73 cases) that increased linearly over time.[165] Most HL cases with HIV were EBV+.

Autoimmune Disease

Analyses of cancer registry linkage and pooled cohort data suggest a positive association between a history of autoimmune disease and HL risks.[166] A Nordic case-control study using population-based linked registry data from Sweden and Denmark on 7,476 Hodgkin lymphoma cases and 18,573 matched controls (no autoimmune disease) reported elevated HL risks for rheumatoid arthritis (OR = 2.7, 95% CI: 1.9–4.0, n_{HL} = 61 cases/50 controls), systemic lupus erythematosus (OR = 5.8, 95% CI: 2.2–15.1, n_{HL} = 15 cases/6 controls), and sarcoidosis (OR = 14.1, 95% CI: 5.4–36.8, n_{HL} = 27 cases/5 controls).[167] In a nested case-control study from the Scandinavian Lymphoma Etiology (SCALE) study involving 585 HL cases and 3,187 population-based controls (no arthritis), self-reported history of rheumatoid arthritis was associated with increased overall cHL risks (OR = 2.63, 95% CI: 1.47–4.70).[168] Subgroup analyses indicated HL risks were higher in mixed-cellularity (OR = 4.25, 95% CI: 1.66–10.9, n_{HL} = 102 cases) and EBV+ (OR = 3.18, 95% CI: 1.23–8.17, n_{HL} = 142 cases) cHL subtypes than the statistically nonsignificant elevations of HL risks in nodular sclerosis (OR = 2.10, 95% CI: 0.96–4.58, n_{HL} = 409 cases) and EBV− (OR = 1.60, 95% CI: 0.64–4.01, n_{HL} = 356) cHL subtypes. The large confidence limits reflect imprecise OR estimates.

Atopy

In the Scandinavian SCALE study, self-reported atopic diseases (asthma, hay fever, atopic dermatitis) were not associated with elevated overall classical HL risks (OR = 0.81, 95% CI: 0.64–1.03, P = 0.09) compared with controls (no atopic disease) consistent with most previous epidemiological studies.[168] In the European, multicenter Epilymph study of 275 classical HL cases and 273 unexposed, age/sex-matched population controls, occupational exposure to eight common protein-derived, high-molecular-weight sensitizing agents was inversely associated with classical Hodgkin lymphoma (OR = 0.62, 95% CI: 0.40–0.98).[169] These agents included animal dander, flour, plant mites, enzymes, and latex antigens.

HISTOLOGY

Hodgkin lymphoma B cell tumors originate in germinal centers or postgerminal center B cells surrounded by a large reactive inflammatory microenvironment comprising lymphocytes, neutrophils, eosinophils, histiocytes, mast cells, macrophages, and plasma cells.[170] The presence of Reed–Sternberg cells in the tumor characterizes Hodgkin lymphoma. The major subtypes of Hodgkin lymphoma (HL) are nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma; the latter has four distinct subtypes (nodular sclerosis, 70–75%; mixed cellularity, 20–25%; lymphocyte rich, 5%; lymphocyte depleted, <1%), primarily reflecting differences in the surrounding nonneoplastic infiltrate and the abundance of Hodgkin–Reed–Sternberg cells. The first two subtypes account for 90% of all classical Hodgkin lymphoma cases.[171] NLPHL typically displays large cells (L&H cells) with a nodular architecture separated by green birefringent, dense collagenous fibrous bands, and single nucleus with multiple, small nucleoli producing a "popcorn-like" appearance. The nonneoplastic microenvironment contains small lymphocytes with histocytes that may form non-necrotizing granulomas. Neutrophils, eosinophils, and plasma cells are rarely present in the background. The mixed-cellularity classical HL subtype displays a diffuse, mixed, inflammatory background without bands of sclerosing fibrosis. A majority of this type of tumor expresses Epstein–Barr-encoded latent membrane protein 1 and EBV small nuclear RNA transcripts including patients without known immunodeficiencies.[140,172] The lymphocyte-depleted subtype frequently occurs in association with HIV; the tumor is diffusely infiltrated with Hodgkin–Reed–Stenberg cells without a significant reactive inflammatory infiltrate. Necrosis may occur in this tumor subtype.

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Hodgkin–Reed–Sternberg cells are usually CD30+/CD15+, whereas the NLPHL lymphocyte predominate cells are CD30−/CD15− and CD45+/CD20+. The Hodgkin and Reed–Sternberg cells are common features of all classic Hodgkin lymphoma subtypes. The Reed–Sternberg cell is a large cell with ≥2 nuclear lobes, separate nucleoli, and an "owl's eyes" appearance, whereas the Hodgkin cell is the mononuclear form of the Reed–Sternberg cell. These most common classical HL cells comprise only 1–2% of the tumor mass with the remaining consisting of nonneoplastic cellular infiltrate (T cells, B cells, eosinophils, macrophages, neutrophils, plasma cells, fibroblasts).[173] These tumors primarily affect the lymph nodes, liver, and spleen.

HOST SUSCEPTIBILITY

Familial aggregation and ethnic variation in HL incidence suggest inherited susceptibility increases Hodgkin lymphoma risks, particularly in monozygotic twins and same-sex sibling pairs with familial HL accounting for ~4–6% of HL cases.[2,174] The role of inherited disease is substantially less in HL than in CLL or NHL.[175] The presence of inherited or acquired immune system abnormalities (e.g., autoimmune diseases, HIV, ataxia-telangiectasia, sarcoidosis) increases HL risks with long latency from the onset of the autoimmune disease to lymphoma diagnosis, suggesting the importance of chronic immune dysregulation. Epstein–Barr virus (EBV)–HL is strongly associated with specific human leukocyte antigen (HLA) complex polymorphisms, including HLA class I alleles with EBV-positive HL and HLA class II polymorphisms with EBV-negative HL.[176]

CLINICAL PRESENTATION

About half the annual incidence of Hodgkin lymphoma occurs in the age group 15–44 years, with a later peak in older adults (>50 years).[177] This tumor typically presents as a painless superficial lymphadenopathy involving cervical, supraclavicular, and mediastinal lymph nodes. Classical HL spreads by contiguity within the lymph network; extension to adjacent and distant viscera occurs late in the clinical course. Extranodal disease is much less common with splenic or bone marrow involvement developing in a minority of patients. B symptoms (recurrent fever, night sweats, weight loss) develop in ~1/3 of HL patients, usually associated with more advanced disease; alcohol-induced pain at disease sites is a unique but rare manifestation of Hodgkin lymphoma. A few HL patients develop severe, unremitting pruritus without obvious skin lesions as a presentation of occult HL.[178] Classical Hodgkin lymphoma is typically an aggressive neoplasm, whereas nodular lymphocyte-predominant HL has a more indolent clinical course and a better prognosis if left untreated.

Hodgkin lymphoma is one of the most curable cancers with current chemotherapy or combined with radiotherapy; however, overall survival in the elderly remains poor and adverse effects (e.g., secondary cancers, treatment-associated cardiovascular disease) are potentially life-limiting.[179] For early-stage disease, the overall survival rate with standard ABVD treatment (adriamycin, bleomycin, vinblastine, dacarbazine) combined with irradiation of involved nodes is >95%. Prognosis varies with HL subtype. Nodular lymphocyte-predominant Hodgkin lymphoma has a good prognosis, whereas lymphocyte-depleted classical Hodgkin lymphoma has a historically poor outcome. The prognosis of adolescents and young adults with HL has dramatically improved over the last several decades, with a 15-year survival rate of ~90–95% as a result of more effective chemotherapy (e.g., PD-1 axis inhibitors, cytotoxic T cell-associated protein 4 inhibitors), better risk stratification, and improved supportive care.[140,171] A relatively small portion of Hodgkin lymphoma patients are refractory or relapse after first-line therapy.

NON-HODGKIN LYMPHOMA (NHL)

Non-Hodgkin lymphoma (NHL) is the 13th most common worldwide cancer with an estimated annual incidence of ~510,000, with ~250,000 annual deaths compared with an estimated ~74,000 new cases and ~20,000 NHL-related deaths in the United States.[1,76] The NHL incidence is increasing throughout the world, regardless of economic development or geography, partly reflecting an aging population and improved reporting. The worldwide incidence rates vary ~5-fold geographically, with a majority occurring in developed countries and lower reported rates in Africa and East/Southeast Asia (2.7/100,000); the highest NHL incidence rates worldwide occur in the United States (13.7/100,000).[1,180] Some NHL subtypes (T cell leukemia/lymphoma, Burkitt lymphoma) are more common in the latter, less developed countries, particularly the African lymphoma belt (Congo, Malawi, Nigeria, Uganda).[181] Follicular lymphomas are uncommon in Europe and rare in Asia, whereas endemic Burkitt lymphoma has an almost exclusive distribution

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with *Plasmodium falciparum* malaria in equatorial Africa. The incidences of T cell, natural killer (NK) cell, and high-grade B cell lymphomas are higher in low- and middle-income countries than in high-income countries.[182]

In most US cancer registries, overall NHL incidence rates increased in the last half of the 20th century beginning in the 1970s, probably reflecting, at least in part, from improved reporting, diagnosis, and case ascertainment; subsequently, the overall rates stabilized in the early 2000s with some subtype, age, sex, and ethnicity differences. The incidences of diffuse large B cell lymphoma, Burkitt lymphoma, marginal zone lymphoma, angioimmunoblastic T cell lymphoma, and mantle cell lymphoma continue to increase, while CLL and lymphoplasmacytic lymphoma/Waldenström macroglobulinemia decrease.[183,184] Non-Hodgkin lymphomas are primarily adult tumors, with <1% of NHL tumors occurring in children under 15 years of age, primarily in children with congenital immune deficiencies (severe combined system immunodeficiency, congenital X-linked immunodeficiency, ataxia-telangiectasia, Wiskott–Aldrich syndrome).[185] NHL accounts for ~7% of pediatric malignancies. The incidence of NHL increases with white ethnicity and male sex; the gender ratio increases with age,[2] whereas the median age varies with subtype. The median age at diagnosis is 65 years for follicular lymphomas compared with 52 years for Burkitt lymphomas and 36 years for mediastinal lymphomas. Overall, the age at diagnosis is younger for T cell than B cell NHL tumors with considerable subtype heterogeneity. The overall male/female NHL ratio indicates a male predominance (1.5/1), with higher ratios (i.e., ~3-fold) in hairy cell leukemia, Burkitt lymphoma, mantle cell lymphoma, and Waldenström macroglobulinemia).[186] The incidences of marginal zone and follicular lymphomas are similar in both sexes, whereas the DLCBL subtype, primary mediastinal B cell lymphoma, occurs more commonly in women.

CARCINOGENESIS

Non-Hodgkin lymphoma (NHL) is one of several major lymphoid neoplasms (e.g., Hodgkin lymphoma, lymphocytic leukemias, multiple myeloma) that includes >45 malignant lymphoproliferative subtypes originating from B cells and >20 from T cells, as displayed in the 2022 World Health Organization revision (Table 60.1). These tumors arise from immature (lymphoblastic) or mature B, T, or natural killer (NK) cells. B cells undergo rearrangement of their immunoglobulin gene segments in the bone marrow before antigen contact. These naïve B cells migrate to lymph nodes and spleen. After encountering antigens, they undergo rapid proliferation to form germinal centers in primary lymphoid follicles with the help of T cells. This process requires double-stranded DNA breaks via somatic hypermutation and class-switch recombination to select high-affinity, nonhost antibodies. This error-prone process promotes lymphomagenesis in the germinal centers, where the lymphoma type depends on the stage of differentiation disrupted. B cell NHLs result from translocations that deregulate gene expression of key transcription factor-producing genes (*BCL6*, *MYC*, *PRDM1*) associated with balancing active pathway-specific enhancers and promoters of B cell maturity. These translocations often involve the immunoglobulin heavy-chain (IGH) locus on chromosome 14q32 and the B cell surface receptors (BCL). Table 60.4 outlines the common aberrant mechanisms associated with lymphomagenesis.

TABLE 60.4. Common mechanistic alterations of lymphogenesis. (Adapted from Armitage et al.).[182]

Mechanism	Genes and Alterations
Enhanced proliferation/survival	Mutation in *CDKN2A* gene, JAK/STAT signaling pathway gene mutations
Upregulation signaling pathways	*CARD11* (immune function) gene, CD79B (B cell antigen receptor), *MYD88* gene (Toll-like receptors and interleukin-1 (IL-1) receptors in early immune responses) mutations
Apoptosis inhibition	BCL upregulation by translocation/gain
Terminal differentiation block	BCL translocation/PRDM1 deletion
Immune escape	PDL1 translocation, CD58, mutations in *B2M* gene
Epigenetic (chromatin remodeling, histone modification)	Mutations in *CREBBP*, *EP300*, *EZH2*, *KMT2D* genes

B Cell NHL

Burkitt Lymphoma

Burkitt lymphoma is an aggressive B cell NHL tumor that exists in three similar morphological, genetic, and immunophenotypic subtypes (endemic, sporadic, immunodeficiency associated); this neoplasm is the fastest-growing human tumor with a 24–48-hour doubling time.[187] In Africa and Papua New Guinea, Burkitt lymphoma is the most common childhood cancer often associated with malaria and Epstein–Barr virus, whereas

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sporadic Burkitt lymphoma accounts for ~30% of childhood (4–5 cases/100,000) and 1–5% of adult lymphomas in developed countries.[188] Malignant Burkitt lymphoma cells typically express B cell lineage (CD20+/CD79a+), with CD10/BCL-6 commonly co-expressed along with an absence of the antiapoptotic protein, BCL-2. The t(8;14)(q24;q32) translocation in this highly aggressive tumor overexpresses the *MYC* proto-oncogene encoding a nuclear phosphoprotein important in cell-cycle progression, apoptosis, and malignant transformation in 70–80% of patients. Variant translocations t(2;8)(p12;q24) and t(8;22)(q24;q11) occur in 10–15% of patients.[189] Other B cell lymphomas may contain these *MYC* translocations.

Little available epidemiological data exist on risk factors associated with Burkitt lymphoma other than infectious agents. Examination of age and gender in a Dutch study of 80 verified childhood and 27 adult cases of Burkitt lymphoma indicated this predominantly male tumor has a bimodal distribution in males (89% children, 78% adults), with peak incidence at 6–10 years in boys and a steadily increasing incidence >65 years in men.[190] Girls and women had similar Burkitt lymphoma risks, with the incidence increasing above the age of 60 years. Children more often displayed extranodal disease (81 vs. 59% adults), with abdominal disease presenting in 60–80% of sporadic cases.[191] The InterLymph Consortium identified 295 Burkitt lymphoma cases and 21,818 controls in 18 case-control studies separating the cases into younger (<50 years) and older (≥50 years) cases.[192] Regardless of age, alcohol consumption was inversely associated with these tumors in the multivariate models comparing any alcohol drinking (≥1 drink monthly) with nondrinkers (aOR= 0.63, 95% CI: 0.40–0.98, $P = 0.001$). Using the basic adjusted model (fixed effects logistic regression adjusted for age, sex, and race/ethnicity) in younger patients, the association with Burkitt lymphoma was inverse for history of allergy (OR = 0.52, 95% CI: 0.30–0.90, $n_{\text{Burkitt lymphoma}} = 21$ cases/1,093 controls, $P = 0.016$) and asthma (OR = 0.35, 95% CI: 0.13–0.95, $n_{\text{Burkitt lymphoma}} = 4$ cases/461 controls, $P = 0.015$). A history of asthma, allergy, atopy, hay fever, or eczema was not associated with Burkitt lymphoma in older patients. In the latter patients, hepatitis C virus seropositivity was associated with increased Burkitt lymphoma risks (OR = 4.1, 95% CI: 1.01–15.4, $n_{\text{Burkitt lymphoma}} = 3$ cases/109 controls, $P = 0.066$) with an imprecise estimate.

Diffuse Large B Cell Lymphoma (DLBCL)

DLBCL is the most common NHL subtype in Western countries, with an age-adjusted incidence of 3.1–5.7/100,000 US/European population; the median age at diagnosis occurs in the sixth decade of life.[193] This anatomically, histologically, and immunophenotypically diverse disease has the following mutations in genes for the three major genetic/phenotypic subtypes: 1) activated B cell (e.g., MYC/BCL6 mutations); 2) germinal center B cell (e.g., MYC/BCL2 mutations); and 3) unclassified origin based on gene-expression profiling. These subtypes differ in genetic aberrations, oncogenic pathway abnormalities, disease presentation, prognosis, therapeutic response, and origin. Major molecular pathways dysregulated in DLBCL include B cell receptor and NF-κB signaling along with chronic inflammation (IL-10 cytokines).[194] Examination of 574 DLBCL biopsy samples using exome and transcriptome sequencing detected four prominent genetic aberration subtypes, including *BN2* (BCL6 fusions/NOTCH2 gene mutations), EZB (EZH2 mutation/BCL2 translocations), *MCD* gene (CD79B/MYD88L265P mutations), and *N1* gene (NOTCH1 mutations).[195]

Multivariate analysis of pooled data in the InterLymph study of 19 European, US, and Australian case-control studies with 4,667 DLBCL cases and 22,639 controls supported a complex, multifactorial etiology of DLBCL.[196] The highest positive odds ratios occurred for B cell activating autoimmune diseases, HCV seropositivity, NHL family history, and higher young adult BMI, whereas reduced DLBCL risks were associated with atopic disease, higher socioeconomic status, and greater recreational sun exposure. Additional risk factors for women, but not men, include field crop/vegetable farm work (aOR = 1.78, 95% CI: 1.22–2.60, $P = 0.004$), hairdressing (aOR =1.65, 95% CI: 1.12–2.41, $P = 0.013$), and seamstress/embroider (aOR = 1.49, 95% CI: 1.13–1.97, $P = 0.005$). The DLBCL risk for the occupation of material handling equipment operator was elevated for men (OR 1.58, 95% CI: 1.02–2.44, $P = 0.047$). Table 60.5 displays the statistically significant positive and inverse associations for DLBCL risk factors based on the InterLymph non-Hodgkin Subtypes Study.

Follicular Lymphoma

Follicular lymphoma (FL) is an indolent lymphoproliferative disorder of germinal center B cells that is the second most common lymphoma in the United States and Western Europe after DLBCL.[13] In the United States, the incidence is ~3.4/100,000, with significant racial differences (~2–3-fold) and a marked increase in incidence at >65 years of age.[186,197] The median age at diagnosis is ~65 years.[198] Age-adjusted FL risks are slightly higher in men than women. Approximately 2–4% of follicular lymphoma cases transform into a

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TABLE 60.5. Statistically significant, self-reported risk factors for diffuse large B cell lymphoma (DLBCL) using data in the InterLymph Non-Hodgkin Subtypes Study from pooled analysis of 19 case-control studies containing 4,667 DLBCL cases and 22,639 controls. Statistically nonsignificant, but positive or inverse odds ratios for DLBCL risks are not included in the table. (Data adapted from Cerhan et al.).[196]

Risk Factor	DLBCL in Cases and Controls	Adjusted Odds Ratio	95% Confidence Interval	$P_{difference}$
	Positive			
B cell activating autoimmune disease	87/157	2.36	1.80–3.09	<0.001
HCV seropositivity	63/152	2.02	1.47–2.76	<0.001
1° NHL family history	110/278	1.95	1.54–2.47	<0.001
Higher young adult BMI	54/173	1.58	1.12–2.23	0.002
	Inverse			
Lifetime alcohol consumption >400 kg[a]	NA	0.57	0.44–0.75	<0.001
First postmenopausal hormone therapy ≥50 years[b]	97/569	0.68	0.52–0.88	0.083
Blood transfusion[a]	NA	0.69	0.57–0.83	<0.001
Higher recreational sun exposure	714/2,983	0.78	0.69–0.89	<0.001
Oral contraceptive use before 1970[b]	128/765	0.78	0.62–1.00	0.014
Atopic disorder	1,315/6,442	0.82	0.76–0.89	<0.001
Higher socioeconomic status	1,296/6,386	0.86	0.79–0.94	0.002

Abbreviations: BMI = body mass index; DLBCL = diffuse large B cell lymphoma; HCV = hepatitis C virus; NHL = non-Hodgkin lymphoma; NA = not available.
[a] Men only. [b] Women only.

more aggressive B cell neoplasm annually, typically diffuse large B cell lymphomas. In a Czechoslovakian study of 1,233 patients with follicular lymphoma grades 1–3A, histologically proven transformation to a more aggressive B cell tumor occurred in 58 cases at a median of 3.0 years from the initial FL diagnosis with a 4% transformation rate at 5 years.[199] Patients typically present with asymptomatic diffuse lymphadenopathy, bone marrow involvement (~70%), splenomegaly, and less commonly (<20%) with B symptoms (fever, weight loss, night sweats) and extranodal involvement.[200] The prognosis for pediatric follicular lymphoma is excellent, whereas the 10-year survival is age-dependent, ranging from 92% for ages 18–49 to 6% for ≥70 years.[198]

Follicular lymphoma has few recognized, mostly modest risk factors. Several observational studies associate follicular lymphoma with cigarette smoking, particularly in women. The California Teachers Study evaluated self-reported baseline cumulative active and passive smoking using Cox proportional hazards models to estimate multivariable-adjusted relative risks of women smokers.[201] For ever-smokers (>100 cigarettes lifetime), the NHL RR was elevated, but statistically nonsignificant (aRR = 1.22, 95% CI: 0.95–1.57, n_{NHL} = 252 cases) after exclusion of passive smoking-exposed, never-smokers (referents). Comparisons of the highest and lowest quintiles of cumulative passive smoking (years) demonstrated a statistically significant aRR for follicular lymphoma (aRR = 2.89, 95% CI: 1.23–6.80, n_{FL} = 26 cases, P_{trend} = 0.01), but no similar exposure-response relationship for DLBCL (P_{trend} = 0.24) or chronic lymphocytic leukemia/small lymphocytic lymphoma (P_{trend} = 0.32). The InterLymph Non-Hodgkin Lymphoma Subtypes Project pooled data from 19 case-control studies involving 3,530 FL cases and 22,639 controls using logistic regression and self-reported baseline questionnaires to estimate age/race/ethnic, sex, study-adjusted odds ratios.[202] Table 60.6 lists statistically significant associations between follicular lymphoma and examined risk factors from this study.

Comparing ever- and never-smokers, the odds ratios for follicular lymphoma were statistically nonsignificant in men (aOR = 0.98, 95% CI: 0.87–1.10, n_{FL} = 987/8,047 controls, $P_{difference}$ = <0.695). The study reported no statistically significant association between FL and autoimmune disease, eczema, HCV seropositivity, hair dye, hormonal drugs, or farming.

Early alterations in follicular lymphomagenesis frequently involve mutations of multiple genes including

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TABLE 60.6. Statistically significant, self-reported risk factors for follicular lymphoma (FL) reported in the InterLymph Non-Hodgkin Subtypes Study from pooled analysis of 19 case-control studies containing 3,530 FL cases and 22,639 controls. Statistically nonsignificant, but positive or inverse odds ratios for overall FL risks are not included in the table. Although the Body Mass Index (BMI) of young women was associated with a statistically significant positive odds ratio, almost all cohort studies have not supported this finding. The epidemiological support for an inverse association between FL and blood transfusions is mixed. The other risk factors are consistent with most epidemiological evidence. Statistically nonsignificant, but positive or inverse odds ratios for overall follicular risks are not included in the table (Data adapted from Linet et al.).[202]

Risk Factor	FL in Cases/Controls	Adjusted Odds Ratio	95% CI	$P_{difference}$
		Positive		
Spray painters[a]	13/22	3.83	1.87–7.84	<0.001
Sjögren syndrome[b]	7/9	3.37	1.23–9.19	0.024
1° NHL family history	96/278	1.99	1.55–2.54	<0.001
BMI as young adult[b]	1,745/9,411	1.25	1.09–1.44	0.948
Ever-cigarette smoking[b]	762/3,643	1.22	1.09–1.37	<0.001
		Inverse		
Bakers/millers	12/158	0.51	0.28–0.93	0.017
University higher education teachers	37/274	0.58	0.41–0.83	0.001
Food allergy[b]	100/583	0.70	0.56–0.88	0.002
Hay fever[b]	272/1,483	0.74	0.63–0.86	<0.001
Highest vs. lowest quartile of recreational sun exposure	505/2,983	0.74	0.65–0.86	0.018
Any current drinking[b,d]	630/3,749	0.79	0.68–0.91	0.002
Any atopic disorder[c]	1,107/6,442	0.87	0.80–0.94	<0.001
Any blood transfusion	297/1,966	0.78	0.68–0.89	<0.001

Abbreviations: CI = Confidence Interval; FL = follicular lymphoma; non-Hodgkin lymphoma, NA = not available; $P_{difference}$ = difference between risk factor and referents.
[a] Men only. [b] Women only. [c] Allergy, asthma, eczema, food allergy, hay fever. [d] ≥1 Drink/month

CREBBP (CREB protein), *EZH2*, and *KMT2D* (*MLL2*).[203] CREB-binding protein is a transcriptional coactivator that affects many genes involved with cell proliferation and differentiation, whereas *EZH2* encodes a histone methyltransferase that suppresses genes involved in cell maturation. The *KMT2D* gene (lysine methyltransferase 2D) produces a histone methyltransferase important for cell development. The t(14;18)(q32;q21) translocation enhances expression of the antiapoptotic protein BCL2, resulting in the blockage of germinal center-associated cell death and tumor proliferation. About 70–90% of FL tumors are t(14;18)-positive; however, this translocation is not unique to follicular lymphoma. Approximately 20–30% of DLBCL and 5–10% of other NHL subtypes also contain this translocation.[13,204] Additionally, the t(14;18) translocation occurs in healthy individuals, indicating this chromosomal abnormality contributes to early lymphogenesis, but is not sufficient alone to cause the disease; hence, multiple genetic and epigenetic events are necessary to produce follicular lymphoma (e.g., altered T cell motility, chromatin modification).[205,206]

Hairy Cell Leukemia

Hairy cell leukemia (HCL) is a rare, indolent mature B cell lymphoproliferative disorder with clear male predominance. In the UK Hematological Malignancy Research Network containing ~3.6 million adult and pediatric incident hematological malignancy cases, the registry identified 55 hairy cell leukemia cases with a median age of 65.7 years.[207] The median age at diagnosis varies in different countries, ranging from 50–65 years in international studies.[208] The estimated annual incidence of hairy cell leukemia was 0.3/100,000 (95% CI: 0.2–0.4) with a male/female ratio of 3.44 (95%

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CI: 1.81–6.98). The HCL incidence has been relatively stable in recent times.[209] Substantial ethnic differences exist in HCL incidence with the rates several-fold higher in Caucasians and Latinos than African Americans or Asians.[210] The typical clinical presentation includes peripheral lymphocytes with characteristic "hairy" cytoplasmic projections, pancytopenia, splenomegaly, and a distinctive phenotype. The life expectancy of HCL patients is close to that of healthy, age-matched adults because of durable remissions in response to purine analogs (e.g., cladribine, pentostatin).[211]

Early case-control studies suggest an association between hairy cell leukemia and several risk factors (e.g., farming operations, tobacco smoking); however, small sample sizes, inadequate study power, and imprecise estimates limit definitive conclusions about causation. A French study of 226 male HCL cases (60% participation rate) and 116 hospital-based referents (57% participation rate) used self-administered questionnaires, expert reviews, and conditional logistic regression to estimate odds ratios for hairy cell leukemia risks.[212] The HCL odds ratio was statistically marginally significant for HCL in all farmers (OR = 1.5, 95% CI: 1.0–2.2, n_{HCL} = 77 cases/116 controls) and significant for farming duration ($OR_{\geq 20\ years}$ = 1.8, 95% CI: 1.1–3.0, n_{HCL} = 59 cases/50 controls) using nonfarmers as referents. For definitive exposures to pesticides, the HCL OR was statistically marginally significant (OR = 1.7, 95% CI: 1.0–2.6, n_{HCL} = 47 cases/65 referents). A French study of 824 lymphoid neoplasms and 752 hospital-based controls identified 36 NHL cases with self-reported lifelong smoking histories based on face-to-face interviews.[157] Ever-smokers were classified as smoking ≥1 cigarette daily for 6 months. Compared with never-smokers, ever-smoking was inversely associated with hairy cell leukemia (OR = 0.2, 95% CI: 0.1–0.5, n_{HCL} = 15 cases/21 controls) with an inverse, but imprecise dose-response relationship comparing the highest and lowest quartiles of duration ($OR_{>31\ years}$ = 0.1, 95% CI: 0.0–0.7, n_{HCL} = 2 cases highest/2 cases lowest) and cumulative consumption ($OR_{>32\ pack\text{-}years}$ = 0.1, 95% CI: 0.0–0.4, n_{HCL} = 1 highest/1 lowest). In a pooled analysis of 154 HCL cases and 8,834 controls in 5 case-control studies from the InterLymph Non-Hodgkin Lymphoma Subtypes Project, cigarette smoking was inversely related to HCL risks.[213] The age/sex/study/race/ethnicity-adjusted odds ratio comparing current smoking status 1 year before diagnosis and nonsmoking referents was inverse and statistically significant (aOR = 0.34, 95% CI: 0.21–0.55, n_{HCL} = 21 cases/2,112 controls). The dose-response for quartiles of cumulative smoking was also significantly inverse, including lifetime pack-years (P = <0.01) and duration (P = <0.01). The association between HCL and ever-working on a farm was not statistically significant (aOR = 1.61, 95% CI: 0.95–2.53, n_{HCL} = 24 cases/1,099 controls, P = 0.067), but duration as a farmer of >10 years was statistically significant (aOR = 1.79, 95% CI: 1.50–5.93, n_{HCL} = 14 cases/609 controls). Alcohol consumption and atopic/autoimmune conditions were not associated with HCL.

Virtually all hairy cell leukemias contain the mutation in *BRAF V600E* (*B-RAF* proto-oncogene, serine/threonine kinase); this abnormality alters the RAS/MAPK (mitogen-activated protein kinase) signaling pathway involved with extranuclear-to-intranuclear communication essential for cell development (proliferation, differentiation, migration, apoptosis).[214]

Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

Proliferation of small B cell lymphocytes, plasmacytoid lymphocytes, and plasma cells characterize lymphoplasmacytic lymphoma (LPL), usually with IgM paraproteins and less often with IgG or other paraproteins. Waldenström macroglobulinemia (WM) is a subset of LPL tumors associated with monoclonal IgM gammopathy and bone marrow involvement. Established risk factors include male gender, older age, white race/ethnicity, and family history of monoclonal IgM gammopathy. Other potential risk factors are chronic immune stimulation, germline susceptibility genes, autoimmune diseases, allergies, and specific infectious diseases. The InterLymph Non-Hodgkin Lymphoma Subtypes used logistic regression models to estimate self-reported risk factors based on pooled data on 374 lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) cases in 11 case-control studies.[215] Table 60.7 lists the statistically significant associations between LPL/WM and specific risk factors based on self-reported exposures. The study results were consistent with autoimmune conditions associated with activated B cells, but not activated T cells. Alcohol consumption and farming were not associated with LPL/WM.

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a recently classified NHL subtype with no confirmed risk factors.[216] Epidemiology data are limited by the delay in the acknowledgment of MCL as an NHL subtype until 1992 and the rare occurrence of this aggressive B cell tumor. MCL tumors originate in the mantle zone of lymphoid follicles accounting for ~2–10% of NHL subtypes, with

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TABLE 60.7. Statistically significant, self-reported risk factors for lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) based on multivariate analysis of pooled data from 374 LPL/WM cases and 2008 WHO lymphoma classifications in 11 predominately population-based case-control studies within the InterLymph Consortium adjusting for age, sex, race/ethnicity, Sjögren syndrome, systemic lupus erythematosus, hay fever, usual adult eight, smoking duration, hepatitis C serology, family history of hematological malignancy, and medical occupation. Statistically nonsignificant, but positive or inverse odds ratios for overall LPL/MM risks are not included in the table. The limited number of exposures and many comparisons limit the power and precision of these estimates. Novel findings included decreased risks for hay fever history and high usual adult weight along with increased risks for cigarette smoking of ≥40 years and working as a physician. (Data adapted from Vajdic et al.).[215]

Risk Factor	LPL/WM in Cases and Controls	Adjusted Odds Ratio	95% Confidence Interval	*P* Value
	Positive			
Sjögren syndrome	3/9	14.0	3.60–54.6	0.002
Systemic lupus erythematosus	4/24	8.23	2.69–25.2	0.003
Medical doctor	6/43	5.54	2.19–14.0	0.002
Hepatitis C virus seropositive	6/95	2.51	1.03–6.17	0.075[a]
Family leukemia history	13/215	2.19	1.21–3.96	0.018[b]
Hematological malignancy family history	21/452	1.64	1.02–2.64	0.060
Cigarette smoking duration (highest quartile, ≥40 years)	57/1,194	1.46	1.04–2.05	0.148
	Inverse			
Usual weight (highest vs. lowest quartile)	79/3,299	0.61	0.44–0.85	0.024[c]
Hay fever	64/2,511	0.73	0.54–0.99	0.017

[a] *P* value using likelihood ratio test. [b] Basic adjusted association using age, sex, race/ethnicity, and study. [c] *P* value using Wald test = 0.021.

an age-adjusted incidence rate of 0.5–1/100,000 inhabitants and a clear male predominance. The median age at diagnosis is 65–70 years with the majority (i.e., ~80%) presenting with advanced Stages III–IV disease. In the French population-based case-control study of 135 MCL patients, the median age at diagnosis was 72 years (range, 30–92 years), with a median net survival time of 41 months (95% CI: 38–62 months).[217] The male/female ratio was 3.9. Characteristic clinical features of MCL at presentation include diffuse lymphadenopathy, anorexia, fatigue, and B symptoms (fever, night sweats, weight loss). The 5-year MCL survival rate ranges from ~70% for lower stages to ~50% for advanced stages.[218]

Although the causes of MCL remain unknown, immunosuppression is not a strong MCL risk factor. Exploratory studies suggest the possible association of MCL with inflammation/infection, antigen presentation, and family malignancy history. The InterLymph Non-Hodgkin Lymphoma Subtypes Project examined MCL risks for self-reported risk factors associated with 557 MCL cases and 13,766 controls using multivariate logistic regression models.[219] Table 60.8 displays the statistically significant MCL risk factors. Alcohol consumption, BMI, and cigarette smoking were not associated with MCL risks.

Mantle cell lymphoma has a distinct genetic profile from other B cell NHL subtypes. These tumors display multiple secondary chromosomal and molecular alterations of genes that target cell cycle and senescence (*ARF*, *BMI1*, *CDK4*, *INK4a*, *RB1*) and interfere with DNA repair (*ATM*, *CHK2*, *TP53*). Exome sequencing of 56 mantle cell lymphoma tumors identified several novel, recurrently mutated genes (POT1, RB1, SMARCA4, WHSC1) along with epigenetic modification of histones.[220] The t(11;14)(q13;q32) translocation of *CCND1* (cyclin D1) gene is a defining feature of mantle cell lymphoma that deregulates cyclin D1, resulting in cell proliferation from overexpression of this key regulator of the cell cycle and G1 phase progression. Pathological MCL characteristics include CD5+, CD20+, and overexpression of the CDK kinase regulator, cyclin D1 (*CCND1* gene).

Marginal Zone Lymphoma

Marginal zone lymphoma is an indolent (low-grade B cell) neoplasm accounting for ~5–10% of NHL subtypes (1.8/100,000) with a median age at presentation

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TABLE 60.8. Statistically significant self-reported risk factors for mantle cell lymphoma (MCL) reported in the InterLymph non-Hodgkin Subtypes Study from a pooled analysis of 13 case-control studies containing 557 MCL cases and 13,766 controls. Statistically nonsignificant, but positive or inverse odds ratios for overall MCL risks are not included in the table. Although the odds ratio for MCL in participants ever-living on a farm was positive and statistically significant, the OR for ever-working on a farm demonstrated no significant association (OR = 1.1, 95% CI: 0.85–1.61, $P = 0.334$). (Data adapted from Smedby et al.).[219]

Risk Factor	MCL in Cases/Controls	Adjusted Odds Ratio	95% CI	*P* Value
	Positive			
Leukemia family history (≥1 1° relative)	19/240	2.01	1.10–3.68	0.012
Hematological malignancy family history (≥1 1° relative)	39/492	1.99	1.39–2.84	<0.001
NHL family history (≥1 1° relative)	16/205	1.95	1.14–3.34	0.024
Electrical/electronic worker	30/460	1.63	1.09–2.44	0.023
Ever-living on farm	102/2,617	1.40	1.03–1.90	0.031
	Inverse			
Hay fever	80/2,727	0.63	0.48–0.82	<0.001
Any atopic disorder	174/5,336	0.74	0.61–0.89	0.001

Abbreviation: CI = Confidence Interval.

of 67 years.[221] Three distinct, heterogeneous types of marginal zone lymphoma (MZL) exist with incidence, distribution, susceptibilities, and risk factors varying between these types, potentially reflecting different marginal-zone B cell origins.[222] Approximately 70% of MZL (EMZL) tumors are extranodal affecting the stomach and less often other gastrointestinal tract sites, eye/adnexa, lung, skin, salivary glands, and thyroid, that typically do not contain organized lymphoid tissues. Extranodal marginal zone lymphomas (also known as mucosa-associated lymphoid tissue, MALT) tumors are small B cell lymphomas strongly associated with inflammatory diseases (i.e., infections, autoimmune diseases) at specific anatomic sites including *Helicobacter pylori* in the stomach, *Campylobacter jejuni* in the small intestine,[223] *Borrelia burgdorferi* (Lyme disease spirochete) in the skin, *Chlamydia psittaci* in the ocular adnexa, Hashimoto thyroiditis in the thyroid, and Sjögren's syndrome in the salivary gland.[172,224] Less common MZL types include splenic MZL (SMZL) and nodal MZL (NMZL); the former is associated with hepatitis C viral (HCV) infections and endemic malaria accounting for ~20% of MZL tumors. NMZL is the least common marginal zone lymphoma type (~10%); this indolent, small B cell, primarily adult lymphoma is also associated with HCV.[225,226] HCV infections occur in ~1/2 of gastric MALT MZL and ~1/3–1/2 of other MALT MZL cases with viremia present in >90% of cases.[227]

For MALT-type EMZL neoplasms, characteristic immunotypes include common B cell-associated antigens CD19+, CD20+, CD22+, CD43±, CD79a+, Bcl-2+, IgM+/CD3−, CD5−, CD10−, CD23−, cyclin DA−, and IgD−, with κ or λ immunoglobulin light-chain restriction. The most common chromosomal translocation is t(11;18)(q21;q21)/*API2-MALT1*; this translocation results in the activation of the NF-κB signaling pathway (regulation of immune response to infection) and inhibition of apoptosis.[228]

The InterLymph Non-Hodgkin Lymphoma Subtypes pooled data from 12 case-control studies identifying 633 extranodal marginal zone lymphomas, 157 nodal marginal zone lymphomas, and 140 splenic marginal zone lymphomas.[229] Based on self-reported questionnaires and/or interviews and adjusted unconditional logistic regression models to estimate overall MZL risks, the study demonstrated statistically significant positive associations with B cell activating autoimmune diseases (e.g., Sjögren syndrome, systemic lupus erythematosus), hepatitis C virus seropositivity, and family history of any hematological or non-Hodgkin lymphoma. Inverse, statistically significant overall MZL risks were associated with the occupation of teaching, recreational sun exposure, and alcohol consumption, as displayed in Table 60.9.

Examination of MZL subtypes demonstrated significant heterogeneity between subtype risks and specific risk factors. The estimated EMZL odds ratio was positive and statistically significant ($P_{trend} \leq 0.05$) for alcohol consumption and family history of any hematological malignancy (but not NHL) or leukemia; NMZL and wine consumption or metalworking; and SMZL and ever-using hair dye, teaching, or general/unspecified

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TABLE 60.9. Statistically significant, self-reported risk factors for marginal zone lymphoma (MZL) based on pooled data from 12 case-control studies in the InterLymph Consortium. Statistically nonsignificant, but positive or inverse odds ratios for overall MZL risks are not included in the table. The study also included estimated risks for the three MZL subtypes; however, the limited number of exposures and many comparisons limit the power and precision of these estimates. (Data adapted from Bracci et al.).[229]

Risk Factor	MZL in Cases/Controls	Adjusted Odds Ratio	95% Confidence Interval	*P* Value
	Positive			
Autoimmune disease (B cell activation)	45/125	5.75	3.97–8.33	<0.001
HCV seropositive	14/95	3.4	1.65–5.60	0.001
Hematological malignancy family history (≥1 1° relative)	78/492	1.73	1.33–2.25	<0.001
NHL family history (≥1 1° relative)	31/205	1.65	1.10–2.46	0.020
	Inverse			
Teacher	36/800	0.50	0.35–0.70	<0.001
Recreation sun exposure (highest quartile)	155/2,983	0.68	0.54–0.85	0.001
Alcohol consumption (highest quartile)	48/888	0.61	0.42–0.88	0.017

laborer.[229] Multiple comparisons and small sample sizes limit the power and precision of these estimates. Some of the statistically significant associations (e.g., hair dye/SMZL, wine consumption/NMZL) are novel findings.

The clinical presentation of MZL tumors depends on the location of the affected tissues. For gastric EMZL, the most common clinical features are epigastric pain, dyspepsia, anemia, melena, hematemesis, and weight loss, whereas B symptoms are rare. The most common extraintestinal site is the lung, with the presentation including cough, dyspnea, and/or chest pain. Ocular adnexal MALT-type MZL occurs more often in women than men, particularly in rural areas with prolonged contact with animals and *Chlamydia psittaci*-associated chronic conjunctivitis.[230] Cutaneous MALT-type MZL is an indolent disease typically confined to the skin with frequent relapses, rarely associated with a life-threatening condition (10-year survival rate ~90%); occasionally spontaneous resolution occurs.[228] The prognosis for indolent MZL tumors is generally good, with overall 5-year survival >90% and 10-year survivals 75–80%.[226,231]

T Cell NHL

Peripheral T Cell Lymphoma

Peripheral T cell lymphomas are markedly heterogeneous category of >20 types of mature T and natural killer (NK) cells based on clinical, molecular, and pathological criteria, resulting in the complex classifications displayed in Table 60.1.[232] These classifications separate T cell NHL tumors arising from NK cells and γ, δ T cell lymphocytes in the nonantigenic *innate* immune system critical for the rapid response to new antigens from the antigen-specific *adaptive* immune system (CD4+/CD8+ α,β T cells, regulatory T cell lymphocytes). The latter system responds slowly, but *specifically*, to new antigens. Recurrent translocations are less common in peripheral lymphomas than in other T cell lymphomas. Although mutations of *TP53* genes are relatively uncommon in peripheral T cell lymphomas, whole-genome sequencing indicates recurrent rearrangements/fusion genes of *TP53*-related genes inhibit p53 protein function.[233]

Mycosis Fungoides and Sézary Syndrome

Mycosis fungoides and Sézary syndrome are rare cutaneous T cell lymphomas, characterized by malignant monoclonal T cell proliferations and an age-adjusted incidence of 0.55/100,00 and 0.01/100,000, respectively.[234] The incidence increases with age. The highest rates occur in blacks and non-Hispanic whites, whereas mycosis fungoides rates are ~50% lower in Hispanics and Asian/Pacific Islanders. The mycosis fungoides/Sézary syndrome (MF/SS) incidence is ~1½-fold higher in men than in women.[235] The few epidemiological studies on these cutaneous T cell neoplasms have identified elderly age, male gender, and African American descent as established risk factors. The InterLymph Non-Hodgkin Lymphoma Subtypes used logistic regression models to examine self-reported risk factors in pooled multivariate analysis of 324 mycosis fungoides/Sézary syndrome cases in 14 case-control studies.[236] Table 60.10 displays the

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TABLE 60.10. Statistically significant, self-reported risk factors for mycosis fungoides/Sézary syndrome (MF/SS) based on pooled data from 14 case-control studies in the InterLymph Consortium using multivariate models adjusted for age, sex, race, and all the variables in this table.[236] Statistically nonsignificant, but positive or inverse odds ratios for overall MF/SS risks are not included in the table. The limited number of exposures and many comparisons limit the power and precision of these estimates. (Adapted from Leiter et al.).[238]

Risk Factor	MF/SS in Cases and Controls	Adjusted Odds Ratio	95% Confidence Interval
Multiple myeloma family history (yes vs. no)	6/36	8.49	3.31–21.80
General carpenter	5/71	4.07	1.54–10.75
Painter	11/194	3.71	1.94–7.07
Eczema history	55/1,460	2.38	1.73–3.29
Crop/vegetable farmworker	9/226	2.37	1.14–4.92
Woodworker	12/324	2.20	1.18–4.08
Body Mass Index ($30–50\ kg/m^2$ vs. $18.5–22.5\ kg/m^2$)	55/2,175	1.57	1.03–2.40
Cigarette smoking (≥40 years vs. nonsmokers)	40/1,742	1.55	1.04–2.31

statistically significant positive associations in this study. The imprecise estimates reflect small sample sizes of these rare cutaneous tumors. This study did not detect significant associations between MF/SS and alcohol consumption, cigarette smoking other than the highest quartile of smoking duration (≥40 years), atopic diseases other than eczema, sun exposure, or specific infectious agents associated with other lymphomas. Patches/plaques of small–medium-sized T cells with cerebriform nuclei infiltrating the epidermis and dermis characterize mycosis fungoides. The prognosis is usually good when diagnosed early with a median survival exceeding 25 years.[237] Sézary syndrome is a more aggressive tumor characterized by lymphadenopathy, erythroderma, and peripheral neoplastic T cell lymphocytes with a median survival of ~5 years.

EXPOSURE

Most non-Hodgkin lymphoma (NHL) cases are sporadic with no identifiable risk factor. NHL is a heterogeneous, multifactorial disease that contains >60 subtypes with further complexity related to age, anatomic site, and gene expression. This diversity, imprecise estimates, and limited statistical power from small sample sizes limit definitive conclusions regarding true associations and exposure-response relationships to a few established risk factors, particularly with NHL subtypes. Established risk factors for NHL include male sex, older age, family history of hematopoietic tumors, certain autoimmune diseases, infections, medications, and immune deficiencies (e.g., HIV/AIDS, organ transplantation, ataxia-telangiectasia); other lifestyle and environmental factors remain controversial. Birth order is not clearly associated with overall NHL risks.[239] Potential lifestyle factors positively associated with NHL include smoking and obesity, whereas an inverse relationship is potentially associated with sun exposure and alcohol consumption. Non-Hodgkin lymphoma subtypes probably have different risk factors, including variations between B and T cell NHL subtype risk factors; however, small sample sizes limit the power to detect associated risk factors. The InterLymph Non-Hodgkin Lymphoma Subtypes Projects used pooled data from 17,471 NHL cases and 23,096 controls in 14 population-based and 6 hospital-based case-control studies to examine the associations between 11 NHL subtypes and self-reported lifestyle, occupation, personal disease history, and family history of hematological cancers.[240] The study population was predominately male (58%) and non-Hispanic whites (93%). Overall, a family history of any hematological cancer in a first-degree relative was the strongest risk factor. B cell-activating autoimmune diseases (i.e., Sjögren syndrome, systemic lupus erythematosus) were strongly associated with certain B cell lymphomas (e.g., marginal zone lymphoma, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, diffuse large B cell lymphoma), whereas T cell-activating autoimmune diseases (e.g., celiac disease, systemic sclerosis/scleroderma) were closely associated with T cell lymphomas (e.g., peripheral T cell lymphoma, mycosis fungoides/Sézary syndrome). Some lifestyle factors (e.g., smoking) and a few occupations (e.g., painting) were modestly associated with some NHL subtypes; however, no consistent patterns emerged.

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Occupation

Self-reported occupation is probably not a strong risk factor for NHL in most populations. Although some observational studies suggest possible lymphomagenic exposures for a few occupations, none of these observational studies clearly establish a causal relationship between any occupational exposure and NHL risks.[241,242] Occupations potentially associated with NHL in exploratory observational studies include farming/agricultural work, meat handling/processing, shoe/leather manufacturing, wood processing, painters, printing/paper industry, painters, medical professionals, hairdressers, and teachers with suspected carcinogens including pesticides, herbicides, benzene and other solvents, paints, varnishes, organic/inorganic dust, aromatic amines, and hair dyes. However, the study results are too inconsistent and heterogeneous to determine definite causal associations because of the lack of accurate exposure data, potential bias, and difficulty controlling confounding. Some occupations identified in these studies are not associated with recognized carcinogenic agents.

Job Classifications

The European Prospective Investigation into Cancer and Nutrition (EPIC) study examined lymphoma risks in 52 occupations associated with suspected carcinogens using self-administered standardized questionnaires to estimate NHL risks.[18] The EPIC study identified 866 incident NHL cases in 348,555 participants followed by a mean of 9 ± 2 years. Using Cox proportional hazard models and multivariate analysis, the adjusted hazard ratios comparing NHL risks in participants ever-working in an occupation with controls (never-working in the occupation) were statistically significant for butchers (aHR = 1.53, 95% CI: 1.05–2.48, n_{NHL} = 28 cases/587 controls) and car repair workers (aHR = 1.50, 95% CI: 1.01–2.00, n_{NHL} = 17 cases/646 controls). The study detected no statistically significant association in the other 50 occupations, including farming, painting, chemical/rubber industry, printing, and the leather industry.

A large US population-based case-control study identified 1,189 histologically confirmed malignant NHL cases (participation rate: 76%) in the National Cancer Institute SEER Program and 982 randomly selected controls (52% participation rate). Using unconditional logistic regression analyses and adjusting for age, sex, ethnicity, and study center, the study examined NHL risks comparing ever- and never-workers in 86 occupations and 97 industries based on computer-assisted personal interviews. Table 60.11 lists the statistically significant positive and inverse NHL risks from this study. Several occupations had at least six NHL cases and none in controls, including supervisors in food/beverage preparation/service, carpet/soft tile installers, drilling/boring machine operators/tenders, religious workers, clergy, and physical therapists. The latter three occupations, purchasing agents/buyers and information clerks, are white-collar occupations, typically without recognized exposure to carcinogens. The study reported no statistically significant increases in follicular or diffuse large B cell lymphomas in any occupation. The occupations involving editors, reporters, public relations specialists, and announcers were associated with 6 NHL cases compared with 18 cases in controls.

A New Zealand study on NHL risks in *a priori* high-risk occupations enrolled 291 incident NHL cases (69% participation rate) and 471 population-based controls (48% participation rate),[243] using unconditional regression analysis to estimate odds ratios for ever- versus never-employment in 235 occupational and 228 industries based on self-reported occupations coded according to the New Zealand Standard Classification of Occupations and the Australian/New Zealand Standard Industrial Classification. The high-risk occupations included bakers/grain millers, drivers, farmers, firefighters, funeral directors, hairdressers, health professionals, leather/shoe workers, machinery mechanics/operators, meat workers, metal workers/welders, painters, printers, teaching professionals, textile workers, and woodworkers. The most robust findings based on semi-Bayes adjustment for multiple comparisons were elevated NHL risk for horticulture/fruit growing (OR = 2.28, 95% CI: 1.37–3.79, n_{NHL} = 43 cases/32 controls), metal product manufacturing (OR = 1.92, 95% CI: 1.12–3.28, n_{NHL} = 33 cases/30 controls), and cleaners (OR = 1.80, 95% CI: 1.11–2.94, n_{NHL} = 34 cases/32 controls). The study did not detect increased NHL risks ($P < 0.05$) for hairdressers, health professionals, leather/shoe workers, painters, printers, teaching professionals, textile workers, or woodworkers.

A pooled analysis of 10,046 NHL cases and 12,025 controls from 10 case-control studies participating in the InterLymph Consortium examined NHL risks in 25 *a priori* occupational groups previously associated with NHL, similar to the groups covered in the New Zealand case-control study listed above.[244] Data on occupations were classified according to the International Standard Classification of Occupations based on self-reported occupations. Using unconditional logistic regression to estimate odds ratios, none of the 24 broad *a priori* occupational groups had a statistically

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TABLE 60.11. Statistically significant adjusted odds ratios in US National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program case-control study of non-Hodgkin lymphoma (NHL) risks in 86 occupations and 97 industries based on self-reported occupations (ever- *versus* never-workers). Large confidence intervals indicate imprecise odds ratio estimates. (Adapted from Schenk et al.).[241]

Description	NHL Cases	NHL Controls	Odds Ratio	95% CI
	Positive			
Launderers/ironers	12	3	3.89	1.06–14.20
Hand packers/packagers	22	7	3.00	1.26–7.14
Purchasing agents/buyers, NEC	17	5	2.79	1.02–7.66
Miscellaneous manual occupation	30	10	2.73	1.31–5.68
Information clerks	44	21	1.83	1.07–3.14
Service occupations except private household/protective[a]	195	138	1.42	1.07–1.86
	Inverse			
Transportation occupations	5	16	0.24	0.09–0.66
Editors, reporters, public relations specialists, announcers	6	18	0.27	0.11–0.69
Financial record processing	47	57	0.65	0.43–0.98
Retail sales occupations	69	82	0.65	0.45–0.92
Post-secondary teachers	51	64	0.66	0.45–0.97
Administrative support including clerks	452	430	0.80	0.66–0.96

Abbreviation: CI = Confidence Interval; NEC = not elsewhere classified.
[a] Women only.

significant positive association ($P < 0.05$) with NHL for ever-employment; however, some specific titles in 10 groups have statistically significant associations, as displayed in Table 60.12.

Subgroup analysis of InterLymph Consortium pooled data suggests different risk factors for the three most common NHL subtypes and some specific occupations and/or job titles; however, some of these associations were not supported by exposure-response relationships. Statistically significant increased risks for diffuse large B cell lymphoma (DLBCL) were associated with ever-employment as field crop farmworkers (OR = 1.48, 95% CI: 1.01–2.17, $P_{\text{heterogeneity}} = 0.61$) and women's hairdressers (OR = 1.60, 95% CI: 1.13–2.27, $P_{\text{heterogeneity}} = 0.03$); however, DLBCL was not associated with long-term employment (>10 years) in either job title. Follicular lymphoma was associated with long-term employment as a medical doctor (OR = 2.23, 95% CI: 1.17–4.26), but not ever-employment (OR = 1.29, 95% CI: 0.77–2.18); the follicular lymphoma risk was also elevated for ever-employment as a spray painter (OR = 2.67, 95% CI: 1.36–5.25). Peripheral T cell lymphoma (PTCL) was associated with ever-employment as an electrical fitter (OR = 2.02, 95% CI: 1.03–3.97), painter (OR = 1.74, 95% CI: 1.07–2.83), textile worker (OR = 1.60, 95% CI: 1.18–2.17, $P_{\text{heterogeneity}} = 0.02$), and woodworkers (OR = 1.54, 95% CI: 1.04–3.50, $P_{\text{heterogeneity}} = 0.15$). PTCL risks were also statistically significant for long-term employment in the latter two job titles with substantial heterogeneity.

