LEAD, TOXICOLOGY

1. Introduction

Lead, lead alloys, and lead compounds have been used for thousands of years for a number of purposes. At least some of the toxic effects to human health caused by these materials have been known or suspected for almost as long. Human health effects associated with exposure to lead and its compounds include, but are not limited to, neurotoxicity, developmental toxicity, renal (kidney) toxicity, cancer, hypertension, impaired hearing acuity, impaired hemoglobin synthesis (anemia), and male reproductive impairment. The previous widespread commercial and consumer uses of lead, the resultant environmental releases of lead, the persistence of lead in the environment, and that many of lead's health effects may occur without overt signs of toxicity has led to significant human exposure to lead and serious human health consequences. Efforts intended to reduce occupational and population exposure to lead have been implemented since the late 1960s. These efforts, largely in the form of regulatory actions, voluntary actions, and increased public awareness, have been highly successful in reducing lead exposure and its associated risks. However, concern about lead as a significant public health problem continues, largely because of epidemiological and experimental evidence regarding the occurrence of adverse human health effects at successively lower levels of lead exposure than previously believed. The U.S. Environmental Protection Agency (EPA) and the U.S. Center for Disease Control consider lead to be a significant and widespread health hazard in the United States.

2. Exposure

Exposure to lead can occur from a variety of occupational or nonoccupational sources. A comprehensive treatise on natural and anthropogenic sources of human lead exposure is available (1), and summarized below.

2.1. Nonoccupational. Humans can absorb lead from: breathing contaminated air, inadvertent ingestion or inhalation of lead-containing dust or particulate matter; consumption of foods that contain lead (eg, foods stored in cans that contained seams sealed with lead-based solder); consumption of water that contains lead (eg, water delivered through copper supply lines in which the joints were connected using lead-based solder); engaging in activities that involve contact with lead-containing materials, eg, do-it-yourself restorations of houses containing lead-based paint, or removal of lead-based paint.

Lead enters the atmosphere from both natural and anthropogenic sources (eg, smelting, mining), but emissions from the latter sources generally contribute more so to elevated atmospheric lead concentrations. Major anthropogenic sources of lead result from the mining and smelting of lead ores, as well as other ores in which lead is a by-product or contaminant. In these processes, lead may be released to land, water, and air. Electrical utilities emit lead in flue gas from the burning of fuels (eg, coal) in which lead is a contaminant. Because of the large quantities of fuel burned by these facilities, large amounts of lead can be released.

Airborne concentrations of lead in the United States have fallen dramatically, however, over the last 30 years, due largely to the phase out of leaded gasoline additives. This has resulted in an overall decrease in lead exposure of the general population via the inhalation route. However, recent studies have also reported that concentrations of airborne lead are sometimes several orders of magnitude higher in urban areas compared to remote regions. Rural areas tend to have lead concentrations falling somewhere between those of urban and remote areas. Thus, urban populations are typically exposed to distinctly higher levels of airborne lead than rural or remote residents.

Concentrations of lead can be elevated in indoor air. Lead in indoor air is directly related to lead in house dust, which poses both an inhalation and an ingestion risk. The predominant sources of indoor air lead are thought to be outdoor air and degraded lead-based paint.

Soil lead can be directly ingested through hand-to-mouth behavior common in children, indirectly ingested through contaminated food, or inhaled when breathing air containing resuspended soil particles. Soil ingestion generally peaks during the second year of life and diminishes thereafter. Lead in soil is derived mainly from atmospheric deposition, both from local sources and long-range transport, and from natural deposits in the surrounding areas. In general, soil in urban and residential areas is contaminated primarily via atmospheric deposition, direct application of agricultural chemicals, and natural mineral weathering of parent rock.

Blood lead levels are typically elevated for people living near lead mines. For example, soil collected at residences near the Tar Creek Superfund Site, which is a lead mining area in northeastern Oklahoma, showed wind-dispersed mine wastes. More than 20% of soils exceeded 500 ppm; and children's blood lead levels tended to be higher when compared to children living outside the area. In this same area, blood lead levels were highest among African American, Mexican American, and poor children.

Lead in drinking water primarily results from corrosion of lead pipes or copper pipe joints welded with lead-based solder within a residence. Very little lead in drinking water comes from utility supplies. The chemical composition of water distribution pipes is of great importance when considering how much lead is leached into drinking water. Copper piping with lead-based solder has largely replaced pure lead piping in the United States. In houses with copper piping and lead-based solder, brass fixtures may contribute as much as 50% of lead in drinking water. The primary type of solder used in the United States was 50–50 tin–lead solder (50% tin, 50% lead) before the Safe Drinking Water Act amendments of 1986 were enacted. Although new or repaired pipes may not use solder containing $>0.2\%$ lead, 50–50 solder still exists in many older structures.

