Biological Factors That Impact Variability of Lead Absorption and Blood Lead Level Estimation in Children: Implications for Child Blood Lead Level Testing Practices

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Abstract **Childhood lead poisoning in the U.S. continues to be a major unresolved child public health issue. One barrier to solving the problem of lead poisoning concerns current child blood lead level (BLL) monitoring practices. In most states, one or two BLL tests administered in early childhood are used to rule out lead exposure. Current knowledge, however, regarding the multiple, complex biological mechanisms that underlie lead absorption and distribution during development suggests that child BLLs should be assumed to be an informative but necessarily fluctuating metric of current child lead exposure. We review some key mechanisms and pathways that influence lead absorption, lead distribution, and the stability of lead in red blood cells. We also consider how each of these factors and their development are likely to drive fluctuations in child BLLs over time. The goal of this special report is to provide a starting point for change in current child BLL testing practices. Solving the problem of child lead exposure will require new approaches to child BLL testing that take into account likely fluctuations in child BLLs.**

Introduction

Lead poisoning in U.S. children continues at staggering rates in selected sectors, particularly among those living in under-resourced communities where older unrenovated housing and lead paint are still major sources of exposure. In over 3,000 U.S. cities, child lead poisoning rates exceed those found in Flint, Michigan, at the height of the crisis (Pell & Schneyer, 2016, 2017). Solving the problem of lead poisoning in U.S. children will require accurate detection of exposed children. In many states, child BLL testing practices rely on single tests among only the youngest children (i.e., 0–5 years) to rule out lead exposure, implicitly assuming that one or two tests in early childhood can accurately reflect a child's ongoing exposure risk.

Lead exposure occurs via inhalation or ingestion. Among children, when exposure is chronic, 99% of absorbed lead is taken up by red blood cells (RBCs) (Agency for Toxic Substances and Disease Registry [ATSDR], 2017; deSilva, 1981) and child lead exposure is most commonly determined from whole blood samples. BLLs reflect circulating lead and, in many cases, exposure occurring in the preceding 28 to 40 days (Griffin et al., 1975; Rabinowitz et al., 1973).

The potent toxicity of lead during development has been attributed to many factors but in particular, lead structurally mimics calcium and causes multitiered damage in calcium-channel dependent pathways, systems, and organ mechanisms (Lidsky & Schneider, 2003). More specifically, Pb^{2+} readily enters RBCs because its radius is slightly smaller than that of Ca^{2+} (Kirberger & Yang, 2008; Simons, 1986a, 1986b). Lead also gains entry to RBCs when the permeability of cell walls shift the processes that are dependent on developmental and individual differences as well as exigencies in the child's environment (Hasan et al., 1967; Riordan & Passow, 1971; Vincent, 1958).

Once absorbed, Pb^{2+} binds to delta-aminolaevulinic acid dehydratase enzyme (ALAD), specifically the three-cysteine site of ALAD, replacing Zn^{2+} and interrupting the second step in heme synthesis (Gonick, 2011; Sakai et al., 1983). The binding affinity of Pb^{2+} is, in fact, greater than that of Zn^{2+} (Boudene et al., 1984; Gonick, 2011).

With regard to individual variability in these processes, there are three *ALAD* common genetic variants (*ALAD-1*, *ALAD-1-2*, and *ALAD-2-2*) that vary in their binding properties and thus their affinity for lead. *ALAD-2-2* has the highest affinity for lead (Gonick, 2011; Pérez-Bravo et al., 2004; Scinicariello et al., 2007) and is associated with higher BLLs in children (Kim et al., 2004; Pérez-Bravo et al., 2004; Scinicariello et al., 2007; Sobin et al., 2009, 2011, 2015; Wetmur et al., 1991). It is logical to suggest that the stability of BLLs over time in children with each of these genetic variants would be expected to differ.