Specific Industrial/Occupational Categories

Farming

The most consistent, but not causal or independent, associations with NHL are farm-related exposures and low-level education.[245] Some studies suggest farmers have a slightly increased NHL risk mostly from case-control studies often reporting statistically nonsignificant increases; the etiology of these increased risks is unclear. Multiple other potential exposures may account for these results besides pesticides, herbicides, and fungicides including study design, infectious agents, fuels, oils, dust, solvents, and lifestyle factors. In a meta-analysis of 18 case-control, 10 mortality/morbidity, and 8 cohort studies (1982–1997) examining the association of farming with NHL risks, 4 studies reported

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TABLE 60.12. Statistically significant ($P < 0.05$) job titles associated with non-Hodgkin lymphoma (NHL) based on pooled analysis of data from the InterLymph Consortium with adjusted odds ratios and 95% confidence limits including comparisons of ever-employed and >10-year employment with never-employed controls.[244] None of the 24 broad, *a priori* occupations including any farming were associated with increased NHL risks, with the exception of female textile workers employed >10 years (OR = 1.23, 95% CI: 1.02–1.50). Some elevated NHL risks in specific job titles are not supported by exposure-response measures (duration of employment), including electrical wiremen, field crop and general farmworkers, women's hairdressers, and general carpenters. Odds ratios and confidence intervals are statistically significant at the $P < 0.05$ level. (Data adapted from t'Mannetje et al.).[29]

Job Title	NHL Cases	NHL Controls	Ever-Employed OR (95% CI)	>10 Years Employment OR (95% CI)
Electrical fitters/related workers	525	589	1.10 (0.98–1.25)	1.24 (1.02–1.50)
Electrical/electronic equipment assemblers	121	145	1.07 (0.84–1.37)	1.86 (1.10–3.12)
Electrical wiremen	177	178	1.24 (1.00–1.54)[c]	1.15 (0.83–1.59)
Farmers – crops	582	573	1.10 (0.97–1.24)	1.18 (1.00–1.41)[c]
Farmers – field crop workers	149	118	1.38 (1.07–1.77)	1.29 (0.91–1.82)
Farmers – general workers	437	404	1.19 (1.03–1.37)	1.19 (0.95–1.50)
Hairdressers, women's[a]	115	113	1.43 (1.08–1.89)	1.39 (0.88–2.19)
Medical doctors[b]	77	82	1.16 (0.84–1.60)	1.87 (1.23–2.85)
Painters – spray	49	29	2.07 (1.30–3.29)[b]	—
Textile workers[a]	728 (total)	773 (total)	1.08 (0.95–1.24)	1.23 (1.02–1.50)
Textile workers – milliners/hatmakers	27	14	2.46 (1.28–4.74)	—
Woodworkers – general carpenters[b]	98	74	1.40 (1.03–1.92)	1.18 (0.71–1.99)

Abbreviation: CI = Confidence Interval.
[a] Women only. [b] Men only. [c] Marginally statistically significant at $P < 0.05$ level.

no association, 11 studies reported an inverse association, and 21 reported a positive association, with 8 being statistically significant.[246] Overall, the positive association was relatively modest with a meta-relative risk for all studies of 1.10 (95% CI: 1.03–1.19) based mainly on case-control studies (metaRR = 1.19, 95% CI: 1.06–1.33). The metaRR for cohort studies was consistent with the null (metaRR = 0.95, 95% CI: 0.85–1.07, n_{NHL} = 8 studies). The metaRR for female farmers demonstrated no association with farming (metaRR = 0.93, 95% CI: 0.82–1.06, n_{NHL} = 11 studies/552 cases). Boffetta and de Vocht added 11 studies, with 4 studies reporting an association and 7 studies reporting no association, to the meta-analysis by Khuder et al.; the metaRR was 1.11 (95% CI: 1.05–1.17) with strong heterogeneity.[242] Subgroup analysis indicated the increased NHL risk involved animal breeding (metaRR = 1.31, 95% CI: 1.08–1.60) rather than crop farming (metaRR = 0.96, 95% CI: 0.83–1.09).

In a New Zealand case-control study, a statistically significant increase ($P < 0.05$) in NHL risks was associated with ever-employment in the agricultural industry for women (OR = 1.72, 95% CI: 1.01–2.92, n_{NHL} = 38 cases/43 controls), but not men (OR = 0.88, 95% CI: 0.53–1.46, n_{NHL} = 37 cases/58 controls).[243] Job titles associated with a statistically significant elevated NHL risk included field crop/vegetable growers (OR = 2.74, 95% CI: 1.04–7.25, n_{NHL} = 12 cases/7 controls) and nursery growers (OR = 3.16, 95% CI: 1.03–9.69, n_{NHL} = 10 cases/5 controls); however, the study reported no clear duration-response relationships between long-term farming occupations and NHL risks. The large confidence limits reflect imprecise estimates and small sample sizes. The multicenter prospective (EPIC) cohort study reported no association between farming or farmworkers and NHL risks.[18] Analysis of pooled data from the InterLymph Consortium suggests field crop farm work was more strongly associated with diffuse large B cell lymphoma than other NHL subtypes.[244]

Meat Workers

The association of meat workers with NHL is inconsistent with no specific causal agent in meat processing identified. The multicenter prospective (EPIC) cohort study reported a statistically significant elevated NHL

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risk in butchers (OR = 1.53, 95% CI: 1.05–2.48, n_{NHL} = 17 cases/646 controls).[18] In contrast, a meta-analysis of nine observational studies of meat processing, butchers, meatpacking, and abattoir workers detected no association between the meat industry and NHL risks (metaRR = 0.99, 95% CI: 0.77–1.29) with substantial heterogeneity.[242] A New Zealand case-control study reported statistically nonsignificant elevated NHL risk in meat processors at the P = <0.05 level (OR = 1.97, 95% CI: 0.97–3.97, n_{NHL} = 22 cases/16 controls).[243] A US study of 268 follicular lymphomas and 1,659 controls reported a positive association between meat packaging/processing and follicular lymphoma (OR = 1.60, 95% CI: 0.99–2.06);[247] however, analysis of pooled data from the InterLymph Consortium detected no statistically significant elevated risks of four common NHL subtypes, including follicular lymphoma with ever- or long-term employment as a meat processor/worker.[244]

Printing Industry

Although most studies of printers and NHL risks are positive, the results are often statistically nonsignificant without demonstrating an exposure-response relationship. Employment as a printer was not associated with a statistically significant elevation of NHL risks in the US National Cancer Institute-SEER case-control (OR = 2.02, 95% CI: 0.79–5.17, n_{NHL} = 17 cases/6 controls),[241] a pooled analysis of InterLymph Consortium data (OR = 0.95, 95% CI: 0.78–1.17, n_{NHL} = 175 cases/230 controls),[244] the New Zealand case-control study (OR = 1.22, 95% CI: 0.43–3.45, n_{NHL} = 8 cases/8 controls), or the multicenter prospective (EPIC)[18] studies. In a meta-analysis of six studies on the printing industry and NHL risks, the metaRR for NHL was statistically significant based on a few cases (metaRR = 1.86, 95% CI: 1.37–2.52) with little heterogeneity or publication bias.[242] Analysis of pooled data from the InterLymph Consortium detected no statistically significant elevated risks in four common NHL subtypes associated with ever- or long-term employment as a printer.[244]

Woodworkers

The association between woodworkers and overall NHL risks is relatively modest and often statistically nonsignificant. This occupation includes a diverse range of workers ranging from sawmill operators and paper pulp workers to forestry workers and carpenters. In a meta-analysis of 11 observational studies on woodworkers, the relative risk for NHL was marginally significant (metaRR = 1.15, 95% CI: 1.00–1.31) with potential publication bias, but no significant heterogeneity.[242] In a pooled analysis of data from the InterLymph Consortium, male general carpenters had a statistically significant elevation of NHL risks (OR = 1.42, 95% CI: 1.04–1.93, n_{NHL} = 98 cases/74 controls), but not woodworkers overall (OR = 1.04, 95% CI: 0.89–1.22, n_{NHL} = 326 cases/352 controls).[244] Peripheral T cell lymphoma risks were significantly elevated in woodworkers who were ever-employed (OR = 1.54, 95% CI: 1.04–2.27) or employed for >10 years (OR = 2.04, 95% CI: 1.19–3.50), but there were no elevations of diffuse large B cell or follicular lymphoma risks. Employment as a woodworker was not associated with elevated NHL risks in the multicenter prospective (EPIC) study.[18]

Teachers

Although some studies of NHL risks in teachers are positive and statistically significant, little data suggest an exposure-response relationship or identify a specific carcinogen (e.g., viral infections). In a meta-analysis of 19 observational studies using random effects models, the metaRR for NHL in the teaching profession was 1.47 (95% CI: 1.34–1.61) with substantial heterogeneity and potential publication bias.[242] Subanalysis indicated no statistically significant difference between primary or secondary teachers, headmasters/principals, or teachers involved with arts/crafts. A New Zealand case-control study detected no statistically significant elevated NHL risks in female preschool/primary (OR = 1.69, 95% CI: 0.82–3.47, n_{NHL} = 16 cases/28 controls) or secondary school (OR = 0.48, 95% CI: 0.13–1.75, n_{NHL} = 3 cases/28 controls) education teachers.[243] The odds ratio for NHL in teachers ever-employed except in postsecondary institutions was not elevated (OR = 1.05, 95% CI: 0.70–1.58, n_{NHL} = 57 cases/45 controls) in the US National Cancer Institute-SEER case-control study.[241] Analysis of pooled data from the InterLymph Consortium detected no statistically significant elevated risks in four common NHL subtypes associated with ever- or long-term employment as preschool or higher education teachers.[244]

Ionizing Radiation

Little data support a strong, statistically significant association between occupational ionizing radiation exposures and NHL. An Australian study of 694 incident NHL cases (85% participation rate) and age/sex/region-matched controls (61% participation rate) examined occupation ionizing/nonionizing radiation exposures and overall NHL risks based on a Finnish job-exposure matrix and self-reported questionnaires/computer-assisted telephone interviews

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on jobs held ≥1 year. The Finish job-exposure matrix assigns annual mean radiation doses to 19 ionizing radiation-exposed jobs, 102 UV radiation-exposed jobs, 4 radiofrequency (RF)-exposed jobs, and 74 extremely low-frequency (ELF) radiation-exposed jobs.[248] Overall, the study did not provide support for a positive association between NHL and cumulative occupational ionizing or nonionizing ELF radiation exposures.[249] Using unexposed controls, the adjusted odds ratio for the highest tertile of ionizing radiation exposure (0.2–19.6 mSv-years) was 0.94 (95% CI: 0.57–1.53, n_{NHL} = 33 cases/35 controls, P_{trend} = 0.81) consistent with US cohort mortality studies.[250,251] The highest tertile of UV radiation exposure was statistically significant only when lagged for 5 or 10 years (OR = 1.48, 95% CI: 1.01–2.18, n_{NHL} = 122 cases/93 controls, P_{trend} = 0.04) consistent with a modest positive effect.

The multicenter European Epilymph study investigated NHL subtype risks for occupational UV radiation exposures based on standardized questionnaires on ever- and never-exposed occupationally to artificial/natural UV radiation and expert evaluation of the intensity (weighted duration) of UV exposure.[252] None of the overall measures of UV exposure reached statistically significant associations with overall NHL risks. Comparing ever- versus never-UV radiation exposures, the adjusted OR was near the null (aOR = 1.02, 95% CI: 0.81–1.29, n_{NHL} = 756 cases/1,320 controls, $P_{heterogeneity}$ = 0.13). Although significant heterogeneity existed ($P_{heterogeneity}$ = 0.02), examination of estimated exposure tertiles on weighted duration in years yielded no evidence of a dose-response relationship (P_{trend} = 0.65). Subgroup analysis suggested an inverse relationship between occupational UV exposure and diffuse large B cell lymphoma (DLBCL) risks. The DLBCL risk was statistically significant for ever- versus never-exposed (aOR = 0.72, 95% CI: 0.54–0.97, $P_{heterogeneity}$ = 0.31) and the third tertile of weighted duration of UV exposure (aOR = 0.62, 95% CI: 0.42–0.92, P_{trend} = 0.21, $P_{heterogeneity}$ = 0.06).

Nonionizing Radiation

In the Finnish population-based case-control study, the adjusted OR was 1.25 (95% CI: 0.91–1.72, n_{NHL} = 147 cases/119 controls, P_{trend} = 0.52) for the highest extremely low frequency (ELF) tertile (3.1–160.4 μT-years) consistent with mortality studies of telecommunications employees[253] and Korean War navy technician veterans.[254] The adjusted odds ratio for the highest RF radiation tertile was imprecise in a few cases (OR = 3.15, 95% CI: 0.63–15.87, n_{NHL} = 6 cases/2 controls, P_{trend} = 0.09).

An Australian study of 694 incident NHL cases and 694 age/sex/region-matched population-based controls examined occupational magnetic field exposure using self-administered postal questionnaires and a US population-based job-exposure matrix.[255] After dividing cumulative magnetic field exposures into quartiles, multivariate logistic regression models estimated the odds ratios comparing NHL risks in the highest (>9.85 μT-years) and lowest (<3.92 μT-years) exposure quartiles. The adjusted odds ratio for NHL for total magnetic field exposure (μT-years) was slight and marginally statistically significant (aOR = 1.18, 95% CI: 1.00–1.48, n_{NHL} = 189 cases/158 controls, P_{trend} = 0.006). The adjusted odds ratio was statistically significant for a 5-year log exposure (aOR = 1.24, 95% CI: 1.05–1.46, n_{NHL} = 184 cases/163 controls, P_{trend} = 0.003).

Chemicals

Agricultural/Horticultural

Pesticides represent a structurally and mechanistically diverse group of chemicals that destroy weeds (herbicides), insects (insecticides), soil/airborne pests (fumigants), and fungi (fungicides). Some epidemiological evidence suggests herbicide and/or pesticide use increases NHL risks.[256] Meta-analyses of farmers and NHL suggest male, but not female, farmers have a slightly elevated risk of developing NHL, but the specific cause (e.g., pesticides, infections) of this increased risk could not be identified.[246,257] Epidemiological data associating increased NHL risks with pesticide exposures are primarily case-control studies with less convincing evidence from cohort studies.[258] Using random effects models, a meta-analysis of 13 case-control studies during 1993–2005 reported a statistically significant meta-OR for occupational pesticide exposure and NHL risks (meta-OR = 1.35; 95% CI: = 1.2–1.5); however, heterogeneity and publication bias were substantial.[259] The modest magnitude of positive study results, inconsistent results across studies, and lack of definite exposure-response relationships limit definite conclusions regarding causality.

Existing data do not associate insect repellants with elevated NHL risks. In a Canadian population-based case-control study using postal questionnaires and structured pesticide exposure telephone interviews, DEET exposure of ≥10 hours annually was not associated with NHL risks (OR = 0.89, 95% CI: 0.71–1.10, n_{NHL} = 239 male cases/801 male controls).[260] Controls were randomly selected male residents from the same Canadian province with no cancer history. The US Agricultural Health Study cohort contained 52,394 private

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pesticide applicators (mostly farmers) enrolled while attending mandatory certification sessions for applying restricted-use pesticides as well as 32,345 spouses.[261] The adjusted hazard ratio for growing up on a farm was associated with a statistically significant elevation of overall NHL risks (HR = 1.51, 95% CI: 1.15–1.98, n_{NHL} = 364 cases) compared with not growing up on a farm (n = 69 cases). Subgroup analysis using polytomous logistic regression models did not detect statistically significant differences in the adjusted overall NHL risk between NHL subtypes ($P_{heterogeneity}$ = 0.98). A history of atopy in applicators was inversely related to overall NHL risks (HR = 0.61, 95% CI: 0.42–0.87, n_{NHL} = 42 atopic cases/6,360 nonatopic cases, P_{trend} = <0.001) based on self-reported physician-diagnosed eczema/hay fever.

Fumigants

Fumigants include methyl bromide and carbon tetrachloride; the latter is rarely used now. In the US Agricultural Health Study cohort on 52,394 private pesticide applicators (mostly farmers), the adjusted relative risk comparing ever-using versus never-using methyl bromide as a fumigant was statistically significant for diffuse large B cell lymphoma (aRR = 1.9, 95% CI: 1.1–3.3, n_{NHL} = 28 cases ever-use cases/86 cases never-use cases), but statistically nonsignificant for overall NHL risks (adjusted OR = 1.1, 95% CI: 0.9–1.5, n_{NHL} = 85 ever-use cases/425 never-use cases).[262] However, the trend for cumulative methyl bromide exposure (lifetime days) was statistically significant for overall NHL risk (P_{trend} = 0.04), but not for diffuse large B cell lymphoma (P_{trend} = 0.67).

The multicenter Cross-Canada Study of Pesticides and Health of 517 male incident NHL cases (67% participation rate) and 1,506 population-based male controls (48% participation rate) examined NHL risks associated with >10 hours of annual exposure to the major chemical classes of pesticides using postal questionnaires and telephone interviews.[263] Compared with unexposed controls, the adjusted NHL odds ratio in carbon tetrachloride-exposed men was statistically significant (adjusted OR = 2.42, 95% CI: 1.19–5.14, n_{NHL} = 13 exposed cases/18 unexposed cases). The adjusted OR for indoor malathion exposure was not statistically significant (aOR = 1.54, 95% CI: 0.74–3.22, n_{NHL} = 12 exposed cases/23 unexposed cases).

Fungicides

Major fungicide classes include phthalimides (captan, captafol), dithiocarbamates (mancozeb, thiram), mercury-containing compounds, and sulfur compounds. Most, but not all, studies report no association between fungicide exposure and statistically significant elevations in NHL risks.[258] The AGRICOH consortium pooled data from 312,270 farmers and agricultural workers from the United States, France, and Norway followed over 3.5 million person-years using the French Agriculture and Cancer, Cancer in the Norwegian Agricultural Population, and the US Agricultural Health study cohorts.[264] Dithiocarbamate (adjusted HR = 0.96, 95% CI: 0.83–1.11, n_{NHL} = 961 cases, I^2 = 0%, $P_{heterogeneity}$ = 0.96) and phthalimide (adjusted HR = 1.10, 95% CI: 0.80–1.52, n_{NHL} = 921 cases, I^2 = 57%, $P_{heterogeneity}$ = 0.10) fungicide exposures were not associated with NHL risks. Subgroup analysis did not demonstrate any statistically significant difference between NHL risk and NHL subtypes (diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, multiple myeloma/plasma cell leukemia). A Swedish study of 910 NHL cases and 1,016 age/sex-matched, national population registry controls examined NHL risks using unconditional logistic regression and self-reported exposure data (postal questionnaires, telephone interviews).[265] Fungicide exposure was not associated with significantly increased NHL risks (OR = 1.11, 95% CI: 0.56, 95% CI: 0.56–2.23, n_{NHL} = 16 cases/18 controls), with no exposure-response relationship or evidence of differences between NHL subtypes. Analysis of data from the US Agricultural Health Study did not demonstrate an association between fungicide exposure (benomyl, captan, chlorothalonil, maneb, mancozeb, metalaxyl) and total NHL cases or specific NHL subtypes.[262] Comparisons included ever- versus never-use and high/low exposure with unexposed controls.

Herbicides

Phenoxyacetic Acid Phenoxyacetic acid herbicides include 2,4-dichlorophenoxyacetic (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), methyl-chlorophenoxyacetic acid (MCPA), and methylchlorophenoxypropionic acid (MCPP). 2,4,5-T and chlorophenol herbicides, but not 2,4-D, MCPA, or MCPP, may be contaminated by dioxins and dibenzofurans during production processes. Early Swedish (RR = 4.8, 95% CI: 2.9–8.1, n_{NHL} = 41 cases/108 controls)[266] and US (OR = 2.2, 95% CI: 1.2–4.1, n_{NHL} = 24 cases/78 controls)[267] case-control studies suggest an association between phenoxy herbicides and NHL risks with statistically significant but imprecise estimates of frequency and duration of use based on self-reported telephone interviews. Later case-control studies were more inconsistent without a strong dose-response relationship; cohort studies of farmers and pesticide applicators

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TABLE 60.13. Adjusted odds ratios of non-Hodgkin lymphoma (NHL) associated with exposure to phenoxyacetic acid herbicides. Pooled data from the A Consortium of Agricultural Cohorts (AGRICOH) did not detect statistically significant inverse relationships with individual phenoxyacid herbicide exposure and null results for individual herbicides within the group. The results for overall phenoxyacid exposure ever- versus never- was inversely statistically significant. The Cross-Canadian Study of Pesticides and Health reported statistically significant odds ratios for phenoxyacid herbicides and individual phenoxyacid herbicides except MCPA. The Swedish University Hospital case-control study also reported statistically significant odds ratios for ever- versus never-phenoxyacid herbicide exposure; however, none of these results demonstrated an exposure-response relationship.

Agent	Exposure Category	Odds Ratio	95% CI	NHL Cases/Controls
	AGRICOH Consortium Cohorts[264]			
Phenoxyacids, overall	Ever vs. never	0.81[a]	0.67–0.98	1,204 cases
2,4-D	Ever vs. never	0.88	0.75–1.04	1,167 cases
MCPA	Ever vs. never	0.81	0.53–1.23	775 cases
MCPP	Ever vs. never	0.94	0.61–1.46	776 cases
	Cross-Canadian Study of Pesticides and Health[263]			
Phenoxyacids, overall	>10-hour vs. <10-hour exposure/year	1.38[b]	1.06–1.81	131/319
2,4-D	>10-hour vs. <10-hour exposure/year	1.32	1.01–1.73	111/293
MCPA	>10 hour vs. <10 hour-exposure/year	1.10	0.60–2.00	17/46
Mecoprop	>10-hour vs. <10- hour exposure/year	2.33	1.58–3.44	53/81
	Swedish University Hospital Case-Control Study[265]			
Phenoxyacids, overall	Ever vs. never	2.0[b]	1.24–3.36	47/26
	≤45 days/year vs. unexposed	2.83[b]	1.47–5.47	32/13
	≥45 days/year vs. unexposed	1.27	0.59–2.70	15/13
2,4-D and/or 2,4,5-T	Ever vs. never	1.61	0.87–2.97	33/21
	≤29 days/year vs. unexposed	2.08	0.99–4.38	21/11
	≥29 days/year vs. unexposed	1.33	0.57–3.13	12/10
MCPA	Ever vs. never	2.81	1.27–6.22	21/9
	≤32 days/year vs. unexposed	3.76	1.35–10.5	15/5
	≥32 days/year vs. unexposed	1.66	0.46–5.96	6/4

Abbreviations: CI = Confidence Interval; 2,4-D = 2,4-dichlorophenoxyacetic acid; 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid; MCPA = 4-chloro-2-methyl-phenoxyacetic acid; MCPP = methylchlorophenoxypropionic acid; mecoprop = phenoxy-2-propionic acid.
[a] Statistically significant inverse relationship. [b] Statistically significant positive relationship.

in the late 1990s and early 2000s reported equivocal results.[258] A 2015 review of cohort and case-control studies did not detect a clear relationship between phenoxyl herbicides and NHL incidence; however, the authors opined that a slight increased NHL risk could not be excluded, but the absolute risk would be small.[268] Table 60.13 displays adjusted odds ratios for overall phenoxyacid herbicides and non-Hodgkin lymphoma risks for pooled results from cohorts in the AGRICOH Consortium along with two case-control studies. In general, the results are less convincing for cohort studies than case-control studies with little evidence of exposure-response relationships.

The IARC classifies 2,4-D as a possible human carcinogen (Group 2B) based on limited evidence of carcinogenicity in experimental animals and inadequate evidence of carcinogenicity in humans.[269] As noted in Table 60.13, the results of observational studies on 2,4-D exposure and NHL are conflicting and mostly statistically nonsignificant. A meta-analysis of 11 case-control studies, 2 nested case-control studies, and 1 cohort study used random and fixed effects models. The summary risk ratio for NHL in ever- versus never-2,4-D users was statistically significant (summary RR = 1.38, 95% CI: 1.07–1.77, $I^2 = 50\%$, $n = 12$ studies, $P_{\text{heterogeneity}} = 0.024$) with moderate heterogeneity.[270] Analysis of only the highest 2,4-D exposure category from 12 studies yielded a statistically significant and higher summary RR (sRR = 1.73, 95% CI: 1.10–2.72, $I^2 = 56\%$, $P_{\text{heterogeneity}} = 0.009$) with moderate heterogeneity. The magnitude of the summary RR ranged from 0.6–13 with 3 of 12 results being statistically significant.

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The meta-analysis did not include data from the large prospective Agricultural Health Study (AHS) cohort. In this cohort, ever- versus never-2,4-D exposure was not associated with NHL (RR = 1.02, 95% CI: 0.54–1.90) after adjustment for age, drinking, family cancer history, education, smoking, and 10 other pesticide exposures with no evidence of an exposure response in cumulative exposure categories ($P_{trend} = 0.77$).[271] An updated meta-analysis of 10 studies including the AHS cohort, reported no association with ever- versus never-use of 2,4-D (sRR = 0.97, 95% CI: 0.79–1.18, $I^2 = 20.4\%$, $P_{heterogeneity} = 0.255$) using random effects models.

Chlorophenols Major chlorophenol herbicides include pentachlorophenol and trichlorophenol; dioxin and dibenzofuran with different toxicities contaminate these herbicides during the production processes. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) may contaminate dichlorophenol or trichlorophenol herbicides, whereas primary contaminants of pentachlorophenol (PCP) include tetrachlorophenol, hexachlorodibenzodioxins, dibenzofurans, and other lower chlorophenols.[272] The IARC considers pentachlorophenol a human carcinogen (Group 1) with sufficient epidemiological and mechanistic evidence of carcinogenicity along with most cohort studies of highly exposed categories demonstrating NHL risks exceeding 2.[273] The IARC classifies 2,4,6-trichlorophenol as a possible human carcinogen (Group 2B) based on inadequate evidence in humans and sufficient evidence in experimental animals.[269] Commercial and technical grades of pentachlorophenol typically contain higher chlorinated dioxins of substantially lower potency than TCDD; the TCDD concentrations in pentachlorophenol are usually not significant.

The Dow Chemical plant in Midland, Michigan, produced trichlorophenols during 1937–1980 and pentachlorophenol during 1942–1980. In fall 2004, serum samples were drawn from 12 TCP-only production workers, 26 PCP-only production workers, and 36 unexposed workers from non-chlorophenol-producing departments (referents).[274] The mean lipid-adjusted serum TCDD concentration in TCP-only production workers was 36.8 ppt (IQR = 7.6–42.6 ppt) compared with 7.8 ppt (IQR = 3.2–8.7 ppt) in PCP-only workers and 6.0 ppt (IQR = 2.4–7.8) in controls.[275]

An early Swedish nested case-control study suggests an association between chlorophenol herbicide exposures and NHL risks, with imprecise exposure-response estimates using unexposed, age/sex/residence-matched controls. The NHL odds ratio was statistically significant for any chlorophenol exposure (OR = 4.8, 95% CI: 2.7–8.8, $n_{NHL} = 35$ cases/35 controls) and any pentachlorophenol exposure ≥1 week continuously or ≥1 month total (OR = 8.8, 95% CI: 3.4–24, $n_{NHL} = 19$ cases/25 controls) based on self-reported questionnaires or telephone review.[266,276] Most subsequent observational studies on herbicide applicators and chlorophenol production workers have not confirmed the Swedish results for chlorophenol compounds containing <4 chlorine molecules.[25,258,277]

A Washington state study of 576 NHL cases and 694 randomly selected controls without cancer did not detect an elevated NHL risk comparing any past occupational chlorophenol herbicide exposure with unexposed controls (OR = 0.99, 95% CI: 0.8–1.2).[278] In a nested case-control study within a multinational cohort of 21,863 workers exposed to phenoxy herbicides, chlorophenols, and/or dioxins, the SMR for non-Hodgkin lymphoma was modestly elevated, but statistically nonsignificant (SMR = 1.39, 95% CI: 0.89–2.06, $n_{NHL} = 24$ deaths) based on self-reported exposure and review by an industrial hygienist.[25] In the same cohort comparing 32 NHL cases ever-exposed to a chlorophenol herbicide and 158 never-exposure controls, the magnitude of the NHL OR was modestly elevated, but statistically nonsignificant (OR = 1.26, 95% CI: 0.52–3.08, $n_{NHL} = 9$ cases/38 controls).[279] The odds ratio for NHL comparing any pentachlorophenol exposure with unexposed controls was elevated, but imprecise and statistically nonsignificant (OR = 2.5, 95% CI: 0.45–17.00, $n_{NHL} = 3$ cases/9 controls). Overall, the IARC considered the associations observed in several studies in different countries consistent with observations of pentachlorophenol exposure-response trends and the elevated risks in the highest pentachlorophenol exposure category from two occupational cohort studies with high-quality exposure assessments. Together, the IARC concluded the evidence was sufficient for a causal association between NHL and pentachlorophenol exposure. Table 60.14 lists the results of the nested case-control and cohort studies used by the IARC to support their conclusion that pentachlorophenol is a human carcinogen.

Triazine Triazine herbicides include atrazine, cyanazine, metribuzin, and simazine. Findings of observational studies on triazine herbicide exposure and NHL risks are inconsistent. In a US study of 200 randomly selected NHL cases and 3 age-matched male controls/case, the NHL odds ratio comparing ever- versus never-triazine herbicide exposure was statistically significant (OR = 2.5, 95% CI: 1.2–5.4, $n_{NHL} = 14$ cases/43 controls).[267] A Midwestern US study of 622 NHL cases in Caucasian men and 1,245 age-matched controls detected no significant association between

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TABLE 60.14. Nest case-control and cohort studies of pentachlorophenol (PCP) production workers exposed only to PCP used by the International Agency for Research on Cancer (IARC) to support their conclusion pentachlorophenol is a human carcinogen with reasonable confidence that chance, bias, and confounding do not account for the positive odds ratios (OR).

Cohort	Study Population	NHL Deaths	Odds Ratio	95% Confidence Interval (CI)	Highest Exposure/OR (95% CI)/Trend)
European/New Zealand nested case-control (Kogevinas M, 1995)[279]	32 exposed/158 unexposed controls	3	2.75	0.45–17.00	4.19 (0.59–29.59)
Canadian cohort. (Demers P, 2006)[280]	27,464 men employed >1 year	92	0.99	0.95–1.05	>5 years/1.71 (0.91–3.24)/P_{trend} = 0.03)
US Dow Chemical (Collins JJ, 2009)[26]	773 men with PCP only exposure from cohort	7	2.8	1.1–5.7[a]	—
US NIOSH cohort. (Ruder A, 2011)[281]	2,122 with PCP only subcohort	9	1.41	0.64–2.67	—

[a] Statistically significant, positive relationship.

self-reported ever-handling atrazine and NHL using unexposed controls as referents (aOR = 1.1, 95% CI: 0.8–1.6, n_{NHL} = 59 cases/108 controls).[282] Logistic models adjusted for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures. Analysis of data from the Agricultural Health prospective cohort study reported no statistically significant exposure-response relationship between NHL risks and quartiles of atrazine use for cumulative lifetime days (P_{trend} = 0.35) or intensity-weighted lifetime days (P_{trend} = 0.14).[283] Pooled analysis of three cohorts in the AGRICOH Consortium demonstrated no association between overall NHL risks and ever-exposure to triazine herbicides (HR = 0.87, 95% CI: 0.74–1.02, n_{NHL} = 1,165 cases), atrazine (HR = 0.97, 95% CI: 0.79–1.18, n_{NHL} = 546 cases), or simazine (HR = 0.92, 95% CI: 0.77–1.09, n_{NHL} = 303 cases).[264] In an Italian multicenter study of 1,145 NHL cases (80% participation rate) and 1,232 age/sex-matched, randomly selected, population-based controls (74% participation rate), the odds ratio for ever- versus never-using atrazine was 0.8 (95% CI: 0.3–2.0, n_{NHL} = 11 male cases) based on self-reported job-specific questionnaires and person interviews.[284]

Glyphosate Glyphosate (*N*-(phosphonomethyl)glycine; Roundup®, Monsanto, St. Louis, Mo.) is a broad-spectrum herbicide that began commercial sales in the United States in 1974; currently, this herbicide is among the most applied herbicides in the world. Although some epidemiological studies suggest an association between glyphosate exposure and non-Hodgkin lymphoma risks, the overall findings are inconsistent with modest exposure-response relationships. Hence, the existence of a causal relationship between NHL and glyphosate exposures remains controversial.[285,286] In 2014, the German Federal Institute for Risk Assessment examined glyphosate toxicity for the European Union; they concluded glyphosate lacked carcinogenic/mutagenic properties as well as evidence of validated or significant increased glyphosate-related carcinogenic risks; however, later in 2019, Germany decided to phase out glyphosate use by 2023 to protect biodiversity as well as the suspected carcinogenicity.[287] The International Agency for Research on Cancer (IARC) reclassified glyphosate as a probable human carcinogen (Group 2A) based on sufficient evidence in experimental animals (rodent hemangiosarcomas and pancreatic islet-cell adenomas, mechanistic evidence of genotoxicity/oxidative stress) and limited epidemiological evidence. In 2016, the Food and Agriculture Organization Panel of Experts on Pesticide Residues in Food/Environment and World Health Organization Core Assessment Group on Pesticide Residues concluded glyphosate was unlikely to pose a carcinogenic risk to humans from dietary exposures, affirming the current Acceptable Daily Intake (ADI) levels.[288] Similarly, other international organizations have classified glyphosate as unlikely to pose a carcinogenic risk to humans, including the Australian Pesticides and Veterinary Medicines Authority, the European Chemical Agency, the European Food Safety Authority, Health Canada, and the New Zealand Environmental Protection Agency. During the review process for glyphosate's classification as a Group E carcinogen (evidence of non-carcinogenicity for humans) in 2019, the US EPA issued an interim decision that the "EPA continues to find that there are no risks to public health when glyphosate is used in accordance with its current label and that glyphosate is not a carcinogen."[289]

A US prospective cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina (Agricultural Health Study) followed a median of

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TABLE 60.15. Summary of five case-control and one cohort study comparing glyphosate exposure and overall non-Hodgkin lymphoma (NHL) risks. A meta-analytic summary estimate of the data from these studies reported a statistically significant meta-risk ratio with modest heterogeneity (metaOR = 1.5, 95% CI: 1.1–2.0, I^2 = 32.7%). Little data support a strong exposure-response relationship between overall non-Hodgkin lymphoma risks and glyphosate exposure, particularly when excluding other pesticide exposure in multivariate analysis. Limited results from case-control studies on associations between non-Hodgkin lymphoma subtypes and glyphosate exposures are also inconsistent. (Adapted from Schinasi and Leon).[291]

Study	Exposure Category	Odds Ratio	95% Confidence Interval	NHL Cases/Controls
Pooled Cross-Canada population-based (McDuffie H, 2001)[263]	≥10 hours/year	1.26	0.87–1.80	51/133
Pooled Swedish population-based case-control (Hardell L, 2002)[292]	≥8 hours/year	3.04 1.85[a]	1.08–8.52 0.55–6.20[a]	8/8
Pooled, US Midwest population-based case-control (De Roos A, 2003)[293]	Ever-used	2.1	1.1–4.0[b]	36/61
US Midwest Agricultural Health Study cohort (De Roos A, 2005)[290]	Ever-used	1.1	0.7–1.9	71 cases
Swedish population-based case-control (Eriksson M, 2008)[265]	Ever-used	2.02	1.10–3.71[c]	29/18
French hospital-based population-based (Orsi L, 2009)[153]	Ever-used	1.0	0.5–2.2	12/24

[a] Multivariate instead of univariate analysis. [b] Multivariate analysis with hierarchical regression yielded a statistically nonsignificant odds ratio (OR = 1.6, 95% CI: 0.9–2.8). [c] The estimated odds ratio became statistically nonsignificant after multivariate analysis for multiple pesticide exposures (OR = 1.51, 95% CI: 0.77–2.94).

6.7 years.[290] The study reported no association with overall NHL risk (aRR = 1.1, 95% CI: 0.7–1.9, n_{NHL} = 92 cases) for ever-glyphosate-exposed pesticide applicators (mostly farmers) followed through 2001 using non-glyphosate-exposed applicators as referents. Comparison of adjusted NHL risks also demonstrated no significant association with the highest and lowest tertiles of glyphosate exposure measures for cumulative exposure days (aRR = 0.9, 95% CI: 0.5–1.6, n_{NHL} = 17 cases, P_{trend} = 0.73) or intensity-weighted exposure days (aRR = 0.8, 95% CI: 0.5–1.4, n_{NHL} = 22 cases, P_{trend} = 0.99). Adjustments included age, demographics, lifestyle factors, and other pesticides. Subgroup analysis of NHL subtypes revealed no differences in glyphosate-related NHL subtype risk with the possible exception of multiple myeloma. In an updated report on this study, ~82.8% of the 54,251 pesticide applicators reported ever-using glyphosate accounting for 79.3% (5,779) of the incident cases. Unlagged analysis of the data yielded no statistically significant association with any cancer site including overall NHL or NHL subtypes as well as the absence of an exposure-response relationship for cumulative glyphosate use. Comparing the highest quartile of lifetime intensity-weighted lifetime days of glyphosate use with unexposed referents, the unlagged rate ratio was 0.87 (95% CI: 0.64–1.20, n_{NHL} = 111 cases, P_{trend} = 0.95). 5-Year and 20-year lagged exposure and unlagged results were similar.

Table 60.15 summarizes the results of 5 case-control and 1 cohort studies on the association between glyphosate exposure and NHL risks. Most of these studies use ever- versus never-use of glyphosate as the exposure category with little data on exposure-response relationships. Evidence for an association between NHL and glyphosate exposure is weaker for cohort studies than case-control studies. A pooled analysis of three large agricultural worker cohorts from the United States, France, and Norway identified 2,430 NHL cases in 316,270 farmers during 3,574,815 person-years of observation.[264] Comparing ever- versus never-use of glyphosate with Cox regression models and random effects meta-analysis, the results for glyphosate were null with moderate heterogeneity (adjusted metaHR = 0.95, 95% CI: 0.77–1.18, n_{NHL} = 1,131 cases, I^2 = 57%, $P_{heterogeneity}$ = 0.10). The estimated HR for diffuse large B cell lymphoma (DLBCL) was marginally elevated (metaHR = 1.36, 95% CI: 1.00–1.85, 221 cases, I^2 = 0%, $P_{heterogeneity}$ = 0.48) with no heterogeneity. Glyphosate exposure was not associated with follicular lymphoma, multiple myeloma, or chronic lymphocytic leukemia/small lymphocytic lymphoma. A pooled analysis of US and Canadian studies (North American Pooled Project) identified 1,690 NHL cases and 5,131 controls including proxy respondents. Comparing ever- versus never-use of glyphosate, the overall age/sex/residence/family cancer history/proxy respondent/personal protective equipment use-adjusted OR

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for NHL was statistically significant (aOR = 1.43, 95% CI: 1.11–1.83 n_{NHL} = 113 cases/244 controls); however, the OR became statistically nonsignificant after adjustment for 2,4-D, dicamba, and malathion use (aOR = 1.13, 0.84–1.51). Overall NHL risks did not increase with increasing duration of glyphosate use. Similarly, the fully adjusted odds ratios for diffuse large B cell (45 cases), follicular (28 cases), and small lymphocytic (15 cases) lymphomas were statistically nonsignificant. Cumulative measures of glyphosate exposure (e.g., >2 days/year) were also inconsistent (e.g., $P_{DLBCL\ trend}$ = 0.2).

Insecticides

Although based on only two cases, a retrospective mortality study of pesticide applicators demonstrated a SMR for non-Hodgkin lymphoma of 7.11 (95% CI: 1.78–28.42) in the group with ≥3 years of employment.[294] Exposure to specific pesticides was not well defined. Population-based case-control studies of Midwestern farmers demonstrated an ~50% increase in NHL risks for farmers using organophosphate insecticides based on proxy interviews; however, the odds ratio decreased significantly to 1.2 when direct interviews were administered.[295]

Carbamates Individual carbamate insecticides include aldicarb, carbaryl (Sevin®), carbofuran, methomyl, and pirimicarb. Table 60.16 lists results from selected case-control and cohort studies on carbaryl exposures and overall NHL risks. For carbamate insecticides, analysis of pooled data from 1,254 NHL cases in the ACRIOCOH consortium demonstrates no association between ever- and never-use of carbamate insecticides and adjusted NHL risks (aHR = 0.94, 95% CI: 0.81–1.08).[264] Additionally, the study did not detect statistically significant increases in common NHL subtype risks. Similarly, analysis of data from the US Agricultural Health Study cohort did not detect statistically significant hazard ratios for common NHL subtype risks and ever-exposure to aldicarb, carbofuran, or carbaryl.[262] Although the magnitude of some cumulative measures of carbamate exposures was positive,[296] the data did not support exposure-response relationships between overall NHL risks and cumulative carbamate exposure tertiles measured in lifetime exposure days (P_{trend} = 0.23–0.87) or intensity-weighted exposure days (P_{trend} = 0.22–0.94) using never-exposed participants as referents.

Organochlorine Organochlorine insecticides are a highly diverse group of chemicals with complex metabolic pathways that may include carcinogenic metabolites. Important organochlorine compounds include aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, lindane, methoxychlor, and toxaphene. Most organochlorine insecticides were banned or severely restricted because of their extremely long half-lives (years–decades). The association between NHL lymphoma risks and overall organochlorine insecticide exposure is inconsistent with cohort studies typically reporting null or statistically nonsignificant results, whereas increased NHL risks are associated with some case-control studies. In a Cross-Canada multicenter study of 517 incident NHL cases and 1,506 population-based male controls (<10 hours/year exposure), the NHL odds ratio in the exposed group (≥10 hours/year exposure) was 1.27 (95% CI: 0.87–1.69, 50 cases/134 controls).[263] In contrast to the Cross-Canada multicenter study, analysis of pooled data from the AGRICOH Consortium cohort demonstrated an inverse association between self-reported ever- versus never-use use of organochlorine insecticides and overall NHL risks (aHR = 0.86, 95% CI: 0.74–0.99,

TABLE 60.16. Selected case-control and cohort studies on ever- versus never-use of carbaryl and overall non-Hodgkin lymphoma risks. Adjustments for multiple pesticide exposures tended to attenuate the odds ratios. Most observational studies on carbamate exposures and NHL risks report statistically nonsignificant results.

Study	Exposure Category	Odds Ratio	95% Confidence Interval	NHL Cases/Controls
Pooled Cross-Canada population-based case-control (McDuffie H, 2009)[263]	≥10 hours/year	2.11[a]	1.21–3.69	25/34
Italian multicenter case-control (Miligi L, 2003)[284]	Ever-used	2.2	0.9–6.4	17 male exposures
Pooled European/American AGRICOH cohort consortium (Leon M, 2019)[264]	Ever-used	0.95	0.83–1.10	651 cases
North American Pooled Project, case-control (Koutros S, 2019)[297]	Ever-used	1.17[a]	0.84–1.64	1,690/5,131
US Midwest Agricultural Health Study cohort (Alavanja M, 2014)[262]	Ever-used	1.0	0.8–1.2	275 ever/225 never-exposed in cohort

[a] Adjusted for multiple pesticide use.

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n_{NHL} = 1,254 cases).[264] The results were fully adjusted for multiple pesticide exposures. Subgroup analysis detected no significant differences in risks between common NHL subtypes and organochlorine insecticide exposures.

The IARC classifies lindane as a human carcinogen (Group 1) based on consistent evidence of an association of lindane exposure with NHL, strong mechanistic evidence (oxidative stress, immunosuppression), and sufficient evidence of carcinogenicity in experimental animals.[298] In the Cross-Canada multicenter study, the association of ever- versus never-use of lindane was associated with a statistically significant increased overall NHL risk (aHR = 2.06, 95% CI: 1.01–4.22, n_{NHL} = 15 cases/23 controls) after full adjustment for multiple pesticide exposures.[263] Analysis of pooled data from the AGRICOH Consortium yielded an inverse, statistically nonsignificant adjusted HR comparing ever- versus never-use of lindane (aHR = 0.87, 95% CI: 0.78–1.01, n_{NHL} = 953 cases).[264] Subgroup analysis detected no significant differences between common NHL subtypes and organochlorine insecticide exposures.

DDT is classified as an IARC probable human carcinogen (Group 2A) based on strong mechanistic data (modulation of receptor-mediated effects, immunosuppression, enhanced oxidative stress), sufficient evidence of carcinogenicity in experimental animals for the metabolite, DDE (but not DDT), and limited human evidence including positive studies on NHL.[299] The Cross-Canada population-based case-control study reported a statistically significant association between self-reported ever- and never-use of DDT after full adjustment, including multiple pesticide exposures (aHR = 1.73, 95% CI: 1.08–2.76, n_{NHL} = 32 cases/59 controls).[263] In contrast, analysis of pooled data from the AGRICOH Consortium cohort demonstrated no association (aHR = 0.92, 95% CI: 0.81–1.04, n_{NHL} = 976 cases), with no evidence for different NHL subtype risks.[264] In a Swedish study of 910 living, incident NHL cases (no proxies) and 1,016 age/sex-matched, national population registry controls using unconditional logistic regression and self-reported DDT exposure data (postal questionnaires, telephone interview), the odds ratio was 1.17 (95% CI: 0.62–2.22, n_{NHL} = 20 cases/19 controls) for total DDT use of ≤37 days and 1.76 (95% CI: 0.97–3.20, n_{NHL} = 30 cases/18 controls) for >37 days total DDT exposure.[265] Comparison of DDT-exposed and unexposed NHL subtypes suggests elevated risks for follicular lymphomas (aOR = 2.14, 95% CI: 1.05–4.40, n_{NHL} = 165 cases) and T cell lymphomas (aOR = 2.88, 95% CI: 1.05–7.95, n_{NHL} = 53 cases).

The IARC classifies dieldrin, and aldrin metabolized to dieldrin, as probably carcinogenic to humans (Group 2A) based on sufficient evidence of carcinogenicity in experimental animals, moderate mechanistic evidence for dieldrin (genotoxicity, oxidative stress, immunosuppression, cell proliferation), and limited evidence of carcinogenicity in humans.[300] Mechanistic evidence for carcinogenicity of aldrin is modest, and human evidence for carcinogenicity is inadequate. Conversion of aldrin to dieldrin occurs in the environment, living organisms, and presumably in humans; however, little evidence is available to determine the extent of absorption or metabolism. In the Cross-Canada Study of 517 NHL cases and 1,506 controls, the elevation of NHL risks for aldrin exposure after full adjustment including multiple pesticide exposures was statistically significant, but imprecise (aOR = 4.19, 95% CI: 1.48–11.96, n_{NHL} = 10 cases/6 controls) based on a few cases.[263] The prospective Agricultural Health Study cohort detected no significant elevated overall NHL risks for ever- versus never-use of aldrin (aRR = 0.9, 95% CI: 0.7–1.1, n_{NHL} = 116 cases/364 controls), dieldrin (aRR = 0.9, 95% CI: 0.6–1.2, n_{NHL} = 35 cases/442 controls), chlordane (aRR = 1.0, 95% CI: 0.8–1.3, n_{NHL} = 136 cases/344 controls), heptachlor (aRR = 1.0, 95% CI: 0.7–1.2, n_{NHL} = 90 cases/384 controls), or toxaphene (aRR = 1.0, 95% CI: 0.7–1.2, n_{NHL} = 79 cases/397 controls).[262] Subgroup analysis demonstrated no statistically significant elevations of common NHL subtype risks. Comparison of cumulative exposure tertiles of lifetime days and intensity-weighted days with unexposed controls detected no exposure-response trends for aldrin (P_{trend} = 0.58 and 0.74, respectively), dieldrin (P_{trend} = 0.47 and 0.84, respectively), chlordane (P_{trend} = 0.43 and 0.16, respectively), heptachlor (P_{trend} = 0.82 and 0.88, respectively), or toxaphene (P_{trend} = 0.50 and 0.38, respectively).

Organophosphorus Organophosphate (OP) insecticides are a diverse group of several hundred organophosphorus compounds with a wide range of toxicities. Major OP insecticides include chlorpyrifos, coumaphos, diazinon, dimethoate, famphur, fonofos, malathion, methidathion, ethyl/methyl parathion, phorate, terbufos, and trichlorfon. Data on NHL risks associated with specific organophosphate insecticides are limited, with inconsistent evidence of a positive association with diazinon, malathion, and terbufos. Analysis of pooled data from three US National Cancer Institute Midwestern studies on male farmers involving 748 NHL cases and 2,236 nonfarming unexposed controls reported statistically significant increased NHL risks in

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farmers ever-exposed to organophosphate insecticides (OR = 1.5, 95% CI: 1.2–1.9, n_{NHL} = 158 cases/279 controls) based on self-reported exposure (26% proxy interviews).[301] The age/residence-adjusted odds ratio was weaker and statistically nonsignificant when only direct interviews were evaluated (OR = 1.2, 95% CI: 0.9–1.6, n_{NHL} = 117 cases/224 controls) compared with only proxy interviews (OR = 3.0, 95% CI: 1.8–5.0, n_{NHL} = 41 cases/55 controls). The odds ratio was positive, but statistically nonsignificant for the highest exposure duration category (≥20 years) using direct (OR = 1.3, 95% CI: 0.8–2.1, n_{cases} = 32 exposed/49 controls) and proxy (OR = 2.4, 95% CI: 0.8–6.7, n_{cases} = 7 exposed/10 controls). Analysis of four NHL subtype risks indicated no clear association with modestly positive, but statistically nonsignificant odds ratios using direct interviews for organophosphate exposure estimates.

A meta-analysis of five cohort, four nested case-control, and one case-control studies using random effects models reported a modestly elevated, statistically significant odds ratio for ever- versus never-exposure to diazinon, malathion, or terbufos (summary OR = 1.22, 95% CI: 1.04–1.43, I^2 = 41.2%, $P_{heterogeneity}$ = 0.032) with moderate heterogeneity.[302] Subgroup analysis indicated significant differences between study designs and overall NHL risks for ever-exposure to the three organophosphate insecticides using unexposed participants as referents. The summary OR for overall NHL risks was null for cohorts (OR = 1.00, 95% CI: 0.85–1.17, $P_{significance}$ = 0.967, I^2 = 1.2%, $P_{heterogenicity}$ = 0.424), whereas NHL risks were statistically significant for case-control (OR = 1.44, 95% CI: 1.14–1.81, $P_{significance}$ = 0.002, I^2 = 29.9%, $P_{heterogenicity}$ = 0.189) and nested case-control (OR = 1.57, 95% CI: = 1.04–2.39, $P_{significance}$ = 0.033, I^2 = 0%, $P_{heterogenicity}$ = 0.571) studies. Adjusting for multiple pesticide use (OR = 1.04, 95% CI: 0.88–1.23, n = 12 studies, $P_{significance}$ = 0.620, I^2 = 14.3%, $P_{heterogenicity}$ = 0.304) and family cancer history (OR = 1.14, 95% CI: 0.89–1.47, n = 9 studies, $P_{significance}$ = 0.300, I^2 = 32.7%, $P_{heterogenicity}$ = 0.157) reduced the overall NHL risks to small, statistically nonsignificant values. Ever-exposure to these organophosphate insecticides was not associated with elevated NHL risks in women (OR = 0.85, 95% CI: 0.56–1.29, n = 3 studies, $P_{significance}$ = 0.441, I^2 = 35.4%, $P_{heterogenicity}$ = 0.213). The authors noted the difficulty in quantifying insecticide exposures based on self-reported questionnaires on ever-exposure rather than internal doses.

Observational studies have not clearly associated increased NHL risks with other organophosphate insecticides, including chlorpyrifos, dichlorvos, dimethoate, parathion, terbufos, or trichlorfon.[303] Although analysis of pooled data from three population-based case-control studies in the US Midwest suggests an elevated NHL risk comparing the ever- and never-use of chlorpyrifos based on a few cases (aOR = 3.2, 95% CI: 1.1–9.2, n_{NHL} = 7 cases/8 controls), other studies have not confirmed these findings.[262,264] In the Agricultural Health Study, the standardized mortality ratio for applicators ever- versus never-using chlorpyrifos was 0.64 (95% CI: 0.29–1.39, n_{NHL} = 10 cases/27 controls).[304] A meta-analysis of three observational studies on ever-exposure to terbufos using unexposed participants as referents and random effects models reported no association with overall NHL risks (summary OR = 1.07, 95% CI: 0.85–1.36, $P_{significance}$ = 0.550, I^2 = 0.0%, $P_{heterogeneity}$ = 0.800).[302]

DIAZINON Although several observational studies associate diazinon with NHL, the overall results are mixed and controversial, as displayed in Table 60.17. The IARC classifies diazinon as a probable human carcinogen (Group 2A) based on strong mechanistic evidence

TABLE 60.17. Odds ratios of selected case-control and cohort studies on non-Hodgkin lymphoma (NHL) risks associated with diazinon exposures.

Study	Exposure Category	Odds Ratio	95% Confidence Interval	NHL Cases/Controls
Pooled Cross-Canada population-based case-control (McDuffie H, 2001)[263]	≥10 hours/year	1.69[a]	1.26–2.27	90/167
Pooled US Midwestern, National Cancer Institute population-based case-control (Waddell B, 2001)[301]	Ever-used	1.7	1.2–2.5	60/93
Pooled European/American AGRICOH cohort consortium (Leon M, 2019)[264]	Ever-used	0.90	0.75–1.09	1,417 exposed cases
North American Pooled Project, case-control (Koutros S, 2019)[297]	Ever-used	1.25[a]	0.90–1.74	85/137
US Midwest Agricultural Health Study cohort (Alavanja M, 2014)[262]	Ever-used	1.0	0.8–1.3	144 ever-/342 never-exposed in cohort

[a] Adjusted for multiple pesticide use.

