Lead Poisoning: An Update

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PRACTICE GAPS

1. Whole blood is used to measure lead, which limits interpretation of blood lead level results.
2. The current lead poisoning intervention level is based on epidemiology, not toxicology.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe updated knowledge about lead poisoning in children.
2. Explain why we use blood lead levels (BLLs), describe limitations in BLL interpretation, highlight the current reasons for intervening for a BLL of 5 μg/dL (0.24 µmol/L), and report the discovery of old lead sources (water and paint) in new locations (schools).
3. Discuss outcomes that support the reversibility of lead effects after treatment.

DEFINING LEAD POISONING

Lead (Pb) poisoning can be assessed at 3 levels: the fundamental biochemical effects, subclinical organ dysfunction, and clinical disease. The presence of Pb in a child's blood sample is an indicator that exposure and absorption have occurred. The blood Pb level (BLL) is a measure of potential toxicity because it is correlated with various health outcomes in groups of children. However, there are limitations to interpreting individual results. What is measured is not plasma Pb, the immediate and most threatening component of blood Pb, which can leave the blood compartment and enter cells. Rather, due to historical laboratory limitations, it is overwhelmingly (~98%) red blood cell Pb content that is assessed. Thus, the BLL is a surrogate measure 2 steps removed from tissue cell Pb, the site of most toxicity. In addition, the reside time (similar to half-life, a term that is strictly defined as the time for radioactivity of an isotope to fall by 50%) of Pb atoms in blood is very different from that in the organs where it accumulates. If Pb atoms are injected into blood, half are gone in approximately 3 weeks. In contrast, those that reach and enter brain cells remain for 1 to 2 years. Most Pb in the body accumulated through long-term exposure is found in the skeleton, where it can remain for years to decades.

Finding Pb in a single blood sample, assuming that it accurately reflects the amount of Pb in the child's blood at that moment and is not due to contamination of the sample or other laboratory issues, does not define duration of Pb

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exposure, Pb accumulation, or degree of toxicity. It does indicate past or current exposure. However, because we have many studies correlating BLLs in populations to health outcomes, it remains the gold standard for assessing the risk of harm. Newer laboratory methods, such as inductively coupled plasma mass spectrometry, that are becoming more widely available enable measurement of nanograms per deciliter amounts of Pb in plasma. These newer methods may allow us to finally define a threshold for Pb toxicity risk using this measure. At the present time, a "safe" BLL has not been determined, ie, any BLL greater than 0 μg/dL (>0 μmol/L) may be associated with toxicity in susceptible people.

BIOCHEMISTRY OF LEAD

Children ingest Pb. Rarely does Pb enter a child's body via inhalation and lung absorption. With few exceptions, Pb compounds do not significantly penetrate skin via topical application to appreciably alter BLLs. Pb does cross the placenta; BLLs in pregnant women and fetuses are highly correlated.

When Pb-containing particles such as paint chips or the dust derived from such chips are swallowed, only a tiny amount is digested sufficiently to cause the release of Pb ions into a liquid phase. This prevents the death that could occur from eating a single premium paint chip of the 1930s and 1940s the size of a child's thumbnail. That chip could contain 500,000 μg of Pb. However, only a few micrograms will be released to become available for absorption. Although Pb atoms have an atomic weight of approximately 207 and calcium (Ca) has an atomic weight of approximately 40, the Pb atom is packed much more densely, yielding a smaller radius. It can slip through Ca channels to enter cells (Fig 1).

Within cells, Pb distributes throughout the cytoplasm and nucleus. Pb binds to proteins via competition with Ca, zinc, and other metals at ionic binding sites as well as to accessible sulfhydryl, amine, phosphate, and carboxyl groups. It induces conformational changes, thereby altering function. For example, calmodulin is a critical protein that normally binds Ca, which activates the protein, making it capable of multiple downstream actions. Pb diminishes those functions (Fig 1). Pathways of molecule production can be affected by Pb at multiple enzymatic steps. Best described is the Pb impairment of the heme pathway (Fig 2). Heme is not only a part of hemoglobin, but also an essential component of cytochrome p450 enzymes that are engaged in steroidogenesis, vitamin D metabolism, detoxification, and fatty acid metabolism. The cytochrome p450 enzyme pathway is so crucial that it is ubiquitously distributed in nearly all cells of the body. Three of the 8 enzymes in the pathway are susceptible to Pb inhibition. The second enzyme, δ-aminolevulinic acid dehydratase (ALAD), is a major Pb binder in erythrocytes and is very sensitive to Pb. BLLs of at least 10 μg/dL (≥0.48 μmol/L) inhibit this enzyme's function sufficiently

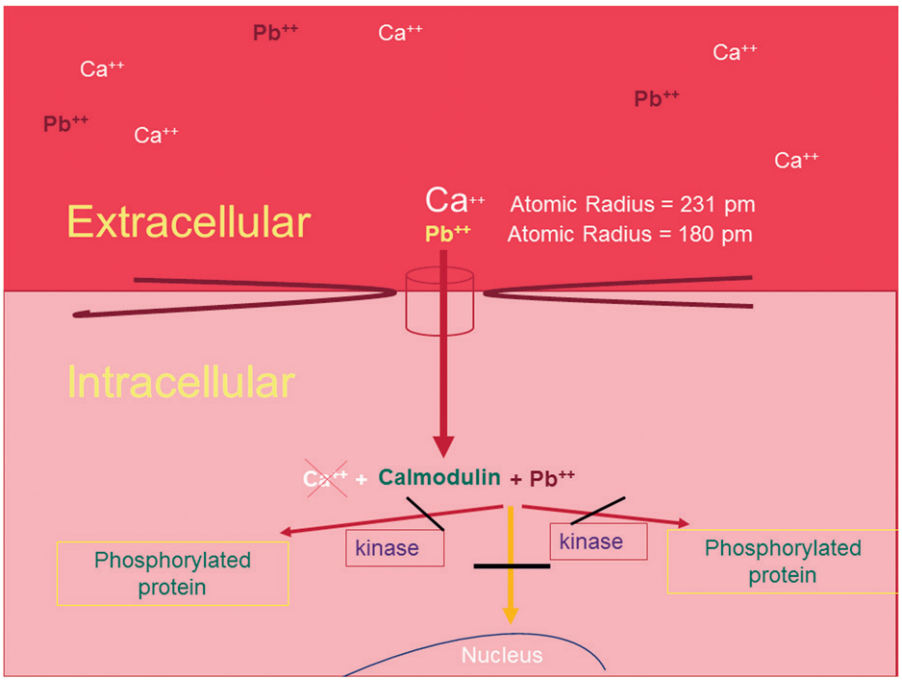

Figure 1. Biochemical lead (Pb) toxicity: Entry pathway into cells and an example of Pb binding to a calcium (Ca) binding protein, which disrupts downstream calmodulin-mediated activity. The darker red area represents the extracellular/blood space; the pink area represents the intracellular space. The thick purple arrow indicates the flow of Pb and Ca ions through the Ca channel. The black crosshatches of arrows indicate Pb-induced dysfunction of the represented enzymes.