Some key absorption mechanisms and their development throughout childhood suggest additional sources of variability and

TABLE 1

Summary of Developmental Influences on Lead Absorption and Re-Release Variability Throughout Childhood

Body System	Mechanism	Source of Variability
Respiratory (lungs)	Lead in gases and particles <100 nm enters via diffusion in alveoli (limited evidence for absorption of particles >100 nm); particles not expelled or ingested are absorbed into the bloodstream	Alveoli densities reach 93% by age 8 (Ahlfeld & Conway, 2014; Dunnill, 1962); full density not reached until approximately age 18 (Narayanan et al., 2012)
Digestive (liver)	Soluble and insoluble lead stored in hepatocytes via metallothionein binding reduces lead in blood	Decreased capacity to metabolize, detoxify, and excrete lead in newborns (Beath, 2003; Gow et al., 2001; Wells, 2017); liver does not fully mature until age 5
Circulatory (red blood cells)	Blood nutrient deficiencies allow lead binding to calcium, iron, and zinc sites	Malnutrition and genetic polymorphisms (*ALAD*) directly impact lead absorption by red blood cells, suggesting variability in lead absorption during childhood (Sobin et al., 2009, 2011, 2015)
Excretory (kidneys)	Metallothionein-bound lead is retained in nephron cell walls; active or passive transport along the nephron can re-release lead into the bloodstream	Mechanisms for filtration and excretion mature at age 2, while full kidney function is not reached until young adulthood (Blane et al., 1985; Čukuranović & Vlajković, 2005)
Endocrine (fat cells)	Initial evidence that lead is stored in fat; fasting, starvation, and exercise can trigger fat metabolism and re-release lead	Initial data suggest insecure food access, irregular eating habits, and/or empty gut can increase vulnerability to lead re-release
Skeletal (bone)	Accumulation in the inert and labile components of cortical and trabecular bone via binding to hydroxyapatite; low calcium blood levels break down hydroxyapatite and lead is re-released from bone into bloodstream	Broken bones, growth spurts during puberty, and deficiencies in bone nutrients can re-release lead into the bloodstream (Janz, 2002; Jones, 2011)
Central nervous system (brain)	Mimics calcium and activates calcium-dependent protein kinase (CDPK), crossing the blood-brain barrier (BBB), possibly disrupting the cohesiveness of the BBB and ability for astrocytes to maintain BBB integrity; inability to regulate the integrity of the BBB may allow for lead to be exchanged more easily between the brain and bloodstream	Nutrient deficiencies and stress can affect BBB integrity (Kadry et al., 2020), suggesting fluctuations in lead absorption through childhood

instability in child BLLs over time. Tables 1 and 2 provide an overview of the detailed information discussed in this special report.

Absorption of Inhaled Lead

Inhaled lead particles follow respiratory system pathways that are relatively well defined. Approximately 30–50% of inhaled lead is retained in the lungs (Chamberlain, 1983; Geiser & Kreyling, 2010) and the duration of respiratory exposure appears to increase absorption (Kastury et al., 2019).

Inhaled lead particles are drawn into the windpipe and bronchi, which have mucus-producing cells where cilia attempt to move dust-laden mucus upward and out of the lungs (Bailey et al., 2007). When trapping fails, dust is absorbed directly by the lung alveoli, a thin barrier of cells between air and blood capillaries (Bailey et al., 2007). In the alveoli, activated macrophages can engulf dust particles, preventing dust from reaching the bloodstream (Hamilton et al., 2008; James et al., 1994).

Absorption of remaining dust depends on particle size and shape; the distribution of particles is determined by air direction and air force. Ultrafine particles (<100 nm) quickly enter the bloodstream via alveoli. Mechanisms by which larger lead particles enter the bloodstream are not well understood, however, particularly in children. Larger lead particles (100 nm–5 μm) are deposited and can remain in different regions of the lungs from months to years before they are eventually absorbed, filtrating from the lungs to the heart and into the bloodstream, or expelled from the lungs and then ingested (Bailey et al., 2007; James et al., 1994; Kastury et al., 2019).