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(genotoxic, but not mutagenic, oxidative stress) and limited human evidence of carcinogenicity, with some positive studies associating diazinon exposure and NHL.[305] In a meta-analysis of seven epidemiology studies using random effects models, the summary odds ratio for NHL comparing ever- and never-use of diazinon was statistically significant with no heterogeneity (OR = 1.39, 95% CI: 1.11–1.73, $P_{\text{significance}} = 0.003$, $I^2 = 0\%$, $P_{\text{heterogenicity}} = 0.668$).[302]

MALATHION The IARC classifies malathion as probably carcinogenic to humans (Group 2A) based on strong mechanistic evidence (genotoxic, but not mutagenic, cell inflammation/proliferation, oxidative stress), sufficient evidence in experimental animals, and limited evidence of carcinogenicity in humans. Although some case-control studies report positive associations between ever- versus never-use of malathion, most of these studies demonstrate no statistically significant differences in NHL risks between exposed and unexposed groups, particularly after adjusting for multiple pesticide exposures and the use of proxy interviews, as displayed in Table 60.18. In a meta-analysis of seven observational studies on ever-exposure to malathion using unexposed participants as referents and random effects models, the odds ratio was statistically nonsignificant with high heterogeneity (summary OR = 1.17, 95% CI: 0.82–1.67, $P_{\text{significance}} = 0.390$, $I^2 = 73.2\%$, $P_{\text{heterogeneity}} = 0.001$).[302]

The odds ratios for common NHL subtypes in ever-users of malathion were not statistically significant in the AGRICOH Consortium Study[264] or the Agricultural Health Study.[262] The latter study suggested an elevated risk for diffuse large B cell lymphoma (aOR = 1.61, 95% CI: 1.16–2.22), but not follicular or small lymphocytic lymphomas. Other cohort studies have not confirmed increased risks for diffuse large B cell lymphoma or other NHL subtypes.[262,264]

Little data support an exposure-response relationship between malathion exposure and NHL risks. North American Pooled Project data suggest an elevated NHL risk for malathion exposures ≥6 years (OR = 1.57, 95% CI: 1.18–210, $P_{\text{trend}} < 0.01$) after adjustment for multiple pesticide exposures. Other observational studies have not confirmed increased NHL risks with cumulative exposure measures. In the Agricultural Health Study,[262] cumulative measures comparing NHL risks in the highest malathion exposure tertile with referents demonstrated no association of NHL risks with total malathion exposure days ($P_{\text{trend}} = 0.63$) or intensity-weighted exposure days ($P_{\text{trend}} = 0.46$).

PYRETHROIDS Pyrethroids are a diverse group of synthetic esters derived from naturally occurring pyrethrins in the Dalmatian pyrethrum plant (*Chrysanthemum cinerariifolium* (Trevir.) Vis.). Major pyrethroid compounds include deltamethrin, esfenvalerate, and permethrin. Little epidemiological data support a positive relationship between pyrethroid/pyrethrin exposures and NHL risks. In the pooled analysis of the ARICOH Consortium, the hazard ratio for ever- versus never-use of pyrethroid insecticides and overall NHL risks was 1.04 (95% CI: 0.90–1.19, $I^2 = 2\%$, $P_{\text{heterogeneity}} = 0.36$); no common NHL subtype was associated with the three pyrethroids, except deltamethrin and chronic lymphocytic leukemia/small lymphocytic lymphoma (HR = 1.48, 95% CI: 1.06–2.07, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.35$).[264] The Agricultural Health Study reported no association between permethrin and overall NHL risks (RR = 1.1, 95% CI: 0.8–1.3, $n_{\text{NHL}} = 112$ cases/363 controls).[262] The hazard ratio for

TABLE 60.18. Odds ratios of selected case-control and cohort studies on non-Hodgkin lymphoma (NHL) risks associated with malathion exposures.

Study	Exposure Category	NHL Odds Ratio	95% Confidence Interval	NHL Cases/Controls
Pooled Cross-Canada population-based case-control (McDuffie H, 2001)[263]	≥10 hours/year	1.77[a]	1.28–2.46	72/127
Pooled US Midwestern, National Cancer Institute population-based case-control (Waddell B, 2001)[301]	Ever-used	1.6	1.2–2.2	91/147
Pooled European/American AGRICOH cohort consortium (Leon M, 2019)[264]	Ever-used	0.98	0.82–1.16	1,208 exposed cases
North American Pooled Project, case-control (Koutros S, 2019)[297]	Ever-used	1.43[a]	1.14–1.81	172/192
US Midwest Agricultural Health Study cohort (Alavanja M, 2014)[262]	Ever-used	0.9	0.8–1.1	332 ever-/163 never-exposed in cohort

[a] Adjusted for multiple pesticide use.

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ever- versus never-use of permethrin and multiple myeloma (but not chronic lymphocytic leukemia/small lymphocytic lymphoma) was statistically significant (HR = 2.2, 95% CI: 1.4–3.5). The study reported no exposure-response relationship between permethrin and NHL risks; cumulative tertiles of permethrin exposure were not associated with total exposure days (P_{trend} = 0.54) or intensity-weighted exposure days (P_{trend} = 0.99). In a Swedish study of 910 NHL cases (78% participation rate) and age/sex-matched, population-based controls, the association between permethrin and overall NHL risks was modestly positive, but statistically nonsignificant (OR = 1.23, 95% CI: 0.48–3.14, n_{NHL} = 9 cases/9 controls).[265]

Solvents

Benzene

Although some rodent models develop malignant lymphomas after prolonged, high-dose benzene exposures,[306] intraspecies differences limit extrapolation to humans. Epidemiological studies report inconsistent and generally modest associations between organic solvents and NHL risks including no definitive exposure-response relationship. An IARC review classified benzene as a human carcinogen with a positive association between benzene exposure and non-Hodgkin lymphoma; however, only a small minority of the Working Group considered benzene a cause of non-Hodgkin lymphoma.[307] Most,[308] but not all,[309] mortality studies and meta-analyses report no association between benzene exposure and overall NHL risks. A meta-analysis of 308,000 petroleum workers (6.6 million person-years), with observations periods 1937–1996, detected 506 NHL deaths versus 561.68 expected. The standardized mortality ratio (SMR) was 0.90 (95% CI: 0.82–0.98).[310] In a systematic review of 11 population-based case-control, 3 nested occupation-based case-control, and 7 occupational benzene cohort studies, 2 of the 21 study groups reported statistically significant elevated NHL risks; these 2 studies involved multiple chemical exposures.[311] Overall, the summary odds ratio for NHL in these 21 groups was 1.04 (95% CI: 0.94–1.14, n_{NHL} = 390 deaths expected/404 deaths observed). Exclusion of the two studies involving multiple chemical exposures yielded a summary OR of 0.96 (95% CI: 0.86–1.06, n_{NHL} = 373.2 deaths expected/359 deaths observed).

In a meta-analysis of 16 case-control (16 incidence/0 mortality) and 6 cohort studies (1984–2007, 2 incidence/4 mortality) on benzene exposure and NHL risks using random effects models, the summary NHL relative risk was 1.23 (95% CI: 1.02–1.48, $P_{heterogeneity}$ = 0.36, I^2 = 8%).[312] Restricting the meta-analysis to 13 studies the authors considered "high exposure" without assigning a specific quantitative measure, the summary NHL RR increased to 1.49 (95% CI: 1.09–2.04, $P_{heterogeneity}$ = 0.25, I^2 = 20%). A meta-analysis of 16 case-control, 6 cohort, and 2 other designs (cancer registrations, death certificates) through fall, 2009 examined NHL risks comparing ever-benzene-exposed and never-benzene-exposed workers, primarily NHL incidence.[313] Of the 24 studies, 22 reported no association; the pooled risk estimate using a random effects model was 1.11 (95% CI: 0.94–1.30, $P_{heterogeneity}$ = 0.001, I^2 = 72.6%) with substantial heterogeneity. Restricting the analysis to six studies using historical benzene measurements, the authors reported little consistent evidence of increasing NHL risks with higher cumulative or intense (duration, peak, mean) benzene exposures. A meta-analysis of 14 case-control studies reporting benzene as an independent analytic variable and 8 cohort or nested case-control studies reporting benzene as a quantitative exposure metric through spring 2009 examined summary relative risk estimates (SRRE) and evaluated exposure-response relationships.[314] The SRRE for all studies was 1.08 (95% CI: 0.93–1.24, $P_{heterogeneity}$ = 0.360). Subgroup analysis did not support an independent association between benzene exposure and NHL, with most estimates statistically nonsignificant. Evaluation of 4 cohort and 1 case-control studies reporting data on cumulative benzene exposures >60 ppm-years yielded a SRRE of 1.08 (95% CI: 0.36–3.24, $P_{heterogeneity}$ = 0.135).

A 15-year, retrospective cohort study examined hematological neoplasm incidence and benzene exposure in 74,828 benzene-exposed Chinese workers and 35,805 nonexposed controls in the same or other Chinese factories employed from 1972–1987 in coatings, rubber, chemical, shoe, or other Chinese industries.[315] Estimation of benzene exposure was based on evaluations by local industrial hygienists and occupational health personnel using job titles, historical benzene measurements, and production information. For all benzene-exposed workers, the mean time-weighted average benzene exposure lagged 1.5 years was 22.5 ppm, with a mean duration of 9.3 years and cumulative exposure of ~698,000 person-years. The relative risk of non-Hodgkin lymphomas in all benzene-exposed workers was positive, but statistically nonsignificant and imprecise (RR = 3.0, 95% CI: 0.9–10.5, n = 16 cases). NHL cases were associated with distant benzene exposure prior to 1972 (15/16, P = 0.005). Dose-response data were difficult to interpret because of small numbers and unstable confidence intervals. Extension of follow-up to 28 years yielded an increased, statistically significant age/sex-adjusted NHL relative risk with a

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wider confidence interval (RR = 3.9, 95% CI: 1.5–13.2, n = 30 exposed cases/4 unexposed cases).[309]

Trichloroethylene

The IARC classifies trichloroethylene as a human carcinogen based primarily on increased renal cancer risks following occupational trichloroethylene (TCE) exposure. Although the IARC suggests a modestly positive association of NHL with trichloroethylene exposure may exist,[316] inconsistent study results, variable exposure measurements, lack of exposure-response relationships/statistically significant risks, and difficulty evaluating numerous NHL subtypes limit definite conclusions on causation. A meta-analysis of 12 cohort and 12 case-control studies involving occupational TCE-exposed workers reported a statistically significant summary relative NHL risk of 1.21 (95% CI: 1.06, I^2 = 35.91, $P_{\text{heterogeneity}}$ = 0.04) with substantial heterogeneity.[16] For cohort studies, the summary RR was 1.52 (95% CI: 1.29–1.79, I^2 = 7.09%, $P_{\text{heterogeneity}}$ = 0.63), whereas the summary RR for case-control studies was not statistically significant (mRR = 1.14, 95% CI: 0.93–1.40, I^2 =10.51%, $P_{\text{heterogeneity}}$ = 0.23). In a Canadian study of 215 men with NHL and 2,341 population and cancer controls, the adjusted OR for NHL in workers with any TCE exposure was not statistically significant (adjusted OR = 1.3, 95% CI: 0.5–3.4, n_{NHL} = 7 cases).[317]

A pooled analysis of four international studies including 2,348 lymphoma cases and 2,462 controls reported an increased risk of some NHL subtypes (e.g., follicular lymphoma/CLL) associated with retrospective assessment of occupational TCE exposure.[318] Overall, NHL risk did not increase by probability, duration, or frequency of TCE exposure; however, restricting analysis to high-probability TCE exposures yielded a modestly positive odds ratio (adjusted OR = 1.4, 95% CI: 0.9–2.1, n_{NHL} = 50 cases/38 controls) but statistically nonsignificant result. Analysis of TCE exposure intensity and NHL risks in a meta-analysis did not reveal any positive pattern consistent with other studies.[16] TCE exposure estimates in a US study of 1,189 NHL cases (76% participation) and 982 unexposed controls (52% participation) suggest a marginally elevated NHL risk in the highest tertile of cumulative exposure (OR = 2.3, 95% CI: 1.0–5.0, n_{NHL} = 24 cases); however, neither overall exposure duration nor intensity was positively associated with NHL.[319] In a German case-control study of 710 lymphoma cases and matched controls, the odds ratio for NHL was marginally elevated in TCE-exposed workers with >35 ppm-years TCE exposure (adjusted OR = 2.1, 95% CI: 1.0–4.8, n_{NHL} = 21 cases/9 controls); however, the trend for cumulative TCE tertiles was not statistically significant (P_{trend} = 0.14).[320] A Nordic cohort study did not detect a positive exposure-response relationship between TCE and NHL; for the high cumulative TCE exposure group, the hazard ratio was 0.95 (95% CI: 0.84–1.06, n_{NHL} = 353 cases) compared with unexposed referents.[321]

Other Solvents

Observational evidence of increased NHL risks following solvent exposures other than benzene remains limited and relatively small. In a hospital-based French study of 244 male NHL cases and 456 age/residence-matched male controls (solvent-unexposed patients in rheumatology or orthopedic wards) using unconditional logistic regression, the overall NHL risk for any lifetime solvent exposure including benzene was marginally significant statistically (OR = 1.4, 95% CI: 1.0–2.0, n_{NHL} = 140 cases/233 controls, P = 0.06) based on self-reported questionnaires and expert reviews.[322] Expert-estimated benzene exposures were usually low (e.g., 81% of 12 definite cases of <1 ppm). The NHL odds ratio was statistically marginally significant for estimated daily job frequency >35% and lifetime exposure duration >15 years, but not for lifetime high-intensity duration or high-average intensity. Subgroup analysis of petroleum, aromatics, halogenated, and oxygenated solvents for overall and intensity with NHL risks yielded a statistically marginally significant OR only for lifetime exposure duration of >15 years to petroleum solvents. The multicenter European population-based case-control Epilymph study reported slightly increased, marginally statistically significant B cell NHL odds ratios for ever-exposed to solvents (OR = 1.1, 95% CI: 1.0–1.3, n_{NHL} = 808 cases/1,009 controls, P_{trend} = 0.00019) as well as for BTX (benzene, toluene, xylene), styrene, and other solvents.[323] Elevation of follicular lymphoma risks was statistically significant for BTX, styrene, and ever-exposed to other solvents. Cumulative exposures were significantly associated with slightly increased risks for B cell NHL (P_{trend} = 0.02) and follicular lymphomas (P_{trend} = 0.02). The US multicenter, population-based National Cancer Institute-SEER study of NHL risks and occupational exposure to chlorinated solvents reported marginally statistically significant elevation of NHL risks (OR = 1.9, 95% CI: 1.00–3.6, n_{NHL} = 34 cases/16 controls, P_{trend} = 0.04) for cumulative carbon tetrachloride exposure (>520 hours) based on computer-assisted personal interviews and expert reviews of 38 job-exposure and task-exposure matrices.[324] The reported NHL risks for other chlorinated solvents (chloroform, methylene chloride, tetrachloroethylene, 1,1,1 trichloroethane) were null.

In a US study of 376 incident female NHL cases and 463 unexposed, population-based female controls

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(56% participation rate), a history of any work or home paint organic solvent exposure was not associated with statistically significant increased, adjusted NHL risks (OR = 1.29, 95% CI: 0.82–2.03) based on telephone interviews (20.5% proxy interviews).[325] None of the nine solvent exposure categories including benzene (aOR = 1.52, 95% CI: 0.41–5.70, n_{NHL} = 7 cases/5 controls) had statistically significant elevations of NHL risks. Exposure duration (P_{trend} = 0.611) and cumulative (P_{trend} = 0.596) solvent exposures were also not associated with statistically significant elevations of NHL risks. A California study of 1,591 NHL cases (72% participation rate) and 2,515 age/sex/residence-matched, population-based controls (78% participation rate) reported no association between NHL and occupational solvent exposures.[326] Using unconditional logistic regression to estimate relative risks and personal interviews (no proxy interviews), the NHL relative risks for ever-solvent exposure were 0.95 (95% CI: 0.80–1.1, n_{NHL} = 73 cases/75 controls) and 0.95 (95% CI: 0.78–1.2, n_{NHL} = 20 cases/20 controls) for medium-high solvent exposures compared with unexposed controls. Subgroup analysis for NHL subtypes demonstrated no significant differences in relative risks for solvent exposures. Investigation of NHL risks for benzene and formaldehyde exposures also yielded null results.

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

TCDD is a persistent contaminant of numerous chemical reactions involving chlorine compounds classified by the International Agency for Research on Cancer (IARC) as human carcinogens (Group 1) based on limited epidemiological evidence and upgraded by a strong mechanism of action in experimental animals.[327] Although the IARC considers TCDD a complete carcinogen capable of causing cancer in all tissue sites based on mechanistic evidence, the IARC classified epidemiological evidence for increased NHL risks after TCDD exposure as limited based on observational studies of military (e.g., Agent Orange use in Vietnam), industrial, and accidental (e.g., Seveso, Italy) exposures. Industrial cohort studies suggest a positive association between NHL mortality and TCDD exposure; however, inconsistent results across other TCDD exposure groups and the lack of clear dose-response relationships limit the classification of any TCDD association as causal.[24]

Agent Orange and Other Vietnam Herbicides

The US Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (IOM Committee) evaluated available medical data on Agent Orange and other herbicide use in Vietnam, as well as background evidence on the association of herbicides and NHL. The IOM Committee determined the medical evidence was sufficient to conclude a positive statistical association existed between herbicide use and increased NHL risks in Vietnam veterans, with reasonable confidence that the association was not related to chance, bias, or confounding.[328] According to the mandate for the IOM Committee, their findings were based on a statistical rather than a strict causal association.

The prospective Air Force Health Study cohort enrolled 1,261 Operation Ranch Hand male veterans involved in aerial Agent Orange and other herbicide spraying in South Vietnam from 1962–1971 with periodic physical examinations and questionnaires from 1982–2002. Controls were 19,101 unexposed male US Air Force veterans assigned to air cargo missions in Southeast Asia during the same time. The median serum TCDD concentrations were 12.4 ppt (range, 0.0–617.7 ppt) for Ranch Hand veterans and 4.2 ppt (range, 0.0–52.8 ppt) for unexposed US Air Force veterans.[329] As of the end of 1999, no death of a TCDD-exposed Ranch Hand veteran was attributed to non-Hodgkin lymphoma.[330] The morbidity portion of the Air Force Health Study enrolled 1,197 Ranch Hand veterans and 1,855 matched controls followed through 2002. Two Ranch Hand veterans developed NHL; their estimated TCDD concentrations at the end of their Vietnam tour were ≤10 and >118.5 ppt.[331] The comparison group had six NHL cases; however, the study size was insufficient to exclude small differences between exposure groups.

The Army Chemical Corps study examined 894 veterans of the US Army Chemical Corps involved with handling, mixing, application, and storage of herbicides during the Vietnam War. Mean lipid-corrected serum TCDD concentrations were much lower than for US Army Chemical Corps members or Ranch Hand veterans ranging from 4.3 ppt (range, 0.8–85.8 ppt) in Army Chemical Corps veterans spraying herbicides in Vietnam to 2.1 ppt (range, 0.4–12.5 ppt) in unexposed veterans stationed outside Vietnam. None of the US Army Chemical Corps veterans stationed in Vietnam developed NHL. The Selected Cancers Study enrolled 1,157 incident NHL cases and 1,776 randomly selected controls using self-reported exposure information from telephone interviews.[332] Compared with Vietnam-era veterans serving outside Vietnam, NHL risk for veterans serving in Vietnam was marginally increased statistically (OR = 1.52, 95% CI: 1.00–2.32, n_{NHL} = 96 cases); however, higher NHL risks appeared in veterans (navy, marine corps, noncombat support units) with much less Agent Orange exposure. NHL risks were not increased

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(OR = 0.89, 95% CI: 0.50–1.58, n_{NHL} = 19 cases) in veterans serving in the area and time period of heaviest spraying (III Corps). No serum TCDD concentrations were available to validate self-reported Agent Orange exposures. Although these studies suggest an association between Vietnam military service and the NHL, the association with Agent Orange is much weaker. Overall, these studies demonstrated no consistent, statistically significant associations or dose-response relationships between Agent Orange or other herbicide exposures and increased NHL risks; however, some of these studies had significant limitations (small sample sizes, inadequate documentation of exposure).

Occupational Cohorts

Considerably higher serum TCDD concentrations occur in TCDD-contaminated herbicide production workers and 2,4,5-T herbicide applicators than in the general population. TCDD-contaminated herbicides primarily involve 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), pentachlorophenol, and trichlorophenol. Some mortality studies of these workers suggest elevated NHL risks; most, but not all, of these studies report statistically nonsignificant increased SMRs. A pooled analysis of 36 cohorts, including 21,863 participants from 12 countries exposed to chlorophenols, phenoxy herbicides, and dioxins, examined NHL mortality using reconstructions of TCDD exposures from company exposure questionnaires, job records, and serum/adipose dioxin concentrations.[25] An estimated 13,831 were classified as TCDD-exposed, whereas 7,553 were considered unexposed. NHL mortality for TCDD-exposed workers was modestly elevated, but statistically nonsignificant (SMR = 1.39, 95% CI: 0.89–2.06, n_{NHL} = 24 deaths) compared with 1.00 (95% CI: 0.46–1.90) for unexposed workers using national data. The SMR for workers with ≥20 years of TCDD exposure was also statistically nonsignificant (SMR = 1.21, 95% CI: 0.15–4.38, n_{NHL} = 2 deaths), with imprecise estimates from the small sample size.

In a US retrospective cohort mortality study of 2,192 Michigan chlorophenol production workers employed from 1930s–1980s, 12% of the trichlorophenol (TCP) and 20% of the pentachlorophenol (PCP) workers developed chloracne.[28] Trichlorophenol production ceased in 1979, whereas pentachlorophenol production ended in 1980. The SMR for NHL in TCP workers was 1.08 (95% CI: 0.52–1.99, n_{NHL} = 10 deaths) with no evidence of a dose-response relationship between SMR tertiles and TCDD concentrations (P_{trend} = 0.630). In a retrospective US mortality study of 2,122 pentachlorophenol (PCP) production workers using US standardized mortality rates, the increased SMR for NHL was statistically significant (SMR = 1.77, 95% CI: 1.03–2.84, n_{NHL} = 17 deaths).[281] Subcohort analysis demonstrated a statistically significant elevated SMR for NHL in 720 workers exposed to TCP *and* PCP (SMR = 2.50, 95% CI: 1.08–4.93, n_{NHL} = 8 deaths), whereas the SMR was not statistically significant for 1,402 PCP workers with no TCP production work (SMR = 1.41, 95% CI: 0.64–2.67, n_{NHL} = 9 deaths). TCP workers typically have much higher serum TCDD than with other dioxin concentrations; PCP workers usually have higher dioxin concentrations than TCDD. An uncontrolled decomposition reaction occurred in a German trichlorophenol plant during 1953, resulting in TCDD contamination of the plant.[333] During cleanup and repair processes, 254 workers were exposed to TCDD, with 56 severe and 45 less severe chloracne cases subsequently developing in these workers. Estimated TCDD doses exceeded 1 μg/kg body weight in 69 workers. No NHL cases occurred in these workers during 40 years of follow-up.

Seveso, Italy, TCDD Incident

Environmental TCDD contamination occurred in Seveso, Italy, during 1976 from a trichlorophenol production plant accident. Long-term surveillance of cancer incidence and mortality revealed some evidence of increased NHL risk in the local community during 25 years of follow-up. The most consistent finding was elevated hematopoietic and lymphoma cancer risks in men and women. The highest increase for non-Hodgkin lymphoma (RR = 2.8, 95% CI: 1.1–7.0) occurred 15 years after the accident about 30 miles north of Milan.[334] Figure 60.4 demonstrates the contamination and reference zones surrounding the accident in Seveso, Italy, with Table 60.19 listing the associated mean TCDD soil concentrations (minimum–maximum), median lipid-adjusted serum TCDD concentration in samples collected from specific zones 1976–1977, and rate ratios for NHL deaths in each zone.[27] No NHL cases occurred in the 18 Seveso residents developing chloracne after the accident (1.7 cases expected).[27]

Environmental Ionizing Radiation

Life Span Study

Initial follow-up studies of 401 NHL cases in Japanese atomic-bomb survivors suggest the possibility of a slight NHL excess (i.e., ~8 cases) in men; however, the evidence is relatively modest and absent in women. Analysis of data from atomic-bomb survivors in the Life Span Study through 2001 did not detect evidence of a statistically significant, dose-related excess non-Hodgkin

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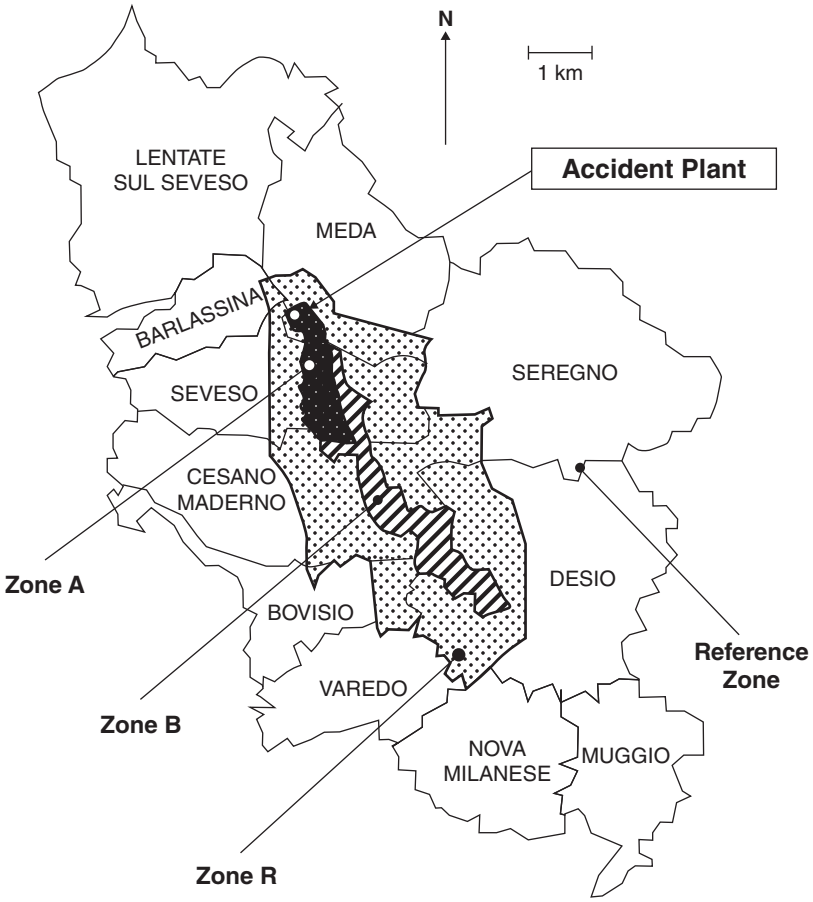


FIGURE 60.4. Seveso, Italy, dioxin contamination zones, including the following: zone A (very high soil contamination); zone B (high soil contamination); zone R (low soil contamination); and the surrounding uncontaminated area. (Adapted from Consonni et al.).[27]

TABLE 60.19. Median serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) concentrations collected from 1976–1977, soil TCDD concentrations, and Non-Hodgkin Lymphoma (NHL) rate ratios for NHL deaths for the three contamination zones around the accident site in Seveso, Italy, based on 25 years of follow-up. (Adapted from Consonni et al.).[27]

Zone (Residents During Accident)	Mean TCDD Soil Concentration (Minimum-Maximum µg/m^3)	Median Serum TCDD Concentration (ppt)	Non-Hodgkin Lymphoma Rate Ratio (Deaths)[d]	Non-Hodgkin Lymphoma 95% Confidence Interval
A (723)	15.5–580.4	447.0[a]	3.35 (3)	1.07–10.46
B (4,821)	1.7–4.3	94.0[b]	1.23 (7)	0.58–2.60
R (15,715)	0.9–1.4	48.0[c]	0.9 (40)	0.71–1.38
Reference (93,224)	Not available	Not available	1.0 (referent)	1.0 (referent)

[a] 296 Samples. [b] 80 Samples. [c] 48 Samples. [d] Adjusted for age, sex, and residence.

lymphoma risk overall.[121] The excess relative rate/Gy was positive in men (ERR/Gy = 0.46, 95% CI: −0.08 to 1.29), but the trend was statistically nonsignificant (P_{trend} = 0.11). In women, the ERR/Gy was near zero (ERR/Gy = 0.02, 95% CI: <−0.44 to 0.64) without evidence of a dose-response relationship (P_{trend} > 0.5).

Sun Exposure

Several case-control studies suggest total and recreational, but not occupational, sun exposure reduces NHL risks by 25–40%;[335,336] however, evidence for a causal or protective effect of sun exposure on NHL

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risks is inconsistent. A pooled analysis of data from 10 European and Australian, mostly population-based case-control studies participating in the International Lymphoma Epidemiology Consortium (InterLymph) compared the highest and lowest quartiles of cumulative total personal (recreational/occupational) and recreational sun exposures based on self-reports and questionnaires.[337] The adjusted estimated odds ratio for the highest quartile of total sun exposure was inverse, but not statistically significant (aOR = 0.87, 95% CI: 0.71–1.05, n_{NHL} = 1,087 cases/1,364 controls) using the lowest quartile as referents and random effects models. For cumulative recreational sun exposure, the comparison was statistically significantly inverse (aOR = 0.76, 95% CI: 0.63–0.91, n_{NHL} = 1,584 cases/2,019 controls). The multicenter European case-control study reported no statistically significant reduction in NHL risks comparing the highest and lowest quartiles of personal indicators of UV radiation exposure (childhood free/school days, adult free/workdays, sunlamp use), except for a modest association between NHL risks and cumulative sunlamp use in hospital-based controls.[252]

Limited data from cohort studies have not supported a protective effect of UV radiation exposure on NHL risks. The US Nurses' Health study identified 1,064 incident NHL cases from 1976–2006 in 115,482 women with follow-up by biennial questionnaires.[338] The study used UV-B flux based on current residence location as a proxy measure for personal sun exposure and dietary vitamin D intake from questionnaire data. None of the comparisons of high and low UV-B flux measurements demonstrated a statistically significant inverse relationship for NHL risks. The multivariable-adjusted relative risk for high UV areas at age 15 years was positive and marginally statistically significant (aRR = 1.21, 95% CI: 1.00–1.47, n_{NHL} = 212 cases/288 controls, P_{trend} = <0.01) using low UV areas as referents. Subgroup analysis yielded no statistical heterogeneity by NHL subtype; however, power was limited by relatively few cases. The Norwegian-Swedish Women's Lifestyle and Health Cohort Study enrolled 104,953 women and identified 158 NHL cases during ~1.6 million years of observation.[339] Using Poisson regression analysis to estimate the association between NHL risks and artificial tanning devices, bathing vacations, and sunburns, the age/residence-adjusted relative NHL risks for all three cumulative measures of sun exposure were near the null. Although several pigmentary characteristics were associated with NHL risks (e.g., ↑ brown hair, ↓ gray/green/blue eyes), the results did not support an association between cumulative sun exposure and NHL risks.

The most common hypothesis for an inverse relationship between sun exposure and NHL risks is vitamin D production; however, little evidence supports vitamin D deficiency as an etiology of NHL risks. A US study of 126 NHL cases and 139 clinic-based controls reported an inverse odds ratio of NHL risks for sunbathing of >1/week (aOR = 0.28, 95% CI: 0.10–0.79, n_{NHL} = 10 cases/98 controls) using never-sun bathers as referents and self-administered surveys for exposure data. In this study, current vitamin D deficiency as measured by radioimmunoassays was not associated with NHL (aOR = 0.86, 95% CI: 0.44–1.68, n_{NHL} = 88 cases/34 controls) or a dose-response relationship comparing high and low tertiles of vitamin D concentrations (P_{trend} = 0.35). The Nurses' Health Study also reported no association between NHL risks and dietary (P_{trend} = 0.35) or total (P_{trend} = 0.22) vitamin D intake.[338]

Lifestyle

Although studies on NHL risks and self-reported smoking, alcohol consumption, and obesity are inconsistent, observational studies have not excluded the effect of lifestyle on NHL subtype risks. Diet probably does not have a prominent role in NHL etiology. Caffeine-containing products (e.g., coffee, tea) are not consistently associated with protective or deleterious effects on NHL risks. Several Italian case-control studies report no clear association between coffee consumption and NHL risks in a country where the average annual per capita coffee consumption is ~600 cups. In a northern Italian study of 429 incident NHL cases and 1,157 hospital-based controls, the estimated relative risk for NHL comparing coffee drinkers and nondrinkers was modestly positive, but not statistically nonsignificant (aRR = 1.2, 95% CI: 0.8–1.7) after adjustment for age, sex, residence, BMI, alcohol consumption, and smoking using multiple logistic regression.[340] The study detected no statistically significant trend between NHL risks and intensity (P_{trend} = 0.11) or duration (P_{trend} = >0.90) of coffee consumption using non-coffee drinkers as referents; however, aRR for the highest quintile of coffee consumption was statistically significant (aRR = 2.2, 95% CI: 1.3–3.9, n_{NHL} = 23 cases/82 controls). The multivariate RR for tea consumption was similar (aRR = 1.2, 95% Ci: 0.9–1.6, n_{NHL} = 95 cases/216 controls) using non-tea drinkers as referents.

Although epidemiological evidence regarding coffee consumption and NHL risks is limited, some data suggest a difference in NHL subtype risks. In a multicenter Italian study of 1,418 NHL cases (1,301 B

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cells, 117 T cells), the fully adjusted odds ratio was positive, but statistically nonsignificant comparing any coffee drinking with nondrinkers for diffuse large B cell lymphoma (OR = 0.95, 95% CI: 0.61–1.5, n_{NHL} = 338 cases).[341] The study reported some evidence of a dose-response for coffee drinking intensity (>4 cups daily, P_{trend} = 0.045) and duration (>4 cups daily for ≥30 years, P_{trend} = 0.001) using ≤2 cups daily coffee users as referents. Although the estimates were imprecise, any coffee drinking was not associated with statistically significant increases in unadjusted T cell lymphoma risks using nondrinkers as referents (OR = 2.3, 95% CI: 0.84–6.4, n_{NHL} = 113 cases). No significant trends were noted in T cell lymphoma risks with increasing intensity or duration of coffee use, using ≤2 cups of daily coffee as referents.

Tobacco Smoking

Findings of epidemiological studies examining tobacco smoking and NHL risks are inconsistent with slightly positive results primarily associated with follicular lymphoma and T cell subtypes in women.[342] In a meta-analysis of 41 case-control (20,143 incident NHL cases) and 9 cohort studies (5,748 incident NHL cases), the pooled-effect estimate for overall NHL risks comparing ever-smokers with nonsmoking referents was marginally significant (pooled-effect estimate = 1.05, 95% CI: 1.00–1.09), primarily reflecting the estimate for T cell NHL subtypes (pooled-effect estimate = 1.23, 95% CI: 1.09–1.38).[33] The International Lymphoma Epidemiology Consortium (InterLymph) examined tobacco smoking and NHL risks in an analysis of nine case-control studies from the United States, Europe, and Australia (6,594 cases; 8,892 controls) using unconditional logistic regression models controlling for age, sex, race, and study center.[343] In contrast to nonsmokers, ever-smokers had a self-reported lifetime history of >100 cigarettes or ≥6 months of regular smoking. The odds ratio for overall NHL in ever-smokers was marginally significant statistically (OR = 1.07, 95% CI: 1.00–1.15, n_{NHL} = 3,765 cases/3,914 controls). The trend among quartiles of cumulative smoking was statistically significant for pack-years ($OR_{\geq 36\ pack\text{-}years}$ = 1.21, 95% CI: 1.09–1.34, n_{NHL} = 1,066 cases/1,194 controls, P_{trend} = 0.01) and smoking duration ($OR_{\geq 36\ years}$ = 1.16, 95% CI: 1.05–1.28, n_{NHL} = 1,197 cases/1,349 controls, P_{trend} = 0.01). Using 2001 WHO NHL subtype classifications, the odds ratio for NHL subtypes among current smokers was statistically significant only for follicular lymphoma (OR = 1.31, 95% CI: 1.12–1.52, n_{FL} = 1,452 cases). A European study of 373 incident follicular lymphoma cases and 818 population-based controls reported a slightly positive, statistically nonsignificant odds ratio for follicular lymphoma in current smokers (OR = 1.12, 95% CI: 0.81–1.56, n_{FL} = 99 cases/177 controls, P_{trend} = 0.62).[344] For women, the magnitude of the odds ratio for follicular lymphoma was higher, but still statistically nonsignificant (OR = 1.42, 95% CI: 0.92–2.21, n_{FL} = 51 cases/112 controls, P_{trend} = 0.16). Analysis of human leukocyte antigen (HLA) class II data and follicular lymphoma risks suggested carrying two shared HLA-DRB1 haplotypes increased follicular lymphoma risks in currently smoking women (OR = 2.52, 95% CI: 1.47–4.34, 18 cases/48 controls, P_{trend} = 0.002).

The Shanghai study of 649 NHL cases (76% participation rate) and 1,298 hospital-based controls demonstrated no association between NHL risks and ever-smokers using never-smokers as referents (OR = 1.04, 95% CI: 0.81–1.35, n_{NHL} = 272 cases/537 controls) with no significant relationship for daily smoking intensity (P_{trend} = 0.36) or duration (P_{trend} = 0.69).[245] Passive smoking was not associated with NHL risks (OR = 0.93, 95% CI: 0.70–1.25, n_{NHL} = 158 cases/350 controls). The prospective Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial examined NHL risks and smoking comparing ever- (≥6 months regular smoking history) and never-smokers based on baseline questionnaire data.[345] Results indicated no association between overall NHL risks or common NHL subtypes and smoking. For current smokers, the age/sex/race/education-adjusted HR for overall NHL risks in current smokers was 0.90 (95% CI: 0.73–1.11, n_{NHL} = 105 cases), whereas the HR for follicular lymphoma was 0.74 (95% CI: 0.42–1.31, n_{FL} = 14 cases). None of the hazard ratios for quartiles in cumulative measures of ever-smokers (duration, packs/day) were statistically significant, including overall NHL and follicular lymphoma risks (P_{trend} 0.365–0.964), except diffuse large B cell lymphoma duration ($HR_{>40\ years}$ = 0.79, 95% CI: 0.49–1.29, n_{DLBCL} = 20 cases). In a Japanese cohort of 1,332 HTLV-1 seropositive participants using never-smokers as referents and followed from 1990–2012, the multivariate hazard ratio for adult T cell leukemia/lymphoma (ATLL) in ever-smokers was 1.64 (95% CI: 0.45–6.06, n_{ATLL} = 10 ever-/15 never-smokers) after adjusting for age, alcohol intake, and geographical area.[346] The multivariate hazard ratios for smoking intensity were statistically significant and demonstrated an exposure-response relationship for 20 cigarettes/day (aHR_{ATLL} = 2.03, 95% CI: 1.13–3.36) and 40 pack-years smoking (aHR_{ATLL} = 2.39, 95% CI: 1.32–4.44).

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Alcohol

Although some case-control[347] and cohort[348] studies on NHL risks and alcohol consumption suggest a modestly inverse relationship, epidemiological evidence is inconsistent and weaker for a dose-response relationship along with variation between NHL subtypes. In a pooled analysis of 9 US and European case-control studies involving 6,492 cases and 8,683 controls from the InterLymph Consortium, the age/sex/ethnic/socioeconomic/study center-adjusted pooled OR comparing current and non-alcohol drinkers was inversely associated with overall NHL risks (aOR = 0.73, 95% CI: 0.64–0.84, n_{NHL} = 1,601 cases/2,392 controls).[349] The NHL risks did not decrease with increased alcohol consumption (P_{trend} = 0.97) with little difference between alcohol beverage types. In current drinkers, the adjusted odds ratios were statistically significant for Burkitt's lymphoma (aOR = 0.29, 95% CI: 0.13–0.64, n_{BL} = 111 cases) and diffuse large B cell lymphoma (aOR = 0.64, 95% CI: 0.53–0.77, n_{DLBCL} = 2,126 cases), but not other common B or T cell lymphomas. A meta-analysis of 21 case-control and 8 cohort studies involving 18,759 NHL cases using random effects models reported an inverse summary relative risk for overall NHL risks comparing current- and non-drinkers (summary RR = 0.85, 95% CI: 0.79–0.91, I^2 = 56.7%) with moderate heterogeneity.[350] The summary RR was statistically significant for case-control studies (RR = 0.80, 95% CI: 0.74–0.87), but not cohort studies (RR = 0.96, 95% CI: 0.88–1.04), with significant heterogeneity between the two estimates ($P_{heterogeneity}$ = 0.001). The summary RR for NHL in heavy alcohol drinkers was inverse and marginally statistically significant (RR = 0.84, 95% CI: 0.70–1.00, n = 7 studies, I^2 = 3.1%). The summary relative risks were similar between men, women, and common NHL subtypes.

The prospective US Cancer Prevention Study II Nutrition Cohort study identified 1,991 incident NHL cases among 43,124 participants.[351] Using Cox proportional hazards regression and nondrinkers as referents, the multivariable-adjusted relative risk was statistically significant and inverse only for >2 drinks daily (RR = 0.78, 95% CI: 0.65–0.93). The study detected little difference in NHL risks between sexes ($P_{interaction}$ = 0.45) or beverage type ($P_{difference}$ = 0.22). Alcohol use and NHL risks were more closely associated with B cell (P_{trend} = 0.005) than T cell subtypes (P_{trend} = 0.76). The Shanghai hospital-based case-control study reported no association between NHL risks and ever- versus never-alcohol consumption (OR 0.92, 95% CI: 0.72–1.19, n_{NHL} = 133 cases/280 controls), with no significant difference in NHL risks between alcohol beverage types.[245] In the prospective Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening cohort of older participants followed a median of 6.4 years, alcohol consumption was not associated with NHL risks comparing the highest alcohol quartile ($OR_{\geq 14\ drinks/week}$ = 0.84, 95% CI: 0.62–1.14, n_{NHL} = 68 cases, P_{trend} = 0.187) with nondrinking referents.[245] Specific alcoholic beverage consumption tertiles were also not associated with NHL risks with the P_{trend} ranging from 0.247–0.455.

Obesity

Pooled analyses of data from case-control studies suggest BMI is associated with slight increases in NHL risks, particularly for diffuse large B cell lymphoma (DLBCL); however, the results are mixed. In a pooled analysis of 18 case-control studies from the InterLymph Consortium (10,453 cases/16,507 controls) using normal weight BMI as referents (18.5–24.99 kg/m^2), the findings demonstrated no association comparing overall NHL risks with obese (BMI = 30–39.99 kg/m^2, OR = 0.97, 95% CI: 0.81–1.15, I^2 = 69.8%) or severely obese (BMI = ≥40 kg/m^2, OR = 0.99, 95% CI: 0.70–1.41, I^2 = 26.8%) participants.[45] The pooled odds ratio for DLBCL in severely obese participants was positive and statistically significant (OR = 1.80, 95% CI: 1.24–2.62, $P_{heterogeneity}$ = 0.40, I^2 = 4.4%); however, increasing 5 kg/m^2-BMI increments was not associated with DLBCL risks. A meta-analysis of 10 cohort studies and 6 case-control studies (21,720 cases) reported modestly elevated overall NHL risks in overweight (BMI = 25–<30 kg/m^2, summary RR = 1.07, 95% CI: 1.01–1.14, I^2 = 57.3%, $P_{heterogeneity}$ = <0.001) and obese (BMI ≥ 30 kg/m^2, summary RR = 1.20, 95% CI: 1.07–1.34, I^2 = 72.1%, $P_{heterogeneity}$ = <0.001) participants using normal weight participants (BMI = <25 kg/m^2) as referents.[352] The summary RR/5 kg/m^2 increase in BMI for overall NHL risks was slightly positive (RR = 1.10, 95% CI: 1.05–1.16, I^2 = 72.9%, $P_{heterogeneity}$ = <0.001). Body weight and height were measured in seven studies and self-reported in nine studies. In obese participants, DLBCL, but not follicular lymphoma, risks were positive and statistically significant (summary RR = 1.40, 95% CI:1.18–1.66, n = 6 studies, I^2 = 39.8%, $P_{heterogeneity}$ = 0.14). The prospective Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial enrolled 14,982 participants aged 55–74 years and followed them for a median of 8.8 years using baseline questionnaires to assess weight and height at age 20 years and baseline.[345] The overall NHL risk was positive and statistically significant for BMI in obese participants

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at baseline (BMI = ≥30 kg/m^2, HR = 1.32, 95% CI: 1.13–1.54, n_{NHL} = 321 cases, P_{trend} = <0.01), particularly for DLBCL risks (HR = 1.58, 95% CI: 1.10–2.27, n_{NHL} = 63 cases, P_{trend} = 0.056). The self-reported BMI at 20 years in obese participants was slightly positive, but statistically nonsignificant (HR = 1.09, 95% CI: 0.72–1.65, n_{NHL} = 23 cases, P_{trend} = <0.001).

A meta-analysis of prospective studies reported slightly elevated overall NHL risks with 5 kg/m^2 increments of BMI in men (RR = 1.09, 95% CI: 1.04–1.14, n = 8 studies, I^2 = 0%, $P_{heterogeneity}$ = 0.69) and women (RR = 1.07, 95% CI: 1.02–1.13, n = 10 studies, I^2 = 44.1%, $P_{heterogeneity}$ = 0.07) with no statistically significant difference between male and female risks ($P_{difference}$ = 0.64).[47] The overall NHL risk for increasing 5-kg/m^2 BMI increments in men and women together was statistically marginally significant (RR = 1.06, 95% CI: 1.00–1.12, I^2 = 0%, $P_{heterogeneity}$ = 0.61). Diffuse large B cell lymphoma incidence in men and women, but not follicular lymphoma incidence, was associated with increasing 5-kg/m^2 BMI increments (RR = 1.13, 95% CI: 1.02–1.26, n = 8 studies, I^2 = 37%, $P_{heterogeneity}$ = 0.13).

The US Women's Health Initiative study identified 1,123 NHL cases in the cohort of postmenopausal women followed for a mean of 11 years using self-administered baseline questionnaires to examine anthropometric factors.[353] Comparing the highest and lowest quartiles, the hazard ratio was marginally statistically significant for height ($HR_{>166.1\,cm}$ = 1.19, 95% CI: 1.00–1.43, n = 300 cases, P_{trend} = 0.02) and statistically significant for DLBCL ($HR_{>166.1\,cm}$ = 1.43, 95% CI: 1.01–2.03, n = 85 cases, P_{trend} = 0.03). The study reported no exposure-response relationship between other anthropometric factors and NHL risks, including abdominal fat (waist circumference, P_{trend} = 0.91; hip circumference, P_{trend} = 0.64; waist-to-hip ratio, P_{trend} = 0.90) or BMI (P_{trend} = 0.77). The hazard ratio for self-reported BMI at age 18 was associated with overall NHL risks ($HR_{\geq 21.8\ kg/m^2}$ = 1.27, 95% CI: 1.01–1.59, n_{NHL} = 178 cases, P_{trend} = 0.09), but not BMI at ages 35 or 50 years. In the US Multiethnic Cohort of 87,079 men and 105,972 women, BMI at age 21 years ($HR_{\geq 30\ kg/m^2}$ = 1.86, 95% CI: 1.02–3.40, n_{NHL} = 11 cases, P_{trend} = 0.27) was a stronger predictor of NHL risks than baseline anthropometric factors, after adjusting for ethnicity, education, alcohol consumption, and baseline age.[46] The NHL incidence was lower in all ethnic groups (African Americans, Latinos, Native Hawaiians, Japanese) than Caucasians, consistent with most of the medical literature. The data suggest a stronger association between NHL risks and follicular lymphoma than DLBCL; however, the risk estimates were unstable for small sample sizes. A meta-analysis of 22 prospective studies on anthropometric factors and NHL risks supported a slightly increased NHL risk and increasing 5-kg/m^2 BMI increment in early adulthood ($HR_{BMI\ age\ 18–21\ years}$ = 1.11, 95% CI: 1.07–1.16, I^2 = 20.3%, $P_{heterogeneity}$ = 0.24) that was stronger than BMI increments reported at other adult ages.[354] Obesity (≥30 kg/m^2) was associated with modestly increased overall NHL risks (HR = 1.13, 95% CI: 1.06–1.20, I^2 = 10.8%, $P_{heterogeneity}$ = 0.328). Measures of abdominal fat (waist circumference, waist-to-hip ratio) were not associated with NHL risks. Among NHL subtypes, DLBCL had the strongest association with anthropometric factors ($HR5\text{-}kg/m^2_{BMI\ increment}$ = 1.11, 95% CI: 1.05–1.16, n = 16 studies, I^2 = 15.2%, $P_{heterogeneity}$ = 0.279).

Diet

Findings from observational studies evaluating the magnitude and consistency of an association between NHL risks and dietary factors are relatively modest and conflicting. No single dietary pattern is conclusively associated with elevated NHL risks. Although results are inconclusive, the strongest dietary factors associated with NHL are animal fat and saturated fat, with suggestive evidence for higher consumption of whole grains and vegetables. Modest alcohol intake lowered NHL risks based primarily on case-control studies.[355] In the US Multiethnic Cohort of >215,000 Caucasians, African Americans, Japanese Americans, Native Hawaiians, and Latinos aged 45–75 at baseline, 939 NHL cases occurred in 10 years of follow-up based on linkage with cancer registries.[356] None of the three dietary patterns (fat/meat, fruit/milk, vegetables) were significantly associated with NHL risks in the total population using Cox regression. Most of the NHL risks in NHL subgroups were statistically nonsignificant; however, some associations were positive (e.g., follicular lymphoma in men and fat/meat diet) based on small sample sizes.

Typically, red meat includes beef, lamb, mutton, pork, and veal, whereas processed meat includes bacon, cured/preserved meats, ham, and sausages. The US NIH-AARP Diet and Health Study enrolled 492,186 participants ($mean_{age}$ = ~62 years; range, 50–71 years) using a baseline self-administered dietary questionnaire, with a subcohort of 302,162 participants receiving a supplemental questionnaire on meat-cooking methods and doneness levels.[357] Proxy respondents and participants with prevalent cancer were excluded from the study. During a mean follow-up of 9 years, the study identified 3,611 incident NHL cases. Using multivariable Cox proportional hazards regression models to compare the

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highest and lowest consumption quintiles, overall NHL risks were not associated with total red meat (HR = 1.01, 95% CI: 0.90–1.14, n = 684 cases, P_{trend} = 0.41), total processed meat (HR = 0.99, 95% CI: 0.89–1.11, n = 691 cases, P_{trend} = 0.45), poultry (HR = 1.00, 95% CI: 0.90–1.12, n = 705 cases, P_{trend} = 0.77), or fish (HR = 1.07, 95% CI: 0.96–1.16, n = 732 cases, P_{trend} = 0.24). Overall, meat cooking and meat processing did not increase overall NHL, DLBCL, or follicular lymphoma risks.

A meta-analysis of 13 population-based case-control, 10 hospital-based case-control, and 10 cohort studies reported a modestly positive, statistically significant association between NHL risks and red meat consumption (summary RR = 1.22, 95% CI: 1.03–1.44, n = 10,149 cases/14 studies, I^2 = 35%).[52] The summary RR (sRR) did not reach statistical significance for processed meat, white meat, or fish/seafood. The sRR for overall dairy consumption was modestly positive and near statistical significance (sRR = 1.26, 95% CI: 0.99–1.60, n = 4,168 cases/6 studies, I^2 = 49%) with moderate heterogeneity. However, cheese (sRR = 1.13, 95% CI: 0.91–1.41, n = 6,969 cases/14 studies, I^2 = 32%) and milk (sRR = 1.12, 95% CI: 0.90–1.38, n = 5,120 cases/8 studies, I^2 = 61%) consumption were not clearly associated with overall NHL risks. None of the dietary factors were associated with statistically significant increased risks for DLBCL or follicular lymphoma. A meta-analysis of four population-based case-control, six hospital-based case-control, and four cohort studies reported a modestly positive, statistically significant pooled relative risk for NHL and red meat comparing the highest and lowest measures of red meat consumption (pooled RR = 1.14, 95% CI: 1.03–1.26, n = 13 studies, I^2 = 24.2%, $P_{heterogeneity}$ = 0.20).[358] Subgroup analysis indicated NHL risk for red meat depended on results from case-control studies (pooled RR = 1.19, 95% CI: 1.06–1.34) rather than cohort studies (pooled RR = 1.08, 95% CI: 0.92–1.26). The pooled RR for processed meat consumption was slightly positive, but statistically nonsignificant (pooled RR = 1.06, 95% CI: 0.98–1.15, n = 11 studies, I^2 = 3.6%, $P_{heterogeneity}$ = 0.41). Sensitivity analysis on five studies demonstrated no statistically significant associations between common NHL subtypes and meat consumption.

Reproductive

The incidence rate for most NHL subtypes is higher in men than women. Some studies suggest an inverse relationship between NHL risks and gravidity (i.e., pregnancies); however, the results are conflicting depending on the limitations of study designs evaluating rare tumors. Overall, the effect of reproductive factors and exogenous hormones on NHL risks is relatively modest.[359] In a systematic review of seven cohort, one nested case-control, eight population-based case-control, and three hospital-based case-control studies, more studies reported inverse relationships (J-shaped pattern) with NHL risks for gravidity than parity (births). The California Teachers study reported an inverse association between gravidity and B cell NHL risks.[360] The InterLymph study also reported an inverse, statistically nonsignificant relationship for follicular lymphoma and gravidity (pooled OR = 0.82, 95% CI: 0.51–1.31, n_{fl} = 117 cases), but not for overall NHL risks (pooled OR = 0.98, 95% CI: 0.75–1.28, n_{NHL} = 547 cases/885 controls, P_{trend} = 0.97).[361] For parity, the findings were null for overall NHL, follicular lymphoma, and DLBCL risks. In the Connecticut Women's case-control study, the age/family NHL history/BMI/menopausal status-adjusted odds ratio for overall NHL risks was inverse and statistically significant in the highest quartile of pregnancies ($OR_{\geq 4 \text{ vs. never}}$ = 0.6, 95% CI: 0.4–0.9, P_{trend} = 0.03) and parity ($OR_{\geq 4 \text{ vs. nulliparous}}$ = 0.6, 95% CI: 0.4–0.9, P_{trend} = 0.008),[362] whereas a UK population-based case-control study demonstrated no association between the highest parity tertile and overall NHL risks.[363] The 1-year lagged age/region-adjusted odds ratio for overall NHL in women with ≥3 births was 1.1 (95% CI: 0.8–1.5, n_{NHL} = 120 cases/112 controls). The NIH-AARP Diet and Health Study Cohort study reported no statistically significant associations between NHL, DLBCL, or follicular lymphoma and parity, age at menarche, age at first birth, or menopausal status at baseline.[359]

Medications

The use of chemotherapy for HL increases secondary NHL risks. Chemotherapeutic drugs (e.g., azathioprine, cyclosporine) associated with the treatment of autoimmune diseases and adverse immune reactions in transplant patients are confounders for assessing NHL risks in these patients. Hormone-based contraception has changed substantially over the previous decades, with high estrogen concentrations in preparations distributed in the 1960s, medium estrogen/progestin doses in the 1970s, and low doses since the 1980s. Additionally, the complex relationship between biological, sociodemographic, and reproductive factors, along with age at consumption and oophorectomy status, may affect NHL risks associated with hormone therapy. Most epidemiological studies on NHL risks

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in hormonal contraceptive users report null findings. The California Teachers Study reported a marginally lower B cell NHL risk in oral contraceptive users, particularly in women starting use at <25 years of age (multivariate-aRR = 0.72, 95% CI: 0.51–0.99); however, the study detected no exposure-response relationship with duration of use.[364] The relative risk of NHL comparing ever- and never-oral contraceptive users was close to 1 in the NIH-AARP Diet and Health Study Cohort[359] and the Connecticut Women's case-control study.[362] In general, case-control studies reported relative risks below 1, and cohort studies typically demonstrated overall null results, except for some NHL subtypes in women with surgical menopause (i.e., no endogenous estrogen).[365]

Although results associating postmenopausal hormone therapy with NHL risks are inconsistent, the overall NHL epidemiological findings are stronger for unopposed estrogen than estrogen/progestin use.[365] Several case-control studies report an inverse relationship between NHL risks and postmenopausal hormone therapy; however, the protective effect of postmenopausal hormone therapy typically is not supported by cohort studies, particularly with some common NHL subtypes (DLBCL, follicular lymphoma). The Women's Health Initiative randomized clinical trial identified 383 incident NHL cases during 13 years of follow-up while comparing conjugated equine estrogen and estrogen plus medroxyprogesterone acetate use.[366] The hazard ratios were similar and close to 1 for both arms of the trial, with no specific NHL subtypes associated with either treatment. The California Teachers Study reported null results comparing ever- versus never-use of postmenopausal hormone use and B cell NHL (RR = 1.05, 95% CI: 0.83–1.33, $n_{\text{B cell NHL}}$ = 299 cases), with no statistically significant associations with common NHL subtypes.[364] Among women with no postmenopausal hormone use and bilateral oophorectomy/hysterectomy, the B cell NHL risk was higher (RR = 3.15, 95% CI: 1.62–6.13) using participants with natural menopause as referents. The US Cancer Prevention Study II Nutrition Cohort identified 616 NHL cases in postmenopausal women during 15 years of follow-up.[367] Using extended Cox regression and never-users as referents, the HR for NHL was positive and statistically significant for ever-users of postmenopausal hormone therapy (HR = 1.29, 95% CI: 1.05–1.58, n_{NHL} = 284 cases), primarily from elevated risks for follicular lymphoma (HR = 1.98, 95% CI: 1.26–3.13, n_{FL} = 51 cases). The hazard ratio for NHL in ever-users of estrogen/progestin was null (HR = 1.02, 95% CI: 0.82–1.39, n_{NHL} = 83 cases). Duration of postmenopausal hormone use was not associated with statistically significant elevation of hazard ratios for NHL ($HR_{\text{current estrogen only use 15+ years}}$ = 1.22, 95% CI: 0.87–1.72, n_{NHL} = 54 cases).

