

## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO LEAD IN THE UNITED STATES

Lead is a naturally occurring metal found in the Earth's crust at about 15–20 mg/kg. In comparison to the two most abundant metals in the Earth, aluminum and iron, lead is a relatively uncommon metal. Lead rarely occurs in its elemental state, but rather its +2 oxidation state in various ores throughout the earth. The most important lead containing ores are galena (PbS), anglesite (PbSO<sub>4</sub>), and cerussite (PbCO<sub>3</sub>). The world's reserves of lead are estimated at  $7.1 \times 10^7$  tons, with over one third located in North America. Levels of lead in the environment (not contained in ore deposits) have increased over the past three centuries as a result of human activity. Human exposure to lead is common and results from the many uses of this metal due to its exceptional properties. The largest industrial use of lead today is for the production of lead batteries, largely used in the automobile industry. Other uses of lead include the production of lead alloys, use in soldering materials, shielding for x-ray machines, and in the manufacture of corrosion and acid resistant materials used in the building industry (see Chapter 5 for more details regarding lead usage).

The greatest potential for human exposure to lead arises from its previous use as an additive in gasoline, which resulted in its widespread dispersal throughout the environment, and its use as a pigment in both interior and exterior paints. Although the use of lead as a gasoline additive has been gradually phased out and completely banned by 1995 in the United States and its use in paints was banned in 1978, human exposure to lead continues because unlike organic chemicals released to the environment, lead does not degrade to other substances. Leaded paint is still prevalent in many older homes in the United States, and peeling or flaking paint contributes to indoor and outdoor dust levels. Prior to World War II, lead-arsenic compounds were used as pesticides, especially in orchards. Because lead does not degrade and is strongly absorbed to soil, the lead released from past uses still remains in the soil. Since the ban on the use of leaded gasoline took effect, lead emissions to the atmosphere have decreased significantly. According to the EPA, atmospheric emissions of lead decreased 93% over the 21-year period of 1982–2002. The atmospheric concentration of lead varies greatly, with the highest levels observed near stationary sources such as lead smelters. Levels of lead in ambient air range from about  $7.6 \times 10^{-5}$   $\mu\text{g}/\text{m}^3$  in remote areas such as Antarctica to  $>10$   $\mu\text{g}/\text{m}^3$  near point sources. The EPA national ambient air quality standard for lead is  $1.5$   $\mu\text{g}/\text{m}^3$ .

## 2. RELEVANCE TO PUBLIC HEALTH

The amount of lead contained in pipes and plumbing fittings have been strictly regulated since 1988; however, human exposure to lead from drinking water still occurs as a consequence of leaching of lead from corroding pipes and fixtures or lead containing solder. Based on several data sets, it is estimated that <1% of the public water systems in the United States have water entering the distribution system with lead levels above 5 µg/L. Copper pipes have replaced lead pipes in most residential plumbing. Section 1417 of the Safe Drinking Water Act, which took effect in August 1998, requires that all pipes, fixtures, and solder be lead-free. However, lead-free means that solders and flux may not contain >0.2% lead, while pipes, pipe fittings, and well pumps may not contain >8% lead. The EPA requires public water distribution systems to reduce the corrosivity of water if >10% of the water samples exceed 15 µg/L of lead.

Occupational exposure to lead occurs for workers in the lead smelting and refining industries, battery manufacturing plants, steel welding or cutting operations, construction, rubber products and plastics industries, printing industries, firing ranges, radiator repair shops, and other industries requiring flame soldering of lead solder. In these occupations, the major routes of lead exposure are inhalation and ingestion of lead-bearing dusts and fumes. In the smelting and refining of lead, mean concentrations of lead in air can reach 4,470 µg/m<sup>3</sup>; in the manufacture of storage batteries, mean airborne concentrations of lead from 50 to 5,400 µg/m<sup>3</sup> have been recorded; and in the breathing zone of welders of structural steel, an average lead concentration of 1,200 µg/m<sup>3</sup> has been found.

Certain populations may be exposed to lead from other sources. Several non-western folk medicines can contain substantial levels of lead. Lead glazing that is applied to some pottery and ceramic ware may leach lead into foods or liquids that are stored in them (see Section 6.4.5 for more information). The FDA regulates the amount of leachable lead from food containers (see Table 8-1).

