

Chapter 23. Toxic Effects of Metals

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Key Points

- Persons at either end of the life span, young children or elderly people, are more susceptible to toxicity from exposure to a particular level of metal than most adults.
- Metals that provoke immune reactions include mercury, gold, platinum, beryllium, chromium, and nickel.
- *Complexation* is the formation of a metal ion complex in which the metal ion is associated with a charged or uncharged electron donor, referred to as a *ligand*.
- *Chelation* occurs when bidentate ligands form ring structures that include the metal ion and the two ligand atoms attached to the metal.
- Metal-protein interactions include binding to numerous enzymes, the metallothioneins, nonspecific binding to proteins such as serum **albumin** or hemoglobin, and specific metal carrier proteins involved in the membrane transport of metals.

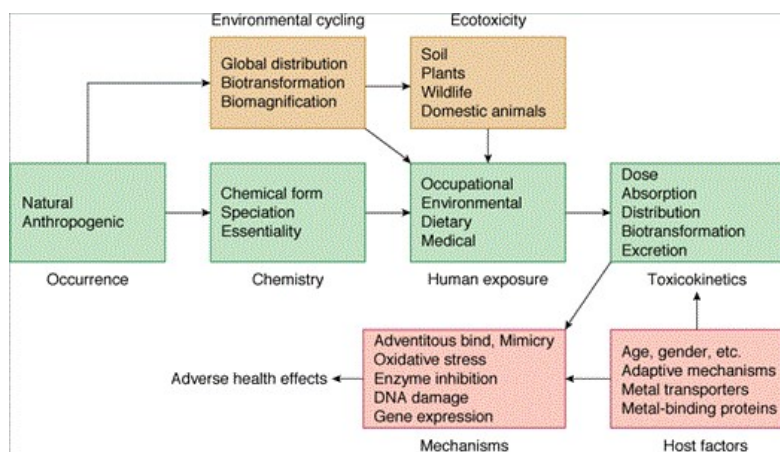
Toxic Effects of Metals: Introduction

What Is a Metal?

Metals are typically defined by physical properties of the element in the solid state. General metal properties include high reflectivity (luster), high electrical conductivity, high thermal conductivity, and mechanical ductility and strength. A toxicologically important characteristic of metals is that they may react in biological systems by losing one or more electrons to form cations.

Many metals have been reported to produce significant toxicity in humans. These include major toxic metals (e.g., lead and cadmium), essential metals (e.g., zinc and **copper**), medicinal metals (e.g., platinum and bismuth), minor toxic metals including metals in emerging technology (e.g., indium and uranium), toxic metalloids (e.g., arsenic and antimony), and certain nonmetallic elemental toxicants (e.g., selenium and fluoride). An overview of metal toxicology is shown in **Figure 23-1**.

Figure 23-1



Source: Klaassen CD, Watkins JB: Casarett & Doull's Essentials of Toxicology, 2nd Edition. <http://www.accesspharmacy.com>
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Overview of metal toxicology.

Metals as Toxicants

Regardless of how safely metals are used in industrial processes or consumer products, some level of human exposure is inevitable. In addition, all living organisms have been forced to deal with these potentially toxic, yet omnipresent, elements. Metals differ from other toxic substances because, as elements, they are neither created nor destroyed by human endeavors. Human use of metals has influenced environmental levels of metals in air, water, soil, and food. Human use of metals can also alter the chemical form or speciation of an element and thereby impact toxic potential. As elemental species, metals are nonbiodegradable. This indestructibility combined with bioaccumulation contributes to the high concern for metals as toxicants.

Movement of Metals in the Environment

Metals are redistributed naturally in the environment by both geologic and biological cycles. Rainwater dissolves rocks and ores and transports materials, including metals, to rivers and underground water (e.g., arsenic), depositing and stripping materials from adjacent soil and eventually transporting these substances to the ocean to be precipitated as sediment or taken up into forming rainwater to be relocated elsewhere. Biological cycles moving metals include biomagnification by plants and animals resulting in incorporation into food cycles. Human industry greatly enhances metal distribution in the global environment by discharge to soil, water, and air. Reports of metal intoxication are common in plants, aquatic organisms, invertebrates, fish, sea mammals, birds, and domestic animals. Not all human toxicity occurs from metals deposited in the biosphere by human activity. For example, chronic arsenic poisoning from high levels of naturally occurring inorganic arsenic in drinking water is a major health issue in many parts of the world. Endemic intoxication from excess fluoride, selenium, or thallium can all occur from natural high environmental levels.

Chemical Mechanisms of Metal Toxicology

Chemically, metals in their ionic form can be very reactive and can interact with biological systems in a large variety of ways. In this regard, a cell presents numerous potential metal-binding ligands. The inhibition of biologically critical enzymes is an important molecular mechanism of metal toxicology.

The metals can show more specific forms of chemical attack through mimicry: acting as mimics of essential metals, they bind to physiological sites that normally are reserved for an essential element. For example, mimicry for, and replacement of, zinc is a mechanism of toxicity for cadmium, copper, and nickel.

Another key chemical reaction in metal toxicology is metal-mediated oxidative damage. Many metals can directly act as catalytic centers for redox reactions with molecular oxygen or other endogenous oxidants, producing oxidative modification of biomolecules such as proteins or DNA. This may be a key step in the carcinogenicity of certain metals. Besides oxygen-based radicals, carbon- and sulfur-based radicals may also occur.

Metals in their ionic form can be very reactive and form DNA and protein adducts in biological systems. They can also induce an array of aberrant gene expression, which, in turn, produces adverse effects.

