CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Lead (Pb) is an element that is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world. A major source of Pb in the U.S. environment has historically been anthropogenic emissions to the atmosphere from combustion of leaded gasoline, which was phased out of use after 1973 and then banned in 1995 (with the exception of fuels for piston-driven aircraft) (EPA 1996a). Pb continued to be used as an anti-knock agent in National Association for Stock Car Auto Racing (NASCAR) fuels until it was phased out beginning in 2008. Deteriorating Pb-based paints from weathered surfaces (which produce highly concentrated Pb debris and dusts) in older housing stock (pre-1978) continues to be a source of childhood Pb poisoning in the United States (CDC 1991, 2012d). The combination of corrosive water and Pb pipes or Pb-soldered joints in either the distribution system or individual houses can create localized zones of high Pb water concentrations (EPA 1989b, 2007a; Hanna-Attisha et al. 2016). Other anthropogenic sources of Pb have included mining and smelting of ore; manufacture of and use of Pb-containing products (e.g., Pb-based paints, pigments, and glazes; electrical shielding; plumbing; storage batteries; solder; and welding fluxes); manufacture and application of Pb-containing pesticides; combustion of coal and oil; and waste incineration.

Pb does not degrade in the environment, although it can exist in various chemical forms (see Section 5.4 for a more detailed discussion of the environmental fate of Pb). Particulate matter containing Pb can be transported through air, water, and soil. In general, atmospheric deposition is the largest source of Pb found in soils not impacted by other local non-air sources (e.g., dust from deteriorating leaded paint). Pb is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for Pb. Pb adsorbs strongly to most soils, which limits the rate of leaching. Soil acidity (pH) and composition are the most important factors affecting solubility, mobility, and phytoavailability of Pb in soil. Other conditions that increase Pb mobility in soil are reducing conditions and high chloride content.

The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. Pb has also been found in a variety of other consumer products including storage batteries, solders, pottery glazes, leaded crystal glassware, cosmetics, hair dyes, jewelry, gun shot and ammunition, relic fishing sinkers, tire weights, and imported children's toys, traditional or folk remedies, and candy/food

packaging. For adults, exposure to levels of Pb beyond background is usually associated with occupational exposures. For children, exposure to high levels of Pb is associated with living in areas contaminated by Pb (e.g., soil or indoor dust in older homes with Pb-based paint). The primary source of Pb exposure to children is from surface dusts (on the ground or entrained) that contain Pb from a variety of sources including deteriorated Pb-based paint (CDC 2009; Lanphear et al. 1998a; Succop et al. 1998). Environmental Pb is particularly accessible to children because of their more intensive hand-to-mouth activity and the proximity of the child breathing zone to Pb entrained from surface dusts. Because Pb is transported from soil very slowly, historic sources of deposition of Pb to soil continue to contribute to current exposures (Laidlaw and Filipelli 2008; Laidlaw et al. 2012). Based on a multimedia Pb exposure modeling analysis for children 1–5 years old at upper percentiles of blood Pb (PbB) levels in the U.S. population, soil and dust ingestion are dominant exposure pathways, but for lower percentiles, other age groups (e.g., younger children), or specific local U.S. locations, the main other exposure sources/ pathways could be important, such as drinking water and food (Zartarian et al. 2017).

PbB has been used as a biomarker of Pb exposure, and periodic surveys of PbB of the U.S. population are conducted by the Centers for Disease Control and Prevention (CDC). Based on data from the National Health and Nutrition Examination Survey (NHANES) (2015–2016, CDC 2018a, 2019), the geometric mean PbB in a representative sample of U.S. adults, ≥20 years old, was 0.920 μg/dL (95% confidence interval [CI] 0.862, 0.982). The geometric mean blood PbB of a representative sample of U.S. children, 1–5 years old, was 0.758 μg/dL (95% CI 0.675, 0.850). PbBs in the U.S. have decreased considerably in the last several decades as a result of removal of Pb from gasoline and restrictions placed on the use of Pb in residential paints (Brody et al. 1994; CDC 2011, 2018a; Pirkle et al. 1994, 1998; Schwartz and Pitcher 1989).

Seasonal variations in blood lead concentration (PbB) levels in children have been observed, with a general trend of increasing PbB during late summer and early fall (Gulson et al. 2008; Johnson and Bretsch 2002; Laidlaw et al. 2005). Seasonal patterns in behavior (e.g., outdoor activities) and weather that promotes re-entrainment and transport of dust Pb (humidity and wind velocity) may contribute to the observed seasonal patterns in PbB (Laidlaw et al. 2005, 2012) and provide additional evidence for surface dusts being a major contributor to child Pb exposure and PbB.