Blood lead levels (PbB) in the general population of the United States have been decreasing over the past 3 decades as regulations regarding lead paint, leaded fuels, and lead-containing plumbing materials have reduced exposure. PbBs measured as a part of the National Health and Nutrition Examination Surveys (NHANES) indicated that from 1976 to 1991, the mean PbBs of the U.S. population aged from 1 to 74 years dropped 78%, from 12.8 to 2.8 µg/dL. The prevalence of PbBs ≥10 µg/dL also decreased sharply from 77.8 to 4.3%. Data from NHANES III, phase II (1991–1994) showed that 4.4% of children aged 1–5 years had PbBs ≥10 µg/dL, and the geometric mean PbBs for children 1–5 years old was 2.7 µg/dL. From the most recent sampling data conducted for 1999–2002, 1.6% of children aged 1–5 years had PbBs ≥10 µg/dL, with a geometric mean PbBs of 1.9 µg/dL (see Section 6.5 for greater

## 2. RELEVANCE TO PUBLIC HEALTH

detail). The Centers for Disease Control and Prevention (CDC) action level for children  $\leq 7$  years of age is 10  $\mu\text{g}/\text{dL}$ . A tiered approach is recommended for managing lead-exposed children (see Section 3.9).

Analysis of lead in whole blood is the most common and accurate method of assessing lead exposure. Erythrocyte protoporphyrin (EP) tests can also be used, but are not as sensitive at low blood lead levels ( $\leq 20 \mu\text{g}/\text{dL}$ ); the screening test of choice is blood lead levels. X-ray fluorescence techniques (XRF) can be used for the determination of lead concentration in bones. Lead partitions to the bone over a lifetime of exposure; therefore, bone lead measurements are a good indicator of cumulative exposure, whereas measurements of lead in blood are more indicative of recent exposure. However, XRF is primarily used in the research area and is not widely available (see Sections 3.3 and 3.6.1 for greater detail).

### 2.2 SUMMARY OF HEALTH EFFECTS

An enormous amount of information is available on the health effects of lead on human health. In fact, the toxic effects of lead have been known for centuries, but the discovery in the past few decades that levels of exposure resulting in relatively low levels of lead in blood (e.g.,  $<20 \mu\text{g}/\text{dL}$ ) are associated with adverse effects in the developing organism is a matter of great concern. Most of the information gathered in modern times regarding lead toxicity comes from studies of workers from a variety of industries and from studies of adults and children in the general population. The most sensitive targets for lead toxicity are the developing nervous system, the hematological and cardiovascular systems, and the kidney. However, due to the multi-modes of action of lead in biological systems, lead could potentially affect any system or organs in the body.

Studies of lead workers suggest that long-term exposure to lead may be associated with increased mortality due to cerebrovascular disease. The same was found in a study of adults from the general population who were hospitalized for lead poisoning during childhood. Population studies suggest that there is a significant association between bone-lead levels and elevated blood pressure. Blood lead levels (PbBs) also have been associated with small elevations in blood pressure. Between the two biomarkers, bone lead appears to be the better predictor. Lead also affects kidney functions; glomerular filtration rate appears to be the function affected at the lowest PbBs. Decreased glomerular filtration rate has been consistently observed in populations with mean PbB  $<20 \mu\text{g}/\text{dL}$  and two studies have reported effects at PbB  $<10 \mu\text{g}/\text{dL}$ . Lead may alter glomerular filtration rate by several mechanisms.

## 2. RELEVANCE TO PUBLIC HEALTH

Lead has long been known to alter the hematological system by inhibiting the activities of several enzymes involved in heme biosynthesis. Particularly sensitive to lead action is  $\delta$ -aminolevulinic acid dehydratase (ALAD). Inhibition of ALAD activity occurs over a wide range of PbBs beginning at  $<10 \mu\text{g/dL}$ . The anemia induced by lead is primarily the result of both inhibition of heme synthesis and shortening of erythrocyte lifespan, but lead also can induce inappropriate production of the hormone erythropoietin leading to inadequate maturation of red cell progenitors, which can contribute to the anemia.

A recent study in children 8–10 years of age suggested that lead accelerates skeletal maturation, which might predispose to osteoporosis in later life. Lead also has been associated with increased occurrence of dental caries in children and periodontal bone loss, which is consistent with delayed mineralization in teeth observed in studies in animals. Current mean PbBs in these cohorts were  $<5 \mu\text{g/dL}$ ; however, the cross-sectional nature of the studies precluded assessment of the exposure history.

Changes in circulating levels of thyroid hormones, particularly serum thyroxine ( $T_4$ ) and thyroid stimulating hormone (TSH), generally occurred in workers having mean PbB  $\geq 40\text{--}60 \mu\text{g/dL}$ . Altered serum levels of reproductive hormones, particularly follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone have been observed at PbB  $\geq 30\text{--}40 \mu\text{g/dL}$ . Lead also has been shown to decrease circulating levels of the active form of vitamin D, 1,25-dihydroxyvitamin D, in children with moderate to high PbB ( $30\text{--}60 \mu\text{g/dL}$ ), but not in children with low to moderate PbB (average lifetime PbB between 4.9 and 23.6  $\mu\text{g/dL}$ , geometric mean, 9.8  $\mu\text{g/dL}$ ). Normal levels of vitamin D are important for maintaining calcium homeostasis.