Factors Impacting Metal Toxicity

Exposure-related factors include dose, route of exposure, duration, and frequency of exposure. Host-based factors that can impact metal toxicity include age at exposure, gender, and capacity for biotransformation. For instance, it is quite clear that younger subjects are often more sensitive to metal intoxication, as, for example, with the neurotoxicity of lead in children. The major pathway of exposure to many toxic metals in children is food, and children consume more calories per pound of body weight than adults. Moreover, children have higher gastrointestinal absorption of metals, particularly lead. Elderly persons are also believed to be generally more susceptible to metal toxicity than younger adults. Lifestyle factors such as smoking or the composition of diet (i.e., alcohol ingestion) may have direct or indirect impacts on the level of metal intoxication.

Adaptive mechanisms can be critical to the toxic effects of metals, and organisms have a variety of ways in which they can adapt to otherwise toxic metal insults. Adaptation can be at the level of uptake, excretion, or long-term storage in a toxicologically inert form. Metal exposure can induce a cascade of molecular/genetic responses that may, in turn, reduce toxicity, such as with metal-induced oxidative stress responses.

Biomarkers of Metal Exposure

Biomarkers of exposure, toxicity, and susceptibility are important in assessing the level of concern with metal intoxication. Exposure biomarkers, such as concentrations in blood, urine, or hair, have long been used with metals. Techniques in molecular toxicology have greatly expanded the possibilities for biomarkers. Thus, in the case of chromium, DNA–protein complexes may serve as a biomarker of both exposure and carcinogenic potential. Also, hair can be useful in assessing variations in exposure to metals over the period of its growth.

Metal-Binding Proteins and Metal Transporters

Protein binding of metals is a critical aspect of essential and toxic metal metabolism. Many different types of proteins play roles in the disposition of metals in the body. Nonspecific binding to proteins, like serum **albumin** or hemoglobin, acts in metal transport and tissue distribution. Proteins with specific metal-binding properties play special roles in the trafficking of specific essential metals, and toxic metals may interact with these proteins through mimicry.

The *metallothioneins* are the best known example of metal-binding proteins. These thiol ligands provide the basis for high-affinity binding of several essential and toxic metals including zinc, cadmium, **copper**, and mercury.

Transferrin is a glycoprotein that binds most of the ferric iron in plasma and helps transport iron across cell membranes. The protein also transports aluminum and manganese. *Ferritin* is primarily a storage protein for iron. It has been suggested that ferrin may serve as a general metal detoxicant protein, because it binds a variety of toxic metals including cadmium, zinc, beryllium, and aluminum.

Ceruloplasmin is a copper-containing glycoprotein oxidase in plasma that converts ferrous iron to ferric iron, which then binds to transferrin. This protein also stimulates iron uptake by a transferrin-independent mechanism.

Pharmacology of Metals

Many metallic chemicals are valuable pharmacological tools in the treatment of human disease, as exemplified by the highly effective use of platinum compounds in cancer chemotherapy. In addition, gallium and titanium complexes are promising metal compounds in cancer chemotherapy. Other medicinal metals used today include aluminum (antacids and buffered analgesics), bismuth (peptic ulcer and *Helicobacter pylori*-associated gastritis), lithium (mania and bipolar disorders), and gold (arthritis).

Treatment of metal poisoning is sometimes used to prevent, or even attempt to reverse, toxicity. The typical strategy is to give metal chelators that will complex the metal and enhance its excretion. Metal chelation therapy should be considered a secondary alternative to reduction or prevention of toxic metal exposures. Such therapy can be used for many different metals including lead, mercury, iron, and arsenic.

Major Toxic Metals

Arsenic

The most common inorganic trivalent arsenic compounds are arsenic trioxide and sodium arsenite, whereas common pentavalent inorganic compounds are sodium arsenate, arsenic pentoxide, and arsenic acid. Important organo-arsenicals include arsenic acid, arsenosugars, and several methylated forms produced as a consequence of inorganic arsenic biotransformation in various organisms, including humans. Arsine (AsH_3) is an important gaseous arsenical.

Occupational exposure to arsenic occurs in the manufacture of pesticides, herbicides, and other agricultural products. High exposure to arsenic fumes and dusts may occur in smelting industries. Environmental arsenic exposure mainly occurs from arsenic-contaminated drinking water, which is often from natural sources. Environmental exposure to arsenic also occurs from burning of coal containing naturally high levels of arsenic. Food, especially seafood, may contribute significantly to daily arsenic intake.

Toxicity

Acute Poisoning

Ingestion of large doses (70 to 180 mg) of inorganic arsenic can be fatal. Symptoms of acute intoxication include fever, anorexia, hepatomegaly, melanosis, cardiac arrhythmia, and, in fatal cases, eventual cardiac failure. Acute arsenic ingestion can damage mucous membranes of the gastrointestinal tract, causing irritation, vesicle formation, and even sloughing. Sensory loss in the peripheral nervous system is the most common neurological effect, appearing at 1 to 2 weeks after large doses and consisting of Wallerian degeneration of axons. Anemia and leucopenia, particularly granulocytopenia, occur a few days following high-dose arsenic exposure and are reversible.

Chronic Toxicity

The skin is a major target organ in chronic inorganic arsenic exposure. Skin cancer is common with protracted high-level arsenical exposure. Liver injury, characteristic of long-term or chronic arsenic exposure, manifests itself initially as jaundice, abdominal pain, and hepatomegaly and may progress to cirrhosis and ascites, even to hepatocellular carcinoma.