During development, absorption is also influenced by lung growth rate and maturity of alveoli. Lungs of children develop throughout childhood up until age 18 (Ahlfeld & Conway, 2014; Narayanan et al., 2012). It is estimated that by age 8 years, only 63% of alveoli have developed (Ahlfeld & Conway, 2014; Dunnill, 1962; Ochs et al., 2004). Fewer alveoli would be expected to result in poorer filtering capacity and higher absorbed lead. Coupled with relatively high respiratory rates, children at different ages have the potential to retain substantial amounts of inhaled lead, especially in the tracheobronchial and alveolar regions (Asgharian et al., 2004). Individual differences in lung development further complicate how and when lead absorption occurs at different ages.

Absorption of Ingested Lead

Compared with inhalation, ingested lead is influenced by relatively more complex and interacting factors including, for example, the bioaccessibility of the lead source, particulate size, site of absorption, individual differences in physiological and molecular lead-uptake processes, lead–nutrient interactions, whether ingestion occurs in an empty or full gut, and developmental and individual differences in the maturity of the gastrointestinal (GI) tract.

The bioaccessibility of a given lead source depends on its chemical form (Deshommes & Prévost, 2012); the chemical form determines the rate of absorption in the GI tract by altering how digestive proteins, gastric fluid pH, and other ions interact with lead (Deshommes et al., 2012). The chemical forms of lead that exist in non-nutritive substances—such as in leaded paint chips, paint dust, and in some contaminated soils—are far more bioaccessible than

the forms of lead commonly found in foods. In vitro digestion models have shown that the bioaccessibility of lead-contaminated soil from pottery industries typically ranges from 28% to 73% (Oomen et al., 2003). In contrast, the bioaccessibility of lead-contaminated soil at mining sites ranges from 2% to 33% (Ruby et al., 1992; von Lindern et al., 2016). The bioaccessibility of lead in water ranges broadly from 1.5% to 100% (Deshommes & Prévost, 2012), while the bioaccessibility of lead-contaminated household dust is from 28% to 100% (Sowers et al., 2021; von Lindern et al., 2016).

Many chemical forms of ingested lead have been identified and include sulfide, chloride, acetate, carbonate, chromate, monoxide, tetroxide, phosphate, and nitrate, all of which are found in the most common child lead hazard sources, but the bioaccessibility will vary depending on their form (speciation) as well as what matrix they are in (ATSDR, 2017) and goes directly into the stomach where multiple internal mechanisms influence both dissolution and speed of absorption. Gastric acid breaks down lead into more soluble forms. Human intestinal fluid studies and animal models have shown that an interacting complex series of chemical, biological, and biophysicochemical factors directly affect absorption of ingested lead, which creates the potential for broad fluctuation of lead in whole blood samples (Liu et al., 2021; Mushak, 1991). Importantly, lead can transform into different lead species in the gut during the digestion process when interactions with native stomach acids increase the lead solubility (Mushak, 1991).

Interestingly, the electrical charge associated with lead influences its diffusion rate in intestinal cells. Ionized forms of lead have higher affinity for intestinal cell junctions that rely on ionic mechanisms for the transport of essential cations including Ca^{2+}, Mg^{2+}, Fe^{2+}, and Na^+ (Jaishankar et al., 2014). For example, lead–bile complexes convert to ionized lead and transport lead into intestinal cells—a process not yet well understood (Oomen et al., 2003).

Lead absorption in the small intestine occurs primarily in the duodenum (upper first sections) via passive diffusion and active transport (Mushak, 1991). In the ileum (third section), micelles form, capture lead in the spaces of the intestines, and are absorbed through the intestinal walls via pinocytosis (Teichmann & Stremmel, 1990). Lead can also pass

TABLE 2

Sources of Variability in Key Lead Absorption Mechanisms by Body System

Body System	Absorption Mechanism	Factors Contributing to Blood Lead Level Variability
Respiratory	• Particles >5.0 μm mainly deposit in the nasopharyngeal region • Particles 2.0–5.0 μm can penetrate the tracheobronchial region • Small particles <0.5 μm and very small particles <1.0 μm can penetrate deep into the alveoli, remaining for months to years • Soluble gases and particles <100 nm enter directly into the bloodstream via diffusion in alveoli	• Lead particulate size • Duration of inhalation • Frequency of exposure • Respiratory rate • Alveoli density • Individual respiratory system differences
Digestive	• Passive and active transport via enterocytes in the gut and small intestine	• Bioaccessibility of lead hazard source • Lead particulate size • Lead chemical form • Absorption site • Lead–nutrient interactions and nutrient deficiencies • Maturity of the gastrointestinal tract • Individual differences in physiological and molecular lead uptake • Food intake variability
Blood	• Active transportation in red blood cells via using calcium- and zinc-activated proteins	• Oxidation stage of lead • Concentration of lead • Nutrient deficiencies • Genetic (*ALAD*) predisposition influencing lead absorption