Altered immune parameters have been described in lead workers with PbB in the range of  $30\text{--}70 \mu\text{g/dL}$ . Reported effects included changes in some T-cell subpopulations, response to T-cell mitogens, and reduced chemotaxis of polymorphonuclear leukocytes. Several studies of children reported significant associations between PbB and increases in serum IgE levels. IgE is the primary mediator for type-I hypersensitivity and is involved in various allergic diseases such as asthma. These findings in children along with results from studies in rodents exposed *in utero* have led some to suggest that lead may be a risk factor for childhood asthma, although a recent relatively large study (4,634 children) found that PbB was less a predictor of asthma than was race.

Exposure to high amounts of lead resulting in PbBs of  $100\text{--}120 \mu\text{g/dL}$  in adults or  $70\text{--}100 \mu\text{g/dL}$  in children produce encephalopathy, a general term that describes various diseases that affect brain function.

## 2. RELEVANCE TO PUBLIC HEALTH

Symptoms develop following prolonged exposure and include dullness, irritability, poor attention span, epigastric pain, constipation, vomiting, convulsions, coma, and death. Lead poisoning in children can leave residual cognitive deficits that can be still detected in adulthood. Neurobehavioral effects including malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libido, dizziness, weakness, and paresthesia have been reported in lead workers with PbBs in the range of 40–80 µg/dL. Also, PbBs between 40 and 80 µg/dL have been associated with neuropsychological effects in lead workers. A recent study of lead workers reported that higher tibia lead was associated with increased prevalence and severity of white matter lesions, as assessed by brain MRI. Studies of older populations with current mean PbBs <10 µg/dL have reported associations between PbB and/or bone lead and poorer performance in neurobehavioral tests. Lead also has been shown to affect nerve conduction velocity and postural balance in workers with PbB in the range of 30–60 µg/dL. Alterations of somatosensory evoked potentials also have been reported in lead workers with mean PbBs in the range of 30–50 µg/dL.

As previously mentioned, one of the major concerns regarding lead toxicity is the cognitive and neurobehavioral deficits that are observed in children exposed to lead. Prospective studies have provided the greatest amount of information. Analyses of these and other studies suggest that an IQ decline of 1–5 points is associated with an increase in PbB of 10 µg/dL. Of special interest and concern are the results of recent studies that have reported neurobehavioral deficits in children associated with PbBs <10 µg/dL and an apparent lack of threshold down to even the lowest PbBs recorded in these studies. Lead also has caused neurobehavioral alterations in developing animals, and at PbBs similar to those reported in children. Studies in animals, particularly in monkeys, have provided key information for the interpretation of a cognitive basis for IQ changes. Studies of children also have shown associations between PbB and growth, delayed sexual maturation in girls, and decreased erythropoietin production.

Some studies of humans occupationally or environmentally exposed to lead have observed associations between PbB and abortion and preterm delivery in women and alterations in sperm and decreased fertility in men. On the other hand, there are several studies that found no significant association between lead exposure and these end points. At least for the effects in males, the threshold PbB appears to be in the range of 30–40 µg/dL. Studies have shown that lead can affect the association of protamines with DNA in sperm cells from exposed males. Lead does so by competing or reducing zinc in protamine P2 *in vivo*, which would leave sperm chromatin and DNA open to damage from other exposures.

*In vitro* mutagenicity studies in microorganisms have yielded mostly negative results for lead, but lead is a clastogenic agent, as shown by the induction of chromosomal aberrations, micronuclei and by sister

## 2. RELEVANCE TO PUBLIC HEALTH

chromatid exchanges in peripheral blood cells from lead workers. Studies of cancer in lead workers have been inconclusive. A meta-analysis of eight major occupational studies on cancer mortality or incidence in workers with high lead exposure concluded that there is some limited evidence of increased risk of lung cancer and stomach cancer, although there might have been confounding with arsenic exposure in the study with highest relative risk of lung cancer. The results also showed a weak evidence for an association with kidney cancer and gliomas. In the only study of the general population available, there was suggestive evidence for an increase risk of cancer mortality in women, but not men, with a threshold PbB of 24 µg/dL. This study used data from the Second National Health and Nutrition Survey (NHANES II) Mortality Study. Lead has produced primarily renal tumors in rodents by a mechanism not yet elucidated. Some nongenotoxic mechanisms that have been proposed for lead-induced cancer include inhibition of DNA synthesis and repair, alterations in cell-to-cell communication, and oxidative damage.