Repeated exposure to low levels of inorganic arsenic can produce peripheral neuropathy. This neuropathy usually begins with sensory changes, such as numbness in the hands and feet, but later may develop into a painful “pins and needles” sensation. Both sensory and motor nerves can be affected, and dying-back axonopathy with demyelination may occur.

Mechanisms of Toxicity

The trivalent compounds of arsenic are the principal toxic forms and pentavalent arsenate is an uncoupler of mitochondrial oxidative phosphorylation. Arsenic and its metabolites have been shown to produce oxidants and oxidative DNA damage, alteration in DNA methylation status and genomic instability, impaired DNA damage repair, and enhanced cell proliferation.

Carcinogenicity

Arsenic is a known human carcinogen, associated with tumors of the skin, lung, and urinary bladder, and possibly kidney, liver, and prostate. Arsenic-induced skin cancers include basal cell carcinomas and squamous cell carcinomas, both arising in areas of arsenic-induced hyperkeratosis. In humans, increased mortality occurs from lung cancer in young adults following in utero exposure to arsenic. Thus, the developing fetus appears to be hypersensitive to arsenic carcinogenesis.

Treatment

For acute arsenic poisoning, treatment is symptomatic, with particular attention to fluid volume replacement and support of blood pressure. The oral chelator [penicillamine](#) or [succimer](#) (2,3-dimercaptosuccinic acid, DMSA) is effective in removing arsenic from the body. For chronic poisoning, chelator therapy has not proven effective in relieving symptoms. The best strategy for preventing chronic arsenic poisoning is by reducing exposure.

Cadmium

About 75 percent of cadmium produced is used in batteries, especially nickel–cadmium batteries. Because of its noncorrosive properties, cadmium has been used in electroplating or galvanizing alloys for corrosion resistance. It is also used as a color pigment for paints and plastics. This metal is produced as a byproduct of zinc and lead smelting.

Exposure

Food is the major source of cadmium for the general population. Many plants readily accumulate cadmium from soil. Both natural and anthropogenic sources of cadmium contamination occur for soil, including fallout of industrial emissions, some fertilizers, soil amendments, and use of cadmium-containing water for irrigation, all resulting in a slow but steady increase in the cadmium content in vegetables over the years. Shellfish and animal liver and kidneys can accumulate relatively high levels of cadmium. Air can be a significant source of direct exposure or environmental contamination. Cigarette smoking is a major nonoccupational source of cadmium exposure.

Inhalation is the dominant route of exposure in occupational settings. Occupations potentially at risk from cadmium exposure include those involved

with refining zinc and lead ores, iron production, cement manufacture, industries involving fossil fuel combustion, the manufacturing of paint pigments, cadmium–nickel batteries, and electroplating.

Toxicity

Acute toxicity from the ingestion of high concentrations of cadmium in the form of heavily contaminated beverages or food causes severe irritation to the gastrointestinal epithelium, leading to nausea, vomiting, and abdominal pain. Inhalation of cadmium fumes or other heated cadmium-containing materials may produce acute pneumonitis with pulmonary edema.

The major long-term toxic effects of low-level cadmium exposure are renal injury, obstructive pulmonary disease, osteoporosis, and cardiovascular disease. Cancer is primarily a concern in occupationally exposed groups. The chronic toxic effects of cadmium are clearly a much greater concern than the rare acute toxic exposures.

Nephrotoxicity

Cadmium is toxic to tubular cells and glomeruli, markedly impairing renal function leading to proteinuria. These lesions consist of initial tubular cell necrosis and degeneration, progressing to an interstitial inflammation and fibrosis. Because of the potential for renal toxicity, there is considerable concern about the levels of dietary cadmium intake for the general population.

Chronic Pulmonary Disease

Cadmium inhalation is toxic to the respiratory system in a fashion related to the dose and duration of exposure. Cadmium-induced obstructive lung disease in humans can be slow in onset, and results from chronic bronchitis, progressive fibrosis of the lower airways, and accompanying alveolar damage leading to emphysema. Pulmonary function is reduced with dyspnea, reduced vital capacity, and increased residual volume.

Other Toxicities

Cadmium toxicity affects calcium metabolism, and associated skeletal changes probably related to calcium loss include bone pain, osteomalacia, and/or osteoporosis. Epidemiologic studies suggest that cadmium may be an etiologic agent for essential hypertension. Heart mitochondria may be the site of the cadmium-induced reduction in myocardial contractility. Epidemiologic studies in humans have suggested a relationship between abnormal behavior and/or decreased intelligence in children and adults exposed to cadmium.

Lead

Lead is a ubiquitous toxic metal and is detectable in practically all phases of the inert environment and in all biological systems. The phasing out of leaded gasoline and the removal of lead from paint, solder, and water supply pipes have significantly lowered blood lead levels in the general population. Lead exposure in children still remains a major health concern.

Exposure

Lead-containing paint is a primary source of lead exposure in children. Major environmental sources of lead for infants and toddlers up to 4 years of age are hand-to-mouth transfer of lead-containing paint chips and dust from floors of older housing. Lead in household dust can also come from outside of the home (i.e., soil). A major route of exposure for the general population is from food and water. Dietary intake of lead has decreased dramatically in recent years. Other potential sources of lead exposure are recreational shooting, hand-loading ammunition, soldering, jewelry making, pottery making, gun smithing, glass polishing, painting, and stained glass crafting.