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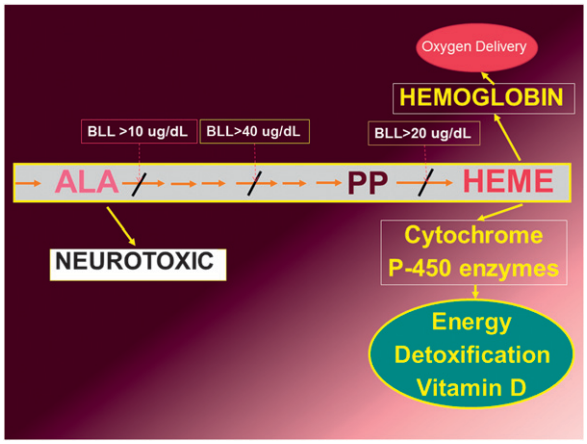

Figure 2. Heme pathway lead (Pb) susceptibility: Representation of the heme pathway. Solid orange arrows indicate enzymes. The black crosshatch indicates that the enzyme is sensitive to Pb. The blood Pb level (BLL) above the enzyme indicates the threshold for effects. Other text indicates effects of substrate or product. ALA=δ-aminolevulinic acid; PP=protoporphyrin.

to raise the concentration of its substrate, δ-aminolevulinic acid. Congenital deficiency of ALAD results in one of the porphyria syndromes, indicating that excess of this enzyme's substrate may be toxic. Of interest, patients who receive chelation therapy for Pb poisoning resulting in a reduction in BLLs have an immediate recovery in ALAD function. Polymorphisms in the *ALAD* gene result in the production of proteins with different Pb binding affinities; these may differentiate populations at risk for Pb toxicity, ie, while the protein's enzymatic function may decline it acts to sequester Pb, thus preventing toxicity elsewhere. The last enzyme in the heme pathway is ferrochelatase. This enzyme promotes the binding of iron (Fe) into protoporphyrin. Pb levels greater than 20 μg/dL (>0.97 μmol/L) are associated with impaired enzyme function, resulting in increased protoporphyrin levels as well as eventually reducing heme production. In children with higher BLLs, the serial measurements of erythrocyte protoporphyrin levels is a useful indicator of not only the effects of Pb but of the success of interventions to reduce a child's body Pb burden. Protoporphyrin levels fall slowly after further Pb ingestion is prevented. In summary, the cellular effects of Pb result not only in reduced essential product production but also in increases in unmetabolized substrate concentrations that can themselves be toxic.

SUBCLINICAL EFFECTS OF LEAD

When enough biochemical disturbances accumulate in an organ, subclinical disease occurs. The organ that seems to be most sensitive to Pb is the brain, and it is the effects on the brain that have largely driven public health efforts to eliminate childhood Pb exposure during the past 40 years or more. Tests of cognitive and behavioral function indicate inverse relationships with BLLs across the age spectrum; it is not limited to children. Indeed, studies of maternal plasma Pb concentrations or BLLs during pregnancy, including the first trimester, find inverse correlations with offspring cognitive scores even 2 years after birth. The estimate of the association between BLLs and IQ-type scores derived from multiple studies of children is an approximately 0.5–IQ point loss for every 1-μg/dL (0.05-μmol/L) increase in BLL, although the association may not be linear. In a composite analysis of 7 longitudinal studies of more than 1,300 children, BLLs of 2 to 10 μg/dL (0.10–0.48 μmol/L) were associated with a 4-point drop in IQ versus an additional 2-point drop for BLLs of 10 to 20 μg/dL (0.48–0.97 μmol/L), indicating a curvilinear relationship.

Other organs are also affected subclinically. Pb inhibits erythropoiesis, in part via reduced erythropoietin production. At high Pb concentrations, red blood cell survival time is shortened. Renal impairment eventually results in gouty nephropathy with a diminished glomerular filtration rate and development of Fanconi syndrome. Spermatogenesis is abnormal, with reduced numbers of sperm and less motile sperm. It seems that no organ is free of Pb effects. Epidemiologic studies link BLLs of 0 to 40 μg/dL (0–1.93 μmol/L) inversely to height in children, although not a sufficient decrease in height to result in endocrinology referrals for short stature. Similar studies indicate reductions in ability to hear across all frequencies, ie, it takes more volume for sounds to be heard as BLLs increase. Blood pressure rises as BLLs increase, initially without symptoms associated with elevated blood pressure.

CLINICAL EFFECTS OF LEAD

Encephalopathy, seizures, and death are rarely reported at BLLs less than 100 μg/dL (<4.83 μmol/L) in children. However, fetal Pb exposure increases the risk of demise at much lower levels. In a study conducted in a Mexico City, Mexico, cohort of women enrolled in the first trimester of pregnancy, the risk of fetal loss doubled in women with initial BLLs of 5 to 10 μg/dL (0.24–0.48 μmol/L) compared with a group with BLLs less than 5 μg/dL (<0.24 μmol/L) and doubled again in the group with BLLs of 10 to 15 μg/dL (0.48–0.72 μmol/L). A recent analysis of adults 20 years and older who had BLLs measured and then tracked over the next 19 years found that the risk of death from cardiovascular causes was increased 70% as

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BLLs varied between 1.0 and 6.7 μg/dL (0.05–0.32 μmol/L) (10th and 90th percentile). No similar studies of mortality risk at low BLLs have been reported in children.

At levels greater than 100 μg/dL (>4.83 μmol/L) the risk of death increases in children. In the United States, there has not been a death attributed to such BLLs in more than 10 years. However, in other parts of the world, lead poisoning is still a killer. Around 2010 and again in 2015, in agrarian regions of northeastern and central Nigeria, public health workers discovered that more than 400 young children had died as a result of lead exposure that came from gold extraction efforts.

