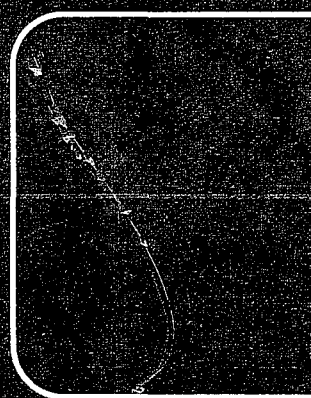


SEVENTH EDITION

Casarett & Doull's

Toxicology

The Basic Science of Poisons



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adenocarcinomas) that frequently metastasized to the lung, liver, and spleen (Kasprzak *et al.*, 1990). The carcinogenic properties of metallic nickel are believed to be due to ionic nickel, which can slowly dissolve in the body from nickel compounds.

Nickel compounds are classified as known human carcinogens (IARC, 1990) based on animal data and sufficient evidence of carcinogenicity from human studies. The IARC (1990) evaluation of nickel and nickel compounds concluded that nickel compounds are carcinogenic to humans based on sufficient evidence in the nickel refining industry and very strong evidence of carcinogenicity of a variety of nickel compounds in experimental studies in rodents. Several cohort studies of workers exposed to various nickel compounds showed an elevated risk of death from lung and nasal cancers (IARC, 1990). An excess risk of lung and nasal cancer was seen in nickel refinery workers exposed primarily to soluble nickel compounds (Anderson *et al.*, 1996).

Lead Lead compounds do not appear to cause genetic damage directly, but may do so through several indirect mechanisms, including inhibition of DNA synthesis and repair, oxidative damage, and interaction with DNA-binding proteins and tumor-suppressor proteins (NTP, 2003). Lead has exhibited conflicting results concerning its genotoxicity; it does not cause mutations in bacteria, but does cause chromosomal aberrations in vitro and in vivo, and causes DNA damage in vivo and in cell-free systems, whereas in mammalian systems, conflicting results were observed. Lead also inhibits the activity of DNA and RNA polymerase in cell-free systems and in mammalian cell cultures. Conflicting results were observed for SCE and micronucleus formation in mammalian test systems.

In studies with laboratory animals, carcinogenicity has been observed for soluble (lead acetate and lead subacetate) and insoluble (lead phosphate, lead chromate) inorganic lead compounds as well as for tetraethyl lead (an organic lead compound), following exposure via oral, injection, and in offspring exposed via the placenta or lactation. Although kidney tumors (including adenomas, carcinomas, and adenocarcinomas) were most frequently associated with lead exposure, tumors of the brain, hematopoietic system, and lung were reported in some studies (IARC, 1980, 1987; Waalkes *et al.*, 1995). Lead also appears to function as a tumor promoter, leading to increased incidence in kidney tumors initiated by *N*-ethyl-*N*-hydroxyethylnitrosamine and *N*-(4'-fluoro-4-biphenyl)acetamide (IARC, 1980, 1987). The mechanisms by which lead causes cancer are not understood.

Lead and lead compounds are classified as reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from studies in experimental animals. Lead exposure has been associated with increased risk of lung, stomach, and bladder cancer in diverse human populations (Fu and Boffetta, 1995; Steenland and Boffetta, 2000; NTP, 2003). Epidemiological studies link lead exposure to increased risk for lung and stomach cancer. However, most studies of lead exposure and cancer reviewed had limitations, including poor exposure assessment and failure to control for confounding factors.

Nongenotoxic (Epigenetic) Carcinogens

A number of chemicals that produce tumors in experimental animals following chronic treatment appear to act via mechanisms not involving direct binding, damage, or interaction of the chemical or its metabolites with DNA (Williams and Whysner, 1996). Based on the lack of genotoxicity, yet their ability to induce tumors in rodent models, these agents have been labeled nongenotoxic carcinogens. The

organ and tissue targets induced by nongenotoxic carcinogens are many times in tissues where a significant incidence of background, spontaneous tumors is seen in the animal model. Prolonged exposure to relatively high levels of chemicals is usually necessary for the production of tumors. In addition, with nongenotoxic carcinogens, tumors are not theoretically expected to occur at exposures below a threshold at which relevant cellular effects are not observed. In contrast to DNA-reactive genotoxic effects, non-DNA reactive mechanisms may be unique to the rodent species used for testing. Certain chemical carcinogens have been well studied and provide examples for the use of mechanistic information in risk assessment. Further, the biochemical modes of action for non-DNA reactive carcinogens are diverse. Examples include agents that function via sustained cytotoxicity, receptor-mediated (e.g., CAR, PPAR α , AhR) effects, hormonal perturbation, as well as the induction of oxidative stress and modulation of methylation status (Table 8-10). Each of these potential mechanisms is discussed in greater detail in the following sections.

Cytotoxicity Cytotoxicity and consequent regenerative hyperplasia is a well-documented mode of action for a variety of non-DNA reactive chemical carcinogens (Dietrich and Swenberg, 1991). Chloroform-induced liver and kidney tumors and melamine-induced bladder tumors are classic examples of chemical carcinogens that are classified as functioning via a cytolethal mode of action (Bull *et al.*, 1986; Butterworth, 1990; Larson *et al.*, 1994; Pereira, 1994; Andersen *et al.*, 1998). Chemicals that function through this mechanism produce sustained cell death, often related to metabolism of

Table 8-10
Proposed Modes of Action for Selected Nongenotoxic Chemical Carcinogens

MODE OF ACTION	EXAMPLE
<i>Cytotoxicity</i>	Chloroform Melamine
α_{2u} -Globulin-binding	D-limonene, 1,4-dichlorobenzene
Receptor mediated: CAR PPAR α	Phenobarbital Trichloroethylene Perchloroethylene Diethylhexylphthalate Fibrates (e.g., clofibrate)
AhR	TCDD Polychlorinated biphenyls (PCBs) Polybrominated biphenyls (PBBs)
Hormonal	Biogenic amines Steroid and peptide hormones DES Phytoestrogens (bisphenol-A) Tamoxifen Phenobarbital
Altered methylation	Phenobarbital Choline deficiency Diethanolamine
Oxidative stress inducers	Ethanol TCDD Lindane Dieldrin Acrylonitrile

IgG, increased serum IgM, and suppression of DTH responses to tuberculin and ovalbumin. In those studies, host resistance to *L. monocytogenes* was diminished. Cytotoxicity by adherent peritoneal cells was suppressed but there was no observed effect on NK cytotoxicity (Vos *et al.*, 1984). In contrast, Van Loveren *et al.* (1990) observed suppressed lung NK cytotoxicity in rats exposed orally to tributyltin oxide. In addition, the lymphoproliferative response of thymocytes to phytohemagglutinin (PHA), concanavalin A, and pokeweed mitogen (PWM) was significantly suppressed. Recent studies also demonstrated that tributyltin oxide modestly suppressed proliferation from lymph nodes in mice sensitized with dinitrochlorobenzene and that the suppression was associated with a modest shift toward a Th2 population (van den Berg *et al.*, 2005).