Diseases

Altered Immunity

Immune deficiency is the most important NHL risk factor; immunocompromised patients including those with HIV/AIDS, immune suppressive therapy, immunosuppressed organ transplant patients, and congenital defects in the immune system have increased relative NHL risks ranging from 10–100-fold.[368,369] The vast majority of HIV-associated NHL neoplasms are B cell tumors with most being extranodal and high grade. In an analysis of 10 US SEER cancer registries with information on HIV status at NHL diagnosis from 1992–2009, 5.9% of 115,643 NHL cases were HIV-infected.[183] The highest percentage of HIV-infected cases in NHL subtypes were Burkitt lymphoma (26.9%), diffuse large B cell (7.8%), and peripheral T cell lymphomas (3.2%), with other subtypes containing ≤1.1% HIV-infected cases.

The strongest NHL risk factors from autoimmune diseases involve Sjögren syndrome, systemic lupus erythematosus, and rheumatoid arthritis.[180] Epidemiological data suggest substantial increased NHL risks ranging over 4-fold occur in patients with autoimmune conditions primarily from B cell activation (e.g., systemic lupus erythematosus,[370] rheumatoid arthritis,[63] psoriasis,[371] Sjögren syndrome, Hashimoto thyroiditis).[372,373] Lymphocytic infiltration of salivary and tear glands characterizes Sjögren syndrome; this autoimmune disease is associated with increased low-grade B cell NHL risks, predominately marginal zone histological types (i.e., extranodal marginal zone mucosa-associated lymphoid tissue, MALT).[374] A meta-analysis of 20 cohort studies using random effects models to evaluate autoimmune disease risk factors reported the highest NHL risks for Sjögren syndrome (mSIR = 18.8, 95% CI: 9.5–37.3), moderate risks for systemic lupus erythematosus (mSIR = 7.4, 95% CI: 3.3–17.0), and lower NHL risks for rheumatoid arthritis (mSIR = 3.9, 95% CI: 2.5–5.9).[375] The large confidence intervals reflect imprecise estimates and high heterogeneity ($I^2 > 70\%$). Results from the InterLymph Consortium indicate autoimmune disorders mediated by B cell responses were associated with increased diffuse large B cell lymphoma risks (OR = 3.11, 95% CI: 2.25–4.30, n_{DLBCL} = 70 ever/2,402 never) and marginal zone lymphoma (OR = 5.80, 95% CI: 3.82–8.80, n_{MZL} = 33 ever/500 never).[376]

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An English study matched a cohort of 471,970 atopic eczema participants (median IQR = 41.1 years, IQR range = 24.9–60.7 years) with 2,239,775 nonatopic eczema individuals (median IQR = 39.8 years, IQR range = 25.9–58.4 years).[377] The hazard ratio for NHL was 1.20 (99% CI: 1.07–1.34) compared with 1.48 (99% CI: 1.07–2.04) for Hodgkin lymphoma after adjustment for confounders. For NHL, the adjusted HR increased with the severity of atopic eczema. The HR for NHL in severe atopic eczema patients was 2.08 (99% CI: 1.42–3.04) compared with nonatopic eczema participants after adjustments. The authors opined that the positive findings in diseases with different etiologies (i.e., NHL, Hodgkin lymphoma) suggest the possibility of detection bias or residual confounding related to immunosuppression. In general, existing evidence of cancer risks in atopic eczema patients is conflicting due to difficulty adjusting for important confounders.

Chronic immune stimulation and T cell dysregulation associated with autoimmune diseases contribute to increased NHL risks; however, autoimmune-associated T cell lymphomas (Crohn's disease, celiac disease) are less common than B cell lymphomas. In a pooled analysis of 8,692 NHL cases and 9,260 controls for 14 case-control studies in the International Lymphoma Epidemiology Consortium, autoimmune conditions mediated by T cell responses were associated with peripheral T cell lymphoma (OR = 2.14, 95% CI: 1.35–3.38, $n_{\text{peripheral T cell lymphoma}}$ = 26 ever/257 never).[376]

Infections

Both viral and bacterial infections are associated with NHL, as displayed in Table 60.20. Rare adult infections associated with elevated NHL subtypes primarily involve *Helicobacter pylori*/gastric mucosa-associated lymphoid tissue lymphoma (MALT)[378] and several viral infections. These infections include Epstein–Barr virus (Burkitt lymphoma, extranodal nasal natural killer/T cell lymphoma), human T cell lymphotropic virus 1 (adult T cell leukemia/lymphoma), human herpesvirus 8 (primary effusion lymphoma), and hepatitis C virus (splenic marginal zone B cell NHL, diffuse large B cell NHL, follicular lymphoma.).[379,380,381] DLBCL is the most frequent aggressive NHL subtype associated with HCV often developing from a preceding low-grade marginal zone lymphoma (MZL); other NHL subtypes associated with HCV infections include lymphoplasmacytic lymphomas, splenic MZL, and non-gastric (MALT) MZL.[382] HTLV-1 is a necessary, but not sufficient cause of adult T cell leukemia/lymphoma; only ~3% of patients infected by this virus develop this lymphoma.[383] Most pediatric infections are not associated with elevated NHL incidence. Extranodal NK- and T cell lymphomas are strongly associated with Epstein–Barr virus infection with substantial geographical variability.

HISTOLOGY

Non-Hodgkin lymphoma (NHL) is a diverse, heterogeneous disease arising from B cells (85–95%) and less commonly T cell lymphocytes (5–15%), with the histological features of each NHL subtype depending on the specific cell of origin and stage of development.[182] These tumors appear mostly in the central lymph nodes (i.e., 70–80%) with the remainder in extranodal reticuloendothelial tissues.

B Cell Lymphomas

Diffuse large B cell and follicular lymphomas are the most common adult, high-grade non-Hodgkin

TABLE 60.20. Infectious agents associated with non-Hodgkin lymphoma (NHL) subtypes. (Adapted from Skrabek et al.).[180]

Infectious Agent	NHL Subtypes
Borrelia burgdorferi (Lyme disease)	Marginal zone lymphoma
Chlamydia psittacosis (Psittacosis)	Marginal zone lymphoma
Coxiella burnetii (Q fever)	Diffuse large B cell lymphoma (DLBCL), follicular lymphoma
Epstein–Barr virus (EBV)	Burkitt lymphoma, nasal NK/T cell lymphoma, posttransplant lymphoproliferative disease
Hepatitis B virus (HBV)	Diffuse large B cell lymphoma (DLBCL) and other NHL subtypes
Hepatitis C virus (HCV)	B cell NHL (splenic marginal zone lymphoma, DLBCL)
Helicobacter pylori	Gastric mucosal-associated lymphoid tissue lymphoma (MALT)
Human herpes virus-8 (HHV-8)	Primary effusion lymphoma
Human T cell lymphotropic virus (HTLV-1)	Adult T cell leukemia/lymphoma
Plasmodium falciparum	Burkitt lymphoma

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lymphomas accounting for ~65% of all NHL lymphomas, with an additional ~5% being marginal zone lymphomas.[384] DLBCL is a heterogeneous disease with three genetically distinct subtypes (germinal center B cell-like, activated B cell-like, unclassified origin) that are now further subclassified.[13] Marginal zone lymphoma subtypes include splenic, nodal, and mucous-associated lymphoid tissue (MALT). The latter is the most frequent marginal zone lymphoma commonly occurring in the stomach associated with t(11;18) translocations and *Helicobacter pylori* infection. Burkitt lymphoma is a highly aggressive, rapidly proliferating B cell NHL with three major morphologically and immunophenotypically similar variants; the endemic type affects young children in equatorial Africa and Papua New Guinea, where *Plasmodium falciparum* malaria is endemic along with EBV. Involvement of the central nervous system may occur. The sporadic type is worldwide, whereas the immunodeficiency-associated HIV-related type affects HIV-infected and immunosuppressed transplant patients. All three types of Burkitt lymphoma are histologically indistinguishable. Lymphoplasmacytic lymphoma is an indolent B cell tumor consisting of a wide spectrum of plasmacytic differentiation (small lymphocytes, plasmacytoid lymphocytes, plasma cells) within the bone marrow that often produce paraproteins (IgG, IgM). Waldenström macroglobulinemia is a type of lymphoplasmacytic lymphoma associated with a monoclonal IgM gammopathy and lymphoplasmacytic bone marrow infiltration.

T Cell Lymphomas

Mature T cell and natural killer (NK) lymphomas are a rare, typically clinically aggressive, very heterogeneous category of >20 subtypes ranging from indolent peripheral-cell lymphoma to more aggressive subtypes (e.g., adult T cell leukemia/lymphoma, hepatosplenic γδT cell lymphoma). Most T cell lymphomas are classified as peripheral T cell lymphomas (~10–15% of all NHL subtypes), most commonly as peripheral T cell lymphoma not otherwise specified, anaplastic large-cell lymphoma, or angioimmunoblastic T cell lymphoma.[385,386] The indolent skin subtypes include cutaneous anaplastic large cell, lymphoid papulosis, and mycosis fungoides as well as other less common T cell lymphoma subtypes. Mycosis fungoides is an indolent and common cutaneous T cell lymphoma that may progress to the more aggressive Sézary syndrome (generalized lymphadenopathy, peripheral blood involvement, erythroderma). Although these two entities previously were considered different expressions of the same disease, genome-wide analysis of cutaneous T cell lymphomas indicates they arise from different memory T cell subsets, resulting in histopathological differences between these tumors.[387]

HOST SUSCEPTIBILITY

Although NHL clusters occur in families, family history of NHL or autoimmune diseases is not a strong risk factor. In a pooled analysis of data from 17 case-control studies collected in the International Lymphoma Epidemiology Consortium (InterLymph) using unconditional logistic regression models with adjustment for confounding, self-reported NHL occurrence in a first-degree relative increased NHL risks (OR = 1.5, 95% CI: 1.2–1.9) unrelated to gender; the 10,211 NHL cases were 93% white.[388] The highest NHL risk occurred in participants having a brother with NHL (OR = 2.8, 95% CI: 1.6–4.8). The NHL risks were similar across NHL subtypes. In a Scandinavian study of 24,728 NHL cases and 55,632 population-based controls using univariate logistic and hierarchical regression models to estimate odds ratios, a personal history of systemic autoimmune disease was associated with up to a 5-fold increased NHL risk. However, the NHL odds ratio for a family history of systemic autoimmune disease was modest, but statistically nonsignificant (OR_h = 1.31, 95% CI: 0.85–2.03, n_{NHL} = 291 cases/533 controls).[389] For most autoimmune disorders, the NHL risk was greater 1–4 years after diagnosis than after 5 years.

Immune system abnormalities represent the strongest NHL risk factor. Similar to cHL (classical Hodgkin lymphoma), congenital or acquired immune deficiencies are strong risk factors for childhood NHL, including autoimmune lymphoproliferative syndrome, combined variable or severe combined immune deficiency, Wiskott–Aldrich syndrome, X-linked hyperimmunoglobulin M syndrome, and X-linked lymphoproliferative disease. Two distinct HLA class II haplotypes are associated with increased follicular lymphoma risks, whereas HLA-B*08 is strongly associated with diffuse large B cell lymphoma.[176]

CLINICAL FEATURES

NHL clinical features vary substantially from an indolent course to an aggressive malignancy depending on subtype, organ involvement, and anatomical area.[390] Consequently, NHL presents with a wide range of symptoms involving any organ in the body depending on the clinical stage. Table 60.21 separates common B cell lymphomas into indolent and aggressive NHL

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TABLE 60.21. B cell non-Hodgkin lymphoma (NHL) indolent and aggressive subtypes. Indolent NHL subtypes are slowly progressive, widespread diseases with few systemic symptoms. These NHL subtypes generally respond to initial therapy, but relapses frequently are fatal. Aggressive lymphomas typically present with rapidly expanding lymph nodes, extranodal involvement, and B symptoms (fever, night sweats, weight loss). These NHL subtypes are rapidly fatal if untreated; however, many are potentially curable. (Adapted from Ninkovic and Lambert).[390]

Indolent B Cell NHL Subtype	Aggressive B Cell NHL Subtype
Extranodal and nodal marginal zone	Burkitt
Follicular	Diffuse large B cell (activated B cell, germinal center B-type, NOS)
Lymphoplasmacytic/Waldenström macroglobulinemia	High-grade B cell, NOS
Mantle cell[a]	Large B cell
Mucosa-associated lymphoid tissue (MALT)	Mantle cell[a]
Splenic marginal zone	Primary diffuse large B cell of central nervous system, Primary mediastinal (thymic)

Abbreviation: NOS = not otherwise specified.
[a] Mantle cell lymphoma sometimes has features of indolent and aggressive B cell subtypes.

subtypes. NHL is primarily an adult cancer except for Burkitt lymphoma (one peak in childhood and the other in the seventh decade of life). The median age at diagnosis for follicular lymphoma is the sixth decade.[391] Higher-grade, indolent NHL subtypes (e.g., follicular lymphoma) typically present with painless lymphadenopathy that fluctuates in size over a long clinical course. Lymphoplasmacytic lymphoma is an indolent B cell lymphoma associated with IgM paraproteinemia (Waldenström macroglobulinemia). Clinical symptoms result from tumor infiltration (bone marrow, liver, lymph nodes, spleen), IgM paraproteinemia (cold agglutinin hemolytic anemia, cryoglobulinemia, hyperviscosity), and IgM paraprotein deposition (amyloidosis, kidney disease, neuropathy). In contrast to Hodgkin lymphoma, aggressive NHL subtypes (e.g., Burkitt lymphoma) may manifest with a rapidly enlarging mass commonly in the abdomen, head, neck, or mediastinum with bowel obstruction, tumor lysis, and/or B symptoms (fever, night sweats, fatigue, weight loss, pruritis). Diagnosis is based on an excisional biopsy of a lymph node or involved organ.

NHL survival rates are poor compared with other hematopoietic malignancies, particularly in young adults with prognosis depending on clinical stage, cell origin, sex, age, and NHL subtypes. Favorable prognosis after the administration of rituximab to anthracycline-containing chemotherapy is better for BN2 and EZB diffuse large B cell lymphoma subtypes than MCD and N1 subtypes; however, MCD and BN2 DLBCL subtypes may respond to therapeutic inhibition of "chronic active" B cell receptor signaling.[195] The prognosis is better for DLBCL subtype tumors originating in germinal centers than peripheral (activated) B cell subtypes. Most T cell lymphomas have similar outcomes with treatment.[392]

MULTIPLE MYELOMA

Abnormal clonal plasma cells in the bone marrow characterize multiple myeloma. This hematological malignancy is part of a range of monoclonal gammopathies that includes monoclonal gammopathy of undetermined significance (MGUS, asymptomatic premalignant plasma cell proliferation) and asymptomatic smoldering multiple myeloma (SMM).[393] Almost all multiple myeloma cases evolve from MGUS;[394] ~3–5% of Europeans of ≥50 years of age have detectable MGUS.[395] Worldwide, multiple myeloma is the 23rd most common cancer with an annual incidence of 160,000 and 106,000 related annual deaths.[1] The incidence varies widely (i.e., 30-fold) internationally, with generally higher rates in developed countries. The annual incidence rate has been relatively stable in the recent past; however, case numbers are increasing in the general population of developed countries due to increased survival and an aging population.[396] The US incidence of multiple myeloma increases from ~8/100,000 persons aged 50–54 years to ~50/100,000 persons aged 80–84 years, according to the Surveillance, Epidemiology, and End Results (SEER) program (https://seer.cancer.gov/statistics/). In the United States and Europe, the annual age-adjusted incidence is ~3–5/100,000 general population,[19] whereas the reported incidences in Western Africa and Southeast Asia are <1/100,000.[397] The recent 5-year trend in the annual incidence rate of multiple myeloma has increased by 2.8% in men and 1.6% in women.[398] Multiple myeloma is 2–3-fold higher in blacks than whites, with relatively lower rates in Asians and Pacific Islanders;[399,400] for African-Americans, multiple myeloma is the most common hematological

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malignancy.[401] Approximately 35,000 new multiple myeloma cases occur in the United States annually, with a male/female ratio of 1.3/1; estimated annual deaths from multiple myeloma are ~13,000.[76] In developed countries, multiple myeloma is the second most common hematological malignancy after non-Hodgkin lymphoma, representing 10–20% of all hematological malignancies.

CARCINOGENESIS

Multiple myeloma is a malignant neoplasm of terminally differentiated, mature B cells (plasma cells) that usually develops in bone marrow and produces monoclonal immunoglobulins (paraproteins) detectable in serum and/or urine. In contrast to primary plasma cell leukemia, multiple myeloma tumor cells are dependent on the bone marrow microenvironment for survival.[402] The multistep accumulation of adverse biological features in secondary plasma cell leukemia allows the spread of malignant plasma cells into the blood. These tumors are very heterogeneous with multiple subclones characterized by distinct gene mutations that independently alter tumor progression.[403] The lack of serum or urinary monoclonal paraproteins does not exclude the diagnosis of multiple myeloma, which occurs infrequently (i.e., <3% of multiple myeloma patients).[404] The tumor cells are strongly bone marrow-dependent, with absent IgM expression and hypermutation of immunoglobulin genes. In contrast to normal plasma cells, multiple myeloma cells retain the potential to reduce their proliferation rate.[405] Almost half of MGUS and multiple myeloma tumors are the hyperdiploid biological subtype with 48−75 chromosomes, primarily 49–56 chromosomes including ≥3 odd-numbered chromosomes (e.g., 3, 5, 7, 9, 11, 15, 19, 21).[406] These tumors lack recurrent immunoglobulin gene translocations. In contrast, the immunoglobulin heavy locus (IgH) chromosome 14 translocations [t(4:14), t(14;16), t(14;20), t(6:14), t(11;14)] characterize nonhyperdiploid subtype of myeloma tumors. This latter tumor subtype has <48 and/or >75 chromosomes, a more aggressive clinical course, and shorter survival compared with the more indolent hyperdiploid subtype.[406] These biological subtypes do not usually change during the course of the disease. Upregulation and overexpression of cyclin D genes are common in hyperdiploid and nonhyperdiploid multiple myeloma tumors, as displayed in Figure 60.5. Other common genetic events in multiple myeloma tumors involve *NRAS*, *KRAS*, and *BRAF* genes, activation of NF-κB pathway, 17p deletions, and rearrangements of the *MYC* gene. The presence of t(14;16), t(14;20), t(6:14), 17p13 (tumor suppressor *P53* gene) deletions, and gains of 1q indicate a worse prognosis.[407]

Multiple myeloma tumors contain currently identified universal driver genes. The Myeloma Genome Project identified 63 apparent driver genes with 17 being potentially actionable including novel putative oncogenes (*IDH1, IDH2, PRKD2, PTPN11*) and, less commonly, putative tumor suppressor genes (*UBR5*, *HUWE1*).[408] These driver genes most often affect various pathways including MEK/ERK (50%), epigenetic regulators (24%), RNA processing (18%), NF-κB signaling (14%), and G_1/S cell-cycle transition (5%). Increasing driver gene abnormalities portends a worse

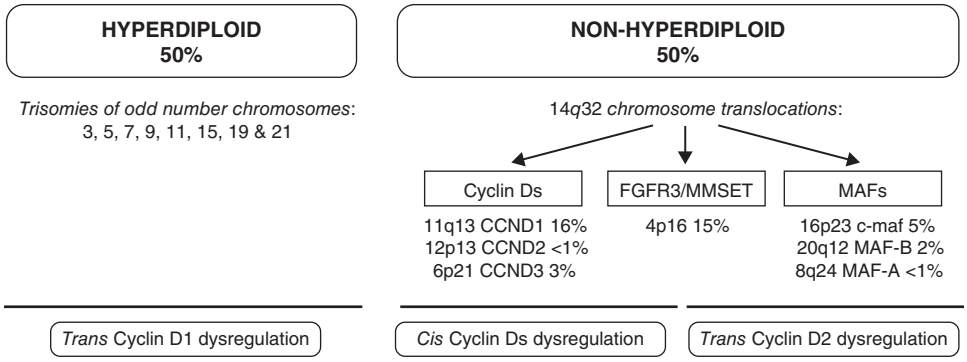


FIGURE 60.5. Cyclin $D_{1\text{-}5}$ dysregulation is common to hyperdiploid and nonhyperdiploid multiple myeloma tumors as well as monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). Most hyperdiploid tumors have biallelic cyclin D_1 *trans*-dysregulation, whereas t(14q32) translocations affect the loci in non-hyperdiploid tumors, as displayed in the figure. The percentage indicates locus frequency. (Adapted from Chesi et al.).[407] *Abbreviations: FGFR3* = fibroblast growth factor receptor 3; *MAF* gene = MAF bZIP transcription factor functions as a transcriptional activator or repressor for several processes including T cell susceptibility to apoptosis; *MMSET* = also known as *NSD2* gene (nuclear receptor-binding SET domain protein 2) involved with normal development.

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prognosis. Translocations involving the immunoglobulin heavy chain locus (IgH) are important primary events in monoclonal gammopathies, including translocation t(11;14) expression of *CCND1*(cyclin D1) important for cell-cycle progression and translocation t(4;14) producing overexpression of *NSD2* (epigenetic dysregulation) and *FGFR3* (fibroblast growth factor receptor 3) genes.[393] Other frequent genetic aberrations include MYC rearrangements and mutations of *KRAS*/*NRAS* genes. The NF-κB pathway involves a transcription factor that regulates the transcription of multiple genes involved with expression of chemokines, proinflammatory cytokines, COX-2, innate/adaptive immunity, cell proliferation, and antiapoptotic genes. Myeloma cells produce several growth factors including insulin-like growth factor 1, interleukin-6, stromal cell-derived factor-1α, and vascular endothelial growth factor that enhance cell proliferation, whereas bone marrow stromal tumor cells produce fibroblast growth factor, tumor necrosis factor-α, and tumor necrosis factor-β.[409]

EXPOSURE

The few well-established risk factors associated with multiple myeloma include older age, male gender, African American ethnicity, monoclonal gammopathy of undetermined significance, and family history of B cell lymphoproliferative disease.

Occupation

Multiple myeloma is not consistently associated with a specific occupational exposure. Low statistical power from small sample sizes and the relative rarity of multiple myeloma complicate accurate quantitation of multiple myeloma associations with specific occupations or industries. Analysis of data from 15 million Nordic residents enrolled in the nationwide registration of 2.8 million incident cancer cases reported a slight, statistically significant multiple myeloma SIR for farmers (pooled SIR = 1.07, 95% CI: 1.03–1.11, n = 2,870 cases).[19] The pooled SIR for gardeners was also slightly elevated, but marginally significant (SIR = 1.07, 95% CI: 1.00–1.16, n = 701 cases), whereas none of the SIRs for the other 52 occupations were statistically significant. A US population-based study of 180 multiple myeloma cases (50% participation rate) and 481 controls (52% participation rate) identified by random dialing used unconditional logistic regression to estimate odds ratios for 135 occupation codes and 143 industry codes.[410] At the P = 0.05 statistical significance level, 9 occupational and 13 industrial categories reached statistical significance. Multiple myeloma was not associated with agricultural occupations based on the self-reported involvement of four cases and seven controls. The odds ratios for multiple myeloma in painters, paperhangers, and plasterers were positive, but statistically nonsignificant with a wide confidence interval (OR = 3.6, 95% CI: 0.7–19, n = 3 exposed/3 control cases). Multiple myeloma was associated with a wide variety of services (e.g., health, religious organizations, transportation services/manufacturing, food/productions, insurance/securities/real estate/business services) with imprecise odds ratios and no clear exposures to carcinogens. An analysis of pooled data from 5 international case-control studies involving 1,959 multiple myeloma cases and 6,192 controls used unconditional regression to estimate odds ratio for multiple myeloma in 98 nonfarming occupations.[411] None of these odds ratios reached statistical significance. The highest reported OR occurred in metal processers (OR = 1.55, 95% CI: 0.98–2.35, n = 58 exposed/212 control cases); glass formers, potters, and related workers (OR = 1.45, 95% CI: 0.75–2.79, n = 14 exposed/39 control cases); and athletes, sportsmen, and related workers (OR = 1.43, 95% CI: 0.35–5.81, n = 6 exposed/21 control cases). A US death certificate study examined 231 industrial and 509 occupational codes in 12,148 multiple myeloma death certificates and 5 age/gender/race-matched controls per case.[412] The results yielded 23 statistically significant odds ratios in 23 occupations and 29 industries. The most consistent, statistically significant increased odds ratio for multiple myeloma occurred in elementary school teachers ($OR_{\text{white females}}$ = 1.5, 95% CI: 1.3–1.7, n = 342 exposed cases; $OR_{\text{white males}}$ = 1.5, 95% CI: 1.2–1.8, n = 140 exposed cases). The odds ratios for the categories of agriculture, forestry, fisheries, and agriculture products/crops were null.

A UK study of 409 multiple myeloma cases and 309 matched hospital controls investigated multiple myeloma risks for workers employed ≥1 year in 18 industries.[413] The relative risk of multiple myeloma was elevated in the food processing/agricultural industries (RR = 1.8, P = 0.002), whereas the RR was statistically nonsignificant for the photographic, petroleum, and painting industries. A proportional mortality ratio (PMR) study of 88,090 Iowa death certificates on white male farmers aged ≥20 years reported a slightly positive and statistically nonsignificant PMR for multiple myeloma (PMR = 1.17, 95% CI: 0.98–1.40, n = 123 cases).[414] A random effects meta-analysis of 32 peer-reviewed, mostly case-control studies of multiple myeloma in farmers reported a modestly elevated metaRR of 1.23 (95% CI: 1.14–1.32).[415] Study heterogeneity was not reported.

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Chemicals

Benzene

Although early data from the Pliofilm cohort suggest a possible link between multiple myeloma and benzene exposure based on four cases, follow-up studies have not consistently reported statistically significant associations between benzene exposure and multiple myeloma.[416,417] The 28-year, retrospective cohort study of over 73,000 benzene-exposed Chinese workers ($Mean_{time\text{-}weighted\ average}$ = 22.5 ppm benzene) identified one multiple myeloma case in exposed workers and three cases in controls (RR = 0.12, 95% CI: 0.01–0.96). Multiple myeloma is a very rarely reported disease in Asia, particularly in young and middle-aged workers.[315] A historical cohort study investigated multiple myeloma risks in 27,919 Norwegian offshore (6,734 upstream operator offshore) workers employed from 1981–2003 in the upstream petroleum industry exposed to benzene in crude oil, natural gas, drilling mud, and other products using Cox proportional hazard regression modeling.[418] Referents included 366,114 non-benzene-exposed Norwegian workers matched by gender, age, and community of residence. The authors surmised that upstream operator offshore workers were the most highly benzene workers; however, quantitative data on benzene concentrations and smoking were not available. The rate ratio for multiple myeloma in these workers was elevated (RR = 2.49, 95% CI: 1.21–5.13, n = 9 operator cases/132 referent cases). All multiple myeloma cases in upstream operator offshore workers occurred in cases with first exposures prior to 1986. The median time between the first year of registered engagement and the diagnosis of multiple myeloma in upstream operators offshore included in the cohort prior to 1986 was 18 years (range, 13–20 years). Examination of cohort studies of benzene-exposed workers suggests the time from first benzene exposure until diagnosis of multiple myeloma in other studies may range up to 20 years.[419]

A meta-analysis of 26 cohort studies examining benzene-exposed workers and multiple myeloma reported a slightly positive, statistically nonsignificant metaRR for multiple myeloma (mRR = 1.12, 95% CI: 0.98–1.27, n = 284 exposed cases).[420] The metaRR for multiple myeloma was more positive for the start of follow-up after 1972 (mRR = 1.26, 95% CI: 0.92–1.71, n = 10 studies/80 exposed cases) than before 1972 (mRR = 1.07, 95% CI: 0.93–1.24, n = 16 studies/204 exposed cases). In the highest category of exposure assessment quality, the metaRR for multiple myeloma was also more positive, but statistically nonsignificant (metaRR = 1.48, 95% CI: 0.96–2.27, n = 8 studies/28 exposed cases) than poorer-quality studies using less robust exposure measures. The exposure-response relationship between benzene exposure and multiple myeloma was unclear in this study.

Chlorinated Solvents

Few studies specifically examine myeloma risks following exposure to chlorinated solvents. Most mortality and cohort studies have not reported increased multiple myeloma risks in trichloroethylene-exposed workers; however, the power of these studies is limited by relatively small case numbers.[421,422] A follow-up study of 14,455 civilian workers at the Hill Air Force Base in Utah investigated cancer mortality and exposure to organic solvents for at least 1 year from 1952–1956, particularly trichlorethylene (TCE).[423] The measures of exposure were ever- versus never-use and tertiles of cumulative TCE exposure using a Cox proportional hazards regression model to estimate relative risk; little quantitative historical data were available. The relative risk of multiple myeloma in the TCE-exposed workers was slightly positive, but statistically nonsignificant (RR = 1.35, 95% CI: 0.62–2.93, n = 25 exposed cases). Examination of tertiles of TCE exposure did not demonstrate a clear exposure-response relationship ($RR_{highest\ cumulative\ tertile}$ = 1.19, 95% CI: 0.40–3.54, n = 7 exposed cases). A population-based US study of 180 multiple myeloma cases identified from Surveillance, Epidemiology, and End Results (SEER) cancer registries in Washington State and Detroit (50% participation rate) and 481 random-dialed controls (52% participation rate) used unconditional logistic regression to estimate odds ratios.[424] Organic solvent exposure was based on job-specific questionnaires and in-person interviews, with no surrogates completing reports of solvent exposure. Comparing ever- versus never-TCE use, the odds ratio for TCE was positive, but statistically nonsignificant (OR = 1.4, 95% CI: 0.9–2.1, n = 66 exposed case/138 control cases). The results demonstrated no significant exposure-response relationship for quartiles of exposure duration (P = 0.41), cumulative exposure (P = 0.10), or cumulative exposure, 10-year lagged (P = 0.08). The study also reported positive odds ratios for 1,1,1-trichloroethane, tetrachloroethylene, and methylene chloride; however, exposure-response relationships did not support a causal association.

Agriculture

The North American Pooled Project investigated pesticide use and multiple myeloma by combining

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data from 3 US and Canadian case-control studies involving 54 multiple myeloma cases and 2,700 age/sex/residence-matched population controls. Exposure categories included ever- versus never-use, duration, and cumulative lifetime days based on self-reports or proxies (35% cases/28% controls) for 2,4-D, captan, carbaryl, chlordane, DDT, glyphosate, lindane, malathion, and methoxychlor.[425] Comparing ever-/never-use, the age/residence/proxy respondents/allergic conditions/rheumatoid arthritis-adjusted odds ratios for chemical pesticide classes (phenoxy herbicides, organochlorine insecticides, organophosphate insecticides, carbamate insecticides) were modestly positive, but statistically nonsignificant. Excluding proxy respondents increased the organochlorine insecticide odds ratio (OR = 1.33, 95% CI: 1.01–1.75, n = 264 exposed/442 control cases); however, odds ratios for the other pesticide classes remained nonsignificant. The adjusted odds ratios of multiple myeloma for specific pesticides were elevated for carbaryl (OR = 2.02, 95 CI: 1.28–3.21, n = 29 exposed/96 control cases), captan (OR = 1.98, 95 CI: 1.04–3.77, n = 15 exposed/40 control cases), and DDT (OR = 1.44, 95 CI: 1.05–1.97, n = 66 exposed/270 control cases) with some evidence of an exposure-response relationship. The odds ratios for the other pesticides were not statistically significant. In a combined random effects and fixed-effects meta-analysis of ever-/never-use of glyphosate, the mRR was modestly positive and marginally significant (mRR = 1.4, 95% CI: 1.0–1.9, n = 4 case-control studies, I^2 = 0.0%, $P_{\text{heterogeneity}}$ = 0.63).[286] Based on an overall evaluation of the medical literature and study limitations, the authors concluded the association was not causal.

Ionizing Radiation

Although early data from the Life Span Study cohort of Japanese atomic-bomb survivors suggested excess mortality from multiple myeloma, later evaluations did not support significant excess morality and reduced point estimates. In an update following 113,011 participants for over 3.6 million person-years from 1950–2001 using Poisson regression methods, analysis of data from atomic-bomb survivors in Hiroshima and Nagasaki did not detect a statistically significant excess of multiple myeloma risks among 136 survivors with adequate data (ERR/Gy = 0.38, 95% CI: −0.23 to 1.36, $P_{\text{difference}}$ = 0.21).[119,121] The authors concluded that the study demonstrated no evidence of radiation-associated excess multiple myeloma risks. Thorotrast® was an X-ray contrast medium during the 1930s–1950s that exposed the patient to chronic α-radiation from thorium deposition in various organs.[426] The standardized mortality rate for multiple myeloma was positive and statistically significant, but imprecise for men (SMR = 9.2, 95% CI: 1.1–425, n = 6 cases); the SMR for women was noncalculable in the absence of multiple myeloma cases.

A pooled cohort of 119,195 US nuclear workers at 4 Department of Energy nuclear weapons facilities reported a mean radiation dose among the cohort of 20 mSv.[251] In contrast to the Life Span Study cohort, multiple myeloma mortality excess relative risk (ERR) was positive and statistically significant, but imprecise (ERR/10 mSv = 3.9%, 95% CI: 0.60–9.5%). Overall mortality was below expectations compared with the general population. The International Nuclear Workers study followed a cohort of 308,297 workers for a total of 8.2 million person-years; the estimated average career absorbed radiation dose to the active red bone marrow was 15.9 mGy (95% CI: 2.1–78.0 mGy).[427] The ERR/Gy for multiple myeloma and immunoproliferative diseases was not statistically significant for a fitted lag of 2 years (ERR/Gy = 1.24, 90% CI: −0.84 to 4.46, $P_{\text{heterogeneity}}$ = 0.626); this lag period represented the maximum likelihood.

Lifestyle

Alcohol consumption, tobacco smoking, and diet are not strongly associated with multiple myeloma, whereas some epidemiology data suggest obesity as defined by BMI, but not waist-to-hip ratio or abdominal girth, may modestly increase multiple myeloma risks.[397,428] Most studies on physical activity and multiple myeloma risks report null results.[429,430] Some epidemiological data suggest alcohol consumption is associated with reduced multiple myeloma risks, particularly in female wine drinkers. Observational studies on multiple myeloma and hormonal factors (hormone replacement therapy, parity, age at first birth) overall do not demonstrate a significant association.[431]

Tobacco Smoking

Most observational studies of tobacco smoking and multiple myeloma have not detected elevated multiple myeloma risks. A meta-analysis examined multiple myeloma risks by pooling data from 27 case-control (4,625 cases/21,591 controls) and 13 cohort (2,228 incident cases/1,852,763 subjects) studies using random effects models.[432] The overall odds ratio for multiple myeloma comparing ever-/never-tobacco smokers was

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null (pooled-RR = 0.92, 95% CI: 0.85–1.00, n = 22 studies, I^2 = 49.9%, $P_{\text{heterogeneity}}$ = 0.005). Similarly, current smokers (pooled-RR = 0.87, 95% CI: 0.74–1.03, n = 24 studies, I^2 = 65.3%, $P_{\text{heterogeneity}}$ = <0.001) and former smokers (pooled-RR = 1.04, 95% CI: 0.96–1.13, n = 23 studies, I^2 = 0%, $P_{\text{heterogeneity}}$ = 0.062) were not associated with increased multiple myeloma risks. A prospective cohort study of 336,381 Swedish construction workers followed for a mean of 22.2 years examined the relationship between self-reported tobacco smoking and 520 incident cases of multiple myeloma using Cox proportional hazards regression models to estimate incidence rate ratios (IRR).[433] Using never-users as referents, the age/BMI-adjusted IRR for multiple myeloma was not statistically significant for current smokers (IRR = 0.96, 95% CI: 0.77–1.20, n = 168 cases) or ex-smokers (IRR = 1.11, 95% CI: 0.86–1.43, n = 102 cases).

Alcohol

Some observational data suggest an inverse relationship between specific alcoholic beverage types and multiple myeloma risks. In a meta-analysis of 8 case-control and 10 cohort studies involving 5,694 multiple myeloma patients using random effects modeling, the relative risk of multiple myeloma comparing ever-users and non-/never-alcohol drinkers was null overall (pooled mRR = 0.97, 95% CI: 0.85–1.10) with the results similar in case-control and cohort studies.[434] Using non-alcohol drinkers as referents, dose-risk analysis indicated an ~15% reduction in multiple myeloma risks for two to four drinks daily. A meta-analysis examined multiple myeloma risks by pooling data from 16 case-control (3,921 cases/19,594 controls) and 10 cohort (3,167 incident cases/2,557,649 subjects) studies using random effects models.[435] Overall, the odds ratio for multiple myeloma comparing ever-and never-alcohol drinkers indicated a statistically significant inverse relationship (pooled-RR = 0.88, 95% CI: 0.79–0.99, n = 22 studies, I^2 = 49.9%, $P_{\text{heterogeneity}}$ = 0.005) with moderate heterogeneity. The pooled RR was stronger for wine drinkers and women, whereas the results for men, beer, and liquor were null.

Obesity

Several epidemiology studies suggest self-reported obesity (BMI = ≥30 kg/m^2) modestly increases multiple myeloma risks. The National Institutes of Health-AARP Diet and Health Study examined multiple myeloma risk using baseline questionnaires from 485,049 participants aged 50–71 years (no proxy respondents) on self-reported height and weight along with state cancer registries to identify multiple myeloma cases.[430] Compared with referents (BMI = 18.5–22.49 kg/m^2), the trend for increasing weight quartiles was statistically significant for baseline weight (P_{trend} = 0.008) and 50 years (P_{trend} = 0.04). The hazard ratios as estimated by Cox proportional hazards regression models were statistically significant for the severely obese category (≥35 kg/m^2) at baseline (HR = 1.55, 95% CI: 1.01–2.39, n = 34 cases) and 50 years (HR = 1.77, 95% CI: 1.05–2.99, n = 18 cases), but not for the overweight categories (25–29.9 kg/m^2). Modeling BMI as a continuous variable with multiple myeloma risks, the hazard ratio/5-kg/m^2 increment in BMI was marginally statistically significant ($HR_{\text{continuous}}$ = 1.10, 95% CI: 1.00–1.22). Waist size and waist-to-hip ratios did not demonstrate a statistically significant relationship with multiple myeloma risks. A Swedish/Finnish cohort study of 70,067 twins used Cox proportional hazards models to estimate hazard ratios for obese (BMI = ≥30 kg/m^2) and overweight participants (BMI = 25–29.99 kg/m^2), with normal weight participants as referents (BMI = 18.50–24.99 kg/m^2).[436] The sex/age/country-adjusted hazard ratio was statistically significant for obese participants (HR = 2.1, 95% CI: 1.1–3.7, n = 13 cases), but not for overweight participants (HR = 1.0, 95% CI: 0.7–1.5, n = 45 cases).

A meta-analysis of 15 cohort studies on multiple myeloma risks reported modestly elevated risks for overweight (summary RR = 1.12, 95% CI: 1.07–1.18, I^2 = 0%, $P_{\text{heterogeneity}}$ = 0.73) and obese participants (summary RR = 1.21, 95% CI: 1.08–1.35, I^2 = 34.1%, $P_{\text{heterogeneity}}$ = 0.07). On a continuous scale, a 5-kg/m^2 increment in BMI was associated with a statistically significant increased multiple myeloma risk ($HR_{\text{continuous}}$ = 1.12, 95% CI: 1.08–1.17, n = 15 studies, $P_{\text{heterogeneity}}$ = 0.41).

Diet

Epidemiology studies on the relationship between diet and multiple myeloma risks are conflicting, with some suggestions of modest inverse effects for fruit, vegetable, and fish consumptions; however, the results are inconclusive.[397] The European Prospective Investigation into Cancer and Nutrition (EPIC) study used Cox proportional hazards regression to estimate the relationship between quartiles of vegetable/fruit intake and multiple myeloma risks based on self-administered dietary assessment instruments covering their diet over the previous 12 months.[437] The hazard ratio for multiple myeloma comparing the highest and lowest quartile of total fruit intake was inverse and statistically significant (HR = 0.60, 95% CI: 0.37–0.98, n = 52

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cases); trends for all other vegetable/fruit categories were statistically nonsignificant including total vegetables (P_{trend} = 0.85), leafy vegetables (P_{trend} = 0.36), onions/garlic (P_{trend} = 0.83), citrus fruits (P_{trend} = 0.15), and hard fruits (P_{trend} = 0.44). Using multivariate analysis, tobacco smoking/ethanol consumption/energy intake/education-adjusted hazard ratios per 100 g of intake were statistically nonsignificant for total vegetable intake (HR = 1.03, 95% CI: 0.90–1.18) and total fruit intake (HR = 0.93, 95% CI: 0.83–1.03). A meta-analysis of four hospital-based case-control, three population-based case-control, and four cohort studies evaluated multiple myeloma risks using random effects models to estimate summary relative risks.[52] The summary relative risk for fish/seafood consumption was marginally inverse (summary RR = 0.71, 95% CI: 0.51–1.00, n = 6 studies/2,238 cases, I^2 = 82%) with high heterogeneity. The result for white meat was null with little heterogeneity, whereas the summary RR for red and processed meats was positive, but statistically nonsignificant with high heterogeneity. For dairy products, the RR was close to null for cheese (RR = 0.94, 95% CI: 0.36–2.41, n = 3 studies/571 cases, I^2 = 67%) and milk (RR = 1.08, 95% CI: 0.46–2.54, n = 3 studies/571 cases, I^2 = 64%).

Diseases

The association of multiple myeloma with autoimmune diseases is inconsistent and relatively modest.[438] A retrospective cohort study of 4,501,578 US veterans used Poisson regression to estimate age/race/latency-adjusted, multiple myeloma relative risks for veterans with autoimmune diseases.[439] The RR was slightly positive and statistically significant (RR = 1.15, 95% CI: 1.02–1.28, n = 362 cases); however, subgroup analysis limiting the cohort to follow-up of ≥10 years reduced the aRR to a statistically nonsignificant value (RR = 1.07, 95% CI: 0.90–1.26, n = 152 cases). In a systematic review and pooled analysis of data from 31 observational studies, the relative risk for multiple myeloma in cases with any autoimmune condition was statistically significant (pooled RR = 1.13, 95% CI: 1.04–1.22, I^2 = 43%, $P_{heterogeneity}$ = ≤0.001) with mild heterogeneity and evidence of publication bias (P_{Egger} = 0.02).[440] The results were driven primarily by statistically significant associations with autoimmune hemolytic anemia (pooled RR = 2.80, 95% CI: 1.37–5.74, n = 3 studies, I^2 = 40.8%, $P_{heterogeneity}$ = 0.18) and pernicious anemia (pooled RR = 1.50, 95% CI: 1.25–1.80, n = 6 studies, I^2 = 27.8%, $P_{heterogeneity}$ = 0.23). The associations between all other autoimmune conditions and multiple myeloma were statistically nonsignificant.

Although to a lesser extent than HL and NHL, severe immune suppression (e.g., HIV, organ transplantation) increases multiple myeloma risks. In a meta-analysis of six cohort studies, the meta-SIR for multiple myeloma was 2.71 (95% CI: 2.13–3.44, n_{MM} = 76 cases, $P_{heterogeneity}$ = 0.78) and 3.12 (95% CI: 2.13–4.57, n_{MM} = 31 cases, $P_{heterogeneity}$ = 0.67) for multiple myeloma in three cohorts of transplant patients.[441] Analysis of data from 98,336 people with AIDS and a population-based cancer registry in the United States and Puerto Rico containing 1,125,098 subjects with cancer aged <70 years investigated multiple myeloma risks.[442] The post-AIDS trend for the relative risk of multiple myeloma was statistically significant (P = 0.01) and the RR was positive, but imprecise and statistically nonsignificant (RR = 4.5, 95% CI: 0·9–13.2). Observational studies on multiple myeloma risks associated with hepatitis C (HCV) are conflicting. A meta-analysis of 6 population-based and 11 hospital-based case-control studies consisting of 11,697 cases and 344,521 controls using random effects models reported a positive, statistically significant pooled odds ratio for multiple myeloma (pooled OR = 2.67, 95% CI: 1.35–5.26; I^2 = 88.1%, $P_{heterogeneity}$ = 0.000) with high heterogeneity.[443] Subgroup analysis indicated the positive odds ratios depended on study design, quality, and HCV prevalence. The multiple myeloma pooled OR was statistically significant for hospital-based case-control studies (pooled OR = 2.17, 95% CI: 1.45–3.24, P = <0.001, I^2 = 49.6%, $P_{heterogeneity}$ = 0.031), but not for population-based case-control studies (pooled OR = 3.17, 95% CI: 0.92–10.87, P = <0.067, I^2 = 95.4%, $P_{heterogeneity}$ = 0.031). Similarly, the pooled OR was statistically significant for multiple myeloma in high- but not moderate- or low-prevalence countries. An earlier meta-analysis of six cohort studies reported statistically significant positive meta-SIRs for HIV/AIDS (SIR = 2.71, 95% CI: 2.13–3.44, n = 6 studies/76 cases, $P_{heterogeneity}$ = 0.76) and immunosuppressed transplant patients (SIR = 3.12, 95% CI: 2.13–4.57, n = 3 studies/31 cases, $P_{heterogeneity}$ = 0.67).[441] The meta-analysis detected no publication bias.

HISTOLOGY

Multiple myeloma is a mature B cell neoplasm derived from plasma cells that consists of two major subtypes (i.e., hyperdiploid, non-hyperdiploid) associated with unique molecular and genetic features. The two major biological classifications of multiple myeloma tumors are morphologically similar; however, these genetic subtypes have unique clinicopathological features

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and different outcomes. The multiple myeloma tumor consists of innate and adaptive immune cells (e.g., regulatory T cells, dendritic cells), bone marrow stromal cells, vascular endothelial cells, osteoclasts, and osteoblasts. The morphological features of plasma cell leukemia and multiple myeloma are similar in the bone marrow, with increased monoclonal plasma cells of variable maturity and diffuse infiltration. The round nucleus is eccentrically located with pyramidal blocks of chromatin arranged against the nuclear membrane creating a characteristic "cartwheel" appearance.[444]

HOST SUSCEPTIBILITY

The relatively frequent occurrence of multiple myeloma in families suggests a family history of B cell lymphoproliferative diseases predisposes to multiple myeloma, particularly among blacks compared with whites.[445,446] In an analysis of 218 multiple myeloma cases in the Icelandic cancer registry, the occurrence of multiple myeloma in a first-degree relative increased the risk of developing multiple myeloma (OR = 2.33, 95% CI: 1.12–4.26, n = 10 cases).[447] Analysis of pooled data from 11 mostly population-based case-control studies in the International Multiple Myeloma Consortium used unconditional logistic regression models to estimate multiple myeloma risks in participants self-reporting 1st-degree relatives with multiple myeloma.[448] The sex/age/education-adjusted odds ratios for multiple myeloma in participants with first-degree relatives were elevated (aOR = 1.90, 95% CI: 1.26–2.87, n = 45 cases/60 controls), particularly for men (aOR = 4.13, 95% CI: 2.17–7.85, n = 25 cases/20 controls). The adjusted odds ratio for African American/black cases was substantially elevated but unstable compared with European American/white cases. A population-based registry linkage study evaluated familial multiple myeloma risks in 8,406 Swedish multiple myeloma cases, 22,490 first-degree relatives, and 16,543 controls.[438] The relative risk of multiple myeloma increased significantly in first-degree relatives of multiple myeloma patients (RR = 1.67, 95% CI: 1.02–2.73, n = 29 cases), particularly in relatives ≥65 years of age at diagnosis (RR = 2.50, 95% CI: 1.19–5.27, n = 17 cases).

CLINICAL FEATURES

Multiple myeloma is an age-related disease primarily of the elderly being rare in young adults (<2% less than 40 years of age) and extremely uncommon (<0.02%) in childhood.[449] The median age at diagnosis of this neoplasm is ~69 years, with only ~25% of cases presenting less than 55 years of age.[450]

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant B cell disorder that precedes the development of almost all multiple myeloma tumors; however, only ~15% of MGUS cases eventually progress to multiple myeloma.[393,451] Plasma cells (MGUS) are age-dependent, appearing in ~4% of individuals >50 years old. MGUS is typically asymptomatic with no end-organ damage and fewer mutated mononuclear immunoglobulins (mIg)/mononuclear bone marrow cells than multiple myeloma. However, some MGUS patients develop primary amyloidosis from the deposition of pathological mIg light chains in various tissues.[405] Smoldering multiple myeloma (SMM) also has no detectable end-organ damage, but the bone marrow mononuclear cell counts and serum mIg concentrations are higher than MGUS. SMM progresses to multiple myeloma in ~10% of cases annually during the first 5 years after diagnosis, then ~5% annually in the next 5 years, and 1% annually after 10 years.[452] Extramedullary multiple myeloma can present with a leukemic phase (plasma cell leukemia). This very aggressive and rare form of plasma cell dyscrasia is classified as *de novo* primary diagnosed at presentation or secondary to relapse/refractory multiple myeloma. Plasma cell leukemia is defined by >20% plasma cells in peripheral blood and $>2\times10^9$ plasma cells/L, with diagnosis occurring ~10 years earlier (median age = 52–65 years) than multiple myeloma or secondary plasma cell leukemia.[453]

The proliferation of protein-producing myeloma cells produces lytic lesions (pathological fractures), bone pain, anemia, renal dysfunction, hypercalcemia, free urinary light chains, and bloodstream hyperviscosity. The most common clinical features of multiple myeloma include anemia, lytic/osteopenic bone disease, hypercalcemia, infections, amyloid deposition in various tissues, and renal failure from obstructing casts of light-chain immunoglobulins; however, some myeloma patients present incidentally without symptoms. Back pain or anemia without a specific cause in an elderly patient suggests the possibility of multiple myeloma. More aggressive multiple myeloma tumors may metastasize to extramedullary locations (e.g., extracellular spaces, liver, spleen) and progress to plasma cell leukemia.

Multiple myeloma is mostly incurable; however, the survival rate has increased substantially over the last few decades.[454] Recent advances in multiple myeloma treatment (proteasome inhibitors, immunomodulatory drugs) resulted in 5-year survival rates of at least 40–50%.[398,455] The introduction of proteasome inhibitors (e.g., bortezomib, carfilzomib, ixazomib), histone deacetylase (HDAC) inhibitors

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(panobinostat), monoclonal antibodies (daratumumab, elotuzumab), and immunomodulating agents (lenalidomide, pomalidomide) along with hemopoietic stem cell transplantation and CAR T cell therapy within the last 15 years has improved median overall survival rate after diagnosis of multiple myeloma from ~3 to up to 8–10 years.[456] Survival after the diagnosis of plasma cell leukemia is short. Historically, the median survival is <1 year with an overall 5-year survival rate of <10% in most studies.[457]

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Chapter 61

SKIN

Excessive UV radiation is the primary risk factor associated with basal cell and squamous cell carcinomas among fair-skinned persons; both UVA and UVB are established carcinogens producing reactive oxygen species, DNA damage, and immunosuppression (↑inflammatory cytokines).[1,2] These two skin cancers arise from epidermal keratinocytes. Although nonmelanoma skin cancer traditionally refers to these two skin cancers, keratinocyte carcinoma is a more accurate term that separates these two cancers from other, relatively rare nonmelanoma cutaneous cancers (adnexal carcinoma, dermatofibrosarcoma protuberans, highly aggressive Merkel cell neuroendocrine carcinoma, primary cutaneous B cell lymphoma, Kaposi sarcoma). Despite many similarities between basal cell and squamous cell carcinomas, high-risk squamous cell carcinoma is a biologically and clinically distinct tumor.[3] Keratinocyte carcinomas are the most common malignancies in the United States, with basal cell carcinomas of the skin 3–4-fold more common than cutaneous squamous cell carcinomas depending on sex, age, skin pigment, and sun-related exposure.[4,5] The exact incidence of keratinocyte carcinomas is unclear because many cancer registries do not include these cancers in local cancer registries, including the US National Cancer Institute's/Surveillance, Epidemiology, and End Results (SEER) program. Both basal and squamous cell carcinomas are more common in sun-exposed areas of the skin.

UV radiation exposure produces an increased risk of squamous cell carcinomas, basal cell carcinomas, and the premalignant lesions of actinic keratosis.[6] Intermittent, excessive sun exposure (lifetime sunburn, childhood sunburn) is a more important risk factor for basal cell carcinoma than squamous cell carcinoma, whereas a high cumulative UV radiation dose (lifetime sun exposure) is a more important risk factor for squamous than basal cell carcinoma.[7] Promoting agents include nonspecific skin irritation (burn scars, decubitus ulcers, chronic sinus tracts), phototoxic agents (8-methoxypsoralen), and chemicals (croton oil, phorbol esters, *n*-dodecane). Radiotherapy-induced skin tumors are uncommon today after recognition of the limited cutaneous carcinogenic risks associated with small fractional radiation doses totaling <1,000 R (9.33 Sv).[8] Table 61.1 lists agents and chemicals classified by the International Agency for Research on Cancer (IARC) as melanoma and keratinocyte carcinoma carcinogens.