Behavioral issues have been linked with BLLs of 20 μg/dL or greater (≥0.97 μmol/L) in school-age children, including attention deficits and disruptive and aggressive activities. Levels of Pb exposure have been highly correlated with violent criminal behavior, after correcting for approximately a 20-year lag time, ie, higher early childhood Pb exposure was associated with higher violent crime rates occurring 20 years later.

Epidemiologic studies also link BLLs with number of dental cavities, indicating a need for careful attention to teeth during the evaluation and treatment of Pb poisoning. Gastrointestinal complaints consist of abdominal pain, constipation, and loss of appetite. Although constant abdominal pain (colic) is associated with BLLs of 50 μg/dL or greater (≥2.42 μmol/L), intermittent recurrent gastrointestinal symptoms were found to be twice as common in young children with BLLs greater than 20 μg/dL (>0.97 μmol/L) compared with those with BLLs less than 20 μg/dL (<0.97 μmol/L): 40% vs 20% in 1 unpublished study.

SOURCES OF PB EXPOSURE

Largely because Pb-containing paint was highly promoted and used in the United States, especially during the first half of the 20th century, the legacy of Pb poisoning continues to the present day. Ingestion of Pb paint or its derivative dust is the main source of Pb poisoning in children. Whereas several countries banned the use of Pb-based paints in the early 20th century, the United States did not set national limits until 1978, when a less than 0.07% cap on allowable Pb content came into effect. The Consumer Product Safety Commission (CPSC) revised that limit to 0.009% in 2009. State and local governments set limits well before the federal government. New York State capped the allowable amount of Pb in paint in 1970, and Baltimore, Maryland, banned Pb paint in 1951. The laws applied to Pb paint were intended for household use; apparently no such limit was imposed on schools. For example, the New York City Department of Education continued Pb paint applications until 1985. This was uncovered in 2019 when a reporter visiting his child's first grade class found paint chips on the floor next to the rug that she sat on. Looking up he saw a crack under the windowsill. He had the paint chips analyzed and found that they were highly leaded. Continuing to collect samples of chips and dust from 4 other schools built before 1985, he found all samples to contain Pb. The published story motivated the Department of Education to conduct a systematic evaluation of New York City classrooms serving 3- to 6-year-olds in schools built before 1985: 20% (~1,800 classrooms) were found to have hazardous Pb paint conditions. Abatement efforts were made during the following summer vacation. Were the kids in those classrooms harmed? No systematic blood Pb testing or comparison of cognitive performance was performed to answer that question. Pb paint in schools is a potential major source of exposure.

Because this versatile metal has hundreds of other commercial uses, Pb can come from many sources. Old sources include the gasoline additive tetraethyl lead. Unlike other Pb compounds, tetraethyl Pb can penetrate skin. Unfortunately, with tetraethyl Pb, while the gasoline's hydrocarbons burned, the Pb was ejected into the air. Tetraethyl Pb use widely disbursed Pb, causing contamination of surfaces, including soil, especially in urban areas. Tetraethyl Pb use was phased out beginning in the 1970s in the United States after being used extensively since its introduction in the 1920s. Food and beverage cans were sealed with Pb solder until the 1980s, which contaminated foods and drinks, particularly those that were acidic. Today, the CPSC and the Food and Drug Administration (FDA) regularly report new items with unacceptably high Pb levels that result in product recalls. Product recalls may include contaminated foods (especially spices), pottery, cooking utensils, traditional medicines, jewelry, cosmetics, toys, crayons, cable sheathing, pipes, furniture, and more (Table 1). Most of these products are imported.

Pb in water resurfaced as a concern in 2014 because of contamination of the Flint, Michigan, water supply when the source was changed. The new water supply corroded old Pb pipes, which released Pb into the drinking water. Similar to paint, Pb pipes were extensively promoted for water company use: for main pipes from water treatment plants, leader pipes connecting water mains in the streets, and pipes within buildings and homes. Pipe connections used Pb solder. Brass faucets contained 8% to 25% Pb. If water is acidic, it can leach Pb from these fixtures. Generally, standing water (from taps not in use for hours) can

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Table 1. Sources of Lead Exposure

SOURCE	COMMENTS
Paint chips/dust	Houses built before 1950, renovations causing lead-laden dust
Contaminated soil	Leaded gasoline use deposited 4–5 million tons of lead in soil; frequent oral mouthing behaviors in children, urban living with higher traffic areas
Air	Leaded gasoline was the dominant source; industrial emissions now account for most airborne lead
Water	Lead-soldered pipes and hot water permits more leaching of lead into the water
Folk remedies	Litargio, Greta, Azarcon, Alkohl, Bali Bali, Coral, Ghasard, Liga, Pay Loo Ah, Reuda, Ayurvedic medicines
Parental occupational exposure	Transportation workers, soldering work, stained glass work, battery reclamation, automobile repair
Other imported sources	Imported toys and foods, ceramics, pottery, cosmetics such as surma (eye makeup in South Asia), soldered pots, kettles

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have the most Pb if the Pb sources are within the property, ie, not from the mains under the streets. This standing water Pb can usually be flushed out by letting water run for 1 to 5 minutes before using. Although BLLs may have increased in tested children living in Flint homes with Pb-containing water, it did not seem that severe poisoning occurred. The discovery raised sufficient concern such that water testing was performed in many other US locations. For the first time, New York State mandated that all of the state's public schools test the tap water. New York City discovered that nearly 90% of its public schools had at least 1 faucet yielding water with Pb over the Environmental Protection Agency (EPA) household water limit of 15 μg/L (15 ppb). Note that this standard is targeted at water-providing companies and is not health based. Currently, the American Academy of Pediatrics recommends that no more than 1 ppb of Pb should be in drinking water. The EPA is in the process of revising its Pb standards, although a drop to 1 ppb is highly unlikely.