Carbamates Carbamate insecticides, which include carbaryl (Sevin), aldicarb, mancozeb, and sodium methylthiocarbamate, are used primarily as insecticides. Similar to the organophosphates, the mechanism of action of the neurotoxic effects involves inhibition of acetylcholinesterase. In an evaluation of humoral immunity following a 2-week exposure to carbaryl in rats, suppression of the IgM PFC response to sRBC was observed following inhalation exposure, but not oral or dermal exposure (Ladics *et al.*, 1994). Conflicting results have been observed in animals exposed to aldicarb or methyl isocyanate, an intermediate in carbamate pesticide production. Deo *et al.* (1987) reported alterations in T cells and lymphoproliferative responses in humans accidentally exposed to methyl isocyanate. In contrast, mice exposed to the same compound showed no significant alterations in immune status (Luster *et al.*, 1986).

Pruett *et al.* (1992a) evaluated the immunotoxicity of sodium methylthiocarbamate, and observed decreased thymus weight, depletion of the CD4⁺/CD8⁺ population of thymocytes, and profound suppression of NK cell activity following both oral and dermal exposure. They also determined that the mechanism by which sodium methylthiocarbamate altered cytokine production from peritoneal macrophages involves inhibition of MAP kinase activity via TLR4 (Pruett *et al.*, 2005). Pruet *et al.* (2006) further determined that the mechanism of cytokine alteration involved depletion of glutathione, alteration of copper-dependent proteins, and induction of stress.

Atrazine Atrazine is an herbicide applied to various agricultural crops to control broad leaf weeds. It is widely used in the United States and it has been detected in soils and groundwater because of its resistance to degradation. Similar to other chemicals discussed, atrazine exhibits immunomodulatory effects. Using offspring of female mice treated with atrazine and challenged with antigen, atrazine induced elevations in T-cell proliferation, cytolytic activity, and antigen-specific B cells (Rowe *et al.*, 2006). In contrast, using young mice directly administered atrazine orally for 14 days, it was determined that atrazine suppressed thymic weight, spleen and thymic cellularity, and B-cell fractions, although CD4⁺ T-cell numbers increased (Filipov *et al.*, 2005). Similarly, in adult mice, it was confirmed that atrazine suppressed thymic weight, and also suppressed splenic weight and decreased the host resistance of the mice to B16F10 melanoma tumors (Karrow *et al.*, 2005). Although the mechanism by which atrazine-induced immune suppression occurred is unclear, atrazine treatment of mice does induce corticosterone levels, indicating that activation of the hypothalamic-pituitary-adrenal axis might be involved (Pruett *et al.*, 2003).

Metals

Generally speaking, metals target multiple organ systems and exert their toxic effects via an interaction of the free metal with the target: enzyme systems, membranes, or cellular organelles. Although specific immunotoxic consequences of metal exposure are well documented in the literature (reviewed in Zelikoff and Thomas, 1998), this section focuses on the four best-studied immunotoxic metals: lead, arsenic, mercury, and cadmium. In considering the immunotoxicity of most metals, it is important to remember that at high concentrations, metals usually exert immunosuppressive effects; however, at lower concentrations, immune enhancement is often observed (Koller, 1980; Vos, 1977). Furthermore, as with most immunotoxic chemicals, it is important to note that exposures to metals are likely not single exposures, although one metal might dominate depending on the exposure conditions (e.g., high levels of mercury in fish or high levels of lead from paint).

Lead By far the most consistent finding in studies evaluating the effects of metals on immune responses is increased susceptibility to pathogens. For lead, decreased resistance to the bacterial pathogens *S. typhimurium*, *Escherichia coli*, and *L. monocytogenes* has been observed. One study suggested that the decreased resistance to *L. monocytogenes* involves a lack of functional IL-12 in lead-exposed mice, which, subsequently, could be related to increased stress in response to infection (Kishikawa *et al.*, 1997).

Studies on the specific effects of lead on functional immunity have demonstrated that lead is immunomodulatory. In rodents exposed to lead, lower antibody titers have been observed (Luster *et al.*, 1978). In addition, children environmentally exposed to lead and infected naturally with *Shigella dysenteriae* had prolonged diarrhea, and occupationally exposed persons reported more colds and influenza, and exhibited suppressed secretory IgA levels, demonstrating lead-induced suppression of humoral immunity. Following in vivo exposure to lead, splenocytes displayed consistently suppressed IgM PFC responses to sRBC. Separation and reconstitution experiments indicated that this suppression is likely due to an effect on macrophage function.

In mechanistic studies (reviewed in McCabe, 1994), an alteration in the ability of the macrophage to process and present antigen to antigen-primed T cells confirmed the previous observation and suggested that lead alters immune recognition. In contrast to other reports concerning the immunosuppressive action of lead on PFC responses, enhancement of the in vitro-generated PFC response appears to be the result of enhancement of B-cell differentiation. This effect may occur at the level of B-cell activation or cytokine responsiveness. And finally, in vitro addition studies indicate that lead shifts the T-cell balance from Th1 to Th2, which can result in either immune enhancement or immune suppression (reviewed in Lawrence and McCabe, 2002). Interestingly, it has been hypothesized that lead exposure might contribute to the development of asthma (Dieter *et al.*, 2004), a predominantly Th2-mediated disease. This theory is consistent with the observation that lead activates the transcription factor NF- κ B (Pyatt *et al.*, 1996), which is an important regulator of several pro-inflammatory cytokines.

Arsenic The literature concerning arsenic-induced immune modulation is fraught with inconsistencies due to differences in speciation of arsenic (which plays a significant role in arsenic toxicity), the route of administration, the concentrations used, and the

fluorescent Ca^{2+} dyes calcium green 1-AM and rhod-2, Heng *et al.* (1999) showed that following application of ethambutol in the presence, but not absence, of glutamate to isolated RGCs, there was a decrease in cytosolic Ca^{2+} and a subsequent increase in mitochondrial Ca^{2+} . Interestingly, the increase in mitochondrial Ca^{2+} resulted in an increase in the mitochondrial membrane potential as measured by the mitochondrial membrane potential sensitive dye JC-1. The authors (Heng *et al.*, 1999) postulate that this latter phenomenon occurs as a result of an ethambutol-mediated chelation of Zn^{2+} from the mitochondrial ATPase inhibitor protein IF1 (Rouslin *et al.*, 1993) that subsequently results in the inhibition of mitochondrial ATP synthesis and elevation of mitochondrial membrane potential. These intriguing ideas have merit; however, many additional experiments will be needed to prove this hypothesis. In addition, the authors suggest that some glutamate antagonists may be useful in decreasing the side effects of ethambutol—a practical suggestion that appears worthy of clinical investigation.

TARGET SITES AND MECHANISMS OF ACTION: THE CENTRAL VISUAL SYSTEM

Many areas of the cerebral cortex are involved in the perception of visual information. The primary visual cortex—called V1, Brodmann's area 17, or striate cortex—receives the primary projections of visual information from the LGN and also from the superior colliculus. Neurons from the LGN project to visual cortex maintaining a topographic representation of the receptive field origin in the retina. The receptive fields in the left and right sides of area 17 reflect the contralateral visual world and representations of the upper and lower regions of the visual field are separated below and above, respectively, the calcarine fissure. Cells in the posterior aspects of the calcarine fissure have receptive fields located in the central part of the retina. Cortical cells progressively deeper in the calcarine fissure have retinal receptive fields that are located more and more peripherally in the retina. The central part of the fovea has tightly packed photoreceptors for resolution of fine detailed images, and the cortical representation of the central fovea is proportionately larger than the peripheral retina in order to accommodate a proportionately larger need for neural image processing. The magnocellular and parvocellular pathways project differently to the histologically defined layers of primary striate visual cortex and then to extrastriate visual areas. The receptive fields of neurons in visual cortex are more complex than the circular center-surround arrangement found in the retina and LGN. Cortical cells respond better to lines of a particular orientation than to simple spots. The receptive fields of cortical cells are thought to represent computational summaries of a number of simpler input signals. As the visual information proceeds from area V1 to extrastriate visual cortical areas, the representation of the visual world reflected in the receptive fields of individual neurons becomes progressively more complex (Horton, 1992).