Toxicity

The toxic effects of lead and the minimum blood level at which an effect is likely to be observed are shown in [Table 23–1](#). Lead can induce a wide range of adverse effects in humans depending on the dose and duration of exposure. The toxic effects range from inhibition of enzymes to the production of severe pathology or death. Children are most sensitive to effects in the central nervous system, whereas peripheral neuropathy, chronic nephropathy, and hypertension are concerns in adults. Other target tissues include the gastrointestinal, immune, skeletal, and reproductive systems. Effects on the

heme biosynthesis provide a sensitive biochemical indicator even in the absence of other detectable effects.

Table 23–1 Summary of lowest observed effect levels for lead-related health effects.

| Effect | Blood Lead Levels, µg/dL | |
|-----------------------------|--------------------------|----------|
| | Adult | Children |
| Neurologic | | |
| Encephalopathy (overt) | 80–100 | 100–120 |
| Hearing deficits | 20 | — |
| IQ deficits | 10–15 | — |
| In utero effects | 10–15 | — |
| Nerve conduction velocity ↓ | 40 | 40 |
| Hematologic | | |
| Anemia | 80–100 | 80–100 |
| U-ALA ↑ | 40 | 40 |
| B-EP ↑ | 15 | 15 |
| ALA-D inhibition | 10 | 10 |
| Renal | | |
| Nephropathy | 40 | 40–60 |
| Vitamin D metabolism | <30? | — |

Neurologic, Neurobehavioral, and Developmental Effects in Children

Symptoms of lead encephalopathy begin with lethargy, vomiting, irritability, loss of appetite, and dizziness, progressing to obvious ataxia, and a reduced level of consciousness, which may progress to coma and death. Recovery is often accompanied by sequelae including epilepsy, mental retardation, and, in some cases, optic neuropathy and blindness.

The most sensitive indicators of adverse neurologic outcomes are psychomotor tests or mental development indices, and broad measures of IQ. Lead may act as a surrogate for calcium and/or disrupt calcium homeostasis. The stimulation of protein kinase C may result in alteration of the blood–brain barrier. Lead affects virtually every neurotransmitter system in the brain, including glutamatergic, dopaminergic, and cholinergic systems. All these systems play a critical role in synaptic plasticity and cellular mechanisms for cognitive function, learning, and memory.

Neurotoxic Effects in Adults

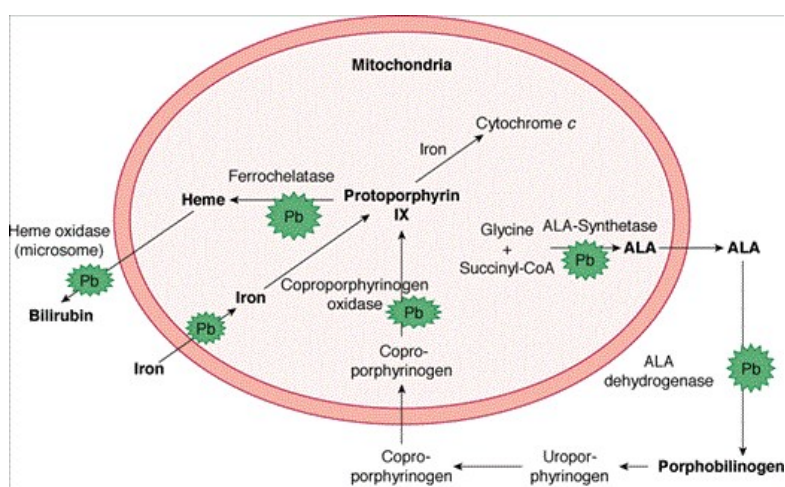
Adults with occupational exposure may demonstrate abnormalities in a number of measures in neurobehavior. Peripheral neuropathy is a classic

manifestation of lead toxicity in adults. Footdrop and wristdrop may be observed in workers with excessive occupational exposure to lead. Peripheral neuropathy is characterized by segmental demyelination and possibly axonal degeneration.

Hematologic Effects

Lead has multiple hematologic effects, ranging from increased urinary porphyrins, coproporphyrins, δ -aminolevulinic acid (ALA), and zinc-protoporphyrin to anemia. The heme biosynthesis pathway and the sites of lead interference are shown in Figure 23-2. The most sensitive effects of lead are the inhibition of δ -aminolevulinic acid dehydratase (ALAD) and ferrochelatase. ALAD catalyzes the condensation of two units of ALA to form porphobilinogen (PBG). Inhibition of ALAD results in accumulation of ALA. Ferrochelatase catalyzes the insertion of iron into the protoporphyrin ring to form heme. Inhibition of ferrochelatase results in accumulation of protoporphyrin IX, which takes the place of heme in the hemoglobin molecule and, as the erythrocytes containing protoporphyrin IX circulate, zinc is chelated at the site usually occupied by iron. Anemia only occurs in very marked cases of lead toxicity.

Figure 23-2



Source: Klaassen CD, Watkins JB, Casarett & Doull's Essentials of Toxicology, 2nd Edition: <http://www.accesspharmacy.com>
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Lead interruption of heme biosynthesis. ALA, δ -aminolevulinic acid; Pb, sites for lead effects. The major lead inhibition sites are ALA dehydrogenase and ferrochelatase.

Renal Toxicity

Acute lead nephrotoxicity consists of proximal tubular dysfunction and can be reversed by treatment with chelating agents. Chronic lead nephrotoxicity consists of interstitial fibrosis and progressive nephron loss, azotemia, and renal failure. Lead nephrotoxicity impairs the renal synthesis of heme-containing enzymes in the kidney, such as heme-containing hydroxylase involved in vitamin D metabolism causing bone effects. Hyperuricemia with gout occurs more frequently in the presence of lead nephropathy.