EPIDEMIOLOGY OF PB

For more than 50 years, the Centers for Disease Control and Prevention (CDC) has been conducting surveys, the NHANES, to determine the general health of the US population. The NHANES II was the first to include BLL measurements in the more than 20,000 participants aged 1 to 70 years (Fig 3). From these data the CDC determined the ages when BLLs are highest and derived the concepts of blood Pb screening to test the groups of children at highest risk. The peak BLLs were observed at ages 2 to 3 years. The original risk factors that were identified were being poor, living in old housing (especially in cities), and belonging to a minority race/ethnicity. Recognizing that environmental exposure combined with nonnutritive

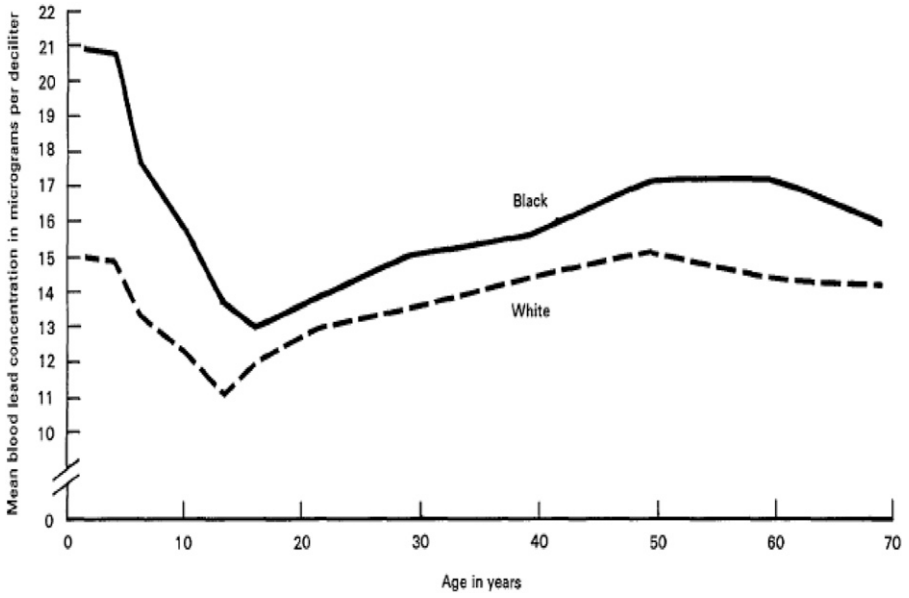

Figure 3. Average blood lead levels (BLLs) in a representative sample of the US population, 1976 to 1980. Although BLLs are highest in preschool-age children, they remain detectable across the pediatric age spectrum. (Reprinted with permission from Annest JL, Mahaffey K. National Center for Health Statistics. Blood lead levels for persons ages 6 months - 74 years, United States, 1976 - 80. *Vital and Health Statistics.* 1984;11(233).)

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hand-to-mouth activity is the combination that results in most Pb poisoning, screening guidelines were developed that indicated the need to test children at ages 1 and 2 years: age 1 year to identify those already ingesting Pb to intervene and prevent further ingestion and again at age 2 years because the ability to walk and climb could increase access to new Pb-containing locations in the child's environments during the period when continuing nonnutritive hand-to-mouth activity is still developmentally normal. Other risk factors were identified later, including being an immigrant from a poor country.

Because ingestion is the main entry route, pica behavior at any age is a risk factor. A careful examination of the relationship between BLLs and age shows that although there is a sharp decline in average BLLs after age 3 years, the drop is only approximately one-third from the peak level. So, for example, if the peak BLL in 2- to 3-year-olds averaged 12 μg/dL (0.58 μmol/L), then the level in 4- to 19-year-olds was approximately 7 to 8 μg/dL (0.34–0.39 μmol/L). In other words, the risk of having Pb poisoning did not decline to zero in the older participants in this cohort (Fig 3). This could reflect bone Pb accumulation that occurred at earlier ages with slow steady release into the bloodstream or new ingestions occurring in either a smaller part of the cohort or to lesser amounts of Pb ingestion. Given that hand-to-mouth activity does not end at age 3 years but declines in prevalence only, it could be that persistent ingestion of Pb dust from contaminated hands is sufficient to account for the occurrence of measurable BLLs in older children. Although epidemiologic data to determine the prevalence of non–food-related hand-to-mouth activity in general populations are lacking, smaller studies are informative. A study of 343 medical students in Poland found that 20% were nail biters at the time of assessment; an additional 27% had previously been nail biters.

Since the 1970s, average BLLs have declined by more than 90%. With that reduction, the severity of Pb poisoning in the United States has also improved dramatically, with the near elimination of Pb-related childhood mortality. Unfortunately, Pb remains a killer in other parts of the world.

UNDERSTANDING BLOOD PB MILESTONES

Although the BLL is our gold standard for determining Pb exposure, ingestion, and risk of toxicity, there are caveats to interpreting BLLs in individual children. As noted previously herein, the BLL is a whole blood measure because most of the Pb is attached to red blood cells and is not in plasma; the reside time is much shorter in blood than in target tissues; BLL does not define duration of exposure or total Pb accumulation, and BLL is not a direct measure of Pb effects. There are testing method concerns. Capillary blood, while convenient to obtain and useful for screening, is subject to contamination and hence false-positives; squeezing hard to obtain the drop of blood may dilute the sample with extracellular fluid, giving a false-negative. Positive screening with capillary blood is to be immediately confirmed with venous sampling. Fingerstick false-negatives are simply not identified. For venous samples, the CDC requires laboratories to have measurement error ranges of less than ±4 μg/dL (±0.19 μmol/L) or 10% to pass proficiency testing for certification. In addition, considering that cognitive scores are the main health outcome measure of concern, we have yet to define a safe BLL, ie, a level below which no discernable health effect can be observed.

So how then should we interpret our gold standard results? (CDC interpretation guide: Tables 2 and 3) The following numbers represent BLLs that should trigger certain clinical responses.

First Number: 5 μg/dL (0.24 μmol/L)

Studies have repeatedly shown that cognitive scores and BLLs are inversely related, with an apparent decline beginning as BLLs increase above 0 μg/dL (0 μmol/L). The implication of this observation is that toxicity is associated with BLLs somewhere between 0 and 1 μg/dL (0 and 0.05 μmol/L). That threshold for effect has not been determined because previous studies used laboratory methods that were unable to accurately measure submicrogram quantities of Pb in blood. In the absence of a defined toxicity BLL threshold, when should interventions begin?