Lead

In addition to the well-documented retinal effects of lead (see above), lead exposure during adulthood or perinatal development produces structural, biochemical, and functional deficits in the visual cortex of humans, nonhuman primates, and rats (Fox *et al.*, 1977; Winneke, 1979; Costa and Fox, 1983; Sborgia *et al.*, 1983; Fox, 1984; Otto *et al.*, 1985; Lilienthal *et al.*, 1988; Reuhl *et al.*, 1989; Murata *et al.*, 1993; Otto and Fox, 1993; Altmann *et al.*, 1994,

1998; Winneke *et al.*, 1994). Quantitative morphometric studies in monkeys exposed to either high levels of lead from birth or infancy to 6 years of age revealed a decrease in visual cortex (areas V1 and V2), cell volume density, and a decrease in the number of initial arborizations among pyramidal neurons (Reuhl *et al.*, 1989). The former results may be due to an absolute decrease in total cell numbers, possibly resulting from lead-induced apoptosis as observed in the retina (Fox *et al.*, 1997; He *et al.*, 2000). This may also account for the decreased density of cholinergic muscarinic receptors found in the visual cortex of adult rats following moderate level developmental lead exposure (Costa and Fox, 1983). The morphometric results on neuronal branching are reminiscent of earlier findings in the neocortex of rats following high level developmental lead exposure (Petit and LeBoutillier, 1979), and recent findings in the somatosensory cortex of rats following low or moderate level developmental lead exposure (Wilson *et al.*, 2000). These alterations could partially contribute to the decreases in contrast sensitivity observed in lead-exposed rats and monkeys (Fox, 1984; Rice, 1998), the alterations in the amplitude and latency measures of the flash and pattern-reversal evoked potentials in lead-exposed children, workers, monkeys, and rats (Fox *et al.*, 1977; Winneke, 1979; Sborgia *et al.*, 1983; Otto *et al.*, 1985; Lilienthal *et al.*, 1988; Murata *et al.*, 1993; Altmann *et al.*, 1994, 1998; Winneke *et al.*, 1994), and the alterations in tasks assessing visual function in lead-exposed children (Winneke *et al.*, 1983; Hansen *et al.*, 1989; Muñoz *et al.*, 1993).

Methylmercury

Methyl mercury became notorious in two episodes of mass poisoning (see chapter 16 entitled "Toxic Responses of the Nervous System"). In the 1950s, industrial discharges of mercury into Minamata Bay in Japan became biomethylated to form methyl mercury, which then accumulated in the food chain and reached toxic concentrations in the fish and shellfish consumed in the surrounding communities. Hundreds of people were poisoned, showing a combination of sensory, motor, and cognitive deficits. A more widespread episode of methyl mercury poisoning affected thousands of Iraqi citizens who mistakenly ground wheat grain into flour that had been treated with methyl mercury as a fungicide and that was intended for planting and not for direct human consumption.

Visual deficits are a prominent feature of methyl mercury intoxication in adult humans, along with several other neurologic manifestations such as difficulties with sensation, gait, memory, and cognition. Methyl mercury poisoned individuals experienced a striking and progressive constriction of the visual field (peripheral scotoma) as patients became progressively less able to see objects in the visual periphery (Iwata, 1977). The narrowing of the visual field gives impression of looking through a long tunnel, hence the term tunnel vision. Visual field constrictions also have been observed in methyl mercury-poisoned monkeys (Merigan, 1979). On autopsy of some of the Minamata patients, focal neurologic degeneration was observed in several brain regions including motor cortex, cerebellum, and calcarine fissure of visual cortex (Takeuchi and Eto, 1977). The histopathologic feature was a destruction of the cortical neural and glial cells, with sparing of the subcortical white matter, optic radiations, and LGN. Monkeys and dogs that were treated experimentally with methyl mercury showed greater damage in the calcarine fissure, associated with higher regional concentrations of protein-bound mercury, than in other brain regions (Yoshino *et al.*, 1966; Berlin *et al.*, 1975). In the Minamata patients, there was a regional distribution of damage observed within striate cortex, such that the

and animal feeds and may cause illness in animals and humans. Intravenous infusion of T-2 toxin in rats causes an initial decrease in heart rate and blood pressure, followed by tachycardia and hypertension and finally by bradycardia and hypotension (McManus *et al.*, 1987). Acute T-2 toxin exposure causes extensive destruction of myocardial capillaries, while repeated dosing promotes thickening of large coronary arteries.

Vitamin D The toxic effects of vitamin D may be related to its structural similarity to 25-hydroxycholesterol, a potent vascular toxin. The manifestations of vitamin D hypervitaminosis include medial degeneration, calcification of the coronary arteries, and smooth muscle cell proliferation in laboratory animals.

β -Amyloid Accumulation of β -amyloid is a major lesion in the brain of Alzheimer's patients. Studies have shown that administration of β -amyloid produces extensive vascular disruption, including endothelial and smooth muscle damage, adhesion and migration of leukocytes across arteries and venules (Thomas *et al.*, 1997). Most importantly, the vascular actions of β -amyloid appear to be distinct from the neurotoxic properties of the peptide. It appears that vascular toxicity of β -amyloid makes contributions to Alzheimer's dementia.

Environmental Pollutants and Industrial Chemicals

The environmental pollutants and industrial chemicals discussed in cardiac toxicity section all have toxic effects on the vascular system. As discussed above, the cardiac effect of some of these agents and pollutants may result primarily from the vascular effect. The by-products of vascular tissue damage or the secreted substances, such as cytokines derived from vascular injury, can affect the heart either directly because of the residual of the vascular system in the heart, or indirectly through blood circulation. In this context, some of the chemicals discussed in the cardiotoxicity will not be further described. Some unique vascular toxicity will be presented.

Carbon Monoxide Carbon monoxide induces focal intimal damage and edema in laboratory animals at a concentration (180 ppm) to which humans may be exposed from environmental sources such as automobile exhaust, tobacco smoke, and fossil fuels. However, it is difficult to distinguish the direct effects of carbon monoxide from those of chemicals such as sulfur oxides, nitrogen oxides, aldehydes, and hydrocarbons on humans because most sources of carbon monoxide are complex mixtures of chemicals. Degenerative changes of myocardial arterioles have been produced experimentally in dogs forced to smoke. Similar changes have also been detected in humans who were heavy smokers and died of noncardiac causes (Wald and Howard, 1975). Tobacco smoke not only exerts a direct atherogenic effect (endothelial injury, changes in lipid profiles, and proliferation of smooth muscle cells), but also facilitates thrombosis by modulation of platelet function and vascular spasm.