BASAL CELL CARCINOMAS

Basal cell carcinoma is the most common worldwide cancer in light-skinned races, with incidence rates continuing to increase as the population ages and lifestyle changes (e.g., clothing, tanning equipment), particularly in young European and US fair-skinned women.[10] Basal cell carcinomas account for >70–80% of epithelial skin tumors, with a propensity for head (e.g., ears) and neck skin in patients of >50 years of age, with an average lifetime basal cell carcinoma risk for white-skinned individuals of ~30%.[11] Together with squamous cell carcinoma, these two keratinocyte carcinomas account for

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TABLE 61.1. International Agency for Research on Cancer (IARC) Classification of cutaneous cancer sites by sufficient and limited evidence of human carcinogenicity. (Adapted from IARC).[9]

Anatomical Site	Carcinogen with *Sufficient* Human Evidence (Group 1)	Carcinogen with *Limited* Human Evidence (Group 2A or 2B)
Melanoma	Polychlorinated biphenyls, solar radiation, ultraviolet-emitting tanning devices, polychlorinated biphenyls	Firefighting (occupation), petroleum refining (occupation)
Keratinocyte carcinomas	Arsenic and inorganic arsenic compounds, azathioprine, coal-tar distillation, coal-tar pitch, cyclosporine, methoxsalen plus ultraviolet A radiation, mineral oils, untreated or mildly treated, shale oils, solar radiation, soot chimney sweep occupation, X- and γ-ray radiation	Creosotes, human immunodeficiency virus type 1 infection, human papillomavirus types 5 and 8 (associated with epidermodysplasia verruciformis), hydrochlorothiazide, nitrogen mustard, (occupational exposures), petroleum refining, ultraviolet-emitting tanning devices, Merkel cell polyomavirus (MCVyP)

~95% of malignant skin cancers.[12] Basal cell carcinoma incident rates vary from >1,000/100,000 person-years in Australia to much lower rates in South America, Asia, and Africa (<1/100,000 person-years). These rates are strongly correlated with geographical latitude and inhabitant pigment status.[13] Basal cell carcinoma incidence varies geographically over 10–25-fold in Caucasians reflecting differences in the annual mean ambient UV radiation dose related to geographical areas (i.e., latitude). The highest incidence occurs closest to the equator.[14] For men of ≥80 years of age, the basal cell carcinoma incidence varied from 475/100,000 ($\text{Mean}_{\text{annual ambient UVR}} = 0.8\,\text{kJ/m}^2$) to 14,173/100,000 ($\text{Mean}_{\text{annual mean ambient UVR}} = 1.8\,\text{kJ/m}^2$).[15] The exact incidence and distribution of basal cell carcinomas are unclear because many basal cell carcinomas are diagnosed clinically without histological confirmation. Many national/regional cancer registries do not include this tumor because of its high prevalence and little to no increased mortality.[16]

CARCINOGENESIS

Basal cell carcinoma is a complex epithelial skin cancer resulting from the interaction of ultraviolet radiation, UVR-sensitive phenotypes, and somatic/germline gene mutations. The major drivers of basal cell carcinoma involve mutations that activate the Sonic Hedgehog signaling pathway (organogenesis, stem-cell maintenance) and involve tumor suppressor genes (patched 1, *PTCH1*; tumor protein p53, *TP53*) with much smaller contributions from mutations in the *SUFU* gene (SUFU-negative regulator of hedgehog signaling). In a genetic profiling study of 293 basal cell carcinomas, additional, more infrequent drivers included mutations in *MYCN* (*MYCN* proto-oncogene, bHLH transcription factor), *PPP6C* (protein phosphatase 6 catalytic subunit), *STK19* (serine/threonine kinase 19), *LATS1* (large tumor suppressor kinase 1), *ERBB2* (erb-b2 receptor tyrosine kinase 2), and *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) genes.[17] Mutations in *MYCN*, *PTPN14*, and *LATS1* genes upregulate the Hippo-YAP pathway involved with cell proliferation, organogenesis, repair, apoptosis, and homeostasis.[18]

The *PATCH1* gene (chromosome 9q22) encodes a protein receptor associated with the upregulation of the Sonic Hedgehog signaling pathway and the development of embryonic structures as well as tumors.[19] Patched-1 and Sonic Hedgehog pathways influence cell growth, cell specialization, and the shape of the developing body (patterning).[20] The absence of Sonic Hedgehog signaling activation and patched-1 protein prevents cell proliferation and division. Somatic PCTH1 mutations occur in the vast majority (i.e., ~90%) of sporadic basal cell carcinomas, with the lack of inhibitor patched-1 protein producing uncontrolled activation of smoothened gene (*SMO*, chromosome 7q32), resulting in resistance of keratinocytes to apoptosis.[21] The cellular translocation of *SMO* interferes with the patched protein and prevents normal inhibition by patched or smoothened (*SMO*). Approximately 30–40% of sporadic basal cell carcinomas contain the PTCH tumor suppressor gene mutation, whereas ~20% contain the SMO (smoothened, frizzled class G-protein-coupled receptor) mutation.[22]

TP53 (chromosome 17p13) gene encodes the tumor suppressor protein p53 involved with DNA repair, cell-cycle arrest, senescence, and apoptosis; somatic mutations in *TP53* occur in a majority of sporadic basal cell carcinomas.[23] Basal cell carcinomas on the head/neck (i.e., more sun-exposed skin areas) more commonly express *TP53* than basal cell carcinomas in

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other sites on the body.[24] In addition to causing genetic mutations, solar radiation induces immunosuppression by altering cytokine expression (IL-3, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor-α, and epidermal dendritic Langerhans cells, CD1a+) along with the formation of reactive oxygen species.[25]

EXPOSURE

Basal cell carcinomas arise from the complex interaction of genetic abnormalities (mutations, signal nucleotide polymorphisms), phenotypic expression (age, light pigment status, tanning ability, personal skin cancer history, childhood sunburn/actinic skin damage), environmental risk factors (intense youth UV radiation exposure, sunbed use, arsenic exposure), and certain medical therapies (immunosuppression, ionizing radiation, PUVA/UVB therapy). The strongest risk factor for basal cell carcinoma is ultraviolet (UV) light, with the risk depending on dose, pattern, sub-types, and age at exposure along with susceptibility factors.[6,26] Compared with UV radiation, all other predisposing risk factors produce small effect sizes including light skin type, immunosuppression, and rare genetic disorders (e.g., albinism, Gorlin syndrome, xeroderma pigmentosum). Little epidemiology data support the substantial influence of dietary factors on basal cell carcinoma risks, including protective effects of carotenoids, selenium, and vitamins.[27]

Ionizing Radiation

Ultraviolet

UV light refers to the portion of the light spectrum wavelength between the visible blue section and soft X-rays and Grenz rays; 6.8% of solar radiation lies in the UV spectrum compared with 54.3% in near-infrared wavelengths and 38.9% in the visible light range (400–760 nm).[28] UVA is the portion of the light UV band between 315 and 400 nm that usually produces photosensitivity reactions rather than malignant tumors. Oxygen and ozone in the stratosphere absorb 77% of UV radiation including all UVC (100–280 nm) and >90% of UVB radiation (280–315 nm). Consequently, >95% of UV solar radiation reaching the earth's surface is UVA capable of inducing mutations in *TP53* in basal keratinocytes.[29] UVB exposure represents 1–5% of solar radiation at the earth's surface, usually accounting for sunburns and oncogenic mutations in epidermal keratinocytes. UVC (200–290 nm) potentially may cause cutaneous erythema and tumors, but this portion of UV radiation seldom penetrates the ozone layer. The development of skin cancer depends on the total UV radiation dose, the UV fractionation dose (i.e., divided UV radiation doses more effectively induce skin cancer),[30] the amount of melanin pigment present in the skin, and the competency of the immune system with the contribution probably greater from the higher energy in UVB than the lower energy in UVA. Absorption of the former occurs primarily in the epidermal area containing DNA and proteins, whereas UVA penetrates the epidermis depositing the UVA radiation mostly in the basal epidermis and dermal fibroblasts. Hence, UVB causes direct effects on DNA and proteins, whereas UVA causes indirect effects involving the generation of reactive oxygen species.[31] UV radiation accounts for most cutaneous damage predisposing white-skinned individuals to basal cell carcinoma, particularly UVB.

Solar

In contrast to the more direct association between squamous cell carcinoma risks and cumulative UVB radiation exposure, the association between solar UV exposure and basal cell carcinoma is more complex and less consistent. Observational studies suggest solar UV radiation will increase basal cell carcinoma risks more when delivered in infrequent, intense increments (i.e., sunburn) than a similar dose delivered continuously over the same total time period, particularly in young individuals.[32,33] Although sun exposure is a very important basal carcinoma risk factor, multiple risk factors (e.g., red/light hair color, light eye color, sunburn sensitivity, sunburn history, north European ancestry) influence the effect of solar radiation on basal cell carcinoma incidence rates. Some observational studies do not support a strong association between various types of solar radiation and basal cell carcinoma. A US population-based, cross-sectional study of 808 white watermen over the age of 30 years (~70% participation rate) and age-matched controls examined the prevalence of basal cell carcinoma and average UVB exposure based on personal interviews, field measurements, and expert analysis.[34] The average annual UVB exposure was similar in 33 watermen with basal cell carcinoma and controls in contrast to the higher UVB radiation exposure in 35 watermen with squamous cell carcinoma. Using logistic-regression models and comparing estimated cumulative UVB exposure to age 60 years between the highest and other UVB exposure quartiles, the prevalence of squamous cell cancer (OR = 2.53, 95% CI: 1.18–5.40), but not basal cell carcinoma, exposure (OR = 1.11, 95% CI: 0.50–2.44) was statistically significant. Using mean daily, erythemal

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weighted ambient UV radiation levels derived from satellite measurements of column ozone, age/sex/study year-adjusted incidence data from 40 selected studies, and Poisson distribution regression analysis to model estimates of basal cell carcinoma incidence, these variables *together* explained 82% of the variability in basal cell carcinoma incidence among adolescent and adult Caucasians.[35] The mean daily UV radiation alone accounted for 37% of the variability.

An Italian hospital-based study of a convenience sample consisting of 166 basal cell carcinoma cases and 158 controls suggests an association between basal cell carcinomas and early, intense, intermittent solar radiation exposure. The multivariate-adjusted basal cell carcinoma risk for the highest tertile of early recreational sun exposure (>8 weeks yearly before age 20 years) was elevated and statistically significant (aOR = 4.5, 95% CI: 1.9–10.5, $n = 53$ cases/30 controls, $P_{\text{trend}} = 0.01$).[36] The wide confidence interval suggests imprecise risk estimates. This and other[37] studies indicate increased basal cell carcinoma risks occur in areas containing sun-induced skin damage (actinic keratoses, solar lentigines), particularly in an individual with a genetic predisposition to sunburn. Approximately 20% of basal cell carcinoma cases occur in non-sun-exposed skin areas of the body.

Artificial UV Sources

The UVA/UVB ratio and intensity differ in tanning beds compared with solar UV radiation. Pre-1980s, mercury sunlamps emitted UVB and UVC wavelengths, whereas tanning beds distributed in the 1980s emitted predominantly UVA radiation (95% UVA/1% UVB).[38] During the 1990s, high-intensity, high-speed devices increased the UVB portion by up to 5%.[39] UVA radiation exposure from tanning devices may exceed midday solar sun UVA exposure depending on the device, with basal cell carcinoma risks being dependent on frequency, duration, and age at use, along with host susceptibility factors.[40]

Several observational studies suggest indoor tanning contributes to basal cell carcinoma risks; however, variation in tanning-bed usage patterns/spectral output over time, control of confounding factors (e.g., solar UV radiation, skin type, tanning ability), and study design issues (e.g., recall bias, small sample sizes, insufficient lag times) complicate the determination of causation. In a meta-analysis of 10 mostly case-control studies using random effects models and never-users as referents, the summary RR for ever-users of indoor tanning was modestly elevated and statistically significant (sRR = 1.29, 95% CI: 1.08–1.53, $I^2 = 36.8\%$, $P_{\text{heterogeneity}} = 0.14$).[41] Other than sunbed use and solar UV exposure, limited epidemiology data suggest lifestyle factors do not strongly influence basal cell carcinoma risks.

Non-ultraviolet

Ionizing radiation increases basal cell carcinoma risks at the irradiation site from medical radiation (e.g., ankylosing spondylitis, acne, *Tinea capitis*, brain tumors), atomic bomb survivors,[42] and radiological technologists. In a US population-based study of 592 basal cell carcinomas identified through a statewide surveillance system and 536 age/sex-matched unexposed controls, the basal cell carcinoma risk in the radiation site comparing ever- versus never-receiving therapeutic radiation was elevated and statistically significant (OR = 3.3, 95% CI: 1.60–6.81), particularly in patients exposed prior to 20 years of age.[43] A US cohort study of 65,304 white, mostly female radiology technologists estimated relative risks for basal cell carcinomas based on baseline mailed questionnaires and Cox proportional hazard models. After a mean follow-up of 10.2 years, a subsequent questionnaire examined skin cancer history and associated risk factors.[44] Approximately one-half of the follow-up questionnaires were confirmed by medical record reviews. Adjusted factors included age, sex, skin complexion, eye and hair color, and self-reported childhood and adult UV exposure. The adjusted RR was categorized by decade using cases first working after 1959 as referents. Table 61.2 displays the results by decade first worked as a radiology technologist.

Occupation

Persons in outdoor occupations (farmers, sailors, gardeners) have a higher incidence of skin cancer compared with persons engaged in indoor occupations.[45] A study of Czechoslovakian uranium miners

TABLE 61.2. Adjusted relative risks for basal cell carcinoma by decade first worked as radiology technologist using ≥1960 basal cell carcinoma incidence as reference.[44] The P_{trend} for the difference between decades and references was statistically significant ($P_{\text{trend}} = <0.001$). Presumably, ionizing radiation doses for the workers were higher in earlier decades; however, the duration of work did not correlate with basal cell carcinoma risks. (Data adapted from Yoshinaga et al.).[44]

Decade	Adjusted Relative Risk	95% CI	Cases in Decade
<1940s	2.16	1.14–4.09	18
1940s	2.04	1.44–2.88	131
1950s	1.42	1.12–1.80	303
≥1960s	1.0[a]		868

Abbreviation: CI = Confidence Interval.
[a] referents.

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detected an increased incidence of basal cell carcinomas predominantly in the cheek and forehead of these workers that, according to the authors, resulted from excessive alpha particle radiation;[46] however, this study has not been replicated in other uranium workers.

Arsenic

Arsenic (As) is a natural constituent of well water in some areas of Bangladesh, India, China, Southwest Taiwan, Northern Chile, and Argentina. Keratinocyte skin cancers (basal cell/squamous cell carcinomas) are well-recognized causes of chronically ingesting high arsenic doses (>100 μg/L) from arsenic-contaminated artesian (tube) well water and medicinal arsenicals.[47] Melanoma is not clearly associated with these arsenic exposures.[48] The threshold for As-induced skin cancer remains controversial in part because of the difficulty in excluding confounders (genetic predisposition, metabolic polymorphisms, UV radiation, socioeconomic status).[49] Skin cancer is the most common neoplasm associated with As ingestion. In a retrospective nationwide population-based survey of keratinocyte cancers, the age-standardized incidence rate of cutaneous basal cell carcinoma was 3–4-fold higher in black foot disease-endemic areas with very high As-contaminated well water than other areas in Taiwan.[50] These rates have decreased in the last several decades due to public health efforts to reduce As contamination. In contrast to UV-induced skin cancers, arsenic-induced basal cell carcinomas typically develop in multiple sites within areas protected from sun exposure.[51]

Occupational As exposure occurs in a variety of industries including mining, manufacturing (agricultural products, electronic semiconductors, glass/pigment production, animal feed additives), and metal smelting. Although As commonly contaminates industrial discharges (metal smelting, coal-fired power generation), epidemiology studies on occupational arsenic exposure and basal cell carcinomas are inconsistent.[52] A multinational European study of 618 incident keratinocyte carcinomas and 527 hospital-based controls examined basal cell carcinoma risks comparing self-reported and expert reviews of ever- versus never-arsenic exposure in the workplace. The age/sex/residence/family history/sun sensitivity/As drinking water-adjusted odds ratio for basal cell cancer was modestly positive and statistically nonsignificant (aOR = 1.22, 95% CI: 0.84–1.75, $n = 113$ cases/80 controls). Basal cell carcinoma risk for the highest tertile of cumulative lifetime was positive and statistically nonsignificant (aOR = 1.47, 95% CI: 0.83–2.58, $n = 39$ cases/25 controls).

Lifestyle

Tobacco Smoking

Current epidemiology data do not associate tobacco smoking with increased basal cell carcinoma risks. Some, but not all, observational studies suggest an inverse relationship between basal cell carcinoma risks and tobacco smoking.[53] An analysis of data from a large UK primary care database (Clinical Practice Research Datalink) compared basal cell carcinoma risks in 6,999 current smokers with 28,058 age/sex-matched nonsmoking controls.[54] The basal cell carcinoma risk for current smokers was inverse and statistically significant (aOR = 0.77, 95% CI: 0.74–0.80). The Australian prospective Nambour Skin Study identified 281 basal cell carcinomas in 1,277 participants with no prior basal cell carcinoma history. Smoking history was assessed at baseline and during updates over 16 years of follow-up. After adjustment for multiple confounders (age, sex, education, occupational sun exposure, sunscreen/β-carotene treatment, country of birth, skin color), the adjusted relative risk was modestly inverse and statistically nonsignificant for current smokers (aRR = 0.69, 95% CI: 0.45–1.05) and minimally positive and nonsignificant for former smokers (aRR = 1.05, 95% CI: 0.84–1.31) using never-smokers as referents.[55] Tobacco-smoking duration and intensity were not clearly associated with basal cell carcinoma risks. In a meta-analysis of 14 studies using random effects models, the odds ratio for basal cell carcinomas was consistent with null results and moderate heterogeneity (OR = 0.95, 95% CI: 0.82–1.09, $I^2 = 59\%$).[56]

Alcohol

Some epidemiology studies suggest alcohol consumption may modestly increase basal cell carcinoma risks;[57] however, observational studies are inconsistent without support for a strong dose-response relationship or a clear mechanism of toxicity.[58,59] Analysis of data from the large UK primary care database (Clinical Practice Research Datalink) reported the smoking-adjusted odds ratio for basal cell carcinoma comparing never- and current-alcohol use was slightly elevated and statistically significant (aOR = 1.19, 95% CI: 1.15–1.23). The data demonstrated no clear dose-response relationships, with the odds ratio for ex-alcohol users being consistent with the null (aOR = 0.96, 95% CI: 0.87–1.05).[54] The Australian Nambour Skin Cancer Study identified basal cell carcinoma risks in 1,360 participants during 11 years of follow-up using alcohol abstainers as referents.[60] The study reported no association between the highest

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category of alcohol consumption (median = 26.3 g/day) and multivariable-adjusted basal cell carcinoma relative risks (maRR = 1.05, 95% CI: 0.65–1.65, $P_{trend} = 0.84$). Specific beverage types in the moderate and high categories of alcohol consumption were not associated with statistically significant elevations of basal cell carcinoma risks ($P_{trend} = 0.16$–0.93). Multivariate adjustment included age, sex, β-carotene use, skin color, smoking, sun exposure, and skin cancer history.

An analysis of data from three prospective cohort studies included 75,209 women in the Nurses' Health Study (1984–2010), 92,556 women in the Nurses' Health Study II (1991–2011), and 43,697 men in the Health Professionals Follow-Up Study (1986–2010).[61] Using Cox proportional hazard models and alcohol abstainers as referents, the multivariable-adjusted basal cell carcinoma risk for the highest quartile of alcohol consumption (≥ 30 g/day) was modestly elevated and statistically significant (aRR = 1.22, 95% CI: 1.15–1.30, $n = 2{,}015$ cases, $P_{heterogeneity} = 0.10$, $P_{trend} = <0.0001$). The elevated risk/daily 10-g increase in alcohol consumption was slight (aRR = 1.06, 95% CI: 1.03–1.10). In a meta-analysis of two hospital-based case-control and four prospective cohort studies using random effects models, the summary relative risk (sRR)/daily 10-g increase in alcohol consumption for basal cell carcinoma compared with alcohol abstainers was slightly elevated and statistically significant (sRR = 1.07, 95% CI: 1.04–1.09, $I^2 = 61.1\%$, $P_{heterogeneity} = 0.008$) with moderate heterogeneity. The risks were higher in the cohort than in case-control studies.[62] The dose-response curve was nonlinear, with the curve flattening above 9-g daily alcohol consumption. The authors suggest a cautious interpretation of the results because of the potential residual confounding.

Caffeine

Some observational studies[36,59] but not all case-control studies,[63,64] suggest caffeine reduces basal cell carcinoma risks in Caucasians; however, the contribution of caffeine or other constituents of coffee to basal cell carcinoma risks is conflicting. An 11-year prospective study on 1,325 randomly selected adult residents of subtropical Australia with mostly fair to medium skin color examined basal cell carcinoma risks in coffee drinkers based on self-reported food-frequency questionnaires administered every 3 years during follow-up using Poisson and negative binomial regression modeling.[65] The fully adjusted basal cell carcinoma relative risk was not associated with total caffeine intake (aRR = 0.96, 95% CI: 0.87–1.05) or tertiles of caffeine intake ($P_{trend} = 0.20$); however, participants with a prior skin cancer history had a statistically significant reduction in basal cell carcinoma risks comparing the highest (four cups daily) and lowest tertiles of caffeine intake (aRR = 0.75, 95% CI: 0.57–0.97, $n = 427$ participants, $P_{trend} = 0.025$). Adjusted confounders included age, sex, skin cancer history, tanning ability, back freckling, treatment allocation, and neck elastosis.

Obesity

Limited data indicate obesity is not a significant independent risk factor for basal cell carcinoma, with some conflicting results from case-control studies.[66] Analysis of data from the large UK primary care database (Clinical Practice Research Datalink) containing 57,123 incident basal cell carcinomas and 57,123 basal cell carcinoma-free controls suggests an inverse association between obesity and basal cell carcinoma risks using normal weight BMI (18.5–24.9 kg/m^2) as referents.[54] The age/sex/alcohol/smoking-adjusted odds ratio for basal cell carcinoma in obese participants (30.0–60.0 kg/m^2) was inverse and statistically significant (aOR = 0.73, 95% CI: 0.70–0.75). The authors opined that the inverse relationship may result from confounding (e.g., lack of outdoor activity, decreased UV radiation exposure). An analysis of pooled data from two large US cohorts (Health Professionals Follow-Up Study, Nurses' Health Study) reported a combined age- and multivariate-adjusted hazard ratio for basal cell carcinoma of 0.75 (95% CI: 0.67–0.83, $n = 509$ cases) for overweight participants (BMI = 25–29.9 kg/m^2) using normal weight participants (BMI = 18.5–24.9 kg/m^2) as controls ($n = 1{,}254$ cases) and controlling for gender.[67] For very obese participants (≥ 35 kg/m^2), the age- and multivariate-adjusted HR was 0.56 (95% CI: 0.36–0.88, $n = 20$ cases, $P_{trend} = <0.0001$).

Medications

Patients with severe psoriasis may receive >100–200 treatments of psoralen plus a portion of UVA radiation (PUVA) or narrow-band UVB (primarily 311–313 nm) treatments. The prospective Psoralen Ultraviolet A Follow-Up Study used univariate and multivariate Poisson regression, negative binomial regression, and Cox proportional hazard models to estimate basal cell cancer risks in 1,380 psoriasis patients receiving PUVA therapy during ~30 years of follow-up.[68] The mean number of PUVA treatments in the 84% receiving UVB radiation was 206 ± 195; the mean age was 44 ± 16 years, with 29% having skin type I/II. Biopsy-proven basal cell cancer occurred in 330 participants (24%), with most developing multiple tumors (1,729 tumors). After adjusting for age/gender/identified confounders and using patients

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with <50 PUVA treatments as referents, the univariate incidence rate ratio for developing ≥1 basal cell carcinoma per year in participants within the highest quintile (>450 PUVA treatments) was elevated and statistically significant (IRR = 3.09, 95% CI: 2.36–4.6). The multivariate incidence rate ratio for basal cell carcinoma in participants receiving >300 UVB treatments was modestly elevated (IRR = 1.40, 95% CI: 1.21–1.63) using participants with <100 treatments as referents. Limited data suggest self-reported use of some photosensitizing medications (e.g., tetracyclines, thiazide diuretics, nonsteroidal anti-inflammatory drugs) may increase basal cell carcinoma risks;[69,70] however, the results are inconsistent and lack dose-response relationships.

Diseases

Several observational studies suggest diseases associated with chronic immunosuppression (e.g., organ transplant patients/immunosuppressive agents) increase basal cell carcinoma risks.[71,72] In an Italian, partially retrospective cohort study of 1,476 renal and 458 heart transplant recipients, 91 patients (4.7%) developed basal cell carcinoma within a median of 6.8 years after transplantation.[73] Approximately 2% (41 with 1st basal cell carcinoma) developed a 2nd basal cell carcinoma; the occurrence of the 2nd basal cell carcinoma was not associated with age at transplantation, transplanted organ type, or immunosuppressive therapy. A New Zealand cohort of 384 renal transplant patients was followed for 35 years (1972–2007).[74] Approximately 4.4% (17 patients) developed basal cell carcinomas as the 1st keratinocyte carcinoma, whereas 18.5% (71 patients) developed squamous cell carcinomas or squamous cell carcinoma *in situ*. The median time to first keratinocyte carcinoma was 18.3 years (95% CI: 14.2–22.9 years). The average number of keratinocyte carcinomas excised per patient was 14 (range, 1–208). Beginning in 1998, immunosuppression regimens mostly included prednisone, azathioprine, and cyclosporine or prednisone, mycophenolate mofetil, and cyclosporine.

Most observation studies have not reported a clear association between basal cell carcinomas and human papillomaviruses (HPV) in immunocompetent patients.[75] In a US population-based study of 525 patients with basal cell carcinomas and 461 control subjects, HPV seropositivity was not associated with basal cell carcinomas (OR = 0.8, 95% CI: 0.6–1.1).[76] A large prospective European study identified 1,990 basal cell carcinoma cases by linking data on serum donors to national cancer registries.[77] The presence of baseline HPV seropositivity did not increase basal cell carcinoma risks for HPV 16 (OR = 1.0, 95% CI: 0.8–1.3, $n_{positive}$ = 159 cases/153 controls) or HPV 18 (OR = 0.9, 95% CI: 0.7–1.1, $n_{positive}$ = 132 cases/147 controls).

HISTOLOGY

Basal cell carcinomas arise from stem cells in the hair follicle infundibulum and adjacent interfollicular mechanosensory touch-dome epithelia. This tumor does not develop from precursor lesion.[78] Both basal and squamous cell carcinomas are more common in sun-exposed skin. The vast majority (95%) of these tumors develop after the age of 40 years, with up to 85% appearing on the head and neck;[79,80] up to 1/3 occur on areas of the head without high sun exposure. In the prospective Psoralen Ultraviolet A Follow-Up Study containing 566 participants with basal cell carcinomas (1,741 total tumors), 54% developed on the trunk, whereas 29% occurred on the trunk/buttocks, 10% on the lower extremities, 7% on the upper extremities, and 0.002% on the genitalia.[68] The four histological subtypes of basal cell carcinoma vary with tumor location. In a retrospective study of 13,457 cases of basal cell carcinoma in 10,245 patients with a mean age of 65 years, the approximate distribution of histological subtypes was nodular (40–70%, translucent, pink or shiny aised lesion), superficial (20–30%, red, flat. scaly lesions with well-defined margins), and morpheaform (5–10%, flat or depressed, light pink or white, sometimes pigmented lesions).[81] The head was the main location for nodular (90%) and morpheaform (95%) subtypes, whereas the trunk was the most common location for the superficial type (46%).

Basal cell carcinomas contain uniform cells with oval/round eosinophilic nuclei, large/dark nuclei, and infrequent atypia. The most common type is nodular basal cell carcinoma with solid, well-defined, irregular, lobulated nests of tumor cells surrounded by dense stroma fibroblasts and mucinous material (mostly hyaluronic acid). Empty peritumoral clefts produce characteristic stromal retractions.[82] The clinical appearance of nodular types includes raised margins, pearly sheen, central ulcerations, and a cystic, pearly sheen, whereas superficial basal cell carcinomas are usually multiple, erythematous macules or plaques with central erosions and bleeding. Sclerosing basal cell carcinomas typically have an atrophic, white appearance. Table 61.3 lists the histology of major basal cell carcinoma histological types.

HOST SUSCEPTIBILITY

Phenotypic risk factors for basal cell cancer include light hair (OR ≈ 1.5–2.5),[83] skin predisposed to sunburns (i.e.,

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TABLE 61.3. Major basal cell carcinoma histological types. (Adapted from Mackiewicz-Wysocka et al.).[82]

Basal Cell Carcinoma Type	Histology
Nodular	Aggregates of basaloid cells have well-defined borders and peripheral cellular palisading with typical clefts. Central necrosis may occur with eosinophilia, granules, and mucin (primarily hyaluronic acid). Aggressive tumors may display mitotic activity; otherwise, mitotic activity is limited. Micronodular subtype is an aggressive subtype with plaque-like shape, well-defined border, myxoid stroma, minimal palisading, skin/grayish color often without ulcerations. Pigmented subtypes of nodular basal cell carcinoma occur predominantly in dark-skinned individuals.
Superficial	Erythematous, well-circumscribed macule with few scales. Painless papules mimic psoriasis or eczema. Nests of basaloid cells extending from epidermis with prominent peripheral palisading and well-demarcated tumor islands. Neoplastic cells resemble primordial germ cells.
Morpheaform/sclerosing	Depressed skin-tone plaque is similar in appearance to scar tissue. Thin, elongated tumor islands without peripheral palisading or stromal retractions. May involve fat and cutaneous annexes with poorly defined borders and non-painful destruction of surrounding tissues.
Metatypical	Mixed histology with more than one type in the neoplasm (e.g., basal and squamous cell carcinomas).

Fitzpatrick skin types I and II, OR ≈ 1.5–4), especially during childhood,[84] excessive chronic sun-induced skin damage (freckles, actinic keratoses, solar elastosis/lentigines), light hair/eye colors (OR ≈ 1.5–2),[85] personal history of a basal cell carcinoma, and age, particularly in men. Persons of Celtic descent are especially susceptible to sun-induced cancers, whereas skin cancer is rare in deeply pigmented races.[86] The melanocortin 1 receptor (*MC1R* gene) is the major determinant of skin pigmentation/hair color expressing eumelanin via binding of α-melanocyte-stimulating hormone. The highly polymorphic *MC1R* gene variants are important risk factors for keratinocyte carcinoma including basal cell carcinoma. Single-stranded conformation polymorphism analysis was followed by sequencing of unknown variants from 153 subjects with squamous cell carcinoma, 284 with nodular basal cell carcinoma, 142 with superficial multifocal basal cell carcinoma, and 385 controls. The study identified 27 *MC1R* variants with the strongest relationship between the *MC1R* variants associated with red hair and light skin. Stratification by skin type and hair color indicates the *MC1R* variates enhance basal cell carcinoma risks independent of other risk factors including phenotype (e.g., hair/skin color).[87,88]

Patients with an abnormal immune system (immunosuppressive therapy, hematological malignancies, acquired immunodeficiency syndrome) are at increased risk of developing primary cutaneous tumors, especially in sun-exposed skin areas. Genetic syndromes predisposed to the early development of basal cell carcinomas include the multisystem, autosomal-dominant basal cell carcinoma syndrome (Gorlin–Goltz syndrome, basal cell nevus syndrome), X-linked-dominant Bazex–Dupre–Christol syndrome, autosomal-dominant Rombo syndrome, albinism, and autosomal-recessive xeroderma pigmentosum (multiple skin cancers).

CLINICAL PRESENTATION

Basal cell carcinomas typically display slow growth and minimal soft tissue invasion. The most common presentation is a smooth, raised pink lesion or a pink to red, flat lesion. The rate of metastasis for basal cell carcinomas is <0.5%. A patient may develop multiple basal cell carcinomas over years or decades, with a typical latent period between UV damage and diagnosis of basal cell carcinoma of 20–50 years.[89] The male/female ratio is ~1.7–2/1.[5] Although the biological behavior and clinical presentation depend on the basal cell carcinoma subtype, this malignant tumor rarely metastasizes (i.e., <0.1–0.5%).[90] Pooled analysis of data from 19 observational studies reported that ~1/3 of patients with an initial basal cell carcinoma later develop another basal cell carcinoma and <5% develop a subsequent squamous cell carcinoma depending on geographical location and UV radiation exposure.[91] Mortality from basal cell carcinoma is extremely low, with little effect on overall cancer mortality or reduced survival.[92] A qualitative review of 12 observational studies did not detect a significant difference in all-cause mortality in patients with basal cell carcinoma, with all studies demonstrating inverse or null results.[93] Using random effects modeling, the authors' meta-analysis of four large retrospective cohort studies detected no increased all-cause mortality in the basal cell carcinoma patients (mRR = 0.92, 95% CI: 0.83–1.02, $I^2 = 99.4\%$, $P_{\text{heterogeneity}} = 0.000\%$) with very high heterogeneity.

The US Preventive Services Task Force recommends counseling children, adolescents, and young adults (<24 years) with fair skin about minimizing UV radiation exposure to reduce skin cancer risks (benefit, moderate to substantial).[94] The expected benefit

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for adults over 24 years of age was considered small. A Cochrane review concluded that available epidemiological data were insufficient to determine if daily sunscreen reduces basal or squamous cell cancer risks.[12] The authors opined that the only random clinical trial reporting no difference in basal or squamous cell carcinoma risks between daily and discretionary sunscreen use was low quality due to a lack of histopathological confirmation and potential confounding. Although sunscreen use may reduce basal cell carcinoma risks from UV radiation exposure, multiple factors limit the prevention of keratinocyte carcinoma, including susceptible skin coverage, appearance of lesions in non-sun-exposed skin areas, previous sun exposure/skin damage history, and age at use. The preventative effects appear stronger for squamous than basal cell carcinomas.[95] The standard measurement of sunscreen protection from UV radiation exposure (sun-protection factor, SPF) assesses UVB rather than UVA protection; consequently, protection against UVA using SPF can be variable.[96]

SQUAMOUS CELL CARCINOMA

The lifetime incidence of squamous cell carcinoma in the United States is ~7–11%, with the rate continuing to increase as the Caucasian population ages and skin cancer screening increases.[97,98] In Europe, the age-standardized squamous cell carcinoma incidence ranges from 9–96/100,000 in men and 5–68/100,000 in women.[99] The rates are up to 499/100,000 for Australian men and 291/100,000 for Australian women.[100] Overall, cutaneous squamous cell carcinoma incidence varies geographically by >10–25-fold in Caucasians, reflecting in part differences in the annual mean ambient UV radiation dose as well as pigmentation. For men ≥80 years of age, the squamous cell carcinoma incidence varied from 79/100,000 ($\text{Mean}_{\text{annual ambient UVR}} = 0.7\,\text{kJ/m}^2$) to 12,149/100,000 ($\text{Mean}_{\text{annual mean ambient UVR}} = 1.8\,\text{kJ/m}^2$).[15,101] Although squamous cell carcinoma is uncommon in dark-skinned individuals, this keratinocyte cancer is the most common skin cancer in African-Americans, Hispanics, and Asians, often occurring in non-sun-exposed areas of the body.

CARCINOGENESIS

Squamous cell carcinoma is an epithelial skin cancer that contains more mutations than most other common malignancies (e.g., lung).[102] UV radiation-induced mutations in *TP53* loss-of-function are the most common tumor suppressor gene mutations in primary and metastatic squamous cell carcinoma, usually with a classic UV signature (CC-TT). These mutations occur early in tumor formation. The mutation rates in the *TP53* gene vary widely, and many other background mutations exist in these tumors. Other potential drivers include Notch pathway (*NOTCH1*/*NOTCH2* genes), *CDKN2A* (cyclin-dependent kinase inhibitor 2A involved with cell-cycle control), and *KNSTRN* (kinetochore gene important for mitotic spindle involved with chromosome segregation and progression of cell cycle into anaphase) genes as well as *HRAS* proto-oncogene (alters GTPase activity important for cellular signal transduction pathways) and *KMT2* methyltransferase family of epigenetic regulators.[103,104] Mutations in *TP53*, *CDKN2A*, and *RAS* are early UV radiation-induced abnormalities; however, other mutations are necessary for tumor formation and expansion. Small noncoding RNAs (microRNAs, MiRs) may contribute to tumor formation by upregulating oncogenic MiRs (e.g., MiR-21) and downregulating tumor suppressor MiRs (MiR-1).[105]

EXPOSURE

Solar radiation and immunosuppression are the primary risk factors for squamous cell carcinomas; other important risk factors include age and fair skin (Fitzpatrick skin types I/II). Less-common, established risk factors include high-dose arsenic and therapeutic radiation exposures along with congenital skin disorders. Less-established risk factors include smoking and HPV infections.

Ionizing Radiation

Ultraviolet

The primary cause of cutaneous squamous cell carcinoma is cumulative sun exposure, whereas the association between basal cell carcinoma and UV radiation is more complex, as reflected in the relatively high occurrence of the latter skin cancer in typically non-sun-exposed areas of the skin.[106] Using mean daily, erythema-weighted ambient UV radiation levels derived from satellite measurements of column ozone, age/sex/study year-adjusted incidence data from 40 selected studies, and Poisson distribution regression analysis to model estimates of cutaneous squamous cell carcinoma incidence, these variables *together* explained 85% of the variability in squamous cell carcinoma

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incidence among adolescent and adult Caucasians.[35] The mean daily UV radiation alone accounted for 40% of the variability. In a meta-analysis of 10 mostly case-control studies using random effects models and never-users as referents, the summary RR for squamous cell carcinomas in ever-users of indoor tanning was modestly elevated and statistically significant (sRR = 1.67, 95% CI: 1.29–2.17, $I^2 = 47.1\%$, $P_{\text{heterogeneity}} = 0.09$) with slight to moderate heterogeneity.[41]

Non-ultraviolet

Soon after the discovery of X-rays in 1895, the association between skin cancer and radiation-induced dermatitis from excessive local ionizing radiation doses became apparent. Most of the early radiation-induced skin cancers were squamous cell carcinomas developing quickly after exposure to very high local cutaneous radiation doses.[107] The association with therapeutic radiation is weaker for squamous cell carcinomas than basal cell carcinomas.[42] A US cohort study of 65,304 white, mostly female radiology technologists estimated relative risks for squamous cell carcinomas comparing ever- versus never-receiving therapeutic radiation based on baseline mailed questionnaires and Cox proportional hazard models.[44] Squamous cell carcinoma was not associated with the decade of first exposure or duration of radiation exposure consistent with the lack of a clear association between squamous cell carcinoma and radiation exposure in the atomic bomb survivor cohort, as displayed in Table 61.4.

In a population-based study of 289 squamous cell carcinomas identified through a statewide surveillance system and 536 age/sex-matched unexposed controls, the squamous cell carcinoma risk in cutaneous radiation sites comparing ever- versus never-receiving therapeutic radiation was elevated and statistically significant (OR = 2.94, 95% CI: 1.30–6.67).[43] The elevated squamous cell carcinoma risk occurred only in irradiated skin, primarily in sun-sensitive phenotypes. The Skin Cancer Prevention Study enrolled 1,690 participants (32% participation rate), with 118 participants developing 179 incident squamous cell carcinomas during an average follow-up of 4 years.[108] Self-reported therapeutic radiation was not associated with an increased rate ratio for squamous cell carcinoma (RR = 1.0, 95% CI: 0.6–1.7). The Life Span Study did not establish a clear dose-response relationship between ionizing radiation exposure and squamous cell carcinomas with a marked difference between squamous cell cancer rates and the two major sites of the atomic bomb survivors, primarily reflecting differences in histological classifications for squamous cell carcinoma *in situ*.[42] Skin cancer is uncommon in Japan.

TABLE 61.4. Adjusted relative risks for squamous cell carcinoma by decade first worked as radiological technologist using ≥1960 squamous cell carcinoma incidence as reference.[44] The P_{trend} for the difference between decades and references was not statistically significant ($P_{\text{trend}} = 0.678$). Presumably, ionizing radiation doses for the workers were higher in earlier decades; the duration of work did not correlate with basal cell carcinoma risks. (Data adapted from Yoshinaga et al.).[44]

Decade	Adjusted Relative Risk	95% CI	Cases per Decade
<1940s	0.69	0.23–2.10	5
1940s	0.81	0.44–1.51	33
1950s	1.52	0.94–2.43	86
≥1960s	1.0[a]		139

Abbreviation: CI = Confidence Interval.
[a] referents.

Occupation

Limited data are available to determine the contribution of occupation to squamous cell carcinoma risks including UV radiation. The Nordic Occupational Cancer Study project linked self-reported occupational information from the censuses in five Nordic countries to cancer registries containing 12.9 million persons born between 1896–1960 and 87,619 incident primary cutaneous squamous cell carcinoma cases.[109] The standardized incidence ratios were increased and statistically significant in 15 of 53 occupations, with outdoor occupations being inconsistently associated with squamous cell carcinoma risks compared with the general working-age population. Generally, the positive risks were relatively weak, as displayed in Table 61.5.

A Canadian study of 180 squamous cell carcinoma cases (80% participation rate) and 406 age-matched controls (71% participation rate) examined squamous cell carcinoma risks using self-reported answers to a standardized questionnaire administered by a trained interviewer.[110] Comparing the highest exposure category with never-exposed controls, the squamous cell carcinoma risks were elevated for insecticides, herbicides, fungicides, petroleum products, grease, diesel fumes, and coal dust. However, the authors opined that the results should be interpreted with caution because of potential selection/information bias in the retrospective data. A German population-based study examined cancer risks in 408 squamous cell carcinoma cases, 224 actinic keratosis class III/Bowen disease cases, and 996 age/sex/phototype/nonoccupational

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TABLE 61.5. Statistically significant elevated squamous cell carcinoma risks in male workers of >50 years of age after categorizing the workers into 53 occupations based on Nordic census data. The association with outdoor work was inconsistent. Occupations associated with outdoor work include seamen, gardeners, fishermen, and woodworkers, whereas mixed indoor/outdoor occupations include transport workers, postal workers, building caretakers, and military personnel. (Data adapted from Alfonso et al.).[109]

Category	Standardized Incidence Ratio	95% CI
Physicians	1.75	1.57–1.95
Assistant nurses	1.36	1.04–1.75
Administrators	1.32	1.27–1.37
Dentists	1.30	1.08–1.56
Military personnel	1.29	1.17–1.41
Religious workers	1.27	1.19–1.36
Public safety workers	1.25	1.16–1.34
Seamen	1.23	1.14–1.32
Teachers	1.20	1.13–1.26
Clerical workers	1.18	1.13–1.23
Sales agents	1.16	1.11–1.20
Technical workers	1.13	1.09–1.16
Printers	1.13	1.02–1.24
Transport workers	1.10	1.03–1.16

Abbreviation: CI = Confidence Interval.

UV exposure-adjusted odds ratios. Total occupation and recreational UV exposure were estimated by the Wittlich algorithm that adjusts for exposure duration, intensity, seasonality, geographic region, reflection, and lifetime skin-exposure areas. Using a standardized erythema dose (SED) of <40th percentile as the referent (<12.6 SED), the squamous cell carcinoma risk in the top 10% of SED (≥6,834.8) was increased and statistically significant (aOR = 1.95, 95% CI: 1.19–3.18, $n = 85$ cases, 41 controls). The estimated nonoccupational UV exposure using <20th percentile (9,136.8 SED) as the referent was not statistically significant (aOR = 1.11, 95% CI: 0.66–1.87, $n = 64$ cases/62 controls).[111]

Polycyclic Aromatic Hydrocarbons and Scrotal Cancer

Complex mixtures of polycyclic aromatic hydrocarbons are well-known skin carcinogens. In 1775, Sir Percival Pott first associated the development of scrotal cancer with exposure to coal soot in chimney sweeps. Scrotal cancer is a rare cancer with a long latent period and mixed histology as reported from small, single-institutional series. The rarity of scrotal cancer significantly limits establishing occupational risk factors for this neoplasm.[112] Analysis of US Surveillance, Epidemiology, and End Results (SEER) cancer registry data identified 471 cancers from 1973–2002, with an age-adjusted incidence rate for scrotal cancer in 2002 of 1/1,000,000 men.[113] Squamous cell carcinoma was the most common histological type (32%), followed by extramammary Paget's disease (21%), basal cell carcinoma (18%), and sarcoma (18%). Squamous cell carcinoma was more common in black than white men, with mortality rates being higher for squamous than other scrotal histological types.

Increases in scrotal cancer incidence occur in patent-fuel workers exposed to coal tar and coal-tar pitches.[114] Creosotes are classified as Group 2A (probable) carcinogens by the IARC, and case reports suggest an increased incidence of scrotal cancer in workers handling creosote-treated timber. Untreated or mildly treated mineral oils are human carcinogens, and exposure to mineral oils (metal machining, jute processing, cotton mule-spinning) produces an increased squamous cell carcinoma incidence, particularly on the scrotum. A case series of 344 scrotal cancers reported that 62% of the cases were exposed to mineral oils with a mean latent period of 34.4 ± 12.1 years.[112] Unprocessed petroleum-based lubricating oils are less carcinogenic than coal tar; solvent refining processes can remove the carcinogenic fraction from petroleum-based oils.[115] More recent studies suggest occupational risk factors do not contribute significantly to squamous cell scrotal cancer incidence. A follow-up study of Scottish shale-oil industry workers employed between 1950 and 1962 demonstrated a significant squamous cell carcinoma excess, primarily of the scrotum.[116] Although the evidence for the association between exposure to shale oil and the development of skin cancer is substantial, a cohort study of 325 workers at a shale-oil demonstration plant did not detect an excess incidence of skin cancer.[117] A downward trend in the incidence of scrotal cancer began in the 1970s, perhaps as a result of improved industrial hygiene.[118]

Petroleum Industry

A prospective Norwegian study of 24,917 male offshore petroleum workers identified 63 squamous cell carcinomas during 13.5 years of follow-up.[119] Although the study reported elevated hazard ratios for crude oil, benzene, and mineral oil comparing unexposed and exposed workers, none of the hazard ratios were statistically significant with very wide confidence intervals. Some measures of dose-response relationships (duration, cumulative) were positive for benzene and crude oil on potentially exposed areas (hand/forearm); however, the findings were inconsistent with unstable confidence intervals.

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Arsenic

Arsenic is a well-recognized human skin carcinogen from the ingestion of arsenic-contaminated well water (e.g., Bangladesh, India, China, Chile, Southwest Taiwan)[120] and arsenic-containing medicines (Chinese proprietary medicine, Fowler's solution, arsenicals) based on observational studies,[121] particularly in areas where black foot disease is endemic. Animal models of As-induced skin cancer have not replicated observational results.[122] Case reports from Chile associate the daily ingestion of 1–1.2-mg arsenic (8-g arsenic total dose) in the drinking water with the development of skin cancers.[123] The latent period was 20–23 years; all patients had palmar hyperkeratosis.

Inorganic trivalent arsenic exposure (e.g., medicinal use of Fowler's solution) is associated with the induction of multiple skin tumor types in non-sun-exposed areas beside squamous cell carcinomas, including intraepidermal carcinomas (Bowen's disease), multiple superficial basal cell carcinomas, and mixed tumors.[124] The English physician Thomas Fowler introduced arsenic as a medicinal agent (Fowler's solution, 1% potassium arsenite) in 1786; subsequently, medicinal applications included the treatment of syphilis, malaria, acute myeloid leukemia, and psoriasis. In 1887, Sir Jonathan Hutchison first associated arsenicals with skin cancer when he reported a case series of skin cancer patients chronically ingesting arsenicals; the carcinomas were all preceded by keratotic lesions.[125] In a retrospective, nationwide, population-based survey of keratinocyte skin cancers, the age-standardized incidence rate of cutaneous basal cell carcinoma was 4–6-fold higher in black foot disease-endemic areas, with very high As-contaminated well water than other areas in Taiwan.[50] Arsenic-induced squamous cell carcinomas develop *de novo* or evolve from areas of Bowen's disease (intraepithelial carcinoma/carcinoma *in situ*) and premalignant skin lesions (hyperpigmentation, hyperkeratosis, depigmentation).[126]

Occupational As exposure is not clearly associated with increased squamous cell carcinoma risks. A multinational European study of 618 incident keratinocyte skin cancers and 527 hospital-based controls comparing ever- versus never-arsenic occupational As exposure reported a positive and statistically nonsignificant odds ratio for squamous cell carcinoma (aOR = 1.54, 95% CI: 0.78–3.02, $n = 23$ cases/80 controls).[52] The odds ratio was adjusted for age, sex, residence, family history, sun sensitivity, and As drinking water exposure. Squamous cell carcinoma risk for the highest tertile of cumulative lifetime was positive and statistically nonsignificant (aOR = 1.54, 95% CI: 0.49–4.85, $n = 5$ cases/25 controls).

Lifestyle

The major causes of squamous cell carcinomas in fair-skinned individuals are solar radiation (sun exposure, sunbed use) and immunosuppression (solid-organ transplant recipients, specific genetic disorders, medical conditions including HIV, chronic lymphocytic leukemia).[127] The association between squamous cell carcinoma and physical activity or dietary factors is relatively weak. Limited epidemiology data suggest dietary factors as significant factors for cutaneous squamous cell carcinoma, including protective effects of carotenoids, selenium, and vitamins.[128]

Tobacco Smoking

The association of smoking with increased squamous cell carcinomas is conflicting with some[53] but not all,[129] studies reporting modest increases in squamous cell carcinoma risks for current smokers. Most of these studies do not report clear dose-response relationships. In a meta-analysis of six studies using random effects models, the odds ratio for squamous cell carcinomas for current smokers was elevated and statistically significant with moderate heterogeneity (OR = 1.52, 95% CI: 1.15–2.01, $I^2 = 64\%$); former smokers exhibited the smallest effect sizes for squamous cell carcinoma (OR = 1.21, 95% CI: 0.94–1.56; $I^2 = 28\%$).[56] An Australian prospective study of 43,794 randomly selected residents of Queensland identified 193 squamous cell carcinomas during 3 years of follow-up.[130] Using Cox proportional hazards models with adjustment for confounders (age, sex, private health insurance, education, skin color, tanning ability, freckles, sunburn (painful, blistering) history, cumulative sun exposure) and never-smokers as referents, the squamous cell carcinoma risk in current smokers was increased and statistically significant (aHR = 2.30, 95% CI: 1.46–3.62). For ever-smokers, the aHR was modestly increased and statistically nonsignificant (aHR = 1.6, 95% CI: 0.92–1.73) based on self-reported baseline questionnaires. The squamous cell carcinoma risks were close to the null for ex-smokers (aHR = 1.05, 95% CI: 0.74–1.48). The data demonstrated no clear dose-response relationship with quartiles of smoking duration ($P_{trend} = 0.117$), intensity in cigarettes/day ($P_{trend} = 0.546$), or cumulative pack-years ($P_{trend} = 0.053$). The authors opined that the results in current smokers should be interpreted with caution because of the lack of elevated risks in ex-smokers, no dose-response relationships, and the absence of a compelling biological mechanism.

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Alcohol

The Australian Nambour Skin Cancer Study reported no significant increased squamous cell carcinoma risks for alcohol users in 1,360 mostly fair-to-medium-skinned participants during 11 years of follow-up with alcohol abstainers as referents.[60] The multivariate-adjusted relative risk for squamous cell carcinoma in the highest alcohol consumption category (26.3 g/day) was consistent with the null (maRR = 0.94, 95% CI: 0.49–1.80, $P_{trend} = 0.38$). Specific beverage types in the moderate and high alcohol consumption categories were not associated with statistically significant elevations of squamous cell carcinoma risks ($P_{trend} = 0.17$–0.97). In a meta-analysis of three prospective cohort studies using random effects models, the summary RR/daily 10-g increase in alcohol consumption for squamous cell carcinoma compared with alcohol abstainers was slightly elevated and statistically significant (sRR = 1.11, 95% CI: 1.06–1.16, $I^2 = 18.8\%$, $P_{heterogeneity} = 0.291$).[62] The small number of studies prevented the evaluation of nonlinearity in the dose-response curve.

Caffeine

Most observational studies do not associate caffeine consumption with the alteration of squamous cell carcinoma risks.[64,65] In a meta-analysis of several cohort and case-control studies, the summary relative risk was close to the null with moderate heterogeneity (sRR = 0.93, 95% CI: 0.68–1.27, $I^2 = 50\%$).[131] These studies demonstrated no clear dose-response relationship between total caffeine or tea consumption and squamous cell carcinoma risks.

Obesity

The association between obesity and squamous cell carcinoma risk is relatively weak. Analysis of pooled data from the US Nurses' Health Study and the Health Professionals Follow-Up Study examined squamous cell carcinoma risks prospectively using normal BMI as referents.[67] The combined, multivariate-adjusted hazard ratio was inverse and statistically significant for mildly obese (BMI = 30–34.9 kg/m^2), mostly Caucasian participants (maHR = 0.68, 95% CI: 0.57–0.80, $n = 178$ cases), and severely obese (BMI $\geq$ 35 kg/m^2) participants (maHR = 0.63, 95% CI: 0.48–0.82, $n = 40$ cases, $P_{trend} = <0.0001$). Multivariate-adjusted variables included gender, sunburn reaction, melanoma family history, severe sunburns, moles, hair color, sun exposure at different age intervals, UV index at residence at different ages, quintiles of physical activity, and history of cardiovascular diseases, type 2 diabetes, and cancer. A 16-year, prospective community-based study of 1,171 Australians reported quartiles of height ($P_{trend} = 0.017$) but not BMI ($P_{trend} = 0.456$) in men, were associated with increased multivariate-adjusted squamous cell carcinoma risks.[132] In women, neither quartiles of height ($P_{trend} = 0.432$) nor BMI ($P_{trend} = 0.492$) were associated with increased risks. The model adjusted for age (years), treatment allocation, squamous cell carcinoma history, elastosis of the neck, freckling of the back, and smoking status.

