2015-Lead-Poisoning

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Taking the Lead on Lead Poisoning:

Policy Proposals to Further Maryland's Goal of Eradicating Childhood Lead Poisoning

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Executive Summary

Though great strides have been made in fighting lead exposure in Maryland, new strategies are necessary to reach children who are left behind by current policy. To make further progress in mitigating lead exposure, we advocate for universal lead testing of Maryland children, stricter requirements on property owners for risk abatement, more funding for lead inspections, and increased education efforts.

The ongoing effort within the Department of Health and Mental Hygiene to make lead testing universal for Maryland children should be supported. The current testing regime targeted toward the "at-risk" and Medicaid populations is based on outdated assumptions about the sources of lead exposure. Universal point-of-care testing is a practical approach which will enable the State to better target its efforts in the future and will ensure that no Maryland child is left behind.

Regulations governing rental units built before 1978 need to be updated to reflect growing evidence of the serious effects of small blood lead concentrations. The current threshold of 10 μg/dL to trigger State intervention is inadequate. We believe that Maryland should follow the CDC's recommendation of 5 μg/dL. While this is only a reference dosage, we believe children living in covered rental units who consistently test at this blood lead level should have access to State lead inspections to ensure that home lead exposure is cut off at the source.

The 2012 expansion of Maryland's lead law resulted in more than 250,000 additional rental units becoming covered by the law.[1] The policy changes we are advocating for would result in more rental units being required to meet the State's risk reduction standard. The current level of staffing for lead inspectors at the Maryland Department of the Environment is

[1] http://news.maryland.gov/mde/2014/07/01/maryland-lead-program-opens-registration-for-rental-properties-built-before-1978/

inadequate to the task of ensuring that all rental units covered by the law are properly protecting tenants. More funding is needed to give the Maryland lead law teeth.

Finally, the State should increase outreach efforts through schools and primary care providers so that families can be aware of the risks and warning signs associated with lead poisoning.

We believe that enacting any and all of these policy changes would make a real difference in the State's campaign against lead poisoning while paying dividends in the form of a lower crime rate and more opportunity for Maryland's most disadvantaged children.

Problem Definition

The tragic death of Freddie Gray and the ensuing unrest in Baltimore has prompted larger discussions about race relations, poverty, and policing in Maryland and across the United States. For Maryland lawmakers, however, a disturbing fact about Gray's childhood should call attention to an issue which continues to impair the development of Maryland's most vulnerable children.

When Freddie Gray was just 22 months old and living in West Baltimore, a test found him to have an astounding 37 μg/dL of lead in his blood, more than 7 times the current threshold at which the CDC urges additional testing.[2] Research has shown that lead poisoning in children under age six severely impedes cognitive development and can lead to behavioral issues such as increased aggression and ADHD. The life story of Freddie Gray supports these associations. Gray was diagnosed with ADHD from a young age and needed special education in school. He never graduated high school and was ultimately arrested more than a dozen times for working in the drug trade.

[2] McCoy, Terrence. "Freddie Gray's Life a Study on the Effects of Lead Paint on Poor Blacks." Washington Post. Accessed August 4, 2015.

Too many Maryland children have their futures poisoned by the lead lurking in their walls. Although Maryland has made great strides in reducing lead poisoning, the most recent report from the Department of the Environment's Lead Poisoning Prevention Program found that in 2013 there were still 371 children in the State with more than 10 μg/dL of lead in their blood while 2251 children had a blood-lead concentration between 5 and 9 μg/dL.[3] As more evidence has shown that even small concentrations of lead can have devastating effects, the CDC has revised its guidelines for intervention down from 10 to 5 μg/dL.

Yet Maryland's State Elimination Plan only calls for the elimination of cases above 10 μg/dL, and substantive State intervention is only triggered at this threshold. While mitigating the most extreme cases of lead poisoning is important, this focus leaves behind the children suffering from blood concentrations below 10 μg/dL. And the fact that only 21.2 percent of Maryland children up to six years old were tested in 2013 means that many more cases could be slipping through the cracks.[4]

The tragic reality is that lead poisoning in Maryland contributes to a vicious cycle of poverty, in the inner city and rural counties alike, by sabotaging the potential of Maryland children. Great strides have been made in mitigating contamination and reducing the number of cases, but progress (particularly for cases above 10 μg/dL, for which there was virtually no change from 2012 to 2013) is stalling. The State needs to reconsider its strategy for eradicating lead poisoning to ensure that every child in Maryland has an opportunity to succeed.

Adverse affects to lead: Crime

Recent studies have shown that there is viable evidence to suggest that low blood lead Pb levels <5 micrograms/deciliter (μg/dL) are associated with aggression, ADHD, and criminal

[3] "Childhood Blood Lead Level Surveillance in Maryland Annual Report 2013." Maryland Department of the Environment. July 2014. Accessed August 4, 2015.
[4] Ibid.

behavior ranging from six year old children to young adults in their early twenties.[5] Children absorb up to 50 percent of lead they ingest, compared with 8 percent for adults making them more susceptible to have higher lead exposure. Adolescents who have had exposure to lead in early childhood have higher rates of incarceration, limited educational achievement, underemployment, and violent behavior compared to the adolescents who were never exposed to lead. Further investigation is vital to strengthen the relationship between early childhood lead exposure as a precursor to crime in early adulthood.

Pennsylvania studies

Herbert Needleman founder of the Alliance to End Childhood Lead Poisoning, and Professor at the Pittsburgh School of Medicine conducted two important studies that helped researchers connect lead exposure in children with negative behavior. The first study he conducted was of 301 young males in the Pittsburgh School System.[6] Needleman discovered that bone lead levels in 12-year-old children were connected to parent and teacher Child Behavior Checklist ratings for aggression, attention and delinquency that were conducted. The children who the parents and teachers documented as having more aggressive behavior had higher blood lead levels.[7] Furthermore, a later study Needleman undertook involved 194 adolescents ages 12-18 that had been previously charged by the Juvenile Court of Allegheny County, Pennsylvania, and 146 non-delinquent adolescents from local high schools in Pittsburgh.[8] The results of the study showed that the delinquents had significantly higher blood lead levels, 11

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[5] Wolpaw, Jessica. "Lead Exposure and Behavior Effects on Antisocial and Risky Behavior Among Children and Adolesents." Amherst. February 1, 2012. Accessed August 4, 2015.

[6] "Toxicological Profile for Lead." CDC. August 1, 2007. Accessed August 4, 2015.

[7] Ibid

[8] Ibid

ppm compared to the non-delinquents 1.5 ppm. Though not every adolescent who has an elevated blood levels is a criminal by any means, the goal of Needleman's studies were to further develop the link between blood lead levels and aggression.

Cincinnati study

A breakthrough long-term study was lead by Kim Dietrich a Professor at the University of Cincinnati College of Medicine. Unlike most other lead exposure studies the Cincinnati study followed participants into adulthood, culminating in more concrete evidence.[9] The study observed 250 individuals with elevated blood lead levels in Cincinnati, Ohio born to women between 1979-1984 who resided in areas who lived in high risk areas for lead-contaminated housing.[10] The blood lead concentrations of the participants was measured on the first or early second trimester of pregnancy and on a quarterly and biannual basis until the child was 6.5 years old.[11] After monitoring the children throughout early adulthood (19-24) the study found that total arrest rates and violent crimes committed went up for every 5 lg/dl (0.24 lmol/l) increase in blood lead concentration. Given the results Dietrich concluded that childhood blood lead concentrations are linked to higher rates of crime.

Baltimore: Crime and Poverty

While some people may still be skeptical about the relationship between lead paint and criminal activity it is impossible to deny that lead exposure has negative health effects. According to Ruth Ann Norton, the executive director of the Coalition to End Childhood Lead

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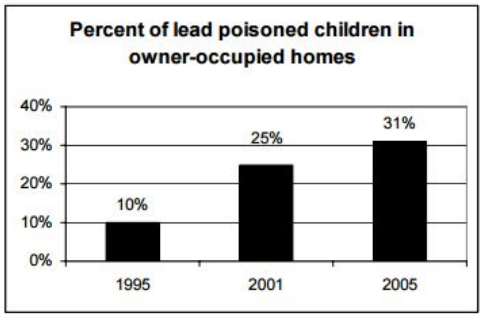
[9] Dietrich, Kim. "Association of Prenatal and Childhood Blood Lead Concentrations with Criminal Arrests in Early Adulthood." PLOS Medicine. May 27, 2008. Accessed August 4, 2015.

[10] Ibid

[11] Ibid

Poisoning,[12] "A child who was poisoned with lead is seven times more likely to drop out of school and six times more likely to end up in the juvenile justice system." This was the case for Freddie Gray who dropped out of school and had multiple arrests ranging from assault to destruction of property.[13] Gray, grew up in Sandtown-Winchester in West Baltimore a neighborhood where children have almost a 6 percent chance of developing elevated blood lead levels, the highest in the State of Maryland.

The connections being made between Gray's lead exposure and criminal activity are not meant to blame his death on lead poisoning. The intention is to shed awareness on the fact lead exposure is still a problem today.[14] For example, even though the rate of lead poisoning in rental properties such as Freddie Gray's has declined, the number of lead poisoning cases in owner occupied units has risen from 10 percent in 1995, to 25 percent in 2001, and reaching 31 percent in 2005.



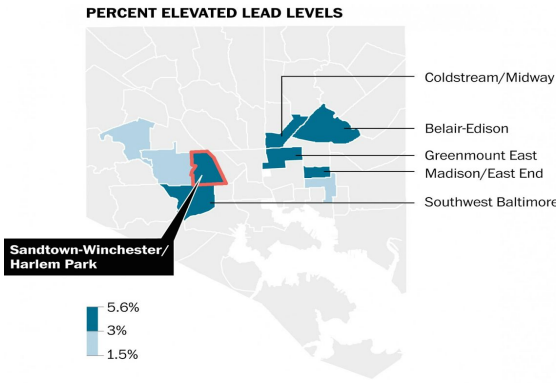
Baltimore City Health Department Snapshot

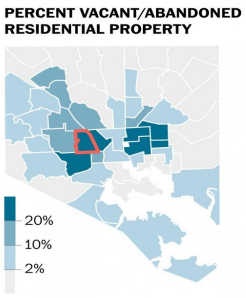
[12] McCoy, Terrence. "Freddie Gray's Life a Study on the Effects of Lead Paint on Poor Blacks." Washington Post. Accessed August 4, 2015.

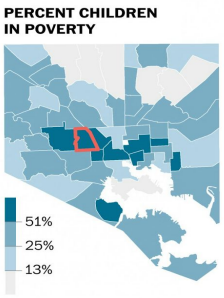
[13] Ibid

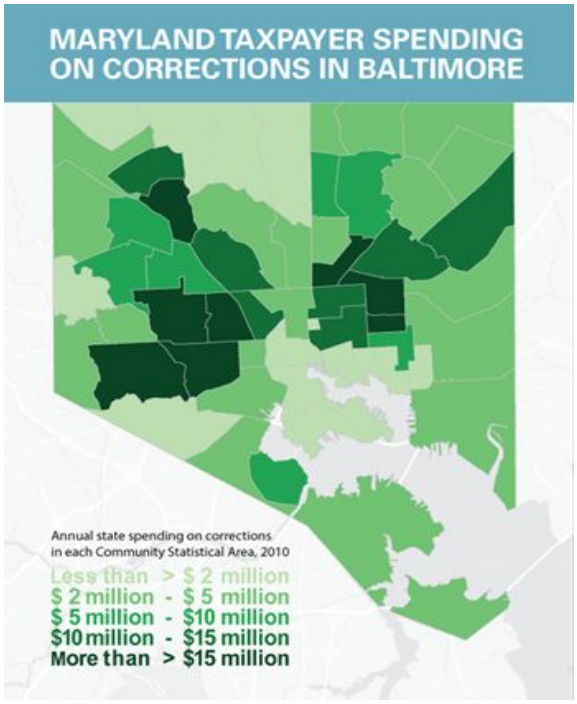
[14] "Lead Poisoning in Baltimore." Baltimore City Health Department. June 12, 2007. Accessed August 4, 2015.

The maps below serve as a guide to illustrate the relationship linking areas of high lead exposure in Baltimore to the amount of taxpayer dollars spent on corrections in those same areas.









Health Effects of Lead

Lead is most damaging to children, especially from zero to 72 months. Although the Centers for Disease Control and Prevention (CDC) and State agencies set "levels of concern," no amount of lead is safe in the body.[15] Lead is harmful for the developing body and primarily affects the neurological system and leads to increased likelihood of ADHD and ADD.

A recent study conducted by several medical experts and published by the US National Library of Medicine found evidence to suggest that low blood lead levels can be linked to ADHD in children.[16] The study monitored 236 children who ranged from 6–17 years old and

[15] http://www.cdc.gov/nceh/lead/

[16] Nigg, Joel, Molly Nikolas, Mark Knottnerus, Kevin Cavanaugh, and Karen Friderici. "Confirmation and Extension of Association of Blood Lead with Attention-Deficit/Hyperactivity Disorder (ADHD) and ADHD

whose blood lead levels ranged from less than 0.3 μg/dL to a maximum of 2.2 μg/dL with a mean of 0.73 μg/dL. It is important to note the blood lead levels observed in the children were the lowest ever studied in association to ADHD. The study sampled four groups one non-ADHD group and three groups ranging in severity of ADHD. The results of the study found that children with ADHD had a higher blood lead level then the children without ADHD. Parent and teacher reports that were conducted on the children helped to solidify the connection between the diagnosis of ADHD and blood lead concentration. The study should be eye opening considering many more children have have blood lead levels between 1–5 μg/dL, which is currently below any accepted standards that require regulatory action.

The link between lead and ADHD is evident in a statement made by Rosalyn Brown the current occupant of Freddie Gray's childhood house, [17] "All these kids that grew up in those houses, they all have ADHD. They have mood swings. They have anxiety," she said. Phil Silva the founder of the Dunedin Multidisciplinary Health and Development Study and Terrie Moffitt a professor at Duke University conducted an academic study on a group of 678 thirteen-year-olds.[18] The study found that 58% of ADHD children became delinquent, compared with only 10% of non-ADHD children.[19] A more recent paper written by Jessica Reyes a

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Symptom Domains at Population-Typical Exposure Levels." US National Library of Medicine; National Institutes of Health. November 23, 2009. Accessed August 4, 2015.

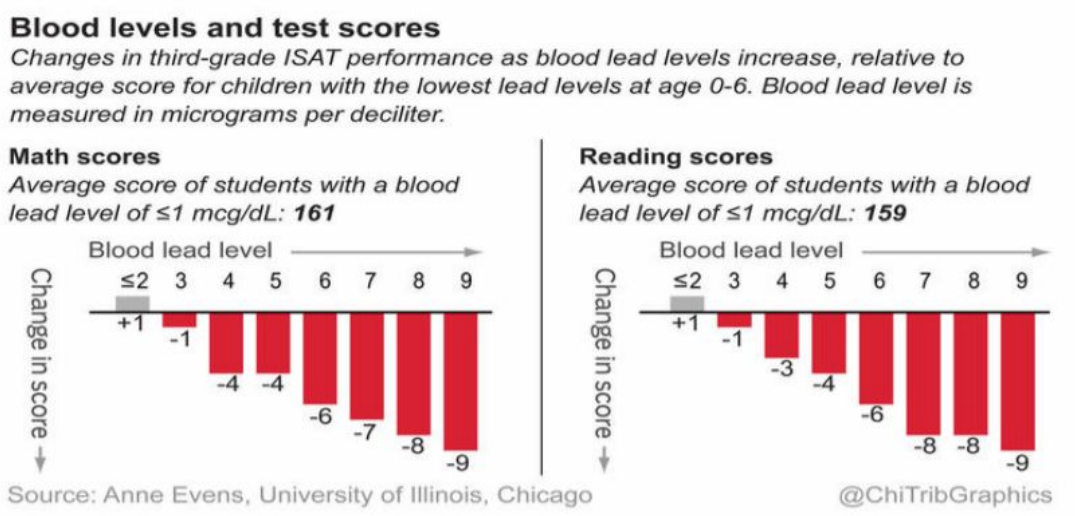
[17] McCoy, Terrence. "Freddie Gray's Life a Study on the Effects of Lead Paint on Poor Blacks." Washington Post. Accessed August 4, 2015.

[18] Moffitt, Terrie E., and Phil A. Silva. "Self-Reported Delinquency, Neuropsychological Deficit, and History of Attention Deficit Disorder." *Journal of Abnormal Child Psychology J Abnorm Child Psychol* 6, no. 5 (1988): 553-69.

[19] Reyes, Jessica. "Lead Exposure and Behavior: Effects on Antisocial and Risky Behavior Among Children and Adolescents." Amherst College. February 1, 2012. Accessed August 5, 2015.

professor at Amherst College cited three independent studies finding children with ADHD are five times more likely to be delinquent than children without ADHD. The increased evidence connecting lead exposure to ADHD even at low levels should trigger an automatic reassessment of current standards.

Lead in the bloodstream also decreases cognitive abilities and executive functioning in the prefrontal cortex, the area that controls aggression, impulse control, and emotional control. A study by the University of Illinois displayed below found that higher blood lead levels resulted in lower IQ scores.



Current Policy

Maryland first began addressing the problems of lead exposure in 1994 when the General Assembly passed a comprehensive lead law aimed at curbing the growing number of citizens with an elevated blood lead level (EBL). This law was aimed at rental home owners, and required every rental unit with lead exposure to be registered with an online registry maintained

by the Department of the Environment (MDE).[20] It also set in a place a Risk Reduction Standard (RRS) which all rental home owners must meet. Rental home owners are required to satisfy a the RRS, a test for lead contaminated dust, after every change of tenancy. This was followed by a physical inspection of the house by an MDE accredited lead inspector to verify the reduced risk of lead exposure.[21] Along with the RRS, after every change in tenancy, the rental home owners are required to give the new tenants a notice of their rights as tenants, as well as educational packets containing information about lead poisoning and the risks of lead exposure.[22]

While Maryland does not require mandatory testing for lead exposure, the State does require testing for children at ages one and two if they are either on Maryland's MEDICAID program or live in designated "at risk" areas for lead exposure.[23] Blood lead testing is most commonly done on children because of the damage done to the development of the brain from lead exposure. Once a lab takes a blood test, all of the results are sent to MDE, which keeps a database of the results of all tests taken in Maryland.[24] If a child tests with a blood level of 10 μg/dL, the MDE must report the child's information to the health department in the local jurisdiction and to the Department of Health and Mental Hygiene (DHMH).[25] At this point, case management ensues from the local health departments. This includes a psychological examination to determine any psychological effects of EBL, as well as an examination of the child's environment and home.[26] While there is follow up monitoring and nutritional guidance

[20] Md. ENVIRONMENT Code Ann. § 6-811
[21] Md. ENVIRONMENT Code Ann. § 6-815
[22] Md. ENVIRONMENT Code Ann. § 6-823
[23] "Childhood Blood Lead Surveillance in Maryland: Annual Report 2013," Maryland Department of the Environment Lead Poisoning Prevention Program. 2013
[24] Md. ENVIRONMENT Code Ann. § 6-303
[25] COMAR 26.02.01.05
[26] Annual Report 2013

for children who test between 5 and 9 μg/dL, there is no mandated coordination with local health departments or DHMH for case management. An environmental history is taken, but that does not constitute a mandated home inspection as it would for children testing with 10 μg/dL.[27]

If a rental owner receives notice of a tenant with an EBL of 10 μg/dL or above, then they are required to satisfy a Modified Risk Reduction Standard in order to reduce further that child's exposure to lead at home.[28] This requires passing a dust test for contaminated dust done by an accredited inspector. If a renter fails to meet this Modified RRS, then MDE and local health departments have the authority to order a home inspection and lead abatement process.[29] Renters must also satisfy the Modified RRS if they receive from their tenants a notice of defect, which states that there is structural damage to the house, such as deteriorating walls or paint chipping.[30] The law, however, only regulates rental home owners and leaves the owner occupied homes without the same level of health standards regarding lead exposure. While owner occupied houses can still receive lead-safe or lead-free certifications from accredited inspectors, they are costly and required extensive work done on both the interior and exterior of the property. More recently, as the 1994 lead law has been expanded to cover homes built between 1950 and 1978 (previously unregulated by the 1994 law, which covered only homes built before 1950) Maryland began regulating the contractors who perform renovations and repairs on all houses built before 1978. This comes through the Environmental Protection Agency's (EPA) Renovation, Repair and Painting Rule (RRP), which states that all contractors working on

[27] Health Care Providers Clinical Recommendations and Follow up Testing: Clinical Recommendations. Maryland Department of the Environment Lead Poisoning Prevention Program http://www.mde.state.md.us/programs/Land/LeadPoisoningPrevention/HealthCareProviders/Pages/Programs/LandPrograms/LeadCoordination/healthcare/healthcare_followupreports.aspx

[28] Md. ENVIRONMENT Code Ann. § 6-819

[29] Annual Report 2013

[30] Md. ENVIRONMENT Code Ann. § 6-819

renovations on houses built before 1978 be accredited through the EPA, or through a State with EPA authorization.[31] The RRP also sets forth certain standards that must be adhered to by all workers performing work in houses built before 1978.[32] This universe of houses includes rental homes, but also applies to owner occupied housing as well.

Universal Testing: Background

In Maryland only children, ages one to two years old living in an at risk area or enrolled on Medicaid have to complete mandatory testing for lead exposure.[33] However, Maryland can still make additional steps to better understand the amount of children at risk. We recommend that the State of Maryland adopt a universal screening tests by way of point of care (POC) testing. POC testing takes place in the doctor's office or in an on-site mobile facility as opposed to in a lab. A recent study was completed on point of care (POC) testing by a Task Force within DHMH to see if (POC) testing is feasible to identify children who have been exposed to lead.

Point of Care Testing: Advantages

By accepting POC testing it will become easier and less time consuming for families in the State to get tested. POC testing will allow for fewer office visits eliminating extra transportation barriers while simultaneously making it a more financially sound option for lower income families. After the doctor administers a test and it is discovered a child has an elevated blood level, proper treatment can start immediately, compared to weeks of waiting for lab test results.[34]A service provider who started using POC testing reported to the Task Force that POC

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[31] 40 C.F.R 745.83

[32] 40 C.F.R 745.85

[33] "Lead Poisoning Prevention Program: Childhood Blood Lead Surveillance in Maryland." November 2002. MDE. Accessed August 2, 2015.

[34] Mitchell, Clifford. "Report to the General Assembly by the Task Force on point of care testing for lead poisoning." January 14, 2015. DHMH. Accessed August 1, 2015.

testing on patients did not disrupt or slow down the flow of the clinic making it attractive to incorporate into the overall testing and vaccinations patients receive.

Point of Care Testing: Barriers

As with any program there some minor setbacks with POC testing. The first being there is no direct electronic reporting system that would allow service providers to send results to the Maryland Childhood Lead Registry (CLR). However, there are two proposed solutions.[35] The first proposal would be fore the service providers to fax reports to the (CLR), which MDE currently allows.[36] The second proposal centers on the State creating a direct data entry platform that service providers can use. It would be similar to an immunization registry where doctors enter vaccination information for their patients directly. This type of system has already been deployed in Rhode Island, Wisconsin, Michigan, and New Jersey.

Another potential barrier includes varying reimbursement rates from insurers for POC testing, sample collection, and counseling. Most health care providers should be able to recover the costs for POC testing but providers from smaller practices have contracts that do not reimburse for lead testing. A potential solution would be for the State to work with Medicaid and private insurers to reevaluate reimbursement rates and the associated costs. Possibly, the most critical aspect of POC testing is having the care providers receive proper training to ensure an accurate test. Without the appropriate training test results patients can receive an inaccurate diagnosis.

[35] Mitchell, Clifford. "Report to the General Assembly by the Task Force on Point of Care Testing for Lead Poisoning." January 14, 2015. DHMH. Accessed August 1, 2015.

[36] Ibid

Point of Care Testing: Costs

In total a service provider should expect to pay $6,581 - $6,790 for the Lead Care Device II, registration, test kit, application fee, and staff time.[37] Should a service provider adopt the POC program it would need to test 434 patients annually under the current Medicaid reimbursement rate of $12.52 per test to breakeven.[38] It is important to note that the Lead Care Device II is the only approved POC test for blood lead levels in the U.S.[39] The device works by collecting a drop of blood that it mixes with reagents. The results are then displayed directly on the devices screen. The test serves the purpose of a screening, and if an elevated blood level is detected the results must be confirmed through a second laboratory method. Currently, the LeadCare II device is not on the accepted CLIA-waived test list creating less incentive for service providers to use it due to extra costs and restrictions. To encourage the use of the POC LeadCare II, it is important that the State of Maryland advocate that the Laboratories Administration put the LeadCare II device on the CLIA-waived test accepted list.

Point of Care Testing: Medicaid

A vital way to expand use of POC lead testing in Maryland is through the Women, Infants, and Children (WIC) program. The WIC program already conducts a blood collection for hemoglobin levels on patients making an additional blood lead test less of a hassle.[40] In 2005 less than one-third of Wisconsin Medicaid children received their mandatory blood lead tests at one to two years of age. [41]However, in 2008 testing went up 40 percent after health care providers

[37] Ibid
[38]Ibid
[39] Ibid
[40]Ibid
[41] Ibid

started using POC testing. This was made possible by Medicaid managed care organizations (MCO's) collaborating with WIC clinics to pay for testing. We recommend that the State of Maryland reach out to WIC clinics to assist them in coordinating with Medicaid MCO's to adopt POC testing. To create another incentive to adopt POC testing the State can recommended that Medicaid MCO's issue individual report cards to service providers to allow them to see if they meet the lead testing requirements.

Universal testing has led to increased testing rates, lower costs, and has made visits more convenient for families. A select number of service care providers in the State have shown that POC testing has been successfully integrated into their routine patient tests. Maryland needs to revise its current standards, encourage departmental collaboration between MDE and DHMH, create incentives for primary care providers to report data, and educate all parties on why increased testing is important to encourage successful implementation of universal testing.

Policy Proposal 1: Lowering "Level of Concern" from 10 µg/dL to 5 µg/dL

The Maryland Department of the Environment (MDE) currently maintains a database consisting of blood lead testing results of all children who have been tested for lead poisoning. As previously stated, the law mandates that these results are sent to MDE by the laboratories that perform blood tests and analyze the results. While all blood tests results are kept by MDE, action is only taken on those children who have tested at or above 10 µg/dL.[42] This action consists of a developmental psychological examination, as well as coordination with local health departments for case management and a physical home inspection. Those who test between 5 and 9 µg/dL,

[42] MDE Childhood Blood Lead Surveillance in Maryland, Annual Report 2013, http://www.mde.state.md.us/programs/land/leadpoisoningprevention/Pages/index.aspx

while still contaminated with dangerous amounts of lead in their bodies, receive follow up monitoring, but no mandated inspection of the child's home environment.

However, as of 2012, the Centers of Disease Control and Prevention lowered the threshold from 10 μg/dL to 5 μg/dL.[43] We propose that Maryland takes a tougher approach against lead and adopt CDC's guidelines. Since no amount of lead is safe in the human body, it is important that Maryland expand its resources to children who continually test with blood lead levels between 5 and 9 μg/dL.

The lowering of the threshold will also place new responsibilities on property owners. Currently, if a child in a rental unit has a blood lead level of 10 μg/dL or higher, the rental unit owner must meet the Risk Reduction Standard (RSS).[44] We propose that if a child tests with a blood lead level between 5 and 9 μg/dL, the rental unit owner and household will first receive a notification and education on possible lead hazards. When the child receives their second blood lead level test (approximately 3 months after the first test) and the BLL is not lower than 5 μg/dL, the rental unit owner will be required to meet the current Risk Reduction Standard. This new practice aims to prevent future exposure to lead and is an earlier intervention than what is currently in place.

With a new adoption of CDC's guidelines for lead blood lead levels, Maryland would solidify its commitment to make sure every household lives lead free.

Policy Proposal 2: Funding Increase for Sustainability

Our proposed policy of extending case management to those who test at levels of 5 to 9 μg/dL will increase the number of children who are referred to local health departments and

[43] http://www.cdc.gov/nceh/lead/ACCLPP/blood_lead_levels.htm
[44] COMAR 26.02.01.05

DHMH. Statistics from the Lead Poisoning Prevention Program's 2013 Annual Report show that while there were 304 new cases of blood lead levels of 10 μg/dL in 2013, there were also 1,724 new children who tested between 5 and 9 μg/dL.[45] Our proposal would, after a second test confirms an elevated blood level, require MDE to notify local health departments and DHMH for around six times more affected children. Additionally, it would require MDE and local health departments to bear significant responsibilities for case management for these children. We feel, however, that if Maryland is serious about eradicating new cases of childhood lead poisoning, then the State should consider expanding its breadth of case management to those children who, while currently under the designated level that triggers management, still contain in their bodies harmful amounts of lead which only will grow with continued exposure.

In Baltimore City, an area which currently sees the highest number of new cases of elevated blood lead levels, the Baltimore City Health Department provides case management for children with elevated blood lead levels at 10 μg/dL or above.[46] The city, in 2013, recorded 170 new cases of elevated blood lead level over 10 μg/dL, while also recording 744 new cases of levels between 5 and 9 μg/dL.[47] Requiring case management for children with confirmed levels of 5 to 9 μg/dL would put a serious burden on the health department's ability to effectively treat the new universe of children requiring management. We propose increasing funds to Baltimore City Health Department to give them the ability to provide quality care and attention to all those who require it. Attention to Baltimore City must remain a priority for the State if it wishes to make further progress. The city has seen substantial success in its fight to eradicate lead

[45] Annual Report 2013
[46] Interview with Horacio Tablada, Deputy Secretary of the Environment. Conducted July 30, 2015
[47] Annual Report 2013

poisoning over the past twenty years, proven by its 96 percent drop in new cases of elevated blood lead levels of 10 μg/dL from 1993 to 2013[48]. However, more can still be done. By increasing the capacity Baltimore City's Health Department to provide effective case management to children testing between 5 and 9 μg/dL, the city can increase the amount of children that they are treating, and in turn, hopefully see a further decrease in new cases of lead poisoning above 10 μg/dL.

Outside of Baltimore City, after local health departments are notified and case management begins, MDE is responsible for conducting environmental assessments of the child home.[49] Currently, MDE provides certified risk assessors to conduct the home assessments, with no cost to the families affected.[50] The cost is paid by the Lead Poisoning Prevention Special Fund and covers the entire State of Maryland outside of Baltimore City.[51] Baltimore city is responsible for 1,121 of the 2,251 total cases of blood levels between 5 and 9 μg/dL in the State, as well as 153 of the 371 total cases of blood levels at 10 μg/dL and above.[52] While the rest of the State is responsible for about half of the blood lead poisoning, representing a substantial increase in the amount of environmental assessments MDE would need to undertake under our proposals. An increase in funds to the Lead Poisoning Prevention Program's Special Fund would allow MDE to adequately provide the assessments that will be needed to make sure the State reduces its exposure to lead. The problem of lead does not only reside in Baltimore City; more rural counties, such as Allegany, Garrett, and Caroline Counties, have seen high percentages of

[48] Ibid
[49] Interview with Paula Montgomery, Lead Poisoning Prevention Program Manager. Conducted July 30, 2015
[50] Interview with Horacio Tablada
[51] Ibid
[52] Annual Report 2013

children testing between 5 and 9 μg/dL.[53] Without providing these children the proper treatment, these children are left to bear the adverse effects of lead in their systems, which is shown to lead to lower test scores and increased aggressive behavior. Increasing funds to the Lead Poisoning Prevention Program's Special Fund will equip MDE to properly and effectively reduce the citizens' risk of lead exposure.

Policy Proposal 3: Increase Education on Lead Poisoning

For families living in rental units in Maryland, they have a right to live in a lead free home. That is why all rental units in Maryland made before 1978 must be registered with the Maryland Department of the Environment.[54] If there is a defect in the house, like chipped paint, the family should notify their landlord to ensure there is no lead hazard. Also, before a family moves into a rental unit, the landlord must prove that the home is safe to live in. However, these rights are not always known to tenants. Tenants also may be afraid to report to their landlord.[55] This is why Maryland must improve its education efforts towards tenants. A child in a rental unit should not experience lead poisoning because his or her parents did not know their rights when it came to living in a lead-free home. Baltimore City currently has a public health campaign to raise awareness about opioid overdoses and Naloxone.[56] These posters and billboards around the city target individuals and households who may benefit from public health campaign. In a similar fashion, Maryland could have a public health campaign in areas of high rental-unit concentration. The posters and billboards would encourage parents to get their children tested and would remind renters of their rights. It is imperative Maryland improve its education efforts

[53] Ibid

[54] http://www.mde.state.md.us/programs/Land/LeadPoisoningPrevention/RentalPropertyOwners/LeadRegistration/Pages/index.aspx

[55] Interview with Horacio Tablada

[56] dontdie.org

on lead poisoning and prevention because it will help households take initiative to invest in their children and communities well-being.

Conclusion

For the State of Maryland to eliminate the remaining cases of lead poisoning it needs to take a comprehensive targeted approach. Today the areas where lead poisoning exists are much more concentrated, primarily in a select number of communities within the City of Baltimore that lead abatement efforts haven't even reached yet. Given the rate of crime that can be tied to lead the State has a choice. It can continue to incarcerate criminals who grow up living in lead exposed houses or it can invest in the future of these children. There is a mutual understanding that there are a limited amount of resources and funds to go around. However, the State will save millions of dollars in funds that would have went to DJS to incarcerate adolescents living in these affected neighborhoods by investing in lead abatement. It has been proven by numerous studies cited within this paper that the most effective way to reduce crime is eliminating lead exposure in urban communities such as in Sandtown-Winchester the neighborhood Freddie Gray grew up in. Even if funds are not immediately available for primary lead prevention measures the first step should start with collaboration between DHR and DHCD. Efforts to reduce lead poisoning should begin inside houses and in affected communities before children end up in Maryland's criminal justice system. If the State seriously considers our proposals we might not be talking about lead poisoning in Maryland by the end of the decade.

case-study_alternative-financing-mechanisms
Uploaded by: Delegate Mosby, Delegate Mosby
Position: FAV

National Center for
HEALTHY HOUSING

ME

Lead Poisoning Prevention Fund

Financing Source: State Fund by Fees
Financing Amount: $650,000 Annually
Focus: Lead (Primary Prevention)

The Maine Legislature established the Lead Poisoning Prevention Fund (22 MRSA c. 252 §1322-E) in 2005. The Lead Poisoning Prevention Fund (LPPF) is administered with the help of an Advisory Board by the Childhood Lead Poisoning Prevention Unit (CLPPU) within the Maine Center for Disease Control and Prevention (CDC) of the Maine Department of Health and Human Services (DHHS). Resources from the LPPF are used to accelerate progress towards eliminating childhood lead poisoning in Maine through statewide and community-based activities that enable the public to identify lead hazards and take precautionary actions to prevent exposure to lead. The Maine CDC awards contracts to organizations to carry out education, outreach and capacity building services in high-risk areas (i.e., the five areas with the highest burden of childhood lead poisoning).

Financing Mechanism

The Maine Legislature established the Lead Poisoning Prevention Fund (22 MRSA c. 252 §1322-E) in 2005. The bill was the outcome of an effort led by a coalition of environmental activists. It authorizes a fee of 25 cents per gallon on all paint sold in Maine. The fee is imposed on paint manufacturers or brand label owners. It provides a waiver for payment for those who sell low quantities. Revenue from the fees fluctuated between$700,000 and $800,000 in the initial years. Revenue decreased during the recession but is currently stable at around $650,000 annually.

The Lead Poisoning Prevention Fund (LPPF) is administered with the help of an Advisory Board by the Childhood Lead Poisoning Prevention Unit (CLPPU) within the Maine Center for Disease Control and Prevention (CDC) of the Maine Department of Health and Human Services (DHHS). Resources from the LPPF are used to accelerate progress towards eliminating childhood lead poisoning in Maine through statewide and community-based activities that enable the public to identify lead hazards and take precautionary actions to prevent exposure to lead.

Through contracts for local education, outreach, and capacity-building services, the Maine CDC disburses funds from the LPPF to communities around the state with the highest burden of children with lead poisoning. The contracts are awarded through a competitive request for proposals (RFP) process. The most recent RFP was published in 2016 for contracts to provide services for up to five years in the five areas in Maine with the highest burden of lead poisoning. Any interested party is eligible to submit a bid in response to the RFP.

Program Overview

Using the resources of the LPPF, the Maine CDC implements education, outreach, and training programs that enable the public to identify lead hazards and take precautionary actions to prevent lead exposure.

According to the LPPF Evaluation Report 2010,[1] program activities and partnerships are designed to:

1. Help parents of young children who live in homes likely to have lead hazards live safely with lead so that their children never become poisoned;
2. Help property owners and managers of rental units likely to have lead hazards provide and maintain lead-safe housing so that child occupants never become poisoned; and,

This brief was made possible through a contract between the W.K. Kellogg Foundation and the National Center for Healthy Housing. The contents of this document are solely the responsibility of the authors and do not necessarily represent the official views of the W.K. Kellogg Foundation.

3. Help property owners of rental units likely to have lead hazards avoid the high costs associated with lead abatement.

Program Operations

The Childhood Lead Poisoning Prevention Unit (CLPPU) of the Maine CDC manages the activities supported by the LPPF. The CLPPU works with the Maine CDC Environmental Public Health Tracking Program to analyze and make publicly available lead poisoning surveillance data for Maine towns, which is used to identify areas at high risk for childhood lead poisoning. The Maine CDC awards contracts to organizations to carry out education, outreach and capacity building services in high-risk areas (i.e., the five areas with the highest burden of childhood lead poisoning). In addition, the Maine CDC conducts statewide prevention activities as directed by the LPPF statute, including a statewide media campaign, a targeted direct mailing to parents of one-year-olds with an offer for a free home lead dust test kit, environmental investigations for all additional units in multifamily buildings where a child has been poisoned, and an online lead-safe housing registry.

Eligible Population Served:

Activities funded by the LPPF are intended to reach:

1. Parents of children under the age of six and expectant parents who live in housing built before 1950 and,
2. Owners of rental units built before 1950.

The LPPF statute directs the Maine CDC to give preference to activities that reach high-risk or underserved populations.

Staffing:

Services are provided by health department employees, contractors, or community-based partners.

Billing for Services:

Services are offered at no cost to community residents.

Outcomes and Evaluation

According to a Maine CDC report, the number of children six years and under who are newly identified with lead poisoning has declined continuously. Data from 2003 through 2013 indicate a significant drop in rates of lead poisoning in three out of the five high-risk areas receiving lead prevention services.[2]

An evaluation report on the LPPF states the following as its most significant achievements during the period between January 1, 2009, and June 30, 2010:

1. Fifty percent of LPPF resources were distributed to community organizations, establishing capacity and infrastructure for education and preventive lead dust testing in homes throughout the state and expanding prevention efforts to far more people than ever before possible.
2. More than 350 homes were tested for lead dust, the most common cause of childhood lead poisoning in Maine. These tests help residents and landlords to identify lead dust and protect children from lead poisoning. Prior to the LPPF, homes were tested only if a child was poisoned there.
3. Increased the number of lead investigations in rental units or owner-occupied homes from 25 in 2007 to 115 during the evaluation period.
4. Three hundred seventy landlords completed lead training courses that are required by the U.S. Environmental Protection Agency. These landlords own at least 2,900 units, two-thirds of which were built before 1950. Pre-1950 buildings often contain lead paint, which can break down into poisonous lead dust.

The Maine CDC also uses the data from the Environmental Public Health Tracking Network data portal annually to monitor and evaluate increases in blood lead screening rates and decreases in lead poisoning in high-risk areas.

Return on Investment:

An earlier study reported a return on investment of $2.34 for every $1 invested from 2006 through 2012.[3]

Lessons Learned

It is important to have data, especially local data, to help people understand the magnitude of the problem in their state and community. Providing data visualizations and maps help communities to understand the place-based nature of lead poisoning and the populations most at risk. It is also important to recognize the necessity of both primary and secondary prevention and deploy funding and staff expertise to both of these types of prevention.

For More Information

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www.mainelegislature.org/legis/statutes/22/title22sec1322-E.html

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[1] Maine Center for Disease Control and Prevention. (2010). Lead Poisoning Prevention Fund evaluation report 2010: A report of findings from the evaluation period: January 2009 through June 2010.
2 Maine Center for Disease Control and Prevention. (2016). Data-driven community lead poisoning prevention.
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Lead Concentrations with Criminal Arrests in EA

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Position: FAV

Association of Prenatal and Childhood Blood Lead Concentrations with Criminal Arrests in Early Adulthood

John Paul Wright, Kim N Dietrich, M. Douglas Ris, Richard W Hornung, Stephanie D Wessel, Bruce P Lanphear, Mona Ho, and Mary N Rae

John Balmes, Academic Editor

Introduction

Early onset of aggressive or violent behavior is a precursor to a life course marred by limited social and educational achievement, incarceration, underemployment, and premature mortality [1,2]. These maladaptive behavioral patterns, which often emerge early in life, remain highly stable [3]. These facts highlight the importance of identifying risk factors that may place youth on an early developmental trajectory toward a career of crime and violence.

A meta-analysis of 34 independent studies identified and prioritized risk factors for serious, violent criminal behavior [4]. The most consistent risk factors were male gender, prenatal exposure to tobacco smoke, having antisocial parents, and low family socioeconomic status. In contrast, few studies have evaluated the consequences of childhood lead exposure as a risk factor for criminal behavior.

Some epidemiological studies have found a relationship between childhood lead exposure and antisocial behavior. In a study of Philadelphia youth, a history of lead poisoning was among the most significant predictors of adolescent delinquency and adult criminality in males [5]. Bone lead levels were associated with delinquent behavior in a retrospective cohort study of 11-year-old Pittsburgh children [6]. In Cincinnati, prenatal and childhood blood lead concentrations were associated with an increased risk for antisocial behavior and delinquency in adolescence [7]. Finally, elevated bone lead levels were observed in juvenile court–adjudicated delinquents residing in Allegheny County, Pennsylvania compared to matched controls [8]. These studies suggest that exposure to environmental lead during childhood is associated with the development of conduct problems and delinquent behavior. In consideration of these findings, it is noteworthy that a number of recent ecological investigations correlating leaded gasoline sales or atmospheric lead levels with crime rates also support an association between lead exposure and criminal behavior [9–12]. Questions remain, however, because these studies were cross-sectional (hence causality cannot be firmly established), relied on indirect measures of lead exposure, or did not follow participants into adulthood.

Here, we report the results of a long-term prospective study on the effects of one potential childhood risk factor of adult arrests, elevated prenatal and childhood blood lead concentrations.

Participants

The Cincinnati Lead Study (CLS) is a birth cohort recruited from late 1979 to early 1984. The CLS enrolled women in their first or early second trimester of pregnancy who attended four prenatal clinics within impoverished Cincinnati neighborhoods with a high concentration of older, lead-contaminated housing [13]. Women were excluded or ineligible if they were known to be addicted to drugs, were known to have diabetes or a neurological or psychiatric condition, or refused prenatal participation. Newborns were excluded if their gestational age was less than 35 wk, birth weight less than 1,500 g, Apgar score at

5 min less than 6, or if genetic or other serious medical issues were present at birth. This process netted 376 newborns who were recruited at birth (i.e., informed oral and written consent was obtained from the mother in the hospital and a blood lead sample was obtained from the newborn). Of these newborns 305 were developmentally examined at the CLS follow-up clinic when they were 3 and 6 mo of age [14]. They were followed up quarterly through age 5 y and semiannually from age 5 to 6.5 y [15].

A total of 250 CLS participants who were between 19 and 24 y of age and had been followed at least through the first 6 y of life participated in the current study. Thus, individuals in the current analysis had serial blood lead concentrations spanning the entire preschool and early school-age period of development. Written informed consent was obtained by the investigator or a senior member of the research staff at each stage of this longitudinal study after it was determined that the participant or the participant's legal guardian understood the nature of the research. This protocol has been reviewed and approved by the institutional review boards of the University of Cincinnati College of Medicine and the Cincinnati Children's Hospital Medical Center.

The 250 participants in this analysis were not substantially different from those with missing data with regard to baseline perinatal characteristics such as birth weight (3,134 versus 3,138 g), sex (50% versus 54% male), 6-y average Hollingshead [16] socioeconomic status (SES) total score (18.0 versus 18.3), years of maternal education (11.2 versus 11.1 y), scores on the Home Observation for Measurement of the Environment (the preschool version of a quantitative observational measure of early nurturing and environmental stimulation [17]) (32.3 versus 33.4), and average childhood blood lead (13.4 versus 14.2 μg/dl).

Exposure and Outcome Assessments

We examined three measures of blood lead. Prenatal maternal blood lead concentration [μg/dl]) was measured during the first or early second trimester of pregnancy. Approximately 50% of the prenatal samples were obtained during the first trimester of pregnancy. The difference between maternal blood lead concentration assessed in the first and second trimesters was not statistically significant ($p = 0.76$) [14]. Postnatal blood lead indices included average childhood blood lead (average of 23 blood lead concentrations obtained quarterly from age 3 to 60 mo and semiannually from 66 to 78 mo), and 6.5-y blood lead. If a 6.5-y blood lead value was not available for a child, we used the blood lead test from 6 y. We selected 6.5 y blood lead over other serial blood lead measures because preliminary analyses indicated that blood lead measured at 6 y was more highly associated with the number of arrests than blood lead measured at other ages. Complete blood lead data were available for 89%–92% of the cohort at any particular quarterly assessment from 3 mo to 5 y of age. Missing postnatal blood lead concentrations were imputed from a weighted average of a within-participant regression of blood lead on age. This imputation was done to avoid excluding those participants who may have one or only a few missing blood lead tests. Prenatal blood lead concentrations were available for 87% (217/250) of the participants.

The primary outcome variable in this study was the individual's number of criminal arrests since turning 18 y of age. We did not collect data on convictions. Arrest is a more proximate measure of criminal behavior than are conviction data. Arrest typically occurs at the scene of the criminal event or immediately thereafter. Arrest decisions, moreover, usually reflect the seriousness of the offense, the offender's prior record, and the desire of the victim to have the individual arrested. Conversely, conviction data are distal indicators of criminal behavior. Actual criminal convictions derived from a trial

represent less than 10% of all criminal arrests. Over 90% of all criminal cases are subject to plea bargaining, in which a plea of “guilty” is usually rewarded with a reduced charge and/or sentence. From the time of arrest it can take upward of 2 y or more before a defendant is tried in a court, or it can take over 1 y from the time of arrest to the time at which a plea deal is accepted by the court. Furthermore, a range of extra-legal variables can enter into the plea and trial process, including the defendant's economic status, support system, and access to quality defense counsel. We should also add that Hamilton County, Ohio (the study's catchment area) makes extensive use of “diversion” programs. These programs select individuals with specified problems or offenses, such as drunken driving or drug abuse and “divert” them from jail or prison into community-based rehabilitation programs. Upon successful completion of the program and a probationary term, many of these programs “erase” the individual's legal conviction, but not the arrest. Finally, at least for this study, arrest data are substantially more complete than are conviction data. Arrest data in Hamilton County, Ohio are compiled into a single county-wide database and are updated at regular intervals. Court data, however, are not updated regularly. This problem is endemic to court systems nationwide, because courts operate at different levels (city, county, state, Federal) and are under the guidance of individual judges.

Data on Criminal Arrests

Data on criminal arrests for participants and their mothers were obtained from a computer search of Hamilton County, Ohio criminal justice records. These records provided information on the nature, number, and disposition of arrests. Two reviewers who were blind to participants' blood lead concentrations independently coded each arrest into one of the following categories: violent offenses (e.g., murder, rape, domestic violence, assault, robbery, or possession of a weapon); offenses against property (e.g., burglary or arson); drug offenses (e.g., trafficking, abuse, or possession); fraud; obstruction of justice; serious motor vehicle offenses (e.g., driving without a license, driving under the influence of alcohol, or driving under suspension); disorderly conduct; and other offenses, which included offenses that did not fit in any previously mentioned category. Minor motor vehicle offenses, such as speeding, safety restraint violations, lights burned out, failing to stop, and pedestrian offenses were excluded from the analyses. We counted the number of arrests and coded the nature of the offense that led to each arrest. If an individual was charged with more than one offense during a single arrest, then the most serious offense was used for classification. Thus, arrest counts were lower than the total number of offenses. Legally determined guilt was not a factor in our coding. Only those offenses that were filed before 31 October 2005 were included in the analyses.

Inter-reviewer differences with respect to arrest and category of offense were resolved by a third reviewer who conducted the initial training for criminal record coding. Interobserver agreement as assessed by Cohen's kappa was 0.93 for maternal offenses and 0.97 for participant offenses.

Statistical Analyses

We used negative binomial regression models to analyze these data because the counts of arrests were overdispersed when originally examined using Poisson regression models [18]. This model provided a very good fit to these data in terms of the estimated scale parameter. These models were used to estimate the association between blood lead concentrations and arrest rates adjusted for other important risk factors. We calculated separate models for each blood lead measure. Our dependent variable was the number of criminal arrests for each participant measured as discrete counts, which were positively skewed. To account for the number of years at risk of arrest, we used the log of current

age as an offset in all models. To control for potential confounding, we examined variables reflecting the effects of other neurotoxicants such as maternal cigarette and marijuana smoking and consumption of narcotics during pregnancy, as well as variables related to adult criminal involvement in prior studies. Our list of candidate covariates included: sex; a validated measure of the quality of early care-giving and environmental stimulation called the Home Observation for Measurement of the Environment (HOME) inventory score [17]; birth weight (g); maternal smoking during pregnancy (half-packs consumed per day); maternal alcohol, marijuana, or narcotic use (Y/N); maternal education level (highest grade); maternal IQ [19]; total prior maternal arrests; SES (average Hollingshead [16] score); number of children in the home; and whether the mother was on public assistance during the participant's childhood (Y/N). Data on fathers or male caregivers in the home were not available, since 84% of the households were headed by the mother or a male caregiver was not consistently present. Continuous covariates were examined using linear, polynomial, and log-transformed functions to assess whether simple linear terms were adequate for adjustment of covariate or confounder influences.

Candidate covariates or confounders remained in the final multivariable models if they were either statistically significant ($p \leq 0.05$) or if their inclusion in the model caused a change of ≥ 10% in the rate ratio estimates for lead, regardless of their level of statistical significance. We tested the interaction of lead by sex, since some studies have indicated that developing male central nervous systems may be more vulnerable than females' to environmental insults leading to later behavioral problems [20]. Before deciding upon a final multivariable model, regression diagnostics for collinearity and influence using the methods described in Belsley, et al. were employed [21]. As a measure of the absolute change in arrest rates between participants with higher levels of blood lead compared to those with lower blood lead levels, we defined attributable risk as the average difference in annual arrest rates between participants at the 95th percentile of blood lead and those at the 5th percentile. All significance tests were two-tailed. Results for blood lead variables are presented as adjusted rate ratios (RR) for total arrests and arrests for violent crimes. All statistical analyses were conducted with SAS (Statistical Analysis System), version 9.1 [22].

Results

The sample was largely African-American (90%), 50% of the participants were male, and 73% of families scored in the lowest two levels of the Hollingshead Four-Factor Index of Social Position [16]. A single female caregiver headed 84% of households.

Mean blood lead concentrations (μg/dl) were 8.3 (0.40 μmol/l) (range 1–26) for maternal prenatal, 13.4 (0.65 μmol/l) (range 4–37) for average childhood, and 8.3 (0.40 μmol/l) (range 2–33) for 6-y. The mean postnatal blood lead concentration of CLS participants increased to a peak of 17.7 (standard deviation [SD] 9.7) μg/dl (0.85 μmol/l) at 21 mo. After age 21 mo, average blood lead concentrations declined to a mean of 8.4 (SD 4.9) μg/dl (0.40 μmol/l) at 6.5 y. At 6.5 y of age, 67 children (26.9%) had a blood lead concentration above 10 μg/dl (0.48 μmol/l) (Table 1). Pearson correlations between blood lead indices examined in this study were 0.32 and 0.28 between prenatal and average childhood and 6-y respectively, and 0.80 between average childhood and 6 y.

Table 1

Characteristics of the Participants and of their Mothers in the Cincinnati Lead Study (*n* =250)

Category	Characteristic	Total (n =250) No. (%) or Mean (SD)	Participant Never Arrested (n =114) No. (%) or Mean (SD)	Participant Ever Arrested (n =136) No. (%) or Mean (SD)
Participant characteristics	Male	125 (50.0%)	34 (29.8%)	91 (66.9%)
	African-American	225 (90.0%)	99 (86.8%)	126 (92.7%)
	Age at study date, y	22.5 (1.5)	21.9 (4.8)	22.5 (4.5)
	Marijuana use	29 (11.6%)	13 (11.4%)	16 (11.8%)
Blood lead, μg/dl[a]	Prenatal blood lead[b]	8.3 (3.8)	7.9 (3.2)	8.7 (4.1)
	Average childhood blood lead	13.4 (6.1)	13.3 (6.7)	13.5 (5.5)
	6-year blood lead	8.3 (4.8)	7.6 (4.3)	8.8 (5.0)
Maternal characteristics	Age at delivery, y	22.5 (4.2)	22.0 (4.0)	22.9 (4.4)
	Maternal IQ (points)	75.3 (9.3)	76.9 (10.4)	73.9 (8.1)
	High school graduate	132 (52.8%)	68 (59.6%)	64 (47.1%)
	HOME inventory at age 3 y (points)	32.3 (6.6)	33.6 (6.3)	31.6 (6.7)
	Socioeconomic status (Hollingshead score)	18.0 (4.8)	18.5 (5.1)	17.8 (4.5)
Marital status	Married	39 (15.6%)	21 (18.4%)	18 (13.2%)
	Single	155 (62.0%)	70 (61.4%)	85 (62.5%)
	Other	56 (22.4%)	23 (20.2%)	33 (24.3%)
Smoked during pregnancy		129 (51.6%)	62 (54.4%)	67 (49.3%)
Number of children in home		3.0 (1.4)	2.9 (1.4)	3.1 (1.3)
Public assistance		190 (76%)	82 (71.9%)	108 (79.4%)

Data presented as n (%) or mean (SD). Average childhood blood lead concentration was defined as the mean of blood lead tests taken from 3 months through the 6-year blood lead test.
[a]To convert blood lead to μmol/l multiply by 0.04826.
[b]n = 217 for prenatal blood lead.
doi:10.1371/journal.pmed.0050101.t001

We identified a total of 800 arrests within the sample. Of these arrests, 108 (14%) were for violent offenses, 90 (11%) involved theft or fraud, 216 (28%) involved drugs, 35 (5%) were for obstruction of justice, 211 (27%) were related to serious motor vehicle offenses, 35 (5%) were for disorderly conduct, and 82 (11%) other. Approximately 55% of participants (62.8% of males, 36.3% of females) had at least one arrest. The mean number of arrests among males was 5.2, which was significantly higher than the mean number of 1.1 for females ($p < 0.001$). The overall mean arrest rate was 0.68 per year after age 18, but the mean arrest rate for males was 4.5 times higher than the female arrest rate (1.1 versus 0.25 per year).

Preliminary analysis of the association between blood lead measures and covariates revealed generally weak correlation coefficients ranging from 0.24 to 0.35, indicating a relatively small potential for confounding. In multivariable regression analyses of the total number of arrests, we found that the associations between prenatal and 6-y blood lead concentrations were statistically significant. In each model, the blood lead association was adjusted for the cofactors of maternal IQ, sex, SES score, and maternal education. The RRs for total arrests increased for each 5 μg/dl (0.24 μmol/l) increment in blood lead concentration; the RRs were 1.40 (95% confidence interval [CI] 1.07–1.85) for prenatal blood lead, 1.07 (95% CI 0.88–1.29) for average childhood blood lead, and 1.27 (95% CI 1.03–1.57) for 6-y blood lead. The attributable risk was 0.48 arrests/year (95% CI 0.29–0.79) for prenatal blood lead, 0.13 (95% CI 0.03–0.33) for average childhood blood lead, and 0.39 (95% CI 0.21–0.68) for 6-y blood lead (Table 2). The rate of total arrests was modeled as a log-linear function of increasing blood lead concentrations for each of the three blood lead assessments: maternal prenatal (Figure 1A), early childhood (Figure 1B), and 6 y (Figure 1C).

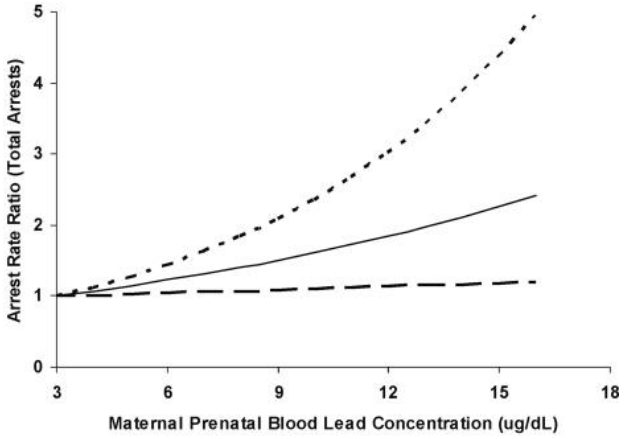
Table 2

Relationship of Prenatal, Early Childhood Average, and Six-Year Blood Lead Concentrations with Total Arrest Rates in Young Adults

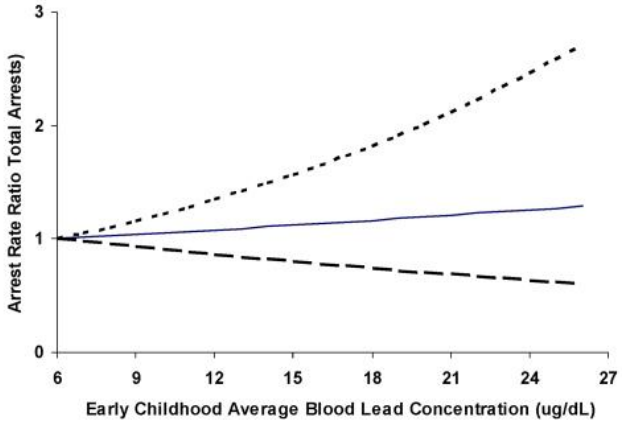
Blood Lead Variable	Median (5th–95th Percentile), μg/dl [a]	Attributable Risk (95% CI), per Year	Rate Ratio for 5 μg/dl Increase in Blood Lead (95% CI)
Prenatal	7.8 (2.9–16.0)	0.48 (0.29–0.79)	1.40 (1.07–1.85)
Early Childhood Average	12.3 (6.0–26.3)	0.13 (0.03–0.33)	1.07 (0.88–1.29)
Six-Year	6.8 (3.4–18.3)	0.39 (0.21–0.68)	1.27 (1.03–1.57)

Estimates adjusted for maternal IQ, sex, SES using the Hollingshead Score, and maternal education level.
[a]To convert blood lead to μmol/l multiply by 0.04826.
doi:10.1371/journal.pmed.0050101.t002

A


Arrest Rate Ratio (Total Arrests)
0
1
2
3
4
5
3
6
9
12
15
18
Maternal Prenatal Blood Lead Concentration (ug/dL)

B


Arrest Rate Ratio Total Arrests)
0
1
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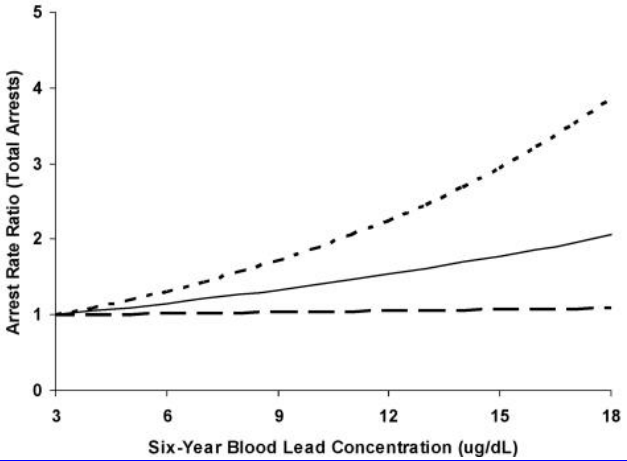
9
12
15
18
21
24
27
Early Childhood Average Blood Lead Concentration (ug/dL)

C


Arrest Rate Ratio (Total Arrests)
0
1
2
3
4
5
3
6
9
12
15
18
Six-Year Blood Lead Concentration (ug/dL)

Adjusted Relationship between Blood Lead Concentration and Arrest Rate Ratio For Total Arrests

Shown are data for maternal prenatal blood lead concentration (A), early childhood average blood lead concentration (B), and 6-year blood lead concentration (C). Rate ratios are plotted as a function of increasing blood lead from the 5th to the 95th percentiles of blood lead relative to participants at the 5th percentile. Dashed lines are 95% confidence intervals. To convert to μmol/l: (μg/dl) × 0.04826.

In multivariable analyses of violent criminal arrests, we found statistically significant associations with both average childhood and 6-y blood lead variables. The RRs for arrests involving violent crimes increased for each 5 μg/dl (0.24 μmol/l) increment in blood lead; the RRs were1.34 (95% CI 0.88–2.03) for prenatal blood lead, 1.30 (95% CI 1.03–1.64) for average childhood blood lead, and 1.48 (95% CI 1.15–1.89) for 6-y blood lead. The attributable risk was 0.055 arrests/year (95% CI 0.026–0.118) for prenatal blood lead, 0.077 (95% CI 0.039–0.156) for average childhood blood lead, and 0.087 (95% CI 0.049–0.152) for 6-y blood lead (Table 3). As with the analyses for total arrests, the rate of arrests for violent offenses was modeled as a log-linear function of each of the blood lead indices: maternal prenatal (Figure 2A), early childhood (Figure 2B), and 6 y (Figure 2C).

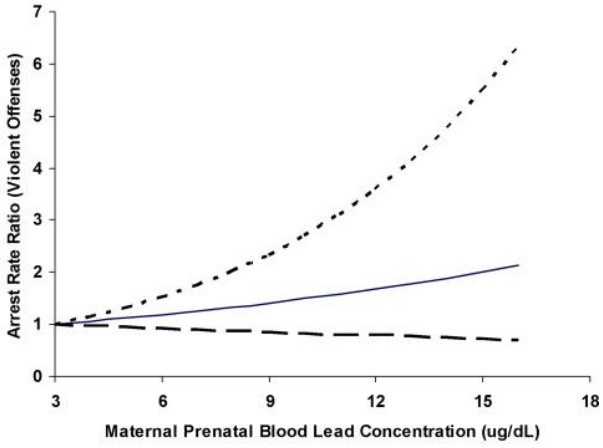
Table 3

Relationship of Prenatal, Early Childhood Average, and Six-Year Blood Lead Concentrations with Violent Crime Arrest Rates in Young Adults

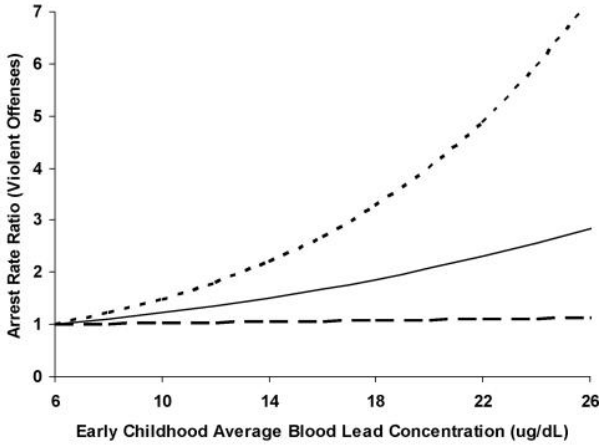
Blood Lead Variable	Median (5th–95th Percentile), μg/dl[a]	Attributable Risk (95% CI), per Year	Rate Ratio for 5 μg/dl Increase in Blood Lead (95% CI)
Prenatal	7.8 (2.9–16.0)	0.055 (0.026–0.118)	1.34 (0.88–2.03)
Early Childhood Average	12.3 (6.0–26.3)	0.077 (0.039–0.156)	1.30 (1.03–1.64)
Six-Year	6.8 (3.4–18.3)	0.087 (0.049–0.152)	1.48 (1.15–1.89)

Estimates adjusted for maternal IQ, sex, SES using the Hollingshead Score, and maternal education level.
[a]To convert blood lead to μmol/l multiply by 0.04826.
doi:10.1371/journal.pmed.0050101.t003

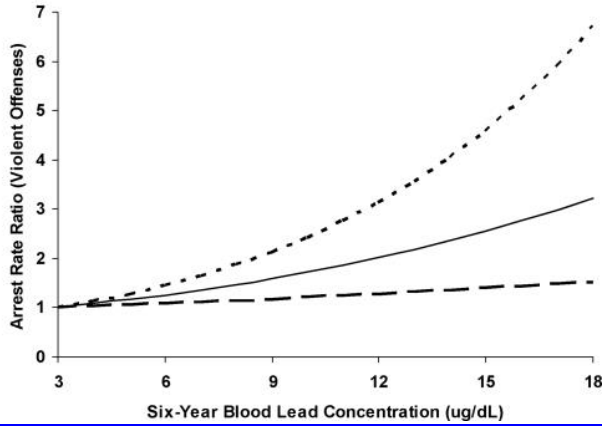
A


Arrest Rate Ratio (Violent Offenses)
0
1
2
3
4
5
6
7
3
6
9
12
15
18
Maternal Prenatal Blood Lead Concentration (ug/dL)

B


Arrest Rate Ratio (Violent Offenses)
0
1
2
3
4
5
6
7
6
10
14
18
22
26
Early Childhood Average Blood Lead Concentration (ug/dL)

C


Arrest Rate Ratio (Violent Offenses)
0
1
2
3
4
5
6
7
3
6
9
12
15
18
Six-Year Blood Lead Concentration (ug/dL)

Adjusted Relationship between Blood Lead Concentration and Arrest Rate Ratio For Violent Offenses

Shown are data for maternal prenatal blood lead concentration (A), early childhood average blood lead concentration (B), and 6-year blood lead concentration (C). Rate ratios are plotted as a function of increasing blood lead from the 5th to the 95th percentiles of blood lead relative to participants at the 5th percentile. Dashed lines are 95% confidence intervals. To convert to μmol/l: (μg/dl) × 0.04826.

