

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of Pb is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of Pb.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 Information on Health Effects

Studies evaluating the health effects of exposure of humans Pb that are discussed in Chapter 2 are summarized in Figure 2-1. The purpose of this figure is to illustrate the information concerning the health effects of Pb. The number of human studies included in the profile for each endpoint is indicated regardless of whether an effect was found.

The health effects of Pb have been extensively studied in humans, including numerous studies in children. Due to the extent of the database in humans, a comprehensive review of the complete epidemiological database is not feasible. Epidemiological studies included in Chapter 2 were selected to identify the major lines of evidence regarding health effects in humans. Because the database of epidemiological studies is so large, animal studies were not included in the profile. Due to the increasing awareness that low-level environmental exposure resulting in blood Pb concentrations (PbB) $<10 \mu\text{g/dL}$ is associated with adverse effects, particularly in children, the primary objective of current research is focused on health effects associated with $\text{PbB} \leq 10 \mu\text{g/dL}$. Additional details on studies with $\text{PbB} \leq 10 \mu\text{g/dL}$, including statistical analyses and assessment of confounding factors, are provided in the *Supporting Document for Epidemiological Studies for Lead*.

Health effects of Pb in humans are not defined in terms of route or duration of exposure. Epidemiological studies on Pb toxicity rely on internal exposure metrics (e.g., PbB), rather than measurements of external

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exposures (e.g., concentration of Pb in water or air) or ingested dose. Furthermore, once absorbed into the body, the health effects of Pb are the same, regardless of the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb can be retained in the body for decades; therefore, health effects of Pb in humans are considered to be associated with chronic exposure, rather than to shorter exposures.

6.2 Identification of Data Needs

A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Increased awareness of the potential adverse consequences of low environmental exposures to Pb has led to changes in U.S. public health policy, with a focus on lowering PbB levels to well below 10 µg/dL (CDC 2012d; EPA 2016b). In 2012, the CDC concluded that the 97.5th percentile of the U.S. PbB distribution (based on NHANES data) should be considered a reference value for identifying children who have "elevated" PbB (CDC 2012d). At that time, the reference was approximately 5 µg/dL, and the value continues to decline (NHANES 2011–2012; CDC 2018a). Therefore, additional epidemiological studies for all health outcomes are needed. The objective of these additional studies would be to define the low end of the dose-response curve (e.g., at PbB ≤5 µg/dL) and to identify threshold levels for health outcomes.

MRLs. Epidemiological studies have identified health effects of Pb in all organ systems. However, exposure thresholds for effects have not been identified, and it is not possible to determine from the epidemiological data which organ system are the most sensitive (i.e., primary) targets for Pb toxicity. Because clear thresholds for these effects have not been identified, MRLs for Pb have not been derived. Additional epidemiological studies would provide more data to further characterize effects; however, as PbBs continue to decline and effects are observed at the lowest PbB examined, identification of control groups has become increasingly difficult. Thus, it is not anticipated that additional epidemiological studies would identify threshold values for Pb-induced toxicity endpoints.

Health Effects. As noted above, epidemiological studies have identified health effects of Pb in every organ system at the lowest PbB evaluated. Additional prospective studies on all health outcomes would

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provide important information to further characterize the effects of Pb and evaluate potential implications for long-term effects. However, as noted above, it is not anticipated that additional epidemiological studies would identify threshold values for health effects.

Epidemiology and Human Dosimetry Studies. Several models of the Pb exposure-biokinetics toxicokinetics in humans have been developed and used in dosimetry studies. Additional studies would be helpful for addressing major uncertainties in these models, including: (1) absence of calibration data for the kinetics of Pb in blood and bone in children in association with exposures that have been quantified with high certainty; (2) absence of calibration data on bone Pb concentrations in adolescents and adults in association with exposures that have been quantified with high certainty; (3) absence of data on the absolute bioavailability of ingested Pb in older children and adolescents; (4) incomplete understanding of Pb kinetics during periods of changing bone metabolism, including adolescence, pregnancy, and menopause; and (5) incomplete understanding of inter- and intra-individual variability in model parameters values in humans. In addition, there is a need for studies that can evaluate or validate model predictions of concentrations of Pb in blood and other tissues in populations in which PbBs are typical of the U.S. population ($\leq 5 \mu\text{g/dL}$).