Medications

PUVA Therapy/Immunomodulation

Long-term immunotherapy in solid-organ transplant patients produces very significant increased squamous cell carcinoma risks compared with immunocompetent persons, as well as increased metastases and mortality rates.[133] Basal and squamous cell carcinoma risks differ substantially in psoriasis patients receiving PUVA therapy, with the incidence being much higher in the latter than in the former. In the prospective Psoralen Ultraviolet A Follow-Up Study using patients with <50 PUVA treatments as referents and Poisson regression, 351 of 1,380 (25%) cohort patients developed 2,973 biopsy-proven squamous cell carcinomas during the 30 years of follow-up.[68] The age/gender/identified confounder-adjusted multivariate incidence rate ratio for developing ≥1 squamous cell carcinoma per year in participants within the highest quintile (>450 PUVA treatments) was elevated and statistically significant (IRR = 9.57, 95% CI: 7.13–12.83). Using participants with <100 UVB treatments as referents, the multivariate incidence rate ratio for squamous cell carcinoma in participants receiving >300 UVB treatments was modestly elevated (IRR = 1.49, 95% CI: 1.32–1.68), similar to the rates for basal cell carcinomas.

Vitamin A

Vitamin A consists of a large number of retinoids (e.g., retinal retinol, retinoic acid); animal-based foods contain preformed vitamin A (retinoic acid), whereas plant-based foods contain provitamin A carotenoids (e.g., α- or β-carotene, β-cryptoxanthin) capable of conversion to retinol and non-provitamin A carotenoids (e.g., lutein, lycopene, zeaxanthin). Animal studies suggest a potential role for vitamin A in chemoprevention of keratinocyte-associated carcinomas including squamous cell carcinoma; however, some clinical studies using retinoids or carotenoids report significant adverse

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effects (liver dysfunction, myalgias/arthralgias, alopecia, headache, hypercholesteremia).[134] A prospective cohort study identified 3,978 squamous cell carcinoma cases in 75,170 women from the Nurses' Health Study and 48,400 men from the Health Professionals Follow-Up Study.[135] Using Cox proportional hazards regression models based on biennial questionnaires and the lowest quintile of dietary vitamin A as the reference, the adjusted pooled multivariable hazard ratio for squamous cell carcinoma in the highest quintile was inverse and statistically significant (HR = 0.86, 95% CI: 0.78–0.96, P_{trend} = <0.001). The results for the second and third quintiles were consistent with the null, whereas the result for the 4th quintile was inverse and statistically nonsignificant. The authors opined that the results indicated future studies are needed to determine the role of vitamin A supplementation on squamous cell carcinoma risks.

Diseases

Immunosuppression

Similar to basal cell carcinomas, several observational studies suggest diseases associated with chronic immunosuppression (e.g., organ transplant patients/immunosuppressive agents, HIV, chronic lymphocyte leukemia)[136] increase squamous cell carcinoma risks. Squamous cell carcinoma/squamous cell carcinoma *in situ* are more common than basal cell carcinomas in these patients.[137,138] In an Italian cohort of 1,934 solid-organ transplant patients, 109 patients (5.6%) developed squamous cell carcinoma within a median of 6.8 years after transplantation.[73] In comparison to squamous cell carcinoma, ~2.6% (50 with 1st basal cell carcinoma) developed a 2nd basal cell carcinoma unrelated to age at transplantation, transplanted organ type, or immunosuppressive therapy. In a New Zealand cohort of 384 renal transplant patients followed for 35 years, squamous cell carcinoma and squamous cell carcinoma *in situ* were ~4-fold more common than basal cell carcinomas.[74] Older age at the first transplant was a predictor of the 1st keratinocyte carcinoma. Low CD4 counts and high viral loads increase squamous cell carcinoma risks in HIV patients compared with HIV-negative persons. In a US observational study of 6,560 HIV+ and 36,821 HIV− non-Hispanic white adults using HIV− participants as referents, the adjusted rate ratio for squamous cell carcinoma in HIV+ participants was 2.6 (95% CI: 2.1–3.2, n = 386 cases HIV+/1,682 cases HIV−) compared with 2.1 (95% CI: 1.8–2.3, n = 136 cases HIV+/479 cases HIV−) for basal cell carcinoma.[139]

Human Papillomavirus

Human papillomavirus (HPV) types consist of five genera (α, β, γ, μ, ν). The association between HPV and squamous cell carcinoma is strongest for β-HPV genus in the external genitalia, perianal area, and nail regions; however, the association is relatively weak and conflicting with an unclear mechanism of action in immunocompetent individuals. Although some data suggest HPV5 and HPV8 may influence the early development of squamous cell carcinomas (e.g., epidermodysplasia verruciformis disorder),[140] current data indicate the presence of the β-HPV genome and E6/7 oncoproteins is not required for tumor promotion or maintenance.[141] In an article by Wang and Aldabagh et al. describing a meta-analysis of 17 case-control studies using inverse variance, random effects modeling, and normal-appearing skin in immunocompetent participants as controls, the pooled effect size for HPV in squamous cell tumors was positive and statistically significant (pooled ES = 2.43, 95% CI: 1.97–5.98, $P_{difference}$ = <0.0001) with little publishing bias (P_{Egger} = 0.23) and high heterogeneity from variation in sampling methods and viral detection techniques. For immunosuppressed patients, the pooled effect size for HPV in cutaneous squamous cell tumors was also positive and statistically significant (pooled ES = 3.01, 95% CI: 2.00–4.52, $P_{difference}$ = <0.0001, n = 12 studies) with mild heterogeneity and no publication bias (P_{Egger} = 0.78). Although the study suggested an association between HPV and squamous cell carcinomas, the authors opined that the study did not imply causality.

In a US population-based study of 252 patients with squamous cell carcinomas and 461 control subjects, the squamous cell carcinoma risk in patients within the β-HPV genus was marginally significant (OR = 1.5, 95% CI: 1.0–2.1), particularly in sun-exposed areas of patients with HPV5 (OR = 1.8, 95% CI: 1.0–3.1).[76] A small portion of squamous cell carcinomas contain high-risk genital human papillomaviruses (HPV), including HPV16 and HPV18. A large, prospective European study identified 633 squamous cell carcinoma cases by linking data on serum donors to national cancer registries.[77] The presence of baseline seropositivity increased cutaneous squamous cell carcinoma risks for HPV16 (OR = 1.6, 95% CI: 1.1–2.6, $n_{positive}$ = 57 cases/37 controls) and HPV18 (OR = 1.7, 95% CI: 1.1–2.5, $n_{positive}$ = 65 cases/41 controls). Only 4 of 79 tumor blocks contained HPV16 DNA, and no HPV18 DNA was detected. The authors opined that the lack of HPV DNA indicated confounding with genital HPV infections accounting for the positive DNA results. HPV is not transcriptionally active in squamous cell carcinomas. Hence, HPV may contribute to the induction but probably not maintenance of these tumors.[142]

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HISTOLOGY

Squamous cell carcinomas develop from the malignant transformation of epidermal keratinocytes or adnexal structures (e.g., pilosebaceous units, eccrine glands). These tumors usually arise from sun-damaged skin or preexisting cutaneous lesions (e.g., scars, ulcers, discoid lupus, chronic radiodermatitis). Squamous cell carcinomas are much more common on the extremities than head or neck in contrast to basal cell carcinomas. In the prospective Psoralen Ultraviolet A Follow-Up Study containing 566 participants with squamous cell carcinomas (2,973 total tumors), 62% developed on the lower extremities and 16% on the upper extremities, whereas 11% occurred on the trunk/buttocks, 9% on the head/neck, and 1% on the genitalia.[68] Squamous cell carcinoma histological types include acantholytic, conventional, lymphoepithelioma-like, spindle-cell, and verrucous, as displayed in Table 61.6.[143]

Keratoacanthoma is a common skin neoplasm in fair-skinned individuals characterized by early proliferation, stabilization, and occasional spontaneous regression; this neoplasm displays characteristics between a benign and malignant tumor.[144] Keratoacanthomas are frequently mislabeled as cutaneous squamous cell carcinomas.

HOST SUSCEPTIBILITY

Inherited skin conditions associated with squamous cell carcinomas include albinism (congenital defect in melanin formation), Bloom syndrome (chromosomal instability), dyskeratosis congenita (telomere maintenance/trafficking), Huriez syndrome, multiple self-healing squamous epithelioma (*TGF*-b signal transduction), epidermodysplasia verruciformis (signal transduction in endoplasmic reticulum), Rothmund–Thomson syndrome (chromosomal instability, telomere maintenance/trafficking), and xeroderma pigmentosum (autosomal-recessive deficiency in DNA nucleotide excision repair).[145] Low-to-moderate-risk susceptibility genes associated with pigment characteristics include genes producing melanocortin 1 receptor (*MC1R*), interferon regulatory factor 4 (*IRF4*), and tyrosinase (*TYR*).[127]

CLINICAL PRESENTATION

The clinical presentation of squamous cell carcinoma depends on tumor location and subtype (e.g., degree of differentiation). The most common presentation is scaly, flat red lesion (*in situ*) or a firm, raised red lesion with erosion or scale (invasive). Actinic keratosis, the precursor lesion, is a scaly, flesh- to pink-colored papule or plaque with an erythematous base that progresses an estimated ~1/200–1/1,000 lesions to squamous cell carcinoma; however, reliable data on monitoring these lesions over time are extremely limited.[146] Bowen's disease (squamous cell carcinoma *in situ*) is an erythematous, well-defined, scaly plaque that is usually asymptomatic; larger lesions may produce pain, tenderness, and/or bleeding. Invasive squamous cell carcinoma usually presents with a persistent ulcer or nonhealing wound that may occur as an indurated or ulcerated lesion (Marjolin ulcer) in a preexisting scar or ulcer. Limited case reports associate squamous cell carcinomas with chronic inflammation in tattoo-induced scars, particularly with red pigment (mercuric sulfide).[147] HPV-induced squamous cell carcinoma typically

TABLE 61.6. Major squamous cell carcinoma histological types. (Adapted from Paolino et al.).[143]

Squamous Cell Carcinoma Type	Histology
Acantholytic	Adenoacanthoma has adenoid pattern with many dyskeratotic cells, often developing in areas of previous radiotherapy.
Conventional	Atypical dermal cells with enlarged, pleomorphic nuclei and atypical mitotic activity. Ulcerated lesions with inflammation (neutrophils, lymphocytes, plasma cells). Aggregates of moderate or poorly differentiated keratinocytes with surrounding desmoplastic stroma may be present.
Lymphoepithelioma-like	Scattered nests of poorly differentiated tumor cells with diffuse lymphocytic infiltrate between epithelial nests. Mainly polygonal in shaped tumor cells with an eosinophilic cytoplasm, containing vesicular nuclei, prominent atypia, numerous mitoses, diffuse lymphoplasmacytic infiltrate surrounding the epithelial nests, and an infiltrating tumor margin.
Spindle-cell	Associated with post-traumatic ulcerated lesions characterized by whorls of spindle cells in the dermis with myxoid stroma and pleomorphic giant cells with atypical mitoses.
Verrucous	Well-differentiated exophytic squamous proliferation with marked papillomatosis, koilocyte-like changes, and little atypia. Rare tumor.

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presents as a new or enlarging warty growth on the anus, vulva, penis, or periungual region. The average age at diagnosis for squamous cell carcinoma is the mid-sixth decade of life, with a predilection for men.[148] Latency for arsenic-induced squamous cell carcinomas may extend to 20–40 years.[149]

Squamous cell carcinomas are usually spread by local invasion rather than distant metastasis via the lymphatic system. The rate of metastasis for squamous cell carcinoma is <2%. The propensity of squamous cell carcinomas to metastasize depends on the location, size (>2 cm), depth of invasion (>2 mm), perineural/lymphovascular involvement (>0.1 mm), and location (ear, temple). Typically, the metastatic rate is ~4–5%, with several-fold higher risk among immunosuppressed patients.[150] In a case series of 264 patients presenting to a Danish dermatology institute during the 1950s with cutaneous squamous cell carcinoma and followed to 1976, 3.3% of 153 patients developed metastases compared with 11% of 55 patients with labial squamous cell carcinoma.[151] The incidence of metastasis in patients with cutaneous squamous cell carcinoma from inflammation and degenerative processes ranged from 10–30%. The parotid gland is the most common site of metastasis.

In-office surgical excision or curettage is the typical treatment for keratinocyte carcinomas with low risk of recurrence. For higher risk lesions, Mohs surgery is usually recommended. This technique involves removing the tumor in stages guided by pathological evaluation of the surgical margins under a microscope to ensure entire removal of the lesion. The recurrence rate after Mohs surgery is ≈3%. These patients have a high risk of addition keratinocyte carcinomas (i.e., 40% over 5 years).

In contrast to basal cell carcinoma, squamous cell carcinoma-associated mortality is significant in elderly and immunosuppressed patients. A quantitative systematic review of 10 mostly retrospective cohort studies suggests squamous cell carcinomas are associated with reduced all-cause mortality.[93] Using random effects modeling and data from four large retrospective cohort studies, the authors reported a statistically significant increased summary relative risk for all-cause mortality in squamous cell carcinoma participants (sRR = 1.25, 95% CI: 1.17–1.32, $I^2 = 98.8\%$, $P_{\text{heterogeneity}} = 0.000$) with very high heterogeneity. In the New Hampshire Skin Cancer Study of 1,125 cases and 1,416 population-based controls followed for an average of 9.5–9.8 years, all-cause mortality was increased in patients with squamous cell carcinoma (aHR = 1.25, 95% CI: 1.01–1.54, $n = 189$ deaths) after adjustment for age, sex, smoking, and nonskin cancer occurrence.[152] The primary means of preventing squamous cell carcinomas in fair-skinned individuals involve the consistent use of sunscreen (SPF 15–SPF 30) along with avoidance of excessive sun exposure. A literature review suggests the addition of DNA repair enzymes or antioxidants may reduce risks.[153] Little data from randomized clinical trials support efficacy of these substances in reducing squamous cell carcinoma risks. Other possible chemopreventive agents include vitamin B_3, nonsteroidal anti-inflammatory drugs, and difluoromethylornithine.

MELANOMA

Melanoma is a multifactorial disease with a variety of genetic and epigenetic causes and heterogenous clinical presentations, resulting in differing origins, UV radiation sensitivity, anatomic site, and mutational profile for melanoma histological subtypes.[154] Worldwide, cutaneous melanoma varies widely accounting for ~230,000 incident cases and ~55,000 deaths annually depending in part on access to primary care and early detection as well as pigmentation and sun exposure. The lowest reported melanoma incidence rates occur in Southeast Asia, whereas the highest rates occur in Caucasian residents of New Zealand and Australia, as displayed in Table 61.7.[155] European melanoma rates are intermediate between these two areas. For the last several decades, melanoma incidence has increased ~3% annually, with some evidence of plateauing in Caucasian population in New Zealand and Australia, particularly in Queensland.[156] Beside geographical location, the age-standardized incidence and body site for melanomas vary between men and women (e.g., ↑ head, neck, and trunk in men; lower ↑ extremities in women).[157] An analysis of 2018 GLOBOCAN data from 185 countries reported age-standardized male/female melanoma incidence rate ratios ranging from 0.68 (95% CI: 0.63–0.73) in Denmark and 0.68 (95% CI: 0.63–0.72) in Belgium to 1.35 (95% CI: 1.33–1.37) in the United States and 1.47 (95% CI: 1.42–1.52) in Australia.[158]

In the United States, melanoma is the fifth most common cause of cancer. Melanoma incidence increases linearly after the age of 25 years before peaking at 50 years and then declining, particularly in women.[159] The incidence of melanoma has decreased recently in adolescents and young adults in contrast to the increased incidence in older populations. Analysis of data from the National Program of Cancer Registries and the Surveillance Epidemiology and End Results

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TABLE 61.7. Estimated age-standardized rate/100,000 population for melanoma incidence and mortality by gender and region. The reported incidence and mortality rates are usually higher in men than women and higher in more-developed than less-developed countries. (Adapted from Torre et al.).[155]

Region	Incidence-Men	Incidence-Women	Mortality-Men	Mortality-Women
World	3.3	2.8	0.9	0.6
More developed	10.2	9.3	2.0	1.2
Less developed	0.8	0.7	0.4	0.3
Africa	1.0	1.1	0.5	0.7
Northern	0.3	0.4	0.2	0.2
Southern	5.0	3.7	1.6	0.8
North America	16.1	12.2	2.6	1.2
South America	2.9	2.2	1.0	0.6
Asia	0.5	0.4	0.3	0.2
Eastern	0.6	0.5	0.4	0.3
Western	1.8	1.6	0.6	0.5
Europe	8.6	8.9	2.0	1.3
Northern	14.0	15.4	2.5	1.6
Southern	8.1	8.3	1.6	1.0
Australia/New Zealand	40.3	30.5	5.9	2.4

(SEER) US Cancer Statistic database reported an increased overall melanoma incidence rate from 200.1 to 229.1/1,000,000 person-years between 2006–2015.[160] The annual percentage change (APC) during that interval increased in men >40 years of age (APC = 1.8%, 95% CI: 1.4–2.1%) and women (APC = 1.8%, 95% CI: 1.4–2.2%). The melanoma incidence decreased for male (APC = −4.4%, 95% CI: −1.7 to −7.0%) and female (APC = −5.4%, 95% CI: −3.3 to −7.4%) adolescents, as well as for male (APC = −3.7%, 95% CI: −2.5 to −4.8%) and female (APC = −3.6%, 95% CI: −2.8 to −4.5%) young adults 20–29 years.

In the United States, the cutaneous melanoma-related death rate accounts for a majority (i.e., ~62–72%) of non-keratinocyte-related skin cancer deaths.[161] However, mortality from melanoma has declined dramatically over the past decade, primarily as a result of more effective screening and effective treatments for advanced disease. In white-skinned races, the cutaneous melanoma incidence is increasing faster than any other malignant tumor, except for lung cancer in women.[162] There is no clear increase in mortality from melanomas in dark-skinned populations. The melanoma risk for young adult women was about twofold higher than that for young adult men. There is no clear increase in mortality from melanomas in dark-skinned populations.

CARCINOGENESIS

Normal melanocytes rarely divide (i.e., <2 times/year); however, melanomas progressively grow in size as point mutations and copy-number alterations increase, resulting in a very high somatic mutational load.[163,164] Cutaneous melanomas usually contain classic ultraviolet-signature mutations including UVA-induced G→T and UVB-induced C→T transitions.[165] Although skin cancers in chronic sun-damaged areas of skin including melanomas, mutate more than almost all other human cancers, all cutaneous melanomas do not contain a unique universal driver.[166,167] The BRAF V600E mutation occurs early in the progression of melanomas. Benign nevi frequently may contain this mutation (i.e., ~80%). In contrast to melanomas, a growth-arrest phase follows transient activation of cell-proliferation by the BRAF-MAPK pathway in benign nevi.[168,169] The latter pathway is a central driver of cell proliferation, differentiation, and survival. About 40–60% of cutaneous melanomas contain the BRAF mutation, and 15–30% contain the NRAS mutation. Although the latter usually occurs in sun-damaged body sites, neither mutation type contains classical UV signature mutations.[170] Progression to precursor lesions (melanocytic nevi, intermediate lesions, melanomas *in situ*) involves the telomerase reverse-transcriptase

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(*TERT* promoter) gene in about ¾ of these tumors, along with tertiary mutations in cell-cycle control genes *CDKN2A* (cyclin-dependent kinase-inhibitor 2A) and/or chromatin remodeling (*ARID1A/1B/D2*, AT-rich interaction domain).[164] Telomere length is positively associated with the nevus count; however, patients with cutaneous melanoma have consistently longer telomeres than healthy persons.[171] Later stages of melanoma metastasis typically include tumor suppressor mutations in *TP53* and *PTEN* (phosphatase-and-tensin homolog, cell-cycle progression control) genes. In a majority of melanomas, these mutations produce overstimulation of several cellular pathways, including MAPK (mitogen-activated protein kinase), PI3K (phosphoinositide 3-kinase, AKT serine-threonine protein kinase family), β-catenin-mediated Wnt signaling, and mTOR (mammalian target of rapamycin) pathways. *BRAF* and *NRAS* are oncogenes within the MAPK pathway, whereas the tumor suppressor gene *NF1* alters regulation of *RAS* (most commonly *NRAS* and less often *KRAS* and *HRAS* genes).[172] Other less-common mutated oncogenes include *RAC1*, *PREX2*, and *ERBB4*. Melanoma cells evade immune checkpoints by alterations of the interferon receptor via Janus-kinase (JAK) and signal-transducer-and-activator-of-transcription (STAT) pathways, resulting in disruption of the programmed-cell-death-protein-1 (PD-1) immune checkpoint.[173] The number of mutations and copy-number alterations varies significantly with melanoma histological type. Dysregulation of the nuclear factor (NF)-κB pathways alters the tumor microenvironment by degrading the extracellular matrix through overexpression of matrix metalloproteinases (e.g., MMP-2, MMP-9); subsequent changes enhance tumor cell invasion and metastasis via the blood.[174]

EXPOSURE

Established risk factors for melanoma include ultraviolet radiation (sun/sunbed exposures, particularly <35 years of age with sunburn), numerous dysplastic/melanocytic nevi, susceptible phenotypes (blue eyes, red/blond hair, fair skin, freckling), 1° family/personal melanoma history, and high socioeconomic status.[175,176] Similar to squamous cell carcinomas, high sunburn frequency throughout life increases melanoma risks. No other environmental risk factor is clearly associated with increased melanoma risks.[177] Although melanomas are more frequent in patients with light skin, most melanomas do not occur on sun-exposed parts of the body. The predominant locations of melanomas are areas exposed to intermittent, intense sunlight (i.e., backs of men, legs of women) rather than skin receiving more constant sun exposure (i.e., face, dorsum of hands). Malignant epithelial tumors (e.g., basal cell, squamous cell carcinomas) occur in the latter areas. Table 61.8 lists the major predisposing factors for developing melanomas. High-risk populations include individuals with red (3-fold ↑ risk) or blond (60% ↑ risk) hair, fair complexion (2-fold risk), and multiple nevi (>20 nevi → 3-fold ↑ risk).[178] Lifestyle (e.g., sun exposure, sunbed use) and genetic and physiological (e.g., immune function) factors determine the number of nevi; increasing the number of nevi, sizes, and types elevates melanoma risks.[179]

TABLE 61.8. Estimated relative risk factors for melanoma. (Adapted from Williams et al.).[179]

Factor	Estimated Relative Risk[a]
Changing pigmentation	Very high
Xeroderma pigmentosum	500
Family history of FAMM[b]	
Previous melanoma	500
Atypical nevi without melanoma history	150
Numerous common nevi	5–65
Atypical nevi	7–20
Giant congenital nevus	5–15
Previous melanoma	9
Lentigo maligna	5–10
Immunosuppressive therapy	4–7
Sun sensitivity	2–3
Excessive sun exposures	2–4
Melanoma in first-degree relative	6–15
Few or no common nevi	0.3
Hispanic or African American	0.0–0.15
Age <15 years	0.01

[a] Average risk = 1. [b] Familial atypical mole or melanoma syndrome.

Ionizing Radiation

Ultraviolet

UV radiation is the major environmental risk factor for melanoma, accounting for up to 70–75% of these tumors, particularly with higher energy UVB producing more DNA damage than oxidative damage (i.e., reactive oxygen species).[180,181] The epidermis absorbs most UVB radiation, with 9–15% of UVB reaching the melanocytes in the basal layer compared with ~50% of UVA radiation.[182] Melanoma risk probably increases with the addition of UVA radiation; however, the exact contribution of these two portions of the UV spectrum remains controversial.[11,183] Although

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UV radiation causes similar types of mutations at the DNA nucleotide level (i.e., UV-signature mutations) in melanoma and keratinocyte skin cancers, the target mutations are different. Epidemiological and molecular genetic data support two distinct types of cutaneous responses to ultraviolet radiation, depending on the delivered dose.[184,185] Early, intense, intermittent sun or sunbed exposure in susceptible phenotypes (multiple nevi, light-skin types) promotes the *BRAF* proto-oncogene serine/threonine kinase (BRAF) pathway and the spreading melanoma subtype.[186,187] About 25–33% of cutaneous melanomas arise from a benign, melanocytic nevus, whereas this percentage increases up to ~50–55% in patients with many nevi.[188] The clinical presentation includes young age at diagnosis, often in axial skin areas and the trunk without evidence of chronic sun damage. Age, skin type, hair color, and melanoma thickness do not influence the presentation of nevi-associated melanomas. The other distinct melanoma type involves *de novo* formation from cumulative sun exposure-induced *NRAS* proto-oncogene GTPase NRAS mutations in chronic sun-related skin-damaged areas with no relation to nevi count. These tumors have a high mutation burden with later age at diagnosis typically occurring on the head and neck.[189] In contrast to cutaneous superficial spreading melanoma, nodular and mucosal melanomas are probably not associated with UV radiation.[154] Superficial spreading melanoma is usually associated with cumulative, low intensity sun damage, whereas lentigo maligna is associated with cumulative, high intensity sun damage (i.e., sunburn).

Non-solar Ultraviolet

Indoor tanning beds now primarily emit UVA radiation (320–400 mm) in contrast to UVB radiation in early models before the 1980s. The International Agency for Research on Cancer classifies the whole ultraviolet spectrum and indoor tanning devices as human carcinogens (Group 1), as noted in Table 61.1. Duration of use and initial use at a younger age modestly increase melanoma risks.[190] Analysis of data from 141,045 women followed a mean of 13.7 years in the prospective Norwegian Women and Cancer Study, which identified 861 women with melanoma.[191] Using Poisson regression to estimate relative risks of melanoma in the highest tertile of indoor tanning use compared with never-users use, the adjusted RR was modestly elevated and statistically significant (aRR = 1.32, 95% CI: 1.08–1.63, $P_{trend} = 0.006$). The adjusted RR for initiation of indoor tanning use before age 30 years was also modestly elevated and statistically significant (aRR = 1.31, 95% CI: 1.07–1.59) using linear regression and never-users as referents. A meta-analysis of 27 case-control (12 population-base, 15 hospital-based), 1 nested case-control, 1 cross-sectional, and 2 prospective cohort studies consisting of 14,956 melanoma cases and 233,106 controls used inverse variance methods with a random effects model to estimate odds ratios.[192] With never-users as referents, the odds ratio for ever-users of indoor tanning was small but statistically significant (OR = 1.16, 95% CI: 1.05–1.28, $I^2 = 52\%$) with moderate heterogeneity. The odds ratios for studies published after 1999 and before 2000 were not statistically significant, suggesting newer tanning technology was not associated with decreased melanoma risks. Evidence for a dose-response relationship was marginal. Comparison of indoor tanning use of >10 times and never-users yielded a modestly increased odds ratio (OR = 1.34, 95% CI: 1.05–1.71, $n = 10$ studies, $I^2 = 66\%$) with moderate heterogeneity. Only three of these studies achieved statistical significance. The melanoma odds ratio for indoor tanning use of 1–10 times was not statistically significant (OR = 1.07, 95% CI: 0.90–1.26, $n = 10$ studies, $I^2 = 43\%$). The authors reported that the quality of the evidence ranged from poor to mediocre.

Occupation

For most malignant melanoma cases, recognized risk factors (UV radiation, genetic susceptibility, skin characteristics) are much more important melanoma risk factors than occupational exposures. Industries with some positive studies include agriculture, airline, electrical, healthcare, research, nuclear, oil, pulp, tannery, and teaching; however, observational studies on melanoma incidence and mortality in these occupations and industries report inconsistent results.[175] Overall, the industries with positive studies lack a common occupational agent, similar ultraviolet radiation exposures, or control for socioeconomic class. Some occupations with substantial outdoor exposure (e.g., farmers, fishermen) do not have consistently elevated malignant melanoma rates. For other occupations, these rates are lower in general than office worker populations.[193] The importance of occupational exposure to chemicals as a cause of malignant melanoma appears small.[194,195]

A mortality study demonstrated elevated proportional mortality ratios for managers and owners, accountants, architects, chemical engineers, gardeners, and nursery workers; however, the lack of an obvious chemical carcinogen in all but the last group limits conclusions regarding causation.[196] Retrospective cohort studies of workers in a chemical plant,[197]

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printing industries,[198] and oil refineries[199] demonstrated increased melanoma risks (i.e., RR < 2). In an Italian study of 100 incident melanoma cases and 200 age/sex/ethnicity/location-matched population controls using logistic-regression models, outdoor occupational sun exposure was associated with a statistically significant elevation of cutaneous melanoma (OR = 2.573, 95% CI: 1.399–4.732).[200] The significance of these studies is limited by the small number of cases, the lack of exposure data, and poor control of confounding variables (e.g., pigmentation). A cohort study of 323,860 Swedish men in the construction industry reported no increased melanoma risks, except for a positive but statistically nonsignificant, increased cutaneous melanoma risk on the head, face, and neck in the high-sun-exposure group (RR = 2.0, 95% CI: 0.8–5.2).[201] An analysis of population-based Bavarian cancer registry calculated the age-adjusted Mantel–Haenszel-type estimates of relative risks in workers classified into outdoor, mixed indoor/outdoor, and indoor categories based on job titles.[202] Using indoor workers as referents, the cutaneous melanoma risk in outdoor male workers was positive but statistically nonsignificant (aRR = 1.5, 95% CI: 0.9–2.5) and close to the null in female outdoor workers (aRR = 1.1, 95% CI: 0.4–3.6).

Lifestyle

UV radiation exposure and skin phenotypic characteristics (e.g., skin color, hair/eye color, freckle density), rather than lifestyle factors, are the major nongenetic risk factors for cutaneous melanomas. Overall, large between-study heterogeneity, small-study effects, and excess significance bias complicate interpretation of the mostly retrospective case-control studies evaluating the influence of lifestyle on cutaneous melanoma risks.[203] Skin color is the main phenotypic melanoma determinate, whereas blue/green/hazel/gray eye and red/blonde hair color are proxies for skin color (i.e., pigmentation) because all three depend on melanin content.[204] Few data support a reduction in melanoma risks with increased physical activity. In a Canadian study of 103 incident melanoma cases in men and 533 population-based controls, the melanoma risk for often engaging in recreational sports and outdoor activities was positive but statistically nonsignificant (OR = 1.24, 95% CI: 0.73–2.12, $n = 54$ cases) compared with referents never or not often engaging in recreational physical activity.[205]

Higher socioeconomic status is consistently associated with increased cutaneous melanoma incidence, particularly in the well-educated. Presentation at the late stage of disease and greater mortality are associated with lower socioeconomic status.[175] Even though blue-collar jobs theoretically involve more sun exposure, melanoma incidence usually occurs more frequently in the higher socioeconomic classes (white-collar, urban, highly educated). Analysis of data from the US population-based cancer registry data (Surveillance, Epidemiology, and End Results Program) at the National Cancer Institute indicated the age-adjusted melanoma rate in Caucasian families with income of >$50,000 (i.e., highest quintile) was 20.54/100,000 compared with 9.19/100,000 in the lowest quintile of Caucasian families (<$12,000).[206] The association may apply only to higher socioeconomic status in later life. A cohort study of 1,824,064 Swedish residents born in 1944–1960 examined the association of early-life socioeconomic position with adult cause-specific mortality using Cox proportional hazards regression models to compare manual and nonmanual social class in early life (0–16 years).[207] The reported age-adjusted hazard ratios demonstrated no evidence of a positive association in men ($aHR_{males} = 1.04$, 95% CI: 0.87–1.25) or women ($aHR_{females} = 0.95$, 95% CI: 0.77–1.16), with no significant differences between the sexes ($P_{difference} = 0.5$). The association with higher socioeconomic status may involve differences in healthcare access (tobacco bias), early diagnosis with thinner tumors, and/or greater recreational UV exposure (solar, sunbeds).

Tobacco

Evidence for an association between smoking and cutaneous melanoma is suggestive of an inverse relationship;[203] however, the association is relatively weak and complex with conflicting data.[175,208] The QSkin Sun and Health Study prospectively enrolled 43,794 residents of Queensland, Australia, aged 40–69 years using a self-reported smoking history in baseline questionnaire.[209] The study identified 247 incident invasive melanoma cases during an average follow-up of 3.5 years. Compared with never-smokers, the fully adjusted hazard ratio for invasive melanoma was inverse and statistically nonsignificant in ever-smokers (aHR = 0.80, 95% CI: 0.62–1.05) and null in current smokers (aHR = 1.01, 95% CI: 0.64–1.61). The inverse association was statistically significant for smoking intensity in cigarettes/day ($P_{trend} = 0.001$), cumulative smoking in pack-years ($P_{trend} = 0.02$), and years since quitting ($P_{trend} = 0.044$), but not duration of smoking ($P_{trend} = 0.1$). The multivariate model adjusted for age, sex, natural skin color, tanning tendency, moles at the age of 21 years, previous excised skin cancers

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and treatment, family melanoma history, childhood sunburn, and cumulative lifetime sun exposure.

Alcohol

Some, primarily case-control, studies suggest alcohol consumption slightly increases cutaneous melanoma risks; however, the data are inconsistent. Several cohort studies reported positive, but statistically nonsignificant, increases in cutaneous melanoma risks.[210,211] A meta-analysis of 14 case-control and 2 cohort studies used random effects models to compare no/light alcohol (≤1 drink/daily) and moderate to heavy drinking (>1 drink daily).[212] The pooled relative risk for cutaneous melanoma for any alcohol consumption using no/occasional drinking as the referent was modestly increased and statistically significant (RR = 1.20, 95% CI: 1.06–1.37, I^2 = 55.6%, $P_{\text{heterogeneity}}$ = 0.003) with moderate heterogeneity. The pooled RR became statistically nonsignificant after adjustment for sun exposure (aRR = 1.15, 95% CI: 0.94–1.41).

Caffeine

The association of coffee with cutaneous melanoma risks remains unclear with conflicting results, whereas most data on tea and decaffeinated coffee consumption and melanoma risks are consistent with null effects.[213,214] In a meta-analysis of 8 cohort and 4 case-control studies involving 832,956 participants using random effects modeling, the pooled relative risk of cutaneous melanoma was inverse and statistically significant for total coffee consumption (pooled RR = 0.80, 95% CI: 0.69–0.93, n = 7,140 cases, I^2 = 53%, $P_{\text{heterogeneity}}$ = 0.014) and marginally significant for caffeinated coffee consumption (pooled RR = 0.85, 95% CI: 0.71–1.01, n = 4,459 cases/5 studies, I^2 = 65%, $P_{\text{heterogeneity}}$ = 0.022) with moderate heterogeneity.[215] Decaffeinated coffee was not associated with statistically significant inverse melanoma risks (pooled RR = 0.92, 95% CI: 0.81–1.05, n = 4,183 cases/6 studies, I^2 = 0.0%, $P_{\text{heterogeneity}}$ = 0.967). The US National Institutes of Health-AARP prospective cohort study identified 2,904 incident cases of malignant melanoma among 447,357 non-Hispanic whites during a median follow-up of 10.5 years.[216] Coffee consumption was self-reported in baseline questionnaires. Using multivariable-adjusted Cox proportional hazard models and non-coffee drinkers as referents, malignant melanoma risk was inverse and statistically significant for the highest total coffee intake category of ≥4 cups daily (HR = 0.80, 95% CI: 0.68–0.93, P_{trend} = 0.01) and caffeinated coffee (HR = 0.75, 95% CI: 0.64–0.89, P_{trend} = 0.01) but not for decaffeinated coffee intake (HR = 0.95, 95% CI: 0.76–1.18, P_{trend} = 0.55). The European Prospective Investigation into Cancer and Nutrition (EPIC) study enrolled 521,324 participants aged 25–70 years; during a median follow-up of 14.9 years, the study identified 2,712 malignant melanomas (93.4% cutaneous melanomas).[213] Coffee categories were based on self-reported consumption in the 12 months preceding enrollment using a validated country-specific dietary questionnaire. Comparing the highest quartile of coffee intake with non-coffee drinkers, the multivariable-adjusted hazard ratio was inverse and statistically significant in men (aHR = 0.47, 95% CI: 0.23–0.94, n = 148 cases, P_{trend} = 0.001) but not women (aHR = 1.10, 95% CI: 0.70–1.72, n = 357 cases, P_{trend} = 0.598). Decaffeinated coffee and tea were not associated with melanoma risks.

The Swedish prospective, population based Västerbotten Intervention Project identified 190 malignant melanomas in 64,603 participants during a median follow-up of 6 years.[217] Using multivariate Cox regression, malignant melanoma risks were not associated with total coffee consumption. Comparing the highest (≥4 cups daily) and lowest (<1 cup daily) coffee-consumption categories, the multivariate hazard ratio for malignant melanoma was 0.97 (95% CI: 0.50–1.89, n = 37 cases, P = 0.939). In the Women's Health Initiative-Observational Study cohort of 66,484 postmenopausal women followed for a mean of 7.7 years, coffee consumption was evaluated by self-administered questionnaires at baseline and the third year of follow-up.[213] Using Cox proportional hazard models adjusted for covariates and nondaily coffee drinkers as referents, melanoma risks were not associated with daily coffee consumption (HR = 0.87, 95% CI: 0.68–1.12) or with increasing coffee consumption (P_{trend} = 0.38).

Obesity

Although some observation studies suggest an association between obesity and cutaneous melanoma,[203] the data are modest and sometimes conflicting, particularly between men and women. A meta-analysis of eight case-control and seven cohort studies in men used BMI = <25 kg/m^2 as referents, BMI = ≥25–<30 kg/m^2 as overweight, BMI = ≥30 kg/m^2 as obese, and fixed effects models unless the data demonstrated substantial heterogeneity ($P_{\text{heterogeneity}}$ = <0.1) to estimate the pooled effect estimate for cutaneous melanoma.[218] The results were similarly elevated for overweight males (pooled effect estimate = 1.31, 95% CI: 1.18–1.45, I^2 = 0.0%, $P_{\text{heterogeneity}}$ = 0.525) and obese males (pooled effect estimate = 1.31, 95% CI: 1.19–1.44, I^2 = 23.2%,

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$P_{heterogeneity}$ = 0.197). For 10 case-control and 6 cohort studies in women, the results demonstrate no significant association between cutaneous melanoma and overweight (pooled effect estimate = 0.98, 95% CI: 0.92–1.05, I^2 = 14.3%, $P_{heterogeneity}$ = 0.789) or obese women (pooled effect estimate = 0.99, 95% CI: 0.83–1.18, I^2 = 40.1%, $P_{heterogeneity}$ = 0.045). The latter analysis applied random effects models with much lower pooled effect estimates for cohort than case-control studies. The authors opined that UV radiation exposure may have confounded the results in women. In a meta-analysis of six studies, the risk ratio per 5 kg/m^2 increase in BMI was weak but positive and statistically significant for malignant melanoma (RR = 1.17, 95% CI: 1.05–1.30, I^2 = 44%, $P_{heterogeneity}$ = 0.004) with slight to moderate heterogeneity.[219] The results indicated no association between obesity and malignant melanoma in women.

Diet

Diet is not strongly associated with cutaneous melanoma risks. Some observational studies suggest the consumption of citrus fruit may increase cutaneous melanoma risks, particularly fruits containing psoralens and other furocoumarins (e.g., grapefruit); however, results are inconclusive.[220] Analysis of data from the US Nurses' Health Study (63,810 women) and the Health Professionals Follow-Up Study (41,622 men) identified 1,840 incident melanomas during 24–26 years of follow-up.[221] Using Cox proportional hazards models to estimate hazard ratios and multivariable analyses to adjust for known melanoma risk factors and potential confounders, the pooled multivariable hazard ratio for melanoma was positive and statistically significant in the highest grapefruit intake category of ≥3 times weekly (aHR = 1.41, 95% CI: 1.10–1.82, n = 125 cases, P_{trend} = <0.001) but not for grapefruit juice (P_{trend} = 0.79). The trend for orange consumption and melanoma risks was not statistically significant (P_{trend} = 0.81) in contrast to orange juice intake (P_{trend} = <0.001). A hospital-based study of 304 cases of cutaneous melanoma and 305 frequency-matched controls used unconditional logistic regression and the lowest intake category as referents.[222] Dietary exposure categories were based on self-reported structured questionnaires, interviews, and a clinical examination for pigmented lesions. The adjusted odds ratio for cutaneous melanoma risks in the highest tertile of citrus fruit consumption category (>5 times weekly) was inverse and statistically significant (aOR = 0.51, 95% CI: 0.32–0.80, P_{trend} = 0.003). The odds ratio was adjusted for age, sex, education, hair color, skin types, nevi, childhood freckles, and childhood sunburns.

Medications

The preponderance of the evidence does not support an increased melanoma risk in women using oral contraceptives or hormone replacement therapy.[223,224] In a meta-analysis of 6 cohort, 12 population-based, and 5 hospital-based case-control studies involving 5,626 histologically confirmed cutaneous melanoma cases, exogenous hormone use was not associated with increased cutaneous melanoma risks.[225] Using random effects models and never-users as referents, the summary relative risks of cutaneous melanoma for ever-users of oral contraceptives were 1.04 (95% CI: 0.92–1.18, I^2 = 42%, $P_{heterogeneity}$ = 0.03) and 1.16 (95% CI: 0.93–1.44, I^2 = 47%, $P_{heterogeneity}$ = 0.05). Dose-response models indicated no significant increase in cutaneous melanoma risk for oral contraceptives or hormone replacement therapy. Cutaneous melanoma risks were not related to age at first use of oral contraceptives or time since first/last use.

Diseases

Melanomas occur more frequently in immunosuppressed patients (solid-organ transplants, hematological malignancies, HIV infections) and chronic inflammatory diseases (e.g., inflammatory bowel disease, psoriasis, rheumatoid arthritis). The small number of cases and large between-study heterogeneity limit definitive conclusions regarding causation.

Parkinson Disease

Although some retrospective studies suggest increased cutaneous melanoma risks in patients with Parkinson disease (levodopa is an intermediary product in melanin synthesis), the data are inconclusive with limited power and very large between-study heterogeneity. A systematic review and meta-analysis of the association between melanoma and Parkinson disease identified 12 publications with only 2 designed explicitly to assess the relationship between melanoma and Parkinson disease; 8 of the eligible studies had <10 cases.[226] Overall, the pooled odds ratio for Parkinson disease in melanoma patients was positive and statistically significant (OR = 2.11, 95% CI: 1.26–3.54, I^2 = 85.4%, $P_{heterogeneity}$ = 0.000%) with very high heterogeneity. In Parkinson disease patients, melanoma risks were positive and statistically significant

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(OR = 3.61, 95% CI: 1.49–8.77, $n = 6$ studies, $I^2 = 89.6\%$, $P_{\text{heterogeneity}} = 0.000\%$) compared with patients without Parkinson disease. The risk of melanoma and Parkinson disease is lower in women than in men. The overall melanoma risk in men in this study was positive and statistically significant (OR = 2.04, 95% CI: 1.55–2.69, $n = 6$ studies, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = 0.539$), whereas melanoma risks were positive but statistically nonsignificant in women (OR = 1.52, 95% CI: 0.85–2.75, $n = 5$ studies, $I^2 = 54.5\%$, $P_{\text{heterogeneity}} = 0.067$). A retrospective cohort study (Rochester Epidemiology Project) in Olmsted County, Minnesota, identified 974 Caucasian patients with Parkinson disease; all these patients were treated with carbidopa–levodopa.[227] Within this cohort, 32 melanomas occurred (29 cutaneous, 3 choroidal melanomas) with only 6 cutaneous melanomas diagnosed after their Parkinson disease. Compared with age/sex-(but not lifestyle)-matched controls, the likelihood of a Parkinson patient having a preexisting melanoma was increased 3.8-fold (95% CI: 2.1–6.8, $P = <0.001$). The melanoma cohort had a similar elevation of Parkinson disease (i.e., 4.2-fold). Using Kaplan–Meier analysis and a log-rank test, melanoma patients had a 35-year cumulative Parkinson disease risk of 11.8% (95% CI: 4.0–19.6%) compared with 2.6% (95% CI: 0.4–4.8%) in controls. The difference was statistically significant ($P = <0.001$). No single unifying mechanism explains this association. Both Parkinson disease and cutaneous melanoma patients accumulate the presynaptic protein, α-synuclein, the main constituent of intraneuronal inclusions (Lewy bodies) in Parkinson disease. This posttranslationally phosphorylated protein occurs in 90% of Parkinsonian brains compared with 4% of normal brains.[228]

Immunosuppression

Melanoma-induced immunosuppression is a complex and heterogeneous process involving several mechanisms, including malignant mutations, downregulation of surface antigens (e.g., histocompatibility complex class I), suppression of the antitumor response by depressing activation and proliferation of regulatory CD4+/CD25+ T cells, blockage of natural killer cell function,[229] and secretion of immunosuppressive cytokines (e.g., indolamine 2,3-dioxygenase, interleukin 10, transforming growth factor β) into the tumor microenvironment.[230,231] These cytokines suppress regulatory T cells and dendritic cells involved with peripheral tolerance.

Compared with the general population, observational studies suggest melanoma incidence increases in several types of immunosuppressed patients, including human immunodeficiency virus infection/AIDS, lymphoproliferative disorders (i.e., chronic lymphocytic leukemia, non-Hodgkin disease), and solid-organ transplant recipients. The latter patients have an increased incidence of many cancers, particularly skin cancers with the risk being much lower for melanoma than keratinocyte cancers. In a review of 17 observation studies on *de novo* melanoma incidence in solid-organ transplant recipients, 8 of the studies reported statistically significant elevated melanoma risks with the relative risk/standardized incidence ratio ranging from 2.14–3.4.[230] Most of the other studies had positive, but statistically nonsignificant, results. Ten patients in the Oxford renal transplant service develop melanomas out of a total of 1,874 transplant patients during 11,942.2 recipient-years of follow-up.[232] The melanoma incidence was ~8 times higher in transplant recipients than the general population, with a mean interval between transplant and melanoma diagnosis of 11 years (median = 8.5 years). For chronic lymphocytic leukemia and non-Hodgkin lymphoma patients, the relative risk/standardized incidence ratio in nine observational studies reporting statistically significantly increased *de novo* melanoma risks ranged from 1.75–6.17.[230] In general, standardized rate ratio for all-cancer incidence in HIV-infected patients increases by 1.5–2-fold. The standardized rate ratio for melanoma in a prospective cohort study of 54,780 HIV-infected persons (Adult and Adolescent Spectrum of HIV Disease Project) was 2.6 (95% CI: 1.9–3.6, $n = 39$ cases).[233]

Reproductive Factors

Malignant melanoma was the most common cancer in women aged 25–29 years, and during pregnancy in a Swedish register-based study on data collected 1963–2007;[234,235] ~1/3 of melanomas occurring in women develop during childbearing years.[236] Although some evidence suggests pregnancy reduces tumor surveillance and melanotic lesions may contain estrogen-sensitive receptors, the clinical relevance of these potential changes is unclear, particularly when most studies indicate pregnancy does not enhance melanoma progression or reduce survival.[237] Observational studies on reproductive factors influencing endogenous hormonal factors (e.g., parity, age at menarche/menopause, age at first birth) report mixed results. In a clinic-based study of 318 cutaneous melanomas and 395 age/race/residence-matched controls, melanoma risks in parous women were positive and marginally significant using nulliparous women as referents

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(aOR = 1.7, 95% CI: 1.00–2.6, $n = 259$ cases/278 controls), particularly in women of <55 years at melanoma diagnosis (aOR = 1.9, 95% CI: 1.2–3.3, $n = 176$ cases/163 controls).[223] Increasing parity was associated with increased melanoma risks ($aOR_{\geq 3\ births} = 2.5$, 95% CI: 1.5–4.3, $n = 108$ cases/98 controls, $P_{trend} = <0.001$) using women with no live births as referents. The odds ratios were adjusted for age, education, study location, dysplastic nevi, freckling, and exogenous hormone use.

A meta-analysis of 14 case-control, 3 nested case-control, and 7 cohort studies involving 16,787 cutaneous melanoma cases reported a slightly increased, statistically significant association between cutaneous melanoma risk and age at first pregnancy (summary RR = 1.011, 95% CI: 1.008–1.013, $n = 8$ studies, $I^2 = 51\%$, $P_{heterogeneity} = 0.06$).[225] Although some summary RR for other reproductive factors were also slightly positive (e.g., fertility drug use, menopausal status), none of the other summary RR for cutaneous melanoma and reproductive factors were statistically significant, including parity, menopausal status, fertility drug use, and age at menarche/menopause. The authors opined that socioeconomic differences may account for excess risks associated with age at first pregnancy.

HISTOLOGY

The epidermis consists of the stratum basale (basal stem cells), spinosum, granulosum, and corneum with melanocytes confined to the stratum basale; cutaneous melanomas arise from melanocytes in the basal epidermal layer. Variation in skin color results from melanocyte activity and melanin production rather than the number of melanocytes. Histological features of pigmented lesions characteristic of cutaneous melanoma include asymmetry, border irregularity, color variegation, recent onset, and diameter of ≥6 mm.[238] Malignant melanomas originate from the transformation of dendritic melanocytes in skin, eye (choroidal layer), leptomeninges, and mucosal epithelia. Although these tumors usually occur in the skin, melanomas can develop in any of these melanocyte-containing tissues. The more common histological categories of melanomas based on their growth patterns are: 1) superficially spreading melanoma (SSM, ≈70%); 2) nodular melanoma (NM, ≈5%); 3) lentigo maligna melanoma (LMM, ≈15%); and 4) desmoplastic melanoma (≈4%). Less common subtypes include amelanotic (2–8%), spitzoid (<2%), and acral (≈1%). Each of these melanoma subtypes can arise from different precursor lesions, gene mutations, and stages of transformation. Superficial spreading melanomas are the most common and slowest-growing (1–5 years) melanomas in Caucasians, comprising ~70% of melanomas. These tumors occur at any age after puberty on any part of the body. Nodular melanomas are the second most common melanoma subtype (15–30%); these tumors display vertical (invasive) growth early, frequently demonstrating nonclassical histological characteristics. Although more common after the age of 50 years, these tumors can occur at any age. Nodular melanomas usually begin on any portion of the skin's surface, whereas superficial spreading melanomas often arise in preexisting nevi.[239] Lentigo maligna melanomas account for ~14% of the melanomas typically appearing on the faces of older Caucasian women as large flat lesions. In contrast to superficial spreading and nodular melanomas, lentigo maligna melanomas occur primarily in sun-exposed areas where sun-related skin damage develops.[240] These melanomas existed in sunlight-exposed areas for many years before becoming deeply invasive. Acral lentiginous melanomas usually appear on the palms, soles, or nail-bed matrix in non-sun-exposed areas of older, dark-skinned patients. These tumors account for only 2–8% of the melanomas in Caucasians compared with ~70% of melanomas in African Americans.[241,242]

HOST SUSCEPTIBILITY

Family/Personal History

A positive family or personal history of melanoma increases melanoma risks and tumor development at younger ages in non-sun-exposed areas. Approximately 6–15% of melanomas occur in patients with a family history of melanoma.[243,244] Many of these patients have dysplastic nevi. In a case series of 102 patients from 49 families presenting with familial cutaneous melanoma to the Massachusetts General Hospital Pigmented Lesion Clinic during an 8-year period, 82% had a personal and/or family history of dysplastic nevi.[245] Analysis of data from the Swedish Family-Cancer Database indicates ~9% of incident melanoma cases have a family history of melanoma.[246] The relative risk of melanoma increased from ~2.5 in individuals with a history of one 1st-degree relative with melanoma to 6.5 for two 1st-degree relatives. The most common family-associated melanoma is familial atypical multiple mole-melanoma (FAMMM) syndrome along with the variant, melanoma-astrocytoma syndrome. The most frequent germline mutation in these patients occurs in *CDKN2A* (cyclin-dependent kinase inhibitor 2A, protein $p16^{INK4A}/p14^{ARF}$) and less often in *CDK4* (cyclin-dependent kinase 4) and *BAP1*

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TABLE 61.9. Meta-analysis results for pooled estimates of proportion and standardized incidence ratios for the occurrence of a subsequent melanoma in a patient previously diagnosed with a melanoma tumor with subgroup analyses on study design and quality. (Modified from van der Leest et al.).[249]

Study Estimate Type	Study Number	Study Result	95% CI
Pooled Proportion Estimates			
Proportion, total studies	47	3.8%	3.3–4.4%
Population-based	11	2.6%	1.9–3.5%
Hospital-based	36	4.3%	3.7–5.2%
Newcastle–Ottawa scale ≥5	13	3.8%	2.9–4.9%
Newcastle–Ottawa scale <5	34	3.8%	3.2–4.6%
Pooled Estimate Standardized Rate Ratio			
Proportion, total studies	12	10.4	8.5–12.3
Population-based	7	7.9	5.7–10.1
Hospital-based	5	17.8	14.1–21.7
Newcastle–Ottawa scale ≥5	7	8.7	6.3–11.0
Newcastle–Ottawa scale <5	5	14.1	10.7–17.5

Abbreviation: CI = Confidence Interval.

(*BRCA1*-associated protein 1) genes.[247] The penetrance of CDKN2A mutation varies in high-risk families geographically ranging from 20% in Australia to 45% in North America and 57% in Europe.[248] Other genetic conditions associated with increased melanoma risks include xeroderma pigmentosum, Lynch syndrome type II, Li–Fraumeni cancer syndrome, and familial retinoblastoma.[243] Pooled analysis of data from 19 observational studies reported the occurrence of subsequent melanomas in patients with an initial basal cell carcinoma of <0.5–1%.[91] Keratinocyte skin cancers are the most common other cancers occurring in familial cutaneous melanoma patients, with pancreatic and breast cancer developing more often in these melanoma-susceptible patients than the general population.

In a meta-analysis of 47 mostly retrospective cohort studies using random effects modeling to calculate estimates, the pooled proportion of subsequent melanomas after an initial incident melanoma case was 3.8% (95% CI: 3.3–4.4%); subgroup analysis indicated a higher difference in hospital-based than population-based studies but no significant difference between higher (Newcastle–Ottawa scale ≥5) and lower quality studies (Newcastle–Ottawa scale of <5), as displayed in Table 61.9.[249]

Compared with the general population, the estimated standardized incidence ratio for a subsequent melanoma was increased to ~10-fold in patients with a prior melanoma (pooled estimate = 10.4, 95% CI: 8.5–12.3, $n = 12$ studies); subgroup analysis indicated differences between hospital-based and population-based studies as well as study quality, as displayed in Table 61.9.