The CDC Lead Advisory Committee has grappled with this question for decades. In 2012 its members chose to use an epidemiologic basis for selecting children most in need of care. Around 2010, an NHANES cohort that included BLL data collected from children 1 to 6 years of age showed that the top 2.5% of the distribution had a BLL of 5 μg/dL or greater (≥0.24 μmol/L). Offering health-care resources for the population in this tail of the BLL distribution curve would mean that, in 2012, approximately 500,000 US children would be eligible for public health and medical intervention nationwide. Using an epidemiologic approach to bypass the question of determining a Pb effect threshold based on a measured BLL meant that as future surveys provided new data, the intervention level for 2.5% of young children with the highest levels could

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Table 2. Actions Based on Blood Lead Levels as per the Centers for Disease Control and Prevention

<5 μg/dL (<0.24 μmol/L)	5–9 μg/dL (0.24–0.43 μmol/L)	>9–19 μg/dL (>0.43–0.92 μmol/L)	>19–44 μg/dL (>0.92–2.13 μmol/L)	>44–69 μg/dL (>2.13–3.33 μmol/L)	>69 μg/dL (≥3.33 μmol/L)
Routine assessment of nutritional and developmental milestones	Routine assessment of nutritional and developmental milestones	Routine assessment of nutritional and developmental milestones	Complete history and physical examination with neurodevelopmental assessment	Complete history and physical examination with neurodevelopmental assessment and complete neurologic examination	Hospitalize and commence chelation therapy in conjunction with consultation with a medical toxicologist or a pediatric environmental health specialty unit
Anticipatory guidance about common sources of lead exposure	Environmental exposure history to identify potential sources of lead and environmental investigation of the home to identify potential sources of lead, as required	Environmental exposure history to identify potential sources of lead and environmental investigation of the home to identify potential sources of lead	Environmental investigation of the home and lead hazard reduction	Environmental investigation of the home and lead hazard reduction	Environmental investigation of the home and lead hazard reduction; child receiving chelation therapy should not return to home until lead hazard remediation is completed
Follow-up blood lead testing at recommended intervals based on child's age according to schedule in Table 3	Follow-up blood lead monitoring at recommended intervals according to schedule in Table 3	Follow-up blood lead monitoring at recommended intervals according to schedule in Table 3	Follow-up blood lead monitoring at recommended intervals according to schedule in Table 3	Follow-up blood lead monitoring at recommended intervals according to schedule in Table 3	Follow-up blood lead monitoring at recommended intervals according to schedule in Table 3
Nutritional counseling related to calcium and iron intake	Nutritional counseling related to calcium and iron intake; consider laboratory work to assess iron status	Laboratory work: – Iron status – Hemoglobin or hematocrit	Laboratory work: – Iron status – Hemoglobin or hematocrit	Laboratory work: – Iron status – Hemoglobin or hematocrit	
			Abdominal radiography (with bowel decontamination if indicated)	Abdominal radiography (with bowel decontamination if indicated)	Abdominal radiography (with bowel decontamination if indicated)
				Oral chelation therapy may be considered in consultation with a medical toxicologist or a pediatric environmental health specialty unit; consider hospitalization if lead-safe home environment cannot be ensured	

readily be adjusted without deliberation. In 2016, a new NHANES cohort found that the 2.5% level had declined to 3.5 μg/dL (0.17 μmol/L). However, the CDC has not adjusted its intervention level as of April 2021.

An interesting phenomenon occurred after the CDC declared 5 μg/dL (0.24 μmol/L) as the intervention level. Although it was based on a cohort representative of young American children in 2010, the number was extrapolated as the intervention threshold to kids of all ages and was adopted by other countries around the world. Thus, although already out of date based on the newer 2016 data, it remains the value that drives clinical and public health efforts for people far beyond the database from which it was derived.

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Table 3. Schedule for Follow-up Blood Lead Testing

VENOUS BLL (μg/dL [μmol/L])	EARLY FOLLOW-UP TESTING (2–4 TESTS AFTER IDENTIFICATION)	LATER FOLLOW-UP TESTING AFTER BLL DECLINING
≥5–9 (≥0.24–0.43)	3 mo[a]	6–9 mo
>9–19 (>0.43–0.92)	1–3 mo[a]	3–6 mo
>19–24 (>0.92–1.16)	1–3 mo[a]	1–3 mo
>24–44 (>1.16–2.13)	2 wk–1 mo	1–mo
>44 (>2.13)	As soon as possible	As soon as possible

[a]Some case managers or health-care providers may choose to repeat blood lead tests on all new patients within a month to ensure that their BLL is not rising more quickly than anticipated.

Seasonal variation of BLLs exists and may be more apparent in colder climate areas. Greater exposure in the summer months may necessitate more frequent follow-up. BLL=blood lead level. Reprinted with permission from Centers for Disease Control and Prevention. Recommended actions based on blood lead level. Available at: https://www.cdc.gov/nceh/lead/advisory/acclpp/actions-blls.htm.

Second Number: 20 μg/dL (0.97 μmol/L)

When is Pb poisoning a clinical disease? The main symptoms of abdominal pain, constipation, inability to concentrate, and disruptive behavior seem to be associated with BLLs greater than 20 μg/dL (>0.97 μmol/L). These symptoms are certainly not Pb specific and occur in children with lower levels. However, the frequency of such complaints seems to be higher in children with BLLs greater than 20 μg/dL (>0.97 μmol/L).

Third Number: 45 μg/dL (2.17 μmol/L)

Chelation treatment, the use of drugs to bind Pb, is indicated for children with levels greater than or equal to 45 μg/dL (≥2.17 μmol/L). Above this level, chelation markedly enhances Pb excretion in most children. The aim of chelation is to prevent further toxicity, at least from removed Pb atoms, which would also be ideally associated with recovery. Unfortunately, the currently available drugs are not very effective in removing Pb from children with BLLs less than 45 μg/dL (<2.17 μmol/L). However, chelation does reduce the BLL at any level. Chelating children with BLLs less than 45 μg/dL (<2.17 μmol/L) not only may be ineffective at inducing Pb diureses but also may cause harm (see the Step 4: Chelation Therapy section later herein). This again highlights another limitation in BLL interpretation.

Fourth Number: 70 μg/dL (3.38 μmol/L)

On a molar ratio basis, the addition of a second chelating agent with a different toxicity profile allows more rapid removal of a greater amount of Pb. In the United States, where chelating agents have been readily available, 2 drugs are used for children with BLLs of 70 μg/dL or greater (≥3.38 μmol/L). However, chelation with even a single agent, such as succimer, markedly reduces Pb-associated mortality in children with BLLs greater than 100 μg/dL (>4.83 μmol/L).

Fifth Number: 100 μg/dL (4.83 μmol/L)

The risk of Pb encephalopathy and death increases at BLLs greater than 100 μg/dL (>4.83 μmol/L), although there are rare reports of encephalopathy occurring at lower levels. Such children require closer observation during chelation because their central nervous system condition may worsen initially. In addition, renal impairment is more likely during treatment at such high levels.