Biomarkers of Exposure and Effect. Measurement of blood Pb concentration is the most widely used biomarker of Pb exposure and is used to identify children who have elevated exposures. Measurement of bone Pb by XRF has been used to estimate Pb body burden in adults, which is a more accurate biomarker of long-term exposure than PbB. Additional studies that could improve and evaluate the validity of non-invasive biomarkers (e.g., hair, saliva, sweat, deciduous teeth, urine) for quantifying exposure would be helpful for population monitoring of Pb exposures and for epidemiology of Pb health effects.

Absorption, Distribution, Metabolism, and Excretion. Studies of Pb absorption are limited to studies in infants and adults. No data are available on the absorption of Pb in older children and adolescents. Additional studies of Pb absorption in this age category would be useful for improving exposure-biokinetic models.

A variety of factors are known to influence the absorption of ingested Pb, including the chemical form of the ingested Pb, the presence of food in the gastrointestinal tract, diet, and nutritional status with respect to calcium, vitamin D, and iron; however, for the most part, the mechanisms by which these interactions occur are not fully understood. This reflects, in part, a lack of understanding of the mechanisms by which

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Pb is absorbed in the gastrointestinal tract, and studies aimed at elucidating such mechanisms would be helpful for developing PBPK models that accurately simulate relationships between Pb exposure and Pb in blood and other target and biomarker tissue.

The quantitative significance of the dermal absorption pathway as a contributor to Pb body burden remains an uncertainty. Few studies are available on Pb absorption after dermal exposure of inorganic Pb compounds in humans. Children may experience extensive dermal contact with Pb in soil, sand, or surface water and suspended sediment (e.g., beach or shoreline exposure scenario), even a low percent absorption across the skin may represent a significant internal dose. Therefore, additional studies designed to quantify dermal absorption of inorganic Pb compounds from both aqueous media and from soil would be helpful for improving PBPK models, in particular, studies that enable measurements to be extrapolated to children.

Comparative Toxicokinetics. Animal models (e.g., swine, mouse) have been used extensively as a model for assessing relative bioavailability of Pb in ingested soil in humans and for evaluating *in vitro* approaches to assessing bioaccessibility of Pb. However, no studies are available in which the absolute or relative bioavailability of ingested Pb has been quantitatively compared in animal models and humans. Such studies would be useful for validating both the *in vivo* swine model and the *in vitro* bioaccessibility model.

Children's Susceptibility. Children are likely to have increased susceptibility to Pb compared to adults for several reasons: increased susceptibility of developing physiological systems compared to mature systems; increased absorption of Pb in children compared to adults; and common childhood behaviors (e.g., hand-to-mouth activity, pica behavior [the compulsive, habitual consumption of nonfood items], proximity of breathing zone to entrained surface dust). In addition, several other factors may affect children's susceptibility to Pb, including (but not limited to) family socio-economic status, parent education, parent alcohol, tobacco, and drug use, allergen exposure, and family history of disease, although these factors may not be unique to children. Additional studies evaluating these factors would provide an increased understanding of relative contributions of these factors to child PbB and associated health effects.

Physical and Chemical Properties. No data needs were identified regarding physical and chemical properties of Pb.

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Production, Import/Export, Use, Release, and Disposal. Continued monitoring of Pb production, import/export, use, release, and disposal would be helpful for identifying sources of potential human exposure. In particular, additional data on releases of Pb from leaded gasoline used in piston-driven engines would be helpful for determining potential contributions of this source to human exposure. Industrial wastes, as well as consumer products, containing Pb are disposed of in municipal and hazardous waste landfills. Current information on the amounts being disposed would be helpful for evaluating potential for exposures to Pb from these sources.

Environmental Fate. Additional information on the atmospheric transformations of organic and inorganic Pb compounds in the atmosphere would be helpful for identifying Pb compounds to which humans are most likely to be exposed by inhalation. Additional data regarding the chemical speciation and the transformation pathways of Pb in soils and water with varying properties such as pH, oxygen content, and salinity would be helpful for improving understanding of the environmental fate of Pb in soils and water.