The results for analyses restricted to arrests for nonviolent crimes were similar to those found for all arrests. Specifically, the RRs for nonviolent arrests for each 5 μg/dl (0.24 μmol/l) in blood lead were 1.40 (95% CI 1.06–1.84) for prenatal blood lead, 1.05 (95% CI 0.86–1.28) for average childhood blood lead, and 1.22 (95% CI 0.97–1.53) for 6-y blood lead.

There was no statistical evidence that the shape of the exposure-response relationship differed by sex with any of the blood lead indices for total arrests or arrests for violent offenses. The interaction term for sex was statistically nonsignificant (*p*-values for interaction term ranged from 0.42 to 0.79). However, the attributable risk for males was considerably higher than for females. For example, the attributable risk for 6-y blood lead rate was 0.85 arrests/year (95% CI 0.48–1.47) for males and 0.18 (95% CI 0.09–0.33) for females.

Discussion

In a prospective birth cohort, we found that prenatal and childhood blood lead concentrations were predictors of adult arrests. Prenatal and 6-y blood lead concentrations were significantly associated with higher RRs for total arrests. Average childhood as well as later (6-y) blood lead concentrations were significantly associated with higher RRs for arrests involving a violent offense. Data from several recent prospective studies suggest that blood lead concentrations in the later preschool years may be more predictive of cognitive and behavioral problems [23]. However, the potential importance of prenatal blood lead concentrations should not be underestimated, as they were predictive of total arrests in our data. The number of arrests in the CLS cohort was significantly higher in males. However, no significant interactions between sex and blood lead with arrest rates were found.

Environmental lead levels as well as crime have dropped over the last 30 y in the US [9]. However, the overall reduction was not uniform; inner-city children, who are predominately African-American, remain particularly vulnerable [24]. Crime and violent crime are concentrated in urban centers in the US where many poor African-Americans reside. One factor in the disproportional representation of African-Americans in crime statistics could well be the historically higher exposures to lead in these communities. Furthermore, recent data from epidemiological studies implicate blood lead concentrations well below the current level of concern adopted by the United States Centers for Disease Control in the development of neurobehavioral deficits [25]. We were unable to explore racial differences in our data since almost all participants were African-American. However, Needleman found that the lead-associated risk for juvenile court-adjudicated delinquency was present in both African-American and white youth, indicating that these findings are not restricted to any one racial or ethnic group [8].

The neurodevelopmental consequences associated with lead exposure in previous studies, such as lower IQ, less tolerance for frustration, deficits in attention, hyperactivity, and weak executive control functions, are potent predictors of delinquent and criminal behaviors [26–29]. Attention deficit

hyperactivity disorder (ADHD) is a common finding among juvenile delinquents, and those with ADHD are more likely to have severe cognitive impairments [30]. ADHD is also a known risk factor for criminal behavior in adulthood [31]. A recent analysis of data from the third National Health and Nutrition Examination Survey (NHANES-III) found that higher blood lead concentrations were significantly associated with ADHD. Children with blood lead concentrations greater than 2 μg/dl were at a 4.1-fold increased risk of ADHD [32]. Similarly, in experiments with rodents, felines, and nonhuman primates, early lead exposure was associated with increased impulsivity, aggression, antagonistic interactions, reduced social play and abnormal mother–infant interaction [33–36]. Childhood lead exposure therefore seems to place individuals at risk for multiple underlying neurobehavioral deficits associated with a higher probability of later criminal behavior.

A number of mechanisms may be at work. Lead interferes with synapse formation, disrupts dopamine systems, and lowers serotonin levels. Lead exposure has been shown to reduce MAO A (monoamine oxidase A) activity, and low MAO A activity has been associated with violent and criminal behaviors [37]. One consequence of these alterations could be neural dysfunction in areas of the brain involved in arousal, emotion, judgment, and behavioral inhibition such as the prefrontal cortex [38].

This study has several limitations. First, most criminal behavior never comes to the attention of authorities; thus, our measure of arrest underestimates actual criminal activity. Had we been able to account for all criminal acts, it is possible that the results of our study may have been different. For example, it could be argued that lead-associated lower intelligence makes it more likely that an offender will be caught (i.e., arrested). However, a recent large-scale prospective study of school-aged children with early blood lead levels similar to those in the CLS suggests that lead impacts social behaviors somewhat independently of IQ [39]. Furthermore, we did not adjust arrest rates for child IQ in our analyses because controlling for a variable that might potentially be on the causal pathway is clearly inappropriate in studies of this kind. Variables along the causal pathway between exposure and outcome cannot be bona fide confounders [40]. Second, we examined only Hamilton County, Ohio records. Although most participants in our cohort continued to reside in Hamilton County, we may have missed some arrests that occurred in other counties. Third, official records of arrest were available only when the participants reached 18 y of age. Thus, the average follow-up was under 5 y. The possibility of bias introduced by nonrandom attrition in the CLS cohort cannot be ruled out, although we found no important differences on key exposure and demographic variables. Fourth, it is always possible in observational studies to have uncontrolled confounding. This can be problematic when it comes to measuring SES, since global assessments of social standing such as the one used in this [16] and many other studies fail to capture all potentially relevant factors [41]. As pointed out by Weiss and Bellinger [42] in their discussion of the social ecology of exposure to environmental pollutants, neurotoxicant exposures are not randomly distributed, but are “chained” to many other risks to normal development that are sometimes quite difficult to partition. Finally, as with all studies of this kind, our measure of dose to the critical organ (brain) was indirect. Blood, as well as other tissues in which lead is often measured such as teeth or bone, are surrogates for dose to the central nervous system.

On the other hand, this study has a number of qualities that contribute to the validity of our findings. To our knowledge this is the first prospective study to directly examine the relationship between early exposure to lead and official documentation of arrests in adulthood. Lead dose as assessed by frequent serial blood lead determinations, assessment of a large number of potentially important covariate factors, and careful documentation of criminal arrests were unique aspects of this investigation.

Furthermore, the sample was relatively homogenous with respect to sociodemographic variables such as SES and ethnicity; thus decreasing the extent to which strong confounding factors might generate spurious associations. Therefore, we conclude that these data implicate early exposure to lead as a risk factor for behaviors leading to criminal arrest.

Acknowledgments

We are grateful to members of the Cincinnati Lead Study cohort and their families for their participation.

Abbreviations

ADHD	attention deficit hyperactivity disorder
CI	confidence interval
RR	rate ratio
SES	socioeconomic status

Footnotes

Author contributions. JPW, KND, MDR, and BPL designed the experiments/the study. SDW and KND collected data or did experiments for the study. RWH, MH and JPW analyzed the data. KND and SDW enrolled patients. JPW and KND wrote the first draft of the paper. JPW, KND, MDR, RWH, SDW, BPL, and MNR contributed to writing the paper.

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Competing Interests: Two of the study's authors, BPL and RH, are on the editorial board of *PLoS Medicine*. BPL and KND sporadically serve as expert witnesses without personal financial gain.

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Lead Poisoning Prevention Fee

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National Center for
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Lead Poisoning Prevention Fund

Financing Source: State Fund by Fees
Financing Amount: $650,000 Annually
Focus: Lead (Primary Prevention)

The Maine Legislature established the Lead Poisoning Prevention Fund (22 MRSA c. 252 §1322-E) in 2005. The Lead Poisoning Prevention Fund (LPPF) is administered with the help of an Advisory Board by the Childhood Lead Poisoning Prevention Unit (CLPPU) within the Maine Center for Disease Control and Prevention (CDC) of the Maine Department of Health and Human Services (DHHS). Resources from the LPPF are used to accelerate progress towards eliminating childhood lead poisoning in Maine through statewide and community-based activities that enable the public to identify lead hazards and take precautionary actions to prevent exposure to lead. The Maine CDC awards contracts to organizations to carry out education, outreach and capacity building services in high-risk areas (i.e., the five areas with the highest burden of childhood lead poisoning).

Financing Mechanism

The Maine Legislature established the Lead Poisoning Prevention Fund (22 MRSA c. 252 §1322-E) in 2005. The bill was the outcome of an effort led by a coalition of environmental activists. It authorizes a fee of 25 cents per gallon on all paint sold in Maine. The fee is imposed on paint manufacturers or brand label owners. It provides a waiver for payment for those who sell low quantities. Revenue from the fees fluctuated between$700,000 and $800,000 in the initial years. Revenue decreased during the recession but is currently stable at around $650,000 annually.

The Lead Poisoning Prevention Fund (LPPF) is administered with the help of an Advisory Board by the Childhood Lead Poisoning Prevention Unit (CLPPU) within the Maine Center for Disease Control and Prevention (CDC) of the Maine Department of Health and Human Services (DHHS). Resources from the LPPF are used to accelerate progress towards eliminating childhood lead poisoning in Maine through statewide and community-based activities that enable the public to identify lead hazards and take precautionary actions to prevent exposure to lead.

Through contracts for local education, outreach, and capacity-building services, the Maine CDC disburses funds from the LPPF to communities around the state with the highest burden of children with lead poisoning. The contracts are awarded through a competitive request for proposals (RFP) process. The most recent RFP was published in 2016 for contracts to provide services for up to five years in the five areas in Maine with the highest burden of lead poisoning. Any interested party is eligible to submit a bid in response to the RFP.

Program Overview

Using the resources of the LPPF, the Maine CDC implements education, outreach, and training programs that enable the public to identify lead hazards and take precautionary actions to prevent lead exposure.

According to the LPPF Evaluation Report 2010,[1] program activities and partnerships are designed to:

1. Help parents of young children who live in homes likely to have lead hazards live safely with lead so that their children never become poisoned;
2. Help property owners and managers of rental units likely to have lead hazards provide and maintain lead-safe housing so that child occupants never become poisoned; and,

This brief was made possible through a contract between the W.K. Kellogg Foundation and the National Center for Healthy Housing. The contents of this document are solely the responsibility of the authors and do not necessarily represent the official views of the W.K. Kellogg Foundation.

3. Help property owners of rental units likely to have lead hazards avoid the high costs associated with lead abatement.

Program Operations

The Childhood Lead Poisoning Prevention Unit (CLPPU) of the Maine CDC manages the activities supported by the LPPF. The CLPPU works with the Maine CDC Environmental Public Health Tracking Program to analyze and make publicly available lead poisoning surveillance data for Maine towns, which is used to identify areas at high risk for childhood lead poisoning. The Maine CDC awards contracts to organizations to carry out education, outreach and capacity building services in high-risk areas (i.e., the five areas with the highest burden of childhood lead poisoning). In addition, the Maine CDC conducts statewide prevention activities as directed by the LPPF statute, including a statewide media campaign, a targeted direct mailing to parents of one-year-olds with an offer for a free home lead dust test kit, environmental investigations for all additional units in multifamily buildings where a child has been poisoned, and an online lead-safe housing registry.

Eligible Population Served:

Activities funded by the LPPF are intended to reach:

1. Parents of children under the age of six and expectant parents who live in housing built before 1950 and,
2. Owners of rental units built before 1950.

The LPPF statute directs the Maine CDC to give preference to activities that reach high-risk or underserved populations.

Staffing:

Services are provided by health department employees, contractors, or community-based partners.

Billing for Services:

Services are offered at no cost to community residents.

Outcomes and Evaluation

According to a Maine CDC report, the number of children six years and under who are newly identified with lead poisoning has declined continuously. Data from 2003 through 2013 indicate a significant drop in rates of lead poisoning in three out of the five high-risk areas receiving lead prevention services.[2]

An evaluation report on the LPPF states the following as its most significant achievements during the period between January 1, 2009, and June 30, 2010:

1. Fifty percent of LPPF resources were distributed to community organizations, establishing capacity and infrastructure for education and preventive lead dust testing in homes throughout the state and expanding prevention efforts to far more people than ever before possible.
2. More than 350 homes were tested for lead dust, the most common cause of childhood lead poisoning in Maine. These tests help residents and landlords to identify lead dust and protect children from lead poisoning. Prior to the LPPF, homes were tested only if a child was poisoned there.
3. Increased the number of lead investigations in rental units or owner-occupied homes from 25 in 2007 to 115 during the evaluation period.
4. Three hundred seventy landlords completed lead training courses that are required by the U.S. Environmental Protection Agency. These landlords own at least 2,900 units, two-thirds of which were built before 1950. Pre-1950 buildings often contain lead paint, which can break down into poisonous lead dust.

The Maine CDC also uses the data from the Environmental Public Health Tracking Network data portal annually to monitor and evaluate increases in blood lead screening rates and decreases in lead poisoning in high-risk areas.

Return on Investment:

An earlier study reported a return on investment of $2.34 for every $1 invested from 2006 through 2012.[3]

Lessons Learned

It is important to have data, especially local data, to help people understand the magnitude of the problem in their state and community. Providing data visualizations and maps help communities to understand the place-based nature of lead poisoning and the populations most at risk. It is also important to recognize the necessity of both primary and secondary prevention and deploy funding and staff expertise to both of these types of prevention.

For More Information

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State Toxicologist, Department of Health and Human Services
Office: 207-287-5189. Email: Andy.E.Smith@maine.gov
www.mainelegislature.org/legis/statutes/22/title22sec1322-E.html

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74492	LeadCare II Label Printer (Ships Soon) See Details	**$459.00**	0
74493	LeadCare II Labels (Ships Soon) See Details	**$39.00**	0

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Lead poisoning in children is a serious chronic disease that can lead to learning difficulties and behavior problems. However, signs of childhood lead poisoning may not be evident right away. The only way to know is through a blood test.

The American Academy of Pediatrics (AAP) recommends that “children should be tested at least once when they are 2 years of age or, ideally, twice, at 1 and 2 years of age, unless lead exposure can be confidently excluded.” [1]

LeadCare II Benefits:

- **Fast and easy** - The simple fingerstick (just two drops of blood) is easier than other tests, which require blood drawn from a vein.
- **Saves time** - no trip to doctor office, no lab send outs required, no follow up calls to lab for results, no redraws due to sample problems.
- **Immediate results** - in 3 minutes you have the information you need.
- **Improved efficiency** - no child lost to “follow up.”

Who is at risk for lead exposure?

Children are considered at risk if any of the following are true[2]

- Child lives in or frequently visits a home or building built before 1950, or a recently renovated home/building built before 1978.
- Child has a sibling or frequent playmate with elevated blood lead levels.
- Child’s parent or principal caregiver works with lead. Examples include: battery recycling or manufacture, lead smelting, lead mining, auto repair, shipbuilding, construction, plumbing, and glass manufacture.[3]
- Child is a recent immigrant, refugee, or foreign adoptee.
- Child has a household member who uses traditional, folk, or ethnic remedies or cosmetics or who routinely eats food imported informally (e.g., by a family member).

Lifelong impact. Lead poisoning can take a serious toll on a growing mind and body, with lifelong effects on cognitive development and behavior[4]. Lead poisoning affects the central nervous system, kidneys, and blood-forming organs. Lead exposure is associated with learning and behavior problems and even reduced income in adulthood.

No safe level. Scientific evidence is growing that even low levels of lead in the blood may cause learning and behavior problems.

Healthy foods. A doctor can advise about simple measures, such as a healthful diet with enough calcium, iron and Vitamin C, to help prevent the effects of lead.

Please Note: LeadCare II products can be sold and shipped only within the United States.

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Report to
The Vermont Legislature

Lead Poisoning Prevention: Report on 2018 Program Outcomes and Activities

In Accordance with 18 V.S.A. § 1756

Submitted to: **Vermont General Assembly**

Submitted by: **Mark Levine MD, Commissioner of Health**

Prepared by: **Division of Environmental Health**

Report Date: **April 15, 2019**

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Lead Poisoning Prevention:
Report on 2018 Program Outcomes and Activities

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Introduction

This annual report on the status of childhood lead poisoning prevention is submitted pursuant to 18 V.S.A. § 1756. Over the past 20 years, Vermont has made steady progress in reducing the number of children with blood lead levels at or above Vermont's current action level of 5 micrograms per deciliter (µg/dL). From 2006 through 2018, the percentage of 1- and 2-year olds with blood lead levels greater than or equal to 5 µg/dL declined (1-year olds from 19.4% to 4.3%, and 2-year olds from 22.5% to 3.8%). In 2018, there were 362 children ages 1 and 2 who had an elevated blood lead level, down from 412 in 2017. In total, 420 children under the age of 6 had an elevated blood lead level in 2018, down from 480 in 2017.

The percentage of 1-year olds tested each year declined from 82% in 2014 to 77% in 2018. The percentage of 2-year olds tested increased from 44% in 2006 to 72% in 2014 and was 70% in 2018.

The mission of the Vermont Department of Health's Healthy Homes Lead Poisoning Prevention Program (Healthy Homes) is to improve the health and safety of all Vermont home environments through surveillance, collaboration, education, and implementation of comprehensive policies and coordinated programmatic activities. Healthy Homes conducts a variety of lead education and outreach activities that are intended for multiple audiences and designed to prevent lead poisoning, encourage lead screening of 1- and 2-year olds, and support case management for children with elevated blood lead levels. For the dollar amount spent by public agencies in Vermont in 2018 to reduce lead hazards and prevent lead poisoning ($2,035,556), the State of Vermont could see a return on investment (ROI) of between $34,604,449 to $449,857,832. This estimate takes into account the national costs of lead hazard control, reduced health care costs, lifetime earnings, tax revenue, special education costs, behavioral disorders, and crime.

In 2019, Healthy Homes will continue working with the U.S. Department of Housing and Urban Development (HUD)-funded partners to reduce lead hazards in the homes of lower-income families, increasing Vermont lead law compliance among rental property owners, reaching out to health care providers to improve screening rates of 1- and 2-year olds, and conducting educational outreach to parents of young children, emphasizing the importance of lead screening.

Measuring Progress

Testing of 1- and 2-year olds is required under law (18 V.S.A. § 1755). A child's exposure to lead can easily be identified through testing and appropriate interventions can be initiated to prevent further exposure to this harmful toxicant. In addition, testing helps inform the development of lead poisoning prevention policies by giving the Department the opportunity to track statewide trends in childhood exposure to lead.

Healthy Homes works toward achieving the goal of universal testing of 1- and 2-year olds in Vermont. Vermont's definition of an elevated blood lead level is 5 µg/dL, which is aligned with the current Centers for Disease Control and Prevention (CDC) reference level. Table 1 presents

2018 data on the number of young children who were tested for lead and the results of those screenings.

Table 1
Blood Lead Tests and Results for Vermont Children ages 0 - <6 years, 2018*

Age	Population	# of Tests	% Tested	# < 5 µg/dL	% < 5 µg/dL	# 5-9 µg/dL	% 5-9 µg/dL	# ≥10 µg/dL	% ≥10 µg/dL
Under 1	5960	168	2.8%	158	94.0%	7	4.2%	*	*
1	6010	4640	77.2%	4440	95.7%	157	3.4%	43	0.9%
2	6080	4224	69.5%	4062	96.2%	133	3.1%	29	0.7%
3	6154	328	5.3%	301	91.8%	25	7.6%	*	*
4	6157	170	2.8%	153	90.0%	12	7.1%	*	*
5	6182	76	1.2%	72	94.7%	*	*	*	*
Total	36544	9606	26.3%	9186	95.6%	337	3.5%	83	0.9%

Notes:

* Indicates fewer than six cases in a category that year. When counts and percentages are based on only a few cases, it is impossible to distinguish random fluctuation from true changes in data
Ages: < 1 year: <11 months, 1 year: 11-22.99 months, 2 years: 23-34.99 months, 3 years: 35-46.99 months, 4 years: 47-58.99 months, 5 years: 59-70.99 months.
Population is the average of census estimates or counts from the three previous years (2015, 2016, 2017).
Data include one blood lead test per child by age: the highest venous test result or if there is no venous test, then the capillary test result. This may result in a child having two tests per calendar year. For example, a child may be born in December 2017, have their 1-year old test in January 2018, and then have their 2-year old test in December 2018.

Figure 1

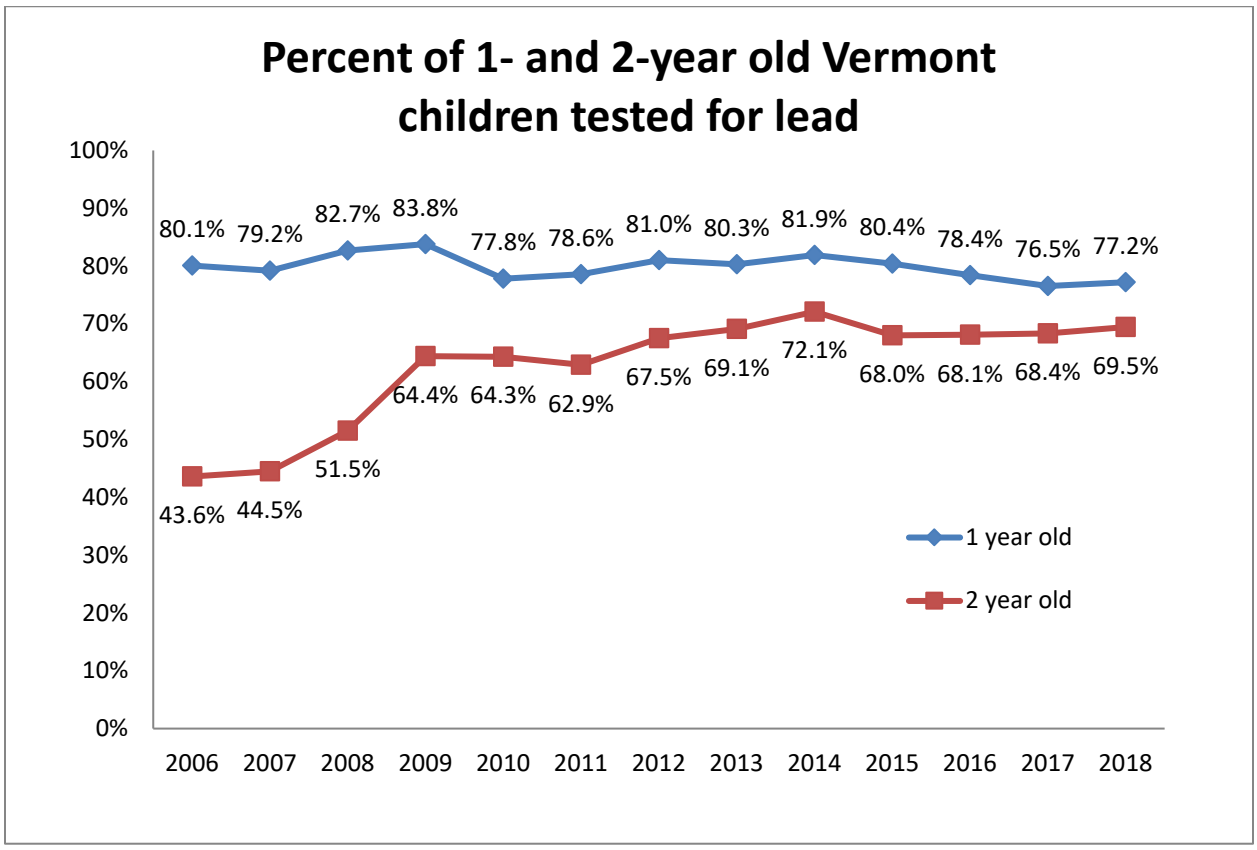

Figure 1 shows the percentage of 1-year olds and the percentage of 2-year olds tested each year from 2006 through 2018. For 1-year olds, about 80% have been tested each year across the time period. However, a steady decrease is observed from 2014 (82%) to 2018 (77%). Statistical analysis indicates that this decrease is statistically significant. For 2-year olds, the percentage tested increased more than 20% between 2006 and 2009. This increase continued until 2014. The percentage of 2-year olds tested has been stagnant from 2015 to 2018.

Figure 2

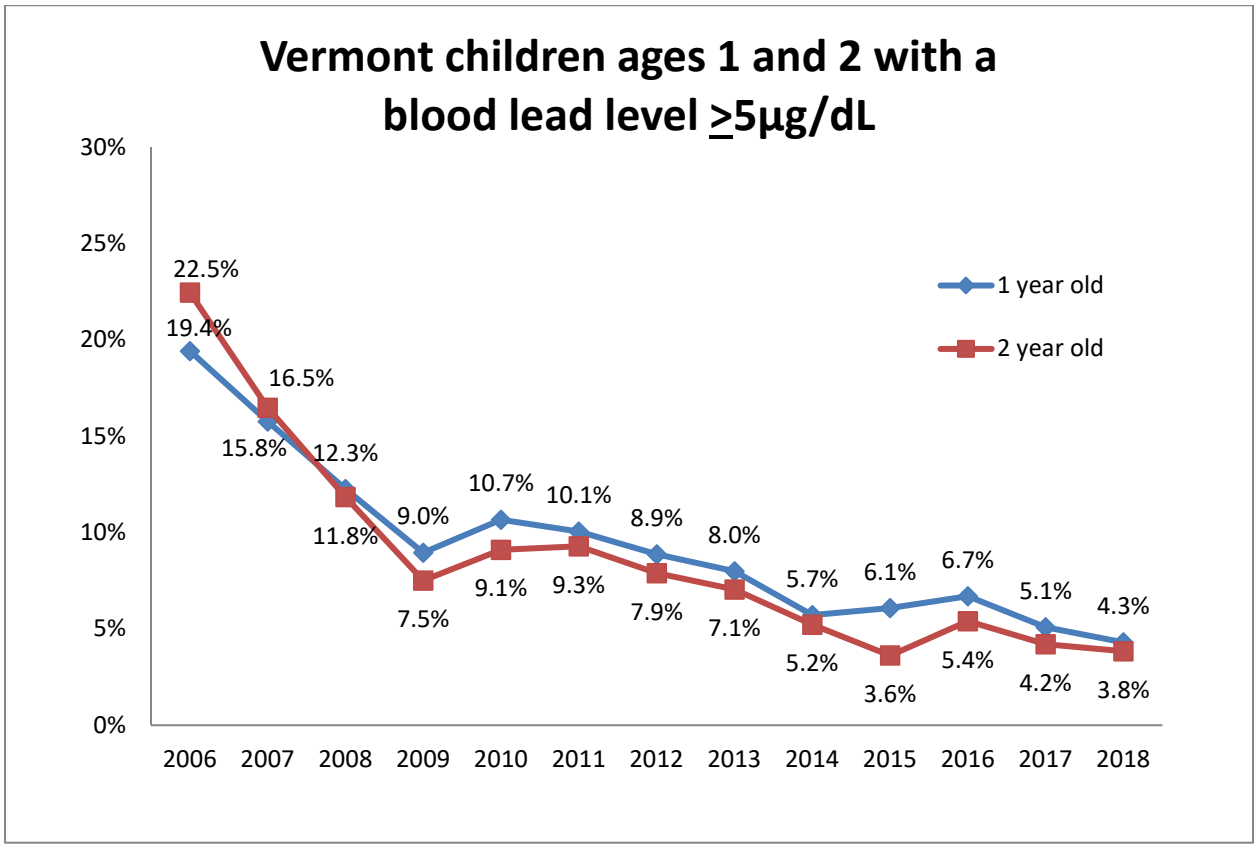

Figure 2 shows the percentage of Vermont 1- and 2-year olds tested who had blood lead levels greater than or equal to 5 µg/dL during the period from 2006 through 2018. This trend shows a decrease in the percentage of 1- and 2-year olds who had elevated blood lead levels.

Barriers to Universal Screening

Lead screening of 1- and 2-year olds is a nationally recognized standard of pediatric care, and Vermont's universal testing requirement is consistent with this standard. As there are no immediate signs or symptoms of lead poisoning, testing is the only way to know if a child has been exposed to lead. Preventing exposure, therefore, is the key to keeping children safe from lead.

In the past, a number of barriers to testing requirements have been identified. Health care providers have indicated that difficulty obtaining blood samples from infants and young children poses a barrier to testing. Health care providers have also voiced concerns about inadequate cost reimbursement for lead testing and lack of insurance coverage for the procedure. Other barriers have included parental opposition to testing and inaccurate beliefs about who is and who is not at risk for lead poisoning.

To understand these barriers, the Vermont Child Health Improvement Program (VCHIP), in partnership with the Health Department, has created a survey to assess perceived barriers to testing. The survey will be sent to all health care providers currently testing 1- and 2-year olds in Vermont in the Spring 2019. Data gathered will be used to outreach to providers with low testing rates, and offering them support and solutions to increase their testing rates in the Fall 2019.

2018 Education and Outreach Activities

In 2018, the Healthy Homes Lead Poisoning Prevention Program continued the cooperative agreement with the Centers for Disease Control or Prevention (CDC) for lead poisoning prevention. This funding supports the Program's efforts to improve the health and safety of all Vermont home environments through surveillance, collaboration, education, and implementation of comprehensive policies and coordinated programmatic activities. In addition, the Program applied for and received one-year of supplemental funding in October 2018 to work on three CDC pre-approved projects: developing provider report cards, creating a simplified reporting system for Lead Care II (in-office blood lead testing machines) users, and developing a social marketing campaign for parents of 1- and 2-year olds to encourage blood lead testing. The overall goal of these three projects is to strengthen blood lead testing and reporting in Vermont.

An integral part of the program is outreach and support for health care providers and education to the public. The program conducts a variety of lead education and outreach activities intended for multiple audiences and designed to prevent lead poisoning, encourage lead screening of 1- and 2-year olds, and support case management for children with elevated blood lead levels. Below is a sample of activities organized by activity type.

Programmatic Activities and Outreach

- Completed a data update on the Healthy Vermonters 2020 dashboard, which displays the percentage of children ages 1 to 5 with venous blood lead levels in the ranges of 5 to 9 µg/dL and 10 µg/dL and above (viewed here: www.healthvermont.gov/scorecard-environment-food-safety).
- Transitioned to the new CDC database, Healthy Housing Lead Poisoning Surveillance System (HHLPSS).
- Standardized the 12 local health office webpages with information on healthy homes and lead poisoning prevention.
- Continued the campaign around vintage, antique, and salvaged items with advertisements in the *NEST*, a quarterly publication of *Seven Days*, and *Green Living* to intended for do-it-yourselfers and homeowners.
- Conducted outreach during Lead Poisoning Prevention Week (October 21-27, 2018) using the Halloween-themed poster and video developed last year. The Department's district offices used these and other materials to conduct additional outreach during the week, which included lobby displays, presentations, social media posts, letters to health care providers, and posters.
- Collaborated with the Asbestos and Lead Regulatory Program to begin the regional rollout (Morrisville area in March and Barre area in June) of a campaign to raise awareness among landlords and tenants with children under six about the required

Essential Maintenance Practices for pre-1978 rental housing that aim to prevent lead poisoning.
- Worked with HUD-funded partners (Vermont Housing Conservation Board and Burlington Lead Program) to reduce lead hazards in the homes of lower-income families.

Targeted Education

- Provided environmental investigations, educational home visits, and follow-ups for 89 families of children with confirmed blood lead levels of 5 µg/dL or greater.
- Mailed 10,560 postcards to families with 10-month-old children and 22-month-old children who were born in Vermont reminding them to have their children tested for lead.
- Mailed 296 packets to families whose children had a blood lead level from 5 µg/dL to 9 µg/dL that include educational materials, follow-up testing recommendations, and a request form for a free dust wipe kit that enables families to test their homes for lead.

Screening Outreach

- Continued education to health care providers via the Department's district offices regarding the need to test children for lead at both 12- and 24-month well-child visits.
- Educated parents at Women, Infants, and Children (WIC) appointments on the importance of getting their children tested for lead.
- Continued back-up lead testing of children at their 18- and/or 30-month WIC appointments who were not tested by their health care providers at 12 and 24 months.
- Continued to work with the Vermont Chapter of American Academy of Pediatrics under a grant to provide the purchase of in-office blood lead testing machines, known as LeadCare II, for selected pediatric and family practices. The grant supports the purchase of the machines and peer-to-peer education and training with the goal of further reducing known barriers to blood lead screening.
- Began a project in partnership with the VCHIP to survey health care providers to determine barriers to testing and to offer support and solutions to providers with low testing rates.
- Included information about lead screening in letters sent by the Early and Periodic Screening, Diagnosis and Treatment Program advising parents that age-appropriate screening tests are recommended and covered by Medicaid.

Future of Vermont's Healthy Homes Lead Poisoning Prevention Program and Recommendations

In 2019, Healthy Homes will continue work to prevent lead poisoning by making homes safer for children and increasing blood lead testing rates for 1- and 2-year olds through educating parents, providing technical assistance to health care providers, and enforcing the lead testing rules. HHLPPP will:

- Continue to:
    - Provide outreach, conduct environmental investigations, and provide case management to families with children that have confirmed elevated blood lead levels.

    - Send reminder postcards with lead testing information to all families whose children were born in Vermont and are ages 10 and 22 months.
- Work with a marketing firm to develop a social marketing campaign focused on parents and caregivers of children under 2 years of age to raise awareness about lead poisoning and testing for their children and to increase testing rates
- Develop and disseminate annual provider report cards on blood lead testing for all medical practices in Vermont who have 30 or more 1- and 2-year-old patients. The goal is to encourage required testing among health care providers by reporting practice-specific testing rates, comparing their rates with those of their peers, and providing education and guidance about blood lead testing.
- Identify health care providers who have not been testing 1- and 2-year olds for lead and work with them to increase their testing rates.
- Continue working with VCHIP to contact health care providers to determine barriers to testing and offer support to increase their testing rates.
- Compile a comprehensive data report with lead poisoning, screening, case management, and housing information that includes geographic information system (GIS) maps featuring areas of elevated blood lead levels, older housing stock, and low-income status.
- Work with Lead Care II users to improve the accuracy and timeliness of lead test reporting.
- Work with town health officers to identify lead hazards in their communities.
- Maintain and create partnerships with internal and external partners, such as:
    - Vermont Housing and Conservation Board
    - Children's Integrated Services
    - Burlington Lead Program
    - Parks Place Lead Safe and Healthy Homes Program
    - Head Start
    - Environmental Public Health Tracking Program
    - Asthma Program
    - Asbestos and Lead Regulatory Program

Estimates of Public and Private Costs

In the public sector, Healthy Homes expended an estimated $631,712 in fiscal year 2018. The Vermont Housing and Conservation Board expended about $990,655 from the Department of Housing and Urban Development (HUD) for lead poisoning prevention in 2018, and the Burlington Lead Program spent an estimated $413,189 in HUD Lead Hazard Control funds. Combined, these organizations spent an estimated $2,035,556 in federal and state funds to reduce lead poisoning in 2018.

A study[1] completed by Dartmouth College as part of the *Get the Lead Out of Vermont* Task Force Report in 2006 estimated direct health care costs of all children with elevated blood lead levels at $51,814 per year and special education costs at $219,841 per year (considered to be an underestimate because they were calculated only for those children with blood lead levels 25 µg/dL or greater). The report also estimated lost future earnings at more than $79 million per year for Vermont children (calculated in 2006 and for children with blood lead levels 5 µg/dL or greater). Screening costs incurred by families, insurers, and health care providers are not represented in these cost estimates.

Another study on the social and economic benefits of lead hazard control (Gould, 2009[2]) estimated a return of $17 to $221 for every dollar spent on lead hazard control. This would suggest that for the $2,035,556 spent in 2018 on reducing lead hazards and preventing poisoning, the State of Vermont could see a return on investment (ROI) of between $34,604,449 to $449,857,832. This estimate takes into account the national costs of lead hazard control, reduced health care costs, lifetime earnings, tax revenue, special education costs, behavioral disorders, and crime. For comparison, the estimated ROI of vaccinations is estimated at between $5.40 to $16.50 for every dollar spent (Zhou et al., 2005[3]).

The Pew Center on the States released an issue brief, *Cutting Lead Poisoning and Public Costs*[4], in 2010. Their research indicated that despite dramatic improvements over the past 30 years, lead poisoning remains a serious hazard for hundreds of thousands of young children in the United States. They concluded that returns on large-scale lead abatement efforts would yield at least $17 for each dollar invested, which translates to a net benefit of $181 to $269 billion. These benefits would be observed in reduced health care utilization, reduced IQ loss, decreased special education needs, higher earnings, and fewer behavior problems and crime.

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[1]Carlson, C., Y. Feng, D. McClurg, and J. Trummel. "The Costs of Lead Poisoning in Vermont." Dartmouth Center for Evaluative Clinical Sciences (CECS) (2006): 1-27. https://ago.vermont.gov/wp-content/uploads/2018/03/The-Cost-of-Lead-Poisoning-in-Vermont.pdf

[2]Gould, E. (2009, July). Childhood lead poisoning: Conservative estimates of the social and economic benefits of lead hazard control. Environmental Health Perspectives, 117(7), 1162-1167. Retrieved February 21, 2017, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2717145/

[3]Zhou F, Santoli J, Messonnier ML, Yusuf HR, Shefer A, Chu SY. 2005. Economic evaluation of the 7-vaccine routine childhood immunization schedule in the United States, 2001. Arch Pediatr Adolesc Med 159:1136–1144

[4]The Pew Center on the States. 2010. Cutting Lead Poisoning and Public Costs. *Partnership for America's Economic Success*, Issue Brief #14. http://www.pewtrusts.org/~/media/assets/2010/02/22/063_10_paes-costs-of-lead-poisoning-brief_web.pdf

Appendix: Statute

18 V.S.A. § 1756. Annual report

(a) The Commissioner shall, at least annually, analyze and summarize all aggregate lead screening and testing information provided by physicians, health care facilities, and laboratories and provide this information to all other local and State agencies involved with case management and lead hazard reduction.

(b) The Commissioner shall also at least annually provide to the General Assembly, the health community, and the general public an analysis and summary of such data and a progress report on the Commissioner's efforts to prevent lead poisoning in young children in a format that is easily understandable to nontechnical readers. The report shall include:

(1) The number and percentage of children under the age of six who have been screened and tested for lead poisoning, and the number found to have lead poisoning at various levels.

(2) Estimates of the public and private costs incurred since July 1, 1993 to prevent, correct, or treat lead poisoning.

(3) An analysis of barriers to universal blood screening of children under the age of six years.

(4) The Commissioner's recommendations for action. (Added 1993, No. 94, § 3.)

LeadReportCLR2018
Uploaded by: Delegate Mosby, Delegate Mosby
Position: FAV

Maryland
Department of the Environment

CHILDHOOD BLOOD LEAD SURVEILLANCE IN MARYLAND

ANNUAL REPORT

October 2019

Calendar Year 2018 Data

Prepared by:
Land and Materials Administration
Lead Poisoning Prevention Program

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Executive Summary

The Maryland Department of the Environment (MDE), Childhood Lead Registry (CLR) performs childhood blood lead surveillance for Maryland. The CLR receives the reports of all blood lead tests conducted on Maryland children 0-18 years of age and provides blood lead test results to the Maryland Department of Health (MDH) including Medicaid, Immunet, and local health departments as needed for case management, and upon request to third parties for research and planning. Since 1995, the CLR has released a comprehensive annual report on statewide childhood blood lead testing and blood lead levels. This current report presents the childhood blood lead test results for calendar year (CY) 2018. All numbers are based on blood lead testing (venous or capillary) on children. The CLR does not receive and does not process any reports on lead screening based on the lead risk assessment questionnaire. With few exceptions all numbers refer to children 0-72 months of age.

CY 2018 Surveillance Highlights

- In CY 2018, the total number of children (0-18 years of age) who were blood lead tested was 142,127. The total number of blood lead test results of children (0-18 years) reported to the CLR was 149,179. A person may have multiple tests in the same year.

- In CY 2018, the total number of children (0-72 months of age) who were blood lead tested was 131,626. The total number of blood lead test results of children (0-72 months of age) reported to the CLR was 138,349. This number in CY 2018 (131,626) remained relatively the same compared to CY 2017 (131,832).

- The number of children (0-72 months of age) identified with a blood lead level of 5-9 µg/dL decreased from 1,661 in CY 2017 to 1,435 in CY 2018, a 13.6% decrease.

- The number of children (0-72 months of age) identified with a blood lead level of ≥10 µg/dL remained relatively stable from 388 in CY 2017 to 390 in CY 2018.

- The number of clinics and other establishments performing Point of Care testing (in-office testing) continues to increase in Maryland from 105 in CY 2017 to 119 in CY 2018.

- During the 2019 Maryland Legislative Session, Chapter 341 was enacted adopting a new Reference Level of ≥5 µg/dL for case management of children 0-72 months of age.

Overview

While the prevalence of blood lead levels ≥10 µg/dL in children in Maryland has declined dramatically over the years (18.0% in 1995, 1.3% in 2005, and 0.3% in 2018), there are still children with historically elevated blood lead levels and a number of children who are newly exposed to lead every year. Children are at the greatest risk from birth to age six while their neurological systems are developing. Exposure to lead can cause long-term neurological damage that may be associated with learning and behavioral problems and with decreased intelligence.

Sources of Childhood Lead Exposure

Lead-based paint hazards continue to be the major source of exposure for children in Maryland. Out of an estimated 2,427,014 residential houses in Maryland more than half (55.0%) were built in or before 1979 (Source: US Census Bureau, 2013-2017 American Community Survey, 5-Year Estimates). Properties built prior to 1978 may have lead-based paint. Although a significant number of residential rental units have been made lead free, there remain untreated units that may cause lead exposure in young residents.

Imported products, parental occupations and hobbies, and occasionally toys may also cause childhood lead poisoning. In-utero exposure to lead may affect fetal development.

The Centers for Disease Control and Prevention (CDC) has determined that there is no "safe" level of lead in a child's blood. As a result of the CDC adopting the lead "Reference Value" of 5µg/dL in 2012, Maryland has implemented guidance for caring for children with blood lead levels between 5-9 µg/dL. Furthermore, during the 2019 legislative session, Maryland adopted the CDC Reference Level for case management of children ages 0-72 months and pregnant women. Effective October 1, 2019, MDE shall notify the parent/guardian and the owner of the Affected Property where the child resides, the results of the test for blood lead levels greater than or equal to the new Reference Level.
In July 2020, all children identified with a blood lead level of ≥5 µg/dL will receive case management.

Statistical Report

In CY 2018, 131,626 children 0-72 months of age were tested for lead exposure statewide. Table One provides a summary of statewide statistics of blood lead testing in 2018.

The number of children tested in CY 2018 (131,626) (Table Two) is similar to the number tested in CY 2017 (131,832). There was a significant decrease in the number of cases with blood lead levels of 5-9 µg/dL (1,661 in CY 2017 vs. 1,435 in CY 2018). The number of cases with a blood lead level ≥10 µg/dL is relatively the same for both years (388 in CY 2017 vs. 390 in CY 2018).

Table One

CY 2018 Statistical Report

Item	Number	*Percent (%)
All Children		
Number of tests	149,179	
Number of children	142,127	
Children 0-72 Months		
Number of tests	138,349	
Number of children	131,626	100.0
Age		
Under One	11,177	8.5
One Year	46,618	35.4
Two Years	43,806	33.3
Three Years	11,030	8.4
Four Years	10,880	8.3
Five Years	8,115	6.2
Sex		
Female	63,834	48.5
Male	66,059	50.2
Undetermined	1,733	1.3
Highest Blood Lead Level (µg/dL)		
≤4	129,801	98.6
5-9	1,435	1.1
10-14	237	0.2
15-19	72	0.1
≥20	81	0.01
Mean BLL (Geometric mean)	1.67	
Blood Specimen		
Capillary	57,218	43.5
Venous	74,107	56.3
Undetermined	301	0.2

*Due to rounding percentage to the first decimal point in this and other tables, the sum of the breakdown percentages may not equal total percentage.

Table Two

Blood Lead Testing of Children 0-72 Months by Jurisdiction in CY 2018[1]

County	Population of Children[2]	Children Tested		Blood Lead Level 5-9 µg/dL						Blood Lead Level ≥10 µg/dL					
				Old Cases[3]		New Cases[4]		Total		Old Cases[5]		New Cases[6]		Total	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Allegany	5,245	1,166	22.2	9	0.8	22	1.9	31	2.7	1	0.1	7	0.6	8	0.7
Anne Arundel	52,090	12,580	24.2	2	0.0	49	0.4	51	0.4	1	0.0	10	0.1	11	0.1
Baltimore	72,559	18,276	25.2	32	0.2	140	0.8	172	0.9	9	0.0	39	0.2	48	0.3
Baltimore City	61,150	15,900	26.0	171	1.1	383	2.4	554	3.5	49	0.3	109	0.7	158	1.0
Calvert	7,741	1,115	14.4	1	0.1	5	0.4	6	0.5	0	0.0	1	0.1	1	0.1
Caroline	3,498	772	22.1	2	0.3	7	0.9	9	1.2	1	0.1	1	0.1	2	0.3
Carroll	14,109	2,814	19.9	2	0.1	30	1.1	32	1.1	2	0.1	7	0.2	9	0.3
Cecil	9,774	1,757	18.0	5	0.3	23	1.3	28	1.6	0	0.0	1	0.1	1	0.1
Charles	14,316	2,934	20.5	0	0.0	22	0.7	22	0.7	1	0.0		0.0	1	0.0
Dorchester	3,023	625	20.7	5	0.8	7	1.1	12	1.9	2	0.3	1	0.2	3	0.5
Frederick	22,661	5,288	23.3	6	0.1	26	0.5	32	0.6	3	0.1	6	0.1	9	0.2
Garrett	2,412	367	15.2	1	0.3	4	1.1	5	1.4	0	0.0		0.0	0	0.0
Harford	22,791	4,993	21.9	2	0.0	32	0.6	34	0.7	2	0.0	5	0.1	7	0.1
Howard	26,693	5,920	22.2	11	0.2	30	0.5	41	0.7	4	0.1	13	0.2	17	0.3
Kent	1,523	210	13.8	2	1.0	2	1.0	4	1.9	0	0.0	1	0.5	1	0.5
Montgomery	96,294	25,808	26.8	20	0.1	112	0.4	132	0.5	3	0.0	32	0.1	35	0.1
Prince George's	87,692	21,843	24.9	37	0.2	147	0.7	184	0.8	13	0.1	38	0.2	51	0.2
Queen Anne's	4,183	809	19.3	0	0.0	7	0.9	7	0.9	0	0.0		0.0	0	0.0
Saint Mary's	11,468	1,688	14.7	1	0.1	11	0.7	12	0.7	0	0.0	1	0.1	1	0.1
Somerset	1,919	403	21.0	1	0.2	3	0.7	4	1.0	0	0.0		0.0	0	0.0
Talbot	2,865	652	22.8	1	0.2	7	1.1	8	1.2	0	0.0	4	0.6	4	0.6
Washington	13,707	2,767	20.2	5	0.2	25	0.9	30	1.1	0	0.0	11	0.4	11	0.4
Wicomico	9,267	2,132	23.0	3	0.1	15	0.7	18	0.8	4	0.2	6	0.3	10	0.5
Worcester	3,504	807	23.0	2	0.2	5	0.6	7	0.9	0	0.0	2	0.2	2	0.2
Total	**550,484**	**131,626**	**23.9**	**321**	**0.2**	**1,114**	**0.8**	**1,435**	**1.1**	**95**	**0.1**	**295**	**0.2**	**390**	**0.3**

1. Table is based on the selection of the highest blood lead test for each child in calendar year 2018 in the order of venous, unknown, or capillary.
2. Adapted from Maryland census population 2010 provided by the Maryland Data Center, Maryland Department of Planning, www.planning.maryland.gov/msdc
3. Children with the blood lead level of 5-9 µg/dL in 2018 and with a history of blood lead level ≥ 5 µg/dL in the past.
4. Children with the very first blood lead level of 5-9 µg/dL in 2018. These children were either not tested in the past or all their tests had blood lead level <5 µg/dL.
5. Children with the blood lead level of ≥10 µg/dL in 2018 and with a history of blood lead level ≥ 10 µg/dL in the past.
6. Children with the very first blood lead level ≥10 µg/dL in 2018. These children may have not been tested in the past or all their blood lead tests had blood lead level <10 µg/dL. This criterion may not necessarily match the criteria for the initiation of environmental case management.

Figure One illustrates the number of children 0-72 months of age tested for lead and those identified with a blood lead level of ≥10 µg/dL from CY 2010 - CY 2018.

Figure One

Number of Children 0-72 Months Tested for Lead and Number Reported to Have Blood Lead Level ≥10 µg/dL: CY 2000 - CY 2018

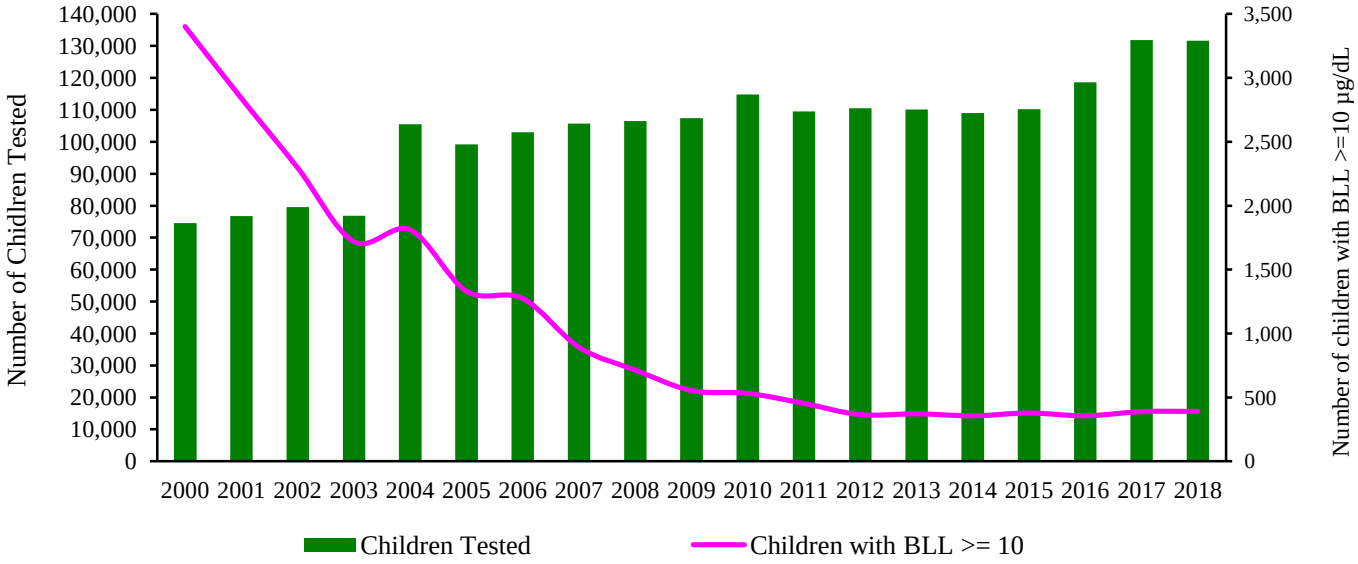
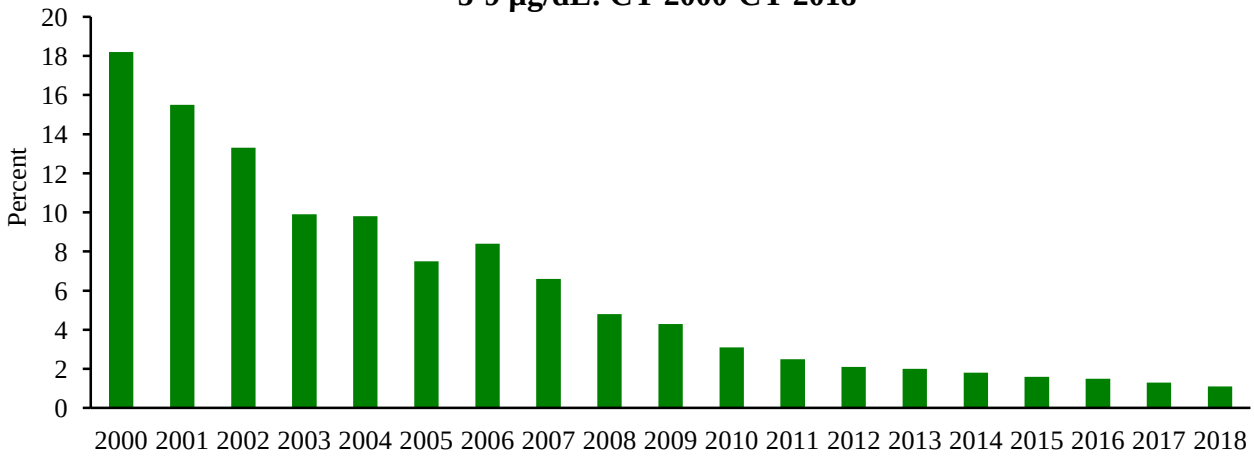


Figure Two illustrates the number of children 0-72 months of age tested for lead and those identified with the highest blood lead level of 5-9 µg/dL from CY 2010 - CY 2018.

Figure Two

Percent of Children 0-72 Months Tested for Lead with the Highest Blood Lead Level 5-9 µg/dL: CY 2000-CY 2018



Point of Care Testing and Universal Testing

The "Point of Care" (POC) testing initiative increased the number of clinics/institutions conducting in-office testing from 105 in CY 2017 to 119 in CY 2018. This in turn increased the percentage of lab reports received by MDE that were derived from POC testing from 35.8% in CY 2017 to 40.5% in CY 2018. All results for POC testing are reported to MDE in hard copy and must be processed manually by MDE.

The data indicates that Universal Testing, which requires all children age one and two years to be tested statewide, has increased lead testing for two year old children, while testing decreased for one year old children. In CY 2018, blood lead testing of children aged one year decreased in 18 counties, while testing of two year olds increased in 14 counties. Eight counties (Baltimore City, and Baltimore, Garrett, Prince George's, Somerset, Washington, Wicomico, and Worcester counties) had a decrease in blood lead testing for both ages. Five counties (Calvert, Caroline, Cecil, Charles, and Queen's Anne counties) had an increase in testing for both ages (Figure Three, Table Three). For a comprehensive overview of Universal Testing, see Appendix C.

Figure Three

Percent of Children One and Two Years Old Tested for Lead
2000-2018

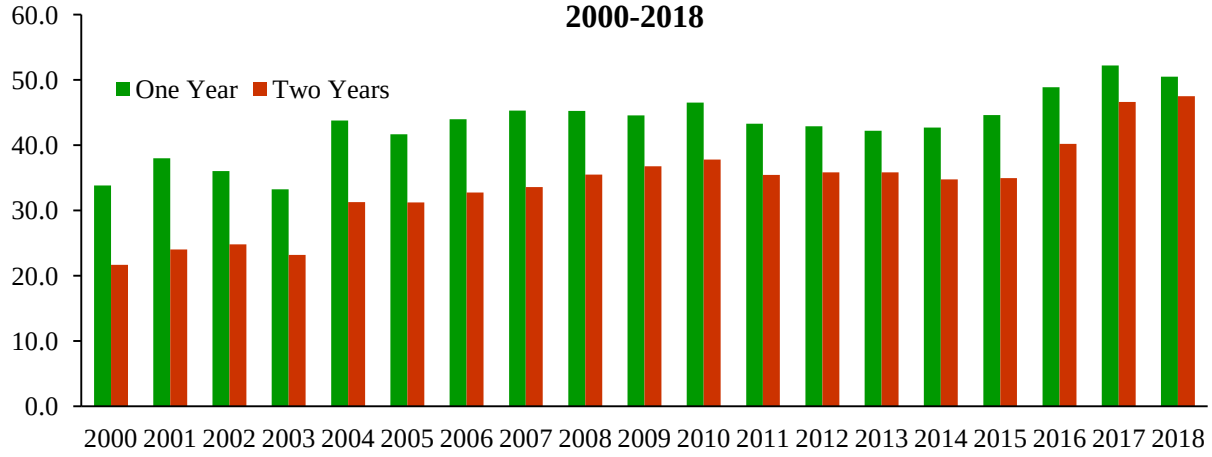


Table Three

Percent of Children Age One and Two Years Tested for Lead in 2017 and 2018

Jurisdiction	One Year Old		Two Years Old	
	CY2017	CY2018	CY2017	CY2018
Allegany	61.0	63.2	57.2	57.2
Anne Arundel	58.2	57.8	49.0	51.3
Baltimore	55.5	55.0	52.3	52.1
Baltimore City	53.9	50.3	52.3	50.0
Calvert	35.6	42.6	23.7	29.0
Caroline	55.2	58.5	51.2	52.2
Carroll	51.9	51.2	37.3	48.7
Cecil	41.4	42.5	25.6	27.3
Charles	43.6	52.9	37.5	40.3
Dorchester	54.8	47.7	45.2	48.4
Frederick	61.9	61.0	49.1	49.6
Garrett	45.8	42.3	38.7	35.6
Harford	47.7	45.1	42.0	48.2
Howard	55.5	53.7	42.5	46.0
Kent	36.0	32.8	28.9	29.2
Montgomery	51.4	47.7	49.9	52.4
Prince George's	47.6	44.7	43.6	42.0
Queen Anne's	47.2	54.7	43.5	46.3
Saint Mary's	42.6	41.6	24.3	25.1
Somerset	60.9	46.6	51.5	50.7
Talbot	56.7	61.3	52.4	48.8
Washington	46.1	44.9	40.8	39.5
Wicomico	59.3	55.6	55.3	52.3
Worcester	66.2	54.0	59.2	59.2
Statewide	52.2	50.5	46.6	47.5

Analysis of Adult ad Childhood Lead Exposure

MDE maintains the Adult Blood Lead Epidemiology and Surveillance (ABLES) database for all adults tested for lead statewide. A data extract was created on all adults with lead exposure in CY's 2017- 2018. The data was then compared with the addresses of children tested and identified with blood lead levels in CY 2018. Within the limitations of both databases (STELLAR and ABLES), the addresses of 58 adults were matched with the addresses of 87 children whose blood lead distribution is presented in Table Four. This data analysis may indicate that an occupational exposure may be a contributing factor to lead exposure.

Table Four

Blood Lead Level of Children 0-72 Months for CY 2018
And Match to Adult Blood Lead CY's 2017- 2018

Blood lead Level	Number of Children	Percent
≤4	77	88.5
5-9	5	5.7
10-14	4	4.6
20-24	1	1.2
Total	87	100.0

Data Quality

The CLR is maintained in the "Systematic Tracking of Elevated Lead Levels and Remediation" (STELLAR) surveillance system, obtained from the CDC, Childhood Lead Poisoning Prevention Program. MDE staff works to improve data quality with respect to completeness, timeliness, and accuracy. Staff keep daily track of reporting to make sure establishments are reporting all blood lead tests in a timely manner. The law requires blood lead results ≥20 μg/dL to be reported to MDE within 24 hours after the result is known. However, upon MDE's request, laboratories/clinics have agreed to report the results of all blood lead tests ≥10 μg/dL within 24 hours. With the CDC's blood lead "Reference Level" now at 5μg/dL, some laboratories report all blood lead tests ≥5 μg/dL within 24 hours.

In CY 2018, 59.5% of all blood lead tests were reported to the CLR through a computer generated electronic data file. This is a decrease of about 5 percentage points for this method of reporting compared to CY 2017 (64.2%) and a decrease of more than 17 percentage points compared to CY 2016 (76.7%). The decrease in electronic reporting is partially due to the increase in the number of establishments (clinics) that use POC instruments to conduct blood lead testing. Currently, the POC instruments only have the ability to produce hard copy reports.
The average time for a blood lead test report from the time the specimen is drawn to the time the report is processed into STELLAR is about 18.3 days. The average time for the report of the first blood lead level ≥10 μg/dL to be processed into the database is about 6 days (Table Five).

Table Five

Days to Process Lab Results into CLR
CY 2018

Days after draw date	Percentage of Blood Lead Reports Processes			
	Electronic Reports	Hard Copy Reports	First Report BLL ≥10	All Reports
≤4 days	16.7	0.3	54.6	10.0
5-9 days	49.5	0.2	36.2	29.5
10-14 days	21.5	0.5	3.8	13.0
15-19 days	5.0	3.0	1.0	4.1
20-24 days	3.0	10.4	0.7	6.0
25-29 days	1.0	20.1	1.3	8.7
≥30 days	3.4	65.6	2.4	28.6
Average/	13.4	38.5	5.9	18.3

MDE works to ensure that the blood lead test reports are complete and, to the extent that is possible, correct. Table Six displays a summary of the completeness of data in blood lead reports for CY 2018.

Table Six

Completeness of Data for CY 2018

Item	Percent Complete
Child's name	100.0
Date of Birth	100.0
Sex/Gender	98.8
Race	51.5
Ethnicity	48.3
Guardian's name	73.2
Sample type	99.7
Test date	100.0
Blood lead level	100.0
Address (geocoded)	87.7
Telephone number	96.9

Blood Lead Laboratory Reporting Requirement

The amended law and regulations* of 2001 and 2002 require that:

1-The following child's demographic data should be included in each blood lead test reported:
- Date of Birth
- Sex
- Race
- Address
- Test date
- Sample type
- Blood lead level

2-Blood lead results ≥20 µg/dL must be reported (via fax) within 24 hours after result is known. All other results must be reported within no later than two weeks.

3-Reporting format should comply with the format designed and provided by the Registry.

4-Data should be provided electronically.

* Environment Article, §6-303, Annotated Code of Maryland and COMAR 26.02.01.

Medical and Environmental Case Management

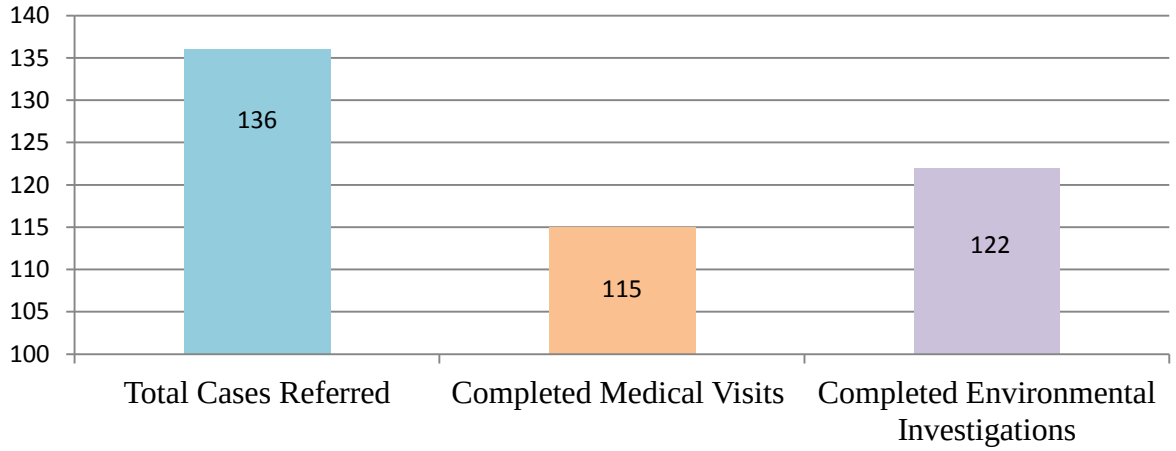
Maryland's Case Management Guidelines ("Guidelines") require medical case management when a child aged 0-72 months is identified with a first time venous or two capillary blood lead tests of ≥10 µg/dL within 12 weeks of each other ("Confirmed Case"). Case management consists of comprehensive medical and environmental case management, coordinated between the health care provider, local health department, and MDE. Services include outreach and education to the family of the identified child, a comprehensive environmental investigation to identify all potential sources of lead exposure, recommendations for lead hazard remediation, and compliance and enforcement as needed on pre-1978 residential rental units. Identifying all potential sources of lead in the child's environment and preventing further exposure are the most important factors in case management of a child. All home visits are arranged with the family based on the availability of the parent or guardian and in accordance with recommendations identified in the Case Management Guidelines.

When a child is diagnosed as a Confirmed Case and is identified to reside in or frequent a pre-1978 residential rental property, MDE or the local health department is required by law to send a Notice of Elevated Blood Lead Level (Notice of EBL) to the rental property owner. Under the law, an owner who receives a Notice of EBL must meet the modified risk reduction standard or provide for the temporary relocation of the tenants to a lead free or lead risk reduced unit within 30 days of receipt of the Notice of EBL.

During CY 2018, there were 235 Confirmed Cases that required medical and environmental case management in Maryland. This was a decrease of 25 Confirmed Cases when compared to CY 2017 (260). Of the total, there were 136 Confirmed Cases in Maryland counties (excluding Baltimore City). This was 43 fewer cases compared to the 179 Confirmed Cases in Maryland counties during CY 2017. See Figure Four for data on completed home visits for medical case management and environmental investigations for Maryland Counties.