The Department of Health and Human Services (DHHS) has determined that lead and lead compounds are reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from animal studies. The EPA has determined that lead is a probable human carcinogen based on sufficient evidence from studies in animals and inadequate evidence in humans. The International Agency for Research on Cancer (IARC) has determined that inorganic lead is probably carcinogenic to humans based on sufficient evidence from studies in animals and limited evidence of carcinogenicity from studies in humans. IARC also determined that organic lead compounds are not classifiable as to their carcinogenicity in humans based on inadequate evidence from studies in humans and animals.

A discussion of the most sensitive end points for lead toxicity, neurodevelopmental, cardiovascular/renal, and hematological, is presented below. The reader is referred to Chapter 3, Health Effects, for information on additional effects.

**Neurodevelopmental Effects.** Lead can impair cognitive function in children and adults, but children are more vulnerable than adults. The increased vulnerability is due in part to the relative importance of exposure pathways (i.e., dust-to-hand-mouth) and differences in toxicokinetics (i.e., absorption of ingested lead). Although the inhalation and oral routes are the main routes of exposure for both adults and children, children are more likely to have contact with contaminated surfaces due to playing on the ground and to hand-to-mouth activities. Furthermore, children absorb a larger fraction of ingested lead than adults. However, perhaps more important is the fact that the developing nervous system is especially susceptible to lead toxicity. During brain development, lead interferes with the

## 2. RELEVANCE TO PUBLIC HEALTH

trimming and pruning of synapses, migration of neurons, and neuron/glia interactions. Alterations of any of these processes may result in failure to establish appropriate connections between structures and eventually in permanently altered functions. Because different brain areas mature at different times, the final outcome of the exposure to lead during development (i.e., *in utero* vs. pediatric exposure) will vary depending on the time of exposure. This has been demonstrated in studies in animals. The time of exposure-specific response appears to have contributed to the failure to identify a “behavioral signature” of lead exposure in children. Other factors that may affect individual vulnerability are certain genetic polymorphisms, such as that for the vitamin D receptor, the lead-binding enzyme ALAD, or the APOE genotype. One important additional factor shown to influence the toxicity of lead is the characteristics of the child’s rearing environment, a modifying factor. It has been argued that effect modification is a property of a true association and should be distinguished from confounding. Effect modification can explain inconsistencies in findings, and if it exists, failure to address it will lead to an error in inference. For example, if social class is an effect modifier of the association between PbB and IQ, and differs between two cohorts, the strength of the association based on these two studies will necessarily be different.

Despite the many factors that can potentially work against finding agreement among studies, the preponderance of the evidence indicates that lead exposure is associated with decrements in cognitive function. Meta-analyses conducted on cross-sectional studies or a combination of cross-sectional and prospective studies suggest that an IQ decline of 1–5 points is associated with an increase in PbB of 10 µg/dL. Most importantly, no threshold for the effects of lead on IQ has been identified. This has been confirmed by a series of recent studies in children that found significant inverse associations between cognitive function and PbBs <10 µg/dL. Moreover, these and other studies have shown that the slope of the lead effects on cognitive variables is steeper (the effect is greater) at lower than at higher PbBs (supra-linear dose-response relationship). However, there is not complete agreement on the interpretation of the lack of linearity in the dose-response relationship among the scientific community. Some have argued, based on a theoretical statistical analysis, that the supra-linear slope is a required outcome of correlations between data distributions where one is log-normally distributed and the other is normally distributed. Perhaps the strongest evidence for nonlinearity is provided by an international pooled analysis of seven prospective studies (details in Section 3.2.4). After testing several models, these investigators determined that the shape of the dose-response was nonlinear insofar as the quadratic and cubic terms for concurrent PbB were statistically significant ( $p < 0.001$ ,  $p = 0.003$ , respectively). Additional support for the steeper slope at low PbB was provided by plotting the individual effects estimates for each of the seven cohorts, adjusted for the same covariates. The plot showed that the studies with the lowest mean PbBs had a