Effects on Cardiovascular System

The pathogenesis of lead-induced hypertension is multifactorial including: (1) inactivation of endogenous nitric oxide and cGMP, possibly through lead-induced reactive oxygen species; (2) changes in the renin-angiotensin-aldosterone system, and increases in sympathetic activity, important humoral components of hypertension; (3) alterations in calcium-activated functions of vascular smooth muscle cells including contractility by decreasing Na^+/K^+ -ATPase activity and stimulation of the $\text{Na}^+/\text{Ca}^{2+}$ exchange pump; and (4) a possible rise in endothelin and thromboxane.

Other Toxic Effects

Lead may affect blood pressure via changes in plasma renin and in urinary kallikrein, alterations in calcium-activated functions of vascular smooth muscle cells, and changes in responsiveness to catecholamines. As an immunosuppressive agent, lead decreases immunoglobulins, peripheral B

lymphocytes, and other components of the immunologic system. Retention and mobilization of lead in bone occur by the same mechanisms involved in regulating calcium influx and efflux. Lead also competes with calcium for gastrointestinal absorption. Lead is known to affect osteoblasts, osteoclasts, and chondrocytes and has been associated with osteoporosis and delays in fracture repair. Lead toxicity has long been associated with sterility and neonatal deaths in humans. Lead, a 2B carcinogen, induces tumors of the respiratory and digestive systems. Epidemiologic studies suggest a relationship between occupational lead exposure and cancer of the lung, brain, and bladder among workers exposed to lead.

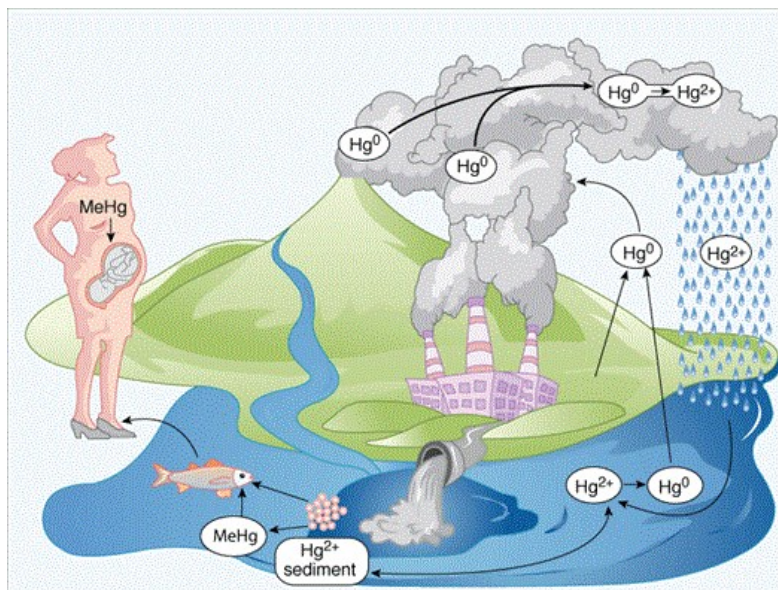
Mercury

Also called quicksilver, metallic mercury is in liquid state at room temperature. Mercury vapor (Hg^0) is much more hazardous than the liquid form. Mercury binds to other elements (such as chlorine, sulfur, or oxygen) to form inorganic mercurous (Hg^+) or mercuric (Hg^{2+}) salts.

Global Cycling and Ecotoxicology

Mercury exemplifies movement of metals in the environment (Figure 23-3). Atmospheric mercury, in the form of mercury vapor (Hg^0), is derived from natural degassing of the earth's crust and through volcanic eruptions as well as from evaporation from oceans and soils. Anthropogenic sources have become a significant contributor to atmospheric mercury. These include emissions from metal mining and smelting (mercury, gold, copper, and zinc), coal combustion, municipal incinerators, and chloralkali industries. Methylmercury enters the aquatic food chain starting with plankton, then herbivorous fish, and finally ascending to carnivorous fish and sea mammals. On the top of the food chain, tissue mercury can rise to levels 1800 to 80,000 times higher than levels in the surrounding water. This biomethylation and bioconcentration result in human exposure to methylmercury through consumption of fish.

Figure 23-3



Source: Klaassen CD, Watkins JB: Casarett & Doull's Essentials of Toxicology, 2nd Edition: <http://www.accesspharmacy.com>
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The movement of mercury in the environment. In nature, mercury vapor (Hg^0), a stable gas, evaporates from the earth's surface (both soil and water) and is emitted by volcanoes. Anthropogenic sources include emissions from coal-burning power stations and municipal incinerators. After ~1 year, mercury vapor is converted to soluble form (Hg^{2+}) and returned to the earth by rainwater. It may be converted back to the vapor by microorganisms and reemitted into the atmosphere. Thus, mercury may recirculate for long periods. Mercury attached to aquatic sediments is subjected to microbial conversion to methylmercury, starting with plankton, then herbivorous fish, and finally ascending to carnivorous fish and sea mammals. This biomethylation and biomagnification result in human exposure to methylmercury through consumption of fish, and pose the health risk to humans, especially the developing fetus.

Exposure

Dietary Exposure

Consumption of fish is the major route of exposure to methylmercury. Inorganic mercury compounds are also found in food. The source of inorganic mercurial is unknown but the amounts ingested are far below known toxic levels. Mercury in the atmosphere and in drinking water is generally so low that it does not constitute an important source of exposure to the general population.