1.2 SUMMARY OF HEALTH EFFECTS

The toxicity of Pb to humans has been known for over 2,000 years, and is not disputed. Early epidemiological studies focused on overt toxicity associated with high occupational exposures. However, during the past few decades, there has been a growing awareness that low-level environmental exposure resulting in PbB <10 μg/dL is associated with adverse effects, particularly in children. PbB levels associated with adverse effects vary by endpoint. Adverse effects occur at PbB <5 μg/dL and for the most studied endpoints (neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental), effects occur at the lowest PbBs studied (≤5 μg/dL). CDC (2018b) states that "no safe blood lead level in children has been identified." As a result, U.S. public health policy has changed to focus on eliminating lead poisoning as a public health problem. CDC considers PbB to be elevated in children when it exceeds a reference value defined as the 97.5th percentile for the U.S. population. The current CDC reference value, based on data from the NHANES 2007–2008 and 2009–2010, is 5 μg/dL. Therefore, the primary objective of current research is on health effects associated with PbB ≤5 μg/dL.

The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children and infants. Information on health effects reviewed below is taken from epidemiological studies that identify the major lines of evidence regarding health effects in humans. Although the literature on adverse effects of Pb in laboratory animals also is extensive, due to the large number of available epidemiological studies, results of animal studies were not considered for the identification of health effects associated with Pb. This potentially leaves out discussion of effects that may have been observed in animal models that have not been studied in humans and that may be future targets of human epidemiology and clinical toxicology studies. Animal studies were included in discussion of mechanisms of toxicity of Pb and toxicokinetics.

To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of μg/dL). Blood Pb concentration reflects both ongoing exposure and Pb stores in bone, which can be transferred to blood. Because of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months and not necessarily the larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI), which may be a better reflection of

exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct, noninvasive measurements of bone Pb concentrations have been used as a metric of long-term exposure on the basis that most of the absorbed Pb retained in the body will reside in bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb is retained in the body for decades. Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect are typically unknown or highly uncertain.

Toxic effects of Pb have been observed in every organ system that has been rigorously studied. Clinical significance of some of the organ system effects at low levels of exposure and blood Pb is more substantial than for others (e.g., neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects). This is not surprising because the mechanisms that induce toxicity are common to all cell types and because Pb is widely distributed throughout the body. Adverse health effects have been observed in these systems at PbB ≤10 μg/dL. Exposure thresholds for effects on specific organ systems have not been identified (i.e., no safe level has been identified). Cognitive deficits in children occurring at the lowest PbBs (≤5 μg/dL) are the best substantiated effects. However, data for some organ systems results are inconsistent, and insufficient data are available to provide information on dose-response relationships. It is also important to note that effects observed in adults, especially older adults, may be due to higher environmental or occupational exposures in the past; therefore, exposure history is an important consideration in epidemiological studies on the health effects of Pb.

The most extensively studied health outcomes, as described below, are neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects. Neurological effects of Pb are of greatest concern because effects are observed in infants and children and may result in life-long decrements in neurological function. Infants are born with a Pb burden derived from maternal transfer *in utero* and subsequently can continue to absorb maternal Pb from ingestion of breast milk. Children are also more vulnerable because of behaviors that increase ingestion of Pb surface dusts (e.g., hand-to-mouth activity) and because gastrointestinal absorption of ingested Pb is higher in children compared to adults, possibly due to a combination of physiological differences and differences in diet and nutrition. The following briefly summarizes health effects of chronic exposure to Pb observed in humans. More detailed information, including reference citations, is provided in Chapter 2.

Neurological Effects in Children. Numerous prospective and large cross-section studies in children provide consistent evidence of decrements in neurological function, including decrements in cognitive function (learning and memory), altered behavior and mood (attention, hyperactivity, impulsivity, irritably, delinquency), and altered neuromotor and neurosensory function (visual-motor integration, dexterity, postural sway, changes in hearing and visual thresholds). These effects have been associated with a PbB range from ≤5 to >50 µg/dL, with numerous studies providing evidence for effects at PbB ≤5 µg/dL. Taken together, studies support the concept that Pb affects cognitive function in children prenatally and/or environmentally exposed to low levels of Pb. No threshold for these effects has been identified (i.e., no safe level has been identified). Decrements in cognitive function increase with PbB, and several PbB-effect models predict that larger decrements in cognitive function would occur when PbB increases from 1 to 10 µg/dL, compared to when PbB increases from levels >10 µg/dL. Supra-linear dose-response relationships for neurological outcomes are discussed in greater detail in Section 2.16 (Neurological). At higher PbB (>30 µg/dL), other neurotoxic effects have been observed, including alterations in nerve function (decrements in fine and gross motor skills, peripheral neuropathy) and encephalopathy.