through the tight spaces between the enterocytes that line the stomach, small intestines, and colon (Kiela & Ghishan, 2016; Mushak, 1991) or can be engulfed by macrophages and/or micelles from the cell membrane of enterocytes. Via these mechanisms, lead can then travel into the bloodstream. While any of these mechanisms can deliver lead into the circulatory system via the liver (Liu et al., 2021; Mushak, 1991), most ingested lead (70–90%) is excreted in urine or feces; sequestered lead can be retained in cells for varying periods of time (Leggett, 1993; O'Flaherty, 1998). Age and maturity of the GI tract influence the functioning of these mechanisms and thus affect lead absorption and excretion.

Eating patterns also affect absorption. Absorption is substantially greater when the stomach is empty (Blake et al., 1983; Blake & Mann, 1983; Heard & Chamberlain, 1982; James et al., 1985), thus the timing of meal and dietary nutrient intake can block

or enhance lead absorption. In children 3–5 years, those who ate breakfast compared with those who did not had lower BLLs after controlling for nutritional and demographic variables (Liu et al., 2011). If a child's stomach is near empty, Pb^{2+} absorption can be as high as 100% (ATSDR, 2017; Heard & Chamberlain, 1982; Rabinowitz et al., 1980). High gut absorption in children has been attributed to developmental and individual differences in calcium-binding proteins and gut acid (Deren, 1971; Mushak, 1991). Also, the risk of exposure from tap water can be increased when children with empty stomachs drink more due to hunger (Heard & Chamberlain, 1982).

Lead in combination with another ion and/or vitamin can facilitate or block absorption of lead in the GI tract. One obvious critical lead–nutrient interaction is with calcium (Blake & Mann, 1983; Elias et al., 2007; Heard & Chamberlain, 1982; Schell et al., 2004; Ziegler et al., 1978). Another critical

interaction is with iron. Similar to calcium, iron deficiencies in children are associated with higher BLLs (Marcus & Schwartz, 1987; Schell et al., 2004; Wolf et al., 2003) and animal studies have shown that lead competes with iron absorption in the intestines (Bannon et al., 2003; Morrison & Quarterman, 1987). Thus, more lead is absorbed when a child is iron deficient, when lead replaces iron in the receptors and/or binding proteins found in the intestines.

With regard to individual differences, there are at least two inherited conditions that directly impact iron metabolism: hemochromatosis and transferrin genes (Hopkins et al., 2008), both of which have been associated with higher BLLs in children. With regard to four clinically recommended nutrients to reduce lead absorption (calcium, iron, vitamin C, and zinc), there is limited evidence that the supplementation of these nutrients prevents lead absorption in nutritionally robust children (Kordas, 2017).

Post-Absorption Mechanisms and Potential for Re-Release

Once in the bloodstream, lead is passed between blood and organs via carrier-mediated transportation (active transport) and diffusion (Leggett, 1993; O'Flaherty, 1998). Absorbed lead is transported via RBCs to soft tissue organs (liver, kidneys, lungs, brain, spleen, muscles, and heart) and exchanged, filtered, and/or trapped to differing degrees, depending on the organ. Ultimately, lead that is not excreted is stored in mineralized tissues (bone and teeth). The amount of lead that remains in the blood rather than transferring to organ tissues depends on multiple shifting factors.

Lead elimination occurs primarily via the kidneys (Lentini et al., 2017). The remaining lead, referred to as total lead body burden, is transported back and forth between the blood system, soft tissue, and mineralizing tissues in a continual process of lead concentration equilibrium (Marcus, 1985; Rabinowitz et al., 1973; Smith et al., 1996). Total lead body burden is dependent on the frequency of lead exposure, concentration, distribution, metabolism, and ability to eliminate lead from the body through urine or feces, as well as developmental and individual differences in the implicated body systems of children.