TREATMENT

There are 4 steps to Pb poisoning prevention and treatment. The first 3 steps apply to almost all situations of Pb exposure. Intervention can be split into preventing Pb poisoning (primary prevention) or mitigating Pb poisoning (secondary prevention).

Step 1: Eliminating Environmental Exposure

Primary prevention of Pb poisoning entails eliminating all sources of environmental exposure. The past extensive use of Pb-containing paint continues to be the most common source of exposure for children in the United States, with millions of residences still containing such paints. Removing Pb paint from areas where children spend time should be an effective and permanent way to diminish cases of Pb poisoning. It is also the most expensive; few if any government bodies require this of home and building owners. A compromise is allowing Pb paint to remain on surfaces but to ensure that those surfaces are covered and sealed, eg, by new sheetrock, and that these covers and seals remain intact. An exception to this strategy applies to Pb-painted friction surfaces such as doors and windows, where rubbing between surfaces can release Pb-containing

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dust. Removal of Pb paint on these surfaces should be undertaken to eliminate this hazard.

For the elimination of old paint, the EPA has developed a method that must be used for Pb paint abatement (removal); these regulations collectively are known as the Renovation, Repair, and Paint Rule. These regulations also include training and certification requirements for contractors. Work practices are designed to prevent the dissemination of Pb paint chips and dust into the work site and beyond and to protect workers from inhaling Pb dust. The EPA sets the standards for allowable dust Pb content on surfaces; these standards are currently under review. The Occupational Safety and Health Administration sets the standards for allowable amounts of Pb in air.

The EPA also has jurisdiction over the Pb content of water meant for consumption. Tap water containing more than 15 μg/L of lead requires further investigation to determine the source of water contamination. Replacing lead-containing fixtures or pipes can result in permanent elimination of these lead sources; using EPA-certified filters can act as an economical alternative if used properly.

The CPSC has jurisdiction over the limit of Pb content in children's products, currently set at 100 ppm. The FDA limits the allowable Pb in food, supplements, and cosmetics. For example, the current limit in bottled water, as opposed to tap water, is 5 ppb; in candy, the maximum level is 0.1 ppm; and in juice, the limit is 50 ppb.

It is unlikely that any of these standards are fully protective in that they are unlikely to prevent BLLs from breaching the 5-μg/dL (0.24-μmol/L) level.

Secondary prevention begins when a child is already identified as Pb poisoned. Typically, the local department of health is responsible for case management. Although triggers for different levels of investigation vary between departments, intervention efforts generally include provision of educational materials about Pb-containing products and how to avoid them, followed by tracking of subsequent BLLs. For higher BLLs, with the definition of "higher" varying between state and local departments of health, a sanitarian is sent to the home to investigate sources of exposure, often beginning with the condition of painted surfaces. X-ray fluorescence instrumentation allows rapid assessment of the presence of Pb on surfaces such as walls. Collection of dust samples from floors and window components adds additional information about possible sources and helps guide efforts to eliminate these sources. Finding Pb paint sources in rental units results in notification of the landlord with instructions to correct the Pb hazards. Enforcement depends on department of health resources, landlords' financial resources, and willingness to comply. Because EPA-certified contractors generally charge more, there is temptation to use untrained workers. Such practice has resulted in marked Pb poisoning in children who remain living in a home while Pb abatement work is underway. It is helpful when primary care providers warn families of the risk of unqualified repairs.

A determination that drinking water is contaminated should lead to a search for the source. Identifying and remediating the source can also be an expensive effort, although the use of appropriate Pb-filtering devices at the tap can at least temporarily reduce Pb content.

Step 2: Eliminating Nonnutritive Hand- or Object-to-Mouth Behavior

Frequently, a single child in a household is the only member with Pb poisoning. Why aren't the siblings and parents also poisoned? A primary reason is that being in a room with Pb is insufficient to cause poisoning. Pb has to find a way into the body, which for children is usually due to nonnutritive hand- or object-to-mouth behavior. Eliminating habitual nonnutritive oral behavior is easier said than done. Developmental "aging out" may be most effective. For older children with persistence of this behavior, numerous strategies have been used. When behavior modification fails, residing in a Pb-safe but not Pb-free environment may not be sufficient to prevent further ingestion. Kids are adept at making holes in walls, thus gaining access to older layers of paint with greater amounts of Pb.

Step 3: Promoting Adequate Nutrition, Especially for Essential Metals and Their Related Vitamins

Pb eaten on an empty stomach is more likely to be absorbed than when eaten with food. Many studies have established that Pb competes with essential elements, especially Ca and Fe, for absorption. Pb is more toxic and is more difficult to remove even with drugs in children with essential metal deficiencies, especially Fe. Correcting such deficiencies is important. However, once deficits are corrected, the continuing prescription of replacement dosages of Ca or Fe does not seem to have any further substantial effects on BLLs. At that point, the normal daily requirements seem to be sufficient. To absorb Ca, vitamin D is essential; to absorb Fe efficiently from nonmeat sources, vitamin C is helpful.

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Step 4: Chelation Therapy

Treatment is guided by the BLL. Currently, there are 4 chelating agents available in the United States (Table 4). The first, British anti-Lewisite (BAL), is no longer in use because it requires deep intramuscular injections every 4 hours, typically with 2 injections at a time, for 3 to 5 days. BAL is toxic, and its odor is nauseating. A second drug, penicillamine, is rarely used. Penicillamine's advantage is that it is taken orally. But penicillamine is a weak chelator, also with a high toxicity profile, and requires months of treatment. Penicillamine also removes essential elements. The decision to use either BAL or penicillamine for lead chelation should be made only in consultation with chelation experts; therefore, they are not included in Table 4. The third drug, calcium disodium ($CaNa_2$) EDTA, can be given intravenously or intramuscularly and has limited and reversible toxicity when administered properly to control rate of delivery and to prevent extravasation. This drug is always given as the Ca salt; giving Na_2EDTA will precipitate hypocalcemia. The most widely used drug, succimer, is also the newest drug. Succimer is a congener of BAL and is administered orally. It has an excellent safety profile, and compared with most of the other agents is less expensive. The quantity of Pb removed during a 5-day course is comparable with $CaNa_2$EDTA. Succimer became available for clinical use in children in 1991. There have been no new agents approved for Pb poisoning since that year. Both drugs (succimer and $CaNa_2$EDTA) are used together for children with BLLs greater than or equal to 70 μg/dL (≥3.38 μmol/L) to enhance Pb excretion, with succimer replacing the earlier use of BAL in this regimen. Historically, a dose of BAL was given 4 hours before the initiation of $CaNa_2$EDTA treatment because it seemed to protect the brain better for severely Pb-poisoned children. Succimer can similarly be given first as a "head start" drug in the current regimen.