## 2. RELEVANCE TO PUBLIC HEALTH

steeper slope compared with studies with higher PbBs. Yet further evidence for nonlinearity was presented when the data were divided at two cut-points *a priori* (maximal PbB above and below 10 µg/dL and above and below 7.5 µg/dL). The investigators then fit separate linear models to the data in each of those ranges and compared the PbB coefficients for the concurrent PbB index. The stratified analyses showed that the effects estimate for children with maximal PbB <7.5 µg/dL was significantly greater ( $p=0.015$ ) than those with a maximal PbB  $\geq 7.5$  µg/dL. Similar results were seen at the cut-off point of 10 µg/dL. A reanalysis of the pooled studies found that a log-linear relationship between PbB and IQ was a better fit within the ranges of PbBs in the studies than was a linear relationship ( $p<0.009$ ). Collectively, the results of the pooled analysis and of additional studies provide suggestive evidence of lead effects on cognitive functions in children at PbBs <10 µg/dL and, possibly as low as 5 µg/dL. It should be stressed, however, that the effects of lead on IQ and other neurobehavioral scores are very small compared with the effects of other factors such as parents' IQ, but is also important to stress that lead exposure, unlike most of those other factors, is highly preventable.

The other aspect that has been questioned regarding the nonlinear shape of the dose-response relationship is the apparent lack of a biological mechanism that could produce this result, and this clearly represents a data need. To explain the nonlinear shape of the dose-response, it was proposed that “the initial damage caused by lead may reflect the disruption of different biological mechanisms than the more severe effects of high exposures that result in encephalopathy or frank mental disability. This might explain why, within the range of exposures not producing overt clinical effects, an increase in PbB beyond a certain level might cause little *additional* impairment in children's cognitive function.”

While measurements of IQ are convenient in that they allow comparison across populations of different demographic and cultural characteristics, and help define the extent of the public health issue, they only partially advance our understanding of the problem of lead-induced behavioral toxicity. It is important to elucidate the underlying basis of the deficits in IQ as well as the behavioral mechanisms that account for them. It was noted that “the answers are critical not only to further define neurobiological mechanisms associated with learning deficits, but also to determine behavioral or neurochemical therapeutic approaches to alleviate them.” Studies in animals have provided answers to some of these questions. Studies in animals have great utility because the possibility of confounding is reduced with the controlled experimental design and genetic factors. In addition, they address specific domains of cognitive function and allow determination of critical periods of exposure. Results of behavioral tests performed primarily in rats and monkeys exposed to lead have suggested that the impaired performance is the result, at least in part, of a combination of distractibility, inability to inhibit inappropriate responding, and perseveration in



## 2. RELEVANCE TO PUBLIC HEALTH

behaviors that are no longer appropriate. Evaluation of children exposed to lead with different subscales of IQ tests in conjunction with assessments of behavior on teacher's rating scales on young school-age children suggest that increased distractibility, impulsivity, short attention span, and inability to follow simple and complex sequences of directions are associated with increased lead body burden. The similarity between neurobehavioral effects in lead-exposed children and in animals, and the fact that the deficits are observed at similar PbBs should stimulate continued research to elucidate the biochemical and morphological substrates that underlie specific behaviors.

Although the decrement of IQ points in children associated with lead exposure is generally small, lead neurotoxicity may have major implications for public health when exposure is considered in terms of large populations and its preventable nature. One study quantified the economic benefits from projected improvements in worker productivity resulting from the reduction in children's exposure to lead in the United States since 1976. Based on data from NHANES (a study designed to provide national estimates of the health and nutritional status of the U.S. civilian noninstitutionalized population aged 2 months and older) and meta-analyses, it was estimated that mean PbBs declined 15.1  $\mu\text{g}/\text{dL}$  between 1976 and 1999 and that IQ scores increased between 0.185 and 0.323 points for each 1  $\mu\text{g}/\text{dL}$  blood lead concentration. It was further estimated that each IQ point raises worker's productivity by 1.76–2.38%, and that the economic benefit for each year's cohort of 3.8 million 2-year-old children ranges from \$110 to \$319 billion. In another study, using an environmentally attributable fraction model, it was estimated that the present value of economic losses in the United States attributable to lead exposure in amounts to \$43.4 billion per year in each annual birth cohort. More recently, one study estimated that mild mental retardation and cardiovascular outcomes resulting from exposure to lead amounts to almost 1% of the global burden of disease, with the highest burden in developing regions.

A related and important issue is whether lead-lowering interventions, such as with chelators, are paralleled by improvement in health outcomes reportedly altered by lead. In one study, improvement in cognitive functions was related to decreases in blood lead but not to chelation treatment. In a multi-center study of 780 children, chelation therapy lowered blood lead by a mean of 4.5  $\mu\text{g}/\text{dL}$  during the 6 months after initiation of treatment, but it did not improve scores on tests of cognition, behavior, or neuropsychological function in children with PbB below 45  $\mu\text{g}/\text{dL}$ . Re-analysis of these data showed that improvement in test scores was associated with greater falls in PbB only in the placebo group. A further evaluation of this cohort showed that chelation therapy lowered blood lead, but produced no benefits in cognitive, behavioral, or neuromotor end points. The conclusion of this series of studies reached by the investigators was that chelation therapy is not indicated in children with moderate blood lead levels.

