observed during childhood lead poisoning. The direct vasoconstrictor
effect of lead may be related to the putative hypertensive re-
response. This effect can be complemented by the ability of lead to
activate the renin–angiotensin–aldosterone system. Lead also di-
rectly affects vascular endothelial and smooth muscle cells. For
instance, lead inhibits the repair process in damaged endothelial
cells (Fujisawa et al., 1997) and modulates spontaneous release of
fibrinolytic proteins from subendothelial cells through intracellu-
lar calcium-independent pathways (Yamamoto et al., 1997). Acute
lead-induced neuropathy may be due to cerebral capillary dysfunc-
tion. 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 throm-
boxane B2 production and platelet responsiveness to arachidonic
acid. Atherosclerosis.

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 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
coronary arterial hyperplasia in humans.

Aromatic Hydrocarbons Aromatic hydrocarbons, including
polycyclic aromatic hydrocarbons and polychlorinated dibenzo-
dioxins, are persistent toxic environmental contaminants. Aromatic
hydrocarbons have been identified as vascular toxins that can initi-
ate 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 hydro-
carbons 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 cr
ical 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 cardio-
vascular 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 ex-
perimental evidence lends support to the vascular effects of inhaled
ambient particles, including endothelial dysfunction and promo-
tion of atherosclerotic lesions. Importantly, these lesions lead to
release or secretion of cytokines and chemokines, worsening car-
diac complications. For instance, PM exposure significantly in-
creases serum total cholesterol concentrations and worsens pre-
mature ventricular complexes of the electrocardiograms that oc-
cur 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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Table 23-1
Blood Lead Levels (BLL) in Children as an Indicator for Risk Assessment

<table>
<thead>
<tr>
<th>BLL (μg/dL)</th>
<th>RISK LEVEL</th>
<th>POTENTIAL EFFECT WITH BLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>I</td>
<td>IQ Deficits (10–15), ALA-D inhibition (10)</td>
</tr>
<tr>
<td>10-14</td>
<td>II, moderate</td>
<td>Developmental effects (10–15)</td>
</tr>
<tr>
<td>15-19</td>
<td>II, moderate</td>
<td>Increased U-ALA (40), decrease nerve, conduction velocity, hearing, vitamin D metabolism</td>
</tr>
<tr>
<td>20-44</td>
<td>III, high</td>
<td>Encehlopathy, anemia (80–100)</td>
</tr>
<tr>
<td>45-69</td>
<td>IV, urgent</td>
<td>Nephropathy, colic (40–60)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>V, emergency</td>
<td>Encephalopathy, anemia (80–100)</td>
</tr>
</tbody>
</table>

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 form at room temperature. The symbol Hg was derived from the Latinized Greek hydrargyrum, meaning “water” and “silver.” Mercury was known in ancient times from 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; Rising, 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 exposure (ATSDR, 1999; Eisler, 2000).

Medicinal Exposure Mercury was an important constituent of drugs for centuries and was used as an ingredient in diuretics, antiseptics, skin irritants, and inactives. 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 been lethal in suicide cases (ATSDR, 1999). A well-known organomericurial 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...
In nature, mercury vapor (Hg\(_0\)), a stable monatomic 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 poses the health risk to humans, especially the developing fetus.

Contact with even a small amount of dimethylmercury (CH\(_3\)CH\(_3\)Hg) can penetrate laboratory gloves resulting in rapid transdermal absorption, delayed cerebellar damage, and death (Nierenberg et al., 1998).

**Toxicokinetics**

**Mercury Vapor** Mercury vapor is readily absorbed (about 80%) in the lungs, rapidly diffuses across alveolar membranes into the blood, and distributes to all tissues in the body due to its high lipid solubility. Once the vapor has entered the cell, it is oxidized to divalent inorganic mercury by tissue and erythrocyte catalase. A significant portion of mercury vapor crosses the blood-brain barrier and placentas before it is oxidized by erythrocytes, and thus shows more neurotoxicity and developmental toxicity compared to administration of inorganic mercury salts which cross membranes less rapidly. After mercury vapor undergoes oxidation, its deposition resembles inorganic mercury. Approximately 10% of mercury vapor is exhaled within a week of exposure, and that converted to inorganic mercury is excreted mainly in urine and feces, with a half-life of about 2 months (ATSDR, 1999; Clarkson et al., 2003). Liquid metallic mercury, such as that swallowed from a broken thermometer, is only poorly absorbed by the gastrointestinal tract (0.01%), is not biologically reactive, and is generally thought to be of little or no toxicological consequence.