Figure Four

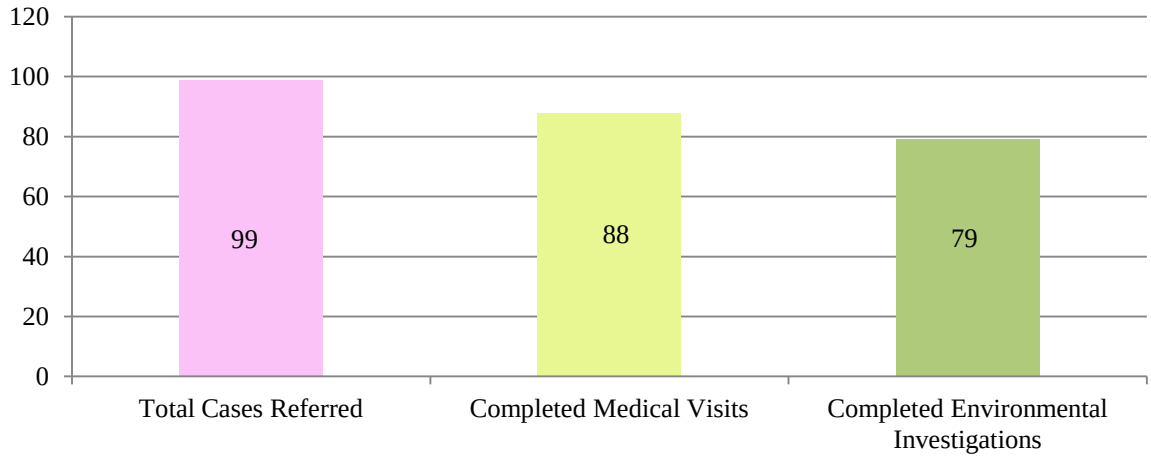
Medical and Environmental Case Outcomes
Statewide* CY 2018



*Excluding Baltimore City Cases

There were 99 Confirmed Cases during CY 2018 in Baltimore City. This was an increase of 18 cases compared to the 81 Confirmed **C**ases in CY 2017. Baltimore City performs all environmental investigations in response to Confirmed Cases. See Table Eight for medical and environmental case outcomes for Baltimore City.

Figure Five
CY 2018
Medical and Environmental Case Outcomes



During CY 2018, of the 136 Confirmed Cases statewide (excluding Baltimore City), 56.6% of the children were identified as residing in a rental property and 43.4% of the children were identified as residing in an owner occupied property. In CY 2018, in Baltimore City, 71.6% of the children were identified as residing in a rental property while 28.4% of the children were identified as residing in an owner occupied property. Table Seven provides a breakdown of Confirmed Cases and housing type identified by jurisdiction.

Sources of Lead Identified During Environmental Investigations

An environmental investigation performed in response to a Confirmed Case is designed to identify all potential lead sources in the child's environment. While exposure to lead paint hazards continues to affect children in all communities across Maryland, exposure from other sources has been observed. For instance, Prince George's County had 33 of the 136 Confirmed Cases in Maryland Counties (excluding Baltimore City). Of the 33 Confirmed Cases, 17 of the children had potentially been exposed to lead prior to their recent arrival to the U.S. There were also a significant number of cases statewide in which cosmetics, such as kohl, and spices purchased outside the U.S. were identified as potential lead hazards during environmental investigations. Figure Six shows the distribution of lead hazards identified by county for CY 2016- CY 2018. Table Eight contains the lead hazards identified for CY 2016- CY 2018 in each jurisdiction.

Table Seven

Property Status of New Cases (≥ 10 µg/dL)
Calendar Year 2018 by Jurisdiction

County	Number Cases	Owner-Occupied						Rental Property					
		Pre-50		1950-1977		Post-1977		Pre-1950		1950-1977		Post-1977	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Allegany	6	4	66.6	0	0.0	0	0.0	1	16.7	0	0.0	1	16.7
Anne Arundel	7	0	0.0	0	0.0	2	28.6	3	42.8	0	0.0	2	28.6
Baltimore	30	8	26.7	3	10.0	3	10.0	0	0.0	11	36.7	5	16.4
Baltimore City	**99**	**28**	**28.3**	**1**	1.0	**0**	0.0	**60**	**60.6**	**8**	**8.1**	**2**	**2.0**
Calvert	1	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Caroline	1	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Carroll	3	1	33.3	0	0.0	0	0.0	2	66.7	0	0.0	0	0.0
Cecil	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Charles	1	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0
Dorchester	1	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Frederick	3	0	0.0	0	0.0	2	66.7	0	0.0	0	0.0	1	33.3
Garrett	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Harford	2	1	50.0	0	0.0	0	0.0	0	0.0	0	0.0	1	50.0
Howard	9	0	0.0	0	0.0	4	44.4	0	0.0	3	33.3	2	22.2
Kent	1	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0
Montgomery	18	2	11.1	2	11.1	3	16.7	2	11.1	6	33.3	3	16.7
Prince George's	33	2	6.1	5	15.1	3	9.1	0	0.0	21	63.6	2	6.1
Queen Anne's	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0.0	0.0
Saint Mary's	1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0
Somerset	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Talbot	3	1	33.3	0	0.0	2	66.7	0	0.0	0	0.0	0	0.0
Washington	9	5	55.6	0	0.0	0	0.0	3	33.3	0	0.0	1	11.1
Wicomico	6	1	16.7	0	0.0	1	16.7	4	66.6	0	0.0	0	0.0
Worcester	1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0
County Total*	**136**	**28**	**20.6**	**11**	**8.1**	**20**	**14.7**	**15**	**11.0**	**42**	**30.9**	**20**	**14.7**
Statewide	**235**	**56**	**23.8**	**12**	**5.1**	**20**	**8.5**	**75**	**31.9**	**50**	**21.3**	**22**	**9.4**

***** Excluding Baltimore City

Figure Six

Distribution of Lead Hazard Type
CY 2016- CY 2018 by Jurisdiction

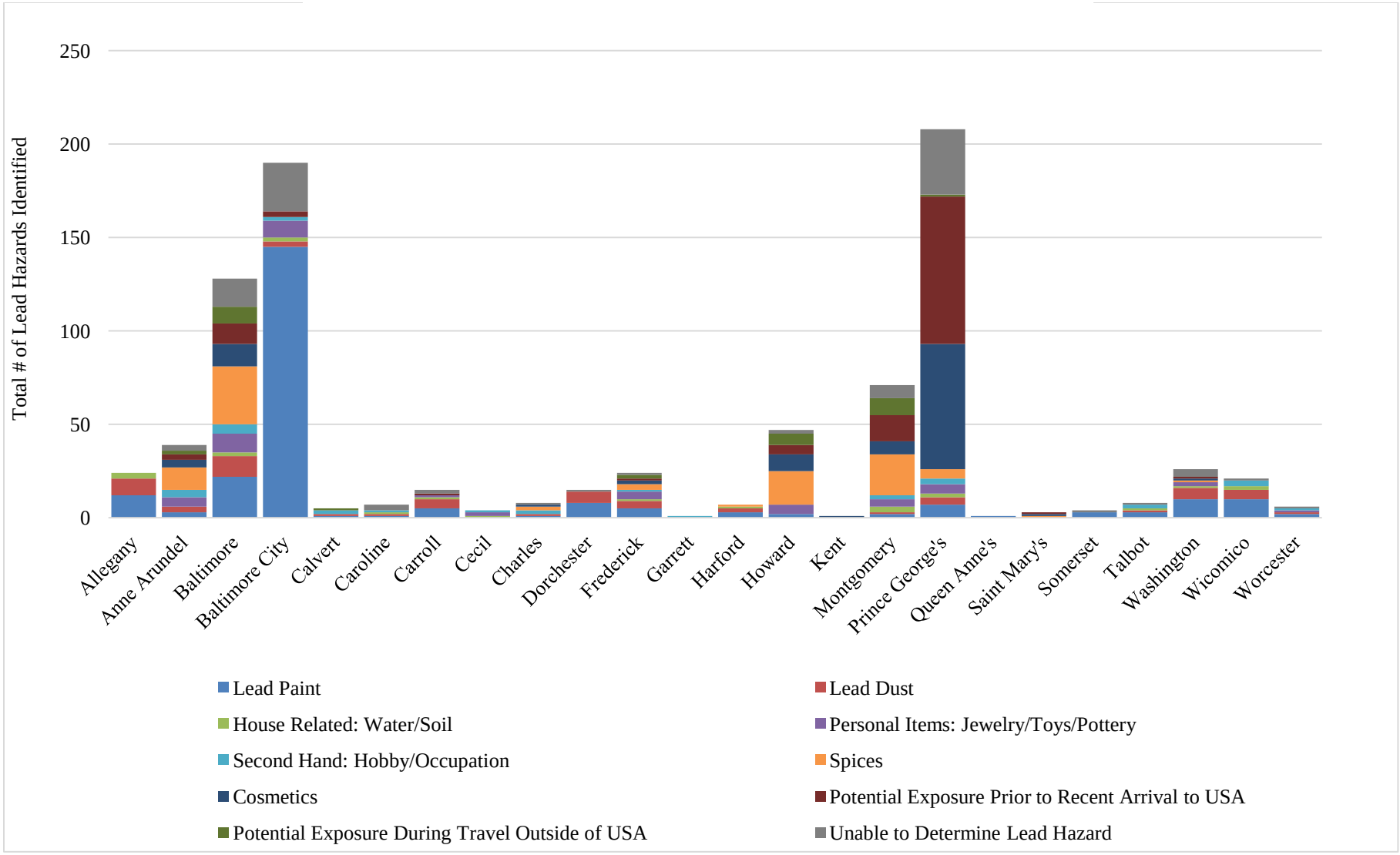


Table Eight

Lead Hazards Identified
Calendar Years 2016-2018 by Jurisdiction

County	Number of Cases	Total Hazards	Lead Paint	Lead Dust	House Related: Water/Soil	Personal Items: Jewelry /Toys/ Pottery	Second Hand: Hobby/ Occupation	Spices	Cosmetics	Potential Exposure Prior to Recent Arrival to USA	Potential Exposure During Travel Outside of USA	Unable to Determine Lead Hazard
Allegany	13	24	12	9	3	0	0	0	0	0	0	0
Anne Arundel	26	39	3	3	0	5	4	12	4	3	2	3
Baltimore	82	128	22	11	2	10	5	31	12	11	9	15
Baltimore City	***188**	**190**	**145**	**3**	**2**	**9**	2	**0**	0	**3**	**0**	**26**
Calvert	2	5	1	1	0	0	2	0	0	0	1	0
Caroline	7	7	1	1	1	0	1	0	0	0	0	3
Carroll	8	15	5	5	1	1	0	0	0	1	0	2
Cecil	4	4	0	0	1	2	1	0	0	0	0	0
Charles	4	8	1	1	0	0	2	2	1	0	0	1
Dorchester	9	15	8	6	0	0	0	0	0	0	0	1
Frederick	15	24	5	4	1	4	1	3	2	1	2	1
Garrett	1	1	0	0	0	0	1	0	0	0	0	0
Harford	6	7	3	2	1	0	0	1	0	0	0	0
Howard	26	47	2	0	0	5	0	18	9	5	6	2
Kent	1	1	0	0	0	0	0	0	1	0	0	0
Montgomery	57	71	2	1	3	4	2	22	7	14	9	7
Prince George's	133	208	7	4	2	5	3	5	67	79	1	35
Queen Anne's	1	1	1	0	0	0	0	0	0	0	0	0
Saint Mary's	1	3	0	0	0	0	0	1	1	1	0	0
Somerset	4	4	3	0	0	0	0	0	0	0	0	1
Talbot	6	8	3	1	1	0	2	0	0	0	0	1
Washington	21	26	10	6	1	2	0	1	1	1	0	4
Wicomico	15	21	10	5	2	0	3	0	0	0	0	1
Worcester	4	6	2	1	0	1	1	0	0	0	0	1
Counties' Total	***446***	***673***	***101***	***61***	***19***	***39***	***28***	***96***	***105***	***116***	***30***	***78***
Statewide	***634**	**863**	**246**	**64**	**21**	**48**	**30**	**96**	**105**	**119**	**30**	**104**

Figures Seven and Eight break down the percentage of each lead hazard found in Maryland counties. Separate pie charts are provided based on housing types and built dates. Figure Nine provide a similar breakdown for Baltimore City. Baltimore City housing mostly consists of pre-1950 housing. Consistent with prior years, lead-based paint hazards remain the most significant contributor of lead exposure in pre-1950 housing for both rental and owner occupied housing.

Figure Seven

Lead Sources Identified in Rental Housing
Maryland Counties CY18 (Excluding Baltimore City)

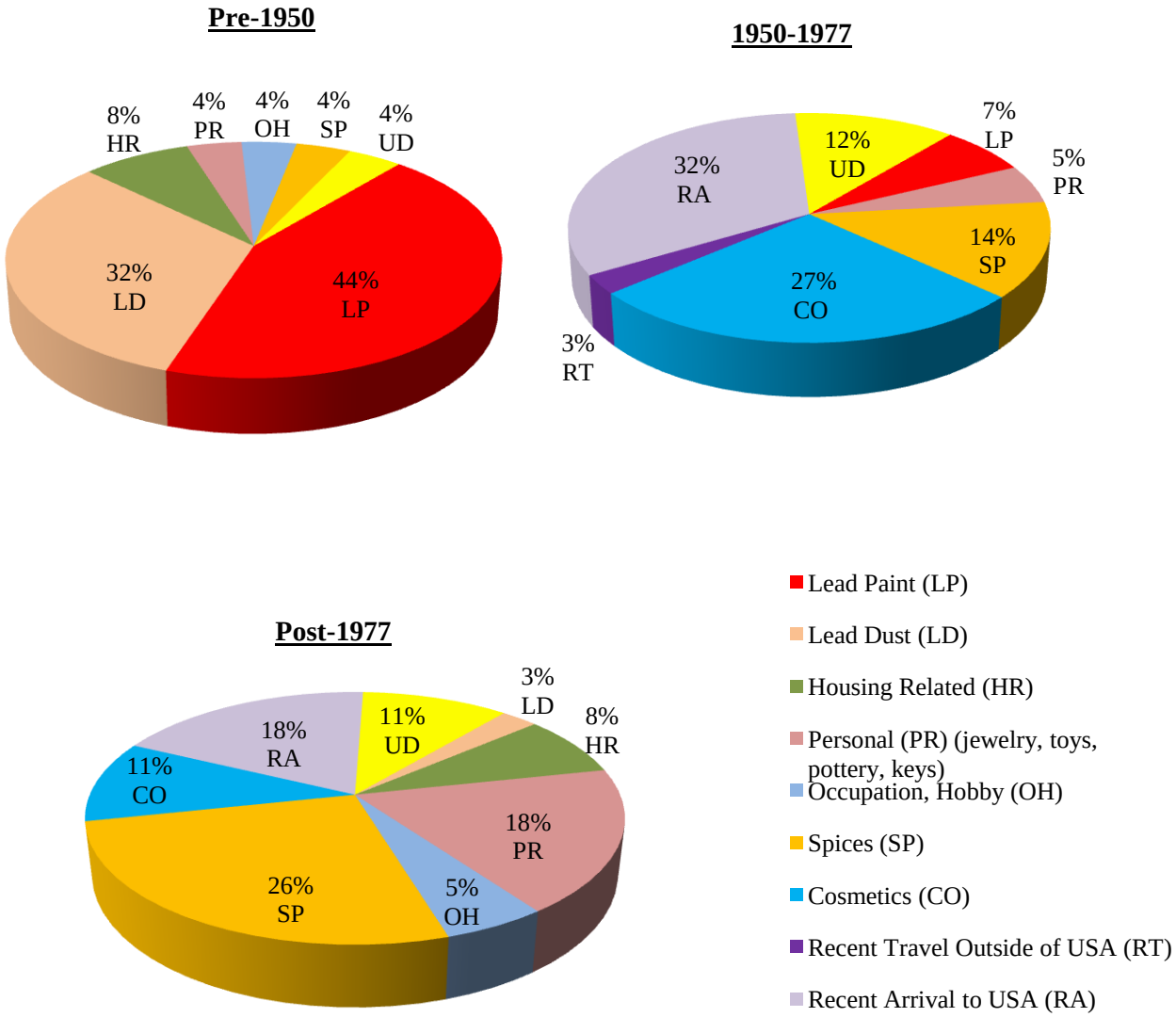


Figure Eight

Lead Sources Identified in Owner Occupied Housing
Maryland Counties CY 2018 (Excluding Baltimore City)

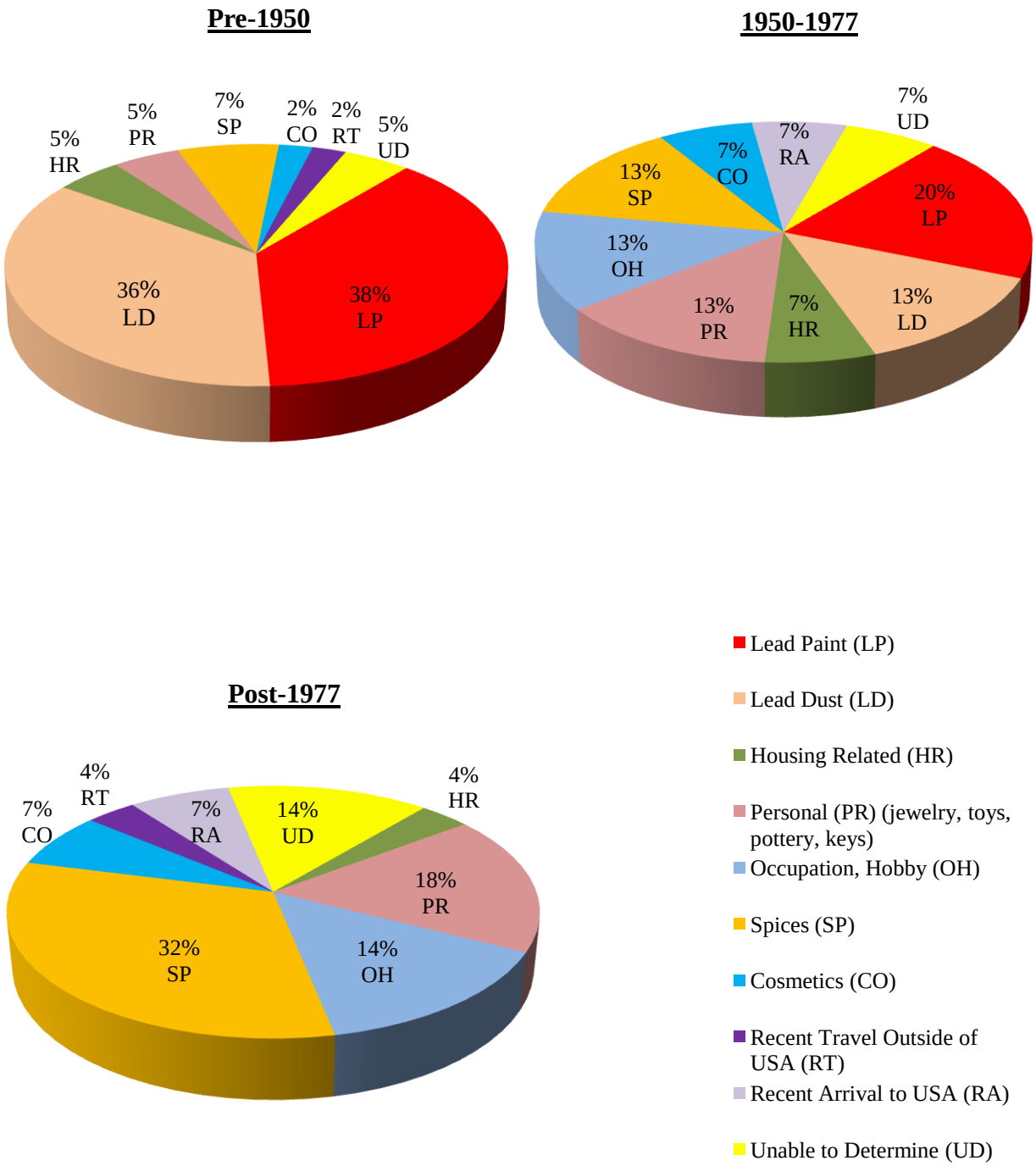
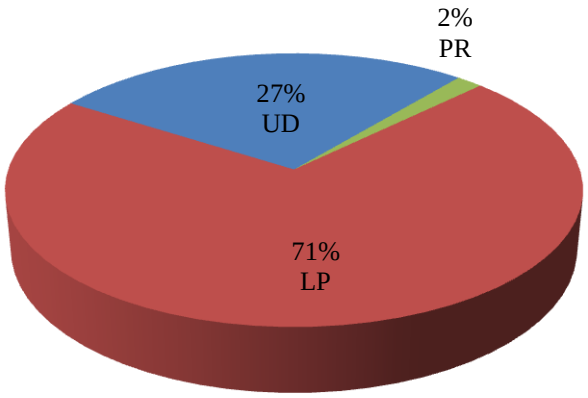
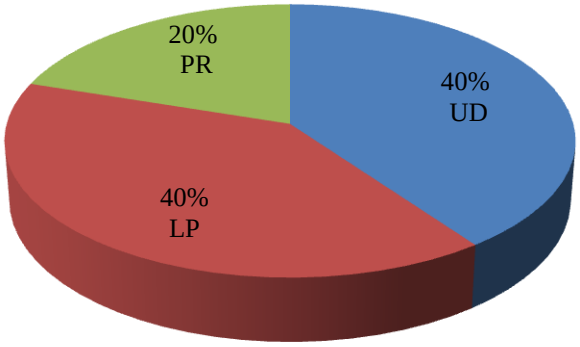


Figure Nine
Lead Sources Identified
Baltimore City CY 2018

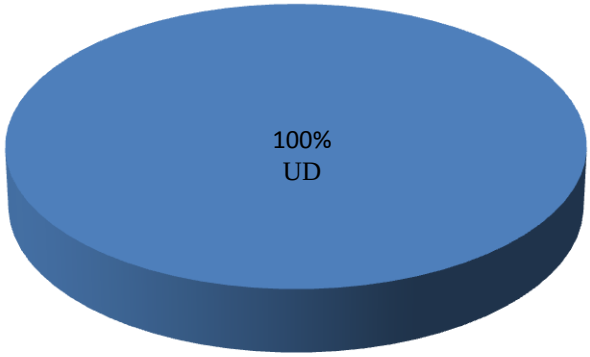
Pre-1950 Rental



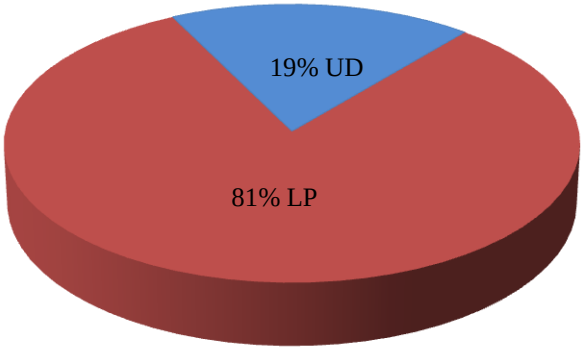
1950-1977 Rental



Post- 1977 Rental



Pre-1950 Owner Occupied*



*There were no Owner Occupied properties identified as being built after 1949

- Lead Paint
- Unable to Determine (UD)
- Personal (jewelry, toys, pottery, keys)

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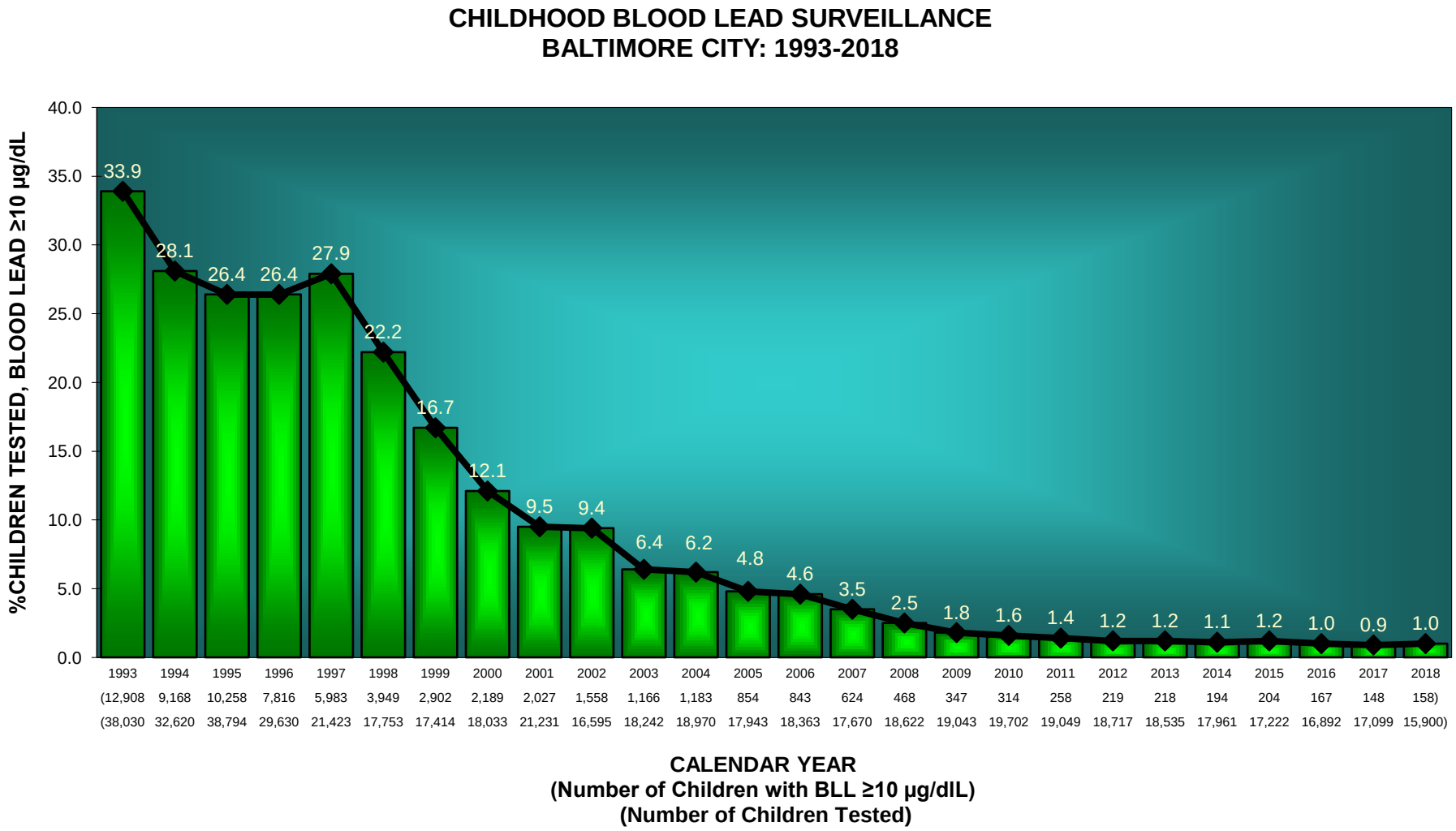
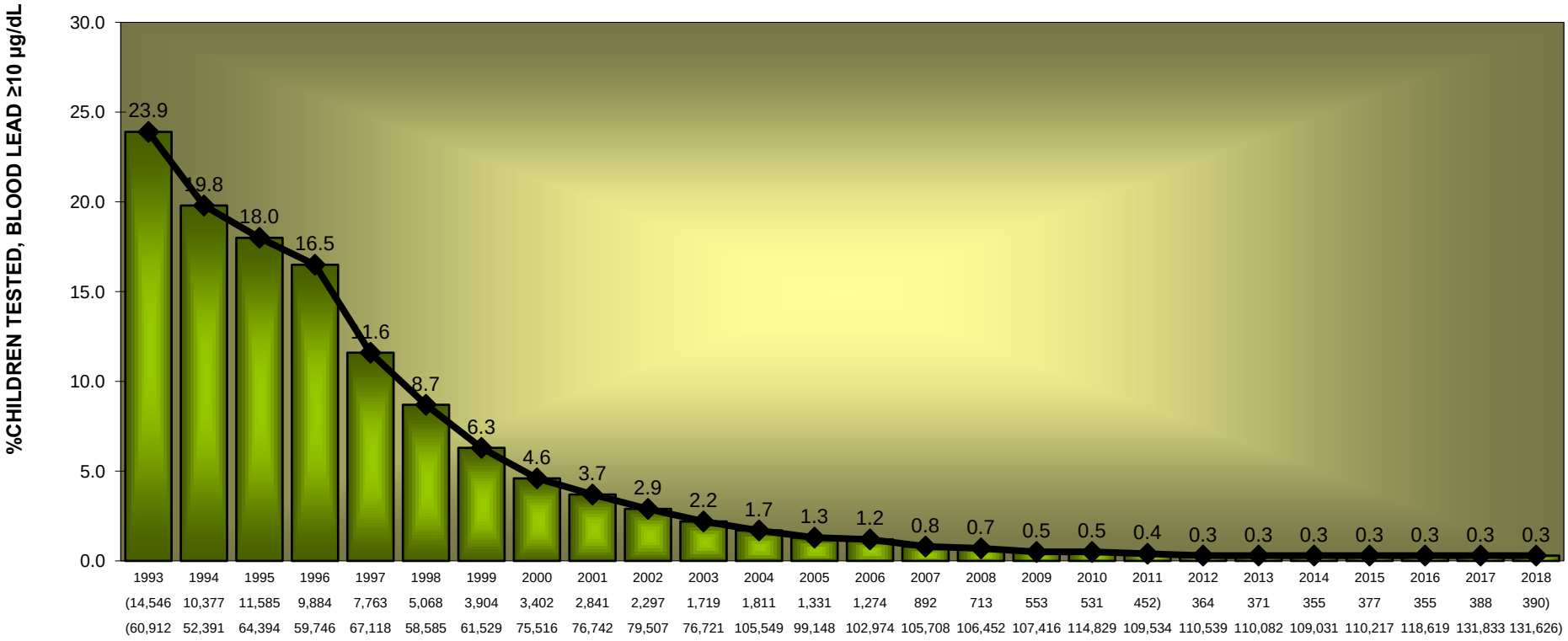
Appendix A


CHILDHOOD BLOOD LEAD SURVEILLANCE
BALTIMORE CITY: 1993-2018
%CHILDREN TESTED, BLOOD LEAD ≥10 µg/dL
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
33.9
28.1
26.4
26.4
27.9
22.2
16.7
12.1
9.5
9.4
6.4
6.2
4.8
4.6
3.5
2.5
1.8
1.6
1.4
1.2
1.2
1.1
1.2
1.0
0.9
1.0
1993 (12,908 (38,030
1994 9,168 32,620
1995 10,258 38,794
1996 7,816 29,630
1997 5,983 21,423
1998 3,949 17,753
1999 2,902 17,414
2000 2,189 18,033
2001 2,027 21,231
2002 1,558 16,595
2003 1,166 18,242
2004 1,183 18,970
2005 854 17,943
2006 843 18,363
2007 624 17,670
2008 468 18,622
2009 347 19,043
2010 314 19,702
2011 258 19,049
2012 219 18,717
2013 218 18,535
2014 194 17,961
2015 204 17,222
2016 167 16,892
2017 148 17,099
2018 158) 15,900)
CALENDAR YEAR
(Number of Children with BLL ≥10 µg/dlL)
(Number of Children Tested)

CHILDHOOD BLOOD LEAD SURVEILLANCE
STATEWIDE 1993-2018



CALENDAR YEAR
(Number of Children with BLL ≥10 µg/dL)
(Number of Children Tested)

Appendix B

Blood Lead Testing of Children One and Two Years old by Jurisdiction in CY 2018

	Population of Children	Children Tested		Blood Lead Level 5-9						Blood Lead Level >=10					
				Old Cases		New Cases		Total		Old Cases		New Cases		Total	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Allegany															
One Year	842	532	63.2	0	0.0	10	1.9	10	1.9	0	0.0	4	0.8	4	0.8
Two Years	880	503	57.2	4	0.8	8	1.6	12	2.4	1	0.2	3	0.6	4	0.8
Total	1,722	1,035	60.1	4	0.4	18	1.7	22	2.1	1	0.1	7	0.7	8	0.8
Anne Arundel															
One Year	8,818	5,098	57.8	0	0.0	25	0.5	25	0.5	0	0.0	3	0.1	3	0.1
Two Years	8,728	4,475	51.3	0	0.0	16	0.4	16	0.4	0	0.0	4	0.1	4	0.1
Total	17,546	9,573	54.6	0	0.0	41	0.4	41	0.4	0	0.0	7	0.1	7	0.1
Baltimore															
One Year	12,372	6,806	55.0	6	0.1	56	0.8	62	0.9	2	0.0	17	0.3	19	0.3
Two Years	12,042	6,272	52.1	12	0.2	48	0.8	60	1.0	4	0.1	10	0.2	14	0.2
Total	24,414	13,078	53.6	18	0.1	104	0.8	122	0.9	6	0.0	27	0.2	33	0.3
Baltimore City															
One Year	10,850	5,457	50.3	20	0.4	161	3.0	181	3.3	3	0.1	44	0.8	47	0.9
Two Years	10,428	5,209	50.0	46	0.9	117	2.2	163	3.1	12	0.2	32	0.6	44	0.8
Total	21,278	10,666	50.1	66	0.6	278	2.6	344	3.2	15	0.1	76	0.7	91	0.9
Calvert															
One Year	1,212	516	42.6	0	0.0	3	0.6	3	0.6	0	0.0	0	0.0	0	0.0
Two Years	1,240	359	29.0	1	0.3	2	0.6	3	0.8	0	0.0	2	0.6	2	0.6
Total	2,452	875	35.7	1	0.1	5	0.6	6	0.7	0	0.0	2	0.2	2	0.2
Caroline															
One Year	571	334	58.5	0	0.0	3	0.9	3	0.9	0	0.0	0	0.0	0	0.0
Two Years	575	300	52.2	1	0.3	4	1.3	5	1.7	1	0.3	1	0.3	2	0.7
Total	1,146	634	55.3	1	0.2	7	1.1	8	1.3	1	0.2	1	0.2	2	0.3

Appendix B continued

Blood Lead Testing of Children One and Two Years old by Jurisdiction in CY 2018

	Population of Children	Children Tested		Blood Lead Level 5-9						Blood Lead Level >=10					
				Old Cases		New Cases		Total		Old Cases		New Cases		Total	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Carroll															
One Year	2,188	1,121	51.2	0	0.0	11	1.0	11	1.0	0	0.0	2	0.2	2	0.2
Two Years	2,272	1,107	48.7	2	0.2	13	1.2	15	1.4	0	0.0	3	0.3	3	0.3
Total	4,460	2,228	50.0	2	0.1	24	1.1	26	1.2	0	0.0	5	0.2	5	0.2
Cecil															
One Year	1,668	709	42.5	1	0.1	9	1.3	10	1.4	0	0.0	0	0.0	0	0.0
Two Years	1,622	443	27.3	3	0.7	9	2.0	12	2.7	0	0.0	0	0.0	0	0.0
Total	3,290	1,152	35.0	4	0.3	18	1.6	22	1.9		0.0	0	0.0	0	0.0
Charles															
One Year	2,301	1,218	52.9	0	0.0	13	1.1	13	1.1	1	0.1	0	0.0	1	0.1
Two Years	2,488	1,003	40.3	0	0.0	6	0.6	6	0.6	0	0.0	0	0.0	0	0.0
Total	4,789	2,221	46.4	0	0.0	19	0.9	19	0.9	1	0.0	0	0.0	1	0.0
Dorchester															
One Year	512	244	47.7	2	0.8	4	1.6	6	2.5	0	0.0	0	0.0	0	0.0
Two Years	519	251	48.4	1	0.4	1	0.4	2	0.8	0	0.0	0	0.0	0	0.0
Total	1,031	495	48.0	3	0.6	5	1.0	8	1.6	0	0.0	0	0.0	0	0.0
Frederick															
One Year	3,592	2,210	61.5	1	0.0	13	0.6	14	0.6	0	0.0	4	0.2	4	0.2
Two Years	3,807	1,890	49.6	2	0.1	7	0.4	9	0.5	2	0.1	1	0.1	3	0.2
Total	7,399	4,100	55.4	3	0.1	20	0.5	23	0.6	2	0.0	5	0.1	7	0.2
Garrett															
One Year	359	152	42.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Two Years	405	144	35.6	1	0.7	4	2.8	5	3.5	0	0.0	0	0.0	0	0.0
Total	764	296	38.7	1	0.3	4	1.4	5	1.7	0	0.0	0	0.0	0	0.0

Appendix B continued

Blood Lead Testing of Children One and Two Years old by Jurisdiction in CY 2018

	Population of Children	Children Tested		Blood Lead Level 5-9						Blood Lead Level >=10					
				Old Cases		New Cases		Total		Old Cases		New Cases		Total	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Harford															
One Year	3,730	1,681	45.1	1	0.1	7	0.4	8	0.5	1	0.1	1	0.1	2	0.1
Two Years	3,752	1,808	48.2	0	0.0	16	0.9	16	0.9	0	0.0	3	0.2	3	0.2
Total	7,482	3,489	46.6	1	0.0	23	0.7	24	0.7	1	0.0	4	0.1	5	0.1
Howard															
One Year	4,223	2,269	53.7	2	0.1	12	0.5	14	0.6	2	0.1	7	0.3	9	0.4
Two Years	4,468	2,055	46.0	5	0.2	7	0.3	12	0.6	1	0.0	3	0.1	4	0.2
Total	8,691	4,324	49.8	7	0.2	19	0.4	26	0.6	3	0.1	10	0.2	13	0.3
Kent															
One Year	258	85	32.9	0	0.0	1	1.2	1	1.2	0	0.0	0	0.0	0	0.0
Two Years	240	70	29.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	498	155	31.1	0	0.0	1	0.6	1	0.6	0	0.0	0	0.0	0	0.0
Montgomery															
One Year	16,116	7,684	47.7	4	0.1	39	0.5	43	0.6	0	0.0	9	0.1	9	0.1
Two Years	16,179	8,475	52.4	9	0.1	30	0.4	39	0.5	1	0.0	14	0.2	15	0.2
Total	32,295	16,159	50.0	13	0.1	69	0.4	82	0.5	1	0.0	23	0.2	24	0.2
Prince George's															
One Year	14,985	6,692	44.7	5	0.1	47	0.7	52	0.8	2	0.0	8	0.1	10	0.1
Two Years	14,700	6,170	42.0	13	0.2	28	0.5	41	0.7	5	0.1	18	0.3	23	0.4
Total	29,685	12,862	43.3	18	0.1	75	0.6	93	0.7	7	0.1	26	0.2	33	0.3
Queen Anne's															
One Year	665	364	54.7	0	0.0	3	0.8	3	0.8	0	0.0	0	0.0	0	0.0
Two Years	669	310	46.3	0	0.0	3	1.0	3	1.0	0	0.0	0	0.0	0	0.0
Total	1,334	674	50.5	0	0.0	6	0.9	6	0.9	0	0.0	0	0.0	0	0.0

Appendix B continued

Blood Lead Testing of Children One and Two Years old by Jurisdiction in CY 2018

	Population of Children	Children Tested		Blood Lead Level 5-9						Blood Lead Level >=10					
				Old Cases		New Cases		Total		Old Cases		New Cases		Total	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Saint Mary's															
One Year	1,877	780	41.6	0	0.0	5	0.6	5	0.6	0	0.0	1	0.3	1	0.3
Two Years	1,876	470	25.1	1	0.2	3	0.6	4	0.9	0	0.0	0	0.0	0	0.0
Total	3,753	1,250	33.3	1	0.1	8	0.6	9	0.7	0	0.0	1	0.2	1	0.2
Somerset															
One Year	326	152	46.6	0	0.0	1	0.7	1	0.7	0	0.0	0	0.0	0	0.0
Two Years	345	175	50.7	0	0.0	1	0.6	1	0.6	0	0.0	0	0.0	0	0.0
Total	671	327	48.7	0	0.0	2	0.6	2	0.6	0	0.0	0	0.0	0	0.0
Talbot															
One Year	504	309	61.3	1	0.3	4	1.3	5	1.6	0	0.0	3	1.0	3	1.0
Two Years	502	245	48.8	0	0.0	1	0.4	1	0.4	0	0.0	0	0.0	0	0.0
Total	1,006	554	55.1	1	0.2	5	0.9	6	1.1	0	0.0	3	0.5	3	0.5
Washington															
One Year	2,220	996	44.9	2	0.2	9	0.9	11	1.1	0	0.0	5	0.5	5	0.5
Two Years	2,319	916	39.5	0	0.0	8	0.9	8	0.9	0	0.0	2	0.2	2	0.2
Total	4,539	1,912	42.1	2	0.1	17	0.9	19	1.0	0	0.0	7	0.4	7	0.4
Wicomico															
One Year	1,596	888	55.6	0	0.0	4	0.5	4	0.5	0	0.0	2	0.2	2	0.2
Two Years	1,548	810	52.3	1	0.1	6	0.7	7	0.9	3	0.4	1	0.1	4	0.5
Total	3,144	1,698	54.0	1	0.1	10	0.6	11	0.6	3	0.2	3	0.2	6	0.4
Worcester															
One Year	594	321	54.0	0	0.0	3	0.9	3	0.9	0	0.0	1	0.3	1	0.3
Two Years	584	346	59.2	2	0.6	2	0.6	4	1.2	0	0.0	1	0.3	1	0.3
Total	1,178	667	56.6	2	0.3	5	0.7	7	1.0	0	0.0	2	0.3	2	0.3

Appendix B continued

Blood Lead Testing of Children One and Two Years old by Jurisdiction in CY 2018

	Population of Children	Children Tested		Blood Lead Level 5-9						Blood Lead Level >=10					
				Old Cases		New Cases		Total		Old Cases		New Cases		Total	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Statewide															
One Year	92,379	46,618	50.5	45	0.1	443	1.0	488	1.0	11	0.0	111	0.2	122	0.3
Two Years	92,188	43,806	47.5	104	0.2	340	0.8	444	1.0	30	0.1	96	0.2	126	0.3
Total	184,567	90,424	49.0	149	0.2	783	0.9	932	1.0	41	0.0	207	0.2	248	0.3

Appendix C

MARYLAND DEPARTMENT OF HEALTH
Maryland Blood Lead Testing Initiative: Interim Progress Report
Evaluation of March 28, 2016 Revision of COMAR 10.11.04

The State of Maryland has several initiatives to increase lead testing and ultimately reduce and eliminate childhood lead poisoning. These initiatives include:

- On April 13, 2015, the Department of Health adopted regulations allowing health care providers increased access to point-of-care testing to screen for elevated levels of lead in children. The amendment to COMAR 10.10.03.02B added whole blood lead testing to the list of tests that qualify for a Letter of Exception, so that providers would have an easier time setting up point of care (POC) testing.
- In October, 2015, the Department of Health released a new "Maryland Testing Targeting Strategy" that established all areas of the state as being "at risk" of lead poisoning. This revised the previous (2000 and 2004) targeting strategies.
- On March 28, 2016, the Department of Health issued final revised regulations (COMAR 10.11.04) requiring providers to test all children born on or after January 1, 2015 at ages 12 and 24 months for lead exposure. Children born before that date were still to be tested under the previous regulation, which requires testing of all children enrolled in Medicaid, all children living in areas identified in the 2004 Testing Targeting Strategy, and children suspected of lead exposure.

In addition to the revised regulations, the Department of Health and the Department of the Environment have conducted extensive outreach to providers and parents through mailings, online bulletins, and outreach through health care organizations. MDH also created a website and two videos, one for parents and one for providers, on the new testing requirements, and issued a set of clinical management guidelines to providers throughout the state.

Interim Results

The statewide average number of children aged 0-72 months tested for lead from CY 2010-2015 was 110,706. In CY 2016, blood lead testing of children 0-72 months was 17.8% higher than the 2010-2015 average, at 118,619 children tested. In CY 2017 testing again increased, and was 19.1% higher than the 2010-2015 average, at 131,832 children tested. In CY 2018 testing remained approximately unchanged from CY 2017 at 131,626 (18.9% higher than the 2010-2015 average).

The statewide number and percentage of children being tested at ages 12 and 24 months increased from an average of 68,892 (2010-2015) to a high of 90,813 in 2017. In 2018, testing at ages 12 and 24 months remained essentially unchanged from 2017 at 90,424 (an increase of 23.4% from the 2010-2015 average and a -0.08% change from 2017). Table C-1 provides a detailed breakdown of the annual change in testing, beginning in 2016.

Table C-1
Change in the Number and Percentage of Children Tested at Age 1 and 2 Years by Jurisdiction in CY 2018, Compared with Average Testing Rate Between 2010 – 2015 and CY 2017 (Source: Maryland Childhood Lead Registry)

County	Blood Lead Testing: Ages 12 and 24 Months									
	Average 2010-2015		2016		2017		2018		% Change 2018 from Baseline*	% Change 2018 from 2017**
	N	%	N	%	N	%	N	%		
Allegany	1,099	66.6	1,068	62.8	1,014	59.1	1,035	60.1	-9.8	1.7
Anne Arundel	5,960	36.2	7,824	45.2	9,371	53.6	9,573	54.6	50.8	1.9
Baltimore	11,302	49.6	12,528	52	13,114	53.9	13,078	53.6	8.1	-0.6
Baltimore City	11,969	59.8	11,172	53.2	11,264	53.1	10,666	50.1	-16.2	-5.6
Calvert	478	20.5	637	26.3	723	29.6	875	35.7	74.1	20.6
Caroline	591	56.1	583	51.6	607	53.2	634	55.3	-1.4	3.9
Carroll	882	20.3	1,424	32.3	1,974	44.4	2,228	50.0	146.3	12.6
Cecil	829	26.7	1,065	32.8	1,102	33.6	1,152	35.0	31.1	4.2
Charles	1,363	30.9	1,763	37.3	1,928	40.4	2,221	46.4	50.2	14.9
Dorchester	515	54.7	496	48.7	513	50	495	48.0	-12.2	-4.0
Frederick	2,048	29.6	3,504	48	4,077	55.3	4,100	55.4	87.2	0.2
Garrett	305	41.2	307	40.8	320	42	296	38.7	-6.1	-7.9
Harford	1,785	24.9	2,676	36.2	3,342	44.8	3,489	46.6	87.1	4.0
Howard	1,566	18.9	2,816	32.8	4,228	48.8	4,324	49.8	163.5	2.0
Kent	192	40.8	169	34.4	162	32.6	155	31.1	-23.8	-4.6
Montgomery	10,584	35	13,766	43.2	16,292	50.6	16,159	50.0	42.9	-1.2
Prince George's	11,086	39.6	12,540	42.8	13,503	45.7	12,862	43.3	9.3	-5.3
Queen Anne's	397	31.5	575	43.7	603	45.4	674	50.5	60.3	11.2
Saint Mary's	1,068	31	1,048	28.3	1,251	33.5	1,250	33.3	7.4	-0.6
Somerset	387	63.4	372	56.1	375	56.1	327	48.7	-23.2	-13.2
Talbot	530	56.5	551	55.5	547	54.5	554	55.1	-2.5	1.1
Washington	1,719	40.6	1,932	43.1	1,960	43.4	1,912	42.1	3.7	-3.0
Wicomico	1,574	54.3	1,625	52.4	1,795	57.3	1,698	54.0	-0.6	-5.8
Worcester	609	54.3	684	58.9	736	62.7	667	56.6	4.2	-9.7
Statewide	68,892	39.7	81,125	44.5	90,813	49.4	90,424	49.0	23.4	-0.8

*Change in the percentage of children tested by jurisdiction and statewide in 2018 compared with the average percentage tested by jurisdiction and statewide 2010 – 2015.

**Change in the percentage of children tested by jurisdiction and statewide in 2018 compared with the percentage tested by jurisdiction and statewide 2017.

This represents a jurisdiction-level increase in the percentage of children tested for lead in many jurisdictions, as shown in Figure C-1 and Table C-1. The largest increases observed were for Howard, Frederick, Harford and Carroll counties, all of which saw increases in their testing rates of more than 85% from 2010-2015 to 2018. Additionally, testing rates in Anne Arundel, Queen Anne's, Charles, and Calvert counties, increased by 50-75%. Cecil and Montgomery counties saw increases of 30-50%. Jurisdiction-level increases in the percentage of children tested for lead largely clustered in Central Maryland (Figure C-1). However, this may due in part to the relatively high 2010-2015 average testing rates in Western and Eastern Maryland (Figure C-2).

Figure C-1

Percentage Change in Children Tested at 12 and 24 months by County in Calendar Year 2018, compared with the Average Percentage of Children Tested between 2010 – 2015 (Source: Maryland Childhood Lead Registry)

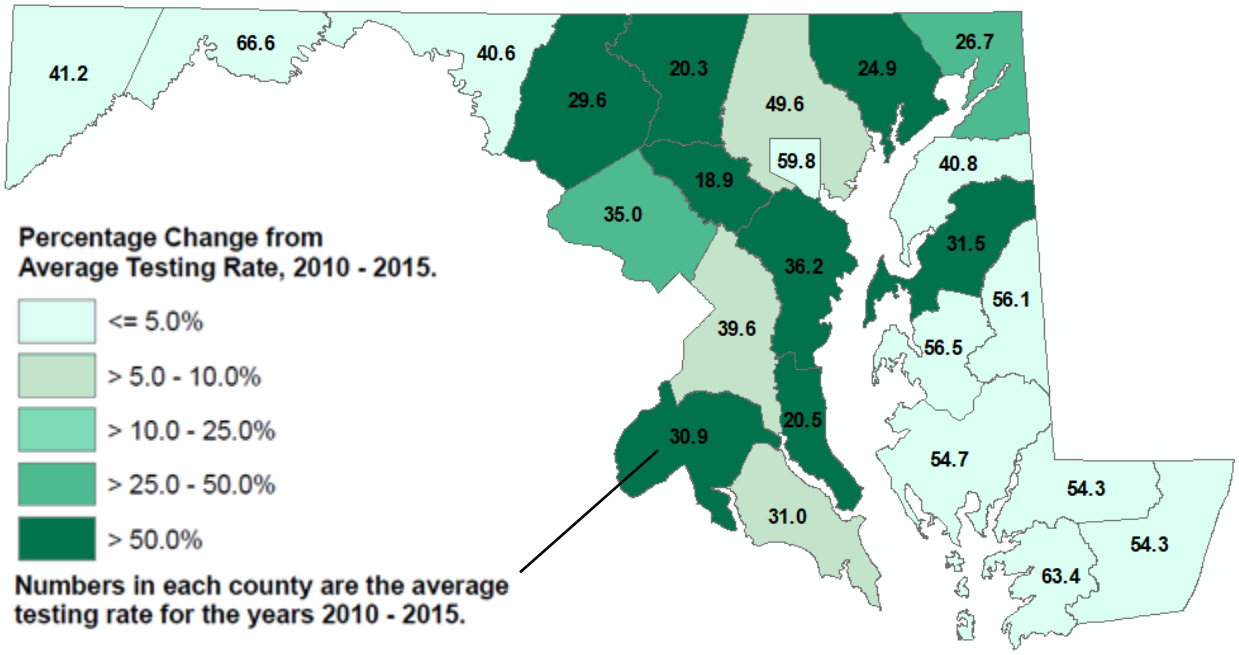
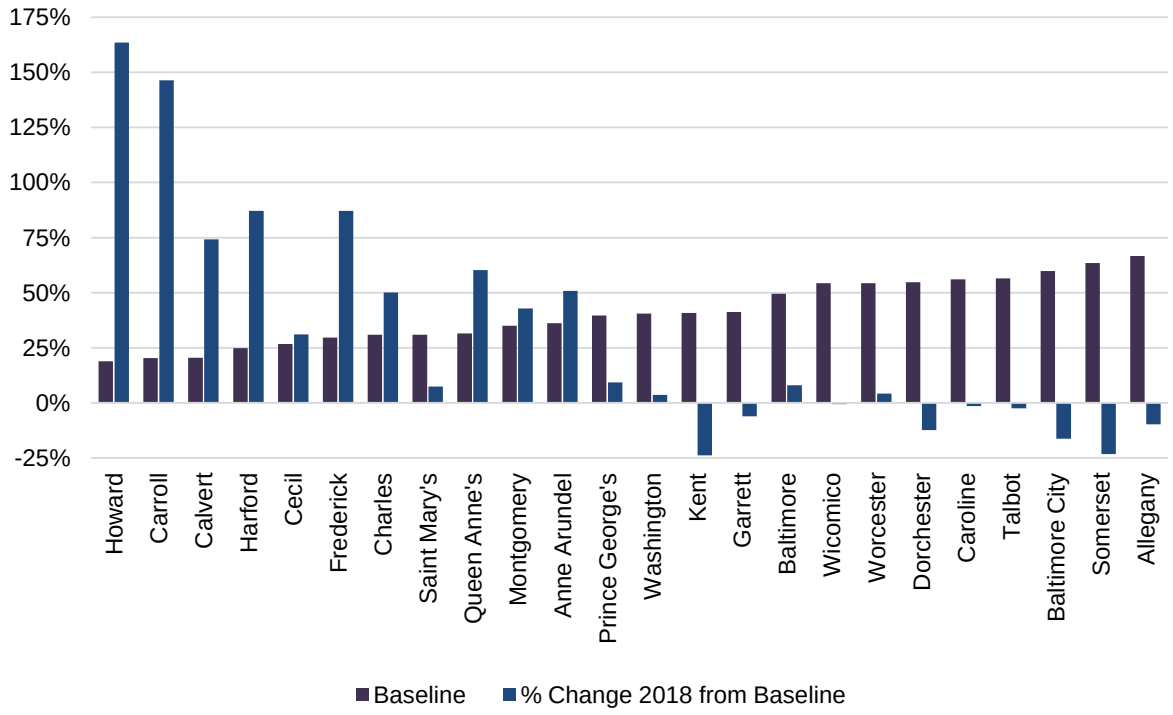


Figure C-2

Percentage Change in Children Tested at 12 and 24 months by County in Calendar Year 2018, compared with the Average Percentage of Children Tested between 2010 – 2015 (Baseline) (Source: Maryland Childhood Lead Registry)

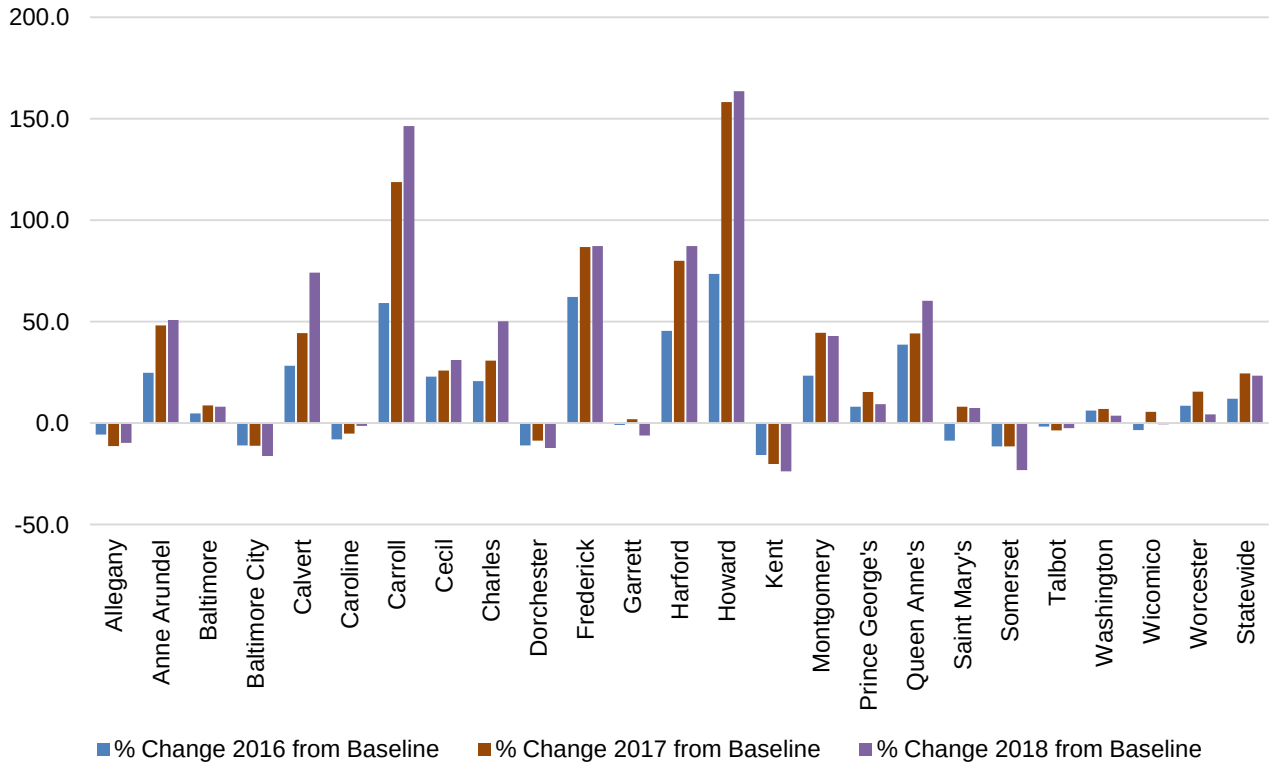


As Figures C-1 and C-2 show, the most significant increases in testing took place in areas with lower average rates during the period 2010 – 2015. While increases were seen in many jurisdictions, there were some areas that experienced small declines in testing rates (Table C-1 and Figure C-2). The reasons for these declines are unclear and could be related to normal fluctuations, or other factors. As will be discussed in the section on next steps, below, these jurisdictions represent opportunities for additional outreach to health care providers in conjunction with local health departments and non-governmental organizations.

Figure C-3 shows that lead testing rates increased statewide and in most jurisdictions year over year from 2010-2015 to 2016 and 2016 to 2017. Calvert and Carroll counties continued to see substantial increases in testing in 2018 compared to 2017. Anne Arundel, Cecil, Charles, Frederick, Harford, Howard, and Queen Anne's also made incremental gains in 2018. Jurisdictions where testing rates did not increase substantially between 2015 and 2017 did not see increases in 2018.

Figure C-3

Percentage Change in Children Tested at 12 and 24 months by County in Calendar Years 2016, 2017, and 2018 compared with the Average Percentage of Children Tested between 2010 – 2015 (Baseline) (Source: Maryland Childhood Lead Registry)



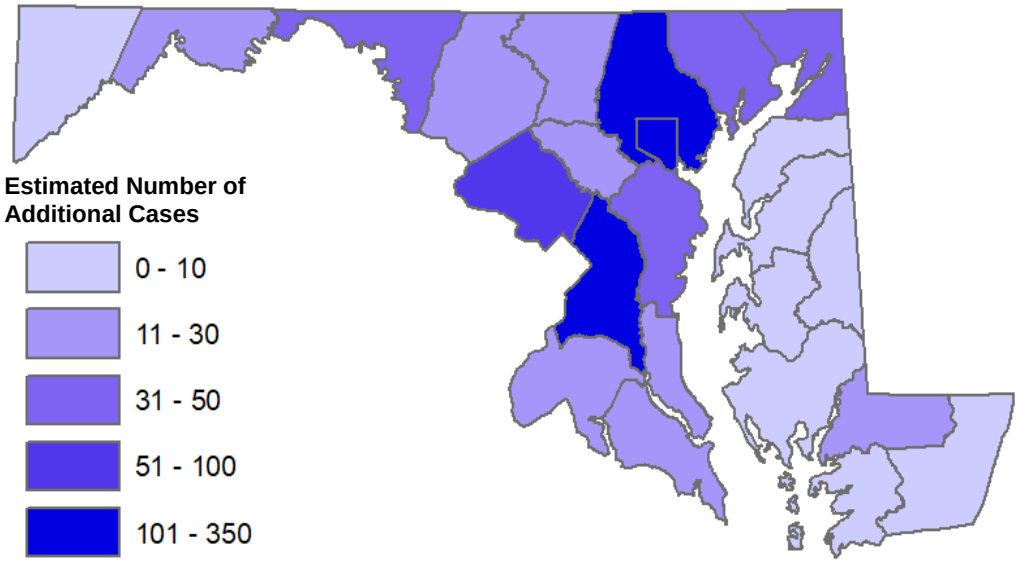
Next Steps

After two- and one-half years of universal testing, increases in blood lead testing at 12 and 24 months have slowed. Statewide, testing rates remained steady from 2017 to 2018 and most jurisdictions that saw an increase in testing between 2015 and 2017 saw smaller increases between 2017 and 2018 (Figure C-3). Perhaps more importantly, the jurisdictions where testing rates did not increase substantially between 2015 and 2017 also did not increase between 2017 and 2018.

Children with first time blood lead levels above 5µg/dL were identified in every jurisdiction in CY 2018. With testing rates below 100% it is likely that, in every jurisdiction, additional lead-exposed children were not identified. Assuming the distribution of lead exposure was the same among children who were and were not tested; we estimated the number of additional children with blood lead levels ≥5 µg/dL who would have been identified with testing rates of 100% (Figure C-4).

Figure C-4

Estimated Number of Additional Cases of Blood Lead Level ≥5 µg/dL Among Children 1 and 2 Years Old by Jurisdiction, Assuming 100% Testing Rates for All 1- and 2-Year-Olds in CY 2018[1]



1.Calculated by applying the jurisdiction rate of "New Cases" among 1- and 2-year-olds tested in CY 2018 to the number of children who were not tested in CY 2018.

Based on these results, the Department of Health and the Department of the Environment will be working with local jurisdictions to focus additional outreach efforts on jurisdictions where the need for outreach is greatest, based on criteria including: (1) jurisdictions where testing rates remain below 50% or actually have declined after three years of universal testing; (2) the total number of children not being tested is greatest; and (3) the likelihood of finding the maximum total number of lead-exposed children is greatest, based on estimates of missed "new cases" of blood lead level ≥5 µg/dL. The departments will continue conducting detailed analysis of blood lead testing data to identify local patterns in testing and to tailor outreach activities.

The Department of Health and the Department of the Environment understand that despite the requirement for testing at 12 and 24 months, parents and children still encounter barriers to blood lead testing. The departments are exploring opportunities to partner with payors, professional societies, local health departments and non-governmental organizations to develop and implement the planned enhanced outreach efforts.

Lead-Screening-Report-Maine a Comparative Report

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Position: FAV

Comparative Assessment of Lead Poisoning Screening Practices in Maine & New England

HEALTH JUSTICE
INNOVATIONS, LLC

March 2019

The "Comparative Assessment of Lead Poisoning Screening Practices in Maine and New England" was commissioned by the Maine Affordable Housing Coalition (MAHC) and prepared by Health Justice Innovations, LLC principals Emily Benfer and John McHugh. MAHC is a membership organization that consists of more than 130 diverse private and public sector organizations committed to ensuring that all Mainers are adequately and affordably housed. Professor Benfer is faculty member and the director of the Health Justice Advocacy Clinic at Columbia Law School. She is a nationally recognized expert on healthy housing and lead poisoning prevention laws and regulations, who has written and lectured extensively on the topic and provided technical advice to advocates and legislators nationwide. She is the 2018 recipient of the David P. Rall Award for advocacy in public health from the American Public Health Association for her work to advance lead poisoning prevention. Dr. McHugh is an assistant professor at Columbia University Mailman School of Public Health. He joined the faculty at Columbia after nearly 10 years at a nationally recognized consulting firm where he worked with hospitals and health systems. Dr. McHugh provided analytical support to the project.

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Table of Contents

1. Process & Objectives

To better understand Maine's ability to prevent and identify cases of childhood lead poisoning, researchers sought to:

- Conduct an independent review of lead screening and lead poisoning trends in Maine
- Compare Maine screening rates to other New England states
- Compare lead screening laws and practices throughout New England

This report provides an overview of lead poisoning rates and screening trends in New England in order to inform a more thorough analysis of state policy and the reforms necessary to protect children from exposure to lead, a debilitating neurotoxin. Data were collected from individual state databases and previously published lead testing annual reports. Maine data was collected from the Maine Environmental Health Public Health Tracking Network website. Where possible, national Center for Disease Control and Prevention (CDC) databases were used to confirm trends and differences across states. Qualitative interviews were conducted with public health department officials in each New England state to provide additional context and identify screening trends and best practices. New England universal screening laws were compared and analyzed. State definitions of lead poisoning and their respective action thresholds were also included in the legal assessment.

2. Lead Poisoning: Overview of the Issue

Maine's current Lead Poisoning Control Act, adopted in 1991, set the goal of eradicating childhood lead poisoning by 2010; yet in 2019, lead poisoning remains a risk to many of Maine's children.[1] One factor contributing to lead poisoning, and the leading source of exposure for children in Maine, is lead paint in older housing.[2] Maine's housing inventory is one of the oldest in the country. 29.8% of Maine housing was built before 1950 as compared to a nationwide median of 17.1%, placing Maine 6th among the 50 states.[3] (Table 1) As a result, a higher proportion of Maine residents are at risk of exposure to lead hazards and lead poisoning. The Federal Centers for Disease Control and Prevention (CDC) guidelines urge universal screening where at least 27% of the housing stock was built before 1950.