Chelation does not remove all the Pb from the body. Because there is residual Pb in the body after chelation, especially in the skeleton, BLLs rebound over the subsequent weeks to months. However, BLLs rarely reach the prechelation level. If that occurs, a new ingestion should be strongly suspected. The current drugs in use do not remove substantial amounts of Pb in children with pretreatment BLLs less than 45 μg/dL (<2.17 μmol/L). Because none of the chelators are specific for Pb, essential metals may be removed in greater amounts in children with lower BLLs, a detrimental effect. Zinc deficiency can impair growth and maturation; Fe deficiency contributes not only to anemia but also to cognitive impairment. Thus, we do not have an effective and safe chelating agent for children with BLLs less than 45 μg/dL (<2.17 μmol/L).

Aside from enhancing Pb excretion, does chelation improve outcomes? As noted earlier, BLLs and ALAD enzymatic activity are inversely related. Changes in BLL are

Table 4. Chelation Therapy

MEDICATION	DOSE	INDICATIONS	ADVERSE EFFECTS	COMMENTS
Succimer[a]	1,050 mg/m^2 per day divided every 8 h for 5 d, then	BLL ≥45 μg/dL (≥2.17 μmol/L)	Transient liver function test abnormalities	First-line drug
			Reversible neutropenia	Must be given in Pb-safe/free environment, ie, hospital for high-dose period
	700 mg/m^2 per day divided every 12 h for 14 d = 19 d total			
	Given orally			
$CaNa_2$EDTA[b]	1,000 mg/m^2 per day continuous intravenous infusion in normal saline or dextrose 5% in water or	BLL ≥45 μg/dL (≥2.17 μmol/L)	Renal dysfunction	Second-line drug for BLL 45–70 μg/dL (2.17–3.38 μmol/L)
		Combined with succimer for BLL ≥70 μg/dL (≥3.38 μmol/L)	Hypokalemia	Hospitalize; monitor for adequate hydration, electrolyte status
	Divided every 6 h for 5 d		Skin irritation if extravasated	
	Maximum=1 g/d			

[a]The total daily dose of succimer is rounded to the nearest 100 mg and then distributed as equally as possible over the 3 daily doses considering that the medication comes in 100-mg capsules. These can be opened and sprinkled in non–metal-containing foods such as apple sauce.
[b]Doses given every 6 hours can be given by intramuscular injection mixed with 1% procaine 1:1 by volume if intravenous injection is unavailable.
Pediatric doses are calculated on a meter squared body surface area basis and not on a per kilogram basis. BLL=blood lead level; $CaNa_2$=-calcium disodium; Pb=lead.

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also inversely related to changes in ALAD activity, ie, if BLLs decline after chelation then ALAD activity rises (Fig 4). As BLLs rebound, ALAD activity declines. On the other hand, erythrocyte protoporphyrin levels continue to fall after chelation even as BLLs rebound, indicating a more permanent effect. At very high BLLs (>100 μg/dL [>4.83 μmol/L]), chelation is associated with a marked reduction in mortality. There are no controlled studies showing cognitive improvement after chelation at lower levels.

ARE THE BRAIN EFFECTS OF PB PERMANENT?

In the preceding paragraph, examples of biochemical reversibility were given. The heme pathway is in brain cells, so it is likely that improvements in function are occurring there as well. However, observational longitudinal studies have repeatedly shown that cognitive scores are inversely related to BLLs regardless of when those levels were determined; if BLLs at age 2 years are associated with IQ scores at 7 years, doesn't that indicate permanent effects? Furthermore, studies of brain size and metabolic activity show differences in the parts of the brain involved in memory/learning and behavior control in young adults with early childhood Pb poisoning.

However, 2 interventional studies that aimed to assess the effects of reducing BLLs and the effect on cognitive scores offer hope that some of the Pb-attributable deficits are recoverable, at least in children.

The first study followed 154 previously untreated 1- to 7-year-old children for 6 months. Enrollment BLLs were 20 to 55 μg/dL (0.97–2.66 μmol/L). Interventions included efforts to reduce exposure, improve nutritional status, and encourage less nonnutritive behavior, and for approximately one-third of enrollees, chelation with $CaNa_2EDTA$.

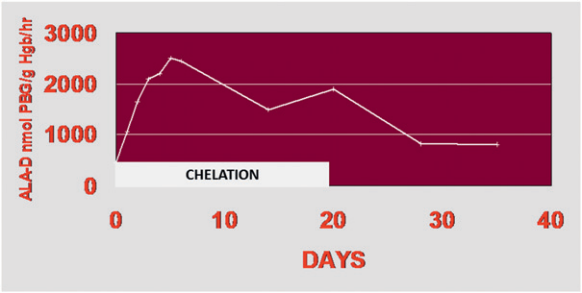

Figure 4. Activity of the heme pathway enzyme δ-aminolevulinic acid dehydratase (ALAD) before, during, and after chelation of children with pretreatment blood lead levels (BLLs) of 45 μg/dL or greater (≥2.17 μmol/L). Enzyme activity, initially depressed, rapidly recovers until falling concomitantly with the postchelation rebound in BLLs (not shown). (Adapted with permission from Graziano J, Lolacono NJ, Moulton T, Mitchell ME, Slavkovich V, Zarate C. Controlled study of meso-2,3-dimercaptosuccinic acid for the management of childhood lead intoxication. *J Pediatr.* 1992;120[1]:133–139.)

The drug was given based on the lead mobilization test result, when a timed urinary Pb sample was collected after a single dose of the drug $CaNa_2EDTA$ was administered to demonstrate effectiveness, or not, in inducing a Pb diuresis. This study found a significant inverse relationship in the change scores in BLL and cognition measures after controlling for confounding variables. The magnitude of change was approximately one-third of an IQ point per 1-μg change in BLL. On average, BLLs declined from 31 μg/dL (1.50 μmol/L) to 24 μg/dL (1.16 μmol/L) over the 6-month study period, and cognitive scores improved.

