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6.2 Toxicology and Exposure

In addition to the brief overview of lead toxicology and exposure presented here, more information is available in the ITRC RISK-3 document, which includes links to USEPA's lead resources. Additionally, see Using Bioavailability Information in Risk Assessment for more information about lead risk assessment.

6.2.1 Environmentally Relevant Exposures

▼*Read more*

Ingestion of lead-contaminated fine soil and dust particulates is the primary pathway of human lead exposure from environmental sources (NTP 2012; Laidlaw et al. 2014; Lanphear et al. 1998; 2003). Lead-based paint is considered the major source of high-dose lead poisoning in the United States (CDC 2005). Dust inhalation, ingestion of contaminated soil, ingestion of contaminated food or drink, use of cookware containing lead, traditional and home medical remedies (Los Angeles Department of Public Health 2016), and some traditional cosmetics, such as kohl, a lead sulfide mineral based eyeliner (FDA 2016) also contribute to lead exposure.

6.2.1.1 Ingestion *Read More*

Lead can be ingested through inadvertently swallowing lead-contaminated soil or dust from hands when eating, drinking, smoking, or applying cosmetics (such as lip balm). Additional lead ingestion sources include:

- incompletely washed produce grown in lead-contaminated soil
- dust settling in or on food and drink or dishes and glasses
- intentional ingestion of soil by young children or people with pica disorder (compulsive soil eaters)

The absorption of lead following ingestion depends on the solubility (bioaccessibility) of lead in the gastrointestinal system as well as the presence or absence of other bioactive agents in the gut. In vitro lead bioaccessibility has been studied in simulated gastric and intestinal phases. These studies conclude that the gastric phase controls lead dissolution from soil and correlates more closely to in vivo animal test results (Ruby et al. 1992; Drexler and Brattin 2007; USEPA 2007c; Juhasz et al. 2009; Smith et al. 2011).

6.2.1.2 Inhalation *Read More*

With the discontinuation of leaded gasoline production and leaded aviation gas for piston-driven aircraft being phased out, inhalation is an exposure pathway of concern mostly for workers in industries that use lead and for home renovation activities (ATSDR 2007b). Inhaled lead is potentially hazardous because approximately 95% of deposited inorganic lead is absorbed (ATSDR 2007b).

6.2.1.3 Dermal *Read More*

Generally, lead uptake by dermal absorption is not an environmentally relevant exposure pathway because of the low dermal permeability of inorganic lead (ATSDR 2007b).

6.2.2 Toxicokinetics

▼*Read more*

Toxicokinetics addresses the disposition of a chemical in humans or animals after exposure occurs. Toxicokinetic studies include an evaluation of the routes and mechanisms of absorption, patterns of distribution throughout the body, metabolism of the chemical, and excretion of metabolites or the unchanged chemical. A thorough review of lead toxicokinetics is included in the Agency for Toxic Substance and Disease Registry (ATSDR) toxicological profile for lead (ATSDR 2007b).

6.2.2.1 Absorption *Read More*

Lead absorption depends on the chemical and physical properties of the lead species as well as the route of exposure, age, health status, physiology, nutritional status, and genetics of the exposed individual. For example, children absorb more lead through gastrointestinal absorption (40–50%) than adults (3–10%) (ATSDR 2007b). The absorbed fraction depends on the presence of food in the GI tract when the lead is ingested. The magnitude of absorption can be much higher after a fast (James, Hilburn, and Blair 1985). The general nutritional status of the exposed individual can also affect lead absorption after ingestion. Dietary deficiencies of calcium, iron, and zinc are known to enhance the adverse effects of lead on cognition and behavioral development (Gover 1995), and people eating a diet deficient in micronutrients are predisposed to toxicity from lead (Peraza et al. 1998).

In human studies, recommended nutritional levels of calcium, phosphorus, and fiber reduced lead absorption (Blake and Mann 1983; James, Hilburn, and Blair 1985). Elevated levels of calcium and phosphorus combined reduced lead absorption more than increased levels of calcium or phosphorus alone (Blake and Mann 1983) and (Heard, Chamberlain, and Sherlock 1983). In the U.S. National Health and Nutrition Examination Survey, children with lower intakes of dietary calcium had increased levels of lead in their blood (Mahaffey, Gartside, and Glueck 1986). Lead may also be reintroduced into the bloodstream at times of calcium deficiency or stress (for example, pregnancy, lactation, or osteoporosis). At these times, the body withdraws calcium from internal stores along with any sequestered lead.

After inhalation, absorption of lead deposited in the respiratory tract may vary and be as high as 95%, depending on the particle size, solubility of the lead species, nose or mouth breathing, and other factors. “In adults about 35-40% of inhaled lead dust is deposited in the lungs, and about 95% of that goes into the blood stream” (Merrill, Morton, and Soileau 2007).