Table 1. Percent of Housing Stock built before 1950
(Top 8 states and New Hampshire)

State	Percent of Housing Built before 1950	Universal Screening	Year Adopted
New York	41.0%	✓	1992
Massachusetts	39.5%	✓	1987
Rhode Island	38.3%	✓	1991
Pennsylvania	34.4%	✗	n/a
Iowa	31.8%	✓	2008
Maine	29.8%	✗	n/a
Connecticut	29.5%	✓	2008
Vermont	29.2%	✓	2011
New Hampshire (ranked #14)	24.2%	✓	2018
United States Median	17.1%	n/a	n/a

The devastating effects of lead exposure on children are undisputed and range from developmental delays that can affect lifelong achievement, to serious muscular and nervous system damage, to immediate or premature death. The most recent empirical research demonstrates that even the lowest levels of exposure can result in permanent brain damage.[4] The severity of the damage correlates with both the level and duration of exposure. The American Academy of

[1] ME. REV. STAT. ANN. TIT. 22, § 1314-A (1991).
[2] Cluett, R; Fleisch, A; Decker, K; Frohmberg, E, Smith, A. *Findings of a Statewide Environmental Lead Inspection Program Targeting Homes of Children with Blood Lead Levels as Low as 5μg/dl.* J. PUB. HEALTH MANAGEMENT & PRACTICE. 25():S76-S83, Jan 2019 doi: 10.1097/PHH.0000000000000869
[3] American Community Survey (www.census.gov/programs-surveys/acs/)
[4] Bruce P. Lanphear et al., *Low-Level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis*, 113 ENVTL. HEALTH. PERSP. 894, 897–99 (2005).

Pediatrics, CDC, and the scientific and medical communities have stated that there is no safe level of lead in the blood,[5] yet most state and federal policies require that a child be lead poisoned before mandating any lead hazard remediation.

Although Maine updated its lead poisoning definition in 2015 to match the CDC reference value of 5 micrograms per deciliter (µg/dL), many state lead poisoning action levels lag behind prevailing scientific evidence and are set well above the CDC reference value. At the same time, the majority of lead poisoning prevention and targeted screening strategies focus on lead-based paint hazards. Scientific research is also focused on the danger of lead exposures in the environment, including soil and water. The 2014 water crisis in Flint, Michigan[6] and the 2017 soil crisis in East Chicago, Indiana[7] highlight the multiple exposures to lead that threaten the health and well-being of many children in the United States.

Costs of lead exposure, both economic and societal, extend well beyond individual children. For example, in Flint, "total related social costs could reach nearly $400 million" according to research conducted by Dr. Peter Muennig at Columbia University's Mailman School of Public Health.[8] In addition to medical costs associated with co-morbidities, lead poisoning results in enormous social costs due to reduced IQ, lowered economic productivity, greater dependence on welfare programs, and increased engagement with the criminal justice system. In a *JAMA Pediatrics* study from 2009, Dr. Muennig estimated that reducing blood lead levels to less than 1 µg/dL would result in "societal benefits amounting to $50,000 per child annually and overall savings of $1.2 trillion by reduced crime and increased rates of on-time high school graduation."[9] In Maine, a 2010 study entitled "Economic Assessment of Children's Health and the Environment in Maine," conducted by Dr. Mary Davis, concluded that "at current levels of lead exposure, each new cohort of babies born in Maine annually will suffer on average a one-point loss in IQ score and, as a result, can expect to earn an aggregate $270 million less over their lifetimes."[10]

An accurate national count of children with lead poisoning is unavailable due to screening rates that are historically low. Many children are not identified until their lead levels surpass the CDC reference value. One mechanism to identify children with elevated blood lead levels as early as possible and to prevent prolonged exposure to lead hazards is through annual mandatory blood

[5] American Academy of Pediatrics, *Childhood Lead Exposure*, https://www.aap.org/en-us/ImagesGen/Lead_infographic.jpg
[6] Merrit Kennedy, *Lead-laced Water in Flint: A Step-By-Step Look at the Makings of a Crisis*, NPR (Apr. 20, 2016) https://www.npr.org/sections/thetwo-way/2016/04/20/465545378/lead-laced-water-in-flint-a-step-by-step-look-at-the-makings-of-a-crisis.
[7] Sarah Reese and Lauren Cross, *Righting an 'Injustice': An Environmental Threat: The East Chicago Crisis One Year Later*, NORTHWEST INDIANA TIMES (Aug. 15, 2017) https://www.nwitimes.com/news/special-section/ec-lead/an-environmental-threat-the-east-chicago-lead-crisis-one-year/article_d19a5de7-5bc0-5292-9fe7-29a6e999ade4.html
[8] Columbia University Mailman School of Public Health, *Lead Poisoning in Flint Could Cost Up to $400 Million*, https://www.mailman.columbia.edu/public-health-now/news/lead-poisoning-flint-could-cost-400-million
[9] Peter Meunnig, *The Social Costs of Childhood Lead Exposure in the Post-Lead Regulation Era*, Arch Pediatr. Adolesc. Med. 844-849 (2009), https://jamanetwork.com/journals/jamapediatrics/fullarticle/382153.
[10] Davis, Mary E. *Economic Assessment of Children's Health and the Environment in Maine*. MAINE POL'Y REV. 19.1(2010):36-44, https://digitalcommons.library.umaine.edu/mpr/vol19/iss1/6

lead level screening in the form of venous or capillary (finger prick) testing. The Centers for Medicare and Medicaid Services (CMS) requires any child enrolled in Medicaid or the Children's Health Insurance Program to receive annual screens at one- and two-years of age, but some states are not in compliance with this mandate and are, thus, leaving children vulnerable to lead poisoning and continued exposure to lead hazards. As discussed in section four, state policies to identify non-Medicaid eligible children with lead poisoning range from universal screening, to targeted screening based on risk, to minimal recommendations or no screening requirement at all. To increase screening rates and the identification of children exposed to lead hazards, twelve states—including all of New England (except Maine), New York, New Jersey, Iowa, Delaware, Louisiana, Maryland—and the District of Columbia have adopted universal screening requirements for all children. These states recognize the well-studied lifelong harms of lead poisoning to children and the economic costs to taxpayers and society as a whole. This is especially relevant to states with older housing inventories (i.e., higher percentages of houses built before 1950) that increase the risk of lead poisoning among children.

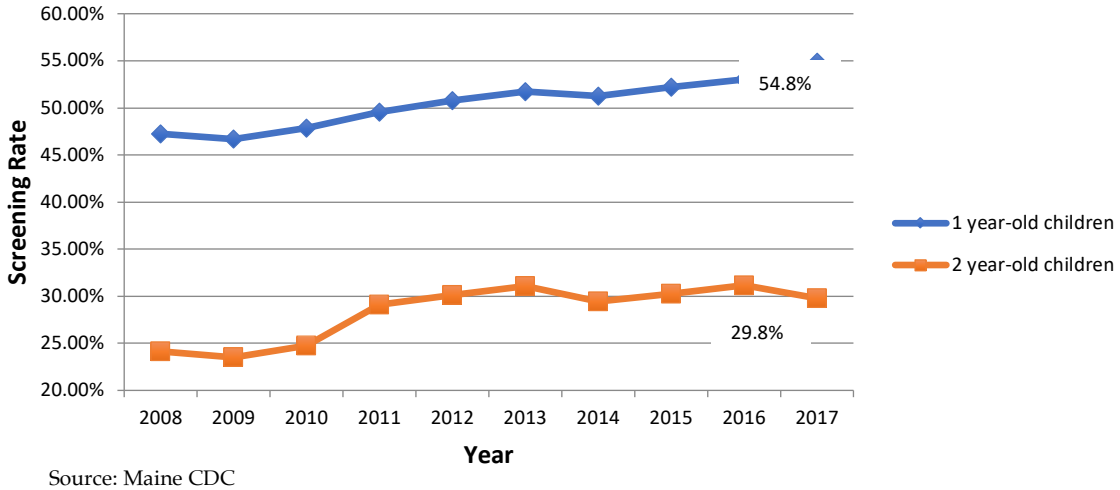
The remainder of this report will document current screening and lead poisoning rates in Maine, provide comparisons to other New England states with universal screening policies, estimate a high-level economic impact, and compare and contrast state laws and practices across New England.

3. Maine & New England State Screening Rates

Maine Screening Rates

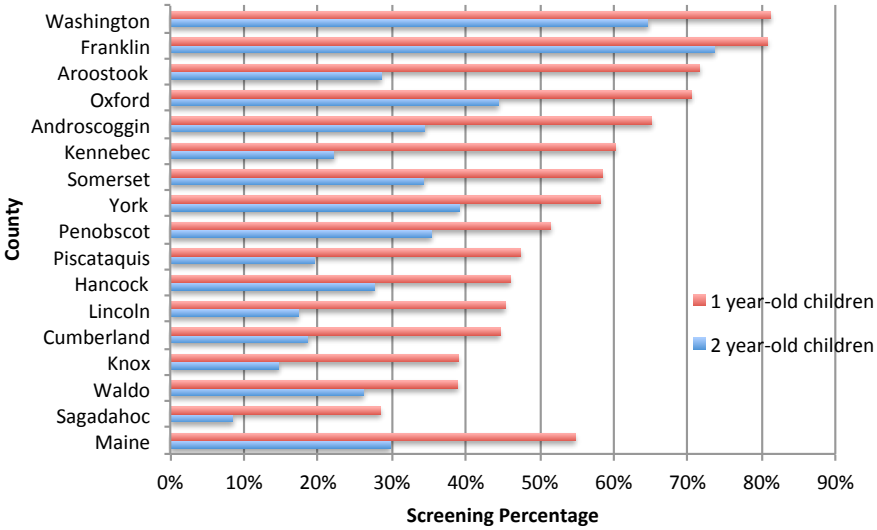
Screening rates in Maine are highly variable depending on the child's location and age. Lead screening rates for 1-year-old children increased from 47.3% in 2008 to 54.8% in 2017. Statewide screening rates for 2-year-old children increased slightly from 24.2% to 29.8%. (Figure 1) Countywide rates were also highly variable in 2017 for both 1- and 2-year-old children, ranging from 28.4% in Sagadahoc County to 81.2% in Washington County for 1-year-old children and from 8.5% in Sagadahoc County to 73.7% in Franklin County for 2-year-old children. (Figure 2)

Figure 1. Statewide Screening Rates, by Calendar Year, 2008-2017



Source: Maine CDC

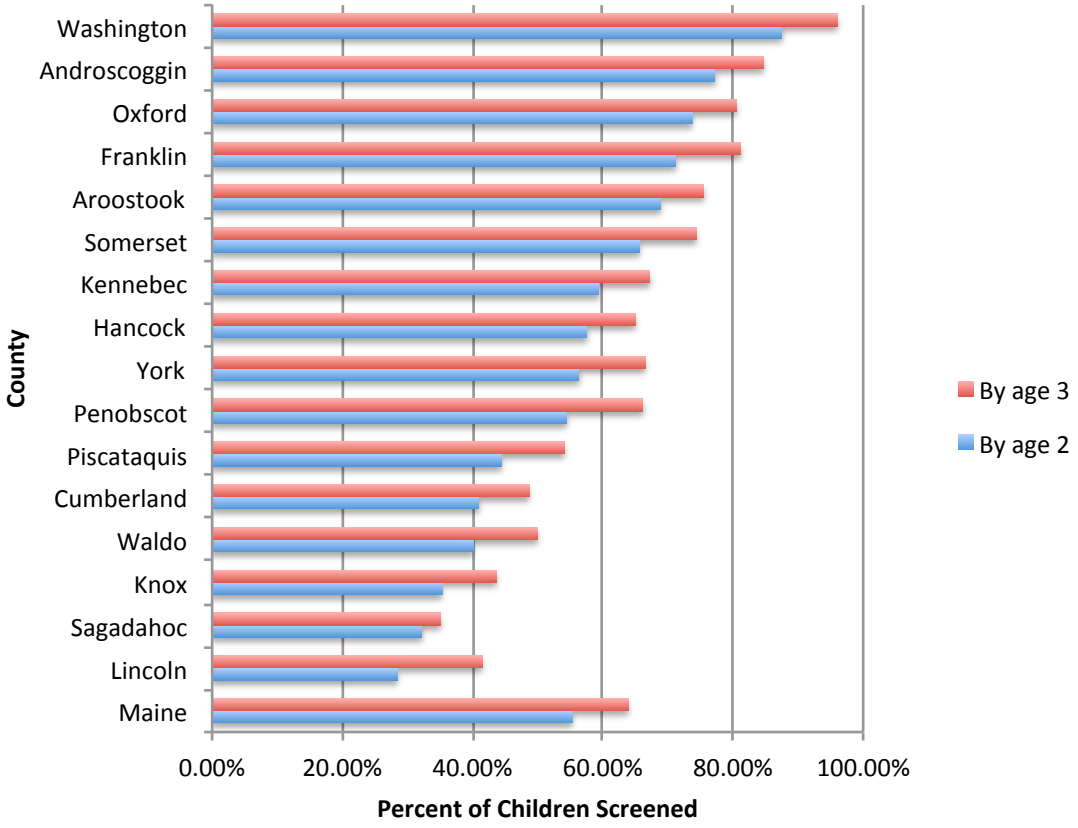
Figure 2. 2017 Screening Rates, by County, 1 and 2 year-old children



Source: Maine CDC

Screening rates can also be examined from a birth cohort perspective. The birth cohort method calculates the screening rate for a cohort of children born in the same year whereas annual screening rates represent the percentage of children screened in a given year. Birth cohort screening rates were also very low. For children born in 2014, lead-screening rates ranged from 28.8% (Lincoln) to 83.7% (Washington) by the time the children reached the age of 2 (2016) and ranged from 34.8% (Sagadahoc) to 95.8% (Washington) by the time the children reached the age of 3 (2017). In the five counties with the highest number of births (Androscoggin, Cumberland, Kennebec, Penobscot, and York), screening rates ranged from 37.4% (Cumberland) to 76.1% (Androscoggin) by the time the children reached age 2 and from 43.5% (Cumberland) to 85.0% (Androscoggin) by the time the children reached age 3. (Figure 3)

Figure 3. Percent of Children Screened for Lead by Age 2 and 3, 2014 Birth Cohort

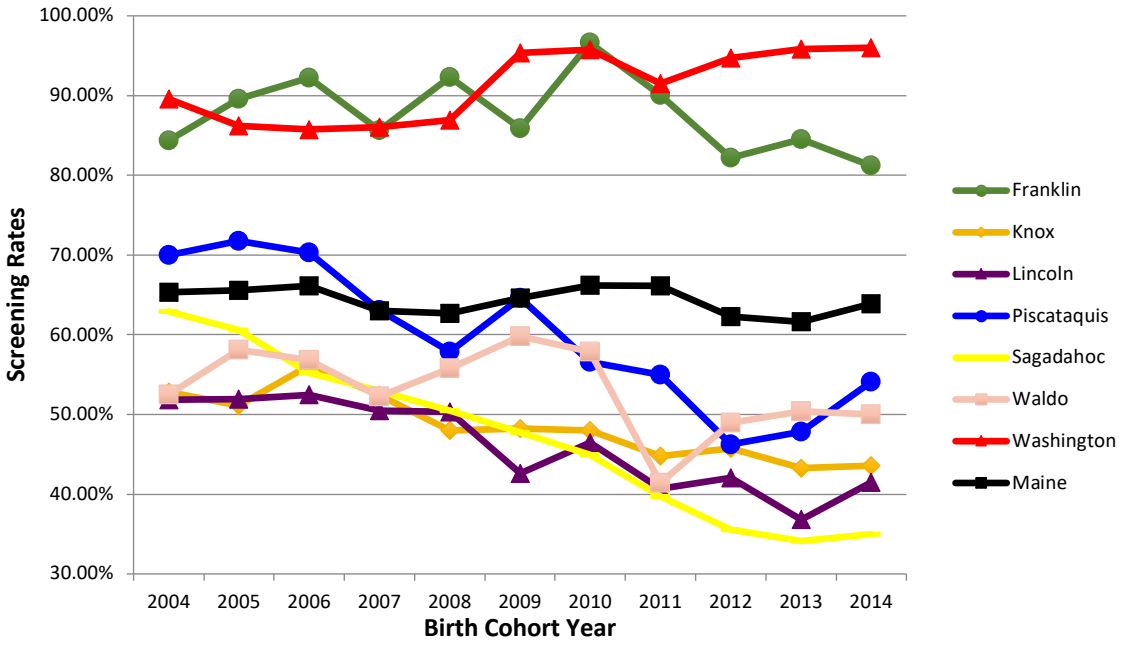


Source: Maine CDC

Maine Screening Rate Trends

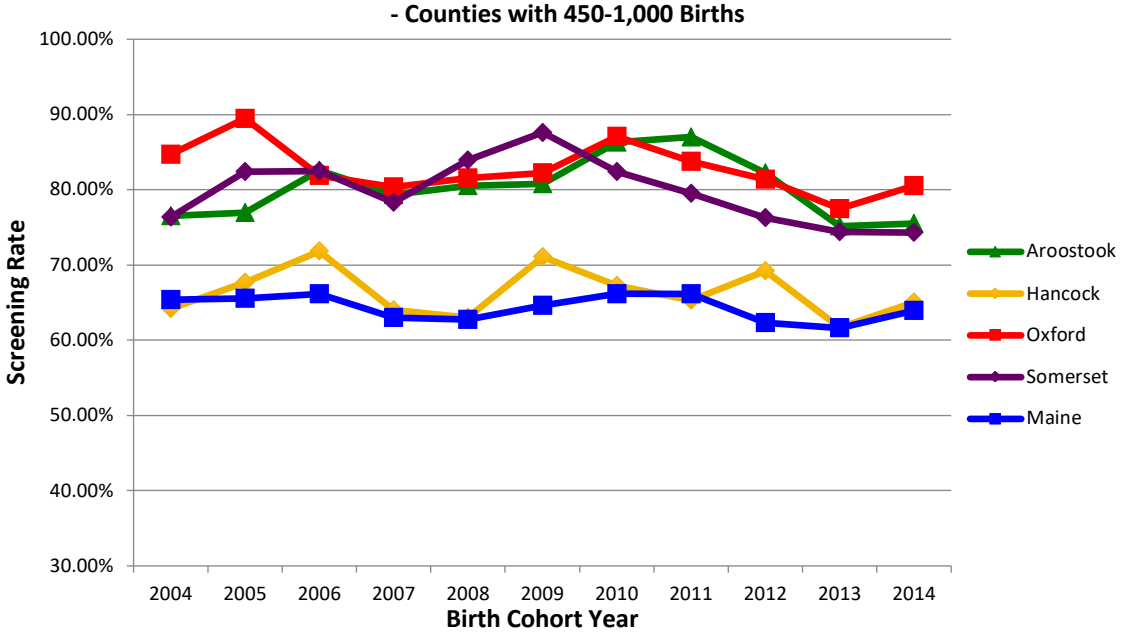
Trends in screening rates are highly variable, with screening rates in the most populous county (Cumberland) actually dropping for the 2004 to 2014 birth cohorts. Very few counties have increased screening rates. (Figures 4a, counties with less than 450 births; 4b, counties with 450-1,000 births; and 4c, counties with greater than 1,000 births)

Figure 4a. Percent of Children Screened before Age 3, by Birth Cohort, 2004-2014 - Counties with Less than 450 Births



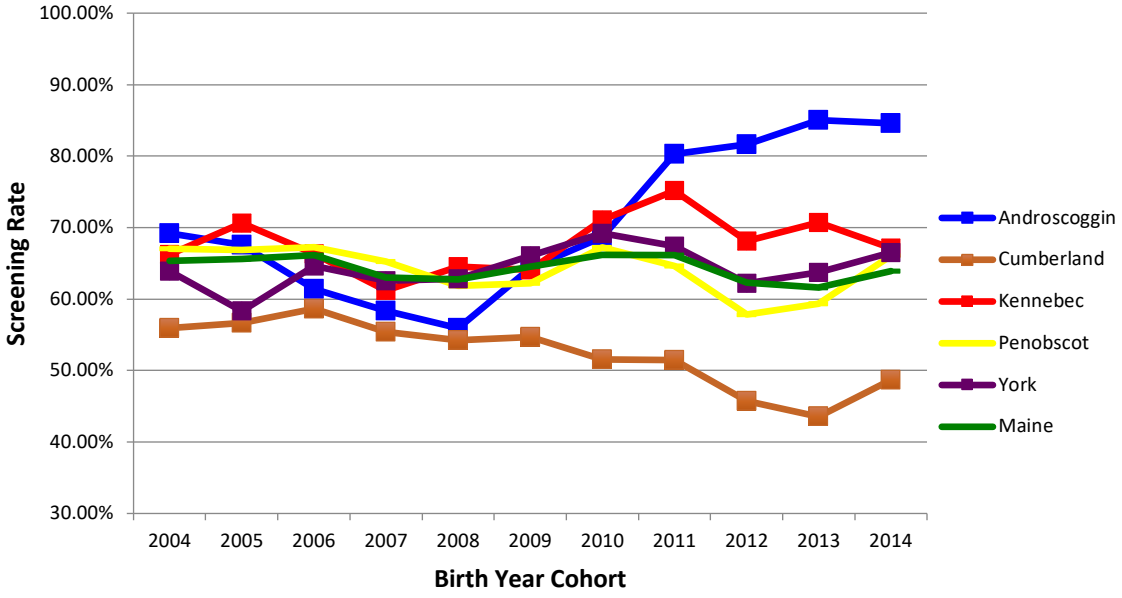
Source: Maine CDC

Figure 4b. Percent of Children Screened before Age 3, by Birth Cohort, 2004-2014 - Counties with 450-1,000 Births



Source: Maine CDC

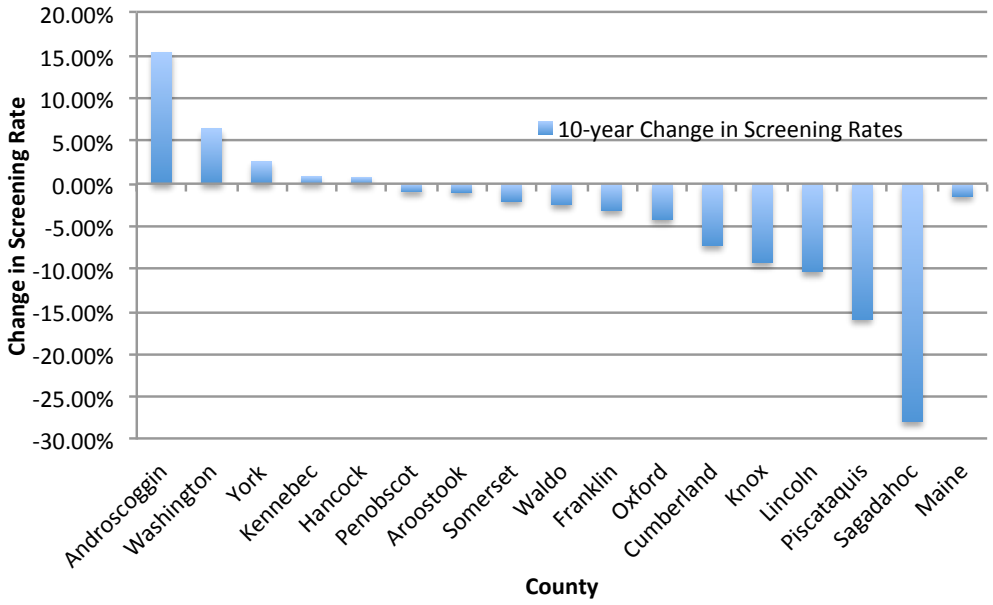
Figure 4c. Percent of Children Screened before Age 3, by Birth Cohort, 2003-2013, Counties with more than 1,000 births



Source: Maine CDC

Androscoggin County stands out as compared to all other counties, with an overall increase in screening rates from 69.2% for the 2004 birth year cohort to 84.6% for the 2014 birth year cohort. Further highlighting the large increase in screening rates in Androscoggin County is the fact that the screening rate declined to a low of 55.9% for the 2008 birth year cohort before increasing by nearly 30 percentage points up to the 2014 birth cohort. See figure 5 for overall changes in screening rates from the 2004 to the 2014 birth cohorts.

Figure 5. Change in Screening Rates, 2004-2014 Birth Cohort Years

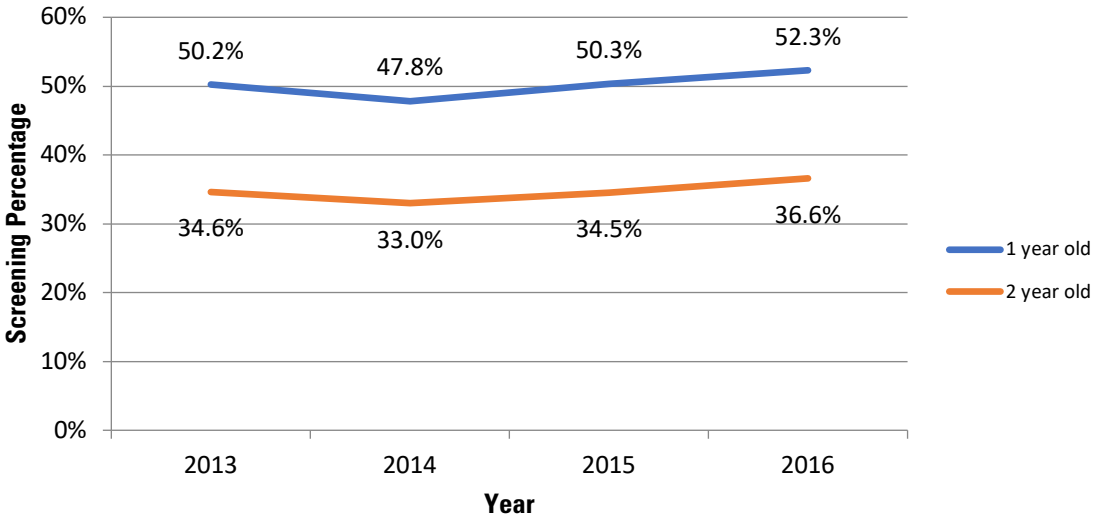


Source: Maine CDC

MaineCare Screening Trends

Given that Maine has not adopted universal screening, it is to be expected that current screening rates are as low as they are. For children enrolled in MaineCare, though, federal law *requires* lead testing be conducted at age 1 and age 2, and Maine is far out of compliance. From 2013 to 2016, the percentage of 1-year-old children that were screened was approximately 52% and the number of 2-year-old children screened was even lower, at around 37%. (Figure 6)

Figure 6. Blood Lead Screening Rates for MaineCare Children, 2013-2016



Source: Maine CDC

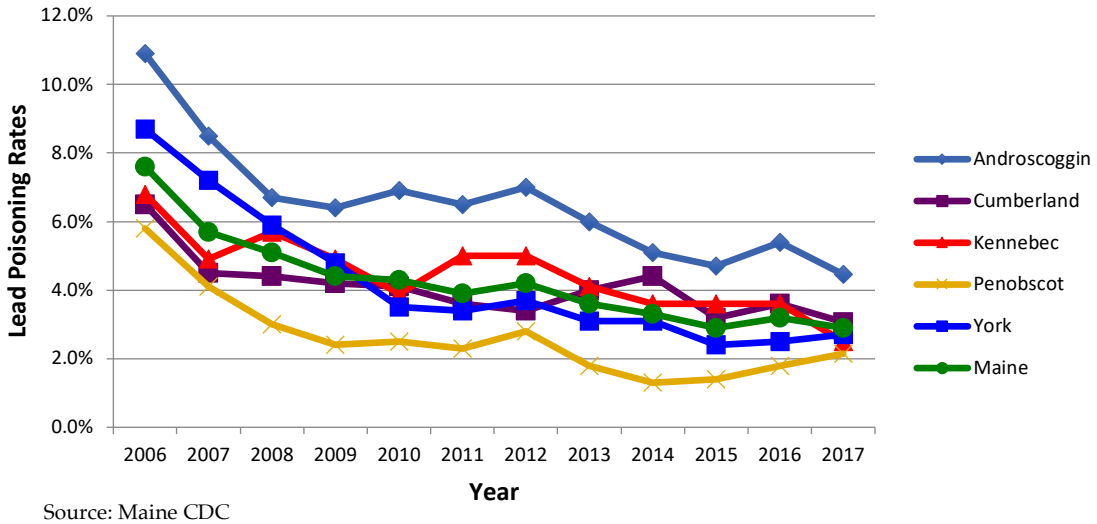
Analysis

Maine's current screening rates, when examined by county, could be described as sporadic. There is a high level of variability across counties, and the majority of counties have experienced a decrease in screening rates when examined by birth cohort. Androscoggin County stands out as an exemplar within the state and perhaps can be studied further to better understand strategies adopted to achieve high rates. As it relates to MaineCare, the state of Maine is not achieving the universal screening standard required by federal law. It will be important to examine the reasons providers are not complying with federal mandates. With screening rates that are relatively low overall and with the most populous county, Cumberland, experiencing declining screening rates based on birth cohort screening percentages, there is most likely a significant number of lead poisoned children who are not being identified and who will potentially suffer lifelong adverse health effects at a tremendous personal and public cost. The estimated cost effects of these "missed" cases are evaluated in section 5 of the report.

Lead Poisoning Rates

Lead poisoning rates fell dramatically from 2006 to 2009 in the 5 most populous counties and in the state. However, lead poisoning rates have remained relatively flat, around 2-4%, from 2009 to 2017. Androscoggin and York counties experienced the greatest decrease in lead poisoning rates, with 6.4 and 6.0 percentage point decreases, respectively, from 2006 to 2017. (Figure 7)

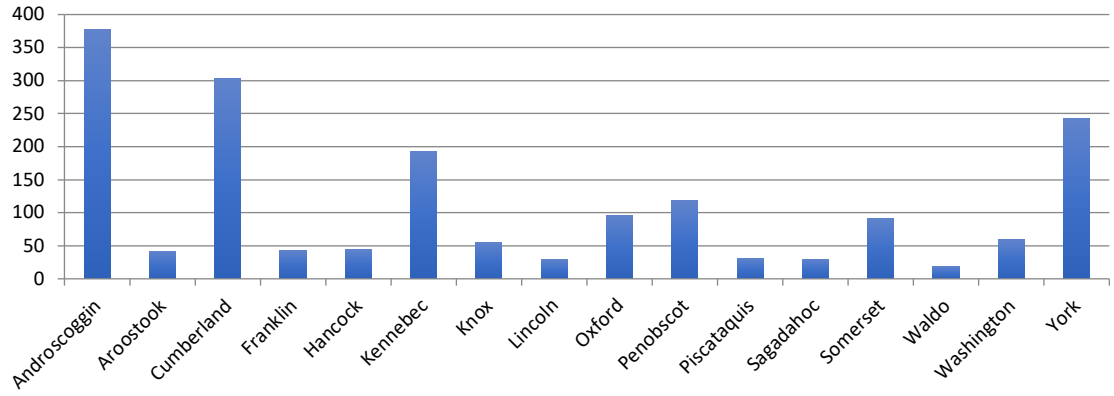
Figure 7. Lead Poisoning Rates, by Most Populous Counties, 2006-2017



Source: Maine CDC

Over the 5-year period from 2013 to 2017, the total estimated number of children with blood lead levels greater than or equal to 5 µg/dL in the state was 1,782. Androscoggin County had the highest number of lead poisoned children with 377, though its high screening rate likely contributes to the higher number of children identified. (See Figure 8 for the total number of children identified by county and screening rates.)

Figure 8. Estimated Lead Poisoned Children Ages 0-3, by County, 2013-2017



Source: Maine CDC

New England State Screening Rate Comparisons

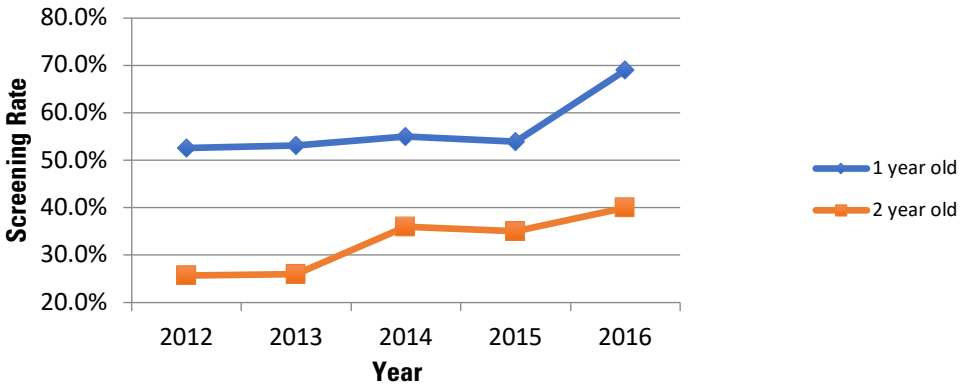
New Hampshire

Prior to 2016, New Hampshire's blood lead level testing rates were static and even declining, with an estimated 52% of 1-year-old children and 26% of 2-year-old children in high-risk, medically designated "universal testing" communities being tested. In 2016, the New Hampshire Division of Public Health Services' Healthy Homes and Lead Poisoning Prevention Program (HHLPPP) developed and implemented a five-part strategy to educate the medical community, increasing the availability of point-of-care blood lead level testing in the pediatric office. As a result of this outreach and education initiative, the HHLPPP observed that in 2016 an additional 2,604 children were tested from the previous year, a 19.4% increase. In 2016, 60.4% of 1-year-old and 33.2% of 2-year-old children statewide were tested.

In January 2018, New Hampshire passed Senate Bill 247, making significant changes to the state's lead laws, including adoption of universal blood lead level testing for all 1-year-old and all 2-year-old children. The state's low blood lead level testing rates, high percentage of pre-1978 housing stock, and large number of children identified each year as being exposed to lead were primary factors that led to New Hampshire's adoption of universal screening. The New Hampshire Chapter of the American Academy of Pediatrics and the pediatric health care community, having been educated on low testing rates, sources of exposure, and the state's prevalence of elevated blood lead levels, were strong advocates for a universal screening requirement.

New Hampshire's universal screening requirement became effective April 9, 2018. The HHLPPP expects the 2018 blood lead level testing surveillance data to demonstrate a greater increase in testing rates due to this change in the lead law.

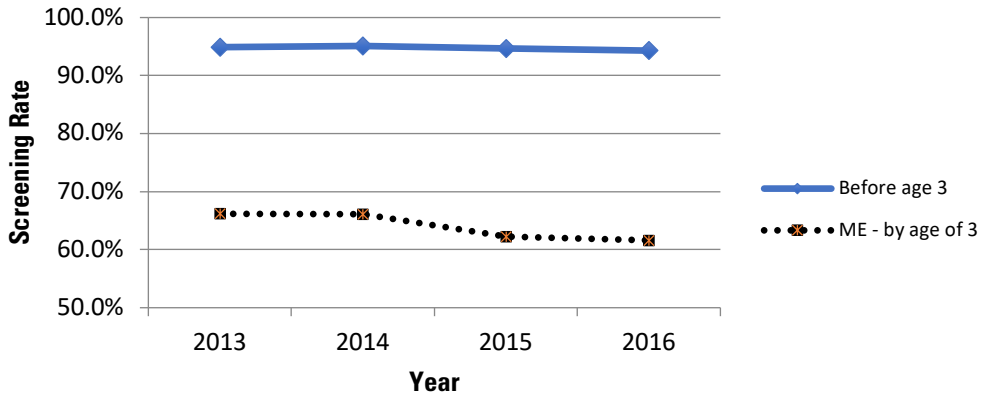
Figure 9. NH Screening Rates (high risk communities), 1 and 2 year olds, 2012-2016



Vermont

In 2005, the Vermont Attorney General and the Commissioner of Health worked with seventy Vermonters to develop a state lead poisoning action plan. The task force recommended the state adopt universal screening to improve identification of lead poisoned children.[11] Vermont adopted universal screening in 2011 and accepts a capillary test for confirmatory purposes. It is estimated that in 2017, 77% of 1-year-old and 68% of 2-year-old children were screened. Screening rates for children before age 3 (i.e., at least one test before turning 3) are around 95% and have remained consistently high since 2013.

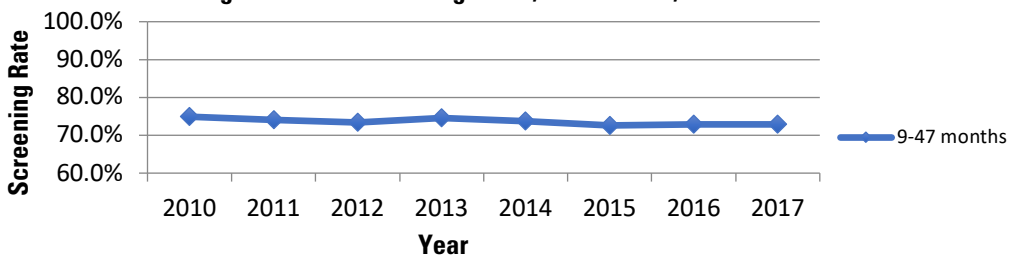
Figure 10. VT Screening Rates, before age of 3, 2013-2016



Massachusetts

Massachusetts enacted the first lead poisoning prevention law in the country in 1971 and adopted universal screening in 1987. The 1971 law emphasized primary prevention and required property owners to permanently control lead-based paint hazards in any house where a child under age 6 resides. The universal screening requirement went into effect in 1990 and requires screening of children once between the ages of 9 and 12 months, again at 2 years of age, and once more at 3 years of age. The state requires venous test sample confirmation of any capillary test that identifies a child with an elevated blood lead level. Since 2010, screening rates have hovered between 70-75% annually.

Figure 11. MA Screening Rates, 9-47 months, 2010-2017



[11] "Get the Lead Out of Vermont," Report to the Vermont Attorney General William H. Sorrell and Acting Commissioner of Health Saron Moffatt (2007).

Rhode Island

Rhode Island adopted universal screening in 1991. The high percentage of housing stock built before 1950 was a major factor in the passage of the universal screening law. For children born in 2015, the percentage of these children with at least one test by January 2019 (age 3-4) was 75.8% and the percentage of these children with two tests was 54.1%. (Figure 12a) For children born in 2012, the percent tested by the age of 3 was 86.1%, rising to 91.7% by the time these children turned 6. (Figure 12b) The CDC reported a slightly higher percentage of children screened at age 3 in 2012 of 91.1%. (Figure 15)

Figure 12a. RI Children born in 2015, testing status as of January 2019

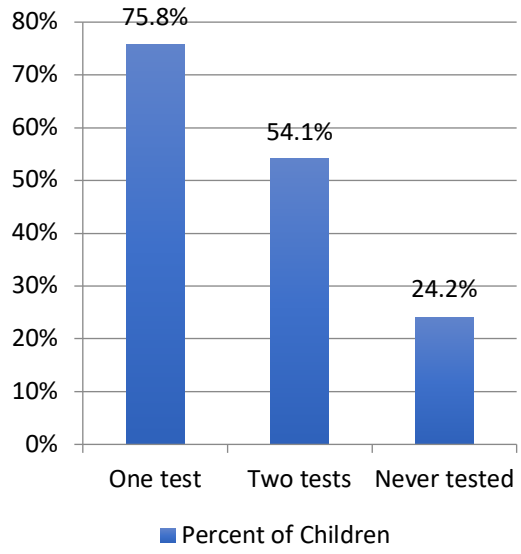
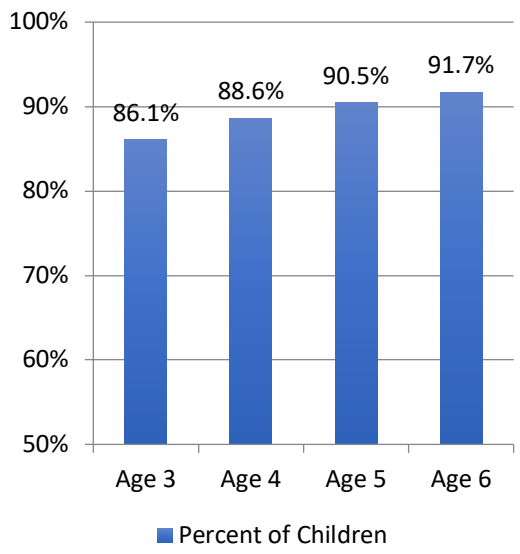


Figure 12b. RI Children born in 2012, testing status by age 3, 4, 5 and 6



Connecticut

Connecticut adopted universal screening in 2008 and the policy went into effect in 2009. Public health officials conducted significant outreach to providers to educate them about the new screening requirements. As a result, screening rates increased significantly. Since that time, screening rates for children 9-35 months old have steadily increased from just below 50% to 74.1% in 2015. To maintain high screening rates, Connecticut contracts with regional treatment centers, located in healthcare systems, that undertake provider and community education events, free medical consultation services, and other measures aimed at identification and primary prevention. Figure 14 shows that the percentage of children screened by the age of 2 in Connecticut has remained between 80 and 85% from 2011-2015 and by the time children reach age 3, the percentage screened is between 95 and 100%.

Figure 13. CT Screening Rates, 9-35 months, 2013-2017

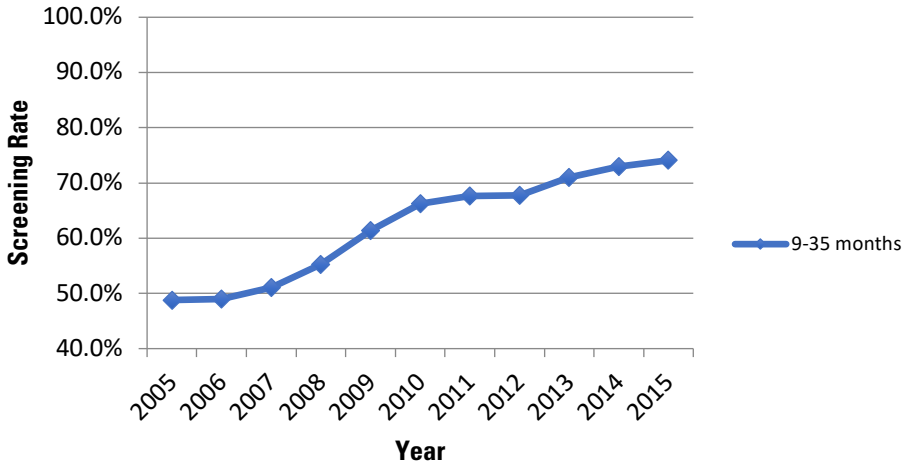
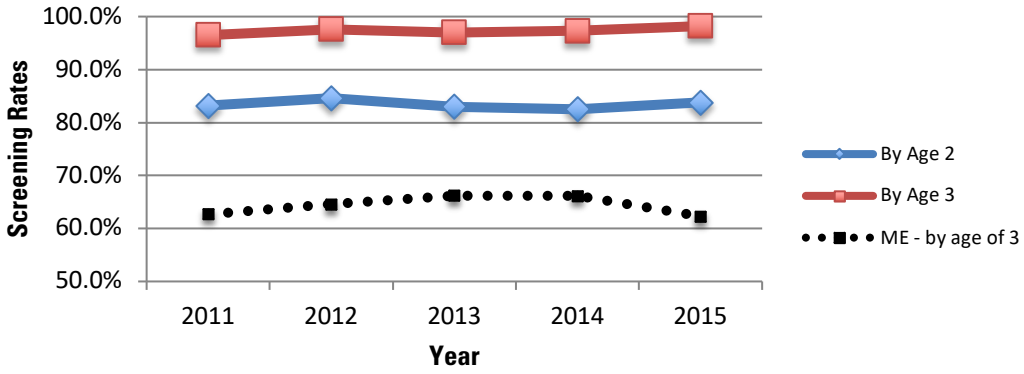
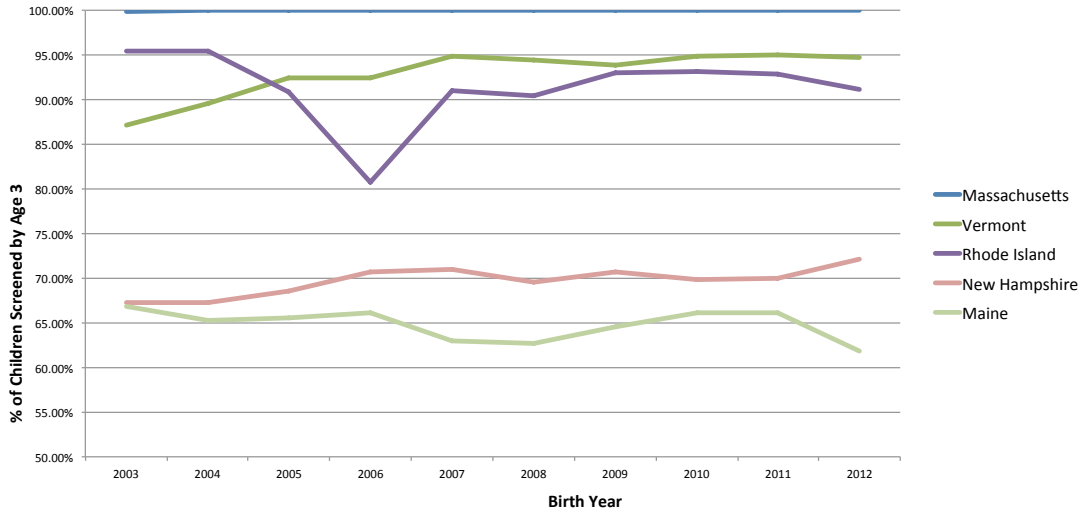


Figure 14. CT Children Screened by Ages 2 and 3, by Year



The federal CDC publishes screening data received from each state, including screening rates by the age of 3 for New England, with the exception of Connecticut, for which data was incomplete in the CDC database. When New England states are compared, Maine is at the bottom of screening rates across New England. (Figure 15) New Hampshire, the only other state in the same range as Maine, was also the only other state without a universal screening law during the time period reflected in the data. As described earlier in this section, New Hampshire adopted universal screening in 2018.

Figure 15. Percent of Children Screened before age 3, by Birth Cohort, 2003-2012



The comparative state analysis shows that where states have adopted universal screening, the overall screening rates are generally well above Maine's.

4. Best Practices & Legal Analysis

Federal Requirements and Recommendations

Since 1987, CMS has mandated that all children enrolled in Medicaid and the Children's Health Insurance Program[12] receive blood lead level screening at ages 12 and 24 months, or between the ages of 24 and 72 months if the child has no record of a past blood lead level screening.[13] If a child is identified with an elevated blood lead level, under "Early, Periodic, Screening, Diagnostic and Testing," Medicaid provides comprehensive coverage for any service that is "medically necessary to correct or ameliorate defects in physical and mental illnesses or conditions … whether or not such service is otherwise covered under the state plan."[14] This includes investigations in the child's home.[15] States also have an obligation to ensure that all Medicaid-eligible children under age 21 receive treatment and care for lead poisoning (even from past exposure), and all Medicaid beneficiaries suffering from the long-term effects of lead poisoning receive appropriate treatment and care, even those over the age of 21.[16]

As recently as the 1990s, the CDC recommended universal screening for all U.S. children, including those not enrolled in Medicaid. Today, CDC guidelines recommend universal screening in communities with at least 27% pre-1950 housing.[17]

State Lead Screening Requirements

State policies for children who are not enrolled in Medicaid range from 1) "universal screening," in which all children's blood lead level must be tested through a capillary or venous blood specimen, 2) "targeted screening," in which a questionnaire is administered and blood lead testing only occurs when a child is identified as high risk, 3) minimal non-mandatory recommendations, to 4) no screening requirement or recommendations at all. States with no formal lead screening policy have screening rates as low as 5% or do not have any reportable data on lead poisoning rates.[18] States that recommend, but do not require any screening have screening rates that range between 4% to 38% of children screened. Six states and Maine have "targeted" screening policies that focus on the

[12] Children under age six are qualify for Medicaid with income up to 160% of the Federal Poverty Line (FPL), or $38,880 for a family of four. MaineCare provides full benefits to children birth to 1-year-old up to 196% of the FPL and children age 0-18 up to 163% of the FPL.
[13] CMS, State Medicaid Manual 5123.2(D)(1).
[14] CMCS Informational Bulletin, November 30, 2016, Center for Medicaid and CHIP Services, *Coverage of Blood Lead Testing for Children Enrolled in Medicaid and the Children's Health Insurance Program at* https://www.medicaid.gov/federal-policy-guidance/downloads/cib113016.pdf.
[15] *Id.*
[16] 42 U.S.C. § 1396d(r)(5); 42 U.S.C. § 1396a(a)(30)(a)
[17] Advisory Committee on Childhood Lead Poisoning Prevention of the Centers for Disease Control and Prevention, Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention, Jan. 4, 2012.
[18] Wyoming, Arkansas, Montana, North Dakota and South Dakota have no formal lead testing policy. SAFER CHEMICALS HEALTHY FAMILIES, CHILDREN AT RISK: GAPS IN STATE LEAD SCREENING POLICIES (2017) at https://saferchemicals.org/sc/wp-content/uploads/2017/01/saferchemicals.org_children-at-risk-report.pdf?x38790.

identification of high-risk children through the administration of a brief parental questionnaire.[19] These screening tools limit blood lead screening to children who meet risk factors in the questionnaire, such as the age of the child's primary residence. For example, the Maine Annual Risk Assessment Questionnaire poses four questions:

1. Does your child spend more than 10 hours per week in any house built before 1950?
2. Does your child spend more than 10 hours per week in any house built before 1978 that was renovated or remodeled within the last six months?
3. Does your child spend time with an adult whose job exposes him/her to lead? (Examples: construction, painting, metalwork)
4. Does your child have a sibling or playmate that has been diagnosed with lead poisoning?[20]

Like most targeted screening states, the questionnaire relies on parental or guardian knowledge, does not consider lead exposure due to lead in water from lead service lines or fixtures, lead in soil near current or former industrial areas or Superfund sites, or legacy lead from leaded gasoline in heavily trafficked areas, among other sources. As a result, children who are chronically exposed to lead hazards may not be screened or receive the interventions necessary to prevent further harm. Many public health experts believe this screening shortfall is one factor in the United States' inability to achieve the goal of eradicating lead poisoning among children.

Twelve states go beyond the targeted approach and require universal screening of all children.

Universal Screening Approaches & Best Practices

Universal screening that requires blood lead level testing of all children is in effect in almost all of New England (Vermont, New Hampshire, Massachusetts, Connecticut and Rhode Island), New Jersey, New York, Maryland, Delaware, Iowa, Louisiana and the District of Columbia. Public health officials in all New England states with universal screening cite to the high percentage of pre-1950 and pre-1978 housing as the primary reason for the adoption of universal screening policies. For states with universal screening, the policy becomes a part of routine well child visits, similar to immunizations, and leaves nothing to individual assessment or chance.

While approaches vary, there are common themes in the universal screening legal requirements among New England states:

- *Age of Screening*: Blood lead level screening typically applies to children at or around 1 and 2 years of age or between 3 and 6 years of age if never screened before. Multiple states extend screening time frames for refugee and migrant populations.

[19] In addition to Maine, Missouri, Illinois, Michigan, Ohio, Virginia, and West Virginia employ a targeted screening strategy. *Id.*

[20] Maine CDC Childhood Lead Poisoning Prevention Unit, Pediatric Blood Lead Screening Guidelines at https://www.maine.gov/dhhs/mecdc/environmental-health/eohp/lead/documents/screening_followup_guidelines_2018.pdf.

- *Proof for School Enrollment*: Almost all states require blood lead level screening prior to school, preschool, or daycare enrollment, though lack of screening is not always a barrier to enrollment.
- *Payer*: The majority of states require insurance policies to cover the cost of blood lead level screening, with one state exemption for small carriers. Where a child is uninsured, the public health department covers the cost of screening.
- *Reporting*: Every universal screening state mandates the reporting of lead screening results.
- *Exemptions*: Some states allow an exemption, and excuse the provider from liability, where a parent refuses the administration of the test.
- *Interventions*: The interventions offered at a positive screening vary from retest in a few months, to case management and parent education, to an environmental investigation.
- *Confirmation*: Some states accept a capillary test as sufficient to meet screening requirements, while others require a venous sample for confirmation.

As demonstrated in the New England state data comparison section of this report, the states with universal testing laws have achieved the highest rates of blood lead level screening nationwide. As a result, they are more likely to identify children with elevated blood lead levels and intervene earlier in the timeline of exposure, thereby preventing high blood lead levels among current and future occupants of a pre-1978 home. According to one public health epidemiologist in a jurisdiction with universal screening, "You know where to focus your efforts. We were able to provide primary prevention funding to the towns that needed it the most. It's important to know who is poisoned and where they are, and then you can focus efforts and tailor to the specific town's needs."[21]

Where New England states achieved high compliance and testing rates, it is attributed to state programs that educate providers and parents, social marketing campaigns, publications, direct outreach to providers, annual progress reports, and reminders about legal obligations through formal letters.[22] In New England states with universal screening, public health officials actively and regularly attempt to increase screening compliance, even when screening rates are high. As one public health official said, "If we are still chelating kids, we have a long way to go."[23] For example, in Vermont, the state is actively working with a marketing company to explore barriers to screening and develop a strategy to increase compliance with universal screening requirements.

All New England states with universal screening engage in constant collaboration with, and education of, healthcare providers. Many states credit the success of their program to a strong healthcare base and active and committed clinicians. None of the states issue penalties for failure to comply with universal screening requirements, opting for a collaborative and supportive approach

[21] Krista Venziano, Epidemiologist 4, Connecticut Lead & Healthy Homes Program, Environmental Licensure Program.
[22] Interviews Between Emily Benfer and New England State Public Health Representatives, December-2018-January 2019. *See* Gail Coppins Gettens & Beverly Baer Drouin, *Successfully Changing a State's Climate to Increase Blood Lead Level Testing, Journal of Public Health Management and Practice*. 25():S31-S36, Jan 2019.
[23] Lori Cragin, MS, PhD, Division Director & State Epidemiologist for Environmental Health, Vermont Department of Health.

to compliance. Multiple states work with primary care providers to identify screening best practices through focus groups, interviews, and surveys.

New England states with universal screening emphasize robust data collection as an important component of universal screening and lead poisoning prevention. Some states have entered into data sharing agreements to allow for constant communication between labs, state epidemiologists, healthcare providers, and care coordinators. The increased data access and analysis helps to raise awareness of strengths and deficiencies in universal screening and lead poisoning prevention programs. For example, some states use the data to create screening "report cards" for healthcare providers that show the provider's screening rate, as compared to the statewide average and the legal requirement. The report cards range from confidential and individual access, to publicly available and widely distributed.

Education is a major component of all New England universal screening programs. Provider education is aimed at correcting misinformation and updates on statewide policies that surpass federal requirements. In some states, like Connecticut, the providers are the teachers contracted to provide training programs for parents and other providers. In others, the public health department provides in person outreach and trainings. Multiple states cater outreach to community needs and hire marketing and media firms to develop appropriate education campaigns and strategies aimed at parents. Multiple states engage in direct outreach to property owners to ensure awareness of legal requirements. New Hampshire sends letters to 200-300 landlords every month. The outreach was considered highly successful, and in one case a property owner of multiple large buildings responded by arranging to certify all maintenance crews in the Renovation, Repair and Painting (RRP) Rule training.

States with the highest screening rates test children at their point of contact with the healthcare system. For example, when New Hampshire educated providers on point of care screening and the various capillary-testing devices available, the model was widely adopted and compliance rates increased. In Rhode Island, a pilot program offered blood lead level testing for clients not compliant with the universal lead screening requirements at Women, Infant and Children offices. Nearly 100% of participants offered the screen accepted.

Because blood lead level screening is covered by private insurance and Medicaid, adopting universal screening does not require significant state funding. However, universal screening does require outreach, education campaigns, and provider support. In addition, universal screening increases the number of children identified with lead poisoning who require interventions. New England states draw from a variety of funding sources, including litigation settlement funds, state budgets, low-interest bank loans for lead abatement or remediation, surcharges on home insurance, and federal funding streams from the U.S. Department of Housing and Urban Development, Environmental Protection Agency, Medicaid funding, and U.S. Department of Agriculture 503(c) rural development grants and low-interest loans, among other sources to respond to children identified with elevated blood lead levels.

New England Lead Poisoning Screening Laws

State	Definition of Lead Poisoning	Action Required	Year Universal Screening Effective	Testing Required	Exemption	Proof of Testing for School Enrollment	Testing Covered by Insurance
ME	5 µg/dL[24]	At 5 µg/dL "inspection of dwelling unit;" "environmental lead investigation"[25]	N/A	Targeted testing based on risk assessment tool[26]	Parent/ guardian refusal due to "sincerely held" religious or philosophical belief	N/A	N/A
CT	"Confirmed blood lead level" ≥5 µg/dL[27]	At 5 µg/dL (venous) and 10 µg/dL (capillary): provide educational materials (effective 2013) 20 µg/dL or 15-19 µg/dL in two tests taken at least three months apart: case management and environmental investigation[28]	2009 (adopted 2008)	Universal screening annually 9 through 35 mos. Children age 36-72 mos. must be tested if no prior test[29]	Parent/ guardian refusal due to religious beliefs[30]	Determined by local public health department	Testing and treatment are covered services for children and pregnant women[31]
MA	"Blood Lead Level of Concern" 5 µg/dL (venous) "Lead Poisoning" 10 µg/dL (venous)[32]	5 µg/dL (venous): follow up care, surveillance and outreach"[33] 10 µg/dL (venous): Lead inspection, case management[34]	1990 (adopted 1987)	Universal screening once between 9 and 12 months and at 2 and 3 years; children who live in high risk communities shall also be screened at age 4; children who are at high risk of exposure are screened at least every 6 months between 6 mos-3 years of age, and again at 4 and 5, and monthly during renovation projects in a pre-1978 home[35]	N/A	Must present evidence of screening prior to daycare, pre-K, Kindergarten enrollment[36]	Testing must be covered by insurance[37]

[24] ME. CODE R. § 10-144-292(3)(Y)
[25] ME. REV. STAT. ANN. TIT. 22, § 1320-A, ME. CODE R. § 10-144-292(4)
[26] ME. REV. STAT. ANN. TIT. 22, § 1317-D
[27] State of Connecticut Department of Public Health, Circular Letter # 2013-27, *Local Health Department Responsibilities as a result of the Updated Childhood Lead Screening Requirements* (April 19, 2013) *at* https://portal.ct.gov/DPH/Environmental-Health/Lead-Poisoning-Prevention-and-Control/-/media/Departments-and-Agencies/DPH/dph/environmental_health/lead/circular_letters/2013/201327LHDResponsibilitiespdf.pdf?la=en.
[28] CON. GEN. STAT. §§19A-110(D), 111(J)(B)-(C)
[29] CONN. GEN. STAT. §19A-11G(A). REQUIREMENTS AND GUIDANCE FOR CHILDHOOD LEAD SCREENING BY HEALTH CARE PROFESSIONALS IN CONNECTICUT, REVISED APRIL 2013 *AT* HTTP://WWW.CT.GOV/DPH/LIB/DPH/ENVIRONMENTAL_HEALTH/LEAD/PDF/SCREENING_REQUIREMENTS-2016.PDF
[30] CONN. GEN. STAT. §19A-11G(B).
[31] CONN. GEN. STAT. § 38A-490D.
[32] 105 MASS. CODE REGS. § 460.020
[33] 105 MASS. CODE REGS. §§ 460.050(F); 460.020
[34] 105 MASS. CODE REGS. §§ 460.020; 460.710
[35] MASS. ANN. LAWS ch. 111, § 193; 105 MASS. CODE REGS. § 460.050
[36] 105 MASS. CODE REGS. § 460.050(E)
[37] 105 MASS. CODE REGS. § 460.060

State	Definition of Lead Poisoning	Action Required	Year Universal Screening Effective	Testing Required	Exemption	Proof of Testing for School Enrollment	Testing Covered by Insurance
NH	3 µg/dL[38]	3 µg/dL: parent and property owner notification (2018)[39] 10 ug/dL (venous or two capillary): inspection of dwelling unit 7.5 µg/dL: inspection of dwelling unit (by July 2019) 5 ug/dL: inspection of dwelling unit; (by July 2021) [40]	2018	Universal screening of all one- and 2-year-old children. Provider may recommend additional testing as warranted[41]	Physician not liable where parental objection or no response to referral; or testing would be detrimental to child[42]	N/A	All insurance plans[43]
RI	5 µg/dL[44]	5 µg/dL: case management 10 ug/dL: comprehensive environmental lead inspection[45]	1991 (adopted)	Universal screening twice between 9-27 months, at least 12 mos. apart before 36 months of age; where elevated, child is tested up to age 6; refugee population screened up to age 16[46]	Sworn statement of parental refusal due to religion[47]	Public/private kindergarten, preschools, childhood education programs, day care centers, childcare programs[48]	All non-supplemental policies cover testing; health department covers testing for children without health insurance[49]
VT	5 µg/dL[50]	5 µg/dL (capillary): educate family[51] 10 µg/dL (capillary): inspection of unit[52]	2011	Universal screening at 12 and 24 months; 36-72 mos. if not previously; to age 16 for migrant children[53]	If parent/ guardian refuses test, provider not liable[54]	N/A	N/A

[38] N.H. REV. STAT. ANN. § 130-A:6;
see also S.B. 247, 2018 LEG., REG. SESS. (N.H. 2018)
[39] N.H. REV. STAT. ANN. § 130-A:6-a
[40] N.H. REV. STAT. ANN. § 130-A:5
see also S.B. 247, 2018 LEG., REG. SESS. (N.H. 2018)
[41] N.H. REV. STAT. ANN. § 130-A:5-a
[42] N.H. REV. STAT. ANN § 130-A:5-a
[43] N.H. REV. STAT. ANN. § 415:6-v.
[44] 216 R.I. CODE R. § 050-15-3.3A(7, 44)
[45] 216 R.I. CODE R. § 050-15-3.3A(50)
https://rules.sos.ri.gov/regulations/part/216-50-15-3
[46] 23 R.I. GEN. LAWS § 24.6; R.I. CODE R. § 3.1(b), 216 R.I. CODE R. §050-15-3.4.1(A)(1)(a) at https://rules.sos.ri.gov/regulations/part/216-50-15-3
[47] 216 R.I. CODE R. § 050-15-3.2.1(A)(4)
[48] 216 R.I. CODE R. § 050-15-3.2.1(A)(3)
[49] 216 R.I. CODE R. § 050-3.4.2.
[50] VT. STAT. ANN. TIT. 18, § 1751(b)(7)
[51] VT. STAT. ANN. TIT. 18, § 1757(b). *Case Management Vermont Department of Health, Pediatric Blood Lead Testing & Case Management Guidelines* (2017), http://www.healthvermont.gov/sites/default/files/documents/pdf/Env_CEH_BLTestingGuidelines.pdf.
[52] VT. STAT. ANN. TIT. 18,§ 1757(c), § 13 140 055(II)(14);(III)
[53] VT. STAT. ANN. TIT. 18, §1755; *Vermont Blood Lead Testing and Reporting Rule, 10-044.*
[54] 18 VSA 1755(c); 13 140 070(II)(1)(d)

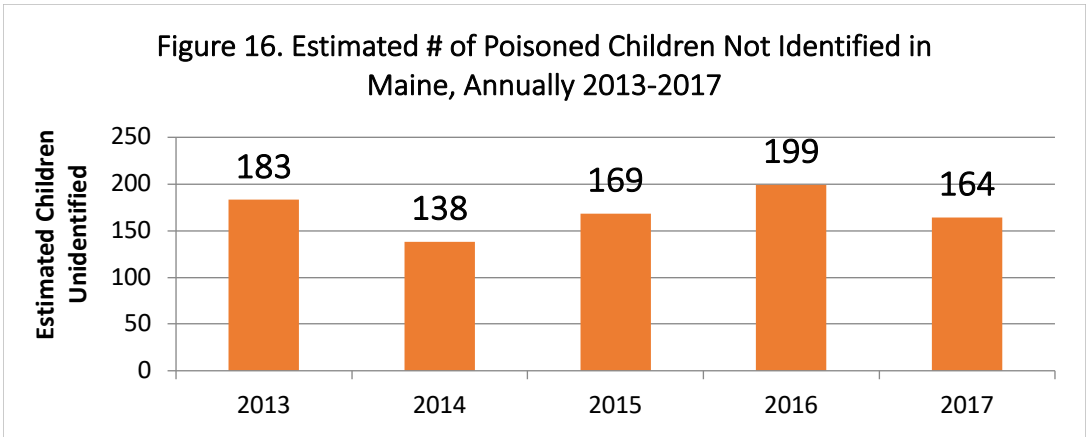
5. Estimated Number of Undiagnosed Children with Lead Poisoning & the Economic Impact

A report in Michigan conducted prior to the Flint crisis estimated that the annual cost of lead exposure was more than $270 million annually, including $112.5 million to tax payers.[55] The report went further and estimated that lead abatement for the 100,000 homes most at risk would cost a total of $600 million, yet would generate annual savings of $190 million annually, a payback period of just over 3 years. In Maine, a study from 2010 estimated the loss in lifetime earnings for lead exposure to be $270 million over the lifetimes of the children considered.[56]

The cost of lead exposure remains extremely high and includes costs related to special education, healthcare, crime, and decreased earnings. The return on investment for controlling lead hazards was estimated between $17 and $221 for every dollar spent, according to a 2009 study from the Economic Policy Institute.[57] More recently, a study from the Health Impact Project in 2017 estimated a return of $1.33 per dollar spent on removing lead hazards from drinking water, $1.39 per dollar spent on eradicating lead paint hazards from older homes, and $3.10 per dollar spent by ensuring contractors comply with the EPA's RRP Rule lead safe practices.[58]

If Maine achieved higher levels of screening, additional children would be confirmed with lead poisoning. To estimate the number of these unidentified children, we applied the screening rate of the highest performing county by the time children reached the age of 3 (Washington County, 95.8% in 2017 for the 2014 cohort) to the total number of children in Maine. Based on this estimate, approximately 164 more children in 2017 would have been identified as lead poisoned, a 50% increase over the actual 2017 confirmed cases. (Figure 16)

[55] Tracy Swinburn, *Costs of Lead Exposure and Remediation: Update* (2016) https://www.ecocenter.org/sites/default/files/Lead.Report.Designed.Final__0.pdf.
[56] Mary E. Davis, *Economic Assessment of Children's Health and the Environment in Maine*, 19 Maine Pol'y Rev. 1 (2010).
[57] Gould, E. Childhood Lead Poisoning: Conservative Estimates of the Social and Economic Benefits of Lead Hazard Control. Environ Health Perspect. 2009 Jul; 117(7): 1162-1167.
[58] Health Impact Project, *10 Policies to Prevent and Respond to Childhood Lead Exposure* (Aug. 2017), https://www.pewtrusts.org/-/media/assets/2017/08/hip_childhood_lead_poisoning_report.pdf.