As is true for lead exposure via inhalation, lead exposure via ingestion of contaminated foods has also decreased in the U.S. population. In general, food lead concentrations have decreased as a direct result of the decrease in airborne emissions of lead from automotive gasoline, as well as the reduction in the use of lead solder in cans. Many older ceramic food containers or items otherwise associated with the consumption of foods or beverages contain lead. For example, crystal wine flasks and the glazing of many older pottery items (eg, plates,

cups) contain lead, and represent a source of exposure to lead, particularly when used to store foods or beverages.

While lead exposure via ingestion of contaminated foods has decreased for the general U.S. population, this general trend is not necessarily true for individuals who consume seafoods harvested from localities contaminated with lead, as seafood organisms may bioaccumulate the lead. Many lead fish advisory warnings, eg, have been issued in specific localities in Idaho and Washington states, and other parts of the United States (2). These advisories warn against human consumption of fish harvested from the specific localities, since the environmental lead contamination in these localities has led to contamination of the fish in the localities. Also, discharges of lead to seawater has been shown to contaminate the edible portions of blue mussels growing in the vicinity of the discharges, and consumption of these mussels can serve as a source of human exposure to lead (3).

In summary, in the United States the elimination of leaded gasoline, lead-based paint, and lead solder has decreased exposure of the general population to lead, as evidenced by a corresponding decrease in blood–lead levels of the U.S. population. However, the potential for high lead exposures remains, particularly in areas near major lead sources or with exposures to lead-based paint or high lead levels in drinking water.

2.2. Occupational. The toxicity of lead following occupational exposure to the metal has been known since antiquity. In developed countries, regulations, engineering advances, and medical surveillance have greatly reduced the incidence of clinical lead poisoning in lead-based industries. However, occupational exposure to lead is still a concern for many workers. Lead smelting and refining have the greatest potential for occupational exposure to inorganic lead, because lead fumes are generated and dust containing lead oxide is deposited in the workplace. Other occupations associated with lead exposure include lead storage battery manufacture; autobody and auto-radiator manufacture and repair; lead recycling; stained glass work; demolition and restoration; and plumbing installation or repair. Elevated blood lead levels have occurred in children of workers who are occupationally exposed to lead. For example, children may be exposed to lead dust brought home on workers' clothing.

Residential renovation and paint removal can also be major sources of lead exposure in workers engaged in such activities. Dry sanding, abrasive blasting, and burning, welding, or heating surfaces covered with lead-based paint typically generate highly dangerous airborne lead levels. Lead-based paints were the predominant coating for U.S. highway bridges for many years. Paint removal during bridge renovation projects has been cited as a major source of occupational lead exposure.

Lead concentrations during industrial paint removal depend largely on the technology used. Generally, abrasive blasting techniques are used, which breaks lead coatings into small particles that can be inhaled or ingested if hands are not washed prior to eating or smoking. Vacuum blasting may reduce occupational exposures.

3. Absorption, Distribution, and Excretion

Detailed discussions on the absorption, distribution, and excretion of lead in humans are available (1,4,5). The principal routes of lead absorption are from the gastrointestinal and respiratory tracts. Gastrointestinal absorption of lead varies with age. Adults absorb ~10% of ingested lead; children absorb up to 40%. Little is known about lead transport across the gastrointestinal mucosa, but it appears that divalent lead and calcium compete for a common transport mechanism, since there is an inverse relationship between the dietary content of calcium and the extent of lead absorption. Absorption of inhaled lead varies with form and concentration. Up to 90% of inhaled lead particles from ambient air may be absorbed.

Infants and children are more susceptible to absorbing lead than adults for several reasons: typical mouthing behavior (eg, thumb and object sucking) can contribute to higher rates of ingestion of lead-contaminated dirt and dust; young children (<5 years of age) absorb a larger fraction of ingested lead than do adults because children absorb more calcium than adults, and lead follows many of the same pathways as calcium in humans; and certain populations of children have relatively high prevalence's of nutrient deficiencies (eg, calcium, iron) that can increase bioavailability of lead. In addition to having greater susceptibility to absorbing lead, infants and children also appear to be more susceptible to bioaccumulating lead in the skeleton, and to the neurological toxicity caused by lead, as indicated by the occurrence of neurotoxic effects in infants and children in association with lower blood lead concentrations compared to adults.

Independent of the route of exposure, some of the absorbed lead is excreted from the body, whereas the fraction that is not excreted is initially distributed to the blood and soft tissues for ~30 days, and then redistributed to the bone. Once in bone, the half-life of lead can be as long as 30 years. Excretion of lead occurs primarily in urine and feces; fecal excretion accounts for approximately one-third of total excretion of absorbed lead. As a result of the shorter and dominant half-life of lead in blood, a quasisteady state between blood lead, excretion of lead, and partitioning of lead to the bone is achieved following 3–6 months of continuous exposure (eg, daily) to lead. Blood lead concentrations may remain approximately constant with continued exposure while lead can continue to bioaccumulate in bone. As a result, lead levels in bone increase with age throughout an individual's lifetime.