Short-term exposure to carbon monoxide is associated with direct damage to vascular endothelial and smooth muscle cells. Injury to endothelial cells increases intimal permeability and allows the interaction of blood constituents with underlying components of the vascular wall. This response may account in part for the ability of carbon monoxide to induce atherosclerotic lesions in several animal

species. The toxic effects of carbon monoxide have been attributed to its reversible interaction with hemoglobin. As a result of this interaction, carboxyhemoglobin decreases the oxygen-carrying capacity of blood, eventually leading to functional anemia. In addition, carbon monoxide interacts with cellular proteins such as myoglobin and cytochrome *c* oxidase and elicits a direct vasodilatory response of the coronary circulation.

Carbon Disulfide Carbon disulfide (dithiocarbonic anhydride) occurs in coal tar and crude petroleum and is commonly used in the manufacture of rayon and soil disinfectants. This chemical has been identified as an atherogenic agent in laboratory animals. The mechanism for carbon disulfide-atheroma production may involve direct injury to the endothelium coupled with hypothyroidism, because thiocarbamate (thiourea), a potent antithyroid substance, is a principal urinary metabolite of carbon disulfide. Carbon disulfide also modifies low-density lipoprotein in vitro and enhances arterial fatty deposits induced by a high-fat diet in mice (Lewis *et al.*, 1999).

1,3-Butadiene Studies have shown that 1,3-butadiene, a chemical used in the production of styrene-butadiene, increases the incidence of cardiac hemangiosarcomas, which are tumors of endothelial origin (Miller and Boorman, 1990). Although hemangiosarcomas have also been observed in the liver, lung, and kidney, cardiac tumors are a major cause of death in animals exposed to this chemical. The toxic effects of 1,3-butadiene are dependent on its metabolic activation by cytochrome *P*450 to toxic epoxide metabolites. The ultimate outcomes of exposure probably are influenced by the rates of glutathione-mediated detoxification of oxidative metabolites.

Metals and Metalloids The vascular toxicity of food- and water-borne elements (selenium, chromium, copper, zinc, cadmium, lead, and mercury) as well as airborne elements (vanadium and lead) involves reactions of metals with sulfhydryl, carboxyl, or phosphate groups. Metals such as cobalt, magnesium, manganese, nickel, cadmium, and lead also interact with and block calcium channels. Intracellular calcium-binding proteins, such as CaM, are biologically relevant targets of heavy metals, including cadmium, mercury and lead, although the contribution of this mechanism to the toxic effects of metals has been fully understood.

Cadmium effects on the vascular system have been studied in the greatest detail. Although cadmium is not preferentially localized in blood vessels relative to other tissues, when present, cadmium is localized in the elastic lamina of large arteries, with particularly high concentrations at arterial branching points (Perry *et al.*, 1989). A large portion of the cadmium that accumulates in the body is tightly bound to hepatic and renal MT. The low MT levels in vascular tissue may actually predispose a person to the toxic effects of cadmium (Perry *et al.*, 1989). Long-term exposure of laboratory animals to low levels of cadmium has been associated with the development of atherosclerosis and hypertension in the absence of other toxic effects. Selenium and zinc inhibit, whereas lead potentiates the hypertensive effects of cadmium. Calcium has antagonistic effect on cadmium-induced high blood pressure. Cadmium increases sodium retention, induces vasoconstriction, increases cardiac output, and produces hyperreninemia. Any one of these mechanisms could account for the putative hypertensive effects of cadmium.

Lead has been shown from epidemiologic studies to be associated with essential hypertension in a large percentage of patients (Batuman *et al.*, 1983). Elevated blood pressure has also been

observed during childhood lead poisoning. The direct vasoconstrictor effect of lead may be related to the putative hypertensive response. This effect can be complemented by the ability of lead to activate the renin-angiotensin-aldosterone system. Lead also directly affects vascular endothelial and smooth muscle cells. For instance, lead inhibits the repair process in damaged endothelial cells (Fujiwara *et al.*, 1997) and modulates spontaneous release of fibrinolytic proteins from subendothelial cells through intracellular calcium-independent pathways (Yamamoto *et al.*, 1997). Acute lead-induced neuropathy may be due to cerebral capillary dysfunction. Inorganic lead alters arterial elasticity and causes sclerosis of renal vessels.

Mercury produces vasoconstriction of preglomerular vessels and disrupts the integrity of the blood-brain barrier. The opening of the blood-brain barrier results in extravasation of plasma protein across vascular walls into adjoining brain tissues. Mercury added to platelet-rich plasma causes a marked increase in platelet thromboxane B₂ production and platelet responsiveness to arachidonic acid.

Arsenic poisoning causes vasodilation and capillary dilation. These actions have been associated with extravasation, transudation of plasma, and decreased intravascular volume. A severe form of arteriosclerosis, blackfoot disease, in Taiwan has been shown to be associated with high levels of arsenic in the soil and water. Blackfoot disease is an endemic peripheral vascular occlusive disease that exhibits arteriosclerosis obliterans and thromboangiitis. The ability of arsenic to induce these changes has been attributed to its effects on vascular endothelial cells. Arsenic has been reported to cause noncirrhotic portal hypertension in humans.

Aromatic Hydrocarbons Aromatic hydrocarbons, including polycyclic aromatic hydrocarbons and polychlorinated dibenzodioxins, are persistent toxic environmental contaminants. Aromatic

hydrocarbons have been identified as vascular toxins that can initiate and/or promote the atherogenic process in experimental animals (Ou and Ramos, 1992). The atherogenic effect is associated with cytochrome P450-mediated conversion of the parent compound to toxic metabolic intermediates, but aromatic hydrocarbons can also initiate the atherogenic process. However, studies have also shown that treatment with several polycyclic hydrocarbons increases the size but not the frequency of atherosclerotic lesions (Albert *et al.*, 1977; Penn and Synder, 1988), suggesting that polycyclic aromatic hydrocarbons act as promoters of the atherosclerotic process. Although additional studies are required to define the "initiating" versus "promotional" actions of polycyclic aromatic hydrocarbons, their ability to readily associate with plasma lipoproteins may play a critical role in vascular toxicity.

Particulate Air Pollution Recent epidemiological studies have provided a strong body of evidence that elevated levels of ambient particulate air pollution (PM) are associated with increased cardiovascular and respiratory morbidity and mortality. Besides the PM effects on cardiomyocytes such as alterations in ion channel function leading to cardiac malfunction, available clinical and experimental evidence lends support to the vascular effects of inhaled ambient particles, including endothelial dysfunction and promotion of atherosclerotic lesions. Importantly, these lesions lead to release or secretion of cytokines and chemokines, worsening cardiac complications. For instance, PM exposure significantly increases serum total endothelin concentrations and worsens premature ventricular complexes of the electrocardiograms that occur in the myocardial infarct rats (Kang *et al.*, 2002). The PM effects on vascular system and the consequences are important health-related topics and further studies are needed to substantiate our current understanding of mechanisms for PM adverse vascular effects.