It is estimated that lead poisoning results in an average loss of lifetime earnings of $723,000 per child.[59] Applying this to the estimated number of undiagnosed children results in a potential loss of earnings in the $77-$119 million range. If we apply the lost earnings to the total number of unidentified and confirmed lead poisoned children, the potential lost earnings falls in the range of $313-$355 million. Applied to the estimated 853 undiagnosed children in Maine, between 2013-2017 there was a potential loss of earnings of approximately $617 million. Applying these lost earnings to the total number of both confirmed and unidentified lead poisoned children in Maine between 2013-2017, the potential total loss is about $1.9 billion. In addition to the economic impact on affected individuals and society, research has demonstrated conclusively that lead poisoning continues to cause increases in health care and special education costs, among others, for communities in Maine and across the nation.

At current screening rates, there are many Maine children with lead poisoning who remain unidentified. The personal and societal costs of this missed public health intervention remain very high.

✦ ✦ ✦

"There is no cure, there is no treatment once the exposure has happened...[universal screening] is the best thing we've got to identify the child who has been exposed to lead and move them away from the hazards to prevent further damage."

~ Health Promotions Advisor, New Hampshire Division of Protective Health Services, Healthy Homes and Lead Poisoning Prevention

[59] National Center for Environmental Health, Centers for Disease Control and Prevention. Grosse et al., *Economic Gains Resulting from the Reduction in Children's Exposure to Lead in the United States,* ENVIRONMENTAL HEALTH PERSPECTIVES 110:563–569, June 2002.

MD 2015 Lead Targeting Plan

Uploaded by: Delegate Mosby, Delegate Mosby
Position: FAV

MARYLAND TARGETING PLAN FOR AREAS AT RISK FOR CHILDHOOD LEAD POISONING

October, 2015

Larry Hogan, Governor

Boyd K. Rutherford, Lieutenant Governor

Van T. Mitchell, Secretary

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EXECUTIVE SUMMARY

This 2015 Targeting Plan for Areas at Risk for Childhood Lead Poisoning revises the previous Targeting Plan, adopted by the Maryland Department of Health and Mental Hygiene (DHMH) in 2004. The 2015 Targeting Plan is based on changes in public health recommendations regarding lead exposure and the changing face of lead exposure in Maryland. The revised 2015 Targeting Plan is part of a comprehensive reassessment of Maryland's public health lead strategy, whose goal is the elimination of lead exposure in the State. The key recommendations in this revised Targeting Plan are:

1. ***Testing of all Maryland children ages 12 and 24 months:*** For a period of three years, all Maryland children under the age of 6 years should be tested for lead exposure at 12 and 24 months of age, based on a determination by DHMH that all ZIP codes and census tracts in the State should be considered "at risk" under the requirements of Maryland Code Annotated, Health-General Article, § 18-106, and Code of Maryland Regulations (COMAR) 10.11.04.
2. ***Re-evaluation of recommendations based on surveillance findings:*** At the end of three years, DHMH will re-evaluate these recommendations, based on the analysis of blood lead testing data developed over the three year period.
3. ***Clinical management:*** Like children with higher blood lead levels, children with blood lead levels of 5 – 9 micrograms per deciliter (mcg/dL) should have a confirmatory test, an assessment of possible sources of lead exposure, an assessment of other vulnerable individuals in the home, and a repeat blood test until it is clear that they do not have ongoing lead exposure.

These recommendations are one part of a comprehensive State strategy to eliminate or control known sources of lead in the environment, conduct surveillance of blood lead levels, ensure appropriate clinical follow-up for those exposed, and provide case management for lead exposed children. The State's Lead Poisoning Prevention Program is based at the Maryland Department of the Environment (MDE) and is conducted in concert with DHMH and local health departments.

In addition to this revised 2015 Targeting Plan, DHMH has also amended its regulations on point-of-care testing (COMAR 10.10.03.02(C)) to make it easier for providers to do lead testing in the office and report the results directly to parents and caregivers. Together with new State laws and regulations governing rental properties and home renovation and repairs, this revised Targeting Plan is intended to move the State towards the goal of eliminating childhood lead exposure in Maryland.

TABLE OF CONTENTS

1. BACKGROUND AND INTRODUCTION

The 2015 Targeting Plan for Areas at Risk of Childhood Lead Poisoning (hereafter referred to as the 2015 Targeting Plan) recommends a revised strategy for testing Maryland children for lead exposure. It is the first comprehensive reassessment of lead testing strategies in the State since 2004 and incorporates new recommendations from the U.S. Centers for Disease Control and Prevention (CDC) regarding blood lead levels that will require follow up action from clinicians, government agencies, and other stakeholders. The 2015 Targeting Plan was also prepared in response to significant changes in both statutory and regulatory requirements, as well as the progress that Maryland has made in reducing lead poisoning cases in the State since 1985.

Exposure to lead remains the most significant and widespread environmental hazard for children in Maryland, although substantial reductions in lead exposure and lead poisoning have also been achieved. While the prevalence of elevated blood lead levels in children in Maryland has declined dramatically over the years, there are still children with persistently elevated blood lead levels from previous exposures, and children who are newly exposed to lead every year (Figure 1). Children are most vulnerable to the adverse effects of lead exposure before age six, a period when their neurological systems are developing and when hand-to-mouth behaviors increase the opportunity for ingestion of lead-containing material. Exposure to lead can cause permanent neurological damage that may be associated with learning disabilities, decreased intelligence, and behavioral problems. Exposure to lead in paint chips and lead-contaminated dust from deteriorated painted surfaces is the primary cause of elevated blood lead levels in young children; however, some old or imported toys, lead-painted pottery, certain hobbies, traditional home remedies or cosmetic items, and clothing contaminated with lead from the workplace are all other possible sources of lead.

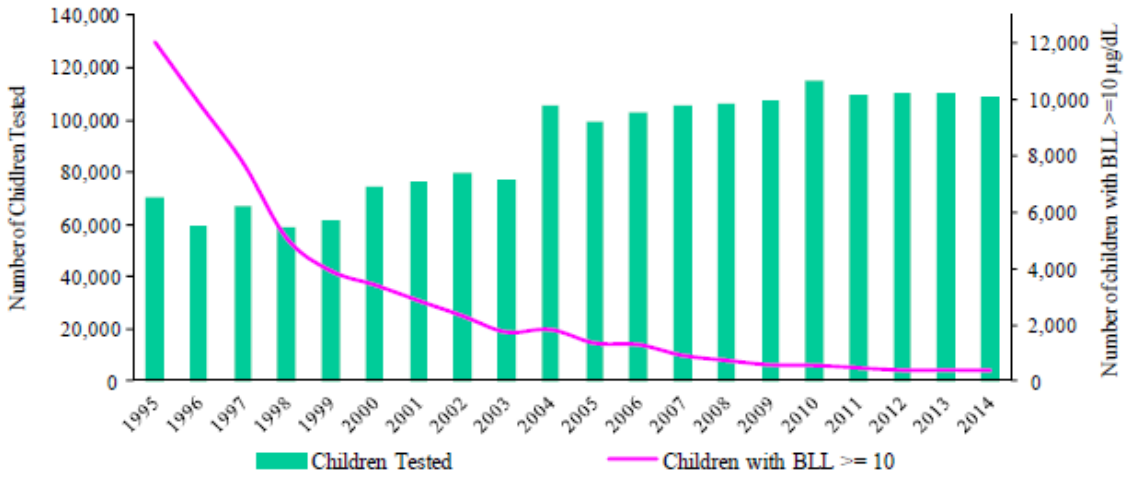

Figure 1. Number of children tested and newly-diagnosed with blood leads ≥10 mcg/dL, 1995-2014 (source = Maryland Department of the Environment, 2015).

The Maryland Department of the Environment (MDE) and and the Department of Health and Mental Hygiene (DHMH) are the principal state agencies charged with lead poisoning prevention. MDE maintains the Maryland Childhood Lead Registry (CLR), conducts enforcement actions, and coordinates with state and local agencies on lead poisoning prevention measures. MDE works in conjunction with the DHMH toward the goal of eliminating childhood lead poisoning through identification and elimination of sources of lead in the environment, surveillance, blood lead testing, coordination of resources, and case management.

2. EVOLUTION OF MARYLAND'S CURRENT TARGETING PLAN

The goal of the State's lead poisoning prevention program is to eliminate lead poisoning in Maryland. The State has made significant progress towards this goal through the identification and elimination of lead sources, such as lead paint in rental housing, and the testing and identification of children with lead exposure. The goal of testing is to identify children exposed to lead as soon as possible so that interventions can effectively address both sources of exposure and the clinical course of action for the child. There is an additional goal of preventing other children from being exposed.

In 1997, the CDC issued a report on childhood lead poisoning (CDC, 1997) revising an earlier recommendation for universal screening (CDC, 1991). The report recommended universal testing of children receiving Medicaid or Supplemental Food Program for Women Infants and Children (WIC) as well as those residing in areas identified as high-risk, and advocated targeted screening for all other children. In response to the public health concern regarding childhood lead poisoning in Maryland and revised CDC guidance, the 1997 Maryland General Assembly enacted House Bill (HB) 1138 as emergency legislation. This bill directed DHMH to establish a Childhood Lead Screening Program to increase awareness of lead poisoning and to ensure testing of children under age six in areas identified as "at risk." HB 1138 suggested specifically targeting childhood blood lead testing to "at risk" areas, specifically those census tracts with large concentrations of pre-1978 housing, as well as those with the highest rates of lead poisoned children, based on CLR surveillance results. In response, DHMH collaborated with various organizations and the University of Maryland to develop the first State Targeting Plan in 2000, identifying geographic areas in Maryland that were at increased risk for childhood lead poisoning (Center for Health Development, 2000).

The most important factors in the 2000 Targeting Plan found to predict the risk of elevated blood levels in a particular ZIP code were: (1) the percentage of pre-1950 housing; (2) median housing value; (3) "poverty index" (based on a formula incorporating the percentage of residents receiving public assistance income, the percentage of female-headed households, and the percentage of families below the poverty threshold); and (4) the percentage of homes built between 1950 and 1979. These variables were then used to identify "at risk" ZIP codes across the entire State.

Legislation enacted by the 2000 General Assembly required testing of children at 12 and 24 months of age residing in these "at risk" areas of the state (Maryland Code Annotated,

Health-General Article § 18-106). Additionally, all children living in Baltimore City or children receiving Medicaid services, regardless of their place of residence, were designated as "at risk," thus requiring testing. A lead exposure risk assessment questionnaire evaluating children for exposures to known sources of lead was also required of all children at their 12 and 24-month doctor's visits regardless of their place of residence. In 2003, a law was passed that required the parent of a child that either previously or currently resided in an "at risk" area to provide documentation of lead testing at first enrollment into pre-kindergarten, kindergarten, or first grade (Maryland Code Annotated, Family Law Article § 5-556.1). Under Maryland law, a child under six years of age must have evidence of appropriate lead screening within 30 days of entering a child care center, family child care home, or non-public nursery school.

In early 2004, DHMH again commissioned the University of Maryland, this time to evaluate and update the 2000 model and Targeting Plan. This update focused on: (1) analysis of the 2000 model variables, (2) reapplication of the 2000 model using data from the 2000 U.S. Census and 2001-2002 CLR data, (3) creation of an updated "at risk" ZIP code list, and (4) development of recommendations for future lead testing in Maryland (Maryland Department of Health and Mental Hygiene, 2004). As a result of this 2004 evaluation, an additional 78 "at risk" ZIP codes were identified. Appendix 1 lists the specific counties and ZIP codes identified as "at risk" as a result of the 2004 revision to the State targeting plan. The results of the updated 2004 Targeting Plan supported targeting outreach and education efforts to increase childhood lead testing in areas at greatest risk, as well as testing all children living in Baltimore City and all children receiving services through Medicaid, as required by Maryland law.

3. REVISION OF FEDERAL AND STATE CLINICAL GUIDELINES FOR LEAD EXPOSURE

In May, 2012, the CDC accepted recommendations from its Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) regarding lowering children's acceptable blood lead levels from 10 mcg/dL to 5 mcg/dL (Advisory Committee on Childhood Lead Poisoning Prevention, 2012; CDC, 2012). This recommendation included eliminating the term "level of concern" (previously set at 10 mcg/dL), and substituting a new term, "reference level," equal to the 97.5th percentile of blood lead measured in children in the National Health and Nutrition Examination Survey (NHANES), which is currently 5 mcg/dL.

DHMH endorsed this recommendation and issued a letter to clinicians on June 7, 2012, recommending that clinicians follow the new CDC guideline and re-test children with blood lead levels of 5 – 9 mcg/dL within three months (Appendix 2). At the time, DHMH also stated that it would follow up on these guidelines with additional guidance on: "the referral and case management process for children with new blood lead tests between 5 and 9 mcg/dL, whether and how far to "look back" for children who previously have had blood lead levels between 5 and 9 mcg/dL, and the appropriate clinical and administrative management of children with historic blood lead levels between 5 and 9 mcg/dL." DHMH subsequently embarked on a detailed analysis of surveillance results for childhood lead exposure in the State in cooperation

with MDE, leading to the current plan. In addition, DHMH has developed recommendations for case management of children with blood lead levels between 5 and 9 mcg/dL, which are being issued separately from this document. The next section describes the rationale for and evaluation of DHMH's revision of the State testing strategy.

4. TARGETING PLAN REVISION: RATIONALE AND EVALUATION

There are four important factors that make this an appropriate time to revise the State's targeting plan. First, it has been a decade since the plan was last re-evaluated; a decade that has seen a significant decline in the number and rate of new cases of childhood lead poisoning. Second, the risk factors for new cases have changed. A decade ago, most of the cases of elevated blood lead were from children in rental units exposed to peeling and chipping lead paint. While these sources are still important, a larger proportion of cases now come from sources including owner-occupied housing, rental housing not previously covered under Maryland law, non-paint sources such as food or consumer products, or sources that cannot be identified. Third, the change in Federal recommendations adopted in 2012 means that a large number of children, who previously might have been tested and had blood lead levels less than 10 mcg/dL or who might not have been tested at all, should now be tested and identified by their primary care providers. And fourth, even under the current targeting plan, many children who should be tested have not been, prompting DHMH to take a fresh look at the entire strategy and assess why testing rates are not as high as recommended.

Three options were evaluated in developing the revised strategy: (1) targeted testing strategy based on lead levels in children tested for lead exposure, using data from the Maryland CLR for the period 2005-2009; (2) targeted testing based on criteria similar to the previous 2000 and 2004 strategies, which used factors such as housing age and demographics in a model to predict the areas of highest lead exposure risk; and (3) designation of all areas of the State as "at risk," which would result in testing of all children under the age of six (the period when children are at greatest risk of permanent damage from lead exposure). These options are described in Table 1 and in more detail in Appendix 3, Methods.

Table 1. Description of testing strategy options evaluated

Testing Strategy	Description of Strategy
Option 1: Testing based on ZIP code distribution of 2005-2009 test results	Lead test results between 2005-2009 for children under age 6 in the Maryland Childhood Lead Registry were used to predict the ZIP codes that would yield the greatest number of children with lead levels ≥ 5 μg/dL (Appendix 3)
Option 2: Testing based on updated Maryland targeting model	"At-risk" areas defined using risk factors similar to 2000, 2004 targeting plans: housing characteristics, population demographics (Appendix 3)
Option 3: Universal testing	All areas of the State are designated "at risk;" all children under 72 months tested at 12, 24 months of age (Appendix 3)

Each option was evaluated according to how well it addressed health disparities, its efficiency in identifying children with elevated lead levels (sensitivity), simplicity, its completeness of coverage, and its potential cost-effectiveness.

The evaluation criteria also included the following assumptions:

- The State should prioritize testing populations that are disproportionately exposed to or affected by lead poisoning.
- All children enrolled in Medicaid should be tested for lead exposure at ages one and two years, as per the current policy.
- Targeting strategies should be designed to maximize the likelihood of identifying children with higher lead levels first, then children with lower levels.
- Any targeting strategy that does not involve universal testing should be simple to administer and understand, so that parents, health care providers, and health care organizations can easily determine whether a particular child should be tested.
- Any targeting strategy that does not involve universal testing should, at a minimum, ensure that all children who are not tested are screened by questionnaire for potential lead exposure, then tested based on suspicion of potential lead exposure.
- Any targeting strategy that does not involve universal testing should also be designed to avoid disproportionate or systematic exclusion of particular groups from testing.
- The testing strategy should be cost-effective; specifically, it should assure that the anticipated large numbers of blood lead levels of 5 – 9 mcg/dL results do not consume resources to the extent that they prevent an adequate response to more severely exposed children.
- The State should provide guidance to health care practitioners and organizations on how to manage children who are tested and found to have blood lead levels between 5 – 9 mcg/dL.

5. FINDINGS AND RECOMMENDATIONS

In developing its recommendations, DHMH has weighed the strengths and weaknesses of each of the three options. The selection of the best strategy depended on a number of factors, including: (1) the estimated number of lead-exposed children identified through selective (i.e., non-universal) testing, as well as the estimated number of lead-exposed children who might be missed; (2) the costs of testing and associated follow-up; (3) the impacts of expanded testing on both the public and the health care system; (4) the potential benefits of identifying children with low-level exposures before they become significantly exposed; and (5) potential limitations of data and models used to analyze each of the targeting strategy options.

The findings of the evaluation are summarized in Table 2, and in more detail in Appendix 4. Using methods similar to those in the 2000 and 2004 Maryland targeting plan, options one and two characterized areas as "high", "moderate," or "low" risk groups. Adoption of the first strategy would result in testing 420,158 children. Of those tested, 293,258 would be expected to have a blood lead level at or above the reference level of 5 mcg/dL and an additional 5,631 children with blood lead levels at or above the reference are expected to miss out on testing. Using the second model, it is expected that 106,570 children would be indicated to receive testing. Of these children, 31,747 are predicted to have a blood lead level at or above the reference and an additional 614 children predicted to have a blood lead level at or above the reference level of 5 mcg/dL are expected to miss testing.

Finding 1: Targeted Testing has Significant Limitations

Any targeted (non-universal) testing strategy would inevitably lead to the exclusion of some at-risk children from testing. Thus, any testing strategy that does not test children in every part of the State will produce a non-representative picture of lead levels in the entire population. For instance, in areas with newer housing, parents and providers may not consider lead testing because lead is considered to be a problem of older inner cities. In addition, the use of historical test data from particular areas could result in biased projections of test results when making inferences to the entire population, although the direction of the bias is not easily predicted. For example, in areas not currently considered "at risk" under the 2004 Targeting Plan, it is possible that testing is more likely to occur in individuals who are suspected of lead exposure, which would bias those results towards higher concentrations in those tested. Furthermore, the use of a model that emphasizes housing characteristics and demographics would underemphasize the role of non-housing-related sources of lead exposure, and would partly ignore the progress Maryland has made in controlling lead paint exposures.

Additionally, a testing strategy that does not test children in every part of the State will produce a non-representative picture of lead levels in the entire population. The population of children who are currently tested for elevated blood lead is also strongly influenced by the 2004 Targeting Plan, which may bias the risk areas identified using any of these revised targeting strategies. In the ZIP codes targeted under the 2004 Targeting Plan, the average percentage of children in the population tested from 2005-2009 ranges from 10 to 61% with a median of 32%,

while in non-targeted areas, the average percentage tested ranges from 0.5 to 46% with a median of 18%.

Since a lower percentage of children from non-at risk ZIP codes are currently tested, the lead levels of children who are tested are unlikely to be representative of the population of children in the area. This could lead either to under-estimation of the "true" population lead level, or over-estimation, depending on whether the few children who are tested are suspected of lead exposure (meaning their levels would likely be higher than other children) or are tested for some other reason, such as access to care (which could lead to misclassification in any direction).

Another limitation of the targeted testing approaches is that they are determined from, and influenced by, population size and 2005-2009 testing rates in the areas. These testing strategies involve a calculation of the predicted number of children with a blood lead level at or above the reference based on this population data. Areas with a large population are more likely to be identified as "at risk," even if they have a lower proportion of tests above the reference level, or a smaller predicted probability. For example, consider ZIP code A with a total population of 100 children and 6/10 (60%) test results above the reference level, and consider ZIP code B with a total population of 1,000 children and 1/10 (10%) test results above the reference level. Targeting approach 1 would result in 60 and 100 children (respectively) estimated to have a blood lead level above reference. Based on this, ZIP code B is more likely to be targeted, although children in ZIP code A may be at greater risk for having a blood lead level above the reference. The implication is that areas with a high proportion of test results ≥5 mcg/dL and a small population are less likely to be targeted than ZIP codes with a large population that have a small proportion of test results ≥5 mcg/dL.

Finding 2: Testing of All Children is More Expensive, but is Easier to Implement, More Equitable, and Provides More Useful Data

Although more costly to implement, a universal testing strategy for a limited time period, based on a determination that all areas of the State should be considered "at risk," is easier and simpler to implement and communicate, and will provide useful data on the true prevalence and distribution of children with elevated blood lead levels in the State. Appendix 5 provides details of the potential costs of the targeting options. This improved understanding of lead risks would ultimately improve future lead testing strategies for the State. The U.S. Census Bureau estimated there were 439,326 children less than 6 years old in 2011. The 2011 MDE Lead Poisoning Prevention Program's annual report indicates that 21.9% of MD children less than 6 years old were tested in 2011 and found 2.5% of those tested had a blood lead level ranging from 5 – 9 mcg/dL, and 0.4% had a blood lead level greater than or equal to 10 mcg/dL. As an upper limit estimate of the "true" number of children with significant lead levels in the State, if the same proportion of tests held in the total population of children, an estimated 12,740 children would be expected to have a blood lead level greater than or equal to 5 mcg/dL.

Testing of all children would be the most expensive of the proposed testing strategies to implement. This strategy also presents an additional issue of how to manage the increased

numbers of children with lead levels in the 5-9 mcg/dL range who would likely be identified if all children were tested. Children with blood lead levels in the 5-9 mcg/dl range would require repeat testing, even though many of them might ultimately not go on to develop higher blood lead levels. However, research has indicated that there is no "safe" level of lead exposure in children, and cognitive effects have been noted in children with increasingly low levels. If adopted, an estimated 10,862 children would require follow-up testing, at an estimated cost of between $471,000 and $831,000 per year for the three years of universal testing. It is likely, however, that most of these children will only require repeat testing to confirm that they are *not* being exposed to lead on an ongoing basis. However, a small, but unknown, number will also be found to have lead exposures, which, if prevented through this early detection, would significantly lower the lifetime costs associated with lead poisoning.

Finding 3: All Testing Options, Including Universal Testing, Offer Significant Returns on Investment When Compared with the Costs of Lead Poisoning

A complete cost-effectiveness analysis is beyond the scope of this document, but it is notable that the greatest rate of IQ loss has been found at blood lead levels *below* 10 mcg/dL (Canfield, 2003). In addition, there are many economic costs associated with lead poisoning including lifetime earnings, tax revenue, special education, criminal justice, and long term health effects. Appendix 9 details a cost-benefit analysis of the lead testing strategy. Using multiple methods from the available literature, the lifetime future earnings saved by reducing blood lead levels in 100% of Maryland children ages one and two, with a blood lead level ≥5 mcg/dL, is between $131-$512 million. Adding on savings from tax revenue, special education, juvenile delinquency, and violent crimes the savings in Maryland range from $143-$556 million.

Using the estimated cost range of the Maryland universal testing strategy and the range of savings in the cost-benefit analysis the return for each dollar invested ranges from $24-$142. This may be an underestimate; there is currently not enough research to estimate a cost from associated health conditions and behavioral problems. The Maryland estimate falls within the range calculated by a nationwide study that found a return of $17-$221 (Gould, 2009). Therefore the cost of any of the proposed strategies pales in comparison to the costs of untreated disease, and maximizing detection efforts should remain paramount.

Recommendation: DHMH Should Find All Areas of the State are "At Risk" and Test All Children Age 12 and 24 Months for a Limited Time Period

Given these considerations, DHMH has determined that all areas of the State should be considered "at risk" for a period of three years, and thus require the testing of all children aged 12 and 24 months. This strategy is most likely to produce a true picture of lead exposures across the State, is easy to administer and understand for all parties involved, and is most likely to move the State towards the goal of eliminating lead poisoning and lead exposure among children. At the end of the three-year period, the State intends to re-evaluate the results and decide whether to

modify the test strategy. Coincident with the adoption of this strategy, DHMH is providing outreach to health care providers on the management of children with blood lead levels of 5 – 9 mcg/dL, anticipating the need to clarify issues such as how long such cases should be followed.

In making this determination, DHMH recognizes that heath care providers, parents, and other stakeholders will need extensive communication regarding testing, test interpretation, and test follow-up. In particular, there may be questions about the need for testing in areas where people have not previously been subject to testing requirements. Outreach and communication will need to address the ease of testing, the importance and value of early identification of lead exposure, the fact that the strategy will be re-evaluated after a period of time, and DHMH's determination that all areas of the State are considered "at risk." Ultimately, this Targeting Plan represents significant progress in the State's efforts to eliminate childhood lead exposure.

Table 2. Evaluation of Targeting Plan Options

Testing Strategy	Estimated number of 1- and 2-year old children to be tested[§]	Estimated number of children with EBL ≥10 mcg/dL[§]	Estimated number of children with EBL 5 – 9 mcg/dL[§]	Prioritizes populations based on disproportionate exposure or effects	Simple for providers, parents to interpret	Ensures screening by questionnaire for children not tested	Addresses disparities observed in current testing	Estimated cost of implementation[§]
Option 1 – Testing based on ZIP code distribution of 2005-2009 test results	91,201 (79,983 Venous, 11,218 Capillary)	1,100 (1,040 Venous, 60 Confirmed Capillary)	7,108 (6,159 Venous, 949 Confirmed Capillary)	May be biased towards areas where testing more likely to be done only in cases of suspected lead poisoning	No	No	No	$2,577,901 - $3,853,697
Option 2 – Testing based on updated Maryland targeting model	108,245 (92,008 Venous, 16,237 Capillary)	1,148 (1,104 Venous, 44 Confirmed Capillary)	8,051 (6,809 Venous, 1,242 Confirmed Capillary)	Assumes exposures primarily related to housing characteristics	No	No	No	$2,904,642 - $4,403,261
Option 3 – Universal testing of all children under 6 at 12 and 24 months	146,037 (124,131 Venous, 21,906 Capillary)	1,548 (1,489 Venous, 59 Confirmed Capillary)	10,862 (9,186 Venous, 1,676 Confirmed Capillary)	Most equitable	Yes	Not applicable	Yes	$3,918,061 – $5,939,876

[§]See Appendix 5, Table A-5.1 for details.

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APPENDIX 1. Current (2015) "At Risk" Areas (Based On 2004 Targeting Plan)

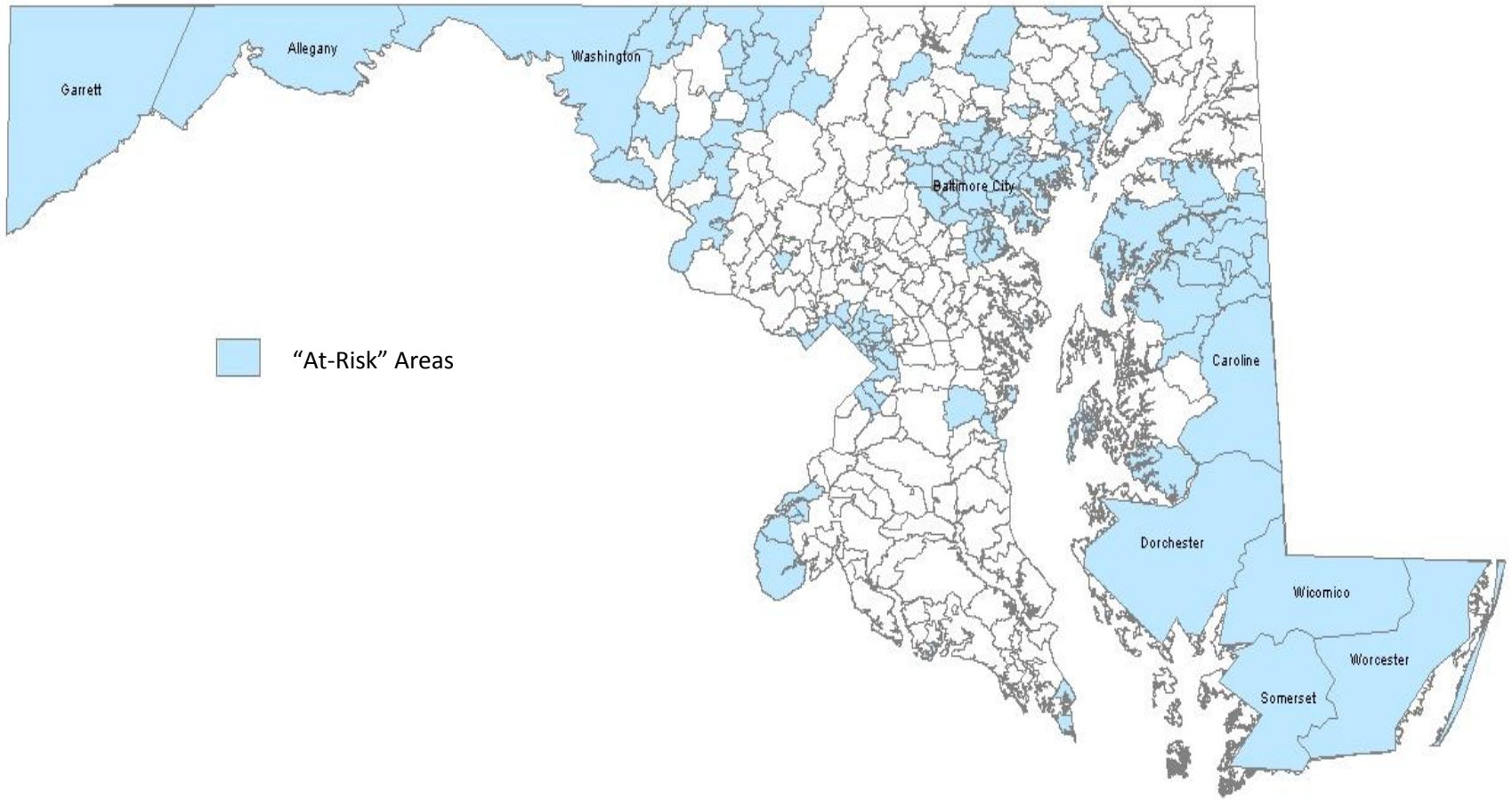


Figure A-1.1. Maryland Lead Targeting Plan, 2004 Revision

Table A-1.1. "At risk" ZIP Codes Identified in the Maryland Lead Targeting Plan, 2004 Revision

Allegany	**Baltimore County**	**Frederick**	**Montgomery**	**Prince George's** (cont.)
ALL	(cont.)	(cont.)	20783	20913
	21239	21719	20787	
Anne Arundel	21244	27127	20812	**Queen Anne's**
20711	21250	21757	20815	21607
20714	21251	21758	20816	21617
20764	21282	21762	20818	21620
20779	21286	21769	20838	21623
21060		21776	20842	21628
21061	**Baltimore City**	21778	20868	21640
21225	ALL	21780	20877	21644
21226		21783	20901	21649
21402	**Calvert**	21787	20910	21651
	20615	21791	20912	21657
Baltimore County	20714	21798	20913	21668
21027				21670
21052	**Caroline**		**Prince George's**	
21071	ALL	**Garrett**	20703	**Somerset**
21082		ALL	20710	ALL
21085	**Carroll**		20712	
21093	21155	**Harford**	20722	**St. Mary's**
21111	21757	21001	20731	20606
21133	21776	21010	20737	20626
21155	21787	21034	20738	20628
21161	21791	21040	20740	20674
21204		21078	20741	20687
21206	**Cecil**	21082	20742	
21207	21913	21085	20743	**Talbot**
21208		21130	20746	21612
21209	**Charles**	21111	20748	21654
21210	20640	21160	20752	21657
21212	20658	21161	20770	21665
21215	20662		20781	21671
21219		**Howard**	20782	21673
21220	**Dorchester**	20763	20783	21676
21221	ALL		20784	
21222		**Kent**	20785	**Washington**
21224	**Frederick**	21610	20787	ALL
21227	20842	21620	20788	
21228	21701	21645	20790	**Wicomico**
21229	21703	21650	20791	ALL
21234	21704	21651	20792	
21236	21716	21661	20799	**Worcester**
21237	21718	21667	20912	ALL

APPENDIX 2. June 7, 2012 Department of Health and Mental Hygiene Letter to Clinicians on New CDC Guidance

STATE OF MARYLAND
DHMH

Maryland Department of Health and Mental Hygiene
201 W. Preston Street • Baltimore, Maryland 21201
Martin O'Malley, Governor – Anthony G. Brown, Lt. Governor – Joshua M. Sharfstein, M.D., Secretary

June 7, 2012

Dear Health Care Provider:

In May, 2012, the U.S. Centers for Disease Control and Prevention (CDC) responded to recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) to revise the guidelines for childhood lead poisoning.

This letter summarizes the Department of Health and Mental Hygiene's (DHMH) recommendations for the prevention, diagnosis, and management of lead poisoning in children. The letter also summarizes the CDC response and rationale, and the current activities of DHMH and the Department of the Environment (MDE) to respond to this change in guidelines.

The key questions for health care providers addressed in this letter are:

- *What are the recommendations of the Advisory Committee on Childhood Lead Poisoning Prevention, and what were CDC's responses to those recommendations?*
- *What blood lead level should trigger a response by a health care provider?*
- *What is the recommendation for children with blood lead levels between 5 and 9 microgram/deciliter (µg/dL)? For children with blood lead levels 10 µg/dL or greater?*
- *Are there changes in the recommendations for which children in Maryland should be screened or tested for possible lead exposure, the screening and testing procedures, or the ages of screening and testing?*

Key Points of Advisory Committee's Recommendations and CDC's Response

The recommendations from the ACCLPP were based on a thorough review of the science of childhood lead poisoning. The ACCLPP's recommendations were based on the weight of evidence from a growing body of studies showing that the effects of lead appear to be irreversible and can occur at levels < 10 µg/dL. Key points of the recommendations are as follows:

- The ACCLPP recommends that the term "level of concern" be eliminated from all future agency policies, guidance documents, and other CDC publications. CDC agreed that the emphasis should be on preventing even these low exposure levels.

- CDC agreed that the agency should use a childhood BLL reference value based on the 97.5th percentile of the population BLL in children ages 1-5 (currently 5 µg/dL) to identify children and environments associated with lead-exposure hazards. The reference value should be periodically updated, based on the most recent population based blood lead surveys among children.

- Clinicians should monitor the health status of all children with a confirmed BLL ≥ 5 µg/dL for subsequent changes in BLL until all recommended environmental investigations and mitigation strategies have been completed, and should notify the family of all affected children of BLL test results in a timely and appropriate manner. Clinicians also should collaborate with local and state health agencies to ensure that the appropriate services and resources are provided to children and their families.

- Both the ACCLPP and CDC emphasized the importance of educating families, service providers, advocates, and public officials on the primary prevention of lead exposure in homes and other child-occupied facilities to ensure that lead hazards are eliminated before children are exposed.

Recommendations for Maryland Health Care Providers

Based on the new CDC recommendations, DHMH, in consultation with the Lead Poisoning Prevention Program at MDE, is taking the following steps. DHMH is currently recommending that all providers follow the guidelines below regarding lead poisoning prevention in children.

1. *There is no change in the recommendations for the age of testing for children in Maryland.* **The requirement remains that children living in zip codes identified as "at-risk") in the Maryland State Targeting Plan (view at-risk zip codes: http://fha.dhmh.maryland.gov/mch/Documents/Lead-revisedatriskareas2004a.pdf), and all children enrolled in Maryland Healthy Kids (EPSDT), should receive a lead test at ages 12 and 24 months.** In addition, all children should be screened for possible lead exposure with questions about peeling, flaking, or chipping paint, as well as other sources of lead exposure. Any child who has potential sources of lead exposure should be tested for lead.

2. *DHMH, consistent with the new CDC guidance, recommends that children with a lead level greater than the new reference level of 5 µg/dL should be retested within 3 months.* In addition, families whose children have a confirmed level greater than 5 µg/dL should receive lead and nutritional education, and be assessed for possible sources of lead exposure.

3. *There has been no change in the Maryland law related to housing and lead levels.* Maryland law still recognizes a level of 10 µg/dL as the level that triggers regulatory action related to rental housing.

Further Recommendations to Come

A number of important policy issues remain to be answered, including the referral and case management process for children with new blood lead tests between 5 and 9 µg/dL, whether and how far to "look back" for children who previously have had blood lead levels between 5 and 9 µg/dL, and the appropriate clinical and administrative management of children with historic blood lead levels between 5 and 9 µg/dL.

DHMH and MDE will work with local health departments to develop recommendations and guidelines for these questions, based on future CDC guidance and on input from key stakeholders. The agencies propose to solicit stakeholder and public input into these decisions through the Maryland Lead Poisoning Prevention Commission. The agencies anticipate updating state guidance this fall..

Resources for Providers

For further information, including resources for parents, providers, tenants, home owners, contractors, and rental owners, data on childhood lead tests in Maryland, and changes in recent laws affected lead, visit the Maryland Lead Poisoning Prevention Program website at: http://mde.maryland.gov/programs/Land/LeadPoisoningPrevention/Pages/Programs/LandPrograms/leadcoordination/index.aspx. You can also call the Childhood Lead Poisoning Prevention program at 410-537-3825. Questions for DHMH can be directed to the Environmental Health help line toll-free at 1-866-703-3266.

Sincerely,

Frances Phillips RN, MHA
Deputy Secretary for Public Health

Clifford S. Mitchell, MS, MD, MPH
Assistant Director for Environmental Health and Food Protection

APPENDIX 3. Methods

This section describes the analytic framework for the project, beginning with a description of the data sources followed by the methods used to prepare the data sets used for the analysis. Next, the methods used to assemble the data to test each of the three different options for a revised lead targeting strategy for Maryland are described.

Data Sources

Maryland childhood lead testing data were downloaded from the Childhood Lead Registry's Systematic Tracking of Elevated Lead Levels and Remediation (STELLAR) data base. Additional property data were obtained from the State Department of Assessments and Taxation (DAT) and MDE Rental Registry data sets. These data were cleaned, geocoded, and then merged using residential addresses. New variables for each address's latitude, longitude, census tract, and county were added using Centrus geocoding software. Detailed descriptions of these data sets and initial data cleaning procedures are in Appendix 6.

The resulting file included record-level information on the basic demographics (age, gender), blood lead test results (sample date, test type, blood lead level), address (street address, latitude, longitude, census tract) and housing characteristics (year of construction, assumed rental status) on each individual child tested in Maryland annually from 2005-2009. Children without valid addresses and children for whom age was unknown were excluded from the analyses. Each child was counted only once in the full project data set for the year in which she/he received a blood lead test, using the highest confirmatory or venous test.

To present a baseline description of lead testing and the characteristics of children tested in Maryland, descriptive statistics were computed on the full project data set. Tables and maps were generated to summarize the characteristics of children who received a blood lead test from January 1, 2005 through December 31, 2009. Both annual and five-year aggregate analyses were performed, retaining each child's highest venous, unknown, or capillary test result (in that order) for the specified time period. Venous samples were considered the most accurate. Samples with an "unknown" type were prioritized over capillary samples because it was possible that some proportion included venous samples. Any decimals in the reported blood lead levels were rounded *down* to the nearest whole number (e.g., a blood lead level of 9.9 would be rounded to 9), because legally, a blood lead level of 9.9 is still considered less than 10. For annual descriptive analyses, each child was counted once per year in the year they received a blood lead test. These results were presented stratified by year. For the 5-year aggregate analysis, each child was counted only once per 5-year period.

Data were prepared and analyzed with SAS Version 9.2. Maps were prepared using ArcGIS ArcMap 10. Tables were prepared using Microsoft Excel 2010.

Targeting Strategy Option 1 (Target Testing Based on the Distribution of Blood Lead Levels in Children Tested between 2005-2009, by ZIP Code)

The first targeting strategy involves testing all 1- and 2-year old children in the State residing in "at risk" areas, as well as all children receiving Medicaid. This strategy defines "risk" based on historically observed test results from the CLR for all children less than 72 months of age tested between 2005 and 2009. This approach assumes that the proportion of children with a test result of 5 mcg/dL or higher is representative of the entire ZIP code. The "expected" number of children with a blood lead level above the CDC reference level of 5 mcg/dL was then calculated based on this assumption.

This approach is based upon the assumption that the risk (probability) of having a blood lead level ≥5 mcg/dL in a population of children *tested* is the same as the *actual* risk (probability) in the population of children residing in that ZIP code. Unlike Strategy Option 2, below, it does not depend on housing characteristics or other predictors, but instead is based solely on the historically observed distribution of blood lead levels from the Maryland Childhood Lead Registry. This assumption is most accurate for areas of the state that already have relatively high testing rates, but is less accurate for areas that traditionally have relatively low rates of testing.

The full project data set was restricted to children less than 6 years of age. This data set was then aggregated over a 5-year period, and the test result of the highest venous, unknown, or capillary was retained, resulting in a data set that included a single record per individual child tested from 2005-2009. Next, the data set was aggregated by ZIP code, obtaining the total number of tests overall and the number of results ≤4 mcg/dL, 5-9 mcg/dL and ≥10 mcg/dL per ZIP code. The proportion of tests at, or above, the current reference level was calculated as the total number of tests with results ≥5 mcg/dL divided by all tests in each ZIP code (Equation 1).

Equation A-3.1. Proportion of Tests at or above CDC Reference Level of 5 mcg/dL

$$\text{Proportion} = \frac{Number\ Results \geq 5 \mu g/dL}{Total\ Number\ of\ Tests}$$

The annual population of children residing in each ZIP code was estimated using the 2000 and 2010 U.S. Census counts of the total number of children less than six years of age in each ZIP code. Procedurally, U.S. Census ZIP Code Tabulation Areas (ZCTAs) were merged using a Geographic Information System (GIS) computer map so that each represented the boundary of each US Post Office ZIP Code. The 2000 Census data were obtained from the 2000 Census summary file compact disk, and Excel files of the 2010 Census data were obtained by MDE from the Maryland Department of Planning. These counts were interpolated to estimate the total annual number of children less than 6 years of age residing in each ZIP code for 2001-

2009. The annual counts of children for each intercensal year were calculated using the accepted premise of a linear change in annual population within the decade. This method, while not as accurate as the 2000 population count, is an accepted method to determine ZIP code population totals for intervening years. The total population change (increase or decrease) from 2000 to 2010 for each ZIP code was divided by 10 (10 years) and a 1/10 increment was added to the total population for the previous year, resulting in an annual estimate of the number of children less than 6 years of age.

The expected number of children with a blood lead level at or above the reference level was calculated by multiplying the proportion of tests at or above the reference level by the estimated population of children less than 6 years of age in each ZIP code.

The list of ZIP codes was sorted in descending order of the proportion of children with a blood lead level ≥5 mcg⁄dL, based on the 2010 population total, and the cumulative percent was calculated. Potential "at risk" ZIP codes were identified by summing the number of children less than 6 years old with an expected blood lead level ≥5 mcg⁄dL in each area, starting with areas with the largest number of children expected to have blood lead levels of 5 mcg⁄dL or greater, until the cumulative total number of cases amounted to 90%, 75%, or 50% of all cases expected in the State. The ZIP codes capturing 90%, 75%, or 50% of the State's total number of children were identified as "at risk."

The computed risk status measure of each ZIP code was merged with other information about each child (ZIP code to child match). The ZIP code polygon-child file was used to identify characteristics of individual children from "at risk" and "non-risk" ZIP codes. Further analyses of this file permitted assessments of the various risk definitions. The Chi-Square test was used to assess whether there were statistically significant differences in the demographic characteristics of "at risk" and "non-risk" areas.

Targeting Strategy Option 2 (Target Testing Based on Updated Maryland 2000 and 2004 Targeting Model)

The second targeting strategy involves testing all children enrolled in Medicaid and all 1- and 2-year old children in the State residing in "at risk" areas, with "risk" defined based on historically observed risk factors such as housing and other demographic data from the U.S. Census. Additional measures from the State Department of Assessments and Taxation (DAT), MDE Rental Registry, MDE Enforcements, and U.S. Census were analyzed to identify potentially new information that could differentiate residential ZIP codes on lead risk. This approach is based upon the assumption that historically identified risk factors (especially lead paint) continue to be the primary influence on a child's risk of lead poisoning in MD and utilizes more recent data to examine the current influence and distribution of these in the state. The assumption underlying this strategy is that a primary risk for lead exposure continues to be lead paint, as in other states in the Northeast United States.

As described above, the initial data consisted of one recorded test per child annually for all children tested from 2005 to 2009. As before, the highest venous, unknown, or capillary

sample was used. The resulting data set was then aggregated by census tract. This data set differed from that in the first strategy in that it included counts of the total number of individual children less than 6 years of age tested and the total number of children with test results that were ≤4 mcg⁄dL and ≥5 mcg⁄dL for each census tract. The percentage of children with tests at or above the CDC reference level (5 mcg/dL) was calculated as the number of children with test results at or above 5 mcg/dL divided by the total number of children in each census tract and multiplied by 100 (Equation 2). The denominator was determined by computing the sum of total children with test results below the reference level (≤4 mcg⁄dL) with total children and those with test results at or above the revised lead reference level (5 mcg/dL) per census tract.

Equation A-3.2. Percentage of Tests At or Above CDC Reference Level

$$\text{Percentage of tests} = \frac{Number\ Results \geq 5\ mcg/dL}{Total\ Number\ of\ Tests} \times 100$$

The 2009 American Community Survey (ACS) 5-year estimate (2005-2009) data set, stratified by census tract, was used for the analysis. The following census tract characteristics were identified as critical to the analysis of the data for the 2000 and 2004 targeting models:

- total number of children less than 6 years of age
- total number of families with children less than 5 years of age below poverty level
- total number of female-headed households with children less than 6 years of age
- number of housing units by age, median housing values
- number of households with public assistance income
- total population by race
- number of occupied and vacant houses
- number of renter- and owner-occupied houses
- median household income

The median household income and housing value for each census tract were used to calculate percentages by census tract. The census tract demographics data were merged with the prepared CLR data containing the counts and the percentage of tests at or above the reference level by census tract number.

Because the CLR data set includes five years of data, the average annual proportion of children tested from 2005-2009 was computed for each census tract. This was the total number of individual children less than 6 years old tested each year divided by the estimated total population of children less than 6 years old per census tract (Equation 3). The ACS 5-year estimated population of children by census tract was used as the annual population estimate. Because the annual denominator came from the population census, each child was counted once per year. For consistency in the numerator, an individual child less than 6 years old was counted

once for each year in which she/he received a lead test. For this measure, an individual child was counted only once per year, provided that the child received a lead test and was less than 6 years of age in that year.

Equation A-3.3. Mean Annual Percentage of Children <6 Years Old Tested

$$\text{Percentage} = \frac{NT\ 2005 + NT\ 2006 + NT\ 2007 + NT\ 2008 + NT\ 2009}{Population\ of\ children < 6\ years\ old} \times 100$$

NT=Number of Children Tested

The dependent variable of interest was census tract "at risk" area versus census tract "non-at risk" area. This census tract risk area was defined as the percentage of unique children with blood lead tests (one single lead test for each child) per census tract at or above the reference level of 5 mcg⁄dL. For census tracts in Maryland, this percentage ranged from 0 to 61%. Four dummy-variable binary measures were created: 25th, 50th, 75th, and 90th percentiles. These percentile cut points were selected to identify high-risk census tracts that included 3, 5, 9, and 17% of test results at or above the four reference cut off values, respectively. For example, using the 50th percentile cut-off, census tracts with greater than or equal to 5% of tests at or above the reference level would be considered "at risk" areas.

Census tract characteristics of areas identified as "at risk" and "non-at risk" were compared for each outcome. Risk and non-risk areas were compared using the two-sample t-test if the dependent variable was continuous. Correlations between the covariates were evaluated using the Pearson's correlation coefficient statistic. Based on the results of these comparisons and the observed correlations between the covariates, a "poverty scale" variable was created. This new poverty scale index was computed by summing the standardized proportion of female-headed households, the proportion of households with public assistance income, and the proportion of families below the poverty level. The mean and standard deviation of each of these variables were calculated and used to generate a "standardized value" (Equation 4 a-c). The standardized values were then averaged, resulting in the poverty scale variable used in the model (Equation 5).

Equation A-3.4. Census Tract Standardized Poverty Variables

a) Female-Headed Household (FHH): Standardized FHH = $\frac{\%FHH(tract) - Mean\%\ FHH(state)}{FHH\ Standard\ Deviation\ (state)}$

b) Public Assistance Income (PA): Standardized PA = $\frac{\%PA(tract) - Mean\%\ PA(state)}{PA\ Standard\ Deviation\ (state)}$

c) Families Below Poverty (FBP): Standardized FBP = $\frac{\%FBP(tract) - Mean\%\ FBP(state)}{FBP\ Standard\ Deviation\ (state)}$

Equation A-3.5. Mean Census Tract Poverty Scale Variable

$$\text{Poverty Scale} = \frac{\text{Standardized FHH+ Standardized PA+ Standardized FBP}}{3}$$

The relationship between the community variables (predictors) and the outcome (being a "risk area") was evaluated by computing crude odds ratios (ORs) and ORs adjusted for the average proportion of children less than 6 years of age tested through logistic regression. To calculate the ORs, census tracts were aggregated into tertiles consisting of low, medium, and high groups for each of the independent variables. To construct these groups, the census tracts were sorted with respect to the independent variable, then cut-off values were identified that divided the population of children into three groups, each containing approximately a third of the census population of children less than 6 years old.

Predictive models for each of the four outcomes (dependent variables) were developed and included covariates historically considered to be significant predictors of lead risk in Maryland, as identified in the earlier models. Logistic regression models were used to evaluate the association between each of these covariates and the dependent variable. Each of the four models was evaluated based on several model criteria. These model assessment criteria included the Hosmer-Lemeshow test, Somers' D statistic, and the area under the receiver operating characteristic (ROC) curve. The area under the ROC curve gives a quantitative indication of each model's ability to distinguish between risk and non-risk census tracts and can range from 0.5 (worst) to 1.0 (ideal). The ROC curve plots the probability of correctly detecting a risk area (sensitivity) and correctly detecting a non-risk area (1 minus specificity).

The results for the models were used to generate a predicted probability for each census tract. The predicted number of children was calculated as the predicted probability of that census tract multiplied by the total population of children less than 6 years of age living in that census tract. Census tracts were then ranked as high, moderate, low, or negligible risk based on the percentage of children predicted to have a blood lead level at or above the reference level in that area. The intervals used here are based on the previous State model; this was done to make the current findings comparable to those from the models used in the previous State targeting plans. For each outcome, census tracts containing 40-100% of the highest number of predicted "at risk" children were classified as high risk; tracts containing 11-39.9% were classified as moderate risk; tracts containing 2-10.9% were classified as low risk; and tracts containing less than 2% were classified as negligible risk. The rankings for each outcome measure were mapped to depict the distribution of risk areas across the state. Under the current State targeting plan, areas classified as high, moderate, and low risk are all targeted (Maryland Code Annotated, Health-General Article § 18-106; see also Maryland General Assembly House Bill 1221 (2000 Session)) .

Targeting Strategy Option 3 (Universal Testing)

The final option for a universal testing strategy would be to test every child in the state at the age of one and two years. The universal testing approach eliminates the need to identify "at risk" areas; rather, the expectation would be that all children in every jurisdiction would be tested at age one, and again at age two. Children older than two years of age who were not previously tested are not assumed to be retrospectively tested in this option.

APPENDIX 4. Results of the Analysis

Descriptive Statistics

The number of individual children (≤18 years old) tested in Maryland increased each year from 113,186 in 2005 to 119,866 in 2009, while the number of children with blood lead levels greater than or equal to 10 mcg/dL decreased. The 181 records for which the child was from a state other than Maryland, or the child's state of residence was unknown (0.01-0.09% annually), were excluded, as were reports for any persons older than 18 years of age. Annually, 59-65% of all children tested in the state were two years old or younger. Completeness of information about a child's race and ethnicity has improved each year. In 2009, however, ethnicity and racial data were still incomplete, with 38% and 46% of tested children's ethnicity and race, respectively, still unknown (these variables were still included, however, because of the importance of addressing historical disparities in lead exposure). Table A-4.1 summarizes the demographic information of all Maryland children who received a blood lead test from 2005-2009.

Of the children less than six years old tested in the State each year, most were from Prince George's County (17.1-18.2%), Baltimore City (16.7-17.7%) or Montgomery County (16.5-17.5%). Table A-4.2 summarizes, by county, the number and percentage of children less than six years old tested each year from 2005-2009. The average annual percentage of census-tract-defined children tested for lead ranged from 2-90% during this 5-year period (Figure A-4.1). The median percentage of blood lead tests at, or above, the reference level for all census tracts in the state was 5%. The percentage of test results at or above the reference level by census tract for all children less than six years old tested ranged from 0.5-61.9% (Figure A-4.2). Summary statistics of all children tested in the state, stratified by blood lead level (≤4, 5-9, and ≥10 mcg/dL), are presented in Table A-4.3.

Table A-4.1. Characteristics of Children Tested for Elevated Blood Lead Levels, Maryland 2005-2009

	2005		2006		2007		2008		2009	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Individual Children Tested:	113,186		115,922		118,197		118,893		119,866	
Sex										
Female	54,366	48.0	55,686	48.0	56,894	48.1	57,789	48.6	57,940	48.3
Male	56,840	50.2	58,377	50.4	60,443	51.1	60,521	50.9	61,212	51.1
Unknown	1,980	1.7	1,859	1.6	860	0.7	583	0.5	714	0.6
Age (years)										
<1	10,178	9.0	10,595	9.1	11,280	9.5	11,360	9.6	10,961	9.1
1	32,108	28.4	34,190	29.5	35,809	30.3	36,307	30.5	36,549	30.5
2	24,208	21.4	26,038	22.5	26,822	22.7	28,349	23.8	29,815	24.9
3	11,659	10.3	11,697	10.1	12,011	10.2	11,616	9.8	11,822	9.9
4	12,016	10.6	11,900	10.3	11,497	9.7	11,006	9.3	10,932	9.1
5	8,827	7.8	8,471	7.3	8,259	7.0	7,845	6.6	7,502	6.3
6-18	14,183	12.5	13,026	11.2	12,516	10.6	12,406	10.4	12,285	10.2
Race										
White	18,009	15.9	20,396	17.6	25,577	21.6	27,222	22.9	27,968	23.3
Black	19,840	17.5	23,601	20.4	27,742	23.5	31,011	26.1	32,371	27.0
Other*	2,198	1.9	2,757	2.4	3,453	2.9	4,231	3.6	3,992	3.3
Unknown	73,139	64.6	69,168	59.7	61,425	52.0	56,429	47.5	55,535	46.3
Ethnicity										
Hispanic	7,776	6.9	10,144	8.8	13,890	11.8	16,300	13.7	17,905	14.9
Non-Hispanic	31,848	28.1	38,112	32.9	46,426	39.3	52,408	44.1	56,428	47.1
Unknown	73,561	65.0	67,663	58.4	57,873	49.0	50,174	42.2	45,518	38.0
Race/ Ethnicity										
White, non-Hispanic	10,812	9.6	12,777	11.0	16,914	14.3	18,311	15.4	18,569	15.5
Black, non-Hispanic	15,421	13.6	18,863	16.3	22,689	19.2	25,877	21.8	27,098	22.6
Other*, non-Hispanic	1,340	1.2	1,596	1.4	2,016	1.7	2,645	2.2	2,619	2.2
Unknown, Non-Hispanic	4,275	3.8	4,876	4.2	4,807	4.1	5,575	4.7	8,142	6.8
Hispanic	7,776	6.9	10,144	8.8	13,890	11.8	16,300	13.7	17,905	14.9
Unknown	73,562	65.0	67,666	58.4	57,881	49.0	50,185	42.2	45,533	38.0
Year Child's Home Built										
Pre 1950	20,042	17.7	20,559	17.7	20,916	17.7	20,899	17.6	21,274	17.7
1950 to <1978	19,885	17.6	20,640	17.8	21,045	17.8	21,864	18.4	21,631	18.0
1978 or After	23,699	20.9	24,650	21.3	25,759	21.8	25,330	21.3	24,703	20.6
Unknown	49,560	43.8	50,073	43.2	50,477	42.7	50,800	42.7	52,258	43.6
Probable Rental Property**										
Yes	18,847	16.7	19,702	17.0	20,200	17.1	20,782	17.5	21,295	17.8
No	47,565	42.0	49,015	42.3	50,254	42.5	50,220	42.2	49,299	41.1
Unknown	46,774	41.3	47,205	40.7	47,743	40.4	47,891	40.3	49,272	41.1
Child Resides in 2004 Target Area										
Yes	65,085	57.5	67,341	58.1	67,688	57.3	68,067	57.3	69,228	57.8
No	47,820	42.2	48,563	41.9	50,493	42.7	50,755	42.7	50,621	42.2
Unknown	281	0.2	18	0.0	16	0.0	71	0.1	17	0.0
Sample Type										
Capillary	15,575	13.8	16,560	14.3	16,119	13.6	15,898	13.4	15,948	13.3
Venous	89,302	78.9	90,340	77.9	92,127	77.9	90,778	76.4	88,935	74.2
Unknown	8,309	7.3	9,022	7.8	9,951	8.4	12,217	10.3	14,983	12.5

* Other Includes Asian/Pacific Islander, Native American/Alaskan and Multiracial

** Probable Rental Properties Identified as those properties in the DAT file where the Owner's Mailing address is not the Property Address

Table A-4.2. Annual Lead Testing Counts and Percentages,* by County for Maryland Children <6 years of age, 2005-2009

	2005		2006		2007		2008		2009	
County	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Allegany	1,035	32.6	1,176	34.8	1,233	34.5	1,325	35.1	1,373	34.6
Anne Arundel	6,618	21.4	6,401	19.4	6,627	18.9	6,829	18.4	7,344	18.7
Baltimore County	15,229	35.7	15,621	34.2	16,511	33.9	15,889	30.8	16,178	29.6
Baltimore City	17,373	47.0	18,206	46.4	17,628	42.4	18,557	42.3	19,074	41.3
Calvert	743	16.1	734	14.9	784	15.0	767	13.8	697	11.9
Caroline	853	44.5	888	42.4	852	37.6	858	35.2	894	34.2
Carroll	1,441	16.4	1,356	14.6	1,422	14.5	1,344	13.1	1,341	12.5
Cecil	1,043	18.4	1,055	17.3	1,188	18.2	1,265	18.3	1,213	16.5
Charles	1,812	21.5	1,918	21.3	2,004	20.9	2,032	19.9	1,839	17.1
Dorchester	623	35.8	696	37.2	678	33.8	680	31.8	732	32.3
Frederick	3,021	22.5	3,121	21.8	3,455	22.7	3,379	20.9	3,183	18.6
Garrett	530	34.6	496	30.8	540	32.0	478	27.1	475	25.8
Harford	2,940	21.3	3,045	20.7	3,355	21.6	3,265	19.9	3,187	18.5
Howard	2,265	13.8	2,187	12.6	2,329	12.7	2,496	12.9	2,490	12.3
Kent	174	19.5	256	26.8	334	32.8	303	28.1	323	28.3
Montgomery	16,348	28.8	17,409	28.6	18,298	28.3	18,616	27.1	18,261	25.2
Prince George's	17,900	34.1	18,581	33.2	18,059	30.4	18,729	29.8	19,621	29.6
Queen Anne's	478	19.0	625	23.4	704	24.8	595	19.8	607	19.2
Somerset	492	45.6	514	44.0	528	42.0	522	38.8	497	34.6
St. Mary's	1,382	21.3	1,551	22.1	1,463	19.4	1,519	18.8	1,527	17.8
Talbot	572	34.9	637	36.1	701	37.0	609	30.1	617	28.7
Washington	3,241	40.5	3,016	35.1	3,069	33.5	3,041	31.2	3,003	29.1
Wicomico	2,097	39.6	2,430	42.5	2,974	48.5	2,419	37.0	2,247	32.3
Worcester	703	32.4	968	42.2	942	39.0	910	35.9	850	32.0

* Denominator used to calculate percentages based on U.S. Census population data.