Nevi

Approximately 25–33% of melanoma tumors arise from preexisting atypical (dysplastic) nevi; these nevi may remain indolent for decades from host immune surveillance until they acquire subsequent mutations in driver genes (e.g., *TERT*, *CDKN2A*).[250,251] Patients with multiple dysplastic nevi (i.e., flat, irregular borders; variegated colors) are particularly susceptible to melanoma transformation. These patients account for a majority of primary cutaneous melanoma patients (52–67%).[252] In a US study of 716 consecutive patients with newly diagnosed melanoma and 1,014 clinic-based controls, the melanoma risk was correlated with the number of small nevi (>2–<5 mm), the presence of large nondysplastic nevi (>5 mm), and the occurrence of dysplastic nevi.[253] The age/sex/center/small nevi-adjusted melanoma RR increased with the number of dysplastic nevi. Melanoma relative risk for the occurrence of one dysplastic nevus was 2.3 (95% CI: 1.4–3.6, $n = 64$ cases/50 controls), whereas the presence of ≥10 was associated with an adjusted melanoma RR of 12 (95% CI: 4.4–31, $n = 55$ cases/6 controls) based on imprecise estimates. Using patients with <25 small nevi as controls, the adjusted melanoma relative risk ranged from 1.8 (1.3–2.5, $n = 163$ cases/190 controls) for patients with 25–49 small nevi to 3.4 (95% CI:

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TABLE 61.10. Anatomical sites of melanomas by gender, with median age at diagnosis in the German Central Malignant Melanoma Registry, 2012. Melanoma was most likely to occur on the trunk in men and the lower extremity in women. Melanomas on the trunk presented at an earlier age in women than men. Approximately 80% of melanomas in patients ≥80 years of age were on the head or neck. Differences in anatomical location and associated sun patterns are consistent with two separate causal pathways for early, intermittent/intense (sunburns) and cumulative, sun-damaging-associated exposures. (Adapted from Leiter et al.).[11]

Anatomical Site	Percentage (%) Men	Percentage (%) Women	Median Age Men at Diagnosis (Years)	Median Age Women at Diagnosis (Years)
Face	7.9	9.7	65	68
Scalp	7.7	2.8	64	67
Neck	2.6	1.8	58	53
Anterior trunk	15.0	7.8	54	41
Posterior trunk	38.1	18.1	57	47
Genital region	0.2	0.5	75	63
Upper extremity	11.6	19.4	57	53
Lower extremity	16.9	39.8	53	50

2.0–5.7, $n = 123$ cases/43 controls) for ≥100 small nevi. The adjusted melanoma RR for congenital nevi was consistent with null results. The sensitivity of specific melanoma histological types varies with different risk factors. The number of nevi appears to be more closely associated with SSM and NM types compared with LLM, whereas total sun exposure and skin type are more important risk factors for LLM than SSM or NM subtypes.[254]

CLINICAL PRESENTATION

Melanomas are malignant tumors of melanocytes that occur primarily in white-skinned races and tend to metastasize early. The overall median age ranges from 57–64 years. The highest melanoma rates occur in older men (>44 years), whereas melanomas usually affect younger women (<45 years) more than younger men, with the peak difference between women and men occurring at age 20–24 years (RR = 2.01, 95% CI: 1.21–3.33).[255] The anatomical site varies with gender; the most common site is the trunk in men and the lower extremity in women, as displayed in Table 61.10. The most common complaint is a new or changing skin lesion.

Melanoma accounts for most skin cancer-related deaths and has a historically poor prognosis for patients with metastases. Relative survival represents the ratio of the overall survival rate for cancer patients to the expected survival of a comparable group of cancer-free individuals. Relative survival depends on the clinical stage of presentation, with the survival rate decreasing with age and being higher in women than men. The difference in rates reflects earlier presentation of melanoma (58 and 65 years, respectively), more localized stage, and dissimilar UV exposure in women than men.[256] Tumor thickness is the most important prognostic factor for primary melanoma.[257] Higher survival rates occur in patients with thin tumors (<1 mm).[258] The stages for melanoma include stage 0 (melanoma *in situ*), stage IA-IIA (localized melanoma), stage IIB/IIC (increased thickness and or ulcerations), stage III (localized spread), and stage IV (distant metastasis). In the United States, the 5-year melanoma-specific survival rate for Stage I (<1-mm thickness, no lymph node involvement, no metastasis) is 98% and 95% for Stage II (1–2-mm thickness, no lymph node involvement, no metastasis). The overall 10-year relative survival rate ranges from approximately 98% for stage IA to 94% for stage IB, 88% for stage IIA to 75% for stage IIC, 88% for stage IIIA to 60 for stage IIIC, and 24% for stage IIID. About 84% of cutaneous melanomas are localized (stages I–II). Treatment with multiple checkpoint inhibitors (programmed cell death protein 1, PD-1), cytotoxic T cell-associated antigen 4, CTLA-4), and multiple tyrosine kinase inhibitors (e.g., BRAF inhibitors targeting the *BRAF* proto-oncogene serine/threonine protein kinases and mitogen-activated protein kinase MAPK signaling) dramatically improved survival in higher melanoma stages.[259] The use of PD-1-based agents and chemotherapy aimed at $BRAF^{V600+}$ melanomas increased overall 5-year survival rates for metastatic melanoma from <10% to 40–50%.[260]

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Chapter 62

SOFT TISSUE AND BONE SARCOMAS

Sarcomas are rare, malignant tumors that originate in mesenchymal tissues within any part of the body, including bones, cartilage, or organs.[1] The dozens of histological types, multiple genetic mutations, and various anatomic sites of this heterogeneous cancer group result in complex interactions between somatic mutations, histology, and clinical courses. For sarcomas, the prognosis of similar histological subtypes varies with location on the body; different sarcoma subtypes in the same location also have variable prognoses. The rarity of these tumors and the many histological subtypes complicate understanding of these interactions.

Sarcomas account for ~1% of adult malignant neoplasms. The rates are relatively higher in younger populations, particularly Ewing sarcomas and osteosarcomas, whereas the median age at presentation for soft tissue sarcomas is the seventh decade. Racial differences also exist in younger populations with relatively higher rates of fibromatous sarcomas in African Americans, liposarcomas in Hispanics, and synovial sarcomas in Caucasians.[2] The annual overall sarcoma age-standardized incidence is ~5/100,000 inhabitants in developed countries, with modest variation between countries; soft tissue sarcomas are ~5–6-fold more common than bone sarcomas. In an analysis of data from the European RARECARE project, the annual age-standardized soft tissue sarcoma incidence was 4.2/100,000 inhabitants ranging from 3.3/100,000 inhabitants of Eastern Europe to 4.7/100,000 in Northern Europe; the overall age-adjusted rate for bone sarcomas was 0.8/100,000.[3] Table 62.1 lists the age-standardized incidence rates by site for soft tissue sarcomas and by histological type for bone sarcomas, along with overall rates in descending order with the most common first.

Most sarcomas are sporadic; ionizing radiation (i.e., therapeutic radiation,[4] atomic bomb survivors[5]) is the only well-recognized risk factor with limited evidence for occupational and environmental causes (e.g., chlorophenols). Epidemiology studies on phenoxyacetic acids[6,7] and chlorophenols[8,9] are inconsistent based on self-reported use and few environmental measurements. Evidence for a causal relationship between specific viruses and sarcomas overall is weak, with the exception of Kaposi sarcoma-associated human herpesvirus (HHV8) and Kaposi sarcoma, particularly in immunosuppressed patients (AIDS, organ transplant chemotherapy).[10] Table 62.2 lists agents and chemicals classified by the International Agency for Research on Cancer (IARC) soft tissue and bone carcinogens.[11]

Sarcomas comprise a heterogeneous group of about 70 uncommon subtypes that include genomically simple tumors with recurrent genetic alterations and genomically complex tumors with extensive genomical rearrangements. Overall, the mutational burden usually is low. Several familial syndromes are associated with increased sarcoma risks, including inherited retinoblastoma (RB mutation, RB transcriptional corepressor 1; certain soft tissue sarcomas, osteosarcoma), Li–Fraumeni syndrome (TP53 mutations, tumor protein p53; certain soft tissue sarcomas, osteosarcoma), and neurofibromatosis 1 (nerve sheath tumors; mutations of *NF1* neurofibromin 1) gene. Epidemiological evidence indicates older adult patients with Paget disease are susceptible to the development of primary and secondary osteosarcomas. Other very

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TABLE 62.1. Annual age-standardized incidence rates per 100,000 inhabitants for soft tissue sarcomas by site and bone cancers by histological type in the Surveillance of Rare Cancers in Europe (RARECARE) project.[3] The rates are listed in descending order of the absolute number of incident cases for each site or histological type. (Data adapted from Stiller et al.).[3]

Site or Histological Type	Age-Standardized Incidence/100,000	Standard Error
Soft Tissue Sarcomas		
Overall soft tissue sarcomas	4.2	<0.1
Limbs	0.9	<0.1
Uterus	0.5	<0.1
Viscera	0.4	<0.1
Superficial trunk	0.4	<0.1
Skin	0.3	<0.1
Retroperitoneum	0.3	<0.1
Head and neck	0.2	<0.1
Central nervous system	0.2	<0.1
Other genitourinary tract soft tissue sarcomas	0.2	<0.1
Breast	0.2	<0.1
Ewing soft tissue sarcoma	0.1	<0.1
Bone Sarcomas		
Overall bone sarcomas	0.8	<0.1
Chondrogenic sarcoma	0.2	<0.1
Osteosarcoma	0.2	<0.1
Ewing bone sarcomas	0.1	<0.1
Gastrointestinal stromal sarcoma	0.1	<0.1

TABLE 62.2. International Agency for Research on Cancer (IARC) Classification of cutaneous cancer sites by sufficient and limited evidence of human carcinogenicity. (Adapted from IARC[11] and Cogliano et al.).[15]

Anatomic Site	Carcinogen with *Sufficient* Human Evidence (Group 1)	Carcinogen with *Limited* Human Evidence (Group 2A or 2B)
Bone	Plutonium, radium-224 and its decay products, radium-226 and its decay products, radium-228 and its decay products, X-radiation, gamma radiation	Iodine radionuclides including ^{131}I
Soft tissue		Polychlorophenols or sodium salts (combined exposures), iodine radionuclides including ^{131}I, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin
Endothelium (Kaposi sarcoma)	Human immunodeficiency virus type 1, Kaposi sarcoma herpesvirus	

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rare syndromes associated with increased osteosarcoma risks include Rothmund–Thomson syndrome (RECQL4 mutation, RecQ-like helicase 4),[12] Bloom syndrome (BLM mutation, BLM RecQ-like helicase), Werner syndrome (*WRN* mutation, Werner syndrome RecQ-like helicase),[13] and McCune–Albright syndrome (GNAS mutation, GNAS complex locus).[14]

SOFT TISSUE SARCOMAS

Soft (connective)-tissue sarcomas arise from primitive mesenchymal cells in any part of the body (head, neck, trunk, internal organs, retroperitoneum, arms, legs) including muscle, fibrous tissue, fat, lymph vessels, blood, and cartilage, with each histological type developing separate characteristics (e.g., risk factors, survival).[7] The reported incidence of these tumors has increased in men; however, the actual incidence and etiology of soft tissue sarcomas are difficult to study because of their low incidence, changing classification, and histological misclassification.[16] The US age-standardized rate (US-ASR) for soft tissue sarcomas in the Surveillance, Epidemiology, and End Results program, excluding Kaposi sarcoma, was 5.49/100,000 person-years for men and 4.60/100,000 person-years for women.[17] In an Austrian study of 5,333 cases collected from 1984–2004, the age-standardized rate was 2.4/100,000 with a male/female ratio of 0.8.[18] The study did not confirm an increase in the soft tissue cancer rate. The international rate varies by ~1.8–5.0 cases/100,000 inhabitants.

CARCINOGENESIS

Soft tissue sarcomas represent a large, complex, heterogeneous group of tumors that arise sporadically, often without specific genetic drivers or chromosomal abnormalities. About 1/3 of soft tissue sarcomas contain specific translocations (e.g., alveolar rhabdomyosarcoma), whereas some have specific mutations (e.g., gastrointestinal stromal tumors) and others lack specific genetic signatures (e.g., leiomyosarcoma, pleomorphic liposarcoma, undifferentiated pleomorphic sarcoma).[19,20] Epigenetic changes in soft tissue sarcomas include DNA methylation (e.g., hypermethylation of *PTEN* promoter region in alveolar rhabdomyosarcoma), histone modification (e.g., upregulation of Jumonji-type histone demethylases by PAX3-FOXO1 fusion gene in alveolar rhabdomyosarcoma), and noncoding RNAs (dysregulation of muscle differentiation transcription factors miRNA-133-1b and miRNA-206 in rhabdomyosarcomas).[21]

EXPOSURE

Ionizing Radiation

The history of primary cancer increases subsequent cancer risks; limited data exist on the exact contribution of radiotherapy to the increased soft tissue sarcoma risks resulting from the susceptibility to secondary cancers and chemotherapy use.

Radiotherapy

Radiation-associated cancers may occur in patients receiving high-dose radiotherapy (i.e., >8–9 Gy). A US study of 565 sarcoma patients with second malignancies identified 160 patients with radiation-associated sarcomas, including 100 soft tissue, 39 osteogenic, and 21 unclassified sarcomas.[22] The median radiation dose was 50 Gy, with malignant fibrous histiocytoma, angiosarcoma/lymphangiosarcoma, and spindle cell sarcoma representing the most common histological types using older classification categories. Given the rarity of soft tissue sarcomas, the overall absolute risk is very small, even with very high radiation doses. A retrospective US study of medical records from 22,306 radiotherapy patients from 1934–1983 identified 18 soft tissue sarcomas in previously radiated patients receiving a radiation dose ranging from 25–70 Gy.[23]

A Finnish study identified 12 soft tissue sarcomas from data in the Finnish Cancer Registry 1953–2000 covering 1.5 million person-years in a cohort of 295,712 primary cancer patients; 75% of these patients were ≥55 years of age.[24] Table 62.3 displays the standardized incidence ratios for soft tissue sarcomas for Finnish primary cancer patients with and without radiotherapy based on age and sex. The standardized incidence ratio for patients with and without radiotherapy was statistically nonsignificant, except soft tissue sarcomas in men ($n = 7$) and women <55 years of age ($n = 34$).

Japanese Atomic Bomb Survivors

The Life Span Study cohort of 80,180 Japanese atomic bomb survivors identified 104 soft tissue sarcomas with a mean latency period between exposure and diagnosis of 36.8 years. The most common histological types were leiomyosarcoma (37 cases) and malignant fibrous histiocytoma (11 cases, now classified as undifferentiated/unclassified).[25] The data suggested a doubling of soft tissue sarcoma risks using a linear dose-response model *above* 1 Gy. The excess relative risk was 1.01/Gy (95% CI: 0.13–2.46, $P = 0.019$) with an excess annual absolute risk of 4.3/100,000 population (95% CI: 1.1–8.9, $P = 0.001$).

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TABLE 62.3. Standardized incidence ratios (SIRs) of bone and soft tissue sarcomas in a Finnish cohort of 295,712 patients with primary cancer diagnosed from 1953–2000.[24] Most of the SIRs in sarcoma patients with a history of radiotherapy were not statistically different than primary cancer patients without a history of radiotherapy. (Data adapted from Virtanen et al.).[24]

Age at Diagnosis (Sex)	Standardized Incidence Ratio	95% CI	Cases
	Soft Tissue Sarcoma		
<55 years (male)	10.0	4.0–20.6[a]	7
≥55 years (male)	1.0	0.2–3.0	3
<55 years (female)	3.1	2.2–4.4[a]	34
≥55 years (female)	1.2	0.7–1.9	18
	Bone Sarcoma		
<55 years (male)	3.6	0.1–19.1	1
≥55 years (male)	0	0.0–5.8	0
<55 years (female)	3.0	1.2–6.1[a]	7
≥55 years (female)	1.4	0.4–3.7	4

[a] Statistically significant at $p = <0.05$. *Abbreviation*: CI = Confidence Interval.

Occupation

An exploratory study analyzed data from the US Selected Cancers Study 1984–1988 and identified 521 incident sarcoma cases and 1,910 age-matched controls.[7] Using self-reported occupational exposures and exact conditional logistic-regression models, the odds ratios for sarcomas classified as dermatofibrosarcoma protuberans ($n = 46$), liposarcoma ($n = 53$), and skeletal sarcoma ($n = 51$) were statistically nonsignificant. Out of the 15 suspected carcinogens, the odds ratio was statistically significant for leiomyosarcoma patients ($n = 67$) exposed to plywood (OR = 2.21, 95% CI: 1.25–3.86) and wood or sawdust (OR = 2.41, 95% CI: 1.38–4.16). The only other statistically significant occupational exposure was herbicide use on a farm 5 years before the study (OR = 2.94, 95% CI: 1.07–7.32). The total number of comparisons was 60.

Human epidemiology evidence for increased soft tissue sarcoma risks following exposure to phenoxy herbicides (2,4-dichlorophenoxyacetic acid, 2,4-D; 2,4,5-trichlorophenoxyacetic acid, 2,4,5-T; 2-methyl-4-chlorophenoxyacetic acid, MCPA, methylchlorophenoxypropionic acid, MCPP, and/or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, TCDD) is limited and inconsistent without strong support for causation.[26,27] A systematic review of 13 cohort and 27 case-control studies reported mostly weak or modest and statistically nonsignificant risks for soft tissue sarcomas in phenoxy herbicide-exposed workers consistent with other reviews.[28] The authors opined that the absolute soft tissue sarcoma risks must be small if there is a true hazard. In a nested case-control study of 4,093 deaths after employment in 5 UK factories manufacturing phenoxy herbicides for a contract spray business, the highest odds ratio for soft tissue sarcoma risks in men working ≥1 year in potentially phenoxy herbicide-exposed jobs was 1.30 (95% CI: 0.30–5.62, $n = 6$ exposed cases/45 exposed controls).[29]

HISTOLOGY

Sarcomas are rare, aggressive tumors with mesenchymal differentiation categorized according to morphology and location in the body. Soft tissue sarcomas are classified according to the normal tissue they resemble. Consequently, sarcomas represent a large, heterogeneous group of >50 distinct histological types in variable locations throughout the body.[30] The World Health Organization (WHO) classifies soft tissue sarcomas as tumors of the extremities, trunk wall, and retroperitoneum rather than internal organs; the latter are considered visceral sarcomas attributable to the organ of origin. The 2013 WHO edition has 11 soft tissue histological subgroups; this WHO classification added gastrointestinal stromal and nerve sheath tumors previously associated with other organs to the soft tissue sarcoma section, along with a new undifferentiated/unclassified sarcoma section.[31] The latter soft tissue tumors now include the tumors previously classified as malignant fibrous histiocytomas (MFH).

A European study of ~13 million inhabitants identified 1,660 sarcomas (968 soft tissue sarcomas, excluding Kaposi sarcoma; 590 visceral sarcomas, including gastrointestinal and endometrial stromal tumors).[32] The newly classified gastrointestinal stromal tumors were

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not included in the study statistics. The most common soft tissue sarcomas were liposarcomas ($n = 254$), leiomyosarcomas ($n = 156$), dermatofibrosarcoma protuberans ($n = 98$), and Kaposi sarcomas ($n = 95$). In an Austrian study evaluating 5,333 soft tissue cancer cases from 1984–2004, the most common subtypes were not otherwise specified (36%), leiomyosarcoma (24%), liposarcoma (12%), malignant fibrous histiocytoma (9%, now classified as undifferentiated/unclassified), and fibrosarcoma (5%).[18] The histological type changes with age; rhabdomyosarcomas are particularly common in the pediatric age group (median age, <20 years), whereas Kaposi sarcoma, fibrohistiocytic tumors, and leiomyosarcoma are more prevalent in adults.[33]

HOST SUSCEPTIBILITY

A small portion of soft tissue tumors are attributed to familial risks, including Li–Fraumeni syndrome, hereditary retinoblastoma, neurofibromatosis type I, Gardner syndrome, and Werner syndrome. Analysis of adjusted standardized incidence ratios (SIR) using data from the nationwide Swedish Family Cancer Database suggests familial soft tissue sarcoma risks are limited to certain histological subtypes.[34] The study identified 17 offspring–parent pairs with concordant soft tissue sarcomas; the SIR was increased and statistically nonsignificant (SIR = 1.60, 95% CI: 0.93–2.56). Most relationships between offspring soft tissue sarcoma subtypes and parental cancers were statistically nonsignificant, except for liposarcoma in offspring with parental bladder cancer and leiomyosarcoma in offspring with parental breast cancer.

CLINICAL PRESENTATION

Although the incidence of soft tissue sarcomas increases exponentially with age, these tumors become a less common portion of total cancers as age progresses, representing ~3% of tumors in the fourth decade of life compared with ~7% of pediatric cancers. Consequently, soft tissue sarcomas are relatively more common during adolescence and young adulthood. In the European study of ~13 million inhabitants, the most common locations for sarcomas (including visceral sarcomas and excluding Kaposi sarcomas) based on the US age-standardized rate per 100,000 person-years were the lower extremity (1.02), trunk wall (0.67), retroperitoneum (0.63), and stomach (0.61).[32] In a retrospective study of 2.6 million insured patients in the German federal state of Saxony, the 1-year relative survival proportion for soft tissue sarcomas was ~88% (95% CI: 80–93%, $n = 1{,}468$ cases) and ~66% (95% CI: 56–76) for relative 5-year survival.[35]

KAPOSI SARCOMA

Kaposi sarcoma is a malignant, cutaneous, or oral mucosal mesenchymal tumor affecting blood and lymphatic vessels. This Kaposi sarcoma herpesvirus-associated (previously known as human herpesvirus type 8, HHV8) tumor manifests most commonly as pink, red, purple, or brown-black skin lesions. Rarely, this cancer develops in the digestive or respiratory systems (i.e., <4%).[36] Originally, this tumor was a rare, indolent disease of elderly Mediterranean and Eastern European descendants in Greece, Italy, and the Middle East, usually with a family history of susceptibility (classic Kaposi sarcoma). Kaposi sarcoma was endemic in South Africa and portions of Sub-Saharan Africa, particularly in men (endemic Kaposi sarcoma).[37] With the onset of AIDS in Western countries, this disease was one of the initial AIDS-defining clinical illnesses along with *Pneumocystis carinii* pneumonia, esophageal/pulmonary candidiasis, tuberculosis, and toxoplasmosis.[38] Currently, most cases are associated with immunosuppression (HIV, solid-organ transplant patients).

In an analysis of data from the European RARECARE project, the age-adjusted annual incidence of Kaposi sarcoma was 0.3/100,000 inhabitants, with the highest incidence in Southern Europe (0.8/100,000).[36] Kaposi sarcoma is the most common malignancy associated with HIV infection. Although HIV infection is neither a necessary nor sufficient condition for the development of Kaposi sarcoma, the presence of HIV increases the incidence and clinical aggressiveness of this tumor.[39]

CARCINOGENESIS

Hyperplasic polyclonal lesions composed primarily of spindle cells from lymphoid endothelia develop from the stimulation of proinflammatory cytokines and growth factors (e.g., basic fibroblast growth factor, interleukin 6, tumor necrosis factor α, vascular endothelial growth factor). Viral oncogenes contribute to the proliferation of these lesions, particularly HHV8, which has a tropism for endothelial cells, keratinocytes, and lymphocytes. Although the presence of this virus is relatively low (i.e., ~10%) in early Kaposi sarcoma, ~90% of the spindles of endothelial cells in the nodular stage contain HHV8 DNA or RNA.[40,41] Immune dysregulation produces various cytokines and growth factors that promote tumor

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growth, including FGF2 (fibroblast growth factor 2), interleukin 6, platelet-derived growth factor, oncostatin M, platelet-derived growth factor, transforming growth factor-β, tumor necrosis factor α, and VEGF (vascular endothelial growth factor).[39]

EXPOSURE

The most important conditions for the development of Kaposi sarcoma involve viral oncogenesis by the Kaposi sarcoma-associated herpesvirus (human herpesvirus-8, HHV8) and cytokine-induced inflammation/proliferation along with some immune suppression. The prevalence of HHV8 infection is high in homosexual men depending on the number of sexual partners; Kaposi sarcoma is independently associated with HHV8.[42] This tumor occurs infrequently in Western women correlating with the relative rarity of HHV8 infections, whereas the male/female ratio is similar in Africa, where HIV is primarily a heterosexually transmitted disease. The incidence of Kaposi sarcoma has declined substantially in Western countries with the advent of highly active antiretroviral therapy.[43]

Several case-control studies suggest BMI may influence soft tissue carcinoma risks. In an Italian study of 217 incident soft tissue sarcomas and 1,297 hospital controls, the soft tissue sarcoma risk for BMI $\geq 30\,kg/m^2$ was increased (OR = 3.28, 95% CI: 1.61–6.69, $n = 33$ cases/172 control cases) using BMI $\leq 20\,kg/m^2$ as controls.[44] The potential for misclassification with self-reported weight, the lack of cohort studies, and the use of hospital controls limit conclusions regarding causation.

HISTOLOGY

The primary histological process in the formation of Kaposi sarcomas is the symmetric, multicentric proliferation of atypical lymphatic and blood vessels. The patch stage is the initial pattern that manifests as a macular lesion consisting of small, irregular endothelium-lined spaces surrounding normal dermal vessels along with an inflammatory lymphocytic infiltrate.[45] Expansion of spindle-cell vascular processes during the plaque stage produces irregular, cleft-like vascular channels containing erythrocytes and hemosiderin deposits along with a perivascular inflammatory infiltrate. As sheets of spindle cells with cytological atypia expand into a network of slit-like vascular spaces, nodules appear during the nodular stage.

CLINICAL PRESENTATION

The clinical course of Kaposi sarcoma is highly variable, ranging from a single indolent lesion to an aggressive, multifocal systemic disease producing widespread hemorrhage and/or organ dysfunction, particularly in AIDS or immunosuppressed solid-organ transplant patients.[46] Classic Kaposi sarcoma is a chronic disease that most commonly affects elderly Mediterranean, European, or Jewish men (10–15 men/1 women, 6th decade of life); the tumor manifests as multiple firm reddish-brown and purple plaques and nodules on the lower extremities, sometimes associated with lymphedema and hyperkeratosis. The clinical course of endemic African, iatrogenic, immunosuppressive, and AIDS-related Kaposi sarcoma is much more variable, ranging from chronic nodular cutaneous lesions to fulminant lymphadenopathic disease rapidly disseminating to visceral organs.[39] Spontaneous remission may occur in iatrogenic Kaposi sarcoma following the cessation of immunosuppressive therapy. Kaposi sarcoma has a relatively good prognosis depending on location, age, and comorbidity; the overall 5-year relative survival rate for all sites in the European RARECARE project was 75% ($n = 1{,}795$ tumors) compared with 25.3% ± 17.1% ($n = 27$ tumors) for digestive system Kaposi sarcomas.[36] The survival rate has improved significantly with the advent of highly active antiretroviral therapy.

LEIOMYOSARCOMA

Leiomyosarcomas are a relatively common type of soft tissue sarcoma that occurs throughout the body; however, the most common are leiomyosarcomas of the uterus. Uterine leiomyosarcomas appear genetically distinct from tumors in other locations.[47,48] Most uterine neoplasms are benign leiomyomas, with leiomyosarcomas representing ~0.1–1% of uterine neoplasms. The annual incidence of uterine leiomyomas is ~0.35/100,000 women, with the incidence about 2-fold higher in black than white women.[17]

CARCINOGENESIS

Leiomyosarcomas usually display complex karyotypes with numerous chromosomal losses and gains.[49] Currently, no single driver gene has been identified. Leiomyosarcomas display a highly heterogeneous genomic landscape with frequent abnormalities in tumor suppressor (*TP53*, *RB1*, *PTEN*) and early development (*ATRX*, *MED12*) genes. Overall, the

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mutational load is relatively low in leiomyosarcomas. The most common genetic changes involve alteration of *TP53* and *MDM2* expression (minichromosome maintenance complex component 2, regulation of helicase activity and genome replication), enhancement of *CDKN2A* (cyclin-dependent kinase inhibitor 2A, p16), and inhibition of λ-smooth muscle isoactin expression.[50] Consistent chromosomal losses include the *PTEN* tumor suppressor via deletions at chromosome 10q23, resulting in hyperactivation of phosphatidylinositol 3-kinase/AKT pathway involved with cell-cycle and apoptosis regulation.[51] Although overexpression of cell-cycle regulatory and apoptotic genes occurs in leiomyosarcoma tumors, other signaling pathways may be important in tumor progression, including the interferon-γ pathway and mutations of the *PSMB9* gene (proteasome 20S subunit beta 9).[52]

EXPOSURE

Leiomyosarcomas are primarily sporadic with no clearly established risk factors reflecting the rarity of these tumors and the difficulty in identifying risk factors in very rare cancers. A pooled analysis of data collected from the Epidemiology of Endometrial Cancer Consortium identified 82 leiomyosarcomas and 28,829 controls.[53] Using polytomous logistic-regression models adjusted for age, race, BMI, menarche, menopausal status, estrogen/progesterone use, smoking, and diabetes, none of the estimated odds ratios for studied risk factors reached statistical significance, including BMI ($P_{trend} = 0.26$), age at menarche ($P_{trend} = 0.44$), or parity ($P_{trend} = 0.12$). The highest odds ratios were reported for diabetic history (OR = 1.91, 95% CI: 0.77–4.77, $n = 10$ cases/1,583 controls, $P_{heterogeneity} = 0.65$), estrogen-only menopausal therapy (OR = 1.63, 95% CI: 0.18–14.95, $n = 6$ cases/2,878 controls, $P_{heterogeneity} = 0.97$), and obesity ≥30 kg/m^2 (OR = 1.56, 95% CI: 0.88–2.77, $n = 23$ cases/4,932 controls, $P_{heterogeneity} = 0.39$). Firm conclusions on causality are restricted by large confidence intervals and limited power. Very rare case reports associate radiotherapy with the subsequent occurrence of leiomyosarcoma;[54] these tumors are too rare to detect elevated risks in the Life Span Study of atomic bomb survivors.

HISTOLOGY

Although most leiomyosarcomas are sporadic, occasional case reports suggest leiomyosarcomas may develop in initially benign leiomyomas; however, distinguishing benign leiomyomas from leiomyosarcomas may be difficult because no single clinical or imaging criterion separates the two neoplasms.[55] These tumors display distinct features of smooth muscle cells. Leiomyosarcomas characteristically are large, soft intramural masses with infiltrative borders, atypical/elongated nuclei, multiple mitotic figures, abundant eosinophilic cytoplasm, and areas of necrosis.

CLINICAL PRESENTATION

Common locations for leiomyosarcomas include the abdomen, retroperitoneum, large blood vessels, and the uterus, with the latter accounting for the majority of these tumors. Overall, leiomyosarcoma incidence increases with age peaking in the seventh decade, whereas most uterine leiomyosarcomas appear in women over 40 years of age with the incidence rapidly increasing over the age of 50 years.[56] The typical uterine leiomyosarcoma patients present with vaginal bleeding, uterine pain/pressure, and a palpable pelvic mass; rarely, hypercalcemia and eosinophilia occur.[57] These aggressive tumors are relatively chemotherapy- and radiotherapy-resistant, resulting in poor survival in advanced stages of the disease. Prognosis depends on tumor size/depth, histological type, and clinical stage. In a follow-up study (median = 9 years) of 71 patients with histologically proven uterine leiomyosarcoma, the overall survival rate was 65%, ranging from 75% for International Federation of Obstetrics and Gynecology (FIGO) Stage I to 14% for Stage II, and 0% for Stages III–IV.[58]

LIPOSARCOMA

Liposarcomas are the most common soft tissue histological type representing ~1/5 of all soft tissue sarcomas with five main subtypes involving: 1) atypical lipomatous tumors/well-differentiated; 2) dedifferentiated; 3) myxoid/round-cell; 4) pleomorphic; and 5) mixed-type. The first two subtypes account for 40–50% of liposarcomas. Well-differentiated and dedifferentiated liposarcomas occur primarily in the retroperitoneum, whereas the extremities are the main location for myxoid and pleomorphic liposarcomas. Well-differentiated and myxoid liposarcomas are low-grade tumors; high-grade tumors include dedifferentiated and pleomorphic liposarcomas.

An analysis of the genomic landscape using SNP arrays and whole-exome sequencing identified known amplified genes (*CDK4*, *HMGA2 MDM2*) and novel genes (*CPM*, *ERBB3*, *IGF1R*, *IGF2*, *LAMA4*, *MIR557*,

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UAP1) along with deletions of chromosome 1p (*RUNX3*, *ARID1A*), chromosome 11q (*ATM*, *CHEK1*), and chromosome 13q14.2 (*MIR15A*, *MIR16-1*).[59] Affected signaling pathways include ErbB, JAK-STAT, MAPK, and Wnt, involving axon development, apoptosis, cell-cycle regulation, and DNA damage repair. Most myxoid and round-cell liposarcomas contain t(12;16) or t(12:22) translocations that produce fusion proteins affecting adipocyte differentiation via the PPARγ (peroxisome proliferator-activated receptor γ) and CEBP proteins (CCAAT-enhancer-binding proteins).[60]

RHABDOMYOSARCOMA

Rhabdomyosarcomas are the most common soft tissue tumors in children and young adults; these tumors are usually high-grade, locally invasive, commonly metastasizing tumors, resulting in poor survival without chemotherapy.[61] These tumors represent 1 of the 10 most common childhood malignancies, with an annual incidence for children and adolescents (< 20 years of age) of 0.004.3 cases/100,000 young population in the United States (i.e., ~350 incident cases/year).[62]

CARCINOGENESIS

Rhabdomyosarcoma is a heterogeneous disease with genetic alterations varying with histological type and age (i.e., children vs. adults). A majority of childhood tumors have the t(2;13)(q35;q14) translocation that fuses the *PAX3* gene (paired box 3) with the *FOXO1A* gene; the former is a transcriptional regulator of embryonic neuromuscular development, whereas the latter is a transcription factor from the forkhead family involved with myogenic growth and differentiation. A less frequent translocation is t(1;13)(p36;q14) that fuses *PAX7* gene (paired box 7) with *FOXO1A* gene; the former is a tumor suppressor involved with fetal development, regulating muscle precursor cell proliferation.[63] The presence of reciprocal translocations and associated fusion genes characterizes the alveolar rhabdomyosarcoma subtype, whereas embryonal rhabdomyosarcomas typically contain gene mutations, copy number changes (chromosomal losses/gains), and allelic losses frequently activating the RAS signaling pathway.[64] Approximately ¼ of childhood alveolar rhabdomyosarcomas contain no translocations.

Common pathways implicated in rhabdomyosarcoma development include nuclear factor-kappa B (NF-κB), YAP (Yes-associated protein 1) transcriptional coactivator, and Hippo, Notch, Wnt, and MEK/ERK signaling pathways.[65] The YAP and Hippo signaling pathways maintain tumor proliferation and antidifferentiation in embryonal rhabdomyosarcomas, while upregulation of Notch signaling and crosstalk with Hedgehog, Hippo, TGF-β, and Wnt pathways inhibit differentiation and promote self-renewing tumor cells.[66,67] In alveolar rhabdomyosarcoma, PAX3/7-FOXO1 fusion genes promote tumorigenesis by suppressing the Hippo signaling pathway and inhibiting myogenic differentiation of tumor cells.[68] Epigenetic changes include deregulation of the NFκB-YY1-induced downregulation of miR-29 tumor suppressor activity.[69]

EXPOSURE

Rhabdomyosarcomas are primarily sporadic with no established risk factors; however, a few rare familial syndromes predispose family members to developing rhabdomyosarcomas. The rarity of these tumors limits studies on environmental, occupational, and lifestyle risk factors.

HISTOLOGY

Although the precise cell of origin is unknown, rhabdomyosarcomas arise from primitive progenitor cells of striated skeletal muscle resembling small, round, blue-cell tumors (desmoplastic, small round-cell, lymphoma, Ewing sarcomas) characteristic of embryonic myogenesis.[1] Rhabdomyosarcomas occur in a variety of anatomical sites other than skeletal muscle. A substantial majority of these tumors stain positive for myoglobin, muscle-specific actin, and polyclonal desmin.[70] Subtype classifications of rhabdomyosarcoma include embryonal, alveolar, botryoid, pleomorphic, and anaplastic; the former two subtypes account for the vast majority of rhabdomyosarcomas in children, whereas the latter three are primarily adult tumors.[65] Embryonal rhabdomyosarcoma displays no distinct architecture, with sheets/nests of typical rhabdomyoblasts and occasional fusiform cells usually appearing in the head, neck, and urogenital regions of infants and young children. The alveolar subtype resembles pulmonary alveoli with fibrovascular septae lined with densely packed tumor cells separated by pseudoalveolar spaces; the latter histological subtype typically occurs in the extremities and parameningeal sites of adolescents.[64] Botryoid rhabdomyosarcomas form hypercellular subepithelial tissue in grape-like polypoid masses lined by epithelium of hollow viscera, usually in

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young children; pleomorphic rhabdomyosarcomas contain intersecting storiform whorls of large spindle cells with irregular, hyperchromatic nuclei and prominent nucleoli.

HOST SUSCEPTIBILITY

Noonan syndrome and related disorders, Costello syndrome, and cardiofaciocutaneous syndrome are a group of developmental malformation syndromes resulting from dysregulation of the RAS/mitogen-activated protein kinase (MAPK) signaling pathway. This pathway mediates early and late developmental processes by controlling cell proliferation, differentiation, senescence, and apoptosis. In a review of 77 peer-reviewed articles reporting 84 cancer patients with these syndromes, 42 patients had Noonan syndrome and 31 had Costello syndrome.[71] Rhabdomyosarcoma was the most common cancer accounting for 1/3 of malignant tumors, primarily Costello syndrome (22 cases) and Noonan syndrome (5 cases).

CLINICAL PRESENTATION

Most children with rhabdomyosarcoma present with local disease manifested by a painless mass surrounded by erythema.[72] Metastatic disease most frequently occurs in the lungs and bones. Although rhabdomyosarcomas can occur in any part of the body, the most common sites include the head and neck (35–40%), genitourinary tract (25%), and extremities (20%). Survival depends on clinical stage, age, site of origin, and histological subtype. The overall 5-year survival rate for rhabdomyosarcoma in children is relatively good (i.e., ~70%) compared with adults (i.e., <18%).[73] In an analysis of prognostic factors for nonmetastatic rhabdomyosarcoma from the Intergroup Rhabdomyosarcoma Studies III/IV, the 5-year failure-free survival rate ranged from 90% for embryonal RMS Stage 1 or 2, group I (localized disease, completely resected) or group IIa (resected tumor with microscopic residual) to 43% in stage 2 or 3 and group III (incomplete resection with gross residual disease) extremity primary tumors.[74] The 5-year survival rate for stage 4 (distant metastatic disease present at onset) is ~30% similar to group III alveolar or undifferentiated sarcoma subtype of rhabdomyosarcoma.[1] In general, the alveolar subtype with the PAX3–FOXO1 fusion genes is more aggressive and at higher risk with a poor prognosis,[75] whereas the embryonal subtype has an intermediate prognosis and the botryoid subtype has a relatively good prognosis.[76]

UNCOMMON SOFT TISSUE SARCOMAS

AGGRESSIVE FIBROMATOSIS

Aggressive fibromatosis (dermoid tumor) is a monoclonal, collagen-forming neoplasm consisting of myofibroblast-like cells. This tumor is locally invasive and occasionally multifocal but rarely metastatic. Although these tumors are rare, aggressive fibromatosis occurs much more commonly in patients with familial adenomatous polyposis;[77] susceptibility to this tumor in patients with familial adenomatous polyposis is associated with an inactivating germline APC gene mutation on chromosome 5q21–q22. Gardner syndrome is a variant of this inherited disease characterized by epidermal cysts, fibromas, intestinal polyposis, osteomas, and sebaceous cysts. Estrogen-related conditions (pregnancy, oral contraceptives) and trauma are suggested risk factors; however, epidemiological evidence of an association is weak and conflicting.[78,79] The most common genetic abnormality in aggressive fibromatosis is a somatic mutation in *CTNNB1* (catenin β1, chromosome 3p21) gene associated with the Wnt/β-catenin signaling pathway affecting cell adhesion and intercellular communication.

Fibrosarcomas are classified as superficial and deep (aggressive or desmoid) types. Superficial fibromatosis neoplasms are smaller, indolent, and lack the somatic β-catenin or mutation in gene *APC*; they develop in knuckles, palm, sole, and penis of predominately Caucasian adult males. Deep (aggressive, desmoid) fibrosarcomas occur in any anatomical location with distinct subsets in the abdominal wall and abdomen (mesentery, retroperitoneum). Extra-abdominal aggressive fibromatosis develops in the proximal extremities, thigh muscles, chest wall, and head and neck of young adults, particularly women.[80] Histologically, the tumor consists of long fascicles of myofibroblasts in parallel with uniform spacing and a hypocellular collagenous stroma; pleomorphism and necrosis are lacking. The typical clinical presentation is a slow-growing, painless plaque or firm, discrete mass with pressure-like symptoms depending on the location. Prognosis is generally good following complete excision of the tumor; however, recurrence may occur.

DERMATOFIBROSARCOMA PROTUBERANS

Dermatofibrosarcoma protuberans is a malignant fibroblastic skin cancer that is the most common

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cutaneous sarcoma.[81] The overall annual incidence is 0.004/100,000 inhabitants with a similar incidence between men and women; the incidence is ~2-fold higher in blacks than whites.[82] These rare tumors typically present as an asymptomatic, indurated, slowly growing plaque that may be flesh-colored or hyperpigmented.[83] Histological examination at this stage demonstrates minimal nuclear atypia, low cellularity, and rare mitotic figures. The subsequent nodular stage consists of firm, brown to reddish-blue or violaceous nodules formed by storiform islands of bland spindle cells, myxomatous areas, less-differentiated foci, and hyperchromatic, deeply lobulated nuclei. Over 90% of these tumors contain t(17;22)(q21;q13) translocations resulting in PDGFB (platelet-derived growth factor subunit B)–COL1A1 (collagen type I alpha 1 chain) fusion gene. This genetic alteration enhances the production of platelet-derived growth factors and the activation of multiple signaling pathways affecting cell differentiation, movement, and proliferation. The absence of the PDGFB–COL1A1 fusion gene in ~8% of these tumors suggests other abnormalities may be involved, including epigenetic (e.g., miRNA-205 downregulation)[84] and genomic alterations (e.g., overexpression of p-ERK, p-STAT3, and thrombospondin-1 proteins).[85] Although dermatofibrosarcoma protuberans can present at any age, the peak incidence occurs between 25–45 years of age on the trunk (40–50%), proximal extremities (30–40%), and head/neck (10–15%).[81] Although this low-grade tumor is locally aggressive and may recur after incision, metastasis is rare. Survival is excellent after complete removal with a 2-year survival rate of 97% and a 5-year survival rate of 92%.[86]

GASTROINTESTINAL STROMAL TUMORS

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumor of the gastrointestinal tract, with an annual incidence of ~0.015/100,000 inhabitants and a similar incidence between men and women. GIST comprise ~20% of soft tissue sarcomas.[87] In 2001, these tumors were the first neoplasms targeted by a cell surface tyrosine kinase receptor inhibitor (i.e., imatinib mesylate) to block the main initiating driver gene mutations KIT and PDGFRA.

CARCINOGENESIS

Early genomic changes in the vast majority (i.e., 75–90%) of gastrointestinal stromal tumors (GIST) involve KIT mutations (*KIT* proto-oncogene receptor tyrosine kinase, chromosome 4q12-exon 11 juxtamembrane domain). The remaining 10–25% of GIST are KIT-negative; overall, up to ~5–7% of GIST have mutations in *PDGFRA* (platelet-derived growth factor receptor α, chromosome 4q12) without KIT mutations, particularly in children with GIST.[88,89] Mutations in *KIT* and *PDGFRA* genes are mutually exclusive. Figure 62.1 displays the chromosomal location of sporadic, hereditary, and secondary gene mutations in GIST. KIT gene mutations produce a protein that activates downstream proliferative and antiapoptotic signaling pathways (mitogen-activated protein kinase, MAK; phosphoinositide-3-kinase, PI3K) without requiring binding to the stem cell factor protein. These pathways increase cell growth, survival of interstitial cells of Cajal, and GIST formation; however, the presence of mutations in *KIT* genes in up to 1/3 of healthy patients without progression to malignancy indicates KIT mutations alone are not sufficient to produce malignant cells.[90] Additionally, a relatively large pool of micro-GIST exists in the general population, providing a reservoir for the development of more advanced neoplasms.[87]

The wild-type, triple-negative tumors (*KIT*/*PDGFRA*/*SDH*-negative) are a heterogeneous group with some tumor development driven by oncogenic mutations downstream of receptor kinases. Alternative potential oncogenic events include activation of mutations in *BRAF* or *RAS*-family genes (*HRAS*, *KRAS*, *NRAS*) along with inactivation of tumor suppressor *NF1* gene (neurofibromin 1). The wild-type GIST (children/adults) usually contains succinate dehydrogenase (SDH) deficiency from inactivation of *SDHA/B/C/D* genes, particularly in younger patients with Carney triad or Carney–Stratakis syndrome.[87] Whole-exome sequencing suggests advanced GIST samples contain a low mutation tumor burden with genomic aberrations mostly affecting tumor suppressor *CDKN2A/B*, *RB1*, and *TP53* genes and copy loss involved with cell-cycle regulation.[91] This study also suggested that a minority of advanced GIST contain mutations in spliceosome-regulating genes (*PRPF18*, *RBMX*, *RBMXL3*, *SF3A2*, *SNRP200*, *U2AF2*). Chromosomal alterations associated with the progression of malignant GIST include deletions of 1p, 9p (*CDKN2A* gene, 9p21.3), 14q, and 22q, particularly tumor suppressors in chromosome 9p, whereas gains in chromosomes 8q and 17q are associated with increased metastasis.[92]

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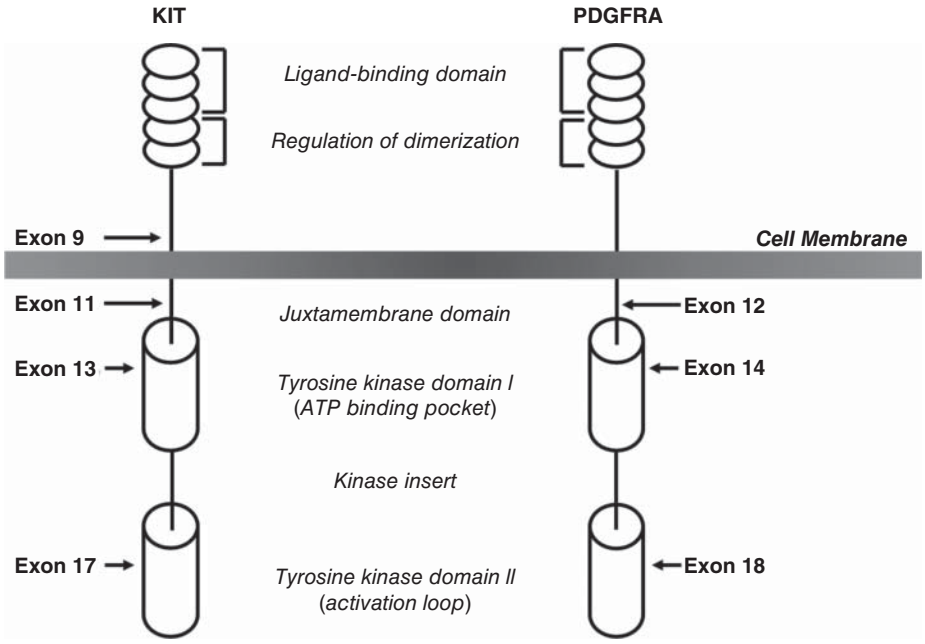


FIGURE 62.1. Schematic view of the locations of mutations in *KIT* (*KIT* proto-oncogene receptor tyrosine kinase) and *PDGFRA* (platelet-derived growth factor receptor alpha) genes in gastrointestinal stromal tumors (GIST). These mutations are mutually exclusive in GIST. The vast majority of GIST contains more of the former than the latter. KIT mutations with PDGFA mutations are much less frequent. Some mutations are sporadic (*PDGFRA* exon 12/18, *KIT* exon 11), whereas a few are hereditary (*PDGFRA* exon 12, *KIT* exon 8/11) or some secondary (*KIT* exon 9/13/14/15/16/17, *PDGFRA* exon 14/18). (Adapted from Joensuu et al.).[87]

EXPOSURE

GIST are primarily sporadic with no established risk factors; however, a few rare familial syndromes predispose family members to the development of GIST. The rarity of these tumors limits study power sufficient to identify environmental, occupational, and lifestyle risk factors.

HISTOLOGY

Most GIST probably originate or share common stem cells with interstitial cells of Cajal located in the outer surface of the gut; these c-*KIT*-positive fibroblast-like cells between intramural neurons and smooth muscle cells regulate peristalsis and the gastrointestinal autonomic nerve system.[88] Previously, these tumors were included with gastrointestinal leiomyosarcomas and schwannomas. Over one-half of GIST occurs in the stomach, ~1/3 in the small intestine, and the remainder in other portions of the gastrointestinal tract (colon and rectum, <5%; esophagus, <1%) and intra-abdominal soft tissue (e.g., retroperitoneum).[93] GIST display diverse histology ranging from small intramural or serosal nodules to large masses with hypocellularity to highly hypercellularity.[94] Histological subtypes include spindle cell, epithelioid, and mixed spindle-epithelioid with a large majority being spindle cell.[95] GIST with mutations in the *PDGFRA* gene typically develop in gastric and omental locations; the neoplasms display cystic, hemorrhagic tumors containing pleomorphic, low-mitotic count epithelioid/plasmacytoid cells with peripheral nuclei in myxoid stroma.[96] GIST with SDH mutations are multinodular/dumbbell-shaped tumors with mucosal ulcerations; histologically, these neoplasms contain fibrous bands in nodules of epithelioid or mixed cells usually with lymphovascular invasion and lymph node metastases.

HOST SUSCEPTIBILITY

Familial GIST results from hereditary mutations in *KIT*/*PDGFRA* genes; rare syndromes include Carney triad (gastric GIST, paraganglioma, pulmonary chondroma), Carney–Stratakis syndrome, and neurofibromatosis type 1 (von Recklinghausen's neurofibromatosis). Heritable mutations occur in *KIT* exon 8, 11, 13, or 17, resulting in increased susceptibility to gastric and small bowel GIST in young adults, whereas germline mutations in *PDGFRA* exon 12 predispose family members to GIST and stomach/small bowel inflammatory fibroid polyps. Patients with Carney's

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triad or Carney–Stratakis syndrome do not have mutations in *KIT* or *PDGFRA* genes. Germline mutations in these patients involve subunits of tumor suppressor succinate dehydrogenase genes (*SDHA*, *SDHB*, *SDHC*, *SDHD*) important in the Krebs cycle and oxidative phosphorylation.[97] Succinate is an intracellular oxygen sensor that stabilizes hypoxia-inducible factor (HIF) and stimulates cell growth in low-oxygen environments. Von Recklinghausen's neurofibromatosis patients with GIST typically are KIT-negative, with <10% of these patients developing GIST.[98,99] Familial GIST accounts for an estimated <0.1% of GIST.[94]

CLINICAL PRESENTATION

Although GIST may develop at any age, the vast majority (i.e., >80%) of cases present over the age of 50 years, with the peak incidence occurring in the sixth to seventh decades of life (median = 60–65 years).[94,100] Clinical manifestations of GIST are diverse, with the clinical course varying from small, indolent nodules to metastatic, life-threatening sarcomas depending on location, type, and stage. Overall, gastrointestinal bleeding and gastric discomfort are the most common features reflecting the stomach as the most common GIST location. Intestinal obstruction, perforated bowel, and hemoperitoneum are rare presenting signs of GIST.[101] Occasional nonspecific symptoms include constipation, diarrhea, dyspepsia, nausea/vomiting, polyuria, and fatigue. Up to ~1/3 of GIST are discovered incidentally during imaging or surgical procedures.[88] GIST have variable malignant potential with prognosis depending on tumor size, mitotic rate, and location. The metastatic risk of small gastric GIST (<5 cm) with low mitotic count is small (3–5%) with a good prognosis. However, the metastatic risk is high for large, intestinal GIST with high mitotic rates. The most common metastases develop in the liver, omentum, and peritoneum, with extra-abdominal metastasis being uncommon.[102]

SYNOVIAL SARCOMAS

Synovial sarcomas are high-grade tumors usually affecting pediatric and young adult patients. The peak incidence occurs in the third decade with 90% appearing before 60 years of age.[103] Although unrelated to synovium, the name of these tumors reflects their resemblance to synovial cells. Histologically, synovial sarcomas display a wide, heterogeneous histological spectrum, characteristics of epithelial cells. Monophasic synovial sarcomas are pure spindle cell tumors, whereas biphasic synovial sarcomas contain spindle cells and epithelioid morphologies. The vast majority of synovial sarcomas have the t(X;18)(p11.2;q11.2) translocation producing the *SS18-SSX* fusion oncogene that inhibits SSX family-induced transcriptional repression. Affected signaling pathways are not well defined.