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Toxicokinetics Absorption of hexavalent chromium compounds is higher (2–10%) than that of trivalent chromium compounds (0.5–2%). Hexavalent chromium readily crosses cell membranes on carriers for sulfate and phosphate, whereas the less insoluble trivalent chromium compounds are absorbed via passive diffusion and phagocytosis. Absorption of inhaled chromium compounds takes place in the lung via transfer across alveolar cell membranes. Dermal absorption depends on the chemical form, the vehicle, and the integrity of the skin. Concentrated potassium chromate may cause chemical burns in the skin that facilitate absorption. Once in the blood, hexavalent chromium is taken up by erythrocytes, whereas trivalent chromium is only loosely associated with erythrocytes. Chromium compounds are distributed to all organs of the body, with high levels in liver, spleen, and kidney. Particles containing chromium can be retained in the lungs for years. Absorbed chromium is excreted primarily in urine. The half-life for excretion of potassium chromium is about 35–40 hours (ATSDR, 2000; Sedman *et al.*, 2006).

Once hexavalent chromium enters cells, it is reduced intracellularly by ascorbic acid, glutathione, and/or cysteine, ultimately to trivalent chromium. It is thought that the toxicity of hexavalent chromium compounds results from damage to cellular components during this process, including the generation of free radicals and the formation of DNA adducts (Zhitkovich, 2005).

Toxicity Toxic effects have been attributed primarily to airborne hexavalent chromium compounds in industrial settings. Hexavalent chromium is corrosive and may cause chronic ulceration and perforation of the nasal septum, as well as chronic ulceration of other skin surfaces (ATSDR, 2000). Hexavalent chromium elicits allergic contact dermatitis among previously sensitized individuals, which is a type-IV allergic reaction inducing skin erythema, pruritus, edema, papule, and scars. The prevalence of chromium sensitivity is less than 1% among the general population (Proctor *et al.*, 1998). Occupational exposure to chromium may be a cause of asthma (Bright *et al.*, 1997). Accidental ingestion of high doses of hexavalent chromium compounds may cause acute renal failure characterized by proteinuria, hematuria, and anuria, but kidney damage from lower-level chronic exposure is equivocal (ATSDR, 2000).

Carcinogenicity Occupational exposure to hexavalent chromium compounds, particularly in the chrome production and pigment industries, is associated with increased risk of lung cancer, and hexavalent chromium-containing compounds are considered to be human carcinogens (IARC, 1990). Hexavalent chromium compounds are genotoxic: A review of more than 700 sets of short-term genotoxicity test results with 32 chromium compounds revealed 88% of hexavalent chromium compounds were positive, as a function of solubility and bioavailability to target cells (De Flora, 2000). Trivalent chromium compounds were generally nongenotoxic, probably because trivalent chromium is not readily taken up by cells (De Flora, 2000). Once hexavalent chromium enters the cell, it is reduced by various intracellular reductants to give reactive trivalent chromium species. During the reduction process, various genetic lesions can be generated, including chromium–DNA adducts, DNA protein cross-links, DNA–chromium intrastrand cross-links, DNA strand breaks, and oxidized DNA bases (O'Brien *et al.*, 2003; Zhitkovich, 2005). Hexavalent chromium compounds are mutagenic, causing base substitutions, deletions, and transversions in bacterial systems, and hypoxanthine guanine phosphoribosyl transferase, *supF* muta-

tions, etc., in mammalian mutagenesis systems (Cohen *et al.*, 1993; O'Brien *et al.*, 2003).

Hexavalent chromium compounds also react with other cellular constituents during the intracellular reduction process. They can cause the generation of reactive oxygen radicals, inhibit protein synthesis and arrest DNA replication. Hexavalent chromium can also cause disturbances of the p53 signaling pathway, cell cycle arrest, apoptosis, interference of DNA damage repair, and neoplastic transformation. All these effects could well play an integrated role in chromium carcinogenesis (O'Brien *et al.*, 2003; Costa and Klein, 2006).

Inhaled chromium compounds can penetrate to many tissues in the body, and thus have the potential to cause cancer at sites other than the lung. Accumulating evidence indicates an association between cancers of the bone, prostate, hematopoietic system, stomach, kidney, and urinary bladder and hexavalent chromium exposure (Costa, 1997). Furthermore, exposure of hexavalent chromium compounds through the drinking water enhances UV-induced skin cancer in the hairless mouse model (Costa and Klein, 2006). An association of hexavalent chromium in the drinking water with stomach cancer has also been reported (Sedman *et al.*, 2006).

Lead

Lead (Pb) has been used by humans for at least 7000 years, because it is widespread, easy to extract, and easy to work with. It is highly malleable and ductile as well as easy to smelt. In the early Bronze Age, lead was used with antimony and arsenic. Lead's elemental symbol Pb, is an abbreviation of its Latin name *plumbum*. Lead in lead compounds primarily exists in the divalent form. Metallic lead (Pb⁰) is resistant to corrosion and can combine other metals to form various alloys. Organolead compounds are dominated by Pb⁴⁺. Inorganic lead compounds are used as pigments in paints, dyes, and ceramic glazes. Organolead compounds were used as gasoline additives. Lead alloys are used in batteries, shields from radiation, water pipes, and ammunition. Environmental lead comes mainly from human activity and is listed as a top toxic substance (ATSDR, 2005c). The phasing out of leaded gasoline, the removal of lead from paint, solder, and water supply pipes have significantly lowered blood lead levels (BLL) in the general population. Lead exposure in children still remains a major health concern. Lead is not biodegradable and the concerns for ecotoxicity of lead are increasing. For instance, the leaded fish sinkers or pellets lost in the bottom of lakes and river banks can be mistaken for stone and ingested by birds causing adverse effects including death (De Francisco *et al.*, 2003).

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 is hand-to-mouth transfer of lead-containing paint chips or dust from floors of older housing (Manton *et al.*, 2000). Lead in household dust can also come from outside of the home and may be related to lead in neighborhood soil (von Lindren *et al.*, 2003). A major route of exposure for the general population is from food and water. Dietary intake of lead has decreased dramatically in recent years, and for infants, toddlers, and young children is <5 µg/day (Manton *et al.*, 2005). A review by the EPA in 2004 found lead levels in 71% of the water systems in the US showed <5 µg Pb/L (ppb). Only 3.6% exceeded the action level of 15 ppb. Lead in urban air is generally higher than rural air. Air lead in rural areas of eastern United States is typically 6–10 ng/m³ (ATSDR, 2005c).

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. Workplace exposure is gradually being reduced. Herbal medicines could be potential sources of lead exposure. Certain Ayurvedic herbal products were found to be contaminated with lead ranging up to 37 mg/g and over 55 cases of lead poisoning have been related to the ingestion of herbal medicines (Patrick, 2006).

Blood lead levels (BLL) are commonly used for monitoring human exposure to lead. The uses of other biomarkers for lead exposure have been critically reviewed (Barbosa *et al.*, 2005).

Toxicokinetics Adults absorb 5–15% of ingested lead and usually retain less than 5% of what is absorbed. Children absorb 42% of ingested lead with 32% retention (Ziegler *et al.*, 1978). Lead absorption can be enhanced by low dietary iron and calcium, especially in children (Mahaffey, 1985). Airborne lead is a minor component of exposure. Lead absorption by the lungs depends on the form (vapor versus particle), particle size, and concentration. About 90% of lead particles in ambient air that are inhaled are small enough to be retained. Absorption of retained lead through alveoli is relatively efficient.