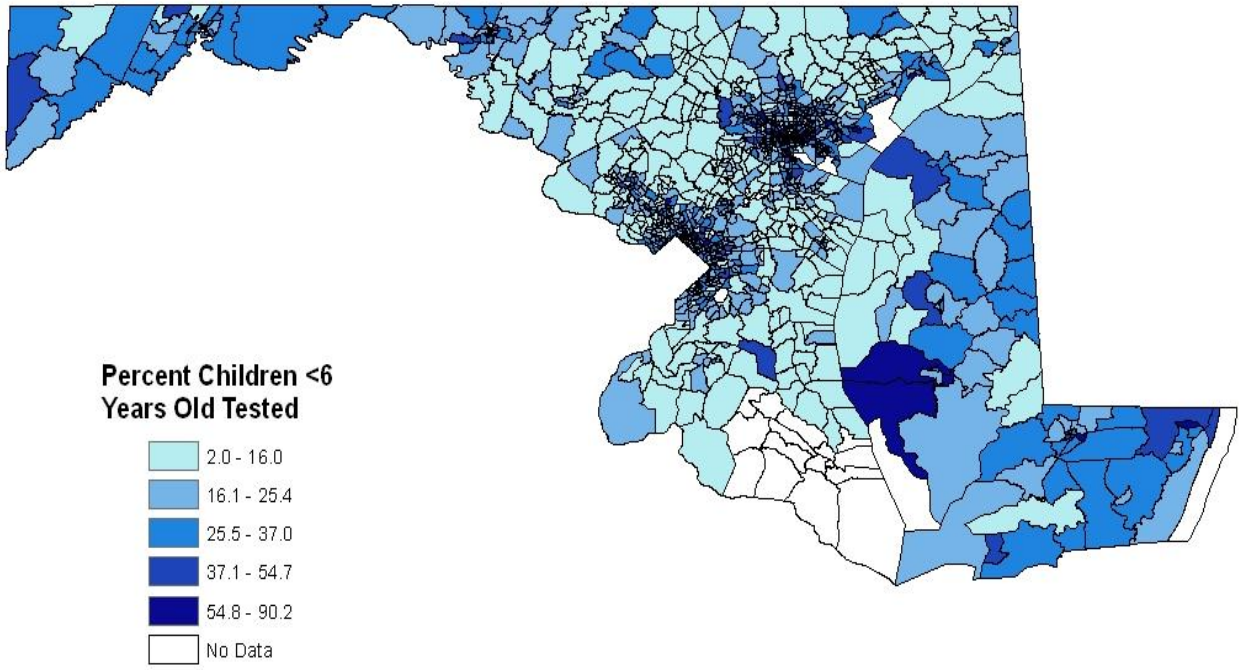


Figure A-4.1. Percent of Children <6 Years Old Tested, by Census Tract, Maryland 2005-2009

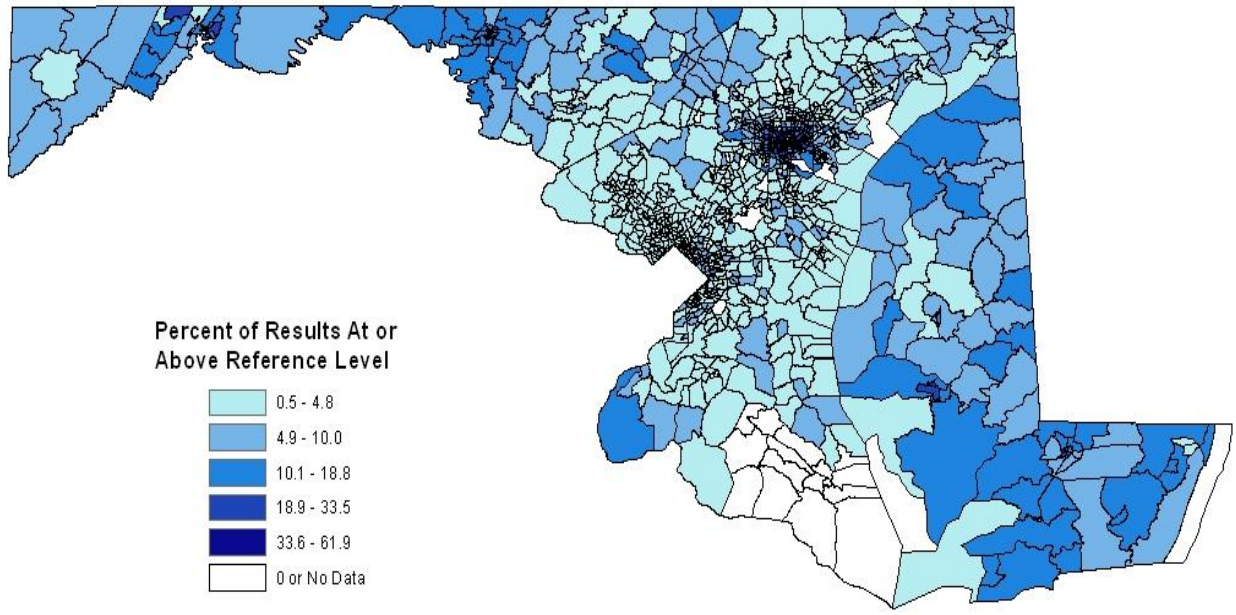


Figure A-4.2. Percent of Blood Lead Test Results ≥5 mcg/dL for Maryland Children <6 years old, by Census Tract, 2005-2009

Table A-4.3. Characteristics of Children Tested for Elevated Blood Lead Levels, by Year and Blood Lead Level, Maryland 2005-2009

Year	2005						2006						2007						2008						2009					
Blood Lead Level	≤ 4		5-9		10+		≤ 4		5-9		10+		≤ 4		5-9		10+		≤ 4		5-9		10+		≤ 4		5-9		10+	
	n	%	n	%	10+	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Individual Children :	103,243		8,428		1,515		104,886		9,692		1,344		109,688		7,546		963		112,598		5,523		772		114,313		4,947		606	
Sex																														
Female	49,815	48.3	3,881	46.0	670	44.2	50,593	48.2	4,504	46.5	589	43.8	53,111	48.4	3,384	44.8	399	41.4	54,961	48.8	2,485	45.0	343	44.4	55,422	48.5	2,267	45.8	251	41.4
Male	51,567	49.9	4,440	52.7	833	55.0	52,577	50.1	5,058	52.2	742	55.2	55,765	50.8	4,116	54.5	562	58.4	57,085	50.7	3,012	54.5	424	54.9	58,221	50.9	2,639	53.3	352	58.1
Unknown	1,861	1.8	107	1.3	12	0.8	1,716	1.6	130	1.3	13	1.0	812	0.7	46	0.6	2	0.2	552	0.5	26	0.5	5	0.6	670	0.6	41	0.8	3	0.5
Age (years)																														
<1	9,751	9.4	372	4.4	55	3.6	10,087	9.6	466	4.8	42	3.1	10,838	9.9	417	5.5	25	2.6	11,039	9.8	293	5.3	28	3.6	10,680	9.3	268	5.4	13	2.1
1	29,411	28.5	2,303	27.3	394	26.0	30,946	29.5	2,870	29.6	374	27.8	33,214	30.3	2,308	30.6	287	29.8	34,346	30.5	1,721	31.2	240	31.1	34,909	30.5	1,479	29.9	161	26.6
2	21,339	20.7	2,453	29.1	416	27.5	22,879	21.8	2,796	28.8	363	27.0	24,352	22.2	2,216	29.4	254	26.4	26,527	23.6	1,608	29.1	214	27.7	28,071	24.6	1,553	31.4	191	31.5
3	10,335	10.0	1,110	13.2	214	14.1	10,360	9.9	1,129	11.6	208	15.5	10,953	10.0	916	12.1	142	14.7	10,892	9.7	617	11.2	107	13.9	11,152	9.8	597	12.1	73	12.0
4	11,030	10.7	808	9.6	178	11.7	10,824	10.3	934	9.6	142	10.6	10,722	9.8	665	8.8	110	11.4	10,424	9.3	505	9.1	77	10.0	10,453	9.1	412	8.3	67	11.1
5	8,180	7.9	544	6.5	103	6.8	7,768	7.4	613	6.3	90	6.7	7,761	7.1	439	5.8	59	6.1	7,466	6.6	333	6.0	46	6.0	7,178	6.3	282	5.7	42	6.9
6-8	7,341	7.1	555	6.6	100	6.6	6,784	6.5	580	6.0	84	6.3	7,006	6.4	387	5.1	62	6.4	7,109	6.3	292	5.3	36	4.7	6,554	5.7	220	4.4	42	6.9
9-11	2,986	2.9	172	2.0	32	2.1	2,674	2.5	181	1.9	21	1.6	2,656	2.4	131	1.7	13	1.3	2,661	2.4	93	1.7	14	1.8	2,872	2.5	84	1.7	8	1.3
12-14	1,782	1.7	80	0.9	16	1.1	1,652	1.6	97	1.0	14	1.0	1,366	1.2	48	0.6	8	0.8	1,331	1.2	38	0.7	6	0.8	1,481	1.3	33	0.7	6	1.0
15-18	1,082	1.0	30	0.4	7	0.5	907	0.9	26	0.3	6	0.4	817	0.7	19	0.3	3	0.3	800	0.7	22	0.4	4	0.5	963	0.8	19	0.4	3	0.5
Race																														
White	16,716	16.2	1,169	13.9	124	8.2	18,787	17.9	1,476	15.2	133	9.9	24,151	22.0	1,295	17.2	131	13.6	26,073	23.2	1,031	18.7	118	15.3	26,849	23.5	1,019	20.6	100	16.5
Black	17,101	16.6	2,247	26.7	492	32.5	20,053	19.1	2,995	30.9	553	41.1	24,823	22.6	2,541	33.7	378	39.3	28,752	25.5	1,956	35.4	303	39.2	30,454	26.6	1,683	34.0	234	38.6
Other*	1,998	1.9	159	1.9	41	2.7	2,483	2.4	229	2.4	45	3.3	3,231	2.9	179	2.4	43	4.5	4,047	3.6	154	2.8	30	3.9	3,856	3.4	123	2.5	13	2.1
Unknown	67,428	65.3	4,853	57.6	858	56.6	63,563	60.6	4,992	51.5	613	45.6	57,483	52.4	3,531	46.8	411	42.7	53,726	47.7	2,382	43.1	277	35.9	53,154	46.5	2,122	42.9	259	42.7
Ethnicity																														
Hispanic	7,452	7.2	271	3.2	53	3.5	9,517	9.1	559	5.8	68	5.1	13,368	12.2	469	6.2	53	5.5	15,903	14.1	341	6.2	56	7.3	17,579	15.4	287	5.8	39	6.4
Non-Hispanic	28,160	27.3	3,018	35.8	670	44.2	33,245	31.7	4,139	42.7	728	54.2	42,527	38.8	3,367	44.6	532	55.2	49,427	43.9	2,529	45.8	452	58.5	53,507	46.8	2,538	51.3	383	63.2
Unknown	67,630	65.5	5,139	61.0	792	52.3	62,123	59.2	4,993	51.5	547	40.7	53,791	49.0	3,710	49.2	372	38.6	47,268	42.0	2,652	48.0	254	32.9	43,224	37.8	2,116	42.8	178	29.4
Race/Ethnicity																														
White, non-Hispanic	10,050	9.7	674	8.0	88	5.8	11,693	11.1	988	10.2	96	7.1	16,051	14.6	776	10.3	87	9.0	17,737	15.8	505	9.1	69	8.9	18,031	15.8	486	9.8	52	8.6
Black, non-Hispanic	13,246	12.8	1,777	21.1	398	26.3	15,868	15.1	2,512	25.9	483	35.9	20,262	18.5	2,094	27.7	333	34.6	24,021	21.3	1,597	28.9	259	33.5	25,529	22.3	1,375	27.8	194	32.0
Other*, non-Hispanic	1,222	1.2	96	1.1	22	1.5	1,435	1.4	132	1.4	29	2.2	1,896	1.7	96	1.3	24	2.5	2,555	2.3	75	1.4	15	1.9	2,528	2.2	82	1.7	9	1.5
Unknown, Non-Hispanic	3,642	3.5	471	5.6	162	10.7	4,249	4.1	507	5.2	120	8.9	4,318	3.9	401	5.3	88	9.1	5,114	4.5	352	6.4	109	14.1	7,419	6.5	595	12.0	128	21.1
Hispanic	7,452	7.2	271	3.2	53	3.5	9,517	9.1	559	5.8	68	5.1	13,368	12.2	469	6.2	53	5.5	15,903	14.1	341	6.2	56	7.3	17,579	15.4	287	5.8	39	6.4
Unknown	67,631	65.5	5,139	61.0	792	52.3	62,124	59.2	4,994	51.5	548	40.8	53,793	49.0	3,710	49.2	378	39.3	47,268	42.0	2,653	48.0	264	34.2	43,227	37.8	2,122	42.9	184	30.4
Year Child's Home Buil																														
Pre 1950	15,625	15.1	3,543	42.0	874	57.7	16,011	15.3	3,712	38.3	836	62.2	17,084	15.6	3,229	42.8	603	62.6	17,883	15.9	2,530	45.8	486	63.0	18,648	16.3	2,254	45.6	372	61.4
1950 to <1978	18,915	18.3	885	10.5	85	5.6	19,339	18.4	1,216	12.5	85	6.3	20,208	18.4	783	10.4	54	5.6	21,239	18.9	569	10.3	56	7.3	21,067	18.4	505	10.2	59	9.7
1978 or After	22,829	22.1	795	9.4	75	5.0	23,527	22.4	1,054	10.9	69	5.1	24,977	22.8	737	9.8	45	4.7	24,801	22.0	486	8.8	43	5.6	24,201	21.2	471	9.5	31	5.1
Unknown	45,874	44.4	3,205	38.0	481	31.7	46,009	43.9	3,710	38.3	354	26.3	47,419	43.2	2,797	37.1	261	27.1	48,675	43.2	1,938	35.1	187	24.2	50,397	44.1	1,717	34.7	144	23.8
Probable Rental Property**																														
Yes	15,624	15.1	2,604	30.9	619	40.9	16,260	15.5	2,840	29.3	602	44.8	17,386	15.9	2,396	31.8	418	43.4	18,577	16.5	1,887	34.2	318	41.2	19,375	16.9	1,664	33.6	256	42.2
No	44,255	42.9	2,852	33.8	458	30.2	45,185	43.1	3,407	35.2	423	31.5	47,381	43.2	2,557	33.9	316	32.8	48,077	42.7	1,855	33.6	288	37.3	47,368	41.4	1,709	34.5	222	36.6
Unknown	43,364	42.0	2,972	35.3	438	28.9	43,441	41.4	3,445	35.5	319	23.7	44,921	41.0	2,593	34.4	229	23.8	45,944	40.8	1,781	32.2	166	21.5	47,570	41.6	1,574	31.8	128	21.1
Child Resides in 2004 Target Area																														
Yes	56,998	55.2	6,765	80.3	1,322	87.3	58,600	55.9	7,556	78.0	1,185	88.2	60,804	55.4	6,029	79.9	855	88.8	62,825	55.8	4,571	82.8	671	86.9	64,629	56.5	4,084	82.6	515	85.0
No	45,990	44.5	1,639	19.4	191	12.6	46,270	44.1	2,134	22.0	159	11.8	48,870	44.6	1,515	20.1	108	11.2	49,707	44.1	947	17.1	101	13.1	49,667	43.4	863	17.4	91	15.0
Unknown	255	0.2	24	0.3	2	0.1	16	0.0	2	0.0	0	0.0	14	0.0	2	0.0	0	0.0	66	0.1	5	0.1	0	0.0	17	0.0	0	0.0	0	0.0

* Other Includes Asian/Pacific Islander, Native American/Alaskan and Multiracial

** Probable Rental Properties Identified as those properties in the DAT file where the Owner's Mailing address is not the Property Address

Targeting Strategy Option 1 (Target Testing Based on the Distribution of Blood Lead Levels in Children Tested between 2005-2009, by ZIP Code)

Estimating Expected Elevated Blood Lead Tests

There were 521,648 blood test results for children less than six years of age. When restricted to the single highest venous, unknown, or capillary test result (in that order) for each child, there were 396,951 individual test results from 2005-2009. In all cases, the highest venous test was used first. If no venous sample was available, the highest result from an unknown sample was used, and if no venous or unknown sample was available, the highest capillary blood lead test result for the given time period was retained. Of these, 78% were venous samples, the most accurate measure of blood lead level; 13% were capillary samples, the least accurate relative to venous tests; and 9% were unknown. An additional 362 records missing ZIP codes were excluded, leaving 396,588 test records for individual children from 595 unique ZIP codes throughout the state.

To calculate the number of children less than six years of age living in each ZIP code by year, annual intercensal estimates were calculated for each ZIP code using the U.S. Census for 2000 and 2010. This resulted in annual population estimates for 450 ZIP codes in the State. These estimates were merged with the aggregated number of tests per ZIP code, producing annual blood lead testing counts and estimated population counts for 450 ZIP codes in the State. A total of 1,991 blood lead tests in the CLR data could not be matched with a corresponding ZIP code and were excluded from further analyses. These ZIP codes may have been added by the U.S. Postal Service after the year 2000, or they may have been incorrectly entered into the STELLAR database and were not valid. For the ZIP codes included in analysis, the percentage of test results greater than, or equal to, the reference level of 5 mcg/dL among children less than 6 years of age ranged from 0.6 to 50% (Figure A-4.3).

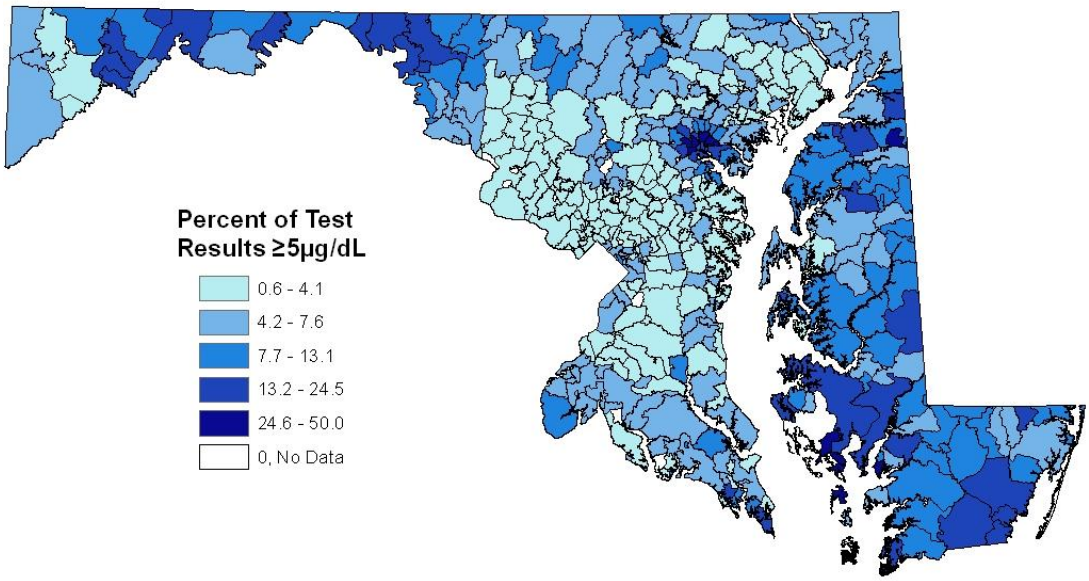


Figure A-4.3. Percent of Blood Lead Test Results ≥5 mcg/dL for Maryland Children <6 years old, by ZIP Code, 2005-2009

An estimate of the total number of children less than six years of age in MD with an elevated blood lead test was computed by applying the observed percentage of test results with levels at or above the reference level in each ZIP code from 2005-2009 to the total population of children in that ZIP code. Based on this analysis, an estimated 28,012 children were expected to have a blood lead level at or above the reference level of 5 mcg/dL. ZIP codes containing a cumulative 90%, 75% and 50% of the expected children with blood lead levels above reference in the State were identified as potential "at risk" areas. Depending on the risk area definition considered, 14,101 to 25, 342 of these children were captured in the identified ZIP code risk areas.

Identifying At Risk ZIP Codes

There were 173 "at risk" ZIP codes identified which would be expected to contain 90% of the children less than six years of age with blood lead levels at, or above, the reference level of 5 mcg/dL (Figure A-4.4, Table A-7.1). The observed percentage of test results at, or above, the reference level from 2005-2009 in these ZIP codes ranged from 1.7% to 38.6% and the total ZIP code populations ranged from 305 to 5,525 children under six years of age. Decreasing the percentage of children to 75% of those children expected to have blood lead levels at, or above, the reference level decreased the number of "at risk" ZIP codes to 95 (Figure A-4.5, Table A-7.2). The observed percentage of test results at, or above, the reference level ranged from 2.1% to 38.6% in these ZIP codes, and the total population of children less than six years of age ranged from 531 to 5,525. If the goal were to identify the "at risk" areas containing 50% of the children expected to have blood lead levels at, or above, the reference level of 5 mcg/dL, 32 ZIP codes were identified (Figure A-4.6, Table A-7.3). The observed percentage of children with test

results at, or above, the reference level ranged from 4.7 to 38.6%, and the total population of children less than six years of age ranged from 1,067 to 5,051 in these ZIP codes.

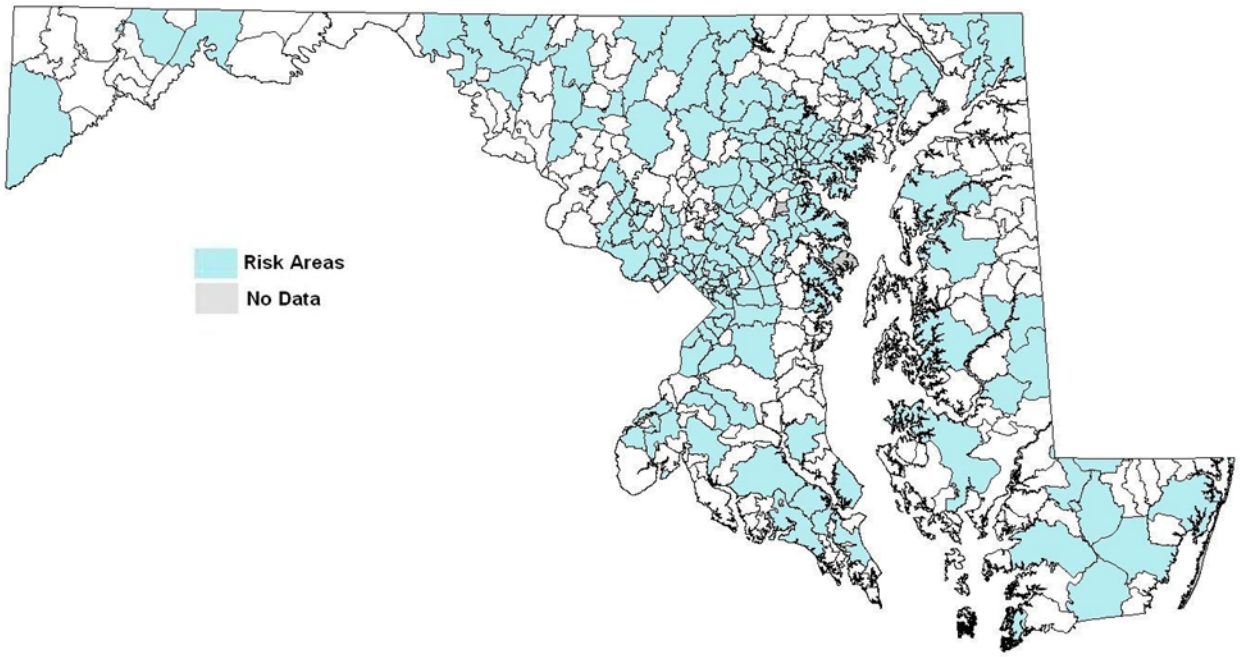


Figure A-4.4. ZIP Codes Capturing a Cumulative 90% of Children Expected to Have a Blood Lead Level ≥5 mcg/dL, Maryland

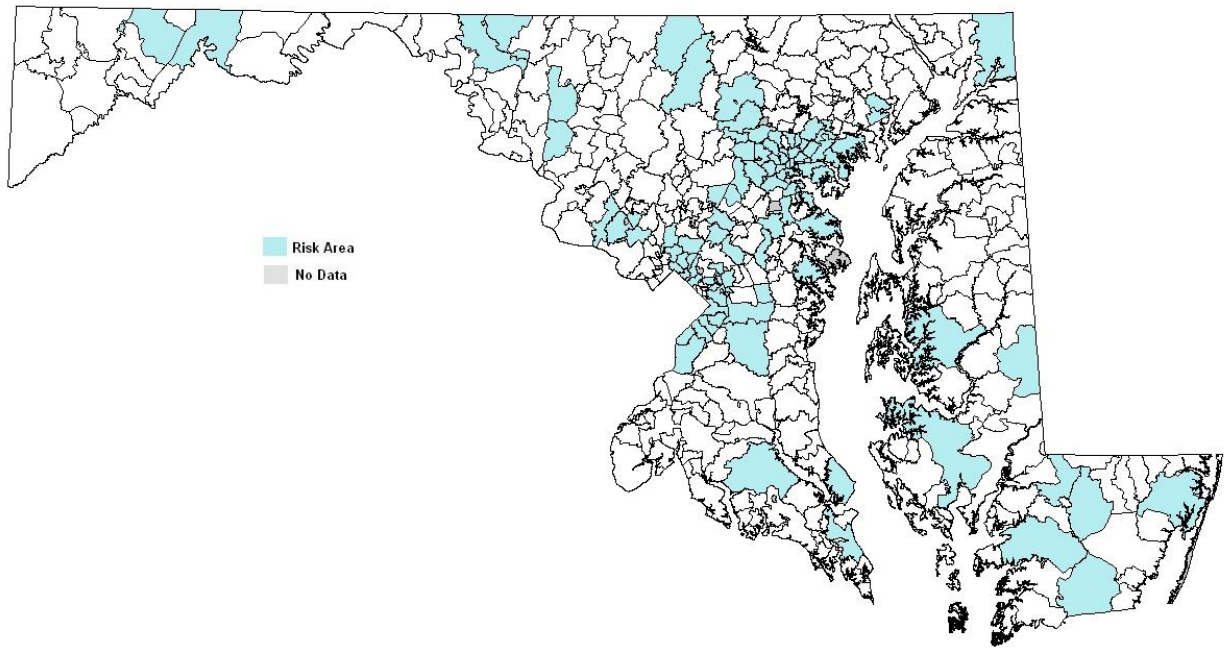


Figure A-4.5. ZIP Codes Capturing a Cumulative 75% of Children Expected to Have a Blood Lead Level ≥5 mcg/dL, Maryland

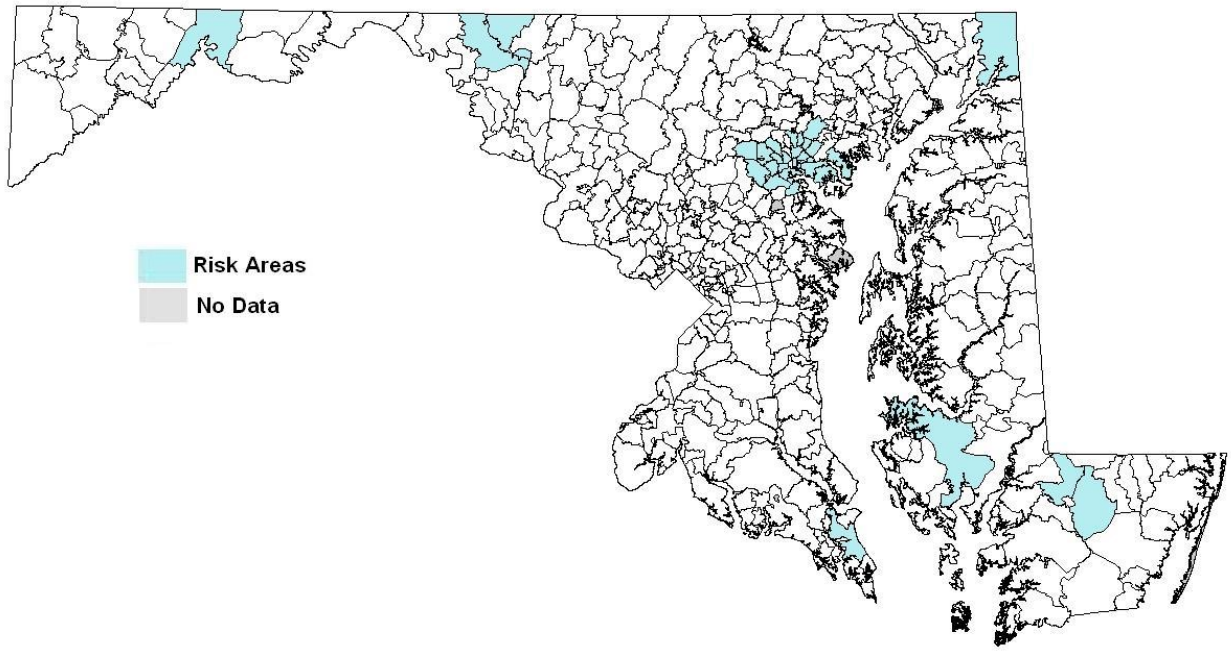


Figure A-4.6. ZIP Codes Capturing a Cumulative 50% of Children Expected to Have a Blood Lead Level ≥5 mcg/dL, Maryland

Comparison of At Risk and Non-Risk Areas

In all cases (90%, 75% and 50% capture areas), more children tested from "at risk" areas were: black (23%, 25%, 26%); resided in properties built before 1950 (16%, 19%, 34%); and resided in a probable rental properties (16%, 17%, 23%; Tables A-4.4, A-4.5, A-4.6). All of these characteristics were significantly associated with residence in a "risk area." Results of Chi-Square analyses are summarized in Table A-4.7. Limited demographic information from the U.S. Census Bureau was included for further comparison of the risk and non-risk ZIP codes (Tables A-7.4, A-7.5, A-7.6). Risk areas had a higher percentage of black residents and renter-occupied housing compared to non-risk areas.

Table A-4.4. Characteristics of Tested Children from Risk (90% of Expected) and Non-Risk Areas, Maryland 2005-2009

Characteristics	90% Expected		Outside Area	
	n	%	n	%
Total Children Tested 05-09	349,983	88.4	44,614	11.6
Characteristics of Children in Area				
Sex				
Female	169,998	48.6	21,419	48.0
Male	176,084	50.3	22,529	50.5
Unknown	3,901	1.1	666	1.5
Age (years)				
<1	34,415	9.8	4,436	9.9
1	112,489	32.1	15,386	34.5
2	91,582	26.2	11,655	26.1
3	39,382	11.3	4,473	10.0
4	41,040	11.7	4,608	10.3
5	31,069	8.9	4,053	9.1
Median Age	2.0	-	2.0	-
Race				
White	67,833	19.4	17,241	38.6
Black	80,234	22.9	4,085	9.2
Other*	10,388	3.0	1,032	2.3
Unknown	191,528	54.7	22,256	49.9
Ethnicity				
Hispanic	38,473	11.0	2,431	5.4
Non-Hispanic	131,872	37.7	17,557	39.4
Unknown	179,638	51.3	24,626	55.2
Year Child's Home Built				
Pre 1950	57,566	16.4	4,240	9.5
1950 to <1978	62,005	17.7	8,246	18.5
1978 or After	75,054	21.4	15,119	33.9
Unknown	155,358	44.4	17,009	38.1
Median Year Built	1965	-	1982	-
Probable Rental Property**				
Yes	56,832	16.2	4,885	10.9
No	146,604	41.9	22,817	51.1
Unknown	146,547	41.9	16,912	37.9
Sample Type				
Capillary	43,919	12.5	7,980	17.9
Venous	276,552	79.0	32,616	73.1
Unknown	29,512	8.4	4,018	9.0
Blood Lead Levels				
≤ 4	322,359	92.1	42,430	95.1
5 - 9	24,299	6.9	2,023	4.5
≥10	3,325	1.0	161	0.4

*Other = Sum of Other, Indian/Alaskan, Hawaiian/Pacific Islander and Multiple Race.

** Probable Rental Property = property assumed to be rental because the owner of the property resided at a different address than the property.

Table A-4.5. Characteristics of Tested Children from Risk (75% of Expected) and Non-Risk Areas, Maryland 2005-2009

Characteristics	75% Expected Cases		Outside Area	
	n	%	n	%
Total Children Tested 05-09	266,627	67.6	127,970	32.4
Characteristics of Children in Area				
Sex				
Female	129,654	48.6	61,763	48.3
Male	134,120	50.3	64,493	50.4
Unknown	2,853	1.1	1,714	1.3
Age (years)				
<1	24,294	9.1	14,577	11.4
1	86,163	32.3	41,712	32.6
2	70,734	26.5	32,503	25.4
3	30,275	11.4	13,580	10.6
4	31,525	11.8	14,123	11.0
5	23,632	8.9	11,490	9.0
Median Age	2.0	-	2.0	-
Race				
White	44,074	16.5	41,000	32.0
Black	67,109	25.2	17,210	13.4
Other*	7,343	2.8	4,077	3.2
Unknown	148,101	55.5	65,683	51.3
Ethnicity				
Hispanic	29,952	11.2	10,952	8.6
Non-Hispanic	99,211	37.2	50,218	39.2
Unknown	137,464	51.6	66,795	52.2
Year Child's Home Built				
Pre 1950	49,883	18.7	11,923	9.3
1950 to <1978	44,503	16.7	25,748	20.1
1978 or After	44,894	16.8	45,279	35.4
Unknown	127,347	47.8	45,020	35.2
Median Built Year	1958	-	1981	-
Probable Rental Property**				
Yes	45,788	17.2	15,929	12.4
No	100,831	37.8	68,590	53.6
Unknown	120,008	45.0	43,451	34.0
Sample Type				
Capillary	29,987	11.2	21,912	17.1
Venous	214,251	80.4	94,917	74.2
Unknown	22,389	8.4	11,141	8.7
Blood Lead Levels				
≤ 4	242,505	91.0	122,284	95.6
5 - 9	21,028	7.9	5,294	4.1
≥10	3,094	1.2	392	0.3

*Other = Sum of Other, Indian/Alaskan, Hawaiian/Pacific Islander and Multiple Race.

** Probable Rental Property = property assumed to be rental because the owner of the property resided at a different address than the property.

Table A-4.6. Characteristics of Tested Children from Risk (50% of Expected) and Non-Risk Areas, Maryland 2005-2009

Characteristics	50% Expected Cases		Outside Area	
	n	%	n	%
Total Children Tested 05-09	109,930	27.9	284,667	72.1
Characteristics of Children in Area				
Sex				
Female	53,336	48.5	138,081	48.5
Male	55,238	50.2	143,375	50.4
Unknown	1,356	1.2	3,211	1.1
Age (years)				
<1	6,993	6.4	31,858	11.2
1	37,054	33.7	90,821	31.9
2	32,098	29.2	71,139	25.0
3	12,673	11.5	31,182	11.0
4	11,923	10.8	33,725	11.8
5	9,188	8.4	25,934	9.1
Median Age	2.0	-	2.0	-
Race				
White	21,972	20.0	63,102	22.2
Black	28,702	26.1	55,617	19.5
Other*	2,152	2.0	9,268	3.3
Unknown	57,104	51.9	156,680	55.0
Ethnicity				
Hispanic	3,603	3.3	37,301	13.1
Non-Hispanic	41,646	37.9	107,783	37.9
Unknown	64,681	58.8	139,583	49.0
Year Child's Home Built				
Pre 1950	37,009	33.7	24,797	8.7
1950 to <1978	11,170	10.2	59,081	20.8
1978 or After	8,066	7.3	82,107	28.8
Unknown	53,685	48.8	118,682	41.7
Median Built Year	1930	-	1977	-
Probable Rental Property**				
Yes	25,635	23.3	36,082	12.7
No	33,095	30.1	136,326	47.9
Unknown	51,200	46.6	112,259	39.4
Sample Type				
Capillary	12,779	11.6	39,120	13.7
Venous	86,788	78.9	222,380	78.1
Unknown	10,363	9.4	23,167	8.1
Blood Lead Levels				
≤ 4	92,476	84.1	272,313	95.7
5 - 9	14,911	13.6	11,411	4.0
≥10	2,543	2.3	943	0.3

*Other = Sum of Other, Indian/Alaskan, Hawaiian/Pacific Islander and Multiple Race.
** Probable Rental Property = property assumed to be rental because the owner of the property resided at a different address than the property.

Table A-4.7. Chi-Square (X^2) Analysis, Comparison of Demographic Characteristics of Risk and Non-Risk Areas for 3 Proposed Risk-Area Definitions (90%, 75%, and 50% Capture Areas)

Risk Area Definition	Statistics	Race	Ethnicity	Year Home Built	Rental Property
Area Capturing 90% of Expected	X^2	9418.21	1151.86	3352.29	1322.14
	*df**	2	1	2	1
	p value	<.0001	<.0001	<.0001	<.0001
Area Capturing 75% of Expected	X^2	14483.70	687.22	15008.98	4200.17
	*df**	2	1	2	1
	p value	<.0001	<.0001	<.0001	<.0001
Area Capturing 50% of Expected	X^2	2015.29	6438.84	55137.43	11554.68
	*df**	2	1	2	1
	p value	<.0001	<.0001	<.0001	<.0001

*df, degrees of freedom

Targeting Strategy Option 2 (Target Testing Based on Updated Maryland Targeting Model)

The second option for a targeting strategy, an update of the targeting model used in the 2000 and 2004 MD lead targeting plans, was based on census tracts rather than ZIP codes. The U.S. Census demographic variables from the American Community Survey (ACS) used in the model were not available at the ZIP code level for the time period of interest (2005-2009). Census tracts were excluded from the analysis if the records contained either "0" or had no data (i.e., missing) for the number of households (n=23), number of families (n=28), number of houses (n=23), or number of children less than 6 years old (n=31). Census tracts were also excluded from if the median housing value was $0 or missing (n=39). After these census tracts were removed, 1,179 census tracts were retained for analysis.

Lead testing data from the CLR excluded children who did not live in the State and children six years of age or older. In addition, if a child was tested more than once in a single year, only the highest test result was used, as noted in previous sections. An additional 10% of remaining records were excluded because they could not be geocoded and, therefore, residential census tract was unknown. This data set was then used to determine the total number of tests for individual children per year per census tract (5-year total, n=469,603 tests) and the total number of individual children tested during the 5-year period per census tract (n=355,740 children). In all cases, the highest venous test was used first. If no venous sample was available, the highest result from an unknown sample was used, and if no venous or unknown sample was available, the highest capillary blood lead test result for the given time period was retained.

When merged by census tract, the CLR and U.S. Census data had 1,179 census tracts in common (Table A-4.8). The merged data set contained 12 census tracts in which the average annual testing rate from 2005-2009 exceeded 100% or was less than 1%. In areas where very

few children are tested, the proportion of test results at or above the reference level is based on a small number of test results and is highly influenced by a single test result. A testing rate greater than 100% indicates that more children were tested in a given census tract than were reported to be living there according to the 2005-2009 ACS. Areas with a testing rate exceeding 100% are likely due to address misclassification or some other error. The proportion of children with a blood lead level at or above the reference level (outcome of interest) is unreliable for census tracts with extremely high or low testing rates; therefore these 12 census tracts, containing 2,381 children tested, were excluded from further analysis. After cleaning and variable preparation 1,167 census tracts, including a total of 346,201 test results for individual children, were retained for analysis (Table A-4.9).

Analysis of Lead Testing Data

The average annual testing rates for children in the 1,179 census tracts ranged from 2 to 90% (Table A-4.8). In a majority of census tracts (46%), the testing rates were 20% or less of the children in the census tract. Table A-4.9 shows the distribution of blood lead levels for 346,201 individual children less than six years of age with known census tracts of residence who were tested for blood lead in MD from 2005-2009.

Table A-4.8. Number of Census Tracts in the Analysis Data Set by Percent of Children Tested, Maryland 2005-2009

Percent of Children Screened	Number of Census Tracts	Percent of Census Tracts
0 to 0.9	2*	0.2
1 to 20	536	45.5
21 to 40	499	42.3
41 to 60	98	8.3
61 to 80	27	2.3
81 to 100	7	0.6
Over 100	10*	0.8

* Excluded from further analyses

Table A-4.9. Number of Individual Children < 6 Years Old Tested per Year, by Blood Lead Level, in the 1,167 Census Tracts Included in Models, Maryland, 2005-2009

Pb Result	Year of Blood Lead Test					Total Children Screened
	2005	2006	2007	2008	2009	
0-4	59,130	58,661	61,517	62,843	77,940	320,091
5-9	5,712	6,254	4,576	3,214	3,252	23,008
10+	1,017	751	528	428	378	3,102
Total	65,859	65,666	66,621	66,485	81,570	346,201

* Highest BLL per Child from 2005-2009. The highest BLL from a venous sample, if no venous then unknown sample type, if no unknown then capillary sample result retained

From 2005-2009, a total of 26,110 individual children tested had a blood lead level at or above the CDC reference level of 5 mcg/dL, of whom 3,102 (12%) had a blood lead level of 10 mcg/dL or greater. Of the 1,167 census tracts included in the analysis, 1,156 (99%) had at least one child with a blood lead level of 5 mcg/dL or above, and 11 (0.9%) census tracts did not have any reported children with a blood lead level at or above reference (Table A-4.10).

Table A-4.10. Census Tracts by Number of Individual* Children with a Blood Lead Level ≥5 mcg/dL, Maryland 2005-2009

Number of Blood Lead Test Results ≥5 mcg/dL	Number of Census Tracts in Model	Total Children With Blood Lead Levels ≥5 mcg/dL, 2005-2009	Total Children <6 Years Old In Tracts**
0	11	0	1,946
1 to 50	1,031	14,444	384,831
51 to 100	84	5,890	33,560
101 to 150	33	4,114	10,968
151 to 200	4	735	1,108
201 to 250	3	643	902
251 to 300	1	284	230
Total	1,167	26,110	433,545

* Highest annual BLL per Individual Child from 2005-2009. The highest BLL from a venous sample, if no venous then unknown sample type, if no unknown then capillary sample result retained.

** Total population of children per census tract based on the 2005-2009 American Community Survey 5-Year Estimate

Many of the covariates were strongly and positively correlated with each other, as might be expected (Table A-4.11). Because many of the covariates were markers of poverty, the percentage of families below poverty level with children less than five years old, percentage of female-headed households with children less than six, and percentage of households with public assistance income were combined into a single poverty scale to be included in the model (as in Sargent, 1995 and Center for Health Development and Management, 2000).

Table A-4.11. Pearson's Correlation Coefficient Values* for Data Set Covariates

	% Female Headed House	% Public Assist. Income	% Families in Poverty	Median House Value	% Houses Pre 50	% Houses 50-79	% Black	% Rental	% Vacant	Median Income	% Screened	% Results ≥5µg/dL
% Female Headed House	-	0.33 <.0001	0.43 <.0001	-0.34 <.0001	0.17 <.0001	0.02 0.4803	0.37 <.0001	0.47 <.0001	0.26 <.0001	-0.42 <.0001	0.16 <.0001	0.28 <.0001
% Public Assist. Income	0.33 <.0001	-	0.46 <.0001	-0.44 <.0001	0.43 <.0001	-0.09 0.0016	0.45 <.0001	0.42 <.0001	0.50 <.0001	-0.48 <.0001	0.34 <.0001	0.62 <.0001
% Families in Poverty	0.43 <.0001	0.46 <.0001	-	-0.38 <.0001	0.36 <.0001	-0.07 0.0107	0.30 <.0001	0.43 <.0001	0.43 <.0001	-0.45 <.0001	0.17 <.0001	0.50 <.0001
Median House Value	-0.34 <.0001	-0.44 <.0001	-0.38 <.0001	-	0.39 <.0001	0.03 0.2943	-0.41 <.0001	-0.39 <.0001	-0.39 <.0001	0.79 <.0001	-0.41 <.0001	-0.51 <.0001
% Pre 50 House	0.17 <.0001	0.43 <.0001	0.36 <.0001	-0.39 <.0001	-	-0.34 <.0001	0.14 <.0001	0.24 <.0001	0.48 <.0001	-0.41 <.0001	0.41 <.0001	0.69 <.0001
% 50-79 house	0.02 0.4803	-0.09 0.002	-0.07 0.01	0.03 0.29	-0.34 <.0001	-	0.10 0.0004	0.06 0.0450	-0.26 <.0001	-0.03 0.2503	0.06 0.0267	-0.28 <.0001
% Black	0.37 <.0001	0.45 <.0001	0.30 <.0001	-0.41 <.0001	0.14 <.0001	0.10 0.0004	-	0.43 <.0001	0.31 <.0001	-0.41 <.0001	0.34 <.0001	0.43 <.0001
% Rental	0.47 <.0001	0.42 <.0001	0.43 <.0001	-0.39 <.0001	0.24 <.0001	0.06 0.0450	0.43 <.0001	-	0.37 <.0001	-0.63 <.0001	0.34 <.0001	0.34 <.0001
% Vacant	0.26 <.0001	0.50 <.0001	0.43 <.0001	-0.39 <.0001	0.48 <.0001	-0.26 <.0001	0.31 <.0001	0.37 <.0001	-	-0.47 <.0001	0.37 <.0001	0.66 <.0001
Median Income	-0.42 <.0001	-0.48 <.0001	-0.45 <.0001	0.79 <.0001	-0.41 <.0001	-0.03 0.2503	-0.41 <.0001	-0.63 <.0001	-0.47 <.0001	-	-0.46 <.0001	-0.52 <.0001
% Screened	0.16 <.0001	0.34 <.0001	0.17 <.0001	-0.41 <.0001	0.41 <.0001	0.06 0.0267	0.34 <.0001	0.34 <.0001	0.37 <.0001	-0.46 <.0001	-	0.46 <.0001
% Results ≥5µg/dL	0.28 <.0001	0.62 <.0001	0.50 <.0001	-0.51 <.0001	0.69 <.0001	-0.28 <.0001	0.43 <.0001	0.34 <.0001	0.66 <.0001	-0.52 <.0001	0.46 <.0001	-

* Pearson's r value (correlation coefficient) is a measure of association indicating the degree to which two variables have a linear relationship, in which one variable varies directly with the other. This value, r, ranges from -1 to +1 with +1 representing a perfect positive linear relationship, and -1 representing a perfect negative linear relationship.

The outcome measure for the logistic regression model was "at risk" or "non-risk" census tract. Because no standard definition of an "at risk" census tract was identified considering the reference level of 5 mcg/dL, four possible definitions were evaluated based on the distribution of blood lead levels at or above reference in Maryland. Census tracts were defined as "at risk" if the percentage of blood lead test results greater than or equal to 5 mcg/dL was at or above the 25th (3%), 50th (5%), 75th (9%), and 90th (17%) percentiles. These represented four different outcome variables. The characteristics of risk and non-risk areas for each of these definitions were then compared (Table A-4.12). Results from the two sample t-test indicated that all measured characteristics of the risk and non-risk tracts were significantly different ($p<0.05$) across all outcome measures (data not shown).

Crude ORs and adjusted ORs for testing rates were calculated for each of the four outcome measures identified; each of the covariates was statistically significant across the

different outcome measures (Table A-4.13). Similar to the findings in earlier versions of the Maryland Lead Targeting Plan, census tracts with a higher percentage of pre-1950 housing still showed a strong association with risk, and the magnitude of the correlation increased as the outcome measure (the proportion of lead tests above the reference level of 5 mcg/dL) increased. Census tracts with greater than 18% old (pre-1950) housing were 6 times more likely to have at least 3% (25th percentile) of lead test results at or above the reference level, 14 times more likely to have at least 5% (50th percentile) of test results at or above reference, and 62 times more likely to have at least 9% (75th percentile) of test results at or above reference compared to census tracts with less than 5% old housing, adjusted for testing rates.

Table A-4.12. Select Census Tract Characteristics, Risk** Compared to Non-Risk Tracts, Maryland 2005-2009

	All Census Tracts	Outcome 1 ≥3% of Tests At or Above CDC Reference† (25th Percentile)		Outcome 2 ≥5% of Tests At or Above CDC Reference (50th Percentile)		Outcome 3 ≥9% of Tests At or Above CDC Reference (75th Percentile)		Outcome 4 ≥17% of Tests At or Above CDC Reference (90th Percentile)	
Characteristics		Non-Risk	Risk	Non-Risk	Risk	Non-Risk	Risk	Non-Risk	Risk
n children ‡	*433,545*	143,293	290,252	273,482	160,063	357,931	75,614	405,868	27,677
total n (%) tracts	*1,167*	*314 (27%)*	*853 (73%)*	*636 (55%)*	*531 (45%)*	*888 (76%)*	*279 (24%)*	*1,052 (90%)*	*115 (10%)*
Median House Value ($)	293,100	372,050	255,700	356,050	213,200	337,300	160,900	315,750	99,800
Median Income ($)	66,797	88,026	59,137	81,053	51,383	75,919	41,098	71,049	31,319
% Rental Properties	31.0	25.2	33.1	26.7	36.1	27.1	43.3	28.7	51.4
% Vacant Properties	9.0	5.1	10.4	5.7	12.9	6.4	17.4	7.3	24.7
% Poverty	3.9	2.0	4.6	2.2	5.9	2.4	8.5	2.9	12.8
% Female Headed Households	3.4	2.4	3.8	2.6	4.3	2.8	5.4	3.0	6.6
% Housing built before 1950	23.0	10.8	27.4	12.3	35.8	15.0	48.3	18.6	63.2
% Housing built 1950-1979	43.0	45.4	42.2	46.3	39.1	45.8	34.2	44.8	26.6
% Residents Black	30.9	15.7	35.4	23.9	39.2	25.4	48.4	26.7	68.6
% Public Assistance Income	2.1	1.0	2.5	1.1	3.3	1.3	4.6	1.6	6.9
% Tested	25.0	19.1	27.2	20.8	30.0	22.0	34.6	23.2	41.7

* Mean values presented, unless otherwise indicated

** Similar to the approach used in prior publications (CDC, 1997), 'Risk" is designated based on a percentage of tests at or above the reference. The prior studies were based on the action level of 10µg/dL and so we assess several levels. Based on CDC 1997 recommendations, tracts with ≥ 12% of blood lead test results ≥ 10 µg/dL were considered high risk areas for lead exposure and poisoning in children

† The CDC Reference level is 5 µg/dL

‡ Number of Children ≤5 years old from the 2005-2009 American Community Survey

Table A-4.13. Community Characteristics by Adjusted‡ Odds Ratios, for 4 Possible of Risk Area Definitions (≥3%, ≥5%, ≥9% and ≥17% of Test Results ≥5 mcg/dL)

Census Tract Characteristics	Aggregated Groups	Number of Tracts	Number of Children ≤5 Years Old in Population	Outcome 1 ≥ 3% of Tests ≥5µg/dL (25th Percentile)		Outcome 2 ≥ 5% of Tests ≥5µg/dL (50th Percentile)		Outcome 3 ≥ 9% of Tests ≥5µg/dL (75th Percentile)		Outcome 4 ≥ 17% of Tests ≥5µg/dL (90th Percentile)	
				Odds Ratio	(95% CI)	Odds Ratio	(95% CI)	Odds Ratio	(95% CI)	Odds Ratio	(95% CI)
Percent of Rental Units	0 - 16.3	394	144,318	1.00		1.00		1.00		1.00	
	16.4 - 38.4	372	144,252	1.18	0.86 , 1.62	1.50 *	1.10 , 2.04	2.80 **	1.76 , 4.44	6.42 *	1.88 , 21.96
	38.5 - 97.7	401	144,975	1.61 *	1.13 , 2.29	1.99 **	1.46 , 2.72	5.41 **	3.48 , 8.40	20.70 **	6.38 , 67.18
Percent of Vacant Housing Units	0 - 3.9	357	143,877	1.00		1.00		1.00		1.00	
	4.0 - 7.6	345	145,081	1.08	0.79 , 1.49	1.27	0.91 , 1.76	2.01 *	1.16 , 3.51	5.17	0.58 , 45.97
	7.7 - 85.7	465	144,587	2.58 **	1.81 , 3.67	4.05 **	2.95 , 5.55	9.78 **	6.01 , 15.92	84.34 **	11.37 , 625.61
Percent Families Below Poverty w/ Children ≤ 5	0	493	157,170	1.00		1.00		1.00		1.00	
	0.1 - 4.9	371	165,498	1.08	0.80 , 1.46	1.02	0.76 , 1.36	1.19	0.80 , 1.77	1.98	0.92 , 4.27
	5.0 - 77.7	303	110,877	2.33 **	1.58 3.42	2.89 **	2.11 , 3.95	4.77 **	3.33 , 6.84	12.92 **	6.80 , 24.53
Percent Female Headed Households w/ Children < 6	0 - 1	436	143,957	1.00		1.00		1.00		1.00	
	1.1 - 3.7	338	144,778	1.12	0.82 , 1.55	0.92	0.68 , 1.25	0.94	0.62 , 1.43	1.19	0.60 , 2.38
	3.8 - 41.4	393	144,810	1.92 *	1.37 , 2.70	1.97 **	1.47 , 2.65	2.90 **	2.04 , 4.12	4.30 **	2.46 , 7.49
Percent Housing Units Built from 1950 to 1979	1.4 - 29.8	350	144,430	1.00		1.00		1.00		1.00	
	29.9 - 50.2	413	144,417	1.54 *	1.09 , 2.18	1.00	0.73 , 1.35	0.58 *	0.41 , 0.83	0.31 **	0.19 , 0.51
	50.3 - 96.6	404	144,698	0.70 *	0.50 , 0.97	0.35 **	0.25 , 0.48	0.14 **	0.09 , 0.22	0.02 **	0.01 , 0.06
Percent Housing Units Built Before 1950	0 - 4.9	291	144,284	1.00		1.00		1.00		1.00	
	5.0 - 18.1	348	144,596	1.69 *	1.22 , 2.34	2.55 **	1.69 , 3.85	5.35 *	1.57 , 18.24	†	--
	18.2 - 91.7	528	144,665	5.51 **	3.79 , 8.01	13.60 **	9.13 , 20.25	61.82 **	19.47 , 196.33	†	--
Median Value of Housing Units	Low - 258,700	479	143,927	1.00		1.00		1.00		1.00	
	258,701 -	343	145,113	0.22 **	0.14 , 0.33	0.16 **	0.12 , 0.22	0.14 **	0.09 , 0.21	0.04 **	0.01 , 0.12
	368,801 - High	345	144,505	0.14 **	0.10 , 0.22	0.10 **	0.07 , 0.14	0.07 **	0.04 , 0.12	0.02 *	0.00 , 0.15
Percent of Black Population	0 - 9.8	433	144,491	1.00		1.00		1.00		1.00	
	9.9 - 34.3	344	144,175	0.89	0.65 , 1.21	0.83	0.61 , 1.13	1.09	0.73 , 1.63	0.80	0.35 , 1.82
	34.4 - 100	390	144,879	2.30 **	1.58 , 3.35	1.53 *	1.13 , 2.08	2.43 **	1.69 , 3.48	5.29 **	2.89 , 9.66
Percent On Public Assist Income	0 - 0.5	388	144,203	1.00		1.00		1.00		1.00	
	0.6 - 1.8	353	144,809	1.39 *	1.02 , 1.91	1.94 **	1.41 , 2.67	1.30	0.81 , 2.08	2.43	0.80 , 7.38
	1.9 - 24.4	426	144,533	2.66 **	1.87 , 3.79	3.68 **	2.69 , 5.03	5.79 **	3.88 , 8.64	17.06 **	6.70 , 43.45
Median Household Income	Low - 59,610	469	144,048	1.00		1.00		1.00		1.00	
	59,611-	366	143,688	0.20 **	0.13 , 0.30	0.21 **	0.16 , 0.29	0.14 **	0.10 , 0.21	0.02 **	0.01 , 0.10
	86,453 - High	332	145,809	0.11 **	0.07 , 0.17	0.09 **	0.06 , 0.14	0.03 **	0.01 , 0.06	†	--

* p<.05

** p<.0001

† '0' cells in the tables therefore OR cannot be calculated

‡ Adjusted for percentage of children screened

The Model

Based on these analyses and the 2000 and 2004 Maryland Targeting Models, the 2013 Maryland Models include the following variables: percentage of pre-1950 housing, median housing value, the constructed poverty scale, the percentage of homes built from 1950-1979 and the average annual percentage of children tested. Models were prepared for each of the four outcome variables described (Table A-4.14). For the more restrictive outcome measures, where risk areas were defined by increasing percentages of tests above the reference level, the area under the ROC curve, Hosmer-Lemeshow test, Somers' D statistic, AIC and SC were all indicative of a better fitting model. Characteristics of the risk and non-risk tracts generally became more homogeneous within each group as the definition of risk area became more restrictive.

Table A-4.14. Comparison of Possible 2013 Maryland Targeting Plan Models

Model Variables	2000 Model* "Original"		Outcome 1 (≥3% Tests ≥RL*)		Outcome 2 (≥5% Tests ≥RL)		Outcome 3 (≥9% Tests ≥RL)		Outcome 4 (≥17% Tests ≥RL)	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
Percent Pre 1950 Housing	0.0162	0.0001	0.0369	<.0001	0.0458	<.0001	0.0488	<.0001	0.0724	<.0001
Poverty Scale	0.5229	0.0001	0.2076	0.2121	0.2992	0.0362	0.7182	<.0001	1.0174	<.0001
Median Housing Value	-0.0114	0.0001	-4.15E-06	<.0001	-0.000007	<.0001	-0.00000869	<.0001	-0.00001	<.0001
Percent 1950-1979 Housin	0.00206	0.0381	-0.00453	0.2124	-0.01260	0.0018	-0.0201	0.0019	-0.0216	0.2320
Percent of Screening	0.0389	0.0001	0.0170	0.0235	0.0121	0.0653	0.0285	0.0004	0.0489	<.0001
Intercept	-4.7097	0.0001	1.6512	<.0001	1.2534	0.0005	-0.3646	0.4979	-4.0775	0.0063
Area Under ROC Curve†	-		0.792		0.865		0.936		0.982	
Conclusion	Not Available		Very Good		Very Good		Excellent		Excellent	
Hosmer and Lemeshow §	-		p=0.0986		p=0.0399		P=0.3816		p=0.8120	
Conclusion	Not Available		Fail to Reject H0, no evidence of poor fit		Reject H_0, conclude poor fit		Fail to Reject H0, no evidence of poor fit		Fail to Reject H0, no evidence of poor fit	
Somers' D¶	0.82		0.583		0.731		0.872		0.965	
AIC ††	Not Available		1108.087		1077.236		640.321		236.747	
SC §§	Not Available		1138.46		1107.609		670.694		267.120	

* The outcome definition for the Original 2000 Maryland model is based on BLL ≥10µg/dL, however the percentage of elevated BLLs used to define a "Risk Area" in this model is unknown. It is assumed to be 12%, based on common practice when the model was developed.
** Reference level. In 2011 CDC defined the reference level for children's' exposure to lead as 5µg/dL.
† Receiver Operating Characteristic (ROC) Curve. The area under the ROC curve gives a quantitative indication of each model's ability to distinguish between risk and non-risk census tracts and ranges from 0.5 (worst) to 1.0 (ideal).
§ The Hosmer and Lemeshow test is a statistical test for goodness of fit for logistic regression models. It assesses whether or not observed rates match expected rates in subgroups of the modeled population.
¶ Somer's D is used to determine the strength and direction of relation between the predicted and actual values of the dependent variable. Its values range from -1.0 (all pairs disagree) to 1.0 (all pairs agree).
†† Akaike Information Criterion (AIC) is used for the comparison of models on the same sample. The model with the smallest AIC is considered the best. The AIC value itself is not meaningful.
§§ Schwarz Criterion (SC) is used to compare between models on the same sample. This measure penalizes for the number of predictors in the model and the model with the smallest SC is considered best. The value itself is not meaningful.

Predicting At-Risk Census Tracts

Logistic regression models were used to assess the risk of a child in a given census tract for having a blood lead level at or above reference, then used to estimate the number of children in that census tract with a blood lead level at or above reference. This analysis was performed for each of the outcomes described. Predicted probabilities based on each of the outcomes modeled ranged from 0 to 0.99, depending on the outcome modeled. When these were applied to the census tract population, the number of children expected to have a blood lead level at or above reference ranged from 0 to 1,179 children (Table A-4.15). Maps were prepared that displayed the level of risk for each census tract in Maryland (Figures A-4.7, A-4.8, A-4.9, A-4.10).

Table A-4.15. Number and Percentage of Census Tracts and Children for Each Level of Risk*, by Model

	Risk Level**	Number of Census Tracts	Percent of Census Tracts	Predicted Number Children at Risk	Total Number of Children Living in Tracts
Original Model Assumed ≥12% of tests 10 mcg/dL	**High**	46	4.0	266 - 666	-
	Moderate	77	6.7	73 - 265	-
	Low	288	20.7	13 - 72	-
	Negligible	790	68.6	0 - 12	-
Model 1 ≥3% of tests at or above RL*	**High**	421	36.1	276 - 1,179	249,657
	Moderate	414	35.5	153 - 275	126,913
	Low	231	19.8	81 - 152	43,588
	Negligible	101	8.7	8 - 81	13,387
Model 2 ≥5% of tests at or above RL*	**High**	347	29.7	179 - 746	174,945
	Moderate	384	32.9	83 - 178	136,873
	Low	255	21.9	36 - 83	74,067
	Negligible	181	15.5	1 - 36	47,660
Model 3 ≥9% of tests at or above RL*	**High**	184	15.8	136 - 618	64,995
	Moderate	293	25.1	37 - 136	109,028
	Low	327	28.0	11 - 37	136,601
	Negligible	363	31.1	0 - 11	122,921
Model 4 ≥17% of tests at or above RL*	**High**	76	6.5	157 - 494	25,491
	Moderate	103	8.8	44 - 154	22,833
	Low	179	15.3	4 - 43	58,246
	Negligible	809	69.3	0 - 4	326,975

* RL= Reference Level; CDC defines this as 5 mcg/dL

** Risk Level Definitions:

High Risk = 40% to 100% of the highest number of children predicted to be at risk;

Moderate Risk = 11% to 39.9% of the highest number of children predicted to be at risk;

Low Risk = 2% to 10.9% of the highest number of children predicted to be at risk; and

Negligible Risk = 0% to 1.9% of the highest number of children predicted to be at risk.