**Inorganic Mercury** Inorganic mercury is poorly absorbed from the gastrointestinal tract. Absorption ranges 7% to 15% of ingested dose, depending on the inorganic compound. A small portion of absorbed inorganic mercury is formed by reduction in tissues and exhaled as mercury vapor. The highest concentration of inorganic mercury is found in kidney, a major target. Renal uptake of mercury salts occurs through two routes: from luminal membranes in renal proximal tubule in the form of the cysteine S-conjugates (Cys-S-Hg-S-Cys) or from the basolateral membrane through organic anion transporters (Bridges and Zalups, 2005). Inorganic mercury salts do not readily pass blood–brain barrier or placenta and are mainly excreted in urine and feces, with a half-life of about 2 months.

**Methylmercury** Methylmercury is well absorbed from the gastrointestinal tract. About 95% of methylmercury ingested from fish is absorbed. It is distributed to all tissues in about 30 hours. About 10% of absorbed methylmercury is distributed to the brain and 5% remains in blood. The concentration in erythrocytes is 20 times that in plasma. Methylmercury is bound to thiol-containing molecules.
such as cysteine (CH$_3$Hg-S-Cys), which mimic methionine to cross the blood–brain barrier and placenta through the neutral amino acid carrier.

Methylmercury avidly accumulates in hair, and although concentrations are proportional to that in blood, they are about 250-fold higher. Thus, hair mercury is often used as an indicator of exposure. Methylmercury undergoes extensive enterohepatic recycling, which can be interrupted to enhance fecal excretion. Methylmercury is slowly metabolized to inorganic mercury by microflora in the intestine (about 1% of the body burden per day). In contrast to inorganic mercury, 90% of the methylmercury is eliminated from the body in the feces, and less than 10% is in the urine, with a half-life of 45–70 days (Clarkson, 2002; Risher et al., 2002; Bridges and Zalups, 2005).

The disposition of ethylmercury is similar to methylmercury. The major differences include that the conversion to inorganic mercury in the body is much faster for ethylmercury, which can result in renal injury. The mercury concentrations in brain are lower for ethylmercury than methylmercury. The half-life for ethylmercury is only 15–20% of that for methylmercury (Clarkson et al., 2003).

**Toxicity**

**Mercury Vapor** Inhalation of mercury vapor at extremely high concentrations may produce an acute, corrosive bronchitis and intestinal pneumonitis and, if not fatal, may be associated with central nervous system effects such as tremor or increased excitability. With acute exposure to mercury vapor, the major effects are on the central nervous system. Early signs are nonspecific, and 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 radiiodine in the thyroid, labile pulse, tachycardia, dermographism, gingivitis, hemolysis, increased uricosuria, or increased excretion of mercury in urine. The pathogenesis is probably immunologically similar to that occurring after exposure to inorganic mercury (ATSDR, 1999; Clarkson, 2002). Mercury vapor release from amalgam is in general too low to cause significant toxicity (Clarkson et al., 2003; Factor-Litvak et al., 2003; Horsted-Bindslev, 2004).

**Inorganic Mercury** Kidney is the major target organ for inorganic mercury (ATSDR, 1999). 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 (Bigazzi, 1999). Exposed persons may develop proteinuria that is reversible after they are removed from exposure. Experimental studies have shown that the pathogenesis has two phases including an early phase characterized by an anti-basement membrane glomerulonephritis, followed by a superimposed immune-complex glomerulonephritis with transiently raised concentrations of circulating immune complexes (Henry et al., 1988). The pathogenesis of the nephropathy in humans appears similar, although antibodies have not been characterized. In humans, the early glomerular nephritis may progress to interstitial immune-complex nephritis (Pelletier and Druet, 1995; Bigazzi, 1999).