Lead in blood is primarily (99%) in erythrocytes bound to hemoglobin, only 1% of circulating lead in serum is available for tissue distribution (ATSDR, 2005c). Lead is initially distributed to soft tissues such as kidney and liver, and then redistributed to skeleton and hair. The half-life of lead in blood is about 30 days. The fraction of lead in bone increases with age from 70% of body burden in childhood to as much as 95% in adulthood, with a half-life of about 20 years. Lead in trabecular bone is more labile and has a shorter turnover time than cortical bone. Lead released from bones may contribute up to 50% of the lead in blood, and is a significant source of endogenous exposure. Bone lead release may be important in adults with accumulated occupational exposure and in women due to bone resorption during pregnancy, lactation, menopause, and from osteoporosis (Silbergeld *et al.*, 1988; Gulson, *et al.*, 2003). Lead crosses the placenta, so that cord blood generally correlates with maternal BLL but is often slightly lower. Lead accumulation in fetal tissues, including brain, is proportional to maternal BLL (Goyer, 1996).

The major route of excretion of absorbed lead is the kidney. Renal excretion of lead is usually through glomerular filtrate with some renal tubular resorption. Fecal excretion via biliary tract accounts for one-third of total excretion of absorbed lead (ATSDR, 2005c).

Physiological-based pharmacokinetic (PBPK) models have been developed for lead risk assessment. The O'Flaherty model is a model for children and adults; The integrated exposure uptake (IEUBK) model is developed by EPA for predicting BLL in children. The Leggett model allows simulation of lifetime exposures and can be used to predict blood lead in both children and adults (ATSDR, 2005c).

Toxicity 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 (Goyer, 1990). Children are most sensitive to effects in the central nervous system, while in adults peripheral neuropathy, chronic nephropathy, and hypertension are concerns. 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.

Neurological, Neurobehavioral, and Developmental Effects in Children Clinically overt lead encephalopathy may occur in children with high exposure to lead, probably at BLL of 70 $\mu\text{g}/\text{dL}$ or higher. 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. The pathological findings at autopsy are severe edema of the brain due to extravasations of fluid from capillaries in the brain. This is accompanied by the loss of neuronal cells and an increase in glial cells. Recovery is often accompanied by sequelae including epilepsy, mental retardation, and, in some cases, optic neuropathy and blindness (Goyer, 1990; Bellinger, 2004; ATSDR, 2005c; Laraque and Trasande, 2005).

The most sensitive indicators of adverse neurological outcomes are psychomotor tests or mental development indices, and broad measures of IQ. Most studies report a 2- to 4-point IQ deficit for each $\mu\text{g}/\text{dL}$ increase in BLL within the range of 5–35 $\mu\text{g}/\text{dL}$. The Centers for Disease Control and Prevention set the goal of eliminating ≥ 10 $\mu\text{g}/\text{dL}$ BLL in children by 2010 (CDC, 2005). However, effects of lead on IQ may occur below this level (Bellinger, 2004). Recent studies found that deficits in cognitive and academic skills could occur with BLL < 5.0 $\mu\text{g}/\text{dL}$ (Lamphear *et al.*, 2000). A study of a cohort of children from pregnancy through 10 years of age found that lead exposure around 28 weeks of gestation is a critical period for later child intellectual development, and lead's effect on IQ occurs with first few μg s of BLL (Schnaas *et al.*, 2006).

Lead can affect the brain by multiple mechanisms (Goyer, 1996; ATSDR, 2005c). Lead may act as a surrogate for calcium and/or disrupt calcium homeostasis. The stimulation of protein kinase C may result in alteration of blood-brain barrier and inhibition of cholinergic modulation of glutamate-related synaptic transmissions. 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 with cumulative exposures resulting from BLL > 40 $\mu\text{g}/\text{dL}$ (Lindgren *et al.*, 1996). Peripheral neuropathy is a classic manifestation of lead toxicity in adults. More than a half-century ago, footdrop and wristdrop characterized the house painter and other workers with excessive occupational exposure to lead but are rare today. Peripheral neuropathy is characterized by segmental demyelination and possibly axonal degeneration. Motor nerve dysfunction, assessed clinically by electrophysiological measurement of nerve conduction velocities, occurred with BLL as low as 40 $\mu\text{g}/\text{dL}$ (Goyer, 1990).

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 Fig. 23-4. 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 phorbobilinogen (PBG). Inhibition of ALAD results in

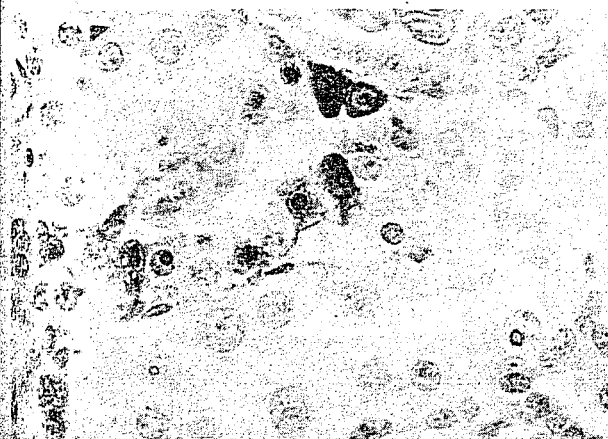


Figure 23-4. Metallothionein Intensity and Localization in Lead-Induced Nuclear Inclusion Bodies from the Kidneys of Wild-type Mice.

Immunohistochemical assessment of a representative section including inclusion bodies showing intense surface staining for metallothionein (dark brown; x400) (From Waalkes *et al.*, 2004c, with permission).

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. Erythrocytes containing zinc-protoporphyrin are intensely fluorescent and may be used to diagnose lead exposure. Feeding lead to experimental animals also raises

heme oxygenase activity, resulting in increases in bilirubin formation. Anemia only occurs in very marked cases of lead toxicity, and is microcytic and hypochromic, as in iron deficiency. The changes in ALAD in peripheral blood and excretion of ALA in urine correlate with BLL and serve as early biochemical indices of lead exposure (ATSDR, 2005c).

Genetic polymorphisms have been identified for alleles of the *ALAD* gene which may affect the toxicokinetics of lead. However, no firm evidence exists for an association between *ALAD* genotype and susceptibility to lead toxicity at background exposures, and thus, population testing for *ALAD* polymorphism is not justified (Kelada *et al.*, 2001).