Synovial sarcomas occur predominantly in older children and young adults at a variety of anatomic sites including viscera. These tumors frequently present as large masses in deep soft tissue associated with local pain/tenderness in extremities, particularly the proximal or middle portions of the lower extremities; cutaneous lesions are rare.[104] Synovial sarcoma is usually a high-grade, aggressive sarcoma with an overall 5-year survival of ~60% and 10-year survival of ~50%.[105]

BONE SARCOMAS

Bone and articular cartilage cancers are rare, accounting for ~0.5% of all human cancers; these tumors may arise from any bone, cartilage, soft tissue, or organ. A retrospective study of 2.6 million insured patients in the German federal state of Saxony identified 671 bone sarcoma cases with approximately equivalent distribution of cases between males and females.[35] The age-adjusted annual bone sarcoma incidence was 2.1/100,000 (95% CI: 0.8–4.8) with ~48% over 50 years of age. Although the incidence of these cancers remains relatively stable, mortality from these tumors has increased in the last few decades. The three main bone neoplasms are osteosarcomas, Ewing sarcomas, and chondrosarcomas. Ewing sarcoma is a disease of childhood and adolescence, whereas osteosarcoma has a bimodal peak in childhood and the eighth decade of life. Chondrosarcoma is primarily a disease of the elderly; these tumors are a heterogeneous group of neoplasms that develop in benign cartilage abnormalities (e.g., enchondroma, osteochondroma). Ollier disease and Maffucci syndrome are rare, nonhereditary disorders associated with the development of multiple, benign enchondromas and susceptibility to the transformation of these neoplasms into chondrosarcomas.[106]

With the exception of Ewing sarcoma, ionizing radiation is the strongest risk factor, particularly bone-seeking radionucleotides (e.g., cesium, plutonium, radium). The attributable incidence of bone sarcomas in the workplace is essentially zero because of the rarity and limited potency of this tumor at typical occupational exposures.[107] A Finnish study identified 20 bone sarcomas from data in the Finnish Cancer Registry 1953–2000

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covering 1.5 million person-years in a cohort of 295,712 primary cancer patients, mostly in patients ≥55 years of age.[24] The only statistically significant increase in SIR for bone sarcoma in radiotherapy patients was in women <55 years of age (SIR = 3.0, 95% CI: 1.2–6.1, $n = 7$ cases), as displayed in Table 62.3; however, the comparison of radiotherapy and non-radiotherapy patients for this subgroup was not statistically significant. The Life Span Study cohort of 80,180 Japanese atomic bomb survivors identified 19 bone-tissue sarcomas with a mean bone marrow radiation dose of 0.43 Gy and a mean latency period between exposure and diagnosis of 29.2 years.[108] Using a linear dose-response model to estimate bone sarcoma risks, the excess relative risk was 7.5/Gy (95% CI: 1.34–23.14) above the threshold dose of 0.85 Gy; the excess absolute risk was 5.75/Gy above the threshold based on an annual incidence of 0.9/100,000 person-years. Rare, hereditary disorders associated with increased bone sarcomas include Mendelian-dominant Li–Fraumeni Syndrome (mutations) in *TP53* autosomal-dominant Retinoblastoma Syndrome (mutations in *RB*), and autosomal-recessive Werner Syndrome (WRN mutation, Werner syndrome RecQ-like helicase).[109] Osteosarcomas and Ewing sarcoma are relatively more common during the second and third decades of life, whereas the incidence of chondrosarcomas increases steadily with age. In a retrospective German study of 2.6 million insured patients in Saxony, the 1-year relative survival proportion for bone sarcomas was ~92% (95% CI: 81–99%, $n = 671$ cases) and ~53% (95% CI: 36–69) for relative 5-year survival.[35]

OSTEOSARCOMA

Osteosarcoma is the most common primary malignant bone tumor, affecting primarily children and adolescents and representing ~5% of childhood cancers (i.e., ~400 US cases/year).[110] The age-adjusted incidence of this rare, high-grade tumor is ~0.005/100,000 population, with half the cases occurring in 10–24-year-old patients.[111] The bimodal distribution peaks in adolescence, followed by a plateau at 25–60 years of age and then a small peak in elderly individuals.[112] Overall, ~900 incident osteosarcoma cases occur in the United States annually. Osteosarcoma varies little with race or gender; the overall male/female ratio is ~1.4:1, except in patients over 60 years when the ratio is near unity.[110] Worldwide, osteosarcoma incidence rates are generally stable.[113]

CARCINOGENESIS

The mutational landscape of osteosarcomas is highly complex; the highly disorganized osteosarcoma genome contains extensive intratumoral heterogeneity with a high rate of somatic mutations (1.2 mutations/megabase) compared with other pediatric tumors. Characteristic features of osteosarcomas include copy number losses/gains, structural variation, increased mutation numbers, and genomic instability. In contrast to Ewing sarcoma, these tumors have no consistent pattern of specific chromosomal translocations, single driver genes, or molecular defects.

Commonly mutated genes in osteosarcomas include the *TP53* and *RB1* tumor suppressor genes along with genes associated with the Notch (*HEY1*, *HES1*, *NOTCH2*), Wnt/β-catenin, and PI3K-mTOR signaling pathways. Notch proteins are important for angiogenesis and normal bone development/homeostasis, whereas the Wnt/β-catenin pathway affects cell growth, normal bone development, and carcinogenesis. The PI3K family of serine/threonine protein kinases regulates the cell cycle, growth, and development. These three pathways are upregulated in osteosarcomas.[112] Long telomeres are common in osteosarcoma; altered lengthening of telomeres that prevents telomere shortening and induces senescence may enhance genomic instability.[114] Epigenetic changes (promotor DNA hypermethylation/hypomethylation, histone modification, long/micro noncoding RNAs) associated with osteosarcomas occur, but the role of these alterations in promoting osteosarcoma formation is not well defined.[115,116]

EXPOSURE

Although most osteosarcomas are sporadic, a few risk factors increase osteosarcoma risks, including radiotherapy, anthracyclines, and alkylating chemotherapeutic agents (e.g., cyclophosphamide, nitrogen mustards). Overall, reproductive risk factors, tobacco smoking, chemicals, diet, and bone trauma are not associated with increased osteosarcoma risks, with the possible exception of early onset of puberty and tall stature;[117] the association between the latter and osteosarcoma is conflicting.[118,119]

Ionizing Radiation

Exposure to ^{226}Ra and ^{228}Ra radionuclides is a well-established cause of osteosarcoma, beginning

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with US female watch dial workers in the 1920s and continuing through the regrowth of the luminous dial industry leading up to World War II.[120] The intravenous diagnostic radiocontrast agent, Thorotrast® (^{232}Th) available from 1930–1955, was also causally associated with osteosarcoma.[121] High-dose therapeutic radiation including treatment of tuberculosis arthritis in the 1920s (e.g., total doses, 50 Gy).[118] The very low radiation doses used in medical imaging (e.g., chest X-rays, CT scans) are not associated with increased osteosarcoma risks.[122]

Occupation

Limited data support an association specifically between farming and osteosarcomas. A retrospective Norwegian study of data on 323,292 offspring followed by 17 years examined incident cancers based on the national agricultural census; bone cancer was not significantly increased in the offspring of farmers (SIR = 122, 95% CI: 83–172, $n = 32$ cases) compared with the total rural population (SIR = 113, 95% CI: 84–149, $n = 51$).[123] Exposure classification was based on information obtained during the agricultural census. A positive association not suspected *a priori* was between parental chicken farming and osteosarcoma in offspring (aRR = 2.90, 95% CI: 1.38–6.11, $n = 12$ cases). Adjustment included birth and calendar year. The specific exposure associated with chicken farming was not identified.

Environmental

Although several ecological studies suggest osteosarcomas are associated with drinking water fluoride concentrations,[124] observational studies are inconsistent and relatively weak.[125,126] A New York study estimated lifetime fluoride exposure from tablets, mouth rinses, toothpaste, dental treatments, and drinking water based on self-reports and population-based estimates of tap water intake.[127] Using the lowest quartile of fluoride intake as referents, childhood osteosarcoma risk in the highest quartile of total fluoride intake was inverse and statistically nonsignificant (OR = 0.41, 95% CI: 0.14–1.22, $n = 27$ cases/17 controls). Comparing the highest tertile of fluorinated water intake with nonexposed referents, the childhood osteosarcoma risk in the highest tertile was consistent with the null (OR = 0.93, 95% CI: 0.31–2.83, $n = 16$ cases/21 controls, $P_{trend} = 0.62$).

Diseases

Several benign conditions that increase bone turnover are associated with increased osteosarcoma risks, including Paget disease, osteochondroma, enchondroma, fibrous dysplasia, and chronic osteomyelitis. Older adults with Paget disease are particularly susceptible to osteosarcoma. An analysis of data from the National Cancer Institute's population-based Surveillance, Epidemiology, and End Results (SEER) Program identified 3,482 incident osteosarcoma cases from 1973–2004.[128] Of 653 osteosarcoma patients in the 60 years and older category, Paget disease patients represented 34% (62 primary tumors, 159 secondary tumors) of the 653 elderly osteosarcoma patients compared with 12% (4 primary tumors, 115 secondary tumors) of the 974 osteosarcoma patients in the 25–59-year-old category and 4% (1 primary tumor, 70 secondary tumors) of the osteosarcoma patients in the ≤24-year-old category.

HISTOLOGY

Osteosarcomas arise from primitive bone-forming mesenchymal cells that produce a broad spectrum of histological appearances. Classic osteosarcoma subtypes include chondroblastic, fibroblastic, and osteoblastic, reflecting the predominant type of matrix present in the tumor; these three subtypes account for ~70–80% of osteosarcomas. The remaining histological variants are very rare, including low- and high-grade surface, parosteal and periosteal, small cell, and telangiectatic osteosarcomas.

HOST SUSCEPTIBILITY

Certain rare genetic disorders predispose patients to osteosarcomas; however, primary bone cancer is not strongly associated with germline mutations or increased familial risks. A small percentage of osteosarcomas result from germline mutations of important tumor suppressor and helicase genes. Rare genetic conditions with germline mutations associated with increased osteosarcoma risks include Li–Fraumeni syndrome (tumor suppressor TP53 mutations), hereditary retinoblastoma, the autosomal-recessive Bloom and Werner syndromes (BLM mutations, BLM RecQ-like helicase), autosomal-recessive Rothmund–Thomson syndrome (RECQL4 mutation, RecQ-like helicase 4), and nonhereditary McCune–Albright syndrome (GNAS1 somatic mutation, GNAS complex

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locus).[129,130] For the highly penetrant, autosomal dominant Li–Fraumeni syndrome, osteosarcoma is a sentinel cancer, with ~70% of Li–Fraumeni syndrome families with a strong history harboring a pathogenic variant of the *TP53* tumor suppressor gene.[131] The cumulative incidence of osteosarcoma in individuals with a germline *TP53* pathogenic variant ranges from 5–11%.[132] A Swedish study of histology-specific bone cancer familial risks in offspring using parental or sibling probands identified 1,327 offspring bone cancers.[133] Only two parent–offspring pairs and one sibling pair had concordant bone cancer; however, the standardized incidence ratios were not statistically significant. The risk of developing osteosarcoma prior to 25 years of age was increased in mothers with melanoma and breast cancer, suggesting Li–Fraumeni syndrome may partly account for the familial association.

CLINICAL PRESENTATION

Osteosarcoma has a bimodal age distribution with the first peak appearing in 10–14-year-olds during the pubertal growth spurt and the second peak in older adults (>65 years). The latter peak commonly occurs in patients with Paget disease or in the transformation of other benign bone lesions.[134] The peak age for these osteosarcomas is the eighth decade. Malignant bone tumors rarely occur prior to 5 years of age. Patients typically present with indolent course of several months of localized bone pain often following trauma; anorexia, fatigue, and weight loss are uncommon. Some osteosarcoma patients have localized swelling and reduced range of motion in the affected extremity; however, few have pathological fractures at the time of presentation.[135] The most common tumor sites are long bones (i.e., ~75%) near metaphyseal growth plates, including the distal femur (knee), proximal tibia, and less frequently the proximal humerus. The tendency to affect extremity bones decreases with increasing age.[136] Metastasis at presentation occurs in ~10–20% of osteosarcoma patients; however, recurrence rates are high (i.e., ≥80%) in patients with localized disease at diagnosis and no subsequent chemotherapy.[137] The lungs are the most common site of metastasis, with involvement of lymph nodes and bone much less frequent.[138] The overall 5-year survival rate is ~60–70%, with complete local resection and multi-agent chemotherapy depending on age, clinical stage, anatomical site, and osteosarcoma subtype, whereas the presence of metastasis at diagnosis is associated with an ~30% 5-year survival.[139] Prior to the 1970s, when surgical resection was the primary treatment, the overall 5-year survival rate was ~20%.[140]

EWING SARCOMA

Ewing sarcomas are very rare and highly malignant, most common bone sarcomas, affecting predominately adolescent and young adult Caucasians. The incidence is higher in males than females; however, the tumor can occur at any age and develop in soft tissue. The overall incidence of Ewing sarcomas is ~0.13/100,000 with little change during the last several decades.[141] Significant differences exist in the pattern of Ewing sarcoma between races; the highest incidence occurs in Caucasians with a 2-fold lower incidence in Asians/Pacific Islanders and a 9-fold lower incidence in African Americans. The estimated age-standardized incidence among children from 1988–1997 was similar for boys and girls aged 0–14 years (0.005–0.006/100,000 population).[142] Among adolescents aged 15–19 years, males had a higher incidence (~0.02/100,000 population) than females (ratio = 1.8/1). An estimated 390 Ewing bone sarcomas and 170 Ewing soft tissue sarcomas occur annually in the United States.[143]

CARCINOGENESIS

This heterogenous tumor has characteristic translocations that produce fusion genes between the *TET*/*FET* (*TLS*/*FUS*, *EWSR1*, *TAF15*) and the *ETS* (E26 transformation-specific) gene families, as demonstrated in Figure 62.2. Typically, fusion genes contain a DNA-binding domain combined with a transcription or growth factor.[144] The vast majority (85–90%) of Ewing sarcomas contain the reciprocal translocation t(11;22)(q22;q12) between *EWSR1* gene (EWS RNA binding protein 1; chromosome 22q12.2) and *FLI1* gene (*FLI-1* proto-oncogene, ETS transcription factor; chromosome 11q24.3); together they produce the EWSR1/FLI1 fusion protein. This fusion protein possesses DNA-binding function of the FLI protein and the transcription regulatory function of the EWS protein. The remaining tumors contain translocations that fuse the *EWSR1* gene with other genes, including the *ETS* gene (*ETS* proto-oncogene family of DNA-binding transcription factors; chromosome 11q24.3), the *FEV* gene (FEV transcription factor, ETS family member; chromosome 2q35), and the *ERG* gene (ETS transcription factor ERG; chromosome 21q22.2). These fusion genes may promote stem cell development, cell senescence, and tumor proliferation; however, the exact function of these fusion genes is not well established. The frequency of mutations in the *TP53* gene is low. Epigenetic changes in Ewing sarcomas

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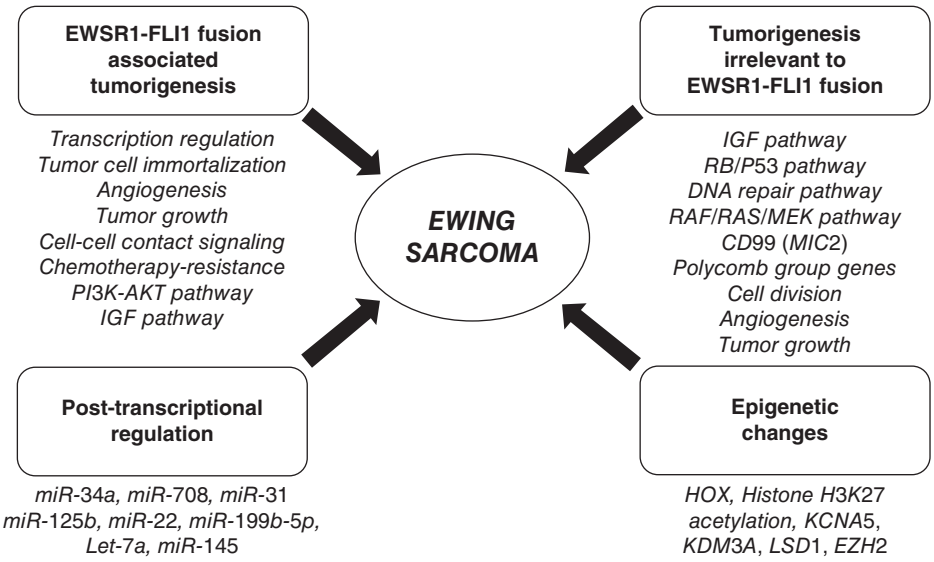


FIGURE 62.2. Translocations (TET/FET and ETS family fusion proteins), signaling pathways, microRNA post-transcriptional modifications, and epigenetic changes (transcriptional modifications) involved with transforming mesenchymal cells in bone and soft tissues into Ewing sarcomas. (Adapted from Salvi et al.).[98]

include *SIRT1* (sirtuin 1)-induced suppression of Notch signaling.

EXPOSURE

Most Ewing sarcomas are sporadic. Small sample sizes limit evaluation of risk factors associated with a rare tumor-like Ewing sarcoma; most studies are case-control, ecological, or descriptive with self-reported exposures. Large cohort studies are difficult to conduct.

Occupation

Several small case-control studies suggest the parental occupation of farming is associated with Ewing sarcomas in offspring; however, the results are inconsistent with imprecise risk estimates. A study of pooled data from 3 case-control studies identified 199 Ewing sarcoma family of tumor (ESFT) cases and 1,451 population-based controls. The odds ratio was positive and statistically significant for a paternal occupation in agriculture (farm owner or laborer) and ESFT in the offspring (OR = 2.3, 95% CI: 1.3–4.1, $n = 19$ cases/61 controls). Although the trend for duration of paternal farming was statistically significant ($P_{\text{trend}} = 0.01$), paternal farming for 1–9 years was not associated with increased ESFT risks (OR = 0.9, 95% CI: 0.4–1.9, $n = 8$ cases/46 controls). The adjusted odds ratio for maternal farming and ESFT in offspring was also positive (aOR = 3.9, 95% CI: 1.6–9.9, $n = 8$ cases/16 controls). Adjustment for the odds ratio included maternal occupation, age, maternal education, and study site.

Environmental

Little epidemiological evidence associates fluoride concentration in water with increased Ewing sarcoma risks. A UK ecological study on water fluoridation and data on Ewing sarcoma risks from population-based cancer registries in England, Scotland, and Wales in 1980–2005 identified 1,650 Ewing sarcoma cases in inhabitants aged ≤49 years. After adjustment for covariates and using negative binomial regression, Ewing sarcoma was not associated with drinking water fluoride concentrations ($P = 0.503$). The relative risk for Ewing sarcoma following a 1-ppm increased fluoride concentration in drinking water was 0.929 (90% CI: 0.773–1.115). The geographical variation in fluoride concentrations did not correlate with Ewing sarcoma risks. A systematic review of water fluoridation and bone cancer risks identified 9 studies comprising 20 separate analyses of bone cancers.[145] Only one study reported excess bone cancers; however, the heterogeneity of outcome measures prevented pooling of the data for meta-analysis.

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HISTOLOGY

Subtypes of the Ewing sarcoma family include Ewing sarcoma of bone, extraosseous Ewing sarcoma, peripheral primitive neuroectodermal tumor, and Askin tumor (Ewing sarcoma of chest wall). Classic Ewing sarcoma is a malignant, small, round cell bone tumor that comprises diffuse sheets or rosettes of uniform cells with round nuclei, fine chromatin, and inconspicuous nucleoli along with scanty, indistinct cytoplasm and occasional necrotic areas; morphological variants include spindled, sclerosing, and clear cell/anaplastic subtypes.[146,147] The cells are round to oval, closely packed, small, undifferentiated cells.

HOST SUSCEPTIBILITY

Familial syndromes are not strongly associated with Ewing sarcomas. In a study of data on 1,327 offspring bone cancers in the nationwide Swedish Family-Cancer Database, Ewing sarcoma was not associated with increased familial risks.[133] Using parents as probands, the SIR for childhood Ewing sarcoma was 1.0 (95% CI: 0.6–1.5, $n = 20$ cases). The SIR for Ewing sarcoma in parents with kidney cancer was positive but statistically nonsignificant (SIR = 2.2, 95% CI: 0.7–5.2, $n = 5$ cases).

CLINICAL PRESENTATION

Ewing sarcoma is a group of highly aggressive tumors primarily of the long bones (i.e., ~80%) and much less of soft tissue tumors in other organs, occurring predominantly in adolescents and young adults; cure rates are low with metastatic potential high for spread to lung and other bones and organs.[148] The peak incidence occurs in 10–20-year-olds, with the rare occurrence of this tumor in patients over 35 years of age. The most common presenting symptom is bone pain for several months and, less commonly, soft tissue swelling and fever. These tumors usually develop in long bones in the lower extremities (femur, tibia) and less commonly in the pelvis, humerus, and ribs. Most cases have localized disease at diagnosis; however, recurrence is common without chemotherapy. Prognosis depends on clinical stage (i.e., metastasis at diagnosis), tumor size (≥8 cm/≥200 mL), and location (i.e., axial vs. appendicular skeleton).[149] A study of 1,631 Ewing sarcoma cases from the US Surveillance, Epidemiology, and End Results (SEER) database reported an overall disease-specific survival rate of 55% at 5 years and 53% at 10 years.[141] Analysis of the SEER database 1991–2010 indicated the 10-year cause-specific survival was ~67% for local disease at diagnosis compared with 28% for patients with metastatic disease.[139]

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Chapter 63

THYROID

In the United States, thyroid cancer is the 6th most common cancer in women and 14th most common in men, with a current total annual estimated incidence of ~52,000 cases.[1] The overall annual thyroid cancer incidence almost tripled (~3% annually) from 4.9 to 14.3/100,000 individuals during the last 2 decades of the 20th century and the 1st decade of the 21st century.[2,3] In a cross-sectional study of individuals below 20 years of age using data from the US Surveillance Epidemiology and End Results (SEER) database, the average percentage increase for overall thyroid cancer incidence in this pediatric age group from 1973–2006 was 1.11% (95% CI: 0.56–1.67%) and 9.56% (95% CI: 5.09–14.22%) for 2006–2013.[4] These differences in incident rates were primarily driven by increased diagnostic imaging and surveillance, particularly papillary thyroid cancer.[5,6] Since then, some evidence suggests the rates are currently stabilizing.[7] Based on data from the US Surveillance Epidemiology and End Results (SEER) Program, the 5-year age-standardized incidence rate for thyroid cancer is ~2.5–3-fold higher in women (21.6/100,000) than men (7.3/100,000).[1,8]

Globally, thyroid cancer is the most pervasive endocrine tumor, with ~255,000 incident cases and ~41,000 deaths in 2017 based on epidemiological data gathered by the Global Health Data Exchange query tool covering 195 countries.[9] In this cross-sectional study, the estimated annual percentage change in age-standardized thyroid cancer incidence for the preceding 27 years was 1.59% (95% CI: 1.51–1.67%). Females accounted for 70% of the age-standardized incidence of thyroid cancer. In the United States, the prevalence of thyroid cancer (i.e., ~900,000 cases) is much higher than the incidence, reflecting the excellent prognosis for this cancer.[10] Worldwide, the mortality rate from thyroid cancer has remained stable for the last four decades.[11] This tumor is the most common endocrine tumor representing over 90% of endocrine cancers and 3.4% of cancers diagnosed annually worldwide. In the United States the 5-year survival rates for thyroid cancer exceed 98%.

CARCINOGENESIS

Substantial differences exist in the genetic alterations associated with the various histological types of thyroid cancer, particularly between follicular and medullary thyroid cancers. The mutation in the *BRAF* gene (*BRAF* proto-oncogene) and the mutant $BRAF^{v600E}$ serine/threonine kinase gene appear during the initiation of 50–70% of papillary thyroid cancers (PTC) and papillary-derived anaplastic thyroid cancers. Mutations of the *RAS* family of oncogenes more frequently occur in follicular than papillary or anaplastic thyroid tumors, as displayed in Table 63.1.[12,13] The *BRAF* oncogene is part of the RAS–MAPK pathway that relays signals downstream to regulate the expression of genes responsible for cell proliferation, differentiation, and apoptosis. Mutations in the *BRAF* gene are mutually exclusive with RET/PTC rearrangements and most other common genetic alterations.[14] The mutations in *BRAF* genes are associated with genetic instability and a poorer prognosis (local recurrence, metastasis,

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TABLE 63.1. Common somatic gene mutations and rearrangements in histological types of thyroid follicle-derived tumors listed as a percentage of total tumor samples from various pathology case series. (Adapted from Carling and Udelsman).[19]

Genetic Alteration	Papillary (%)	Follicular (%)	Poorly Differentiated (%)	Anaplastic (%)
		Mutations		
BRAF	29–70	0	0–13	0–12
CTNNB1	0	0	0–25	66
RAS	0–21	40–53	18–27	20–60
TP53	0–5	0–9	17–38	67–88
		Rearrangements		
NTRK1	5–13	—	—	—
PPARG	0	25–63	0	0
RET/PTC	13–36	0	0–13	0

Abbreviations: BRAF = B-type Raf kinase; *CTNNB1* = β-catenin 1; *NTRK1* = neurotrophic receptor tyrosine kinase 1; *PPARG* = peroxisome proliferator-activated receptor γ; *PTC* = papillary thyroid cancer; *RET* = *RET* proto-oncogene.

advanced clinical stage).[15] All thyroid tumors with mutations in $BRAF^{V600E}$ are considered malignant.[16] RET/PTC is an interchromosomal rearrangement of an oncogene common in papillary thyroid cancer that produces an activated serine/threonine kinase, resulting in stimulation of the RAS–RAF–MAPK signaling cascade.[17] In a mutational analysis of 72 papillary thyroid carcinomas, mutations in $BRAF^{V660E}$ occurred in 38 (44.4%) of the tumors compared with 26 (36.1%) with RET/PTC rearrangements; 22 (30.5%) contained neither genetic alteration.[18] These chimeric oncoproteins develop almost exclusively in papillary thyroid cancers.

The *RAS* family of GTP-binding proteins regulates cell growth via the MAPK and PI3K–AKT pathways. The most frequent mutations in *RAS* genes in order of the most common are first *NRAS*, *HRAS*, and *KRAS*, primarily occurring in poorly differentiated, anaplastic, and medullary thyroid cancers. Mutations in *NRAS* genes preferentially activate the PI3K–AKT pathway, whereas mutations in *KRAS* genes are preferential activators of the MAPK pathway. Mutations in *RAS* act upstream of mutations in *BRAF* genes; the two mutations are usually mutually exclusive.[14] Mutations in *RAS* genes and PAX8/PPARγ (PPARG) rearrangements are mutually exclusive and the primary oncogenic drivers in follicular thyroid cancers.[16] These two genetic alterations are not specific and occur in both follicular thyroid carcinomas and adenomas, although at a lower rate in the latter.[12]

Most early thyroid cancer mutations affect three main signaling pathways: 1) RAS–RAF–MEK–MAPK (mitogen-activated protein kinase) pathway that helps regulate cell proliferation by transmitting growth signals from the plasma membrane to the nucleus; 2) calcium–calmodulin pathway that produces an important component of calcium-mediated cellular signal transduction; and 3) the PI3K–AKT–mTOR pathway that is essential for protein synthesis, development, cell proliferation, and cell survival.[20] Most of the mutations in oncocytic thyroid carcinoma (Hürthle cell carcinoma) involve the mTOR signaling pathway. RAS mutations and RET/PTC rearrangements also stimulate the growth of benign thyroid nodules without excess transformation into malignant neoplasms;[21,22] these benign thyroid nodules grow faster with than without these genetic alterations.[23]

Novel fusion oncogenes occurring during the initial stage include the *PAX8*-peroxisome proliferator-activated receptor λ (PPARλ) translocation in follicular thyroid tumors and the RET (*RET* proto-oncogene) chromosomal rearrangement in papillary thyroid carcinomas.[24] Although most thyroid cancers harbor mutations in *BRAF* genes remain indolent, the presence of a mutation in *BRAF* gene is associated with a more advanced tumor stage at diagnosis and worse prognosis (higher recurrence/mortality).[25] More aggressive tumors also develop alterations of the PI3K–AKT–mTOR pathway associated with cell development, cell proliferation, and survival; inactivation of the TP53 tumor suppressor pathway; and antiapoptotic mutations in *TERT* genes causing reactivation of telomerase reverse transcriptase.[26,27] The latter is a catalytic protein subunit of telomerase

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important for maintenance of chromosomal integrity and genomic stability. Mutations in *TERT* promoter genes typically do not occur in benign thyroid nodules and are uncommon in papillary thyroid cancers, whereas the prevalence of these mutations in poorly differentiated and anaplastic thyroid cancers usually exceeds 40%.[28]

MiRNAs are a group of >2,000 small, noncoding RNAs that have key roles in posttranscription gene regulation by repressing or degrading mRNA in the cytosol and altering gene expression. Most alterations of miRNAs involve downregulation rather than upregulation, which is usually associated with a less differentiated state.[29] Compared with normal thyroid tissues, overexpression of miRNAs-146b, miRNA-221, and miRNA-222 is associated with increased papillary thyroid tumor progression (local recurrence, metastasis, $BRAF^{V600E}$ mutation).[30,31] In a Chinese study of 36 papillary thyroid cancer tumors and 15 benign thyroid nodular goiter samples, the presence of miRNA-30-3p, miRNA-146b-5p, and miRNA-199b-5p was statistically different in the two tissues.[32] MiRNA-30-3p was downregulated, whereas the other two miRNAs were upregulated. The genes associated with these miRNAs remain unclear.

EXPOSURE

The main risk factor for thyroid cancer is ionizing radiation, particularly papillary thyroid cancer in children exposed to high-dose therapeutic or external radiation at doses from 0.1–60 Gy.[33] Other risk factors include benign thyroid diseases, iodine deficiency, and family history of thyroid cancer. Currently, epidemiological studies indicate electromagnetic field exposures and cell phone use are not associated with increased thyroid cancer risks. In a US study of 462 thyroid cancer cases and 498 population-based controls using multivariate unconditional logistic regression to estimate odds ratios, the OR for thyroid cancer in cell phone users was 1.05 (95% CI: 0.74–1.48) using nonusers as referents. The study reported no statistically significant association with cumulative cell phone use.[34] A Swedish study of ~3 million workers followed for 19 years reported no association between extremely low-frequency magnetic fields and thyroid cancer based on three job-exposure matrices.[35] Few epidemiological data indicate lifestyle is a significant risk factor for thyroid cancer; several studies suggest a modest positive association between BMI and thyroid cancer risks and an inverse association with smoking. Current smoking produces a modest dose-dependent reduction in thyroid cancer risks, particularly for papillary thyroid cancer, with the risk in former smokers approaching never-smoker risks within several years of cessation.[36,37]

Ionizing Radiation

Ionizing radiation is a well-established cause of thyroid cancer from radioactive fallout (e.g., post-Chernobyl radioiodine release, Japanese atomic bomb survivors) and high-dose cervical radiotherapy, particularly following radiation exposure during childhood. Thyroid cancer was the first solid tumor associated with an increased incidence among Japanese atomic bomb survivors.[38] Analysis of pooled data from 5 cohort (Japanese atomic bomb survivors, children treated for *Tinea capitis*, enlarged tonsils or thymus) and 2 case-control (cervical cancer, childhood cancer) studies involving ~120,000 participants covering ~3 million person-years identified almost 700 incident thyroid cancers.[39] For children of <15 years of age, the best fit for the data was a linear dose-response curve down to 0.1 Gy, with the curve beginning to level off at >10 Gy based on limited data at the high doses. The excess relative risk/Gy for thyroid cancer in these children was 7.7 (95% CI: 2.1–28.7) reflecting small sample sizes and imprecise estimates. Although the excess risk persisted for 30–40 years, the risk was small 20 years after exposure and depended strongly on the age at exposure. Only two cases occurred within 5 years of initial radiation exposure. Similarly, the minimum latency period for diagnosis of thyroid cancers following the Chernobyl accident was 4–5 years; however, minimum latency postradiation time periods in most studies are 5–10 years with the highest risks in the 10–15-year time period and diminishing risks after 20 years' postexposure.[33]

Radiotherapy

A pooled analysis of thyroid cancer incidence in 2 cohort and 2 nested case-control studies involving radiotherapy for 16,757 patients treated for childhood cancers identified 187 incident primary thyroid cancers.[40] The excessive relative risk of thyroid cancer followed a linear exponential model through 10 Gy, then leveled before declining at >30 Gy. The peak estimated RR was 14.9 (95% CI: 8.2–24.5) at 15.9 Gy. The estimated RR at 1 Gy was 3.2 (95% CI: 2.2–5.3) compared with 8.7 (95% CI: 3.1–29.7) at 1 Gy in the Ron et al. study.[39] The Childhood Cancer Survivor Study identified 119 subsequent thyroid cancers in cancer patients living at least 5 years after treatment.[40] The dose-response relationship

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between a second primary thyroid cancer and radiation dose followed a linear exponential quadratic model with the relative risk peaking at ~20 Gy before declining; the peak RR was 14.6 (95% CI: 6.8–31.5). Sex (risk ↑ in females), time since exposure, and age at exposure (risk ↑ with younger age at exposure) were significant modifiers of radiation-induced thyroid cancer risks. The overall mean initial radiation dose was 11.3 Gy (range, 0–67.3 Gy). Chemotherapy administration did not confound the association between radiation and subsequent primary thyroid cancer risks.

A Portuguese study followed children receiving radiation therapy for *Tinea capitis* from 1950–1963 until 2012.[41] For children administered radiation doses of 3.25–4.75 Gy (325–475 R), the SIR for subsequent thyroid cancer was 2.93 (95% CI: 2.13–3.94, $n = 36$ female/8 male cases) compared with 4.05 (95% CI: 1.09–10.4, $n = 4$ female/0 male cases) for children receiving ≥6.3 Gy (630 R). An Israeli study examined thyroid cancer risks in 10,834 children receiving relatively low radiation doses (mean = 0.093 Gy; range, 0.0045–0.495 Gy) for *T. capitis*. During a median follow-up of 46 years (range, 1–54 years), the study identified 159 thyroid cancers. The peak ERR/Gy was 20.2 (95% CI: 11.8–32.3) with the value increasing during the second decade after exposure, peaking during the third decade, and decreasing dramatically during the fourth decade after exposure.

Environment

Chernobyl Nuclear Power Plant

The Chernobyl nuclear power plant accident produced the largest, uncontrolled environmental release of radioactive material by a civilian operation; the explosion and fire affected Southern Belarus, four oblasts (states) of the Russian Federation, and Northern Ukraine. High thyroid doses resulted from the ingestion of short-lived ($t^{½} = 8$ days) ^{131}I-contaminated milk among children;[42] external environmental radiation exposure was relatively low except for cleanup and emergency workers. The first thyroid cancer cases presented 4–5 years postexposure, primarily in children exposed at age ≤10 years. By 2005, over 6,800 cases of thyroid cancer were reported by UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) in children from contaminated areas under 18 years of age, with most of these children being under 14 years of age; 15 fatalities were associated with these cases.[43] Little epidemiological evidence supports an increased thyroid cancer incidence in adults or children born after the Chernobyl accident. Although initially these mostly (i.e., 95%) papillary thyroid tumors were considered more aggressive than sporadic cases, subsequent studies indicated the high rates of recurrence (30%) and metastases (60–70% cervical lymph nodes, 10–15% distant) with low mortality (<1%) reflecting age at onset and solid papillary thyroid cancer histology rather than radiation-induced effects.[44,45]

Some studies suggest the genetic alterations in radiation-induced and sporadic thyroid cancer differ. In targeted next-generation sequencing and RNA-Seq on 65 papillary thyroid cancers from the Ukrainian-American cohort of children exposed at <18 years of age, driver mutations consisted of 26.2% point mutations and 70.8% fusion genes.[46] Novel driver fusion genes included POR-BRAF (cytochrome p450 oxidoreductase-*BRAF* proto-oncogene, serine/threonine kinase) and *STRN-ALK* (striatin-ALK receptor tyrosine kinase) alterations. The point mutations appeared at lower radiation doses (mean = 0.2 Gy; range, 0.013–1.05 Gy) than fusion genes (mean = 1.4 Gy; range, 0.009–6.15 Gy). The percentage of fusion genes increased to 87.8% in tumors receiving radiation doses of ≥0.3 Gy. In contrast, sporadic papillary thyroid cancers are driven primarily by point mutations. Chromosomal rearrangements are not unique to radiation-induced papillary cancers.

Fukushima Daiichi

The Japanese Fukushima Daiichi Nuclear Power Plant accidentally released 900 pBq of radiation (500 pBq ^{131}I, 10 pBq ^{137}Cs) from March 10–13, 2011; these doses represent 10% and 30% of the radiation doses released during the Chernobyl nuclear reactor explosion and fire, respectively.[47] The 2013 UNSCEAR report estimated the absorbed thyroid dose in Fukushima residents ranged from 0.047–0.083 Gy and higher in non-evacuated residents (0.036–0.795 Gy),[48] whereas the 2012 WHO report estimated a range of 0.1–0.2 Gy.[49] Although an ecological study done on 2-phase screening of 300,476 (81.7% participation rate) Fukushima residents of ≤18 years of age between October 2011 and March 2014 and a 2nd round of 270,489 (70.9% participation rate) residents between May 2014 and March 2016 suggests an increased thyroid cancer incidence,[50] further studies are necessary because of insufficient follow-up times (minimum latency: 4–5 years) and the difficulty separating prevalence and incidence.

Marshall Islands BRAVO Atmospheric Nuclear Test

On March 1, 1954, a 15-megaton nuclear weapons test heavily contaminated the inhabitants of four atolls east

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of Bikini Island in the northern Pacific Ocean with nuclear fallout from radioactive iodides (^{131}I, ^{131}I isotopes) and external γ radiation. Thyroid cancer risks and radiation exposure estimates are uncertain; however, the fallout delivered high-dose radiation based on the high incidence of acute radiation sickness in residents of Rongelap Atoll and the subsequent high incidence of thyroid nodules in Marshall islanders followed from 1954–1985.[51] Almost all Marshall islanders had thyroidectomies in the United States; hence, the true thyroid cancer incidence is unclear. Ecological studies of fallout from the Nevada Test Site have not associated the relatively low radiation doses with elevated thyroid cancer risks.[52]

Occupation

Occupations potentially exposed to ionizing radiation include radiologists and radiology technologists, particularly interventional radiologists, nuclear industry and disaster cleanup workers, military personnel in weapon production and testing, underground miners, plutonium and reactor fuel manufacturing workers, airline pilots (UV radiation), and radium-dial painting (historical). Although childhood ionizing radiation exposure is a well-recognized thyroid cancer risk factor, the association of thyroid cancer with low–moderate occupational ionizing radiation exposures in adults is less clear.

Chernobyl cleanup workers (liquidators) received external radiation exposure from radioactive materials deposited on the ground and building surfaces, particularly in the 30-km Chernobyl zone in 1986. These mostly male workers represented approximately half of the recovery workers during 1986–1991. A study of a Ukrainian cohort of 150,813 male liquidators identified 196 incident thyroid cancer cases; the mean age at exposure was the early 30s.[53] The overall SIR was 3.50 (95% CI: 3.04–4.03) compared with 3.86 (95% CI: 3.26–4.57) for liquidators' first cleaning in the Chernobyl zone in 1986.

The Nordic Occupational Cancer Project collected occupational data and 2.8 million incident cancer cases from 15 million inhabitants from Denmark, Finland, Iceland, Norway, and Sweden aged 30–64 years based on self-administered census information from 1960–1990 and follow-up for 45 years.[54] Thyroid cancer risks in various occupations were modest and inconsistent. These risks were highest in Iceland and were attributed in part to differences in diagnostic criteria. Table 63.2 lists the statistically significant increases in the standardized incidence ratio for thyroid cancer in specific occupations based on the census data; none of the comparisons

TABLE 63.2. Statistically significant standardized incident ratios (SIRs) for thyroid cancer in occupations of 15 million men and women covered by the Nordic Occupational Cancer Project (NOCP). For comparison, the SIRs for both men and women in occupations with statistically significant increases were included; none of the comparisons in the same occupations were positive and statistically significant for both men and women. (Adapted from Pukkala et al.).[54]

Occupation (Sex)	Standardized Incidence Ratio	95% CI	Observed Thyroid Cases
Fishermen (male)	1.32[a]	1.07–1.62	93
Fishermen (female)	1.22[a]	0.33–3.12	4
Public safety workers (male)	1.25[a]	1.04–1.50	112
Public safety workers (female)	0.71	0.34–1.30	10
Clerical workers (male)	1.20[a]	1.06–1.35	264
Clerical workers (female)	0.92	0.88–0.97	1,538
Farmers (male)	0.95	0.88–1.02	639
Farmers (female)	1.18[a]	1.07–1.30	420
Teachers (male)	1.15[b]	1.00–1.32	199
Teachers (female)	0.99	0.91–1.07	566
Building caretakers (male)	1.10	0.87–1.38	75
Building caretakers (female)	1.08[a]	1.01–1.15	827

[a] Statistically significant. [b] Marginally significant statistically. *Abbreviation*: CI = Confidence Interval.

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between men and women for the same occupation were both positive and statistically significant. In a review of 30 studies including thyroid cancer risks in various occupations, the most consistent associations existed between thyroid cancer and radiation-exposed workers or healthcare occupations (primarily direct interaction with X-ray technology). The associations with pesticide-exposed workers and agricultural occupations were suggestive but inconsistent.[55] Exposure classifications were generally subject to misclassification and wide estimates based on small sample sizes and exposures based on self-reports, occupational categories, or generic job-exposure matrices. Most of the statistically significant associations in the Nordic study were not supported by the review; the Nordic study did not report any increased thyroid cancer risks in healthcare occupations.

In the US Radiologic Technologists cohort of 89,897 members following a mean of 21 years, the mean cumulative occupational thyroid radiation dose was 0.057 Gy (range, 0–1.6 Gy) based on self-reports, historical data, and individual film badge measurements when available.[56] Using Poisson regression to estimate excess relative thyroid cancer risks, the adjusted ERR/0.1 Gy was −0.05 (95% CI: <−0.10 to 0.34, $n = 476$ cases). Adjustments included age, sex, birth year, body mass index, and pack-year smoking. Similarly, the US Radiologic Technologists Study did not report a significant association between thyroid cancer incidence and fluoroscopically guided interventional procedures.[57] Using Cox proportional hazard models and never-working with these procedures as referents, the adjusted hazard ratio for thyroid cancer was 0.91 (95% CI: 0.61–1.38, $n = 32$ ever/96 never cases).

Reproduction

The several-fold higher risk of thyroid cancer in women and the excess thyroid cancer risk during reproductive years suggest reproductive history, menstruation, and/or estrogen status may affect thyroid cancer risks; however, epidemiological studies do not support a strong role for these factors in the etiology of thyroid cancer. The European Prospective Investigation into Cancer and Nutrition (EPIC) study reported no association between differentiated thyroid cancer risks and age at menarche or menopause, menopausal status, breastfeeding, or parity.[58] Although a positive Cox proportional hazards regression model indicated a positive association between thyroid cancer risks and infertility problems, a recent pregnancy, and surgical vs. natural menopause, the authors opined that enhanced surveillance may account for some or all of the increased risks. The Japan Public Health Center-Based Prospective Study of 54,776 women aged 40–69 years identified 187 incident thyroid cancers.[59] Using Cox proportional hazard regression modeling, analysis indicated an inverse association between age at menarche and thyroid cancer risks for premenopausal women (HR = 0.83/1-year increase, 95% CI: 0.70–0.98, $P_{trend} = 0.03$), but not postmenopausal women. The association was positive for surgical vs. natural menopause (HR = 2.34, 95% CI: 1.43–3.84). In a meta-analysis of 24 prospective studies including 5,434 thyroid cancer cases, thyroid cancer was not associated with age at menarche, oral contraceptive use, or parity.[60] Surgical menopause (summary RR = 1.43, 95% CI: 1.15–1.78) and increasing age at first pregnancy/birth (sRR = 1.56, 95% CI: 1.01–2.42) were positively associated with thyroid cancer risks.

Obesity

Some case-control and prospective studies suggest a modest positive association between obesity and differentiated thyroid carcinomas, primarily papillary thyroid cancer in women.[61,62] The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort of ~370,000 women and ~150,00 men aged 35–69 years followed for 5.4 million person-years used Cox proportional hazard models to estimate hazard ratios and BMI of 18.5–24.9 kg/m^2 as referents.[63] The HR for differentiated thyroid cancer in obese participants (BMI ≥ 30 kg/m^2) was modestly positive but statistically nonsignificant in women (HR = 1.19, 95% CI: 0.89–1.59, $n = 66$ cases, $P_{trend} = 0.057$) and unrelated (HR = 0.40, 95% CI: 0.13–1.19, $n = 4$ cases, $P_{trend} = 0.449$) in men. Comparisons of tertiles of waist circumference and waist-to-hip ratio were similar to the BMI values in women (positive, nonsignificant) and men (no association). In a pooled analysis of 5 US prospective studies involving 413,979 women and 434,953 men followed for a mean of 10.3 years, the study identified 768 thyroid cancers in women and 388 thyroid cancers in men.[64] The hazard ratio for obese men and women combined was 1.53 (95% CI: 1.31–1.79) using normal weight (18.5–24.9 kg/m^2) as referents. BMI was positively associated with baseline age in women but not in men. The multivariable-adjusted HR for thyroid cancer per 5-kg/m^2 increase in BMI was positive and nonsignificant in men (aHR = 1.21, 95% CI: 0.97–1.49, $I^2 = 54.3\%$, $P_{heterogeneity} = 0.09$) and positive and significant in women (aHR = 1.16, 95% CI: 1.08–1.24, $I^2 = 0\%$, $P_{heterogeneity} = 0.48$).

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Medications

Interpretation of epidemiology studies on the association of thyroid cancer with chemotherapy use is complicated by the frequent use of combined chemotherapy, the attenuation of chemotherapy-associated risks with increasing radiation doses and conflicting results. In a pooled analysis of data from two cohort and two case-control studies on thyroid cancer in childhood cancer survivors using patients without chemotherapy or radiation treatment as referents, the overall RR for developing thyroid cancer in patients treated with chemotherapy was positive but statistically nonsignificant (RR = 2.4, 95% CI: 0.5–12.3); the estimated RR was imprecise.[40] Similarly, the RR for thyroid cancer following the use of alkylating agents was 3.2 (95% CI: 0.8–12.8) and 3.1 (95% CI: 0.9–10.9) for bleomycin. The RR for anthracyclines was positive and statistically significant (RR = 4.5, 95% CI: 1.3–15.7) but imprecise. The P_{trend} for increasing quartiles of 5-Gy radiation doses on decreasing thyroid cancer risks in chemotherapy patients was statistically significant for alkylating agents ($P_{\text{trend}} = 0.01$) and bleomycin ($P_{\text{trend}} = 0.11$) but not for overall chemotherapy ($P_{\text{trend}} = 0.01$) or anthracyclines ($P_{\text{trend}} = 0.12$).

HISTOLOGY

Most thyroid nodules are small, nonpalpable nodules often identified during routine imaging studies. Over 90–95% of these nodules do not progress to cancer.[65] The histological classification of thyroid cancer consists of a heterogeneous group of three well-differentiated subtypes (papillary, follicular, medullary), poorly differentiated, and anaplastic.[66] Papillary, follicular, and some anaplastic subtypes arise from follicular cells, whereas medullary thyroid cancer is a rare neuroendocrine tumor originating in parafollicular C cells. The latter produces calcitonin rather than thyroid hormones. Traditionally, Hürthle cell carcinoma was considered a variant of follicular thyroid cancer and included with follicular thyroid cancer in studies; however, recent evidence suggests the biological behavior and genetic alteration of the two tumors differ.[67] The World Health Organization (WHO) now classifies Hürthle cell carcinoma (oncocytic thyroid carcinoma) and follicular thyroid cancer separately.[68] In countries with sufficient dietary iodine, the papillary subtype accounts for ~92% of thyroid cancer cases compared with ~6% for follicular, ~0.1–2% for medullary, and ~0.075% for anaplastic.[11]

The histology of papillary thyroid cancer is relatively straightforward, whereas follicular thyroid cancer histology is much more complicated; the latter lacks the cellular and nuclear atypia (e.g., nuclear enlargement/overlap, irregular/elongated nuclear contours, optically clear nucleoplasm) present in papillary thyroid cancers. Papillary thyroid carcinomas characteristically demonstrate papillae; however, some variants are follicular variants with no papillary areas.[19] Rare but aggressive papillary thyroid variants include tall-cell, columnar-cell, diffuse sclerosing, solid, Hob-mail, and follicular variants.[69] These tumors display irregular borders invading thyroid parenchyma and lymphatic spaces, resulting in microscopic multimodal lesions and regional lymph-node metastases. Stromal reactions include desmoplasia, myxoid areas, elastosis, fibromatosis-like changes, and amyloid formation.[66]

Follicular adenomas and carcinomas appear similar cytologically, with the difference being capsular or vascular invasion on histological slides; both neoplasms contain somatic mutations in *RAS* genes and PAX8/PPARλ rearrangements.[70] Follicular thyroid carcinomas are more common in iodine-deficient areas than nonendemic goiter areas, with the incidence ratio of papillary/follicular thyroid cancers being relatively lower in iodine-deficient countries.[71] Excessive Hürthle cells (polygonal cells with abundant eosinophilic granular cytoplasm) do not increase malignancy risks except in the presence of Hashimoto thyroiditis. Anaplastic carcinomas are the most heterogeneous, highly aggressive subtype of thyroid cancer consisting of a mixture of epithelioid, pleomorphic giant, and spindle cells with variable combinations of desmoplastic, hyalinized, and sclerotic stoma.[66] Medullary thyroid cancer is typically well differentiated, monoclonal, and not encapsulated; however, papillary and medullary thyroid cancer may develop concurrently, particularly in patients with familial medullary carcinoma and multiple endocrine neoplasia syndrome.

HOST SUSCEPTIBILITY

Hereditary thyroid neoplasms arising from calcitonin-producing C cells are called familial medullary thyroid carcinomas, whereas familial thyroid cancers developing from follicular cells are known as familial nonmedullary thyroid carcinoma or familial follicular cell-derived carcinoma. Familial medullary thyroid cancers are part of the autosomal-dominant multiple endocrine neoplasia syndrome; ~1/4 of medullary thyroid tumors occur in patients with this inherited syndrome.[72] Germline mutations in *RET* genes predispose patients with multiple endocrine neoplasia type 2A or 2B syndrome to medullary thyroid cancer.[73] Of

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all cancer sites, the familial risk of thyroid cancer is one of the highest, with increased risks extending beyond the immediate family, particularly medullary thyroid carcinomas.[74]

At least 5% of follicular cell-derived, papillary, and follicular thyroid carcinomas have a thyroid cancer family history. In a population-based Nordic cohort of 63,495 1st-degree relatives of 11,206 nonmedullary thyroid cancer patients, the overall thyroid cancer risk in individuals with a parent, child, or singleton sibling with papillary thyroid cancer increased by ~3-fold over the general population.[75] The risk increased significantly for individuals with multiple affected relatives or twin siblings. The lifetime cumulative thyroid cancer risk (0–84 years) in close female relatives of a papillary thyroid cancer patient was 2.1% (95% CI: 1.73–2.49%, $n = 146$ cases) and 0.8% (95% CI: 0.53–1.00%, $n = 51$ cases) in male relatives.

Familial nonmedullary thyroid cancers consist of two categories of rare hereditary cancer syndromes involving: 1) prominence of non-thyroid tumors; or 2) prominence of nonmedullary thyroid tumors.[76] The former category includes: autosomal-dominant Carney complex (germline mutation in *PRKAR1α* genes); autosomal-dominant Cowden syndrome from germline mutations in multiple genes (*AKT1*, *KLLN*, *PTEN*, *PIK3CA*, *SDH*, *SEC23B*); autosomal-recessive Werner syndrome (germline mutation in *WRN*); McCune–Albright syndrome (germline mutation in *GNAS*); autosomal-dominant DICER1 syndrome (germline mutation in *DICER1*); Pendred syndrome; and autosomal-dominant familial adenomatous polyposis (germline mutation in *APC*). The latter category includes familial papillary thyroid carcinoma with papillary renal cell carcinoma (germline mutation in *PRN*), autosomal-dominant familial papillary carcinoma with multinodular goiter from germline mutations in *MNG1* and *PTCSC3*, and autosomal-dominant familial papillary thyroid carcinoma with (Hürthle cell) or without oxyphilic staining. Germline alterations in Cowden syndrome with follicular thyroid cancer also involve mutations in *RASAL1* (RAS protein activator like 1) from the GAP1 family of GTPase-activating proteins.[77] Most familial thyroid cancers are more aggressive than sporadic thyroid tumors, manifested by extrathyroidal invasion, lymph-node metastasis, and earlier age at onset.

TABLE 63.3. Prevalence, clinical features, and genetic alterations associated with specific histological subtypes. Percentages are approximations based on estimates of the range of values in the medical literature. The genetic changes are listed in order of most common to least common. The epidemiology of follicular thyroid cancer is more difficult to study than papillary cancer because of the changing diagnostic criteria over time; hence, the estimates in the table for follicular thyroid cancer are wide. (Adapted from Forte et al.).[29]

Features	Papillary	Follicular	Poorly Differentiated	Undifferentiated	Medullary
Prevalence	75–80%	10–15%	<7%	2%	<5%
Lymph-node metastasis	<50%	<5%	30–80%	40%	50%
Distant metastasis	5–7%	20%	30–80%	20–50%	15%
5-Year survival	SI-II: 100% SIII: 93% SIV: 51%	SI-II: 100% SIII: 71% SIV: 50%	50% overall	7% overall	86% overall
Genes commonly altered	*BRAF* *RET*/PTC *NTRK1* *RAS*	*RAS* *PPARG* (rearrangement)	*TP53* *RAS* *CTNNB1* *RET* (rearrangement) *BRAF*	*TP53* *CTNNB1* *RAS* *BRAF*	*RET*
Genes uncommonly altered	*TP53* *BRAF* (rearrangement)	*TP53*			

Abbreviations: BRAF = *BRAF* proto-oncogene, serine/threonine kinase; *CTNNB1* = β1-cadherin-associated protein, also known as β-catenin; *NTRK1* = neurotrophic receptor tyrosine kinase 1; *PPARG* = peroxisome proliferator activated receptor gamma, nuclear receptor subfamily; *RAS* = resistance to audiogenic seizures; *RET* = *RET* proto-oncogene, tyrosine protein kinase family; *TP53* = tumor suppressor p53 protein; SI–IV = clinical stages.

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CLINICAL PRESENTATION

Most well-differentiated thyroid cancer are asymptomatic on presentation with the diagnosis resulting from incidental findings on diagnostic imaging or physical examination. The clinical course of thyroid cancer varies widely; most papillary and follicular subtypes display an indolent course with low mortality, whereas anaplastic thyroid cancers are usually aggressive malignancies unresponsive to iodine radiotherapy. Medullary thyroid cancer typically presents as a solitary nodule in the fourth to sixth decade of life, often with metastasis to cervical lymph nodes. Symptoms may include diarrhea and flushing; hyperthyroidism occurs rarely in follicular thyroid carcinoma.[16] Anaplastic thyroid cancer is a rare neoplasm that typically presents as a rapidly growing, firm, 8–9-cm neck mass with or without cervical adenopathy; symptoms include dysphagia, dyspnea, and hoarseness.[78] This thyroid subtype may present as a *de novo* tumor or coexist with differentiated thyroid cancer. Distant metastatic sites include the lungs and less commonly bone and brain. Metastases outside the neck and mediastinum occur in 1–2% of papillary thyroid cancer patients and 2–5% of follicular thyroid cancer cases.[79] In contrast to papillary thyroid cancer, recurrence of follicular thyroid cancer is usually associated with distant rather than lymph-node metastases.[80]

Papillary thyroid cancer has an excellent prognosis; however, ~25% of these patients develop local recurrence during long-term follow-up. In a retrospective review of 269 patients with papillary thyroid cancer, 11% of the recurrences appeared >20 years after the initial diagnosis.[81] Follicular thyroid cancer including Hürthle cell carcinoma and poorly differentiated thyroid cancers are high-risk tumors because of their tendency to metastasize through the blood, particularly to the lungs and bone.

Survival depends on tumor histology, age at diagnosis, and clinical stage. The overall 5-year survival rate for papillary thyroid cancer is extremely high (men, 99%; women, 99.8%), whereas the 5-year survival rate for anaplastic thyroid cancer is much lower (i.e., <10%).[8] In contrast to most solid cancers, regional lymph-node metastasis in well-differentiated thyroid tumors correlates with local recurrence but not strongly with overall survival.[82] Table 63.3 displays approximate percentages of prevalence, clinical features (lymph-node/distant metastases), 5-year survival, and common genetic alterations associated with thyroid cancer histological types based on an analysis by Forte et al.[29] Total thyroidectomy with or without radioactive iodine is curative in most cases of well-differentiated thyroid cancer.

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