Furthermore, several mechanisms facilitate or oppose the distribution of lead into tissues. Simple diffusion and carrier proteins for calcium facilitate the transfer of lead into soft tissues (Rădulescu & Lundgren, 2019). In contrast, plasma proteins such as albumin, transferrin, globulin, and lipoproteins oppose and limit distribution by binding to lead molecules (Gonick, 2011). Unbound lead passes through capillary endothelial cells into the extravascular space for tissue storage. Of note, the immaturity of this mechanism in young children does not allow tissue absorption and reabsorption, leaving greater amounts of lead in circulating blood. Site-specific proteins and interstitial conditions can also contribute to BLLs (Table 1).

Two mechanisms in the liver act simultaneously to remove lead from blood and retain lead in hepatocytes (Braet & Wisse, 2002). Inorganic lead, the most common form absorbed by children, is stored in the liver via the fenestrate, a layer of endothelial cells with scattered small and large pores lining the liver sinusoids (ATSDR, 2017; Beath, 2003). A second retention mechanism involves metallothionein, an intracellular protein that, once bound to lead, ensures that the lead does not exit hepatocytes (Gonick, 2011). The hepatocytes, submucosal and mucosal layers, and bile duct size do not mature in young children until the age of 2 years (Gow et al., 2001; Wells, 2017); the transition to a single cell wall of hepatocytes is not complete until age 5 years (Morgan & Hartroft, 1961). Thus, depending on the age of the child and individual differences in development, these mechanisms might or might not be mature enough to consistently metabolize, detoxify, and/or excrete lead, contributing to increased or fluctuating BLLs (Allegaert et al., 2007; Gow et al., 2001; Wells, 2017).

Reabsorption of lead into the kidney is another mechanism that influences BLLs. Lead is reabsorbed through active or passive transport mechanisms along three main sections of the nephron: the proximal convoluted tubule (via both passive and active transportation), predominately in the ascending limb of the loop of Henle (mainly via active transportation), and the distal convoluted tubule (mainly via passive transportation) (Fowler & DuVal, 1991; Kwon et al., 2015). When lead binds to metallothionein, it is retained in the cell wall of the nephron (Fowler & DuVal, 1991). Another pathway for reabsorption of lead is by erythrophagocytosis effected via macrophages in the epithelial cells that line the proximal convoluted tubule (Kwon et al., 2015). Thus, lead in degrading RBCs is engulfed and removed; reabsorbed lead is then transported to the peritubular capillary network, eventually leading into the bloodstream. Lead that is not reabsorbed exits the nephron as urine.

The mechanisms responsible for kidney filtration and excretion mature at different ages. Nephrons and tubular structures continue to grow until approximately 1 year; kidney excretion mechanisms (via the parenchyma) mature when the child is approximately 7 months (Čukuranović & Vlajković, 2005; Weinstein & Anderson, 2010). Kidney perfusion and glomerular filtration rates reach full capacity by approximately 2 years; urine concentration capacity matures by 18 months; and renal blood flow by 1 year. Importantly however, full renal function is not complete until young adulthood (approximately 25 years) (Čukuranović & Vlajković, 2005; Davies & Shock, 1950; Levey et al., 2003; Weinstein & Anderson, 2010). The kidneys do not reach maximum functional capacity until early to middle adulthood (between 20 and 30 years) (Blane et al., 1985; Čukuranović & Vlajković, 2005). These age-related factors necessarily influence the amount of lead detectable in circulating whole blood.

Individual differences in children are also important to consider. For example, lead can be stored in body fat. While lead concentrations in fat might be lower than in other types of tissues initially, with chronic exposure they can begin to equal BLL concentrations (Mikalsen et al., 2019; Riedt et al., 2009). Lead stored in fat can be re-released into the bloodstream when fat reserves are mobilized, such as during fasting, hunger, starvation, or exercise (Mikalsen et al., 2019; Riedt et al., 2009). Thus, children with insecure food access or irregular eating habits, who are likely to be at highest environmental risk of lead exposure, might mobilize fat stores more frequently (Dhurandhar, 2016; Pan et al., 2012; Tester et al., 2020).