Neurological Effects in Adults. Epidemiological studies in adults demonstrate decrements in neurological function associated with PbB. All of the cognitive and neurobehavioral effects of Pb observed in children also have been observed in adults associated with PbB ranging from ≤10 to >50 µg/dL, with evidence of effects occurring at PbB ≤5 µg/dL. At higher PbB (>30 µg/dL), other observed neurotoxic effects include peripheral neuropathy, psychiatric symptoms (depression, panic disorders, anxiety, hostility, confusion, anger, and schizophrenia), and changes in regional brain volumes and neurochemistry. It is not clear if cognitive decrements are related to exposures that occurred during adulthood or during periods of nervous system development (e.g., prenatal and childhood exposures) or if effects are due to cumulative exposure. Results of a few studies that have followed children to early adulthood show an association between child PbB and behavioral and neuroanatomical changes in adults, suggesting a possible impact of exposures on childhood to adult outcomes.

Renal Effects. Adverse renal effects of Pb are well-established in numerous epidemiological studies. Studies show consistent evidence of renal damage and reduced renal function associated with a wide range of PbB (≤10–50 µg/dL), with several studies providing evidence for effects at PbB ≤5 µg/dL. Deficits in renal function include enzymuria, proteinuria, impaired transport of organic anions and glucose, and depressed glomerular filtration rate (GFR). At higher PbB (>30 µg/dL), Pb-induced nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, interstitial fibrosis,

and tubular necrosis. Note that Pb-induced decrements in renal function can lead to higher Pb body burden due to decreased excretion of Pb (i.e., reverse causality). In addition, other causes of decreased renal function could result in an increased body burden of Pb.

Cardiovascular Effects. A large number of epidemiological studies in adults show adverse cardiovascular effects associated with a PbB range from ≤5 to >50 µg/dL. Effects on blood pressure is the most-studied cardiovascular outcome, with studies showing increased systolic and diastolic blood pressure, with some evidence of effects occurring at PbB ≤5 µg/dL. A few studies show increased blood pressure in children and pregnant women. Nawrot et al. (2002) estimated that with doubling of PbB (for example, from 5 to 10 µg/dL), systolic and diastolic blood pressure would increase by 1 and 0.6 millimeters of mercury, respectively. Other cardiovascular effects include increased risk of hypertension and heart disease, atherosclerosis, altered cardiac conduction, cardiac disease, and increased mortality due to cardiovascular disease. A recent study concluded that low-level environmental Pb exposure is an important risk factor for cardiovascular disease mortality (Lanphear et al. 2018).

Hematological Effects. The toxicity of Pb to the hematological system of humans has been established in numerous studies in adults and children. Exposure to Pb causes dose-dependent decreases in heme synthesis through inhibition of the enzyme delta-aminolevulinic acid dehydratase (δ-ALAD). At PbB ≤10 µg/dL, decreased blood hemoglobin is observed; however, it should be noted that the magnitude of this decrease is typically small and may not represent a biologically significant change. As PbB increases, further decreases in blood hemoglobin and loss of erythrocytes due to a Pb-induced increased membrane fragility results in the development of anemia (NAS 2013). Other effects of Pb on the hematological system include decreased activity of other erythrocyte enzymes (pyrimidine 5'-nucleotidase or red blood cell membrane Ca^{2+}/Mg^{2+}ATPase) and altered levels of plasma erythropoietin (a hormone that stimulates red blood cell formation); however, fewer studies on these endpoints have been published and study results are mixed.

Immunological Effects. Epidemiological studies provide evidence that Pb exposure can perturb the immune systems of children and adults. Evidence for this derives from changes in various indicators of humoral and cell-mediated immunity in association with increasing PbB. Effects have been observed in populations that had average PbB <10 µg/dL. These effects are consistent with more extensive studies conducted in animal models and isolated immune cells that have shown that Pb can perturb the humoral and cell-mediated immune systems, leading to sensitization, autoimmunity, and inflammation (EPA 2014c; NAS 2013).

Reproductive Effects in Males. Health effects of Pb on the male reproductive system have been evaluated in numerous epidemiological studies. Effects include damage to sperm (decreased sperm count, concentration, motility, and viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm), possible alterations in serum levels of reproductive hormones (testosterone, estradiol, luteinizing hormone [LH], and follicle-stimulating hormone [FSH]), decreased fertility, and histopathological changes to the testes. Severity of these effects increases with PbB. Studies conducted in populations with mean PbB ≤10 µg/dL provide evidence of damage to sperm, although effects are more consistently observed at PbB >10 µg/dL. Regarding effects on serum levels of reproductive hormones, results of available studies for PbB ranging from ≤10 to >50 µg/dL are inconsistent; thus, Pb-induced effects on circulating reproductive hormones are not firmly established. At higher PbB (>10 µg/dL), a few studies provide evidence of more severe effects, including decreased fertility and histopathological damage to testes.