**Methylmercury** The major human health effect from exposure to methylmercury is neurotoxicity. Clinical manifestations of neurotoxicity include parasthesia (a numbness and tingling sensation around the mouth, 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. Neuropathological observations have shown that the cortex of the cerebrum and cerebellum are selectively involved with focal necrosis of neurons, lysis, and phagocytosis, and replacement by glial cells. These changes are most prominent in the deeper fissures (sulci), as in the visual cortex and insula. The overall acute effect is cerebral edema, but with prolonged destruction of gray matter and subsequent gliosis, cerebral atrophy results (Takeuchi, 1977). A study of the Iraq epidemic of methylmercury exposure (Bakir et al., 1973) has provided dose–response estimates of the body burden of mercury required for the onset and frequency of symptoms (Fig. 23–7).

**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 (ATSDR, 1999; Clarkson, 2002). Mercury causes overexpression of metallothionein and glutathione system-related genes in rat tissues (Brambila et al., 2002; Liu et al., 2003), probably as an adaptive mechanism.

**Sensitive Sub-populations** Early life stages are particularly vulnerable to mercury intoxication (Counter and Buchanan, 2004). In Minamata, Japan, pregnant women who consumed fish contaminated with methylmercury, manifested mild or minimal symptoms, but gave birth to infants with severe developmental disabilities, raising initial concerns for mercury as a developmental toxicant.
Methylmercury crosses the placenta and reaches the fetus, and is concentrated to a level in fetal brain at least 5–7 times that of maternal blood (Clarkson, 2002). Prenatal methylmercury exposure at high levels can induce widespread damage to the fetal brain. However, the observed effects from low-level exposures are inconsistent (Counter and Buchanan, 2004; Davidson et al., 2004). In the Seychelles Children Development Study, a group with significant methylmercury exposure from a diet predominantly of fish was studied for adverse developmental effects. These children were examined six times over 11 years using extensive batteries of age-appropriate developmental end-points, but no convincing associations were found except for delayed walking (Davidson et al., 2006). The National Research Council reviewed the epidemiologic studies relating in utero methylmercury exposure and fetal neurological development. It concluded that the current EPA reference dose (RfD) for methylmercury of 0.1 µg/kg per day or 5.8 µg/L cord blood is scientifically justifiable for protection of human health (NRC, 2000). The RfD is equivalent to 12 ppm methylmercury in maternal hair.

The safety of thimerosal (ethylmercury) used in childhood vaccines has also received extensive attention. A recent review indicates that thimerosal is safe at the doses used in vaccines, except for a potential for local hypersensitivity (Clarkson et al., 2003). However, some infants may be exposed to cumulative levels of mercury during the first six months of life that may exceed EPA recommendations (Ball et al., 2001). Steps have been rapidly taken to remove thimerosal from vaccines in the US by switching to single-dose vials that do not require preservatives. Nonetheless, the World Health Organization concluded that it is safe to continue using thimerosal in vaccines, which is important for developing countries where it is essential to use multidose vials (Clarkson et al., 2003).

Although the use of mercury amalgam in children can contribute to mercury exposure, the exposure is too low to cause significant toxicological effects (DeRouen et al., 2006).

Acrodynia occurred in children chronically exposed to inorganic mercury compounds in teething powder and diaper disinfectants, as well as to organomercurials. Acrodynia is characterized by pink hands and feet (also called Pink Disease). These subjects are photophobic and suffer from joint pains (Clarkson, 2002).

**Treatment**  Therapy for mercury poisoning should be directed toward lowering the concentration of mercury at the critical organ or site of injury. For the most severe cases, particularly with acute renal failure, hemodialysis may be the first measure, along with administration of chelating agents for mercury, such as cysteine, EDTA, BAL, or penicillamine. Caution should be taken to avoid inappropriate use of chelating agents in putative mercury poisoning patients (Risher and Amber, 2005).