Occupational Exposure

Inhalation of mercury vapor may occur from working in the chloralkali industry. Occupational exposure may occur during manufacture of a variety of scientific instruments and electrical control devices, in dentistry where mercury amalgams are used in tooth restoration, and in the extraction of gold.

Accidental Exposure

Elemental mercury exposure can occur from broken elemental mercury containers, medicinal devices, barometers, and melting tooth amalgam fillings to recover silver. Inhalation of large amounts of mercury vapor can be deadly.

Toxicity

Mercury Vapor

Inhalation of mercury vapor at extremely high concentrations may produce an acute, corrosive bronchitis and interstitial pneumonitis and, if not fatal, may be associated with central nervous system effects such as tremor or increased excitability. This condition has been termed the *asthenic-vegetative syndrome* or *micromercurialism*. Identification of the syndrome requires neurasthenic symptoms and three or more of the following clinical findings: tremor, enlargement of the thyroid, increased uptake of radioiodine in the thyroid, labile pulse, tachycardia, dermographism, gingivitis, hematologic changes, or increased excretion of mercury in urine.

Inorganic Mercury

The kidney is the major target organ for inorganic mercury. Although a high dose of mercuric chloride is directly toxic to renal tubular cells, chronic low-dose exposure to mercury salts may induce an immunologic glomerular disease. Exposed persons may develop proteinuria that is reversible after they are removed from exposure.

Methylmercury

The major human health effect from exposure to methylmercury is neurotoxicity. Clinical manifestations of neurotoxicity include paresthesia (a numbness and tingling sensation around the mouth and lips) and ataxia, manifested as a clumsy, stumbling gait, and difficulty in swallowing and articulating words. Other signs include neurasthenia (a generalized sensation of weakness), vision and hearing loss, and spasticity and tremor. These may finally progress to coma and death. The overall acute effect is cerebral edema, but with prolonged destruction of gray matter and subsequent gliosis, cerebral atrophy results.

Mechanism of Toxicity

High-affinity binding of divalent mercury to sulfhydryl groups of proteins in the cells is an important mechanism for producing nonspecific cell injury or even cell death. Other general mechanisms, such as the interruption of microtubule formation, inhibition of enzymes, oxidative stress, interruption of protein and DNA synthesis, and autoimmune responses, have also been proposed. Mercury causes overexpression of metallothionein and glutathione system-related genes in rat tissues.

Nickel

Metallic nickel is produced from sulfide and silicate-oxide ores. Nickel is used in various metal alloys, including stainless steels, and in electroplating.

Occupational exposure to nickel occurs by inhalation of nickel-containing aerosols, dusts, or fumes, or dermal contact in workers engaged in nickel production (mining, milling, refinery, etc.) and nickel-using operations (melting, electroplating, welding, nickel–cadmium batteries, etc.). Nickel is ubiquitous in nature, and the general population is exposed to low levels of nickel in air, cigarette smoke, water, and food.

Toxicity

Contact Dermatitis

Nickel-induced contact dermatitis is the most common adverse health effect from nickel exposure and is found in 10 to 20 percent of the general population. It can result from exposure to airborne nickel, liquid nickel solutions, or prolonged skin contact with metal items containing nickel, such as coins and jewelry.

Nickel Carbonyl Poisoning

Nickel carbonyl is extremely toxic. Intoxication begins with headache, nausea, vomiting, and epigastric or chest pain, followed by cough, hyperpnea, cyanosis, gastrointestinal symptoms, and weakness. The symptoms may be accompanied by fever and leukocytosis. More severe cases can progress to pneumonia, respiratory failure, and eventually to cerebral edema and death.

Carcinogenicity

Nickel is a respiratory tract carcinogen in nickel-refining industry workers. Risks are highest for lung and nasal cancers among workers heavily exposed to nickel sulfide, nickel oxide, and metallic nickel.

Essential Metals with Potential for Toxicity

This group includes eight metals generally accepted as essential: cobalt, copper, iron, magnesium, manganese, molybdenum, selenium, and zinc. All can produce some target organ toxicity ([Table 23–2](#)).

Table 23–2 Toxicity of several metals.

| Metal | CNS | GI Tract | Lung | Kidney | Liver | Heart | Blood | Skin |
|-----------|-----|----------|------|--------|-------|-------|-------|------|
| Aluminum | * | | * | | | | | |
| Arsenic | * | * | * | * | * | | * | |
| Beryllium | | | * | | | | | * |
| Bismuth | | | | * | * | | | * |
| Cadmium | * | * | * | * | * | * | | |
| Chromium | * | | * | * | * | | | * |
| Cobalt | * | * | * | | | * | | * |
| Copper | | * | | | | | * | |
| Iron | * | * | * | | * | | * | |
| Lead | * | * | | * | | | * | * |
| Manganese | * | | * | | | | | |
| Mercury | * | * | * | * | | | | |
| Nickel | * | | * | | | | | * |
| Selenium | | * | | * | | | | * |
| Zinc | | * | | | | | * | |

Copper

Food, beverages, and drinking water are major sources of exposure in the general population. Copper exposure in industry is primarily from inhaled particulates in mining or metal fumes in smelting operations, welding, or related activities.

Toxicity

The most commonly reported adverse health effects of excess oral copper intake are gastrointestinal distress. Nausea, vomiting, and abdominal pain have been reported shortly after drinking solutions of copper sulfate or beverages stored in containers that readily release copper. Ingestion of drinking water with >3 mg Cu/L will produce gastrointestinal symptoms. Ingestion of large amounts of copper salts, most frequently copper sulfate, may produce hepatic necrosis and death.