6.2.2.2 Distribution *Read More*

The distribution of lead throughout the body is independent of the route of absorption. Most lead that is absorbed into the bloodstream is transported to bone, with small amounts transported to teeth and soft tissues such as the liver. Lead accumulates in bone over most of the human lifespan but is turned over as the processes of remodeling and resorption progress. The elimination half-life of lead depends on factors including age and exposure history, which determines bone lead levels. The elimination half-life of lead is approximately 1 month in blood, 1-1.5 months in soft tissue, and decades in bone (ATSDR 2007b; CDC 2013).

6.2.2.3 Metabolism *Read More*

Inorganic lead generally forms complexes with several proteins, such as albumin and globulins, and nonprotein ligands, such as low molecular weight sulfhydryls. Lead metabolism is known to inhibit heme synthesis and erythrocyte lifespan. Heme synthesis is altered by disruption of the major intracellular ligand in red blood cells, delta-aminolevulinic acid dehydratase (ALAD). ALAD activity has been inversely correlated with BLL in both lead workers and urban study subjects never exposed occupationally (Gurer-Orhan, Sabır, and Özgüneş 2004; Hernberg and Nikkanen 1970). Organic (alkyl) lead compounds are metabolized in the liver. Studies of organic lead workers have found that tertraethyl lead is excreted as diethyl, ethyl, and inorganic lead (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang, Zhang, and He 1994).

6.2.2.4 Excretion *Read More*

Absorbed lead is excreted primarily in urine and feces, independent of the route of exposure. Other routes of excretion include sweat, saliva, hair, fingernails, and breast milk (Rabinowitz, Wetherill, and Kopple 1976).

6.2.3 Toxicodynamics

▼*Read more*

Toxicodynamics addresses the toxicological effects of a chemical in humans and other animals. A thorough review of lead toxicodynamics is included in the ATSDR toxicological profile for lead (NTP 2012).

6.2.3.1 Systemic Effects *Read More*

Toxicity is generally correlated with BLL because the toxic effects of blood-borne contaminants are independent of exposure route and because BLL is easier to obtain than bone lead concentrations. BLL also better indicates recent lead exposures, but is not useful for chronic measurements due to exposure fluctuations. Acute duration exposures to low doses of lead cause few adverse effects; however, exposure to higher concentrations may be associated with gastrointestinal effects, liver and kidney damage, and hypertension. Additionally, neurological effects can include mental dullness, restlessness, irritability, attention deficits, headaches, hallucinations, and encephalopathy (see Table 6-1).

Table 6-1. Effects of lead exposure on human organ systems (adapted from ATSDR 2007b, Table 3-1)

Exposure Duration	Target Organ	Blood Lead Concentration (µg/dL)	Effects
Acute	Cardiovascular system	48–120	Hypertension
	Kidney	48–80	Generally reversible, including tubular dysfunction and nephritis
	Neurological system	80–100	Encephalopathy in children
	Liver	Various	Inhibition of heme synthesis
	Gastrointestinal system	60–400	Cramps, vomiting, anorexia, and constipation
Chronic	Blood	40–50	Anemia
	Neurological system	40–120	Various neurological effects, including dizziness, fatigue, sleep disturbance, headache, irritability, lethargy, malaise, slurred speech and convulsions. Muscle weakness, paresthesia, ataxia, tremors, and paralysis may also occur.
		> 2	In children, developmental lead neurotoxicity and IQ decrements
	Kidney	Various	Nephropathy, including glomerular sclerosis, interstitial fibrosis, proximal tubular nephropathy, and decreased glomerular filtration rate
	Cardiovascular system	Various	Arrhythmias
	Gastrointestinal system	40–200	Nausea, vomiting, anorexia, constipation, and abdominal cramps in children and adults
	Liver	Various	Hepatitis

6.2.3.2 Reproductive and Developmental Effects *Read More*

Chronic exposure to lead may cause adverse reproductive effects in both males and females. Effects in females include an increased risk of spontaneous abortion and premature delivery (Nordstrom, Beckman, and Nordensen 1979; Borja-Aburto et al. 1999). In males, occupational exposure that results in BLL concentrations of 44 µg/dL or greater results in low sperm count (Bonde and Kolstad 1997). Total sperm count and concentration decreases with increasing BLL in Pb smelter workers (Alexander et al. 1998), while a significant decrease in fertility occurs among lead battery workers (Gennart et al. 1992).