## 2. RELEVANCE TO PUBLIC HEALTH

Thus, it appears that lead abatement must remain the primary approach in the public health management of lead poisoning.

**Cardiovascular/Renal Effects.** Although lead has been shown to produce various cardiovascular and renal effects in animals, end points of greatest concern for humans at low exposures and low PbB are elevations in systemic blood pressure and decrements in glomerular filtration rate. These effects may be mechanistically related and, furthermore, can be confounders and covariables in epidemiological studies. Decrements in glomerular filtration rate may contribute to elevations in blood pressure, and elevated blood pressure may predispose people to glomerular disease.

**Effects on Blood Pressure.** Numerous covariables and confounders affect studies of associations between PbB and blood pressure, including, age, body mass, race, smoking, alcohol consumption, ongoing or family history of cardiovascular/renal disease, and various dietary factors. Varying approaches and breadth of inclusion of these may account for some of the disparity of results that have been reported. Including confounders in a regression model will attenuate the apparent association between lead exposure and the measured health outcome. Measurement error may also be an important factor. Blood pressure estimates based on multiple measurements or, preferably, 24-hour ambulatory measurements, are more reproducible than single measurements. Few studies have employed such techniques and, when used, have not found significant associations between PbB and blood pressure.

An additional limitation of blood lead studies, in general, is that PbB may not provide the ideal biomarker for long-term exposure to target tissues that contribute a hypertensive effect of lead. Bone lead appears to be a better predictor of lead-induced elevations in blood pressure than PbB. In a recent prospective analysis of the Normative Aging Study, higher tibial lead levels, but not PbBs, were associated with higher systolic blood pressure and abnormalities in electrocardiographic conduction.

Chronic lead exposure increases blood pressure in rats through diverse mechanisms that include alterations in neurohumoral control of peripheral vascular resistance, heart rate, and cardiac output (see Section 3.4.2). Studies conducted in animal models provide strong evidence for the plausibility of lead elevating blood pressure in humans. Meta-analyses of the epidemiological findings have found a persistent trend in the data that supports a relatively weak, but significant association. Quantitatively, this association amounts to an increase in systolic blood pressure of approximately 1 mmHg with each doubling of PbB. The results of more recent epidemiology studies indicate that the lead contribution to elevated blood pressure is more pronounced in middle age than at younger ages. A longitudinal study of

## 2. RELEVANCE TO PUBLIC HEALTH

males, mean age 67 years, found positive associations between systolic blood pressure and bone lead concentrations, and increased risk of hypertension in association with increased bone lead concentration. Based on this study, an increase in patella bone lead from the midpoint of the lowest quintile (12.0  $\mu\text{g/g}$ ) to the highest quintile (53.0  $\mu\text{g/g}$ ) was associated with a 1.71-fold increase in hypertension risk (rate-ratio, 95%; confidence interval [CI], 1.08–2.71). A case-control study of women, ages >55 years, found increased risk of hypertension in association with increased bone lead concentration. In this study, an increase in patella bone lead from 6 to 31  $\mu\text{g/g}$  was associated with a 1.86-fold (odds ratio [OR], 95%; CI, 1.09–3.19) increase in risk of hypertension. A large-scale cross-sectional analysis of the NHANES III data on males and females, age 40–59 years, found increasing risk for hypertension in association with increasing PbB, with higher risks in postmenopausal women than in premenopausal women. Risks of diastolic hypertension for pre- and postmenopausal women, combined, who were in the highest blood lead quartile (mean, 6.4  $\mu\text{g/dL}$ ; range, 3.0–31.1) was predicted to be 3.4-fold higher (OR, 95%; CI, 1.3–8.7) than that of women in the lowest quartile (mean, 1  $\mu\text{g/dL}$ ; range, 0.5–1.6); corresponding risks for postmenopausal women were 8.1 times greater (OR, 95%; CI, 2.6–24.7) (highest vs. lowest quartile). The results of two analyses of the NHANES III data on adult subjects provides evidence for an association between increasing PbB and increasing blood pressure that is more pronounced in blacks than whites. Lead exposures during infancy and childhood (reflected in PbB) have been associated with increased blood pressure and altered responses to acute pressor stresses in childhood. Lead poisoning in childhood has also been associated with hypertension during adulthood in the absence of clinically significant renal disease and discernable elevations in PbB.