The second study was a multicenter, blinded, randomized, placebo-controlled trial to test the efficacy of succimer on cognitive and other outcomes. Seven hundred eighty children approximately 2 years of age were treated with either succimer or placebo up to 3 times in the first 6 months of the study and then followed to age 4 years when analyses were performed. Unlike the earlier study, children in this study had lower pretreatment BLLs of 20 to 44 μg/dL (0.97–2.13 μmol/L), with a mean BLL of 26 μg/dL (1.26 μmol/L). BLLs were repeatedly measured, and cognitive scores were obtained at the beginning and end of a 2-year period. Although BLLs were lower at the end of 6 months in the succimer-treated group, the average BLLs of the 2 groups converged by 1 year. They remained statistically indistinguishable after 2 years of study. Similarly, the average cognitive scores in the now 4-year-olds were also indistinguishable. The investigators concluded that succimer treatment of 2-year-olds in this BLL range was ineffective at improving cognitive outcomes or BLLs. The investigators subsequently reanalyzed their data using the statistical approach of the earlier intervention study. Instead of 2 group comparisons of means they now performed regression analyses looking at change in BLL versus change in cognitive scores. As in the former study, an inverse relationship between the change scores was observed, ie, for any given change in BLLs over time, cognitive scores moved in the opposite direction (eg, if BLLs declined, cognitive scores improved). They further discovered that this relationship occurred only in the placebo group. The magnitude of the relationship was also comparable: for every 1-μg/dL (0.05-μmol/L) change in BLLs, cognitive scores changed 0.4 U. However, no relationship between the change scores was observed in the chelated group. One inference of this finding is that succimer not only was ineffective at improving scores on average but also was potentially interfering with possible recovery in children whose BLLs were declining.

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Summary

1. Based on level A epidemiologic data, the epidemiology of the gold standard for assessing lead (Pb) exposure and absorption in young children, blood Pb levels (BLLs), shows a public health success story during the past 50 years.
2. However, during the same period, our knowledge about Pb toxicity has pushed the BLL of concern lower and lower. We still do not have a safe BLL below which we cannot demonstrate toxicity. Based on level A observational studies, some Pb effects on the brain are permanent.
3. Based on level A epidemiologic evidence, in lieu of a BLL toxicity threshold, the CDC has chosen to direct intervention efforts at children with the highest levels, which in a 2010 nationally representative cohort was at least 5 μg/dL (≥0.24 μmol/L).
4. Based on level B evidence, Pb interventions have not changed substantially in recent decades: identifying and eliminating sources of exposure, usually Pb-based paint; reducing nonnutritive hand- or object-to-mouth activity; preventing Pb-containing dust ingestion; eliminating nutritional deficiency states for essential elements, especially calcium and iron; and, for a small subgroup of children with BLLs of 45 μg/dL or greater (≥2.17 μmol/L), chelation therapy.
5. Although the magnitude of Pb poisoning in the United States has been reduced, new sources of exposure are continually being discovered, as well as old sources in new locations, such as water fountains and walls in schools. Based on level A evidence from epidemiologic data, because enormous amounts of Pb have been disseminated throughout the United States, millions of children likely will continue to become Pb poisoned in the coming decades. Based on level A evidence from epidemiologic studies, in other countries, Pb poisoning still has lethal outcomes.
6. Based on level D evidence, the primary care provider is in the prime position to prevent the possibility of Pb poisoning from becoming a reality through assessments of patients, education of caregivers, and advocacy to eliminate exposure.

References for this article can be found at http://pedsinreview.aappublications.org/content/42/No. 6/302.

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PIR QUIZ

1. A 3-year-old boy in your practice has a blood lead level (BLL) of 2 μg/dL (0.10 μmol/L) on capillary blood lead screening. Which of the following is the most appropriate recommendation(s) to be provided to the child's parents at this time?

   A. Begin chelation therapy.
   B. Follow up with a repeated capillary BLL.
   C. Indicate that there may be a risk for toxicity in genetically susceptible individuals. Provide anticipatory guidance and follow-up lead levels at recommended intervals.
   D. Reassure the family that there is no need for concern and that the BLL is a safe level.
   E. Refer the child to developmental pediatrics for neurodevelopmental assessment.

2. The parents of a 2-year-old girl come to your office concerned that she just swallowed a paint chip from their apartment. They live in a very old apartment building, and the landlord has been fined for not following Environmental Protection Agency guidelines. They report that the child is asymptomatic and acting normal. Which of the following is the most appropriate course of action at this time?

   A. Administer syrup of ipecac.
   B. Hospitalize the child and start chelation therapy.
   C. Perform abdominal radiography.
   D. Reassure the family that although the paint chip may contain a large amount of lead, only a very small amount will be absorbed.
   E. Send the child to the emergency department for gastric lavage.

3. A 4-year-old girl new to your practice is seen in the clinic for her health supervision visit. The family is originally from South Asia and recently moved to the area. They live in a luxurious, newly built suburban home, and they drink bottled water. The family frequently travels back and forth to Singapore for business. They also see relatives and bring back a lot of the food ingredients to cook traditional food. Both parents are executives, and they work in nearby offices. Which of the following sources of lead poses the highest risk for potential lead exposure in this patient?

   A. Chipping paint.
   B. Cosmetics.
   C. Industrial emissions.
   D. Occupational exposures.
   E. Spices.

4. A 2-year-old boy was found to have a capillary lead level of 25 μg/dL (1.21 μmol/L)on a routine screen for his 2-year health supervision visit. He is otherwise healthy and is having no symptoms. His physical examination findings are normal. Which of the following is the most appropriate immediate next step in the managementof this patient?

   A. Begin outpatient oral chelation therapy.
   B. Hospitalize because a lead-safe home environment cannot immediately be ensured.
   C. Obtain abdominal radiographs.
   D. Perform an environmental investigation of the home.
   E. Repeat lead level with a venous sample.

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5. A 5-year-old boy undergoes chelation therapy with succimer and calcium disodium EDTA for a blood venous lead level of 75 μg/dL (3.62 μmol/L). The patient also exhibits evidence of cognitive dysfunction on neuropsychiatric testing. Which of the following best describes the expected course to be seen asa result of chelation therapy?

   A. An immediate rebound in BLLs to greater than the level before chelation.
   B. Complete and immediate reversal of cognitive dysfunction.
   C. Complete removal of all the lead from the body with a single chelation course.
   D. Rebound increase in erythrocyte protoporphyrin levels as BLLs rebound.
   E. Release over weeks to months after chelation of residual lead that has accumulated in the body, especially the skeleton.

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Lead Poisoning: An Update

Morri Markowitz

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