Hereditary Disease of Copper Metabolism

Wilson's Disease

This is an autosomal recessive genetic disorder of copper metabolism characterized by the excessive accumulation of copper in liver, brain, kidneys, and cornea. Serum ceruloplasmin is low and serum copper not bound to ceruloplasmin is elevated. Urinary excretion of copper is high. Clinical abnormalities of the nervous system, liver, kidneys, and cornea are related to copper accumulation. Patients with Wilson's disease have impaired biliary excretion of copper, which is believed to be the fundamental cause of the copper overload. Reversal of abnormal copper metabolism is achieved by liver transplantation, confirming that the basic defect is in the liver. Clinical improvement can be achieved with chelation therapy.

Iron

Iron is an essential metal for erythropoiesis and a key component of hemoglobin, myoglobin, heme enzymes, metalloflavoprotein enzymes, and mitochondrial enzymes. In biological systems, iron mainly exists as the ferrous (+2) and ferric (+3) forms. Toxicologic considerations are important in terms of iron deficiency, accidental acute exposures, and chronic iron overload due to idiopathic hemochromatosis or as a consequence of excess dietary iron or frequent blood transfusions.

Toxicity

Acute iron poisoning from accidental ingestion of iron-containing dietary supplements is the most common cause of acute toxicity. Severe toxicity occurs after the ingestion of more than 0.5 g of iron or 2.5 g of ferrous sulfate. Toxicity occurs about 1 to 6 h after ingestion. Symptoms include abdominal pain, diarrhea, and vomiting. Of particular concern are pallor or cyanosis, metabolic acidosis, and cardiac collapse. Death may occur in severely poisoned children within 24 h.

Chronic iron toxicity from iron overload in adults is a relatively common problem. There are three basic ways in which excessive amounts of iron can accumulate in the body: (1) hereditary hemochromatosis due to abnormal absorption of iron from the intestinal tract, (2) excess intake via the diet or from oral iron preparations, and (3) repeated blood transfusions for some form of refractory anemia (*transfusional siderosis*). Increased body iron may play a role in the development of cardiovascular disease. It is suspected that iron may act as a catalyst to produce free radical damage resulting in arteriosclerosis and ischemic heart disease. Some neurodegenerative disorders associated with aberrant iron metabolism in the brain include neuroferritinopathy, aceruloplasminemia, and manganism.

Zinc

An essential metal, zinc deficiency results in severe health consequences. However, zinc toxicity is relatively uncommon and occurs only at very high exposure levels. Zinc is present in most foodstuffs, water, and air. Occupational exposure to dusts and fumes of metallic zinc occurs in zinc mining and smelting. The zinc content of substances in contact with galvanized copper or plastic pipes may be high.

Essentiality and Deficiency

More than 300 catalytically active zinc metalloenzymes and 2000 zinc-dependent transcription factors exist. Zinc participates in a wide variety of metabolic processes, supports a healthy immune system, and is essential for normal growth and development during pregnancy, childhood, and adolescence. Zinc deficiency is related to poor dietary zinc intake, dietary phytate intake, chronic illness, or oversupplementation with iron or copper. Symptoms of zinc deficiency include growth retardation, appetite loss, alopecia, diarrhea, impaired immune function, cognitive impairments, dermatitis, delayed healing of wounds, taste abnormalities, and impaired sexual function. Therapeutic uses of zinc include the treatment of acute diarrhea in infants with severe zinc deficiency, the treatment of common cold by its antiviral and immunomodulatory effects, therapy for Wilson's disease to help reduce copper burden and to induce metallothionein, and the prevention of blindness in age-related macular degeneration.

Toxicity

Gastrointestinal distress and diarrhea have been reported following ingestion of beverages standing in galvanized cans. Following inhalation of zinc oxide, and to a lesser extent other zinc compounds, the most common effect is "metal-fume fever" characterized by fever, chest pain, chills, cough, dyspnea, nausea, muscle soreness, fatigue, and leukocytosis. Acute inhalation of high levels of zinc chloride as in the military use of "smoke bombs" results in more pronounced damage to the mucous membrane including interstitial edema, fibrosis, pneumonitis, bronchial mucosal edema, and ulceration. Following long-term exposure to lower doses of zinc, symptoms generally result from a decreased dietary copper absorption, leading to early symptoms of copper deficiency, such as decreased erythrocyte number or decreased hematocrit.

Neuronal Toxicity

Excess zinc released by oxidants can act as a potent neurotoxin, contributing to excitotoxic brain injury. The release of excess, toxic free zinc could be a factor that sets the stage for the later development of Alzheimer's disease.

Metals Related to Medical Therapy

Metals that are used to treat a number of human illnesses, including aluminum, bismuth, gold, lithium, and platinum, exert some toxicity (Table 23–2).

Aluminum

Chemical compounds of aluminum occur typically in the trivalent valence state (Al^{3+}). As a hard trivalent ion, aluminum binds strongly to oxygen-donor ligands such as citrate and phosphate. Human exposure to aluminum comes primarily from food and secondarily from drinking water. Occupational exposures to aluminum occur during mining and processing, as well as in aluminum welding.

Toxicity

Most cases of aluminum toxicity in humans are observed in patients with chronic renal failure, or in persons exposed to aluminum in the workplace, with the lung, bone, and central nervous system as major target organs. Aluminum can produce developmental effects.