In adults, >90% of the total body burden of lead is found in the skeleton; whereas, bone accounts for ~70% of the lead body burden in children. This large pool of lead in bone can serve to maintain blood lead levels (ie, serve as an internal source of exposure) long after external exposure to lead has ended. Bone lead stores can contribute substantially to blood lead, and maternal bone lead can be transferred to the fetus during pregnancy, and to breast milk and nursing infants during lactation. Transfer of bone lead stores to blood can also be accelerated during other physiological or pathological states of bone loss, such as osteoporosis that occurs in disease or with advanced age. Hence, lead stored in bone from external exposures that occurred years, even decades, earlier

may serve as an internal source of lead exposure later in life in the individual in whom the lead has accumulated or, in the case of pregnant or nursing females who have previously accumulated lead, to the fetus or nursing infant.

There is evidence indicating that certain human subpopulations may have greater susceptibility than others to bioaccumulate lead. Specifically, there is evidence indicating that infants and children, African Americans, and individuals that have one of three genes are more susceptible to bioaccumulating lead. Regarding infants and children, results from both animal (6–8) and human studies (9–11) indicate that bioaccumulation of lead in infants and children undergoing rapid growth is greater than it is in adults.

Regarding African Americans, studies have shown that African Americans have increased risk for having higher blood lead levels compared to Caucasians, even after controlling for income and urban status (11,12). It is currently unknown, however, what factors contribute to this disparity. Nonetheless, there is evidence suggesting that higher blood lead levels in African Americans are due to ethnic–race differences in bone and calcium metabolism (13,14); slower rates of bone turnover, lower urinary calcium excretion; diminished rates of bone mineralization and bone formation, increased circulating parathyroid hormone; differences in the vitamin D endocrine system (15); and greater calcium absorption and deposition (16). Because lead behaves similarly to calcium, and is modulated by the same ions and hormones, the above differences may cause African Americans to accumulate relatively larger quantities of lead in the bone than Caucasians, potentially making African Americans more susceptible to bioaccumulating lead.

At least three polymorphic genes have been identified that may potentially increase the absorption and bioaccumulation of lead in humans that have any one of the genes (1,17). The first gene is the gene coding for delta-aminolevulinic acid dehydrates (ALAD), an enzyme of heme biosynthesis, which exists in two polymorphic forms. The resulting isozymes have been shown to affect the blood and bone lead levels in human populations. The effects of ALAD in lead intoxication have also been studied in laboratory mice that differ in the genetic dose for this enzyme. The second gene is the vitamin D receptor (VDR) gene. The VDR is involved in calcium absorption through the gastrointestinal tract and into calcium-rich tissues, eg, bone. Recent findings suggest that VDR polymorphism may influence the accumulation of lead in bone (1,17). The third gene that may influence lead is the hemochromatosis gene coding for the HE protein.

4. Toxicity

The toxicity of lead to humans is well known and characterized. Comprehensive discussions on the toxicity of lead to humans are available (1,4,5,18), and summarized here. Human health effects associated with exposure to lead and its compounds include, but are not limited to, toxicity to the central and peripheral nervous systems, developmental toxicity, renal (kidney) toxicity, cancer, hypertension, impaired hearing acuity, impaired hemoglobin synthesis (anemia), and male reproductive impairment. When compared to adults, infants and children

are more susceptible to lead exposure and are more sensitive to the neurotoxic effects of lead.

The toxicity of lead to the kidney is manifested by chronic nephropathy and appears to result from long-term, relatively high dose exposure to lead. It appears that the toxicity of lead to the kidney results from effects on the cells lining the proximal tubules. Lead inhibits the metabolic activation of vitamin D in these cells, and induces the formation of dense lead–protein complexes, causing a progressive destruction of the proximal tubules. Lead has been implicated in causing hypertension as a result of a direct action on vascular smooth muscle, as well as the toxic effects on the kidneys.

Lead-induced anemia results from impairment of heme biosynthesis and acceleration of red blood cell destruction. Lead-induced inhibition of heme biosynthesis is caused by inhibition of 5-aminolevulinic acid dehydratase and ferrochelatase, which starts to occur at blood lead levels of 10–20 μg/dL and 25–30 μg/dL, respectively. Anemia, however, is not manifested until higher levels are reached.