Reproductive Effects in Females. Compared to studies of male reproductive effects, the epidemiologic literature database for effects of Pb on the female reproductive system is smaller, with most epidemiological studies conducted in populations with mean PbB ≤10 µg/dL. Studies provide some evidence of alterations in serum reproductive hormone levels (estradiol, LH, and FSH), decreased fertility, increased spontaneous abortion, increased preterm birth, and earlier age at onset of menopause. However, results are inconsistent, with several studies reporting no association between PbB and female reproductive effects.

Developmental Effects (Excluding Neurodevelopmental). Numerous epidemiological studies have evaluated developmental outcomes, with most studies conducted in populations with maternal and/or umbilical cord PbB ≤10 µg/dL. Some studies provide evidence of decreased birth size (weight, length, head circumference), decreased child growth (weight, height, head circumference, trunk length, leg length, arm length, body mass index [BMI]), and delayed onset of puberty in males and females. Although it is difficult to assess dose-dependence for developmental effects within the relatively narrow range of PbB (≤10 µg/dL) in most studies, dose-related decreases in birth weight have been observed in populations with PbB ≤10 µg/dL. Although studies provide evidence of associations between PbB and developmental outcomes, results are inconsistent and several studies, including prospective studies, show no associations with non-neurodevelopmental outcomes.

Other Health Effects Associated with Pb. In addition to the effects summarized above, health effects to other organ systems have been reported. The epidemiological databases for these effects are much less extensive than for the effects reviewed above. Effects described below occur over a wide range of PbBs, including PbB ≤10 µg/dL. However, results for most endpoints are inconsistent and insufficient data are available to provide information on dose-response relationships.

- ***Respiratory Effects.*** Associations have been observed between PbB and decreased lung function, increased bronchial hyperreactivity, symptoms of respiratory disease, and increased risk of respiratory diseases (e.g., asthma and obstructive lung disease).
- ***Endocrine Effects (Excluding Reproductive Hormones).*** Studies in adults, adolescents, and children show effects on thyroid function, cortisol levels, vitamin D levels, and serum levels of growth factors. Effects on thyroid function are the most studied effect, although results do not demonstrate a consistent pattern of effect.
- ***Hepatic Effects.*** Most studies were conducted in workers with PbB >10 µg/dL. Several studies show altered plasma levels of liver enzymes, although no consistent pattern of effects has been observed. Liver enlargement and increased gall bladder wall thickness have been associated with PbB.
- ***Musculoskeletal Effects.*** Studies provide evidence of bone loss, increased markers of bone metabolism/turn over, and adverse periodontal and dental effects (periodontal bone loss, tooth loss, periodontal disease, dental caries) in adults and children.
- ***Gastrointestinal Effects.*** Gastrointestinal colic is a predominant clinical symptom of acute Pb poisoning. Epidemiological studies provide evidence of gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea, and/or constipation) associated with PbB ranging from 8 µg/dL to approximately 100 µg/dL. However, most studies are survey or cross-sectional studies of small populations of workers.
- ***Body Weight Effects.*** A few studies evaluating effects of PbB ≤10 µg/dL on body weight provide some evidence of decreased body weight in children and adults, although inconsistent results have been reported.
- ***Ocular Effects (Excluding Neurological Effects).*** Limited data provide some evidence that exposure to Pb is associated with macular degeneration in adults and increased risk of cataracts.

Cancer. Numerous epidemiological studies have evaluated associations between Pb exposure and cancer. Although studies provide limited evidence of carcinogenicity of Pb in humans, results are inconsistent, with several negative studies, and interpretation of data may be limited due to confounding

factors (e.g., smoking status, family history of cancer, co-exposure to other carcinogens). At PbB ≤10 µg/dL, increased risks were reported for all cancers and lung cancer. At PbB >10 µg/dL, increased risks were observed for all cancer, respiratory tract cancer, stomach cancer, intestinal cancer, cancer of the larynx, and glioma.

The Department of Health and Human Services classified Pb and Pb compounds as reasonably anticipated to be human carcinogens (NTP 2016). In 1988, EPA classified Pb as a probable human carcinogen based on sufficient evidence in animals; evidence in humans was considered inadequate (IRIS 2004). The International Agency for Research on Cancer (IARC) has classified inorganic Pb compounds as probably carcinogenic to humans (Group 2A) based on sufficient evidence in animals and limited evidence in humans; evidence for organic Pb compounds was considered to be inadequate in humans and animals (IARC 2006).

1.3 MINIMAL RISK LEVELS (MRLs)

As reviewed in Section 1.2, epidemiological studies have evaluated the health effects of Pb in all organ systems. For the most studied endpoints (neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental), effects occur at the lowest PbBs studied (≤5 µg/dL). Because the lowest PbBs are associated with serious adverse effects (e.g., declining cognitive function in children), MRLs for Pb have not been derived.