Numerous studies have shown cognitive impairment at BLL above 10 µg/dL (CDC 2012). In addition, a decline of 1.37 IQ points for each 1 µg/dL increase in BLL under 10 µg/dL has been calculated (Canfield et al. 2003). In children, increasing BLL was significantly associated with decreasing body stature and head circumference (Ballew et al. 1999). In children, increased BLL is positively correlated with increased dental cavities (Moss, Lanphear, and Auinger 1999). Encephalopathy (impaired brain function) in children was associated with BLL of 90 to 800µg/dL (mean 330 µg/dL), with death occurring at a mean of 327 µg/dL (NAS 1972). Lead toxicology is an area of ongoing research and regulatory evaluation, the details of which are beyond the scope of this document.

6.2.3.3 Genotoxic Effects *Read More*

Genotoxic studies suggest that lead is a clastogenic agent, potentially inducing disruption or breakage of chromosomes. The effects reported after occupational exposures include chromosomal aberrations, induction of micronuclei, and sister chromatid exchanges in peripheral blood cells (ATSDR 2007b), Section 3.2.7 and references).

6.2.3.4 Carcinogenicity *Read More*

The International Agency for Research on Cancer (IARC 2006) has concluded that inorganic lead compounds are likely carcinogenic to humans. The IARC noted that data from animal studies indicates carcinogenicity, but there is limited human exposure data providing direct evidence of human carcinogenicity. The U.S. Department of Health and Human Services has determined that lead and lead compounds are reasonably anticipated to be human carcinogens (NTP 2014). Animal studies show that lead is carcinogenic, producing renal tumors in mice (ATSDR 2007b).

6.2.4 Factors that May Reduce Lead Bioavailability from Soil

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In general, the bioavailability of lead-contaminated soil is lower than the bioavailability of lead in foodstuffs (Zia et al. 2011). The solubility of lead-bearing minerals or precipitates, the extent of lead desorption from soil particles in the gut, or both are the primary mechanisms that mitigate the bioavailability of ingested lead-contaminated soil. Once ingested, the fraction of lead mineral dissolution or desorption, or both from soil relative to the lead absorption across the intestinal epithelium defines the limiting process crucial to quantifying lead oral bioavailability. Lead mineral solubility and soil desorption are discussed separately, as are in vitro approaches.

Different mineral species of lead have different dissolution constants and dissolve under acidic gut conditions with variable rates and extents. Thus, both mineral equilibria and dissolution kinetics are important considerations because bioavailability may or may not reflect equilibrium conditions, which depend on the mineral surface area and gut retention time. These conditions are reflected in the solubility product constant (K_{sp}), which is the equilibrium constant for a mineral dissolving in a solution (water, soil, or gastric). The log value of K_{sp} represents the molar equilibrium concentration in solution, and in general the more soluble a given mineral, the faster dissolution occurs. The solubility products for numerous lead minerals have been recorded and are presented in Table 6-2. As log K_{sp} decreases, the less soluble the mineral is in solution.

Table 6-2. Solubility products of select minerals (Lindsay 1979)

Mineral	**Log K_{sp}**
PbO (yellow)	12.89
PbO (red)	12.72
$PbCO_3$ (cerussite)	4.65
$Pb_3(CO_3)_2(OH)_2$ (hydrocerussite)	-1.80
$PbSO_4$ (anglesite)	-7.79
$PbMoO_4$ (wulfenite)	-16.04
$Pb_5(PO_4)_3Cl$ (chloropyromorphite)	-25.05
PbS (galena)	-27.51

The soil matrix can adsorb lead or promote lead mineral formation when lead concentrations are above mineral saturation, indices greatly affecting lead oral bioavailability. Both electrostatic reactions with negatively charged soil surfaces and covalent reactions with soil organic matter (SOM) and amorphous iron, manganese, and aluminum oxides are relevant to varying extent. Lead typically exhibits an S-shaped adsorption curve as a function of pH on soil minerals and SOM. Thus, at a low pH, lead adsorption is limited (more in solution), adsorption sharply increases between pH 5 to 7, and maximum adsorption occurs beyond pH 7. Under gut conditions, both mineral and adsorbed forms of lead can be released into the gastrointestinal solution as freely dissolved ions (in addition to other elements in the matrix) because of the acidic conditions. Upon transfer to the intestinal tract, where pH is higher, the precipitation of amorphous oxide minerals may promote readsorption of lead to those minerals, which in turn limits absorption into the body (Beak et al. 2006b; 2008). Consequently, most lead in vitro bioaccessibility methods demonstrate that the gastric phase better predicts RBA than simulated conditions of the intestinal tract. Lead IVBA in a gastric assay is strongly correlated with in vivo RBA, even though lead is absorbed in the small intestine (Drexler and Brattin 2007).