***Effects in Renal Glomerular Filtration.*** Classic lead nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, and interstitial fibrosis and related functional deficits, including enzymuria, low- and high-molecular weight proteinuria, impaired transport of organic anions and glucose, and depressed glomerular filtration rate. In humans, the overall dose-effect pattern suggests an increasing severity of nephrotoxicity associated with increasing PbB, with effects on glomerular filtration evident at PbBs below 10  $\mu\text{g/dL}$ , enzymuria and proteinuria becoming evident above 30  $\mu\text{g/dL}$ , and severe deficits in function and pathological changes occurring in association with PbB exceeding 50  $\mu\text{g/dL}$ . Thus, the renal effects of greatest concern, at low exposures (i.e., low PbB), are on glomerular filtration.

The results of epidemiological studies of general populations have shown a significant effect of age on the relationship between glomerular filtration rate (assessed from creatinine clearance of serum creatinine concentration) and PbB (see Section 3.2.2. Renal Effects). Furthermore, as noted previously, hypertension can be both a confounder in studies of associations between lead exposure and creatinine

## 2. RELEVANCE TO PUBLIC HEALTH

clearance as well as a covariable with lead exposure. Another important complication in the assessment of associations between lead exposure and adverse effects on glomerular filtration is the potential confounding effect of decrements in glomerular filtration rate and increased lead body burden. Lead exposure has also been associated with increases in glomerular filtration rate. This may represent a benign outcome or a potentially adverse hyperfiltration, which may contribute to subsequent adverse renal effects. Increases in glomerular filtration rate have been observed in the early phases of development of chronic renal injury in rats. When age and other covariables that might contribute to glomerular disease are factored into the dose-response analysis, decreased glomerular filtration rate has been consistently observed in populations that have average PbBs <20 µg/dL, with some studies finding effects at PbBs <10 µg/dL (see Section 3.2.2, Table 3-4). Two studies provide evidence for an effect at lead concentrations below 10 µg/dL. A longitudinal study found a significant relationship between increasing serum creatinine concentration and increasing PbB below 10 µg/dL. A cross-sectional analysis of data from the NHANES III found increased risk of chronic renal disease (defined as severely depressed glomerular filtration rate) in association with PbB <6 µg/dL. The confounding and covariable effects of hypertension are also relevant to the interpretation of the regression coefficients reported in these studies. Given the evidence for an association between lead exposure and hypertension, and that decrements in glomerular filtration rate can be a contributor to hypertension, it is possible that the reported hypertension-adjusted regression coefficients may underestimate the actual slope of the PbB relationship with serum concentration of creatinine or creatinine clearance.

**Hematological Effects.** The adverse hematological effects of lead are mainly the result of its perturbation of the heme biosynthesis pathway. The activity of ALAD, an enzyme occurring early in the heme synthesis pathway, is negatively correlated with PbBs between 5 and 95 µg/dL. Although inhibition of ALAD occurs at very low exposure levels, there is some controversy as to the toxicological significance of a depression in ALAD activity in the absence of a detectable effect on hemoglobin levels. Nevertheless, because the impairment of heme synthesis has a far-ranging impact not limited to the hemopoietic system, there is concern that developing organisms might be particularly susceptible.

A potential consequence of the inhibition of heme synthesis is a decreased formation of mixed function oxidases in the liver resulting in impaired metabolism of endogenous compounds, as well as impaired detoxification of xenobiotics. Mitochondrial cytochrome oxidase is another heme-requiring protein that could be affected by heme synthesis inhibition. In addition, tryptophan pyrrolase, a hepatic heme-requiring enzyme system, is inhibited via the reduction in the free hepatic heme pool. This could ultimately lead to increased levels of the neurotransmitter serotonin in the brain and increased aberrant

## 2. RELEVANCE TO PUBLIC HEALTH

neurotransmission in serotonergic pathways. Inhibition of heme synthesis also results in increased levels of  $\delta$ -aminolevulinic acid (ALA), which has a structure similar to that of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and therefore, interferes with GABA neurotransmission. Finally, a prospective study of children with moderate PbB (25–40  $\mu\text{g}/\text{dL}$ ) and hemoglobin levels within normal limits found that serum erythropoietin (EPO) was positively associated with PbB at ages 4.5 and 6.5 years, but the magnitude of the association gradually declined from 4.5 to 12 years. EPO is a glycoprotein hormone produced in the kidney that regulates both steady-state and accelerated erythrocyte production. This suggested that in nonanemic children with moderate PbB, hyperproduction of EPO is necessary to maintain normal hemoglobin concentrations. The decline in slope with age suggested that the compensatory mechanism gradually begins to fail due to direct lead-induced inhibition of EPO production or indirectly through toxic effects of lead on the kidney. Inhibition of EPO production may contribute to lead-induced anemia. Anemia occurs at PbBs of  $\geq 20 \mu\text{g}/\text{dL}$ .