Approximately one half of the lead that the body absorbs is stored in bone/mineralized tissues, accounting for an estimated 74% of the total lead body burden in children (Barry, 1975, 1981). The storage is relatively temporary, however, because bone tissue re-releases lead via different types of biological processes. Depending on the type and duration of expo-

sure, from 40–70% of circulating lead can come from stores in the bones (Smith et al., 1996).

How and when lead is re-released into the bloodstream depends on the concentration of lead in the outer layers of the bone and the body's demand for calcium (Dowd et al., 2001; Stojsavljević et al., 2019). Lead accumulates in the inert and labile components of cortical and trabecular bone. The inert component is closer to the center of the bone, which can store lead for decades. The labile component is located toward the outer layers of the bone and can easily exchange lead from bone to blood (Stojsavljević et al., 2019). Lead stored in the inert component can mobilize to the labile component with time or in situations where the body releases calcium from the bone, such as when a child suffers a broken bone.

The mechanism by which lead is exchanged between blood and bone mimics that of calcium exchange. Lead can bind to hydroxyapatite (a calcium phosphate mineral that serves as a calcium reserve for the body) and fluctuates according to the concentration of calcium found in the blood (Dowd et al., 2001; Pounds et al., 1991; Saisa-ard et al., 2014). Deficiencies in calcium, phosphorus, and vitamin D result in higher lead bone storage and more frequent re-release (Jones, 2011).

Bone growth in children creates multiple opportunities for lead to be reintroduced into the bloodstream. The largest growth spurt occurs during puberty when there is a greater demand for hydroxyapatite formation (Stagi et al., 2013). Females reach full height at approximately 15 years and continue to build bone mass until 21 years. Males grow until approximately 18 years and build bone mass up to 12 months after reaching full height (Jones, 2011). Also, lead is released during states of high bone turnover such as following bone fractures or in children with conditions that prevent bone mass formation (e.g., osteoporosis, conditions that limit physical activity) (Janz, 2002). Age-based differences, individual differences in stored bone-forming nutrients, and bone injuries can all explain BLL spikes in some older children.

Summary

Current practices for BLL testing in children that rely on one or two BLL tests administered to only the youngest children (i.e., 0–5 years) are not aligned with knowledge regarding the complexity of lead absorption, transport, and disposition in the body throughout childhood and adolescence. In the respiratory system, lead deposition and absorption rates are complex and depend on many changing factors, including lead particulate size, length, frequency of exposure, respiratory rate, where in the lungs lead particulates are deposited, and importantly, individual differences in the development of the lungs and alveoli.

Ingested lead is influenced by complex interactions of chemical, biological, biophysicicochemical, and behavioral factors related to dietary intake, dietary deficiencies, and maturity of the GI tract. These interactions of factors can be additive, antagonistic, or synergistic. Once in the bloodstream, lead absorption by RBCs is influenced by common (*ALAD*) genetic variants and by ongoing fluctuations in calcium, iron, and zinc levels. Additional age-dependent factors facilitate and oppose the distribution of lead into tissues and re-release of lead into the circulatory system.

Current approaches for BLL testing in children inadvertently do not take into account the likely fluctuations in child BLLs described previously in this article. As Sobin et al. (2022) discussed, a revision of current practices is needed to ensure feasibility for monitoring highest-risk children. Suggested revisions include:

- Acceptance of capillary samples for final determination of lead poisoning, with electronic documentation of "clean" collection methods submitted by workers.
- New guidance specifying analysis of capillary samples by inductively coupled plasma mass spectrometry or graphite furnace atomic absorption spectrometry with documented level of detection ≤0.2 µg/dL.
- Adaptation of universal testing and monitoring guidance that is census tract-specific for children from birth to 10 years.

These changes to current practices can immediately increase our national capacity for inclusive and equitable detection and monitoring of BLLs, particularly for dangerous lower-range BLLs in children in the U.S. ❧

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