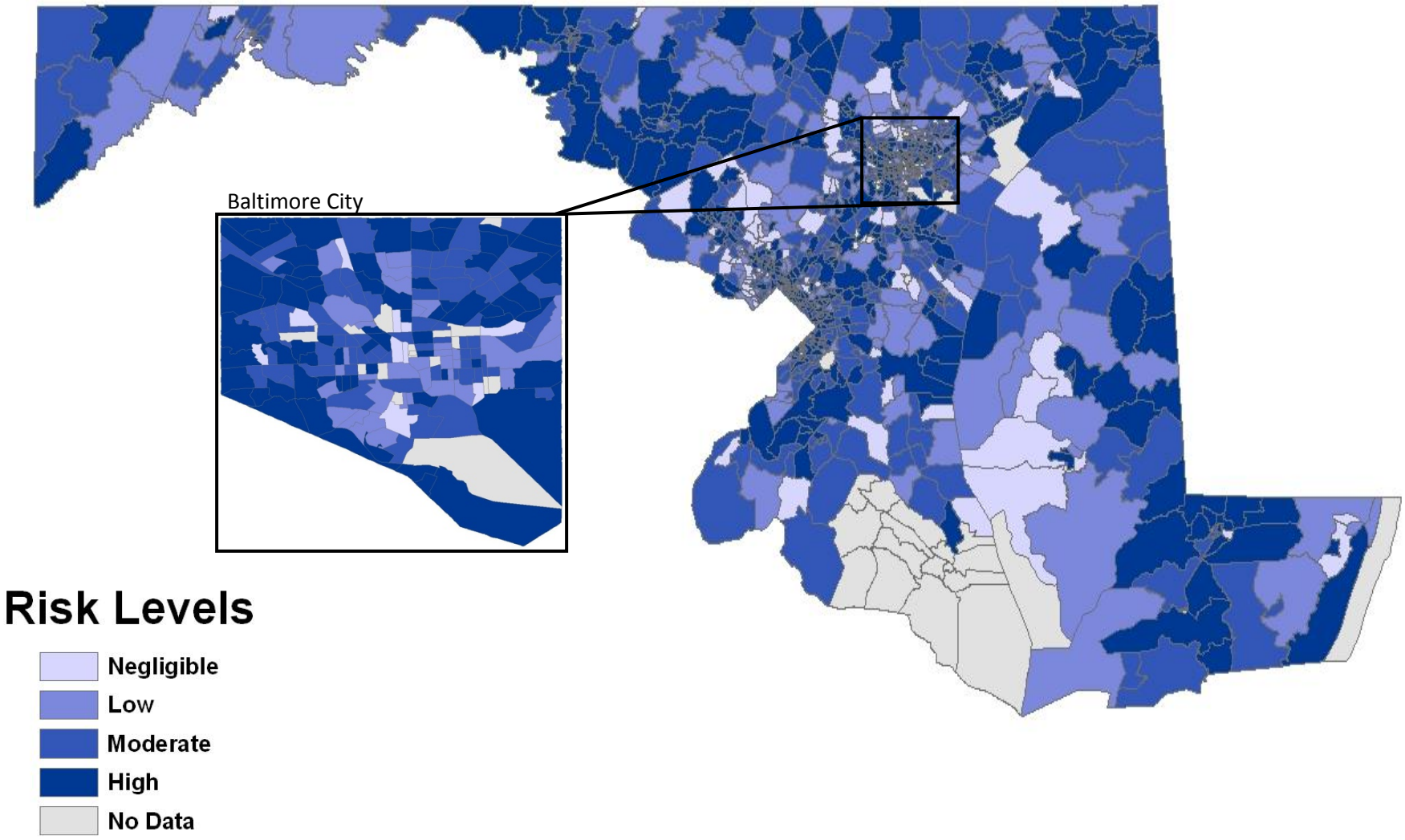


Figure A-4.7. Predicted Risk Areas, Model 1: Modeled risk area defined as a census tract with ≥3% of tests at or above the reference level

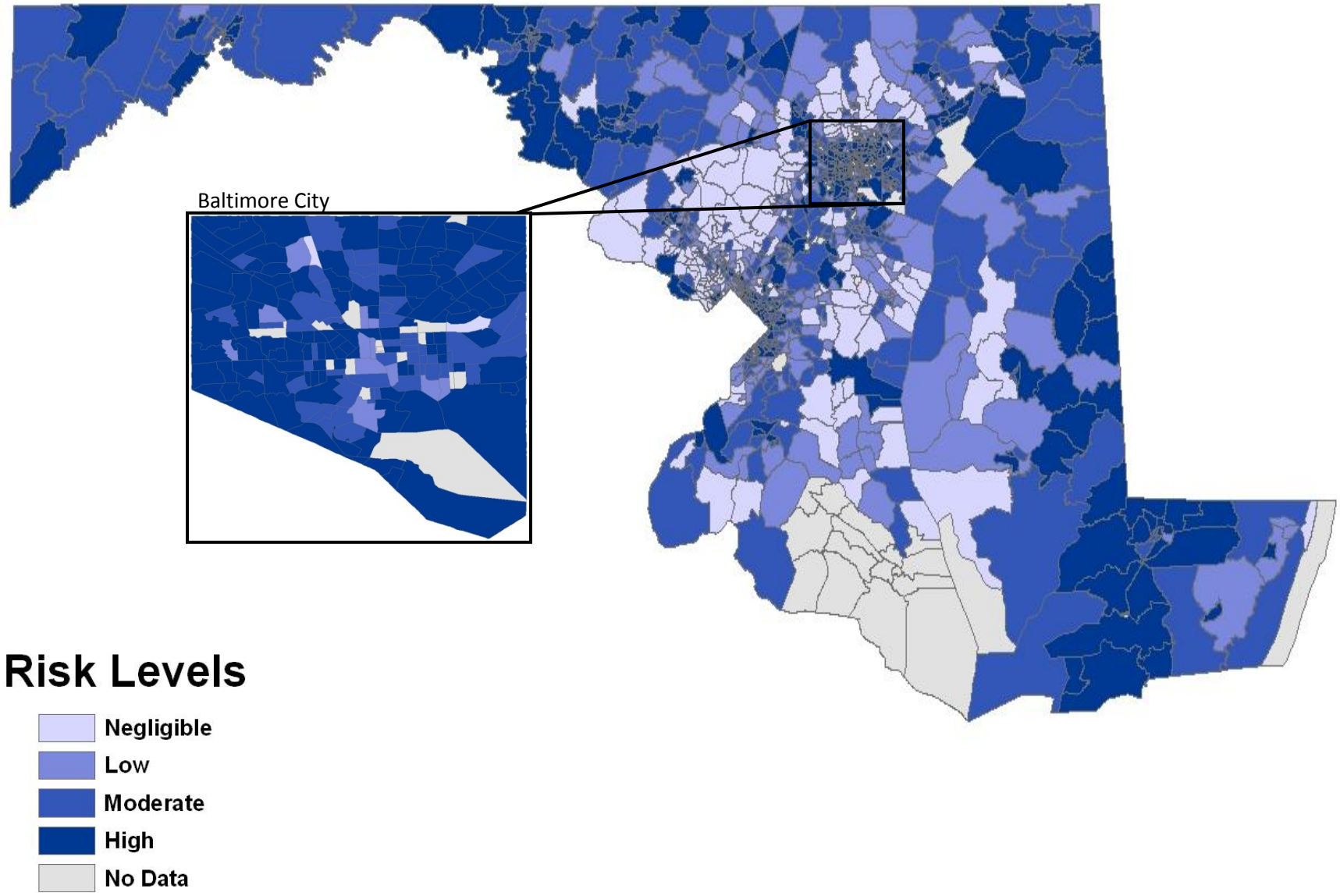


Figure A-4.8. Predicted Risk Areas, Model 2: Modeled risk area defined as a census tract with ≥5% of tests at or above the reference level

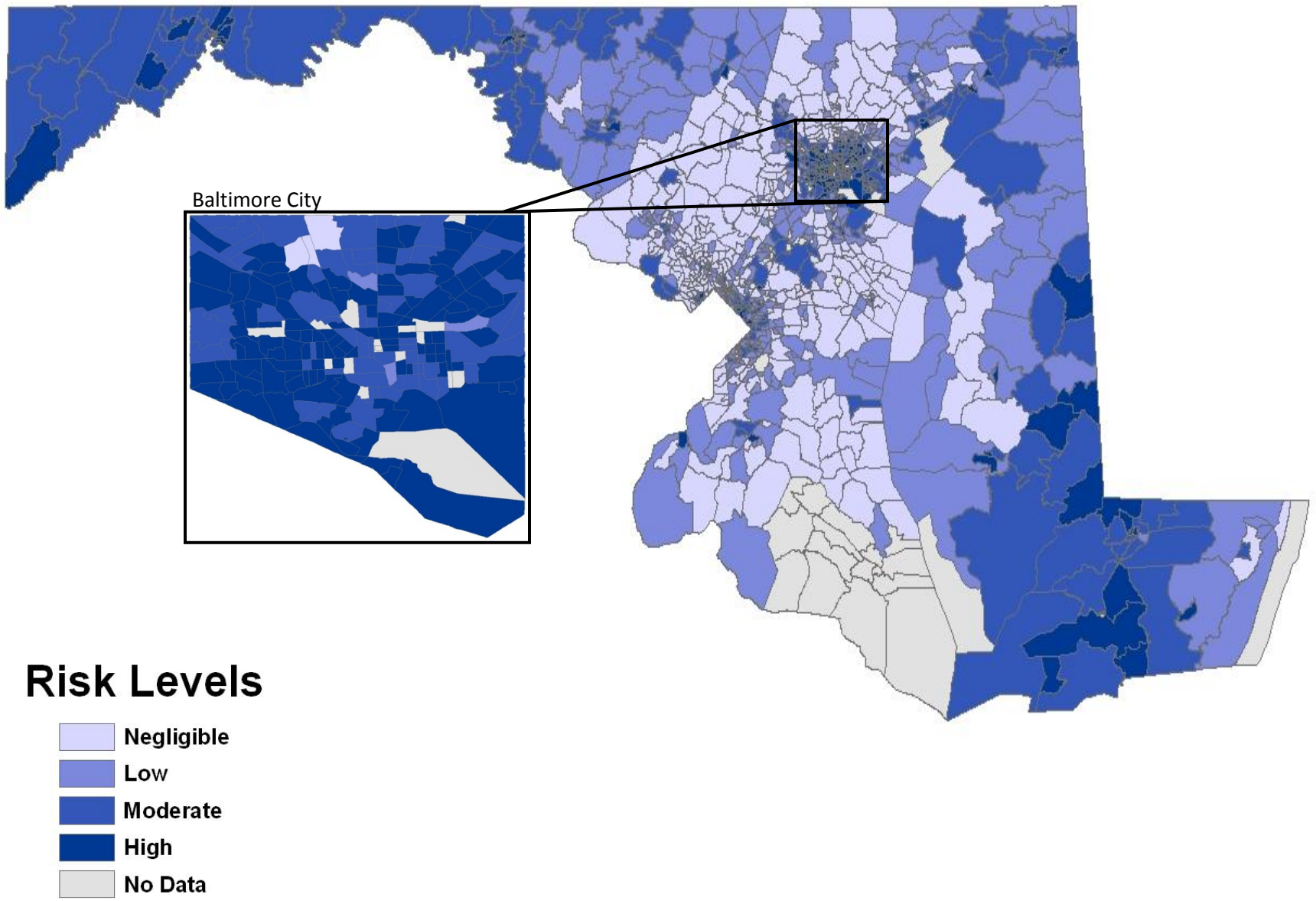


Figure A-4.9. Predicted Risk Areas, Model 3: Modeled risk area defined as a census tract with ≥9% of tests at or above the reference level

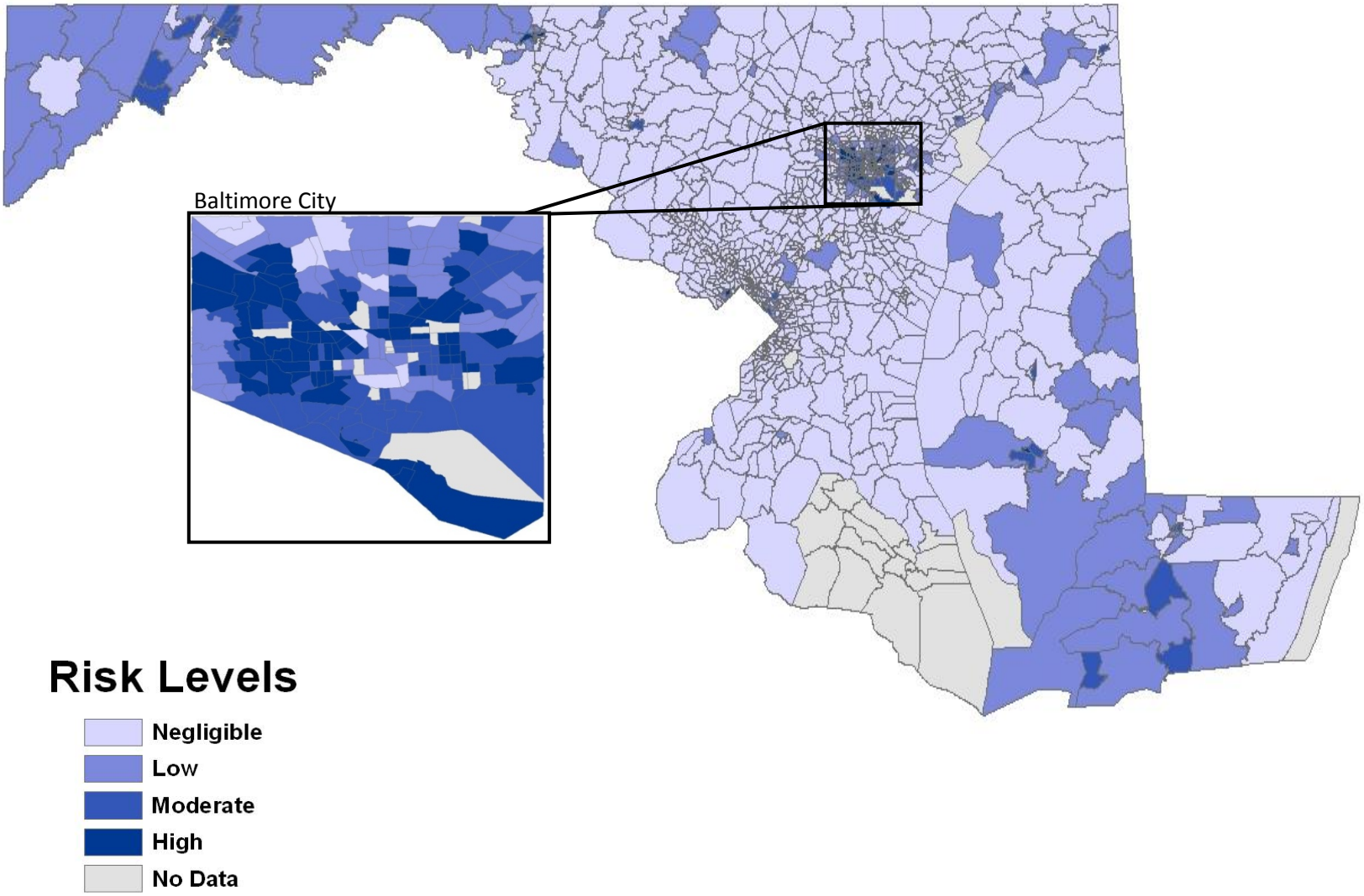


Figure A-4.10. Predicted Risk Areas, Model 4: Modeled risk area defined as a census tract with ≥17% of tests at or above the reference level

Targeting Strategy Option 3 (Universal Testing)

The third option for a targeting strategy would be universal testing for all children of appropriate age in Maryland. This strategy would require that all children be tested at one year and two years of age, regardless of place of residence or any other consideration. This strategy would be recommended for a period of *three years*, enough time to develop a more complete understanding of the actual distribution of blood lead levels throughout the State. This strategy requires no modeling or data analysis. Table A-4.16 lists the estimated number of 1- and 2-year old children living in each county and Baltimore City, based on the 2010 U.S. Census.

Table A-4.16. Estimated Number* of 1- and 2-Year Old Children to be Tested under a Universal Testing Strategy, by County

County	Number
Allegany	1,362
Anne Arundel	13,884
Baltimore	19,316
Calvert	1,939
Caroline	905
Carroll	3,529
Cecil	2,602
Charles	3,791
Dorchester	815
Frederick	5,857
Garrett	603
Harford	5,921
Howard	6,880
Kent	393
Montgomery	25,559
Prince George's	23,489
Queen Anne's	1,054
St. Mary's	2,969
Somerset	530
Talbot	795
Washington	3,592
Wicomico	2,486
Worcester	930
Baltimore City	16,836
Total	146,037

* Based on the 2010 U.S. Census

APPENDIX 5. Potential Costs of Testing Targeting Options

This section deals exclusively with the costs of implementing the lead testing strategies, not with potential benefits. The projected costs of the three options presented in this document are complex, and depend on numerous assumptions. One overarching complexity is the change in the global health care system brought about by implementation of the Affordable Care Act (ACA). This includes a significant increase in Medicaid enrollment as well as insurance coverage, in general. The increase in Medicaid coverage for children means that even without any change in "at risk" ZIP codes, more children should be tested by their providers. Other potential results of the ACA could be changes in hospitalization costs for children diagnosed with elevated blood lead levels, although it is impossible to predict what those changes might be. The cost estimates presented are therefore necessarily simplified and subject to considerable uncertainty.

The three options were compared as to their relative costs of implementation, using current reimbursement rates provided to DHMH by health care providers and organizations involved in lead prevention, as well as directly from Medicaid. The cost comparison included "typical" costs for blood lead testing, costs of follow-up, and an estimate of the percentage of capillary tests that would be confirmed by venous testing, based on the following assumptions (Table A-5.1):

- 13% of elevated capillary tests (≥10 mcg/dL) would be less than 10 mcg/dL when repeated by venous testing (false positives)
- Reimbursement rate for blood lead test is $15 - $25
- A "typical" environmental investigation for a child with a confirmed elevated blood lead (≥10 mcg/dL) would cost approximately $370 if performed by a public agency or $630 if conducted by a private firm.

In the first option, based on the distribution of test results at or above the reference level observed from 2005-2009, the different selection areas would potentially "miss" children estimated to be "at risk." To capture 100% of expected children with blood lead levels at or above the reference, all areas would have to be targeted (universal testing). Capturing 90% of expected children with blood lead levels at or above the reference would involve targeting 173 "at risk" ZIP codes. Adoption of this strategy would result in an estimated 126,016 1- and 2-year old children receiving a lead test the first year, with 10,042 (8.0% of tests) of these estimated to have a blood lead level at or above the reference level. This approach would "miss" an estimated 972 1- and 2-year old children living in non-targeted ZIP codes who, although not tested, would still be expected to have a blood lead level at or above the reference level. If, instead of 90%, the goal were to identify 75% of children expected to have a blood lead level at or above the reference level, 95 ZIP codes would be targeted as "at risk." This strategy would result in an estimated 91,201 1- and 2-year old children receiving a blood test, identifying an estimated 8,320

(9.1% of tests) children and "missing" an estimated 2,445 children expected to have a blood lead level at or above the reference level. Finally, a strategy based on identifying 50% of expected children with blood lead levels at or above the reference would target 32 ZIP codes as "at risk." This strategy would result in an estimated 32,580 children being tested, identifying 5,274 (16.2% of tests) children estimated to have a blood lead level at or above the reference level and "missing" 4,925 children expected to have a blood lead level at or above the reference level.

Using the most conservative assumptions for the second targeted testing approach, census tracts with 3 or more percent of test results at or above the reference level were identified as "at risk." The results of this model identified 421 "high" risk census tracts with a total of 179,681 children less than 6 years of age predicted to have a blood lead level ≥5 mcg/dL; 414 census tracts as "moderate" risk areas with a total of 86,740 children less than 6 years of age predicted to have a blood lead level ≥5 mcg/dL; 231 "low" risk census tracts with a total of 26,837 children less than 6 years of age predicted to have a blood lead level ≥5 mcg/dL; and 4 "negligible" risk census tracts with a total of 5,631 children less than 6 years of age predicted to have a blood lead level ≥ 5 mcg/dL. For the least conservative model, a risk area was defined as a census tract with greater than or equal to 17% of blood lead tests at or above the reference level. The results identified 76 "high" risk census tracts with a total of 19,570 children less than 6 years of age predicted to have a blood lead level ≥ 5 mcg/dL; 103 census tracts as "moderate" risk areas with a total of 9,303 children less than 6 years of age predicted to have a blood lead level ≥5 mcg/dL; 179 "low" risk census tracts with a total of 2,874 children less than 6 years of age predicted to have a blood lead level ≥5 mcg/dL; and 809 "negligible" risk census tracts with a total of 614 children less than 6 years of age predicted to have a blood lead level ≥5 mcg/dL. Details of the cost analysis are presented in Tables A-5.2, A-5.3, A-5.4.

Table A-5.1. Crude Projected Cost Analysis, Three Targeting Strategy Options, Maryland

Targeting Strategy Option	Estimated number of 1- and 2-year old children to be tested	Estimated number of children with EBL ≥10 mcg/dL§	Estimated number of children with EBL 5 – 9 mcg/dL§	Cost of Testing¶	Costs of Follow-Up for EBL ≥10 mcg/dL††	Cost of Follow-Up for EBL 5 – 9 mcg/dL§§	Total Estimated Cost
Option 1 – Target testing based on the distribution of 2005-2009 test results, by ZIP Code*	91,201 (79,983 Venous, 11,218 Capillary)	1,100 (1,040 Venous, 60 Confirmed Capillary)	7,108 (6,159 Venous, 949 Confirmed Capillary)	$1,320,146 - $2,324,713	$949,242 – $985,435	$308,513 - $543,549	$2,577,901 - $3,853,697
Option 2 – Target testing based on an updated MD Targeting Model**	108,245 (92,008 Venous, 16,237 Capillary)	1,148 (1,104 Venous, 44 Confirmed Capillary)	8,051 (6,809 Venous, 1,242 Confirmed Capillary)	$1,564,844 - $2,759,165	$990,702 - $1,028,436	$349,097 - $615,660	$2,904,642 - $4,403,261
Option 3 – Universal testing	146,037 (124,131 Venous, 21,906 Capillary)	1,548 (1,489 Venous, 59 Confirmed Capillary)	10,862 (9,186 Venous, 1,676 Confirmed Capillary)	$2,111,184 - $3,722,483	$1,335,895 - $1,386,776	$470,983 – $830,617	$3,918,061 – $5,939,876

* This estimate was prepared considering the area containing 75% of children expected to be "at risk," representing the "middle" estimate.

** This estimate was prepared based on model 3, with the modeled outcome of interest "risk area" defined as a census tract with ≥9% of tests at or above the reference level.

§ Represents venous test results and confirmed capillary results. 90% of capillary tests are assumed to be true positives in these analyses.

¶ The Cost per Test is based on Maryland Medicaid 2013 Clinical Diagnostic Laboratory Fee Schedule, with a low range of reimbursement assumed to be: Venous sample = $12.37 +$2.19 = $14.56; Capillary test =:$12.37 + $1.50= $13.87. The high range is assumed to be: Venous sample = $22.49 + $3.00 = $19.64; Capillary sample = $22.49 + $3.00 = $19.64.

†† Based on estimates of follow-up testing (3 tests/year), home inspection and testing ($715), nurse home visit ($48.75), case coordination ($55.63).

§§ Cost per Year: 3 follow-up tests per year (re-test every 3 months), following the initial screening test.

See Tables A-5.2 – A-5.4 for details.

Table A-5.2. Low and high range estimates for targeting strategy option 1.

Option 1* - Low Range					Option 1* - High Range			
	Estimated number of 1 and 2 year old children to be tested	**Cost/Test**	**Total Screening Test Cost**			**Estimated number of 1 and 2 year old children to be tested**	**Cost/Test**	**Total Screening Test Cost**
Venous	79,983	$15	$1,164,552		**Venous**	79,983	$25	$2,038,767
Capillary	11,218	$14	$155,594		**Capillary**	11,218	$25	$285,947
Cost of Screening	91201		$1,320,146		**Cost of Screening**	91201		$2,324,713
5-9 mcg/dL Follow-up X 1 year	**Estimated number of children with EBL 5 – 9 mcg/dL**	**follow-up Cost per Year**	**Total Follow-up Testing Cost**		**5-9 mcg/dL follow-up X 1 year**	**Estimated number of children with EBL 5 – 9 mcg/dL**	**follow-up Cost per Year**	**Total Follow-up Testing Cost**
Venous tests	6,159	$44	$269,025		**Venous**	6,159	$76	$470,979
Capillary tests	949	$42	$39,488		**Capillary**	949	$76	$72,570
Cost of 5-9 mcg/dL follow-up	7,108		$308,513		**Cost of 5-9 mcg/dL follow-up**	7,108		$543,549

≥10 mcg/dL follow-up X 1 year	Estimated number of children with EBL ≥ 10 mcg/dL	follow-up Cost per Year	Total Follow-up Testing Cost		≥10 mcg/dL follow-up X 1 year	Estimated number of children with EBL ≥ 10 mcg/dL	follow-up Cost per Year	Total Follow-up Testing Cost
Venous	1,040	$44	$45,427		**Venous**	1,040	$76	$79,529
Capillary	60	$42	$2,497		**Capillary**	60	$76	$4,588
MDE Inspection X1	1,100	$715	$786,500		**MDE Inspection X1**	1,100	$715	$786,500
MDE Case Coordination X1 year	1,100	$56	$61,193		**MDE Case Coordination X1 year**	1,100	$56	$61,193
Nurse visit X1	1,100	$49	$53,625		**Nurse visit X1**	1,100	$49	$53,625
Cost of ≥10 mcg/dL follow-up			$949,242		**Cost of ≥10 mcg/dL follow-up**			$985,435
Total Estimated Cost			**$2,577,901**		**Total Estimated Cost**			**$3,853,697**

Table A-5.3. Low and high range estimates for targeting strategy option 2.

Option 2** - Low Range					Option 2** - High Range			
	Estimated number of 1 and 2 year old children to be tested	**Cost per Test**	**Total Screening Test Cost**			**Estimated number of 1 and 2 year old children to be tested**	**Cost per Test**	**Total Screening Test Cost**
Venous	92,008	$15	$1,339,636		**Venous**	92,008	$25	$2,345,284
Capillary	16,237	$14	$225,207		**Capillary**	16,237	$25	$413,881
Cost of Screening	108,245		$1,564,844		**Cost of Screening**	108,245		$2,759,165
5-9 mcg/dL follow-up X 1 year	**Estimated number of children with EBL 5-9 mcg/dL**	**follow-up Cost per Year**	**Total Follow-up Testing Cost**		**5-9 mcg/dL follow-up X 1 year**	**Estimated number of children with EBL 5-9 mcg/dL**	**follow-up Cost per Year**	**Total Follow-up Testing Cost**
Venous	6,809	$44	$297,417		**Venous**	6,809	$76	$520,684
Capillary	1,242	$42	$51,680		**Capillary**	1,242	$76	$94,976
Cost of 5-9 mcg/dL follow-up	8,051		$349,097		**Cost of 5-9 mcg/dL follow-up**	8,051		$615,660
≥10 mcg/dL follow-up X 1	**Estimated number of children with EBL ≥ 10**	**follow-up Cost per Year**	**Total Follow-up Testing Cost**		**≥10 mcg/dL follow-up X 1**	**Estimated number of children with EBL ≥10**	**follow-up Cost per Year**	**Total Follow-up Testing Cost**

year (3 tests)	mcg/dL				year (3 tests)	mcg/dL		
venous	1,104	$44	$48,223		**venous**	1,104	$76	$84,423
Capillary	44	$42	$1,831		**Capillary**	44	$76	$3,365
MDE Inspection X1	1,148	$715	$820,820		**MDE Inspection X1**	1,148	$715	$820,820
MDE Case Coordination X1 year	1,148	$56	$63,863		**MDE Case Coordination X1 year**	1,148	$56	$63,863
Nurse visit X1	1,148	$49	$55,965		**Nurse visit X1**	1,148	$49	$55,965
Cost of ≥10 mcg/dL follow-up			$990,702		**Cost of ≥10 mcg/dL follow-up**			$1,028,436
Total Estimated Cost			**$2,904,642**		**Total Estimated Cost**			**$4,403,261**

Table A-5.4. Low and high range estimates for targeting strategy option 3.

Option 3 - Low Range					Option 3 - High Range			
	Estimated number of 1 and 2 year old children to be tested	**Cost per Test**	**Total Screening Test Cost**			**Estimated number of 1 and 2 year old children to be tested**	**Cost per Test**	**Total Screening Test Cost**
Venous	124,131	$15	$1,807,347		**Venous**	124,131	$25	$3,164,099
Capillary	21,906	$14	$303,836		**Capillary**	21,906	$25	$558,384
Cost of Screening	146,037		$2,111,184		**Cost of Screening**	146,037		$3,722,483
5-9 mcg/dL follow-up X 1 year	**Estimated number of children with EBL 5 – 9 mcg/dL**	**follow-up Cost per Year**	**Total Follow-up Testing Cost**		**5-9 mcg/dL follow-up X 1 year**	**Estimated number of children with EBL 5 – 9 mcg/dL**	**follow-up Cost per Year**	**Total Follow-up Testing Cost**
Venous	9,186	$44	$401,244		**Venous**	9,186	$76	$702,453
Capillary	1,676	$42	$69,738		**Capillary**	1,676	$76	$128,164
Cost of 5-9 mcg/dL follow-up	10,862		$470,983		**Cost of 5-9 mcg/dL follow-up**	10,862		$830,617

≥10 mcg/dL Follow-up X 1 year	Estimated # of children with EBL ≥ 10 mcg/dL	follow-up Cost per Year	Total Follow-up Testing Cost		≥10 mcg/dL follow-up X 1 year	Estimated # of children with EBL ≥10 mcg/dL	follow-up Cost per Year	Total Follow-up Testing Cost
venous	1,489	$ 44	$65,040		**venous**	1,489	$76	$113,864
Capillary	59	$ 42	$2,455		**Capillary**	59	$76	$4,512
MDE Inspection X1	1,548	$715	$1,106,820		**MDE Inspection X1**	1,548	$715	$1,106,820
MDE Case Coordination X1 year	1,548	$56	$86,115		**MDE Case Coordination X1 year**	1,548	$56	$86,115
Nurse visit X1	1,548	$49	$75,465		**Nurse visit X1**	1,548	$49	$75,465
Cost of ≥10 mcg/dL follow-up			$1,335,895		**Cost of ≥10 mcg/dL follow-up**			$1,386,776
Total Estimated Cost			**$3,918,061**		**Total Estimated Cost**			**$5,939,876**

Cost Projection Assumptions for tables A-5.2 – A-5.4 – Low Range

1) Cost per Test: Based on Maryland Medicaid 2013 Clinical Diagnostic Laboratory Fee Schedule.
   Venous: $12.37 +$2.19 = $14.56
   Capillary: $12.37 + $1.50= $13.87
2) Cost per Year: 3 follow-up tests per year (i.e., a test every 3 months), following the initial screening test.
3) Inspection by MDE inspection is done if blood lead level is ≥10 mcg/dL
4) Follow-up testing process is constant, (i.e., all capillary testing or all venous testing)
5) Nurse visit is done in coordination with MDE investigation; of note, MD law requires only for levels ≥15 mcg/dL, but majority of counties perform visits in conjunction with MDE.
6) Excludes physician visit costs since tests are likely performed in conjunction with routine preventive care visits.
7) Total Estimated Cost: Σ Cost Tests + Cost 10 mcg/dL (follow-up) + Cost 5-9 mcg/dL (follow-up)
8) 100% utilization of Health Department and MDE services with no loss to follow-up.

* This estimate was prepared considering the area containing 75% of children expected to be "at risk," representing the "middle" estimate.

** This estimate was prepared based on model 3, with the modeled outcome of interest "risk area" defined as a census tract with ≥9% of tests at or above the reference level.

Cost Projection Assumptions for tables A-5.2 – A-5.4 – High Range

1) Cost per Test: Based on Medicare 2013 Clinical Diagnostic Laboratory Fee Schedule.
   Venous: $22.49 + $3.00=$19.64
   Capillary: $22.49 + $3.00=$19.64 (*code 36416 is N/A to Medicare)
2) Cost per Year: 3 follow-up tests per year (i.e., a test every 3 months), following the initial screening test.
3) Public MDE inspection is done if blood lead level is ≥10 mcg/dL
4) Follow-up testing process is constant, (i.e., all capillary testing or all venous testing)
5) Nurse visit is done in coordination with MDE investigation; of note, MD law requires only for levels ≥15 mcg/dL, but majority of counties perform visits in conjunction with MDE.
6) Excludes physician visit cost since tests are likely performed in conjunction with routine preventive care visits.
7) Total Estimated Cost: Σ Cost Tests + Cost 10 mcg/dL follow-up + Cost 5-9 mcg/dL follow-up
8) 100% utilization of Health Department and MDE services.

* This estimate was prepared considering the area containing 75% of children expected to be "at risk," representing the "middle" estimate.

** This estimate was prepared based on model 3, with the modeled outcome of interest "risk area" defined as a census tract with ≥9% of tests at or above the reference level.

APPENDIX 6. Detailed Description of Data Sources

1. Data Sets

The following data sets were used to assess the current picture of lead testing in MD and to make recommendations for revising the targeting plan. The Systematic Tracking of Elevated Lead Levels & Remediation (STELLAR) database was used to generate descriptive summary tables on the characteristics of children tested in MD. These fields were also aggregated by county, ZIP code, and census tract to be used for analysis in targeting strategy options 1 and 2.

- **Systematic Tracking of Elevated Lead Levels & Remediation (STELLAR) Database, MDE CLR:** The STELLAR database stores the results of all childhood blood lead tests in the State and includes information on actual blood lead level, as well as geographic and demographic information. Records of all tests performed in the 5-year period from January 1, 2005 through December 31, 2009 were extracted from the STELLAR database. Records for children receiving a blood lead test in multiple years, or who had multiple tests within a given year, were counted only once for each year in which they were tested. The record of venous test with the highest blood lead level annually was retained for each child who had multiple tests in a given year. For children with more than one test, of which there was no venous result, the highest result where the test type was "unknown" was retained. Unknown test types were retained as a second priority because some proportion of these is likely to be venous tests. Finally, for children who received multiple tests in a given year, none of which were venous or "unknown," the highest capillary result was retained. This selection process resulted in a total of 586,264 individual records in the project data set (Figure A-6.1). Note the resulting data set contains no more than one test per year for each of the 5 years included, for children of all ages. In later analyses, these individual records were further restricted to include only children less than 6 years of age and aggregated to determine a total incidence for the 5-year period. Table A-6.1 summarizes the variables included in this initial project data set.

Figure A-6.1. STELLAR Data Set Processing

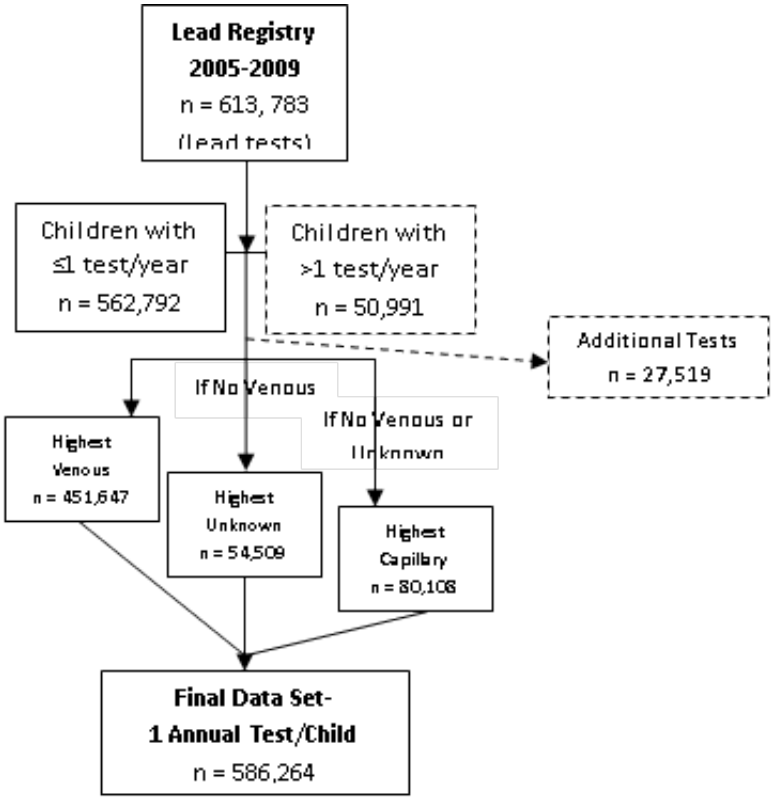


Table A-6.1. STELLAR Data Fields

Description	Field Name	Source	Notes
Stellar Id Number	CHILD_ID	STELLAR	Unique identifier for each child
Child's Address:			
- Street	ASSEMADDR	STELLAR	
- State	ADDRSTATE	STELLAR	
- City	ADDR_CITY	STELLAR	
- ZIP Code	ADDR_ZIP	STELLAR	
- County	ADDR_CNTY	STELLAR	
Child's Date of Birth	DOB_CHILD	STELLAR	
Child's Age (years)	SampleAgeY	STELLAR*	Calculated: sample date - DOB
Address-Latitude	LATITUDE	STELLAR*	Geocoded CLR addresses in Centrus
Address-Longitude	LONGITUDE	STELLAR*	Geocoded CLR addresses in Centrus
Address-Census Tract	CENSUSTRAC	STELLAR*	Geocoded CLR addresses in Centrus
Result (Blood Lead Level)	PBB_REST	STELLAR	
Child's race	RACE	STELLAR	
Date Test Sample Drawn	SAMP_DATE	STELLAR	
Sample Year	SampYear	STELLAR*	Year extracted from sample date
Sample (Venous, Capillary)	SAMP_TYPE	STELLAR	
Lab Id	LAB_ID	STELLAR	
Child's Sex	SEX	STELLAR	
Total number of tests per year for an individual child	count1	STELLAR*	Count number of records per child per year

* Fields added to data set. These were not exported from STELLAR but were created using fields from STELLAR.

- **American Community Survey (ACS), U.S. Census Bureau:** All demographic information utilized in the logistic regression analyses was obtained from the U.S. Census Bureau's ACS through the American FactFinder web tool. Excel files of select demographic characteristics by census tract were downloaded, modified, and utilized in the logistic regression model. The specific table for each of the variables is indicated under 'Notes' in the table. Variables were merged with a census tract level-aggregated CLR data set based on census tract ID number. Table A-6.2 summarizes the fields included in this data set.

Table A-6.2. American Community Survey Data Fields

Description	Field Name	Source	Notes
Census Tract ID Number	CensusTract	ACS	
Total number of residents ≤ 5 years old	LE5yo	ACS*	B09001: POPULATION UNDER 18 YEARS BY AGE
Number of renter-occupied housing units	nRenterOcc	ACS	B25002: OCCUPANCY STATUS
Number of occupied housing units	nOccupied	ACS	B25032: TENURE BY UNITS IN STRUCTURE
Percent Rental Housing	PercRental	ACS*	PercRental=(nRenterOcc/nOccupied)*100
Number of vacant housing units	nVacant	ACS	B25002: OCCUPANCY STATUS
Total number of housing units	nAllHouses	ACS	B25032: TENURE BY UNITS IN STRUCTURE
Percent vacant housing units	PercVacant	ACS*	PercVacant=(nVacant/nAllHouses)*100
Total number of families	TotalFam	ACS	B17006: POVERTY STATUS IN THE PAST 12 MONTHS OF RELATED CHILDREN UNDER 18 YEARS BY FAMILY TYPE BY AGE OF RELATED CHILDREN UNDER 18 YEARS
Sum of all family types below poverty with children <5 years old	povWChLT5	ACS*	Sum (married couple, male-headed household, female-headed household) below poverty with children less than 5 years old (B17006)
Percent of families below poverty level with children >5	PercPov	ACS*	PercPov=(povWChLT5/TotalFam)*100
Number female-headed households with children >6	FHHn	ACS	B11004: FAMILY TYPE BY PRESENCE AND AGE OF RELATED CHILDREN UNDER 18 YEARS
Percent female-headed households with children >6	PercFHH	ACS*	PercFHH=(FHHn/TotalFam)*100
Number housing units built from 1970 - 1979	Npre50	ACS*	B25034: YEAR STRUCTURE BUILT [Sum number built 1939 and before and from 1940-1949]
Number housing units built pre-1950	N50_79	ACS*	B25034: YEAR STRUCTURE BUILT [Sum number built 1950-1959, 1960-1969 and 1970-1979]
Percent housing units built from 1970 - 1979	Perc50_79	ACS*	Perc50_79=(N50_79/nAllHouses)*100

Table A-6.2. American Community Survey Data Fields –CONTINUED

Description	Field Name	Source	Notes
Percent housing units built pre-1950	PercPre50	ACS*	PercPre50=(Npre50/nAllHouses)*100
Median value of housing units	MedHousVal	ACS	B25077: MEDIAN VALUE (DOLLARS)
Number of black persons	nBlack	ACS	B02001: RACE
Total number of persons (all races)	nAllRaces	ACS	B02001: RACE
Percent black population	PercBlack	ACS*	PercBlack=(nBlack/nAllRaces)*100
Number households with public assistance income	PA_INCn	ACS	B19057: PUBLIC ASSISTANCE INCOME IN THE PAST 12 MONTHS FOR HOUSEHOLDS
Total number of households	TotalHHn	ACS	B19057: PUBLIC ASSISTANCE INCOME IN THE PAST 12 MONTHS FOR HOUSEHOLDS
Percent households with public assistance income	PercPaInc	ACS*	PercPaInc = (PA_INCn/TotalHHn)*100
Median household income	MedianInc	ACS	B19013: MEDIAN HOUSEHOLD INCOME IN THE PAST 12 MONTHS (IN 2009 INFLATION-ADJUSTED DOLLARS)

* Fields added to data set. These were not directly exported from FactFinder but were created/calculated using fields from the data sets downloaded.

- **2010 Decennial Census, U.S. Census Bureau:** A limited selection of demographic characteristics of ZIP codes is available from the 2010 U.S. Census tables. These characteristics were used for comparing the ZIP codes identified as risk and non-risk under targeting strategy option 1 (identification of expected risk areas based on observed test results). Excel files of select demographic characteristics by ZIP code were downloaded using the U.S. Census American FactFinder web tool. These files were prepared and merged into the ZIP code level-aggregated project data set based on ZIP code. Table A-6.3 summarizes the Census variables included in this data set.

Table A-6.3. 2010 Decennial Census Data Fields

Description	Field Name	Source	Notes
Number residents white	White	2010 SF1	P3: RACE
Number residents black	Black	2010 SF1	P3: RACE
Number residents other race	OthRace	2010 SF1*	P3: RACE—Sum of Other, Indian/Alaskan, Hawaiian/Pacific Islander and Multiple Race
Number residents all races (total)	AllRaces	2010 SF1	P3: RACE
Percent residents white	pWhite	2010 SF1*	pWhite=(nWhite/nAllRaces)*100
Percent residents black	pBlack	2010 SF1*	pBlack=(nBlack/nAllRaces)*100
Percent residents other race	pOther	2010 SF1*	pOther=(nOther/nAllRaces)*100
Number occupied housing units	OccupiedUnit	2010 SF1	H3: OCCUPANCY STATUS
Number vacant housing units	VacantUnit	2010 SF1	H3: OCCUPANCY STATUS
Number housing units	TotalUnit_V	2010 SF1	H3: OCCUPANCY STATUS
Percent occupied housing units	pOccupied	2010 SF1*	pOccupied=(OccupiedUnit/TotalUnit_V)*100
Percent vacant housing	pVacant	2010 SF1*	pVacant=(VacantUnit/TotalUnit_V)*100
Number owner occupied housing units	OwnerOccUnits	2010 Demographic Profile	DP21: HOUSING TENURE
Number rental housing units	pRentrOc	2010 Demographic Profile	DP21: HOUSING TENURE
Number housing units	TotalUnits_R	2010 Demographic Profile	DP21: HOUSING TENURE
Percent owner occupied housing	pOwnerOcc	2010 Demographic Profile*	pOwnerOc=(OwnerOccUnits/TotalUnits_R)*100
Percent rental housing	pRentrOc	2010 Demographic Profile*	pRentrOc=(RenterOccUnits/TotalUnits_R)*100
Males/females <1 year old	MLT1/FLT1	2010 Census	2010 Population of Children <5 years old
Males/females 1 year old	M1/F1	2010 Census	2010 Population of Children <5 years old
Males/females 2 years old	M2/F2	2010 Census	2010 Population of Children <5 years old
Males/females 3 years old	M3/F3	2010 Census	2010 Population of Children <5 years old

Table A-6.3. 2010 Decennial Census Data Fields (Continued)

Description	Field Name	Source	Notes
Males/females 4 years old	M4/F4	2010 Census	2010 Population of Children <5 years old
Males/females 5 years old	M5/F5	2010 Census	2010 Population of Children <5 years old
Total number males ≤5 years old	MLE5	2010 Census*	MLE5= MLT1+M1+M2+M3+M5+M5
Total number females ≤5 years old	FLE5	2010 Census*	FLE5= FLT1+F1+F2+F3+F5+F5
Total number children ≤5 years old	TotLE5	2010 Census*	TotLE5= MLE5+ FLE5

* Fields added to data set. These were not directly exported from FactFinder, but were created/calculated using fields from the data sets downloaded.
SF= Summary File

2. Exploratory Data Sets

The following data sets were evaluated as potential data sources to be used in assessing and revising the MD lead targeting plan. Due to noted limitations, these sources were used only to provide limited descriptive information on children in the CLR or were eliminated from these analyses.

- **Department of Assessments & Taxation (DAT) Real Property Data, 2011, Obtained from MDE:** The State DAT Real Property database contains records of all residential and non-residential properties in MD and is created and intended to be used for taxation purposes. The variables in this file, including year of construction and property use, and the feasibility of merging the data with the CLR data, were explored to determine whether this data set could be used as a more robust source of information on the housing characteristics in MD. The file was used for two purposes: (1) to provide a detailed summary of housing characteristics in the State and (2) to provide specific housing information on all children in the CLR. This would allow a comparison of blood lead levels by the specific housing characteristics of individual children.

  Data files from DAT were obtained from MDE, which receives updated files from DAT on a monthly basis. The files were stored as '.txt' files by MDE, and the project team contacted the DAT for the data schematic to enable further use of these data. Fields in this data set on the year of construction, the most recent transfer date, owner occupancy, and property use were investigated further.

  The files used were received by MDE in 2011. The .txt files were converted to SAS data sets, and efforts were made to eliminate non-residential properties (e.g. parking garages, undeveloped land, boat slips, etc.). Following data set cleaning, the file was geocoded in Centrus to include latitude, longitude, and census tract for each property. Of the 1,841,023 records remaining after cleaning, 1,463,558 (79.5%) were successfully geocoded in Centrus. Although attempts were made to remove

non-residential properties, some may not have been captured by the exclusion criteria used and remained in the data set.

Following discussions with representatives at the DAT, the project team concluded that it would not be possible to use the DAT files to create a detailed summary of the housing stock in MD, as there was no way to definitively identify occupied residential properties or renter- versus owner-occupied properties using the fields available in the data set. Limited information on the construction year was merged with the CLR data in order to provide more specific information on the age of properties inhabited by individual children who had received a blood lead test in MD. Variables merged into the project data set are summarized in Table A-6.4. Further attempts at using these data were abandoned.

The DAT file was matched with the CLR data set using a multi-tiered approach, first by matching based upon geocoded latitude and longitude (57 % of overall data matched), and then matching the remaining observations by the address fields ZIP code, street number, and street name (1.4 % of overall data matched). Finally, the address fields for the remaining fields were cleaned and re-geocoded in Centrus, and a final merge by latitude and longitude was done (0.20 % of remaining addresses matched). This approach resulted in an overall 58.9% match of CLR records to an address in the DAT file. The processes for this merge are outlined in Figure A-6.2, and Table A-6.5 summarizes the overall results for the three data matching methods. The percentage of STELLAR addresses in each ZIP code that failed to match to a DAT record was mapped to assess whether there appeared to be a geographic pattern to addresses that failed to match (Figure A-6.3).

Table A-6.4. DAT Data Fields

Description	**Field Name**	**Source**	**Notes**
Property Latitude	N_LAT	DAT*	Geocoded property addresses in Centrus
Property Longitude	N_LON	DAT*	Geocoded property addresses in Centrus
Year property was built	YEARBUILT	DAT	
Rental property estimate	RENTALest	DAT*	Assume rental property if owner's mailing address is different that the property address
* Fields added to data set. These were not included in the original file but were created using fields from the file.			

Figure A-6.2. CLR - DAT Merge Process

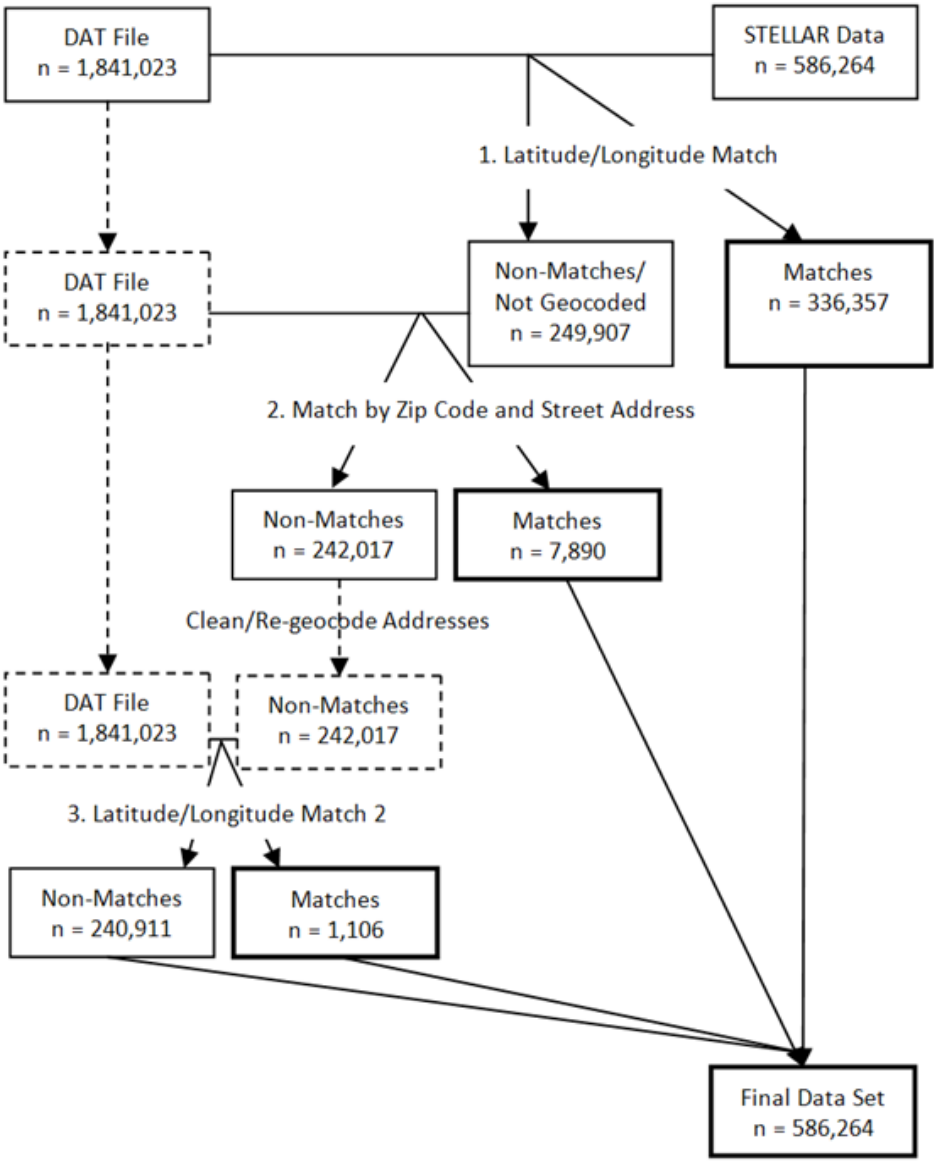
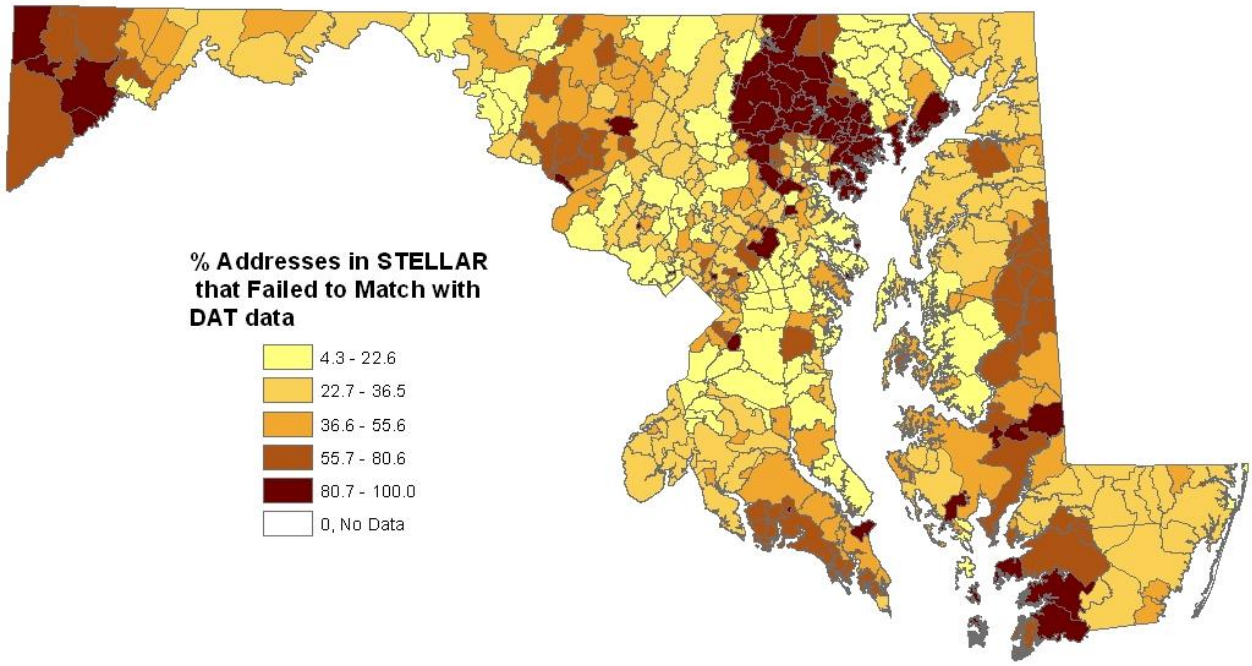


Table A-6.5. CLR - DAT Merge Results

Merge Approach	Matches	
	N	%
Attempt 1: Latitude/Longitude Merge	334,742	57.1
Attempt 2: Address Field Merge	312,721	53.3
Attempt 3: Combination of 1 & 2	345,353	58.9

Figure A-6.3. Percent of Childhood Lead Registry Addresses that Failed to Match to a DAT Address Record, by ZIP Code, Maryland 2005-2009



- **Rental Registry, MDE**: Information on registered rental properties in the State was obtained from MDE and used to determine the percentage of children in the CLR residing in registered rental properties and to assess the blood lead levels of these children.

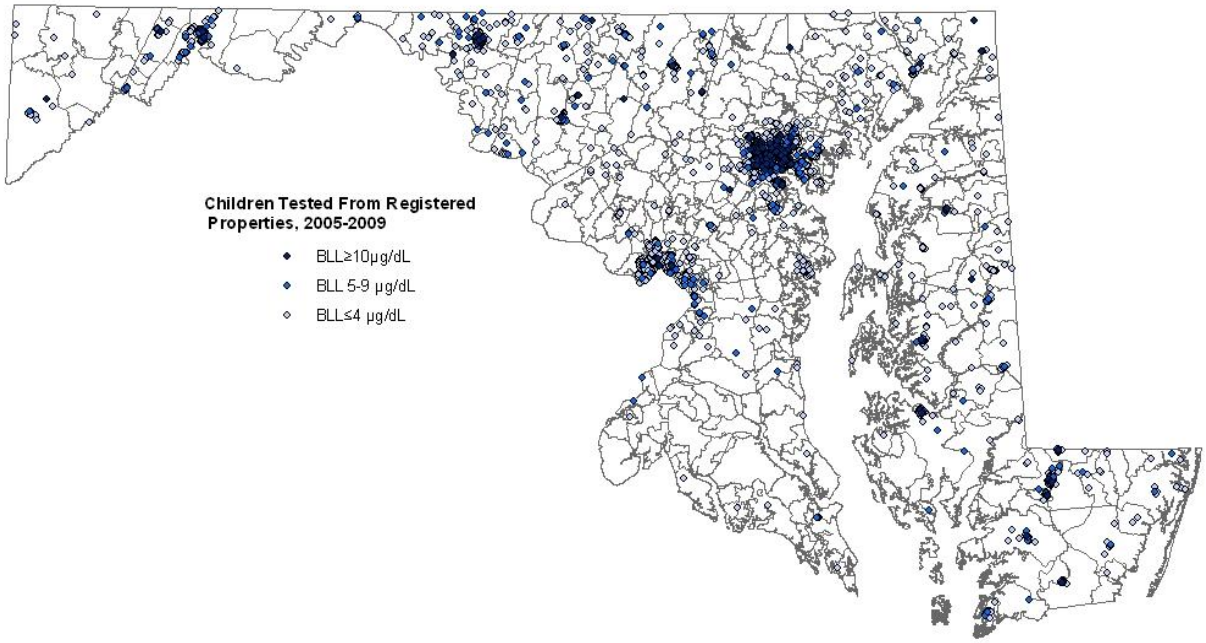
  Excel files of properties annually registered with MDE's Rental Registry from 2005-2009 were obtained. These files included the address, construction year, and identification number for all registered properties. The data sets provided had one noted limitation: only those properties currently registered as of September 2012 were included. If a property had been registered between 2005 and 2009 and later removed in a subsequent year, it was not included in the provided

data sets. This limitation could potentially lead to error when retrospectively estimating the number of properties registered annually.

The addresses provided were matched to the addresses of children tested in the CLR by ZIP code, street name, and street number. This match was done separately for each year (i.e. addresses of children tested in 2005 were matched to the addresses of properties registered in 2005, and so on). Therefore, only properties registered in the year a child was tested would have matched. Annually, 2.3-3.3% of individual addresses with children tested matched to a property in the Rental Registry.

This data set was used to identify additional rental properties in the CLR-DAT file. Blood lead levels of individual children from registered rental properties were mapped (Figure A-6.4), but no further uses for this data set were identified.

Figure A-6.4. Children from Registered Rental Properties and Blood Lead Levels, Maryland 2005-2009 *(all children)*



- **Environmental Investigations Enforcement Database, MDE:** This data set was investigated to provide further information on sources of exposure for children with elevated blood lead levels. As efforts have succeeded in reducing exposures to children from pre-1950 rental housing, other sources, including owner-occupied housing, imported potteries, home remedies, or other exposures have become more prevalent. The MDE enforcements data contained information on the source(s) of lead exposure identified for investigated cases (Table A-6.6).

  Data sets containing records of all enforcements investigations from 2005-2009 were obtained from the Lead Poisoning Prevention Program's Lead Enforcement Division at MDE. This data contained

records of 702 inspections for different sites/children, representing an estimated 570 unique children (in some cases, there were multiple addresses inspected for a single child). Upon preliminary analysis, several limitations to these data were identified. These data represented only a small subset of the population of the children in the State—from 2005-2009, investigations were performed only for cases with a blood lead level at or above 15 mcg/dL. Since this data set captured exposure information only for those children with the most elevated blood levels, it may not accurately represent lead exposures for all children in the State. Further, this data set provided no information on the source of exposure for children with blood lead levels from 5 to 14 mcg/dL. Due to this limitation, the investigations data set was unable to be utilized in any of the targeting models assessed.

The records in the enforcements data set also did not contain an identifier that allowed them to be directly matched to a record in STELLAR. Therefore, matching the two data sets was based on the open text fields containing the child's name and/or address information. A child with records at different addresses or with different names or name spellings may not be identified as matching. Due to the limitations previously identified, this match was not attempted.

The data in this system may be used as anecdotal information; however, due to the limited subset of children for whom this information in available, the difficulties matching records to individual children in STELLAR, and other characteristics of this system, further attempts to utilize this data source for any quantitative analysis were abandoned.

Table A-6.6. Lead Exposure Sources* Identified by MDE Investigations, 2005-2009

Source Identified	Non-Paint Source	Defective Paint	Blinds	Dust	Ceramics	Hobbies	Industry	Make-up	Occupation	Renovations	Soil	Toys	Other**
Yes	375	81	42	252	15	3	1	19	18	29	40	25	159
No	327	621	660	450	687	699	701	683	684	673	662	667	-

* Multiple sources may have been identified at one address. Also, multiple addresses may have been inspected for a single child.

** "Other" includes Other (155), Bullets (1), Sinkers (3)

- **Baltimore City STELLAR, Baltimore City Health Department, Obtained from MDE:** Baltimore City utilizes their own version of STELLAR and captures additional environmental information on cases for which they perform an investigation. While Baltimore City accounts for the largest number of individuals with elevated blood lead levels, this data set still represents only a subset of children in the state and not the state overall.

- **Medicaid Data:** A list of Medicaid enrolled children would have been used to determine the percentage of children in the project data set who had received a lead test. Unfortunately, we were unable to obtain this information for these analyses.

APPENDIX 7. Supplemental Data Tables

Table A-7.1. Targeted Areas Containing 90% Expected "At-Risk" Children

Zip Codes with 90% of Expected					
Allegany	**Baltimore City**	**Cecil**	**Howard, *Cont.***	**Prince Georges, *Cont.***	**Somerset**
21502 *	21201 *	21901	21043	20708	21817 *
21532 *	21202 *	21911	21044	20710 *	21853 *
	21205 *	21921	21045	20712 *	
Anne Arundel	21206 *		21046	20715	**Talbot**
20724	21209 *	**Charles**	21075	20716	21601
21012	21210 *	20601		20720	
21037	21211 *	20602	**Kent**	20721	**Washington**
21060 *	21212 *	20603	21620 *	20722 *	21713 *
21061 *	21213 *	20640 *		20735	21722 *
21108	21214 *	20646	**Montgomery**	20737 *	21740 *
21113	21215 *		20814	20740 *	21742 *
21114	21216 *	**Dorchester**	20815 *	20743 *	21783 *
21122	21217 *	21613 *	20817	20744	21795 *
21144	21218 *	21643 *	20832	20745	
21226 *	21223 *		20850	20746 *	**Wicomico**
21401	21224 *	**Frederick**	20852	20747	21801 *
21403	21225 *	21701 *	20853	20748 *	21804 *
	21229 *	21702	20854	20770 *	21826 *
Baltimore Co.	21230 *	21703 *	20866	20772	21875 *
21030	21231 *	21771	20871	20774	
21093 *	21239 *	21788	20874	20781 *	**Worcester**
21117	**Calvert**		20876	20782 *	21811 *
21133 *	20657	**Garrett**	20877	20783 *	21842 *
21136	20678	21550 *	20878	20784 *	21851 *
21204 *			20879	20785 *	21863 *
21207 *	**Caroline**	**Harford**	20886		
21208 *	21629 *	21001 *	20901		
21219 *	21632 *	21009	20902	**Queen Annes**	
21220 *		21014	20903	21617 *	
21221 *	**Carroll**	21015	20904		
21222 *	21048	21040 *	20906	**Saint Marys**	
21227 *	21074	21047	20910	20619	
21228 *	21102	21050	20912	20636	
21234 *	21157	21078 *		20650	
21236 *	21158		**Prince Georges**	20653	
21237 *	21784	**Howard**	20705	20659	
21244 *	21787 *	20723	20706		
21286 *	21791 *	21042	20707		

* Zip Code Considered "At Risk" in the 2004 Targeting Plan

Table A-7.2. Targeted Areas Containing 75% Expected "At-Risk" Children

Zip Codes with 75% of Expected					
Allegany	**Baltimore, *Cont.***	**Calvert**	**Harford**	**Prince George's**	**Saint Marys**
21502 *	21236 *	20657	21009	20706	20653
21532 *	21237 *		21040 *	20707	20659
	21244 *	**Caroline**		20708	
		21632 *	**Howard**	20716	
Anne Arundel	**Baltimore City**		20723	20737 *	**Somerset**
21061 *	21201 *	**Carroll**	21043	20743 *	21853 *
21113	21202 *	21157	21044	20744	
21122	21205 *	21158	21045	20745	
21144	21206 *			20746 *	**Talbot**
21226 *	21209 *	**Cecil**	**Kent**	20747	21601
21401	21211 *	21921	-	20748 *	
	21212 *			20770 *	
	21213 *	**Charles**	**Montgomery**	20772	**Washington**
Baltimore	21214 *	-	20850	20774	21740 *
21117	21215 *		20874	20782 *	21742 *
21133 *	21216 *	**Dorchester**	20877	20783 *	
21136	21217 *	21613 *	20878	20784 *	**Wicomico**
21207 *	21218 *		20901	20785 *	21801 *
21208 *	21223 *	**Frederick**	20902		21804 *
21220 *	21224 *	21702	20903	**Queen Annes**	
21221 *	21225 *	21703 *	20904	-	
21222 *	21229 *		20906		**Worcester**
21227 *	21230 *	**Garrett**	20910		21811 *
21228 *	21231 *	-	20912		21851 *
21234 *	21239 *				

* Zip Code Considered "At Risk" in the 2004 Targeting Plan

Table A-7.3. Targeted Areas Containing 50% Expected "At-Risk" Children

Zip Codes with 50% of Expected					
Allegany	**Baltimore City**	**Baltimore City, *Cont.***	**Cecil**	**Howard**	**Somerset**
21502 *	21202 *		21921	-	-
	21205 *	21225 *		**Kent**	**Talbot**
Anne Arundel	21206 *	21229 *	**Charles**	-	-
-	21212 *	21230 *	-	**Montgomery**	**Washington**
Baltimore	21213 *	21231 *	**Dorchester**	-	21740 *
21207 *	21214 *	21239 *	21613 *	**Prince Georges**	21742 *
21221 *	21215 *			-	
21222 *	21216 *	**Calvert**	**Frederick**	**Queen Annes**	**Wicomico**
21227 *	21217 *	-	-	-	21801 *
21228 *	21218 *	**Caroline**	**Garrett**	**Saint Marys**	21804 *
21234 *	21223 *	-	-	20653	
21244 *	21224 *	**Carroll**	**Harford**		**Worcester**

* Zip Code Considered "At Risk" in the 2004 Targeting Plan

Table A-7.4. Comparison of ZIP Codes containing 90% of Expected Children with Blood Lead Levels ≥5 mcg/dL to other ZIP Codes

Characteristics		90% Expected Cases Area		Outside Area	
		n	**%**	**n**	**%**
Total Zip Codes		173	38.4	277	61.6
Total Children In ≤5 Zip Codes*		374,621	86.0	61,018	14.0
Zip Code Characteristics					
Sex, Total Children*					
	Female	183,725	49.0	29,882	49.0
	Male	190,896	51.0	31,136	51.0
Age (years), Total Children*					
	<1	62,224	16.6	9,062	14.9
	1	62,271	16.6	9,546	15.6
	2	63,745	17.0	9,978	16.4
	3	63,355	16.9	10,437	17.1
	4	61,860	16.5	10,740	17.6
	5	61,166	16.3	11,255	18.4
Race, by Median Percent**					
	White	-	63.3	-	88.5
	Black	-	22.0	-	6.1
	Other	-	8.4	-	4.0
Median Percent Occupied**					
	Occupied	-	93.3	-	90.8
	Vacant	-	6.7	-	9.2
Median Percent Rentals***					
	Owner Occupied	-	67.3	-	83.2
	Renter Occupied	-	66.2	-	16.8

* 2010 Population of children ≤5 years old
** 2010 Census, Summary File 1
*** 2010 Census, Demographic Profile

Table A-7.5. Comparison of ZIP Codes containing 75% of Expected Children with Blood Lead Levels ≥5 mcg/dL to other ZIP Codes

Characteristics	75% Expected Cases Area		Outside Area	
	n	**%**	**n**	**%**
Total Zip Codes	95	21.1	355	78.9
Total Children In ≤5 Zip Codes*	267,247	61.3	168,392	38.7
Zip Code Characteristics				
Sex, Total Children*				
Female	135,988	50.9	82,348	48.9
Male	131,259	49.1	86,044	51.1
Age (years), Total Children*				
<1	45,481	17.0	25,805	15.3
1	45,301	17.0	26,516	15.7
2	45,900	17.2	27,823	16.5
3	44,912	16.8	28,880	17.2
4	43,288	16.2	29,312	17.4
5	42,365	15.9	30,056	17.8
Race, by Median Percent**				
White	-	51.6	-	87.0
Black	-	28.9	-	6.5
Other	-	9.1	-	4.4
Median Percent Occupied**				
Occupied	-	93.1	-	92.4
Vacant	-	6.9	-	7.6
Median Percent Rentals***				
Owner Occupied	-	61.2	-	81.9
Renter Occupied	-	38.8	-	18.1

* 2010 Population of children ≤5 years old
** 2010 Census, Summary File 1
*** 2010 Census, Demographic Profile

Table A-7.6. Comparison of ZIP Codes containing 50% of Expected Children with Blood Lead Levels ≥5 mcg/dL to other ZIP Codes

Characteristics	50% Expected Cases Area		Outside Area	
	n	**%**	**n**	**%**
Total Zip Codes	32	7.1	418	92.9
Total Children In ≤5 Zip Codes*	95,116	21.8	340,523	78.2
Zip Code Characteristics				
Sex, Total Children*				
Female	46,904	49.3	166,703	49.0
Male	48,212	50.7	173,820	51.0
Age (years), Total Children*				
<1	16,308	17.1	54,978	16.1
1	16,207	17.0	55,610	16.3
2	16,373	17.2	57,350	16.8
3	16,042	16.9	57,750	17.0
4	15,250	16.0	57,350	16.8
5	14,936	15.7	57,485	16.9
Race, by Median Percent**				
White	-	54.4	-	84.9
Black	-	37.6	-	8.2
Other	-	6.8	-	4.9
Median Percent Occupied**				
Occupied	-	90.1	-	92.8
Vacant	-	9.9	-	7.2
Median Percent Rentals***				
Owner Occupied	-	57.2	-	80.7
Renter Occupied	-	42.8	-	19.3

* 2010 Population of children ≤5 years old
** 2010 Census, Summary File 1
*** 2010 Census, Demographic Profile

APPENDIX 8. Acronyms and Abbreviations

mcg/dL – micrograms/deciliter

ACS – American Community Survey

CDC – U. S. Centers for Disease Control and Prevention

CLR – Childhood Lead Registry

DAT – Maryland State Department of Assessment and Taxation

DHMH – Maryland Department of Health and Mental Hygiene

MDE – Maryland Department of the Environment

STELLAR – Systematic Tracking of Elevated Lead Levels and Remediation

APPENDIX 9. Cost-Benefit Analysis of Lead Testing Strategy

This section estimates the lifetime cost-benefits of reducing blood lead levels in 100% of Maryland children, ages 1 and 2, who have a blood lead level ≥5 mcg/dL, in a three-year period. Many studies have detailed the economic expenses associated with lead exposures. This analysis estimates the cost-benefits associated with a decrease in lead exposure in the following areas: lifetime earnings, tax revenue, special education, and criminal justice. A recent nationwide study found a return of $17-$221 for every dollar spent on lead hazard controls (Gould, 2009).