### 2.3 LEAD DOSE-RESPONSE RELATIONSHIPS

MRLs were not derived for lead because a clear threshold for some of the more sensitive effects in humans has not been identified. In addition, deriving an MRL would overlook the significant body of PbB literature. These data suggest that certain subtle neurobehavioral effects in children may occur at very low PbBs. In lieu of MRLs, ATSDR has developed a framework to guide decisions at lead sites. This approach utilizes site-specific exposure data to estimate internal doses as measured by PbBs (see Appendix D).

Epidemiological studies and clinical observations provide evidence for a progression of adverse health effects of lead in humans that occur in association with PbBs ranging from  $<10$  to  $>60 \mu\text{g}/\text{dL}$  (Table 2-1). At the low end of the blood lead concentration range, adverse effects include delays and/or impaired development of the nervous system, delayed sexual maturation, neurobehavioral effects, increased blood pressure, depressed renal glomerular filtration rate, and inhibition of pathways in heme synthesis. Although fewer studies have examined associations between health outcomes and bone lead concentrations, recent studies provide evidence for adverse effects occurring in association with bone lead concentrations in excess of  $10 \mu\text{g}/\text{g}$  (e.g., cardiovascular/renal, neurobehavioral effects).

The timing of exposure, in addition to the exposure intensity, appears to be an important variable in the exposure-response relationship for lead. Exposures that occur during pre- and postnatal development, which result in PbBs of  $10 \mu\text{g}/\text{dL}$  or less, produce delays or impairments of neurological and sexual

## 2. RELEVANCE TO PUBLIC HEALTH

**Table 2-1. Blood and Bone Lead Concentrations Corresponding to Adverse Health Effects**

Age	Effect	Blood lead <sup>a</sup> (µg/dL)	Bone lead <sup>a</sup> (µg/g)
Children	Depressed ALAD	<5	ND
Children	Neurodevelopmental effects	<10	ND
Children	Sexual maturation	<10	ND
Children	Depressed vitamin D	>15	ND
Children	Elevated EP	>15	ND
Children	Depressed NCV	>30	ND
Children	Depressed hemoglobin	>40	ND
Children	Colic	>60	ND
Adults (elderly)	Neurobehavioral effects	>4	>30
Adults	Depressed ALAD	<5	ND
Adults	Depressed GFR	<10	>10
Adults	Elevated blood pressure	<10	>10
Adults	Elevated EP (females)	>20	ND
Adults	Enzymuria/proteinuria	>30	ND
Adults	Peripheral neuropathy	>40	ND
Adults	Neurobehavioral effects	>40	ND
Adults	Altered thyroid hormone	>40	ND
Adults	Reduced fertility	>40	ND
Adults	Depressed hemoglobin	>50	ND

<sup>a</sup>Concentration range associated with effect.

ALAD =  $\delta$ -aminolevulinic acid dehydratase; EP = erythrocyte protoporphyrin; GFR = glomerular filtration rate; NCV = nerve conduction velocity; ND = no data

## 2. RELEVANCE TO PUBLIC HEALTH

development. Cognitive deficits, hypertension, and depressed glomerular filtration rate have been observed in older adults (>60 years and/or postmenopause) in association with PbBs <10 µg/dL. This may reflect a higher vulnerability with age and/or the effects of cumulative life-time exposures that are less evident in younger populations that have lower time-integrated exposures.

The epidemiological literature provides a basis for associating specific biomarkers (e.g., PbB, bone lead concentration) with adverse health effects. Prediction of health outcomes that might result from any given environmental exposure requires an understanding of the relationships between environmental exposure (level, frequency, duration), human physiology and behaviors that result in intake of lead (e.g., ingestion of dust, drinking water, inhalation), and lead biokinetics. Models that predict PbBs corresponding to specific exposure scenarios have been used in this context for the purpose of assessing lead health risks. Two general approaches have been explored: (1) integrated exposure-biokinetics models that simulate lead exposure, intake, absorption, tissue distribution, and excretion of lead in humans; and (2) slope factor models that predict PbB based on an empirically-derived linear parameter relating exposure level, or rate of lead absorption, to PbB. Descriptions of exposure-biokinetics and slope factor models that have been used or have potential use in assessing exposure-effect relationships in human populations are described in Section 3.3.5 and in Appendix D.