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, azotaemia and renal failure (Goyer, 1989). A characteristic microscopic change is the presence of intranuclear inclusion bodies (Fig. 23-5). By light microscopy the inclusions are dense, homogeneous, and are eosinophilic with hematoxylin and eosin staining. The bodies are composed of a lead-protein complex. The protein is acidic and contains large amounts of aspartic and glutamic acids with little cystine. The inclusion bodies are a form of aggresome accumulating large amounts of lead in a relatively inert, nontoxic state. Metallothionein-null mice cannot form inclusion bodies following lead treatment and are hyper-sensitive to lead-induced nephropathy and carcinogenesis, suggesting that lead inclusion body formation requires metallothionein as a participant (Qu *et al.*, 2002; Waalkes *et al.*, 2004c). In fact, metallothionein is found on the outer surface of lead inclusion bodies, indicating

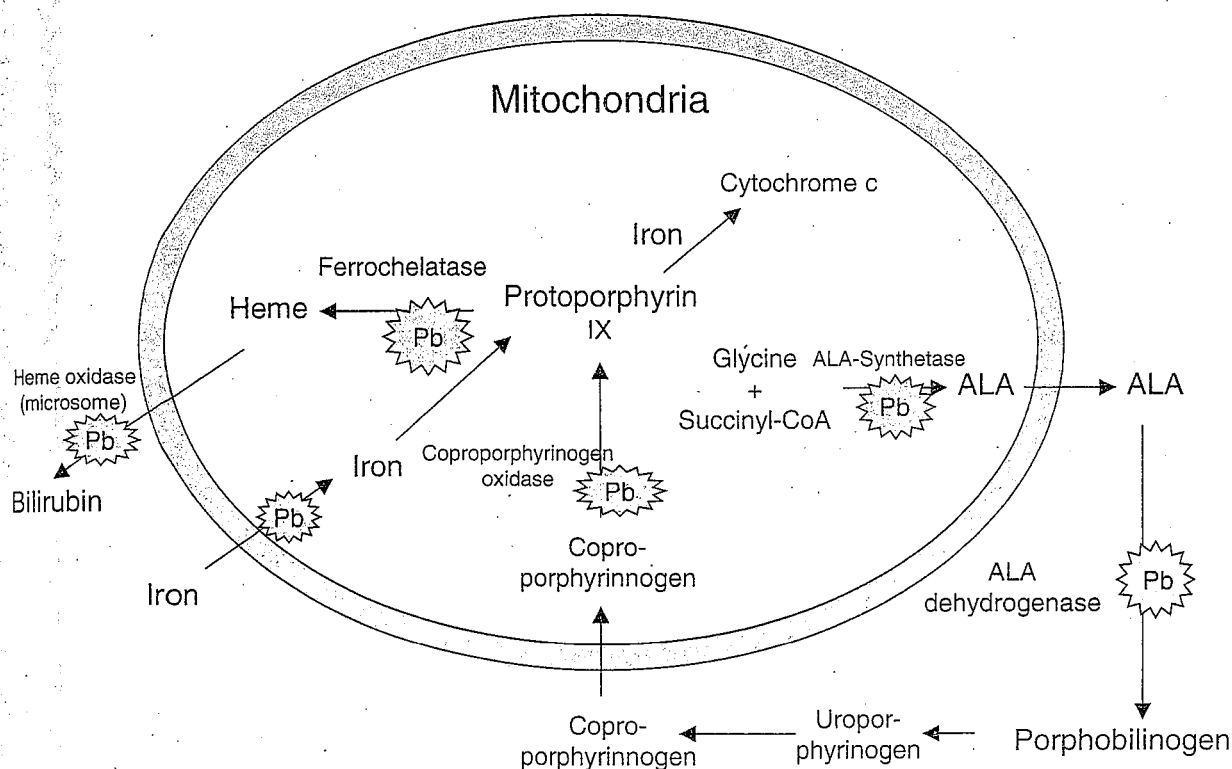


Figure 23-5. Lead Interruption of Heme Biosynthesis.

ALA, δ -aminolevulinic; Pb, sites for lead effects. The major lead inhibition sites are ALA dehydrogenase and ferrochelatase.

that it may transport the metal to the forming inclusion (Waalkes *et al.*, 2004c). 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 (ATSDR, 2005c). Hyperuricemia with gout occur more frequently in the presence of lead nephropathy (Batuman, 1993). Lead nephropathy is also a cause of hypertension (Gonick and Behari, 2002).

Effects on Cardiovascular System There is evidence of a causal relationship between lead exposure and hypertension (Gonick and Behari, 2002; ATSDR, 2005c). A study related bone lead with blood pressure in a cohort of 590 men that indicated an increase in hypertension for individuals with elevated bone lead (Hu *et al.*, 1996). Analysis of data from the National Health and Nutrition Examination Survey (NHANES II) for the U.S. population, including BLL and blood pressure measurements in a general population (5803 people aged 12–74), found a correlation between BLL at relatively low levels and blood pressure (Harlan, 1988). An epidemiology reappraisal using meta-analysis of 58,518 subjects from both the general population and occupationally exposed groups from 1980 to 2001 suggested a weak, but significant association between BLL and blood pressure (Nawrot *et al.*, 2002). Elevated blood pressure is more pronounced in middle age than at young age (ATSDR, 2005c).

A review of chronic lead exposure on blood pressure in experimental animals indicated that at lower doses, lead consistently produced hypertension effects, whereas at higher doses results are inconsistent (Victory, 1988). 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 rennin-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 $\text{Na}^+/\text{Ca}^{++}$ exchange pump; and (4) a possible rise in endothelin and thromboxane (Gonick and Behari, 2002; Vaziri and Sica, 2004).

Immunotoxicity The developing immune system is sensitive to toxic effects of lead (Dietert *et al.*, 2004). A hallmark of lead-induced immunotoxicity is a pronounced shift in the balance in T helper cell function toward Th2 responses at the expense of Th1 functions, resulting in elevated IgE levels. Increased IgE levels and inflammatory cytokines were found in lead-exposed neonatal rodents, and there is an association between BLL and elevated IgE levels in children (Karmaus *et al.*, 2005; Luebke *et al.*, 2006). Thus, lead immunotoxicity might be a risk factor for childhood asthma (Dietert *et al.*, 2004). In experimental animals, lead has been shown to target macrophages and T cells, especially CD4^+ T cells. In occupational exposure, lead-associated changes include altered T-cell subpopulations, reduced immunoglobulin levels, and reduced polymorphonuclear leukocyte chemotactic activity (Dietert *et al.*, 2004; Luebke *et al.*, 2006).

Bone Effects Lead has an extremely long half-life in bone, accounting for over 90% of the body lead in adults. Lead can affect bone by interfering with metabolic and homeostatic mechanisms including parathyroid hormone, calcitonin, vitamin D, and other hormones that influence calcium metabolism. Lead substitutes for calcium in bone (Pounds *et al.*, 1991). Lead is known to affect osteoblasts, osteoclasts, and chondrocytes and has been associated with osteoporosis and delays in fracture repair (Carmouche *et al.*,

2005). In children exposed to lead, a higher bone mineral density (BMD) was observed. This may be due to accelerated bone maturation through inhibition of parathyroid hormone-related peptide, may ultimately result in lower peak BMD in young adulthood, and might predispose subjects to osteoporosis later in life (Campbell *et al.*, 2004). A positive association between lead exposure and dental caries in children has been shown in a number of studies. Lead is deposited in teeth, inhibits mineralization of enamel and dentine, and affects metabolism of the cells in the dental pulp (ATSDR, 2005c).

Other Effects Lead colic is a major gastrointestinal symptom of severe lead poisoning, and is characterized by abdominal pain, nausea, vomiting, constipation, and cramps (ATSDR, 2005c). It is rarely seen today.

Lead-induced gametotoxic effects have been demonstrated in both male and female animals (Goyer, 1990). There is also evidence that lead may disrupt the hypothalamic-pituitary-gonadal axis. An increase in the maternal BLL may also contribute to premature birth and reduced birth weight (ATSDR, 2005c).