Chelation therapy is not very helpful for alkyl mercury exposure. Biliary excretion and reabsorption by the intestine can be interrupted by oral administration of a nonabsorbable thiol resin, which can bind mercury and enhance fecal excretion (Clarkson, 2002).

**Nickel**

Nickel (Ni) has been in use since ancient times. However, because the ores of nickel were easily mistaken for ores of silver, a more complete understanding of this metal and its specific use dates to more contemporary times. In 1751, nickel was first isolated from the ore kupfernickel (niccolite) for which it is named. Metallic nickel is produced from sulfide and silicate-oxide ores. In the US ~20,000 metric tons of nickel are used each year. Nickel is used in various metal alloys, including stainless steels and in electroplating. Major properties of nickel alloys include strength, corrosion resistance, and good thermal and electrical conductivity. Occupational exposure to nickel occurs by inhalation of nickel-containing aerosols, dusts, or fumes, or dermal contact in engaged in nickel production (mining, milling, refinery, etc.) and nickel-using operations (melting, electroplating, welding, nickel–cadmium batteries, etc.) (ATSDR, 2005d). Nickel is ubiquitous in nature, and the general population is exposed to low levels of nickel in air, cigarette smoke, water, and food. These exposures are generally too low to be of toxicological concern (Kasprzak et al., 2003). Nickel has various oxidation states but the +2 oxidation state is the most prevalent form in biosystems. The major soluble nickel compounds are nickel acetate, nickel chloride, nickel sulfate, and nickel nitrate. Important water-insoluble nickel compounds include nickel sulfide, nickel subsulfide, nickel oxide, nickel carbonyl, and nickel carbonate (ATSDR, 2005d).

**Toxicokinetics** Inhaled nickel particles are deposited in the respiratory tract and, as with all inhaled particles, the site of deposition depends on the particle size. Large particles (5–30 µm) deposit in the nasopharyngeal area via impaction, smaller particles (1–5 µm) enter the trachea and bronchial region by sedimentation, and particles smaller than 1 µm enter the alveolar space. About 25–35% of the inhaled nickel that is retained in the lungs is absorbed into the blood. The insoluble nickel particles can be taken up into cells by phagocytosis. In the skin the rate of absorption depends on the rate of penetration into the epidermis, which differs for different chemical forms of nickel. In humans, about 27% of a single oral dose of nickel in drinking water is absorbed, whereas only about 1% is absorbed when nickel is given with food. Intestinal nickel absorption occurs through calcium or iron channels, or by the divalent metal transport protein-1 (ATSDR, 2005d).

The main transport proteins of nickel in blood are albumin, histidine, and α2-microglobulin. Nickelplasmin and metallocortin also bind and transport nickel. Following inhalation exposure, nickel is distributed to the lungs, skin, kidneys, liver, pituitary, and adrenal. The half-life of nickel is 1–3 days for nickel sulfate, 5 days for nickel sulfide, and more than 100 days for nickel oxide (ATSDR, 2005d). Absorbed nickel is excreted into urine. Urinary nickel correlates closely with exposure to airborne levels of insoluble nickel compounds. Thus, urinary nickel may serve as a suitable measure of current nickel exposure.

The marked differences in carcinogenic activities of various nickel compounds may be due to differences in delivery of nickel to specific cells and subcellular target molecules. For example, injection of animals with crystalline nickel sulfide or crystalline nickel sulfide results in a high incidence of tumors at the site of injection sites, although tumors are not observed in animals similarly injected with soluble nickel sulfate. The crystalline nickel particles can be actively phagocytized and deliver larger quantities of nickel ions into the nucleus than water-soluble nickel compounds (Kasprzak et al., 2003; Costa et al., 2005).

Essentiality of nickel in higher organisms is questionable, though nickel may be nutritionally essential for some plants, bacteria, and invertebrates. Nickel deficiency syndromes have not been reported in humans and nickel-dependent enzymes or cofactors are unknown (Denkhaus and Kalinow, 2002).