Lung and Bone Toxicity

Occupational exposure to aluminum dust can produce lung fibrosis in humans. Osteomalacia has been associated with excessive intake of aluminum-containing antacids in otherwise healthy individuals. This is assumed to be due to interference with intestinal phosphate absorption. Osteomalacia also can occur in uremic patients exposed to aluminum in the dialysis fluid. In these patients, osteomalacia may be a direct effect of aluminum on bone mineralization as bone levels are high.

Neurotoxicity

Aluminum is neurotoxic to experimental animals, with wide species and age variations. In susceptible animals, such as rabbits and cats, the most prominent early pathologic change is the accumulation of neurofibrillary tangles (NFTs) in large neurons, proximal axons, and dendrites of neurons of many brain regions. This is associated with loss of synapses and atrophy of the dendritic tree. In other species, impairment of cognitive and motor function and behavioral abnormalities are often observed.

Dialysis Dementia

A progressive, neurologic syndrome has been reported in patients on long-term intermittent hemodialysis for chronic renal failure. The first symptom in these patients is a speech disorder followed by dementia, convulsions, and myoclonus. The disorder, which typically arises after 3 to 7 years of dialysis treatment, may be due to aluminum intoxication. The aluminum content of brain, muscle, and bone increases in these patients. Sources of the excess aluminum may be from oral aluminum hydroxide commonly given to these patients or from aluminum in dialysis fluid derived from the tap water used to prepare the dialysate fluid. The high serum aluminum concentrations may be related to increased parathyroid hormone levels that are due to low blood calcium and osteodystrophy common in patients with chronic renal disease. The syndrome may be prevented by avoiding the use of aluminum-containing oral phosphate binders and by monitoring of aluminum in the dialysate.

Alzheimer's Disease

A possible relationship between aluminum and Alzheimer's disease has been a matter of speculation for decades. Elevated aluminum levels in Alzheimer's brains may be a consequence and not a cause of the disease. The reduced effectiveness of the blood–brain barrier in Alzheimer's might allow more aluminum into the brain. Also, recent studies have raised the possibility that the staining methods in earlier studies may have led to aluminum contamination. There are conflicting conclusions from studies examining the role of aluminum in Alzheimer's disease. However, there is increasing evidence suggesting a link between aluminum in the brain and other neurodegenerative diseases.

Lithium

Lithium is used in batteries, alloys, catalysts, photographic materials, and the space industry. Lithium hydride produces hydrogen on contact with water and is used in manufacturing electronic tubes, in ceramics, and in chemical analysis. Groundwater contamination with lithium from man-made waste disposal could be a risk factor for the aquatic environment. Lithium carbonate and lithium citrate are widely used for mania and bipolar disorders.

Toxicokinetics

Lithium is readily absorbed from the gastrointestinal tract. It is distributed to total body water with higher levels in kidney, thyroid, and bone as compared with other tissues. Excretion is chiefly through the kidneys with 80 percent of the filtered lithium reabsorbed. Lithium can substitute for sodium or potassium on several transport proteins.

Toxicity

Except for lithium hydride, no other salts are considered hazardous, nor is the metal very toxic itself. Lithium hydride is intensely corrosive and may produce burns on the skin because of the formation of hydroxides. The toxic responses to lithium include neuromuscular changes (tremor, muscle hyperirritability, and ataxia), central nervous system disorders (blackout spells, epileptic seizures, slurred speech, coma, psychosomatic retardation, and increased thirst), cardiovascular disturbances (cardiac arrhythmia, hypertension, and circulatory collapse), gastrointestinal symptoms (anorexia, nausea, and vomiting), and renal damage (albuminuria and glycosuria).

Chronic lithium nephrotoxicity and interstitial nephritis may occur with long-term exposure even when lithium levels remain within the therapeutic range. Chronic lithium-induced neurotoxicity, nephritis, and thyroid dysfunction may occur, especially in susceptible patients with nephrogenic diabetes insipidus, older age, abnormal thyroid function, and impaired renal function.

Platinum

Platinum compounds are used as automobile catalysts, in jewelry, in electronics, and in dental alloys.

Toxicity

Platinum can produce profound hypersensitivity reactions in susceptible individuals. The signs of hypersensitivity include urticaria, contact dermatitis of skin, and respiratory distress, ranging from irritation to an asthmatic syndrome, following exposure to platinum dust. The skin and respiratory changes, *platinosis*, are mainly confined to persons with a history of industrial exposure to soluble compounds such as sodium chloroplatinate.

Antitumor Effects of Platinum Complexes

The platinum-coordinated complexes are important antitumor agents, including cisplatin, carboplatin, and oxaliplatin. They are routinely administered, often in combination with other anticancer drugs, in the treatment of a wide spectrum of malignancies, especially advanced testicular cancer and also cancers of head and neck, bladder, esophagus, lung, and ovary.

Carcinogenic Effects of Platinum Complexes

Although cisplatin has antitumor activity in humans, it is considered to be a probable carcinogen in humans and is clearly carcinogenic in rodents. In fact, in mice deficient in metallothionein, cisplatin can induce tumors at clinically relevant doses.

Toxicities of Platinum Antitumor Complexes

Cisplatin produces proximal and distal tubular cell injury, mainly in the corticomedullary region, where the concentration of platinum is highest. Hearing loss can occur and can be unilateral or bilateral but tends to be more frequent and severe with repeated doses. Marked nausea and vomiting occur in most patients receiving the platinum complexes but can be controlled with ondansetron or high dose of corticosteroids.

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