Carcinogenicity The association of lead exposure with increased human cancer risk was strengthened by recent studies (ATSDR, 2005c), and inorganic lead compounds were recently reclassified as probably carcinogenic to humans (IARC, 2004). A study of a cohort of 20,700 workers coexposed to lead and engine exhaust found a 1.4 fold increase in the overall cancer incidence and a 1.8 fold increase in lung cancer among those who ever had elevated BLLs (Anttila *et al.*, 1995). Another epidemiological study of 27,060 brain cancer cases and 108,240 controls that died of nonmalignant disease in US from 1984 to 1992 provides evidence for a potential link between occupational exposure to lead and brain cancer (Cocco *et al.*, 1998). A meta-analysis of published data on cancer incidence among workers in various industries with lead exposure indicates a significant excess of cancer deaths from stomach cancer, lung cancer, and bladder cancer (Fu and Boffetta, 1995). Analysis of eight principal studies with well-documented lead exposures suggests associations of lead exposure with increased lung and stomach cancers (Steenland and Boffetta, 2000). However, workers were not only exposed to lead alone, and exposures to other potential carcinogens such as arsenic, cadmium, and engine exhausts could confound these interpretations. Lead does not appear to be directly genotoxic *in vivo* or *in vitro*, and lead may interact with other toxicants to facilitate chemical carcinogenesis (Silbergeld, 2003).

Lead is a nephrocarcinogen in adult rodents (Waalkes *et al.*, 1995, 2004c; IARC, 2006). Lead-induced renal tumors also occur after perinatal exposure in the absence of the extensive chronic nephropathy (Waalkes *et al.*, 1995). Metallothionein-null mice, which do not form lead inclusion bodies, are hypersensitive to lead-induced proliferative lesions of the kidney (Waalkes *et al.*, 2004c).

Several mechanisms have been proposed for lead-induced carcinogenesis, including regenerative repair, inhibition of DNA synthesis or repair, generation of reactive oxygen species with oxidative damage to DNA, substitution of lead for zinc in transcriptional regulators, interaction with DNA-binding proteins, and aberrant gene expression (Silbergeld *et al.*, 2000; Qu *et al.*, 2002; Silbergeld, 2003).

Treatment Chelation therapy is warranted in workmen with BLL > 60 $\mu\text{g}/\text{dL}$. For children, criteria have been established (Laraque and

Table 23-1

Blood Lead Levels (BLL) in Children as an Indicator for Risk Assessment

BLL ($\mu\text{g/dL}$)	RISK LEVEL	POTENTIAL EFFECT WITH BLL ($\mu\text{g/dL}$)
<10	I	
10–14	II, moderate	IQ Deficits (10–15), ALA-D inhibition (10)
15–19	II, moderate	Developmental effects (10–15)
20–44	III, high	Increased U-ALA (40), decrease nerve, conduction velocity, hearing, vitamin D metabolism
45–69	IV, urgent	Nephropathy, colic (40–60)
>70	V, emergency	Encephalopathy, anemia (80–100)

Trasande, 2005) that may serve as guidelines to assist in evaluating the individual case with potential health effects (Table 23-1). The oral chelating agent dimercaptosuccinic acid (DMSA, also called Succimer) has advantages over EDTA in that it can be given orally and is effective in temporarily reducing BLL. However, DMSA does not improve long-term BLL in children, nor reduce brain lead levels beyond the cessation of lead exposure alone (Cremin *et al.*, 1999; O'Connor and Rich, 1999). A recent study shows that DMSA lowered BLL in children, but had no detectable benefit on learning and behavior (Dietrich *et al.*, 2004).

Mercury

Mercury (Hg) was named after the Greco-Roman god known for swift flight. Also called quicksilver, metallic mercury is in liquid state at room temperature. The symbol Hg was derived from the Latinized Greek *hydrargyrum*, meaning “water” and “silver.” Mercury was known in ancient times from ~1500 BC. By 500 BC mercury was used to make amalgams with other metals. 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^{1+}) or mercuric (Hg^{2+}) salts. This metal can form a number of stable organometallic compounds by attaching to one or two carbon atoms. Methylmercury (CH_3Hg^+ , or MeHg) is the toxicologically most important organic form (ATSDR, 1999). Mercurial compounds have characteristic toxicokinetics and health effects that depend on oxidation state and associated organic species.

Global Cycling and Ecotoxicology Mercury exemplifies movement of metals in the environment (Fig. 23-6). 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. Mercury vapor is a chemically stable monatomic gas and its residence time in atmosphere is about one year. Thus, mercury is globally distributed even from point resources. Eventually, it is oxidized to a water-soluble inorganic form (Hg^{2+}) and returned to the earth's surface in rainwater. At this stage, the metal may be reduced back to mercury vapor and returned to the atmosphere, or it may be methylated by microorgan-

isms present in sediments of bodies of fresh and ocean water. This natural biomethylation reaction produces methylmercury (MeHg). 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 (Clarkson, 2002; Risher *et al.*, 2002). Organomercurial compounds are generally more toxic than inorganic mercury to aquatic organisms, aquatic invertebrates, fish, plants, and birds. Organisms in the larval stages are generally more sensitive to toxic effects of mercury (Boening, 2000).

Exposure

Dietary Exposure Consumption of fish is the major route of exposure to methylmercury. Unlike the case of polychlorinated biphenyls, which are also deposited in fat, cooking the fish does not lower the methylmercury content. 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 they do not constitute an important source of exposure to the general population (ATSDR, 1999; Clarkson, 2002).

Occupational Exposure Inhalation of mercury vapor can occur from the working environment, as in the chloralkali industry, where mercury is used as a cathode in the electrolysis of brine. Occupational exposure may also occur during manufacture of a variety of scientific instruments and electrical control devices, and in dentistry where mercury amalgams are used in tooth restoration. In the processing of and extraction of gold, especially in developing countries, large quantities of metallic mercury are used to form an amalgam with gold. The amalgam is then heated to drive off the mercury, resulting in a substantial atmospheric release (ATSDR, 1999; Eisler, 2003).

Medicinal Exposure Mercury was an important constituent of drugs for centuries and was used as an ingredient in diuretics, anti-septics, skin ointments, and laxatives. These uses have largely been replaced by safer drugs. Thimerosal contains the ethylmercury radical attached to the sulfur group of thiosalicylate (49.6% mercury by weight as ethylmercury), and has been used as a preservative in many vaccines since 1930s. The use of mercury amalgam in dental restoration releases mercury vapor in the oral cavity and can result in increased mercury body burden. However, the amounts are low compared to occupational exposure (Clarkson *et al.*, 2003).

Accidental Exposure Fatal mercury poisonings come mainly from accidental exposure. Elemental mercury spills can occur in many ways, such as from broken elemental mercury containers, medicinal devices, barometers, and from melting tooth amalgam fillings to recover silver. Inhalation of large amount of mercury vapor can be deadly (Baughman, 2006). Oral ingestion of large amounts of inorganic mercury chloride has also been lethal in suicide cases (ATSDR, 1999). A well-known organomercurial poisoning episode was from consumption of fish contaminated with methylmercury from industrial waste in Minamata, Japan. Consumption of grains and rice treated with methylmercury or ethylmercury as fungicides