Bioavailability from Environmental Media. Studies conducted in animal models show that oral RBA of soil Pb varies depending upon the Pb mineralogy and physical characteristics of the Pb in the soil. There is only one published study that assessed the bioavailability of Pb in humans (adults) who ingested hazardous waste site soil. Additional studies of this type would provide an improved basis for estimating Pb uptake in people who are exposed to Pb in soil. No studies have measured oral RBA of surface dusts. Since this is an important exposure pathway, especially in urban environments, studies of oral Pb RBA of surface dusts collected from various types of indoor and outdoor surfaces, including those impacted by paint Pb, would be helpful.

Recent interest in the use of soil-amending agents (e.g., phosphate) to reduce soil Pb bioavailability, would be served by additional studies directed at developing methods for monitoring the magnitude and persistence of the effect of amending agents on Pb bioavailability and for predicting the magnitude of the effect for improved design of amending projects.

Food Chain Bioaccumulation. No data needs were identified regarding food chain bioaccumulation.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of Pb in contaminated media at hazardous waste sites are needed so that the information obtained on levels of Pb in the environment can be used in combination with the known body burden of Pb to assess the potential

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risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Continued monitoring of Pb levels in air, drinking water, and diet (e.g., food and bottled water) would be helpful for evaluating potential for exposures to Pb from these sources. Continued testing of consumer products would be helpful for identifying potential localized sources of human exposure (e.g., ceramics, cosmetics, jewelry, toys).

Exposure Levels in Humans. Continued updating of national (e.g., NHANES) and regional surveys of Pb biomarkers (e.g., PbB) would be helpful for assessing temporal and demographic trends in Pb exposure in the U.S. population as well as for evaluating associations between Pb exposure and health metrics (e.g., those included in the NHANES), and for evaluating models that relate exposure to PbB.

Exposures of Children. Since an important variable in estimating Pb intakes from measurements of surface dust Pb levels is the rate of surface dust ingestion, improved estimates of soil ingestion would increase confidence in predictions of Pb intakes associated with exposures to Pb in surface dusts. In some contexts, exposure to surface dust Pb is measured in terms of Pb loading ($\mu\text{g}/\text{Pb}/\text{cm}^2$ of surface area available for contact); however, Pb loading measurements do not provide a direct way of estimating Pb ingestion without corresponding estimates of dust loading and surface dust ingestion rates. Improved methods for translating measurements of Pb loading into estimates of surface dust Pb concentration or surface dust Pb intake would be helpful for improving models for predicting exposure-Pb relationships in children.

6.3 Ongoing Studies

Ongoing studies on Pb are outlined in Table 6-1. Note that the studies listed below are funded by the National Institute of Health (NIH) and do not include ongoing studies that are funded by other sources.

Table 6-1. Ongoing Studies on Lead (Pb)

Investigator	Affiliation	Research description	Sponsor
D'Sa, VA	Memorial Hospital of Rhode Island	Longitudinal study on the relationship between PbB and myelination and neurite density in children ages 12–24 months	NICHHD
Guilarte, TR	Florida International University	Mechanism of action study in rats to evaluate the role the NMDA receptor in Pb-induced neurotoxicity	NIEHS

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Table 6-1. Ongoing Studies on Lead (Pb)

Investigator	Affiliation	Research description	Sponsor
Guilarte, TR	Florida International University	Study in rats to evaluate presynaptic mechanisms of Pb-induced neurotoxicity	NIEHS
Murphy, MP	University of Kentucky	Study in rats to evaluate mechanism of Pb-induced neurotoxicity	NIEHS
Sandler, DP	NIEHS	Epidemiological study examining Pb and other neurotoxins as risk factors for amyotrophic lateral sclerosis	NIEHS
Steenland, NK	Emory University	Epidemiological study examining mortality and renal disease in Pb-exposed workers	NIOSH
Bhattacharya, A	University of Cincinnati	Epidemiological study on the effects of early exposure to Pb as a risk for bone health later in life in African-American women	NIEHS
Wright, RO	Icahn School of Medicine Mount Sinai	Epidemiological study in children on the link between Pb exposure, stress, and neurological development	NIEHS

NICHD = National Institute of Child Health and Human Development; NIEHS = National Institute of Environmental Health Sciences; NIOSH = National Institute of Occupational Safety and Health; NMDA = N-methyl-D-aspartate; PbB = blood lead concentration

Source: NIH Reporter 2017