The most severe neurological effect of lead in adults or children is lead encephalopathy, which is a general term to describe various diseases that affect function of the central nervous system. Early symptoms that may develop within weeks of initial exposure include irritability, poor attention span, headache, muscular tremor, loss of memory, and hallucinations. The condition may then worsen, sometimes abruptly, to delirium, convulsions, paralysis, coma, and death. In adults, exposure to lead has often been associated with other signs of toxicity to the central nervous system. Numerous case reports and small cohort studies that describe a higher incidence of these symptoms, including malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libido, dizziness, weakness, and paresthesia at blood lead levels that range from ~40 to 120 μg/dL following acute-, intermediate-, and chronic-duration occupational exposure. In addition, numerous studies have reported neuropsychological effects in lead workers. Blood lead levels in these studies ranged between 40 and 80 μg/dL. For example, lead workers exhibited greater levels of conflict in interpersonal relationships compared with unexposed workers. In another study, lead workers (45–60 μg/dL) performed much worse than workers with lower PbB on neurobehavioral tests, with general performance on cognitive and visual–motor coordination tasks and verbal reasoning ability most markedly impaired.

The toxicity of lead to the central nervous systems of infants and children is well known. These effects are primarily neurobehavioral in nature, and are manifested in the form of impaired intellectual function. Results of some recent studies indicate that the lead-induced neurobehavioral effects in children occur when blood lead concentrations are <10 μg/dL (4). Other studies suggest that there may be no threshold for the effects of lead on intellectual function (4).

In the peripheral nervous system, motor axons are the principal target for lead. Lead-induced pathological changes in these fibers include segmental demyelination and axonal degeneration. Extensor muscle palsy with wrist drop or ankle drop is the classic clinical manifestation of this toxicity. Lead-induced central nervous system toxicity, or lead encephalopathy, is the most serious manifestation of lead toxicity. It is more common in children than in adults.

The toxicity is believed to arise from demyelination and nerve degeneration. Early signs of lead encephalopathy include clumsiness, vertigo, ataxia, falling, headaches, insomnia, restlessness, and irritability. If untreated, delerium, tonic–clonic convulsions, mental retardation, and even death may ensue.

Lead is known to cause reproductive and developmental toxicity. Decreased sperm counts and abnormal sperm development have been reported in male workers heavily exposed to lead. Increased incidences of spontaneous abortion have been reported in female lead workers as well as in the wives of male lead workers. Lead crosses the placenta and has been found to cause irreversible neurologic impairment to the fetus at maternal blood levels as low as 15–20 μg/dL.

5. Detection and Treatment of Lead Poisoning

The classic clinical manifestations of lead poisoning include gastrointestinal disturbances (eg, vomiting, diarrhea, constipation, or intestinal spasms), anemia, renal failure, hyperuricemia or gout, hypertension, reproductive impairment, peripheral nerve injury manifested by wrist or ankle drop, and neuropsychological impairment. In children, the classic signs are delayed growth and deficits in psychometric intelligence, speech and language processing, attention, and classroom performance. Overt lead encephalopathy may occur in children having high lead exposure. The gastrointestinal syndrome is more prevalent in adults; the central nervous system syndrome is usually more common in children. Because all of these symptoms occur with other illnesses, misdiagnosis of lead poisoning may occur unless it is suspected and a detailed patient history is obtained.

More specific indications of lead poisoning are increased blood and urine levels of lead or 5-aminolevulinic acid [106-60-5]. Measurement of erythrocytic protoporphyrin or zinc protoporphyrin has been described as being a diagnostic test in the detection of lead poisoning. However, as epidemiological and experimental data continually indicate that the toxic effects of lead occur at blood levels lower than previously believed, these protoporphyrin assays are not sensitive enough for reliable quantification of the lower levels of lead believed to be clinically significant. Protoporphyrin assays are more useful as indicators of recent, high lead exposure. Measurement of bone lead content is a more definitive approach for assessing chronic lead exposure and total body lead burden. X-ray fluorescence, an analytical technique for determining bone lead content, is a noninvasive and relatively rapid approach for assessing chronic lead exposure and total body burden of lead. It is not useful for determining acute lead exposure. From a practical standpoint, blood lead is most useful in determining exposures.

The treatment of lead poisoning has been extensively reviewed (5,18). Lead in the blood is removed by administration of chelating agents, eg, *meso*-2,3-dimercaptosuccinic acid [304-55-2], $C_4H_6O_4S_2$, ethylenediaminetetraacetic acid [60-00-4] (EDTA), $C_{10}H_{16}N_2O_8$, dimercaprol [59-51-9], $C_3H_8OS_2$, or D-penicillamine [52-67-5], $C_5H_{11}NO_2S$. These agents form stable lead chelates, which are then excreted in the urine or feces. Chelation therapy, however, should not be used indiscriminately because there are potential hazards associated with the use of these agents. Other treatment measures include proper nutrition, eg,

lead absorption is facilitated by iron deficiency, and removal of the patient from the source of lead to prevent continued exposure.

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