Lifetime Earnings

Lead poisoning is linked to cognitive and behavioral impairment, even at levels below 10 mcg/dL (Canfield, 2003). The loss of IQ points is considered irreversible and is calculated once rather than yearly. Lost IQ points are associated with both fewer years of schooling and a lower probability of participation in the workforce (Salkever, 1995). The lifetime earnings saved are the total savings if 100% of Maryland children are tested, and children with a EBL ≥5 mcg/dL have their blood lead levels reduced to the 'background' level of 1.36 mcg/dL (2012 geometric mean blood lead level in Maryland children ages 1-2).

Lanphear et al. estimate that children with a blood lead level between 2-10 mcg/dL, 10-20 mcg/dL, and 20-30 mcg/dL lose 0.513, 0.19, and 1.1 IQ points per 1 mcg/dL blood lead level respectively (Lanphear, 2005). In Table A-9.1 Lanphear's IQ estimate is used with Gould's IQ value estimate of $21,014 per one IQ point (adjusted for inflation to 2015 USD) to find total savings of $183,505,165. All inflation adjustments in this analysis have been done using the Bureau of Labor Statistics (BLS) Consumer Price Index inflation calculator.

Table A-9.2 shows a second method for calculating lost future income. Landrigan et al. calculated the economic consequences of lead exposure at the national geometric mean blood level using an analysis by Salkever (Landrigan, 2002; Salkever, 1995). In Maryland the geometric mean blood lead level is 1.37 mcg/dL for boys and 1.35 mcg/dL for girls ages 1-2. Table A-9.2 uses the calculation from Schwartz et al. of 0.245 IQ points lost per 1 mcg/dL; and 2.1% and 3.6% lifetime earnings lost for boys and girls respectively (Schwartz, 1994; Salkever, 1995). Grosse et al. calculated the expected lifetime earnings by sex and age in the United States in 2007 (Grosse, 2009). The expected lifetime earnings for children 0-4 years old by sex was adjusted to 2015 U.S. dollars. The estimate of total lifetime earnings saved using the Landrigan method is $130,595,692. Using an IQ loss estimate from a newer study by Canfield et al. instead of the Schwartz estimate the total lifetime earnings estimate increases to $512,077,044 (Canfield, 2003). Canfield estimates, the IQ loss per 1 mcg/dL to be 1.22 points for children with an EBL <10 mcg/dL and 0.35 for all children.

The estimates for the lifetime earnings saved in Maryland children range from $130-$512 million. Assuming an average income tax rate of 5%, eliminating high lead exposure (blood lead level ≥5 mcg/dL) in Maryland would save the state $7-$26 million per cohort in tax revenue.

Table A-9.1. Lifetime Earnings Saved, in Maryland Children 1-2 years of age

EBL	MD Children per EBL Group	Geometric Mean EBL*	Average Reduction in blood lead level	Average IQ Point Loss Avoided per 1 mcg/dL	Total Avoided IQ Loss	Total lifetime earnings
5-9	3,327	6.0	4.7	0.513	7,966	$167,396,367
10-20	359	12.6	11.2	0.19	767	$16,108,798
≥20	108	27.2	25.8	0.11	307	$6,449,481
Total	3,794				8,732	**$183,505,165**

* Maryland 2012 lead data, Children 1-2 years of age

Table A-9.2. Lifetime Earnings Saved, in Maryland Children 1-2 years of age, Landrigan Method

	MD Children with EBL ≥5	Geometric Mean EBL*	Average Reduction in Blood Lead Level	Average IQ Point Loss Avoided per Person	Average Gain in Lifetime Earnings	Average Lifetime Earnings per Person	Total Lifetime Earnings
Boys	1,897	6.84	5.48	1.34	2.8%	$1,213,225	$64,672,653
Girls	1,897	6.81	5.46	1.34	4.9%	$715,669	$65,923,040
Total	3,794						**$130,595,692**

* Maryland 2012 lead data, Children 1-2 years of age

Special Education

The cognitive impairment associated with lead is also linked to the need for special education. It is estimated that 20% of children with a blood lead level ≥25 mcg/dL and 10% of children with a blood lead level ≥10 mcg/dL require special education (Schwartz, 1994; Pichery, 2011). The annual cost of additional special education used in Table A-9.3 is from the Maryland Special Education Expenditure project, which calculated the total education spending in Maryland in the 2001-2002 school year to be $1.8 billion (Parrish, 2003). Table A-9.3 shows the cost of three years of special education discounted by 3% for five years. The total education savings of $1,934,767 are discounted for five years to match the age that children start school (Stefanak, 2005).

Table A-9.3. Special Education Savings

Maryland children with EBL ≥ 25	51
Estimated percent of children with EBL ≥ 25 mcg/dL who require special education	20%
Maryland children with EBL 10-25	416
Estimated percent of children with EBL ≥ 10 mcg/dL who require special education	10%
Estimated number of children needing special education	52
Cost of special education per school-aged student in the 2001-2002 school year in Maryland	$14,440
Discounted cost per year	$12,456
Total discounted savings for three years of special education for one cohort of children	**$1,934,767**

Criminal Justice

Levin's Population Attributable Risk (Equation A-9.1) was used to estimate juvenile justice expenditures (Gordis, 2009). In a study of adolescents arrested as delinquents, the adjusted odds ratio for having bone lead levels ≥25 ppm was: OR=4.0 (95% CI, 1.4-11.1) (Needleman, 2002). It is assumed that children with a blood lead level ≥10 mcg/dL have neurological damage comparable to the adolescents in Needleman's study (Stefanak, 2005). The expected number of children with a blood lead level ≥10 mcg/dL in Maryland is used along with Needleman's odds ratio to calculate Levin's Population Attributable Risk (Equation A-9.1). The estimated cost of juvenile services used here may be an underestimation; the calculated attributable risk (1.0%) is much lower than risks cited in other studies (10% in Korfmacher, 2003; 11% in Stefanak, 2005). Table A-9.4 shows the cost of state operated juvenile facilities due to lead exposure using the calculated attributable risk (Maryland Department of Juvenile Services, 2014). The final estimate of $2,080,395 is discounted by 3% for 15 years. The 15 year discounting period and the three years of facility costs are a reflection of the majority of juvenile justice costs incurring between the ages of 15-18 (Stefanak, 2005).

Equation A-9.1. Levin's Population Attributable Risk

a) Risk in total population= $(Risk\ in\ exposed \times Prevalence\ in\ target\ population) + [Risk\ in\ unexposed \times (1 - Prevalence\ in\ target\ population)]$

$$=(4 \times 0.003) + [1 \times (1 - 0.003)] = 1.01$$

b) Percent population attributable risk= $\left(\frac{Risk\ in\ total\ population - Risk\ in\ unexposed}{Risk\ in\ total\ populaation}\right) \times 100$

$$= \left(\frac{1.01-1}{1.01}\right) \times 100 = 1.0\%$$

Studies have also estimated the cost of violent crimes due to lead exposure. Gould et al. calculates the lead linked crimes per 100,000 residents that could be prevented with a 1 mcg/dL

reduction in average preschool blood lead level (Gould, 2009). The number of lead linked crimes shown in Table A-9.5 are adjusted from Gould using the rate of each type of crime in Maryland (Governor's Office of Crime Control & prevention, 2013). Instead of calculating the savings of a 1 mcg/dL reduction, the savings were calculated as if all Maryland children ages 1-2 with a blood lead level ≥5 mcg/dL were reduced to the geometric mean blood lead level of 1.36 mcg/dL. This reduction changes the geometric mean blood lead level from 1.36 mcg/dL to 1.30 mcg/dL (ΔBlood lead level=0.06). McCollister et al. calculates tangible costs from victim costs, criminal justice costs, and crime career costs (McCollister, 2010). Crime career costs were removed from this analysis since they are calculated from lost future earnings and that calculation is done separately in this analysis (Table A-9.1 and Table A-9.2). McCollister also does a calculation for intangible costs that include indirect losses suffered by crime victims, including pain and suffering, decreased quality of life, and psychological distress. In Maryland the tangible costs are estimated to be $2.2 million, and the total tangible and intangible costs are estimated to be over $14 million (Table A-9.5).

Table A-9.4. Savings from Reductions in Juvenile Delinquency

2014 Costs of MD Department of Juvenile Services State Operated Facilities	$111,659,988
Fraction of juvenile delinquents attributable to lead poisoning	1.0%
Lead poisoning attributable cost per year adjusted to 2015 USD	$1,080,396
Total discounted savings for three years (3% for 15 years)	**$2,080,395**

Table A-9.5. Savings from Reductions in Violent Crime

Crime	Crimes per 100,000 MD Residents in 2013	Lead-linked Crimes per 100,000 MD Residents	Total Avoided Lead Linked Crimes	Tangible Costs per Crime in 2015 USD	Total Tangible Costs Avoided Annually
Burglaries	537.9	0.94	55	$5,489	$336,114
Robberies	170.1	0.04	2	$17,126	$44,455
Aggravated assaults	271.3	0.83	49	$17,341	$937,595
Rape	19.7	0.04	3	$32,035	$91,666
Murder	6.5	0.01	1	$1,129,869	$827,428
Totals			110	$1,201,860	**$2,237,258**

Cost-Benefit Analysis Summary

The total savings of reducing blood lead levels in 100% of one cohort of Maryland children, ages 1 and 2, that have a blood lead level ≥5 mcg/dL is in the range of $143-$556 million (Table A-9.6). The long term health effects and behavioral problems resulting from lead

are an additional cost to society not included in this estimate. These include attention deficit-hyperactivity disorder (ADHD), adult hypertension, stroke, and osteoporosis. Quantifying the cost of these diseases due to lead has not been done for this analysis due to a lack of research and data, but is assumed to be high. Using the estimated cost of universal testing and the range of savings in the cost-benefit analysis (Table A-9.6) the return for each dollar invested ranges from $24-$142 (low range of this estimate excludes intangible crime savings).

Table A-9.6. Summary of Cost-Benefits

Benefit	Estimated Savings for One Cohort of Children
Lifetime Earnings	$131-$512 million
Tax Revenue	$7-$26 million
Special Education	$1.9 million
Juvenile Delinquency	$2 million
Violent Crime Tangible Costs	$2.2 million
Violent Crime Intangible Costs	$12 million
Total savings	**$143-$556 million**

Toxicological Profile for Lead

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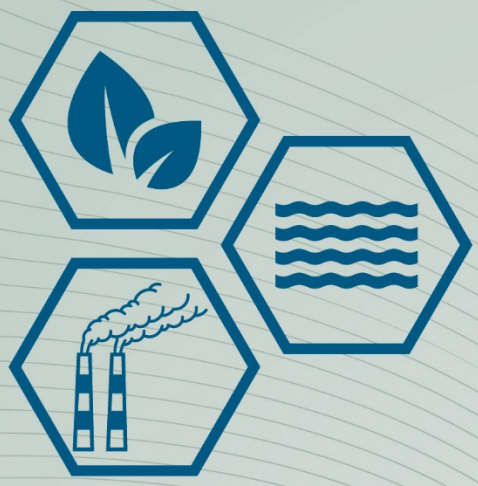

Toxicological Profile for Lead

Draft for Public Comment

May 2019

ATSDR
U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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VERSION HISTORY

Date	Description
May 2019	Draft for public comment toxicological profile released
August 2007	Final toxicological profile released
April 1993	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

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

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

The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. Pb has also been found in a variety of other consumer products including storage batteries, solders, pottery glazes, leaded crystal glassware, cosmetics, hair dyes, jewelry, gun shot and ammunition, relic fishing sinkers, tire weights, and imported children's toys, traditional or folk remedies, and candy/food packaging. For adults, exposure to levels of Pb beyond background is usually associated with occupational exposures. For children, exposure to high levels of Pb is associated with living in areas

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

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

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

1.2 SUMMARY OF HEALTH EFFECTS

The toxicity of Pb to humans has been known for over 2,000 years, and is not disputed. Early epidemiological studies focused on overt toxicity associated with high occupational exposures. However, during the past few decades, there has been a growing awareness that low-level environmental exposure

resulting in PbB <10 µg/dL is associated with adverse effects, particularly in children. Currently, it is accepted that adverse effects occur at PbB <5 µg/dL and for the most studied endpoints (neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental), effects occur at the lowest PbBs studied (≤5 µg/dL). CDC (2018b) states that "no safe blood lead level in children has been identified." As a result, U.S. public health policy has changed to focus on lowering PbB levels to well below 10 µg/dL. CDC considers PbB to be elevated in children when it exceeds a reference value defined as the 97.5th percentile for the U.S. population. The current CDC reference value, based on data from NHANES 2007–2009 and 2009–2010, is 5 µg/dL. Therefore, the primary objective of current research is on health effects associated with PbB ≤5 µg/dL.

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

To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of µg/dL). Blood Pb concentration reflects both ongoing exposure and Pb stores in bone, which can be transferred to blood. Because of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months and not necessarily the larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI), which may be a better reflection of exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct, noninvasive measurements of bone Pb concentrations have been used as a metric of long-term exposure on the basis that most of the absorbed Pb retained in the body will reside in bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone

Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb is retained in the body for decades. Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect are typically unknown or highly uncertain.

Adverse health effects of Pb have been observed in every organ system. This is because the mechanisms that induce toxicity are common to all cell types and because Pb is widely distributed throughout the body. Health effects of Pb have been observed in all organ systems over a wide PbB range (≤5–>50 μg/dL). Exposure thresholds for effects on specific organ systems have not been identified (i.e., no safe level has been identified). Cognitive deficits in children occurring at the lowest PbB concentrations (≤5 μg/dL) are the best substantiated effects. However, data for some organ systems results are inconsistent, and insufficient data are available to provide information on dose-response relationships. It is also important to note that effects observed in adults, especially older adults, may be due to higher environmental or occupational exposures in the past; therefore, exposure history is an important consideration in epidemiological studies on the health effects of Pb.

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

Neurological Effects in Children. Numerous prospective and large cross-section studies in children provide consistent evidence of decrements in neurological function, including decrements in cognitive function (learning and memory), altered behavior and mood (attention, hyperactivity, impulsivity, irritably, delinquency), and altered neuromotor and neurosensory function (visual-motor integration, dexterity, postural sway, changes in hearing and visual thresholds). These effects have been associated with a PbB range from ≤5 to >50 μg/dL, with numerous studies providing evidence for effects at PbB ≤5 μg/dL. Taken together, studies support the concept that Pb affects cognitive function in

children prenatally and/or environmentally exposed to low levels of Pb. No threshold for these effects has been identified (i.e., no safe level has been identified). Decrements in cognitive function increase with PbB, and several PbB-effect models predict that larger decrements in cognitive function would occur when PbB increases from 1 to 10 µg/dL, compared to when PbB increases from levels >10 µg/dL. Supra-linear dose-response relationships for neurological outcomes are discussed in greater detail in Section 2.16 (Neurological). At higher PbB (>30 µg/dL), other neurotoxic effects have been observed, including alterations in nerve function (decrements in fine and gross motor skills, peripheral neuropathy) and encephalopathy.

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

Renal Effects. Adverse renal effects of Pb are well-established in numerous epidemiological studies. Studies show consistent evidence of renal damage and reduced renal function associated with a wide range of PbB (≤10–50 µg/dL), with several studies providing evidence for effects at PbB ≤5 µg/dL. Deficits in renal function include enzymuria, proteinuria, impaired transport of organic anions and glucose, and depressed glomerular filtration rate (GFR). At higher PbB (>30 µg/dL), Pb-induced nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, interstitial fibrosis, and tubular necrosis. Note that Pb-induced decrements in renal function can lead to higher Pb body burden due to decreased excretion of Pb (i.e., reverse causality). In addition, other causes of decreased renal function could result in an increased body burden of Pb.

Cardiovascular Effects. A large number of epidemiological studies in adults show adverse cardiovascular effects associated with a PbB range from ≤5 to >50 µg/dL. Effects on blood pressure is the most-studied cardiovascular outcome, with studies showing increased systolic and diastolic blood

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

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

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

Reproductive Effects in Males. Health effects of Pb on the male reproductive system have been evaluated in numerous epidemiological studies. Effects include damage to sperm (decreased sperm count, concentration, motility, and viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm), possible alterations in serum levels of reproductive hormones (testosterone, estradiol, luteinizing hormone [LH], and follicle-stimulating hormone [FSH]), decreased fertility, and histopathological changes to the testes. Severity of these effects increases with PbB. Studies

conducted in populations with mean PbB ≤10 μg/dL provide evidence of damage to sperm, although effects are more consistently observed at PbB >10 μg/dL. Regarding effects on serum levels of reproductive hormones, results of available studies for PbB ranging from ≤10 to >50 μg/dL are inconsistent; thus, Pb-induced effects on circulating reproductive hormones are not firmly established. At higher PbB (>10 μg/dL), a few studies provide evidence of more severe effects, including decreased fertility and histopathological damage to testes.

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

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

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

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

Cancer. Numerous epidemiological studies have evaluated associations between Pb exposure and cancer. Although studies provide limited evidence of carcinogenicity of Pb in humans, results are inconsistent, with several negative studies, and interpretation of data may be limited due to confounding factors (e.g., smoking status, family history of cancer, co-exposure to other carcinogens). At PbB ≤10 µg/dL, increased risks were reported for all cancers and lung cancer. At PbB >10 µg/dL, increased risks were observed for all cancer, respiratory tract cancer, stomach cancer, intestinal cancer, cancer of the larynx, and glioma.

The Department of Health and Human Services classified Pb and Pb compounds as reasonably anticipated to be human carcinogens (NTP 2016). In 1988, EPA classified Pb as a probable human carcinogen based

on sufficient evidence in animals; evidence in humans was considered inadequate (IRIS 2004). The International Agency for Research on Cancer (IARC) has classified inorganic Pb compounds as probably carcinogenic to humans (Group 2A) based on sufficient evidence in animals and limited evidence in humans; evidence for organic Pb compounds was considered to be inadequate in humans and animals (IARC 2006).

1.3 MINIMAL RISK LEVELS (MRLs)

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

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of lead (Pb). It contains descriptions and evaluations of epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others identify potential health effects in persons with elevated PbB, the information in this section is organized by health effect.

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of epidemiology studies included in this chapter of the profile.

Since development of the 2007 Toxicological Profile on Lead (ATSDR 2007), results of numerous epidemiological studies have prompted growing attention to the adverse health effects of Pb exposures that result in blood Pb concentrations (PbB) of <10 µg/dL (EPA 2014c). Awareness of the potential adverse consequences of such exposures has led to changes in U.S. public health policy, with a focus on lowering PbB levels to well below 10 µg/dL (CDC 2012d; EPA 2016b). In 2012, CDC established a PbB reference value for lead, replacing the 10 µg/dL level of concern. The reference value is based on the 97.5th percentile of the PbB distribution among children 1–5 years of age in the United States, using data generated by NHANES (CDC 2012d). At that time, the PbB reference was approximately 5 µg/dL (NHANES 2011–2012) (CDC 2018a). The reference value would be updated every 4 years using the two most recent NHANES surveys and would be used in recommendations for follow-up evaluations and identification of high-risk childhood populations (CDC 2012d). It is likely that PbB values among children will continue to decline; therefore, the primary focus of this toxicological profile is on health effects associated with low Pb exposure (i.e., those observed at PbB ≤5 µg/dL). Detailed information on effects at PbB ≤10 µg/dL is also presented to examine potential exposure-response relationships. Information on health effects observed at higher PbB levels (>10 µg/dL) is also included to provide a comprehensive overview of the adverse effects of Pb.

Literature Search Strategy. The literature on health effects of Pb in humans is enormous, with countless epidemiological studies in workers and the general population, including children. Due to the extent of the Pb database in humans, it is impossible to cite all, or even most, of the studies on health effects of Pb; thus, this profile does not attempt to provide a comprehensive review of all literature; instead, the profile summarizes the major lines of epidemiological evidence regarding health effects in humans. Although the literature database on adverse effects of Pb in laboratory animals is also extensive, given the large number of studies available in humans, animal studies are not included in this toxicological profile. For a recent review of studies in animal models, the reader should consult the EPA's Integrated Science Assessment for Lead (EPA 2014c).

The following were used as primary sources to identify literature on health effects of Pb:

- The previous Toxicological Profile for Lead (ATSDR 2007) was used to identify literature published through 2007.
- The EPA (2014c) Integrated Science Assessment for Lead was used to identify literature published from 2006 to 2013.
- Literature searches were conducted from 2013 to 2016 to identify studies published after EPA (2014c).

In addition, recent reviews by NTP (2012) and NAS (2013) were consulted. As anticipated, the literature search revealed an extensive epidemiological database of literature published since 2013. To narrow the evaluation to those studies of greatest utility identifying health effects of low exposures to Pb exposure, a series of inclusion criteria were defined; only studies meeting the criteria were considered for inclusion in the toxicological profile. These criteria are described further in Appendix B. Data from selected studies were tabulated and discussed in subsequent sections of this chapter.

Duration of Exposure. Typically, toxicological profiles organize the discussion of health effects according to exposure duration categories. However, this is not a particularly informative approach to the discussion of Pb epidemiology. The epidemiologic study of Pb toxicity in human populations has relied on internal dose metrics (PbB, bone Pb) for evaluating associations between health outcomes. These metrics are considered to represent relatively recent exposure history, in the case of PbB, and longer-term cumulative exposure, in the case of CBLI or bone Pb. However, neither metric offers a confident estimate of exposure duration or of changes in lead exposure over time (including peak exposure periods that may have occurred in the past), and, in general, the complete exposure history is not known. Health

outcomes associated with acute exposures is available from clinical case studies of Pb poisoning (see Section 2.2). However, even in these cases, the exposure duration that proceeded the identification of the case is rarely known with certainty.

Routes of Exposure. For the general population, exposure to Pb occurs primarily via the oral route, with some contribution from the inhalation route, whereas inhalation exposures can be more important in occupational settings, depending on particle size. In addition, occupational exposure to organic Pb compounds may involve dermal absorption as a significant exposure route. This profile does not attempt to separate health effects by route of exposure. As noted previously, epidemiology studies have relied on internal dose metrics (PbB, bone Pb), which reflect Pb body burden (to varying degrees), irrespective of the route of exposure. The primary systemic toxic effects of Pb are the same regardless of the route of entry into the body,

Exposure Metric. To quantify exposure in humans, data are expressed in terms of absorbed Pb, and not in terms of external exposure levels (e.g., concentration in water) or dose (e.g., mg/kg/day). The most common metric of absorbed dose for Pb is the concentration of lead in blood (PbB), although other measures of exposure (e.g., concentration of Pb in bone, hair, teeth, or urine) are used; however, measurements of Pb in urine, teeth, and hair are not as reliable as measurements in blood or bone. PbB mainly reflects exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of Pb in bone (see Section 3.1). Pb in bone is considered a biomarker of cumulative or long-term exposure because Pb accumulates in bone over the lifetime and most of the Pb body burden resides in bone. Most of the body burden of Pb (the total amount of Pb in the body) is distributed to the bone, with approximately 94 and 76% of the body burden found in bone in adults and children, respectively. The remainder is distributed to blood and soft tissues. However, the concentration of Pb in blood can vary considerably with age and physiology/lifestage (e.g., pregnancy, lactation, menopause). For this reason, measurement of Pb in bone has seen wider application in epidemiological studies of adults in which measures of cumulative lifetime exposures are of interest. However, bone Pb measurements require specialized radiologic equipment (e.g., K-shell x-ray fluorescence; XRF) and, as a result, are used less commonly than PbB in human epidemiology. Since most of the epidemiology has relied on PbB as the dose metric, this profile has focused on describing dose-response relationships based on PbB to facilitate comparisons across studies and endpoints. This approach also aligns with public health practices, which rely on PbB for evaluating elevated exposures to Pb (CDC 2012d; EPA 2016b). However, it is recognized that some health outcomes may be correlated with cumulative exposure, in which case, bone Pb may be a better dose metric than PbB. For these

outcomes, short-term variation in PbB may contribute to exposure classification error (i.e., the same PbB could be observed in individuals who have different bone Pb). The exposure history of the subjects may also be an important factor in determining associations observed between outcomes and blood or bone Pb. Some studies of historically exposed occupational populations (e.g., former workers) have found stronger associations between bone Pb and health outcomes than with PbB, while some studies of concurrently exposed populations have found stronger associations with PbB (Shih et al. 2007).

Confounding Factors and Effect Modifiers. Bias can occur in epidemiological studies when the background risk of the outcome being measured is not the same in the exposed and reference groups. Confounders are variables that affect the measured outcome and are also associated with the Pb exposure metric (e.g., PbB, bone Pb). For example, Pb body burden increases with age; therefore, age can be a confounding factor if it is also a risk factor for the outcome (e.g., renal or cardiovascular disease). Not adjusting for confounders may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on whether it is a negative or positive confounding variable. Effect modifiers are variables that affect the measured outcome independently of the Pb exposure metric. For example, renal disease from any cause can affect blood pressure and, thereby, could interact with Pb to change blood pressure. Effect modifiers can also be confounders, if they are associated with the Pb exposure metric (e.g., socio-economic status [SES] and cognitive development). Failure to account for important effect modifiers can result in underestimation or overestimation of the apparent strength of the association, depending on the direction of the effect of the modifying variable. Confounding factors and effect modifiers are discussed in greater detail in sections that describe specific categories of health effects.

Overview of Health Effects of Pb. The health effects of Pb are diverse, and exposure to Pb is associated with toxicity to every organ system. This is not surprising because the mechanisms of action associated with Pb-induced toxicity, including perturbations of ion homeostasis and transport, protein binding, oxidative stress, and inflammation, are common to all cell types. In addition, Pb is widely distributed throughout the body, and has been measured in all tissues evaluated (see Section 3.1.2). For all organ systems, toxicity has been observed at PbB $\leq$10 μg/dL. Neurological effects of Pb are of greatest concern because effects are observed in infants and children; furthermore, these effects may result in life-long decrements in neurological function. Children are also more vulnerable because of behaviors that increase ingestion of Pb surface dusts (e.g., hand-to-mouth activity) and because gastrointestinal absorption of ingested Pb is higher in children compared to adults, possibly due to a combination of physiological differences and differences in diet and nutrition. The weight-of-evidence for all adverse

health effects is strongly supported by studies in animal models and *in vitro* systems; see EPA (2014c) for a review of this literature.

Effects observed in association with PbB are briefly described below. Note that for some of the effects listed below, study results are not consistent, which limits interpretation of observations; this is reviewed in more detail in subsequent sections for each organ system in Chapter 2. The most extensive epidemiological databases examining Pb are for neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects.

- **Neurological Effects:**
  - **Children.** Decreased cognitive function; altered mood and behaviors that may contribute to learning deficits, altered neuromotor and neurosensory function, peripheral neuropathy, and encephalopathy.
  - **Adults.** Decreased cognitive function including attention, memory, and learning; altered neuromotor and neurosensory function; altered mood and behavior; and decreased peripheral nerve conduction velocity.

- **Renal Effects.** Decreased GFR, proteinuria, enzymuria, impaired tubular transport, and histopathological damage.

- **Cardiovascular Effects.** Increased systolic and diastolic blood pressure, increased risk of hypertension, atherosclerosis, altered cardiac conduction, increased risk of heart disease, and increased mortality due to cardiovascular disease.

- **Hematological Effects.** Inhibition of δ-ALAD leading to decreased blood hemoglobin and anemia, decreased activity of other erythrocyte enzymes, and altered plasma erythropoietin (EPO) levels.

- **Immunological Effects.** Perturbation of humoral and cell-mediated immune systems, decreased resistance to disease, sensitization, autoimmunity, and inflammation.

- **Reproductive Effects:**
  - **Males.** Effects on sperm, alterations in semen quality, decreased fertility, histopathological damage to the testes, and possible altered serum concentrations of reproductive hormones.
  - **Females.** Possible alterations in serum concentrations of reproductive hormones, decreased fertility, spontaneous abortion, preterm birth, and decreased age at the onset of menopause.

- **Developmental Effects.** Decreased birth weight and size, decreased anthropometric measures in children, and delayed onset of puberty in males and females.

Other health outcomes associated with PbB include the following:

- **Respiratory Effects.** Decreased lung function, increased bronchial hyperreactivity, increased risk of asthma, and obstructive lung disease.

- **Hepatic Effects.** Possible increases in plasma liver enzymes and cholesterol, enlarged liver, and increased thickness of gall bladder wall.

- **Endocrine Effects.** Possible alterations in serum of thyroid hormones, altered cortisol responses, alteration in serum growth factors, and decreased serum vitamin D levels.

- **Gastrointestinal Effects.** Abdominal pain/colic, nausea, vomiting, and diarrhea and/or constipation.

- **Musculoskeletal Effects.** Bone loss, osteoporosis, dental caries, tooth loss, and periodontitis.

- **Ocular Effects.** Possible macular degeneration and cataracts.

- **Cancer.** Increased risk of cancer, including all cancers, cancer of the respiratory tract, intestinal tract, and larynx, and glioma.

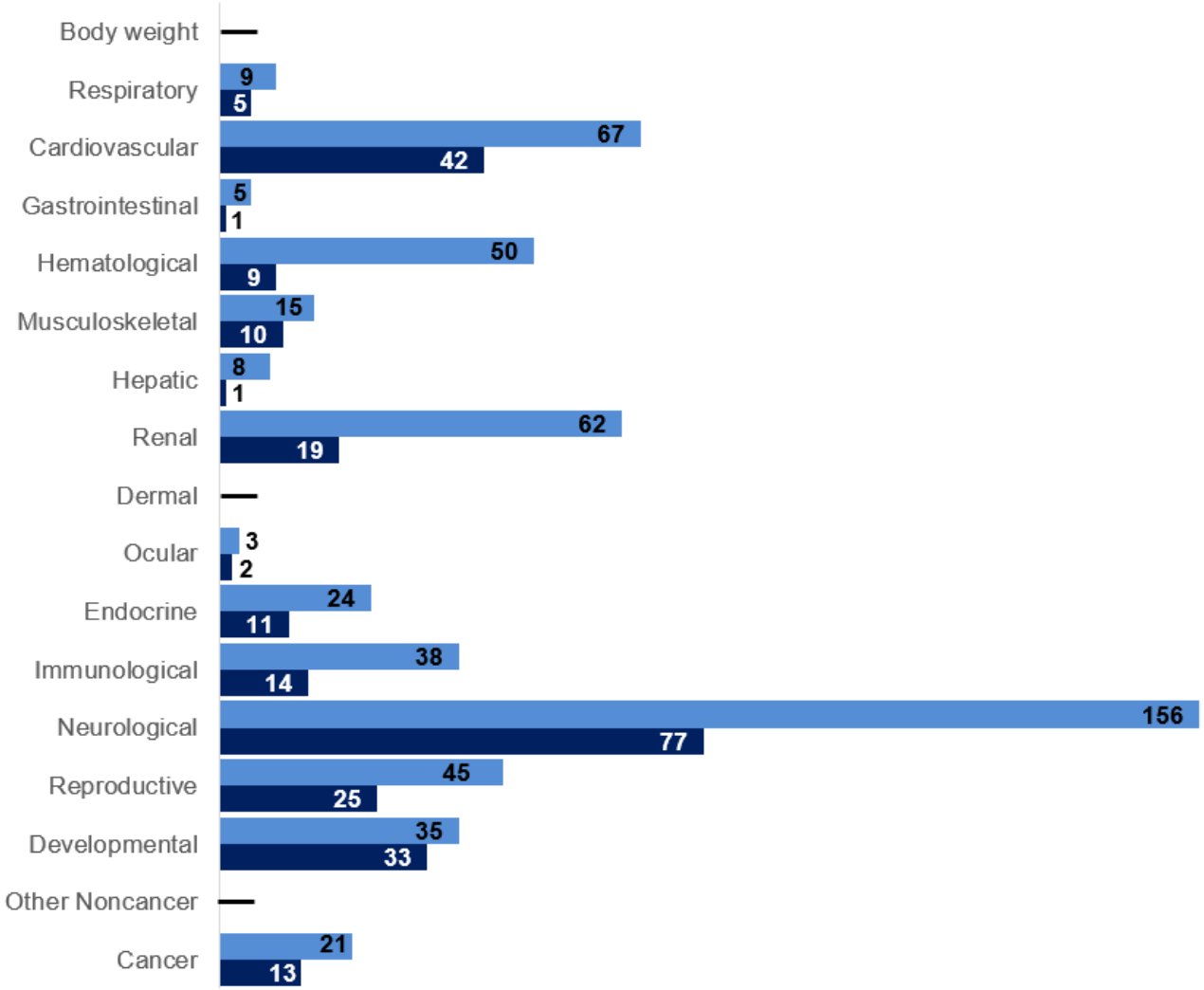
Many specific health effect endpoints have been evaluated in numerous studies. To provide the reader with a weight-of-evidence for these endpoints, the profile indicates if results are consistent and corroborated in numerous studies or if results are inconsistent (or mixed).

Figure 2-1 shows the numbers of epidemiological studies included in this chapter of the toxicological profile, based on health outcome studied. The number of studies evaluating effects at PbB ≤10 µg/dL also is indicated. The PbB ≤10 µg/dL was selected to evaluate effects at the lowest PbB (e.g., ≤5 µg/dL) and to evaluate potential exposure-response relationships for PbB ≤10 µg/dL. As noted above, due to the enormous number of epidemiological studies published, the profile does not attempt to provide a comprehensive review of all literature. Therefore, this figure should not be interpreted as depicting all epidemiological studies that have been published on Pb toxicity.

Figure 2-1. Overview of the Number of Studies Examining Associations Between PbB and Health Effects[a]

Most studies examined the potential cardiovascular, renal, and neurological effects of lead

A subset of studies evaluating health effects for **PbB ≤10 µg/dL** compared to **all PbB studies** (counts represent studies examining endpoint)



[a]Includes studies discussed in Chapter 2. A total of 540 epidemiological studies (including those finding no effect) have examined toxicity; some studies examined multiple endpoints.

2.2 ACUTE LEAD TOXICITY

Overview. No controlled studies in humans have evaluated the acute toxicity of Pb (acute Pb poisoning). Available information is anecdotal, obtained from numerous case reports. Thus, data are not sufficient to establish a dose-response relationship for acute toxicity relative to PbB. Acute Pb toxicity is characterized by symptoms of abdominal pain/colic, vomiting, constipation, peripheral neuropathy, and cerebral edema and encephalopathy, which can lead to seizures, coma, and death. Children are more susceptible than adults to acute Pb poisoning. Additional information on toxicity of ingested Pb debris (e.g., Pb shot) is provided in Appendix C.

Rather than reviewing numerous case reports, the information presented below was taken from the following reviews: Beers et al. (1999); Chisolm (1977); Klaassen (2001); Landrigan (1995); NAS (1972a); Needleman (2004); and Skerfving and Bergdahl (2015). Citations are only specifically noted below if quantitative information is discussed.

Confounding Factors, Effect Modifiers, and Uncertainties. There are several uncertainties from case reports on acute toxicity of Pb. Therefore, it is difficult to establish dose-response relationships for acute toxicity relative to PbB. Uncertainties include:

- Baseline PbB data are rarely available.
- There is a lack of quantitative data on the dose of Pb ingested.
- No information on the fractional absorption of ingested Pb.
- Time from ingestion of Pb to development of symptoms of acute Pb toxicity is often unknown.
- Time from ingestion of Pb to first clinical evaluation and PbB assessment is often unknown.
- Gastrointestinal symptoms and general malaise are typically the first symptoms of acute Pb toxicity to appear; these general symptoms are often attributed to other causes, leading to an initial misdiagnosis or delay in diagnosis.
- Data to develop PbB time-concentration curves are incomplete.
- Numerous factors may contribute to individual susceptibility to acute Pb exposure, including age, intercurrent illness, underlying developmental issues, dietary and nutritional status, concurrent medication use, and exposure to other chemicals.

Clinical Presentation of Acute Pb Toxicity. The onset of acute toxicity is rapid, usually occurring within 1–5 days of exposure. The main organ systems involved are the gastrointestinal, hematological, and

neurological systems. Signs and symptoms increase in severity with increasing PbB, ranging from mild to severe. Gastrointestinal effects include abdominal colic/pain, nausea, vomiting, diarrhea, and constipation. Massive loss of gastrointestinal fluids can lead to dehydration. Hematological effects include decreased hemoglobin synthesis, anemia, and acute hemolytic crisis characterized by anemia and hemoglobinuria. Numerous neurological symptoms are associated with acute Pb toxicity, including headache, hyperirritability, decreased activity, paresthesia, muscle pain and weakness, ataxic gait, decreased consciousness, cerebral edema leading to seizures and coma, encephalopathy, and death. Other reported symptoms include astringency of the mouth, metallic taste in the mouth, and thirst.

Susceptibility of Children. Children are more susceptible than adults to Pb poisoning because the fractional absorption of ingested Pb is higher than in adults and the developing central nervous system is more vulnerable to toxicity compared to a fully developed nervous system (Needleman 2004). In addition to being more sensitive than adults, acute toxicity in children may have long-lasting effects. For example, children who recover from acute encephalopathy can have long-term decreases in cognitive abilities, attention deficits, and impaired behavior. Children are also susceptible due to increased exposure.

Dose-Response Relationship for Acute Toxicity Relative to PbB. As noted above, data from case reports are not sufficient to establish a dose-response relationship for acute toxicity relative to PbB. Some general observations can be made from available reports; however, dose-response relationships are highly uncertain and may not apply to individuals acutely exposed to Pb. At PbB <30 µg/dL, signs and symptoms of acute toxicity typically are not observed. This should not be interpreted to mean that no Pb-induced adverse effects (e.g., decreased hemoglobin synthesis) occur at PbB <30 µg/dL, but that symptoms causing individuals to seek medical intervention (e.g., abdominal colic and vomiting) typically are not observed at PbB <30 µg/dL. As PbBs increase to >30 µg/dL, signs and symptoms of gastrointestinal and neurological toxicity are observed, with severity increasing with PbB. Pb-induced encephalopathy has been reported at PbB <100 µg/dL, but is more commonly associated with PbB >100 µg/dL (NAS 1972b). In a review of 96 cases of death due to acute Pb poisoning in children, death occurred at PbB >100 µg/dL (NAS 1972b).

2.3 DEATH

Overview. Numerous epidemiological studies have investigated associations between Pb exposure and death. Studies include exposure of workers and general populations, and report a wide range of PbB levels. In the general population, studies have shown significant associations between PbB and mortality

due to disease of blood and blood-forming organs. In occupationally exposed individuals, mortality due to infection, endocrine diseases, and digestive diseases were associated with PbB in male workers, but not female workers, while mortality due to respiratory disease was associated with PbB in a cohort of male workers. In addition, studies of the general population and Pb occupations show an association between PbB and cumulative "all-cause" mortality (including cancer). However, results are inconsistent and interpretation may be limited due to confounding factors. Studies assessing associations between PbB and mortality due to cardiovascular diseases and cancer are discussed in Sections 2.5 and 2.19, respectively, and are not reviewed here.

The following causes of death have been associated with PbB:

- ≤10 µg/dL:
    - Increased risk of death from all causes (including cancer and cardiovascular disease); evaluated in a few studies with generally consistent results.
- >10 µg/dL:
    - Increased risk of death from all causes (including cancer and cardiovascular disease); evaluated in several studies with positive associations in some studies.
    - Increased risk of death from chronic or unspecific nephritis or non-malignant kidney disease; evaluated in several studies with positive associations in some studies.
    - Increase risk of death from infection; demonstrated in one study.
    - Increased risk of death from endocrine disease; demonstrated in one study.
    - Increased risk of death from digestive disease; evaluated in several studies with positive associations in some studies.
    - Increased risk of death from diseases of the blood and blood forming organs; demonstrated in one study.
    - Increased risk of death from respiratory diseases (emphysema, pneumonia, and other respiratory diseases); evaluated in several studies with positive associations in some studies.

Confounding Factors and Effect Modifiers. Numerous factors can influence results of epidemiological studies evaluating associations between Pb exposure and mortality, including age, sex, BMI, ethnicity, poverty level, education, alcohol consumption, smoking status, hypertension, diabetes, family history of diseases, activity level, total cholesterol, postmenopausal status, nutritional status, and co-exposure with other metals (i.e., arsenic or cadmium). Failure to account for these factors may attenuate or strengthen

the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Measures of Exposure. Studies examining the association between Pb exposure and mortality evaluate exposure by measurement of PbB.

Characterization of Effects. Numerous epidemiological studies have assessed associations between PbB and mortality. Studies of general populations and workers are briefly summarized in Table 2-1. In the general population, at PbB ≤10 µg/dL, a positive dose-response relationship was suggested for all-cause mortality and mortality due to coronary heart disease (Khalil et al. 2009, 2010; Menke et al. 2006; Schober et al. 2006), although Weisskopf et al. (2009) did not show an increased risk for all-cause mortality. At >10 µg/dL, results of occupational exposure and general population studies are mixed and do not establish a pattern of effects or exposure-response relationships. In the general population, findings of the Lustberg and Silbergeld (2002) study suggested dose-response for PbB and all-cause mortality. In Pb workers, a dose-effect relationship was observed for all-cause mortality and mortality due to endocrine disease, infection, and digestive disease (Chowdhury et al. 2014; Kim et al. 2015), although Malcolm and Barnett (1982) did not observe a dose-effect relationship between Pb and all-cause mortality in Pb battery workers.

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
PbB ≤10 µg/dL			
Cheung et al. 2013 Cross-sectional study; n=3,482 (NHANES III)	Mean (SE): 4.44 (0.14)	All-cause mortality[c]	**OR: 1.045 (1.013 1.079)***
Khalil et al. 2009, 2010 Prospective cohort study; n=533 women (age 65–87 years)	Quintiles • Q1: <4 • Q2: 4 • Q3: 5 • Q4: 6–7 • Q5: >7	All-cause mortality[c]	HR Q1 (reference) HR Q2: 0.80 (0.45,1.42) HR Q3: 0.70 (0.39, 1.24) HR Q4: 0.60 (0.34, 1.06) HR Q5: 1.20 (0.69, 2.09) **p-trend=0.905***
Khalil et al. 2009 Prospective cohort study; n=533 women (age 65–87 years)	Mean: 5.3 <8 (n=453) ≥8 (n=79)	All-cause mortality[c]	**Adjusted HR ≥8 µg/dL: 1.59 (1.02, 2.49); p=0.041***
		All-cause mortality excluding deaths due to cancer and cardiovascular disease	Adjusted HR ≥8 µg/dL: 1.22 (0.48, 3.10); p=0.673
Menke et al. 2006 Longitudinal study; n=13,946 (NHANES 1988–1994; mean age 44.4 years)	Mean: 2.58 Tertiles: • T1: <1.93 • T2: 1.94–3.62 • T3: ≥3.62	All-cause mortality[c]	Adjusted HR T1 (reference) T2: 0.91 (0.72, 1.15) **T3: 1.25 (1.04, 1.51)*** **p-trend=0.002***
Neuberger et al. 2009 Retrospective cohort study; mortality data from Oklahoma State Department of Health; 1999–2001	5.8	Tuberculosis	SMR: 0.0 (0.0, 10.80)
		Bronchitis, emphysema, asthma	SMR: 1.10 (0.863, 13.84)
		Kidney disease	SMR: 0.984 (0.573, 1.576)

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
Schober et al. 2006 Longitudinal study; n=9,757 (NHANES III; age ≥40 years)	Tertiles • T1: <5; mean 2.6 • T2: 5–9; mean 6.3 • T3: >10, mean 11.8	All-cause mortality[c]	**RR T2: 1.24 (1.05, 1.48)*** **RR T3: 1.59 (1.28, 1.98); p-trend<0.001**
Weisskopf et al. 2009 Longitudinal study; n=868 men (Normative Aging Study; age 21–80 years)	Mean (SD): 5.6 (3.4) Tertiles: • T1: <4 • T2: 4–6 • T3: >6	All-cause mortality[c]	Adjusted HR • T1: 1 (reference) • T2: 0.99 (0.71–1.37) • T3: 1.01 (0.71–1.44) p-trend=0.92
PbB >10 µg/dL			
Chowdhury et al. 2014 Survey study; n=58,368 male workers (mean age 38.9 years)	Quartiles • Q1: 0- <5 • Q2: 5- <25 • Q3: 25- <40 • Q4: ≥40	All-cause mortality[c]	**SMR Q4: 0.80 (0.75, 0.84)** SMR overall: 0.69 (0.66, 0.71)
		Chronic obstructive pulmonary disease	SMR Q4: 0.86 (0.64, 1.12) SMR overall: 0.65 (0.54, 0.78)
		Chronic renal disease	SMR Q4: 1.01 (0.58, 1.64) SMR overall: 0.65 (0.44, 0.93)
Cooper 1988; Cooper et al. 1985 Cohort study; n=4,519 battery workers; 2,300 smelters	Mean • Battery (n=1326): 62.7 • Smelters (n=537): 79.7	Nonmalignant respiratory disease	Battery PMR: 0.90 (0.74, 1.10) Smelter PMR: 0.76 (0.53, 1.11)
		Cirrhosis of the liver	Battery PMR:1.29 (0.96, 1.73) Smelter PMR: 0.63 (0.35, 1.15)
		Chronic or unspecified nephritis	**Battery PMR: 2.06 (1.26, 3.18)*; p<0.01** Smelter PMR: 1.86 (0.80, 3.66)
		Chronic nephritis	Battery PMR: 1.48 (0.88, 2.49) Smelter PMR: 1.20 (0.50, 2.86)

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
Kim et al. 2015 Cross-sectional study; n=81,067 inorganic Pb workers (54,788 males; 26,279 females; age 20–≤50 years)	Mean (SD) • Males: 8.8 (8.5) • Females 5.8 (5.4) Tertiles: • T1: <10 • T2: 10–20 • T3: >20	All-cause mortality[c]	**Males: RR T3: 1.36 (1.03, 1.79)*; p<0.05** Females: RR T3: 1.30 (0.41, 4.16)
		Non-malignant death	Males: RR T3: 0.95 (0.56, 1.51) Females RR T3: 0.99 (0.13, 7.19)
		Infection	**Males: RR T2: 3.73 (1.06, 13.06)*; p<0.05** Females: Not reported
		Endocrine disease	Males: RR T3: 4.25 (0.90, 20.04)*; p<0.1 Females: Not reported
		Respiratory disease	Males: RR T2: 1.46 (0.28, 7.49) Females: RR T2: 3.49 (0.31, 39.05)
		Digestive disease	**Males: RR T3: 3.23 (1.33, 7.86)*; p<0.05** Females: RR T2: 3.66 (0.33, 40.70)
Lundstrom et al. 1997 Retrospective cohort study; n=3,979 workers	Mean: • In 1950: 62.2 • In 1987: 33.2	All-cause mortality[c]	Total cohort SMR: 0.9 (0.8, 1.0)
		Respiratory disease	Total cohort SMR: 0.4 (0.2, 0.8)
		Digestive organs	Total cohort SMR: 0.6 (0.3, 1.1)
Lustberg and Silbergeld 2002 Longitudinal study; n=4,292; age 30–74 years (NHANES II)	Tertiles: • T1 (n=818): <10 • T2 (n=2,735): 10–19 • T3 (n=637): 20–29	All-cause mortality[c]	RR T2: 1.17 (0.90, 1.52) **RR T3: 1.46 (1.14, 1.86)***
Malcolm and Barnett 1982 Retrospective cohort study; n=754 Pb battery workers	Group1 (non-occupational exposed): not reported Group 2: (light occupational lead exposure): mean 57 Group 3: (high occupational lead exposure): not reported	All-cause mortality[c]	Group 3 SMR: 1.07; p=0.134

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
McDonald and Potter 1996 Prospective cohort study; n=454 pediatric patients diagnosed with Pb poisoning, Massachusetts, 1923–1966, followed through 1991	Mean 113	Diseases of the blood and blood forming organs	**SMR: 9.68 (1.95, 28.28)***
		Nervous-system and sense-organ diseases	SMR: 2.86 (0.57, 8.35)
		Respiratory diseases	SMR: 1.95 (0.78, 4.02)
		Pneumonia	SMR: 2.10 (0.68, 4.90)
		Digestive system diseases	SMR: 1.37 (0.44, 3.21)
		Genitourinary system diseases	SMR: 1.69 (0.02, 9.43)
		Chronic nephritis	SMR: 5.00 (0.06, 27.82)
		All-cause mortality[c]	**SMR: 1.74 (1.40, 2.15)***
McElvenny et al. 2015 Cohort study; n=9,122 workers; mean age 29.2 years	Mean (SD): 44.3 (22.7) Range: 2.3–321.5	All-cause mortality[c]	**Males: SMR 1.10 (1.06, 1.14)*** Females: SMR 1.00 (0.91, 1.09) **Total SMR: 1.09 (1.05, 1.12)***
		Respiratory system diseases	**Males: SMR: 1.17 (1.06,1.30)*** Females: SMR: 1.24 (0.98, 1.57) **Total SMR: 1.18 (1.08, 1.30)***
		Digestive system diseases	**Males: SMR: 1.22 (1.03, 1.45)*** Females: SMR: 0.84 (0.52, 1.35) Total SMR: 1.16 (0.99, 1.36)
		Genitourinary diseases	Males: SMR: 1.02 (0.72,1.44) Females: SMR: 0.67 (0.28, 1.60) Total SMR: 0.95 (0.69, 1.31)
		Non-malignant kidney disease	Males: SMR: 1.30 (0.76, 2.24) Total SMR: 1.29 (0.79. 2.11

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
Selevan et al. 1985 Retrospective cohort study; n=1,987 male workers	Mean: 56.3	All tuberculosis	SMR: 1.39 (0.69, 2.49)
		Diseases of the central nervous system	SMR: 0.84 (0.61, 1.12)
		Diseases of the respiratory system	SMR: 1.25 (0.92, 1.66)
		Other respiratory diseases	**SMR: 1.87 (1.28, 2.64)***
		Diseases of the digestive system	SMR: 0.51 (0.26, 0.89)
		Diseases of the genitourinary system	SMR: 0.93 (0.42, 1.77)
		Chronic and unspecified nephritis and other renal sclerosis	SMR: 1.92 (0.88, 3.64)
		All other	SMR: 0.88 (0.67, 1.14)
Steenland et al. 1992 Cohort study (same cohort as Selevan et al. 1985); n=1,990 male smelter workers	Mean: 56.3	All-cause mortality[c]	**SMR: 1.07 (1.00, 1.14)***
		Non-malignant respiratory disease	**SMR: 1.44 (1.16, 1.77)***
		Emphysema	**SMR: 2.20 (1.45, 3.20)***
		Pneumonia and other respiratory disease	**SMR: 1.88 (1.34, 2.56)***
		Acute kidney disease	SMR: 0.91 (0.02, 5.07)
		Chronic kidney disease	SMR: 1.26 (0.54, 2.49)

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
Wong and Harris et al. 2000 Cohort study; n=4,519 battery workers; 2,300 smelters (same cohort as Cooper et al. 1985)	Mean: • All workers: 64.0 • Battery workers: 62.7 • Smelters: 79.7	All-cause mortality[c]	**SMR: 1.045 (1.012, 1.08)*; p<0.01**

[a]Studies assessing death due to cardiovascular disease and cancer are discussed in Sections 2.5 and 2.19, respectively.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[c]Includes cancer and/or cardiovascular deaths.

CI = confidence interval; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PbB = blood lead concentration; PMR = proportionate mortality ratio; RR = rate ratio or relative risk; SD = standard deviation; SE = standard error; SMR = standard mortality ratio

2.4 BODY WEIGHT

Overview. Compared to other health effect endpoints, there is little information on Pb exposure and body weight measures. However, a few epidemiological studies have evaluated effects of Pb exposure on body weight in children, adolescents, and adults. The studies reviewed below focused on effects at PbB ≤10 µg/dL. Negative associations have been observed between PbB and BMI, and decreased risks of being overweight or obese have been reported. However, some studies did not observe associations and one study reported a positive association between PbB and the risk of obesity in women.

Note that studies evaluating the effects of exposure to Pb on birth weight are reviewed in Section 2.18 (Developmental).

The following effects on body weight have been associated with PbB ≤10 µg/dL:

- Decreased BMI and risk of being overweight or obese in children and adolescents; observed in a few studies.
- Decreased BMI and risk of being overweight or obese in adults; not corroborated.
- Increased risk of obesity in women; not corroborated.

Measures of Exposure. Most studies evaluating effects of chronic Pb exposure on body weight evaluate exposure by measurement of PbB. A few other studies examining associations between Pb exposure and body weight used Pb concentration in urine, bone, and/or dentin as biomarkers of exposure; however, these studies did not report PbB (Kim et al. 1995; Padilla et al. 2010; Shao et al. 2017).

Confounding Factors and Effect Modifiers. Numerous factors contribute to body weight (or BMI), including age, sex, race, nutrition, diet, daily activity level, intercurrent illness, genetic pre-disposition for body type, income level, education, and alcohol and tobacco use. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Effects at Blood Pb Levels ≤10 µg/dL. Results of studies evaluating effects of PbB ≤10 µg/dL on body weight are briefly summarized in Table 2-2 and an overview of results is provided in Table 2-3; study details are provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 1. Studies have been conducted in children and adolescents (Burns et al. 2017; Cassidy-Bushrow et al. 2016; Hauser et al. 2008; Scinicariello et al. 2013) and adults (Scinicariello et al. 2013; Wang et al. 2015). The largest study evaluating associations between PbB and body weight is a study of children, adolescents, and adults participating in NHANES, 1999–2006; this study included adjustments for numerous confounding factors (see the *Supporting Document for Epidemiological Studies for Lead*, Table 1) (Scinicariello et al. 2013). In children and adolescents (n=10,693), results show a negative association between PbB and BMI-Z score and risk of being overweight or obese. In a smaller study in children (n=131), negative associations were observed between PbB and BMI and BMI-Z score (Cassidy-Bushrow et al. 2016). Other studies in small populations of boys showed no associations between weight, BMI and/or BMI-Z score (Burns et al. 2017; Hauser et al. 2008). Results of studies in adults are mixed. The largest study in adults (n=15,899) shows negative associations between PbB and BMI and risk of being overweight and obese, with a negative trend (p-trend: ≤0.01) over quartiles (Scinicariello et al. 2013). No association was observed between PbB and BMI in a small study on women (n=107) (Ronco et al. 2010) or a larger study in men (n=2235) (Wang et al. 2015). In contrast, the risk of being obese was increased in a large population (n=3323) of women (Wang et al. 2015). Thus, except for the Wang et al. (2015) study, available studies show either no association or a negative association between PbB ≤10 µg/dL and body weight and/or BMI.

Mechanisms of Action. The mechanisms involved in the development of Pb-induced changes in body weight have not been established. However, alterations of the hypothalamic-pituitary-adrenal axis, stress-induced elevations in glucocorticoid levels, oxidative stress, and altered lipid metabolism have been proposed (reviewed by Scinicariello et al. 2013; Shao et al. 2017; Wang et al. 2015).

Table 2-2. Summary of Epidemiological Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Burns et al. 2017 Prospective cohort of 481 Russian boys enrolled at age 8–9 years and followed until age 18 years	Median 3.0	HT-Z score	**Adjusted β (95% CI), HT-Z score per unit lnPbB: -0.26 (-0.40, -0.13); p<0.001***
		BMI-Z score	Adjusted β (95% CI), BMI-Z score per unit lnPbB: -0.14 (-0.31, 0.04); p=0.12
Cassidy-Bushrow et al. 2016 Birth cohort of 131 children, 2–3 years of age	Mean (SD): 2.45 (2.53)	BMI	**Adjusted RR (95% CI) for BMI ≥85th percentile 0.57 (0.33, 0.98); p=0.041***
		BMI-Z score	**Adjusted β (95% CI) for BMI Z-score: -0.35 (-0.60, -0.10); p=0.012***
Hauser et al. 2008 Cross-sectional study of 489 boys, 8–9 years of age	Mean: 3	Weight	Adjusted β (95% CI), per unit log-PbB: -0.761 (-1.54, 0.02); p=0.067
		BMI	Adjusted β (95% CI), per unit log-PbB: -0.107 (-0.44, 0.23); p=0.53
Ronco 2010 Cross-sectional study of 107 women of childbearing age (median age: 27 years) from Chile; data collection period not reported	Median • All: 1.0 • Low weight: 1.7 • Normal weight: 2.3 • Overweight: 1.0	BMI	No differences in PbB were observed between BMI categories

Table 2-2. Summary of Epidemiological Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Scinicariello et al. 2013 Cross-sectional study of children and adolescents (n=10,693; age 3–19 years) adults (n=15,899, age ≥20 years) using NHANES data (1999–2006)	Gmean (SE) • Children/adolescents: 1.12 (0.02) • Adults: 1.59 (0.02) • Quartiles (all): o Q1: ≤0.70 o Q2: 0.71–1.09 o Q3: 1.10–1.60 o Q4: ≥1.61	BMI-Z score (children and adolescents)	**Adjusted β (SE) (BMI Z-score per PbB quartile):** • **Q3: −0.15 (0.06); p=0.01*** • **Q4: -0.33 (0.07); p ≤ 0.01*** • **p-trend: ≤0.01***
		Overweight (children and adolescents)	**Adjusted OR for Q4: 0.67 (0.52, 0.88)***
		Obesity (children and adolescents)	**Adjusted OR** • **Q3: 0.70 (0.54, 0.90)*** • **Q4: 0.42 (0.30, 0.59)***
		BMI (adults)	**Adjusted β (SE) (BMI per quartile):** • **Q2: −0.90 (0.20); p ≤ 0.01*** • **Q3: −1.41 (0.22); p ≤0.01*** • **Q4: −2.58 (0.25); p ≤0.01*** • **p-trend: ≤0.01***
		Overweight (adults)	**Adjusted OR for Q4: 0.79 (0.65–0.95)***
		Obesity (adults)	**Adjusted OR** • **Q2: 0.76 (0.66–0.87)*** • **Q3: 0.66 (0.56–0.77)*** • **Q4: 0.42 (0.35–0.50)***

Table 2-2. Summary of Epidemiological Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Wang et al. 2015 Cross-sectional study of 5,558 adults (men: 2,235, ages 39–65 years; women: 3,323, ages 40–65 years) from 16 locations in China	**PbB:** Men • Median: 4.40 • Quartiles: o Q1: ≤2.90 o Q2: 2.90–4.40 o Q3: 4.40–6.22 o Q4: ≥6.23 Women: • Median: 3.78 • Quartiles: o Q1: ≤2.51 o Q2: 2.51–3.77 o Q3: 3.78–5.43 o Q4: ≥5.44	BMI	β (SE) per PbB quartile • Men o Q4: 0.01 (0.20) o p-trend: 0.82 • **Women** o **Q4: 0.59 (0.17); p<0.05*** o **p-trend: <0.001***
		Overweight	Adjusted OR • Men o Q4: 0.95 (0.72,1.26) o p-trend: 0.74 • Women o Q4: 1.16 (0.92, 1.46) o p-trend: 0.07
		Obesity	Adjusted OR • Men o Q4: 0.88 (0.48, 1.61) o p-trend: 0.99 • **Women** o **Q4: 1.86 (1.16, 2.98)*** o **p-trend: <0.01***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 1 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb.

BMI = body mass index; BMI-Z = BMI z-scores; CI = confidence interval; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; RR = risk ratio; SD = standard deviation; SE = standard error

Table 2-3. Effects on Body Weight Associated with Mean Blood Lead Concentrations (PbBs) ≤10 µg[a]

Mean PbB (µg/dL)	Population (n)[b]	Weight	BMI	BMI-Z score	Overweight	Obese	Reference
3.0	C (481 boys)	–	–	0	–	–	Burns et al. 2017
2.45	C (131)	–	↓	↓	–	–	Cassidy-Bushrow et al. 2016
3	C (489 boys)	0	0	–	–	–	Hauser et al. 2008
1.0	A (107 women)	–	0	–	–	–	Ronco et al. 2010
1.12	C, Ad (10,693)[c]	–	–	↓	↓	↓	Scinicariello et al. 2013
1.59	A (15,899)[c]	–	↓	–	↓	↓	Scinicariello et al. 2013
4.40	A (2,235, men)	–	0	–	0	0	Wang et al. 2015
3.78	A (3,323, women)	–	0	–	0	↑	Wang et al. 2015

[a]↑ = increased; ↓ = decreased; 0 = no change; – = not assessed.
[b]Unless otherwise specified, study was conducted in males and females.
[c]Participants from the National Health and Nutrition Examination Survey 1999–2006.

A = adults; Ad = adolescents; BMI = body mass index; BMI-Z = BMI z-scores; C = children

2.5 RESPIRATORY

Overview. Few epidemiological studies have evaluated respiratory effects associated with exposure to Pb; those that are available include cross-sectional studies in adults and prospective and cross-sectional studies in children. Associations have been observed between PbB and decreased lung function, increased bronchial hyperreactivity, increased number and severity of symptoms of respiratory disease, and increased risk of respiratory diseases (e.g., asthma and obstructive lung disease). Although most studies found associations between respiratory effects and PbB, other studies did not observe associations.

The following respiratory effects have been associated with PbB:

- ≤10 µg/dL:
  - Decreased lung function; corroborated in a few studies.
  - Increased bronchial hyperreactivity.
  - Increased risk of asthma and obstructive lung disease; evaluated in a few studies with mixed results.

- >10 µg/dL:
    - Decreased lung function.
    - Symptoms of respiratory disease (e.g., shortness of breath).
    - Increased risk/prevalence of asthma; evaluated in a few studies with mixed results.

Measures of Exposure. Studies evaluating the association between respiratory effects and Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. The etiology for most respiratory diseases is multifactorial; therefore, several factors may contribute to clinical findings. Factors that may contribute to the development of respiratory diseases include poor housing conditions, exposure to allergens (e.g., pet dander, seasonal allergies), exposure to tobacco smoke and other respiratory irritants, and asthma compounded by obesity (Ali and Ulirk 2013). In addition, Aligne et al. (2000) reported that children living in urban settings have an increased risk of asthma. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. General trends for studies showing a relationship between PbB and respiratory effects are shown in Table 2-4. Compared to other toxicological endpoints (e.g., neurological or cardiovascular effects), few studies have evaluated adverse respiratory effects associated with PbB. Data are from cross-sectional studies in adults (Bagci et al. 2004; Bener et al. 2001; Chung et al. 2015; Min et al. 2008a; Pugh Smith and Nriagu 2011; Rokadia and Agarwal 2013), and prospective (Joseph et al. 2005; Rabinowitz et al. 1990) and cross-sectional (Wells et al. 2014) studies in children. Over a range of PbBs that includes PbB ≤10 µg/dL and PbB >50 µg/dL, studies provide evidence for effects in Pb workers compared to controls or associations between PbB and decreased pulmonary function tests indicative of obstructive pulmonary disease (forced expiratory volume in 1 second [FEV_1], FEV_1/forced vital capacity [FVC] ratio, forced expiratory flow at 25–75% of FVC [$FEF_{25–75}$]), increased bronchial hyperreactivity (indicative of asthma), symptoms of respiratory disease (cough, shortness of breath), and increased risk of respiratory diseases (e.g., asthma and obstructive lung disease). With the exception of a prospective study in children, which showed no increased risk of asthma at umbilical cord PbB ≥10 µg/dL compared to <10 µg/dL (Rabinowitz et al. 1990), studies showed positive associations between PbB and respiratory effects.

Table 2-4. Overview of Respiratory Effects in Adults and Children Chronically Exposed to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Decreased lung function	Chung et al. 2015
	Increased bronchial responsiveness	Min et al. 2008a
	Lung disease (asthma and obstructive lung disease)	Joseph et al. 2005; Rokadia and Agarwal 2013; Wells et al. 2014
>10–30	Lung disease (asthma)	Pugh Smith and Nriagu 2011
>30–50	Decreased lung function	Bagci et al. 2004
>50	Symptoms of lung disease (phlegm)	Bener et al. 2001
	Lung disease (asthma)	Bener et al. 2001

Effect at Blood Pb Levels ≤10 µg/dL. Results of studies evaluating respiratory effects of PbB ≤10 µg/dL are summarized in Table 2-5, with study details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 2. Studies show associations between PbB ≤10 µg/dL and decreased lung function, increased bronchial hyperreactivity, and increased risk of asthma; findings are consistent with obstructive lung disease. In adults, a cross-sectional study evaluating lung function showed an increased FEV_1/FVC ratio in a population with mean PbB of 2.50 µg/dL; results are consistent with obstructive airway disease (Chung et al. 2015). Increased bronchial reactivity in response to methacholine challenge, consistent with a diagnosis of asthma, was observed in adults with mean PbB of 2.96 µg/dL (Min et al. 2008a). In addition, risk of obstructive lung disease was observed in a large NHANES population of adults with a mean PbB of 1.73 µg/dL (Rokadia and Agarwal 2013). Studies in children examining associations between PbB and risk of asthma do not provide consistent results. A large prospective study showed an increased risk of asthma in black children with PbB <5 and ≥5 µg/dL compared to white children with PbB <5 µg/dL; however, no increased risk was observed for white children with PbB ≥5 µg/dL compared to white children with PbB <5 µg/dL. A large cross-sectional study of children participating in NHANES did not observe an association between PbB (mean 1.07 µg/dL) and asthma, with or without atopy (Wells et al. 2014).

Mechanisms of Action. General mechanisms of respiratory toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of toxicity to the respiratory system. EPA (2014c) specifically noted that oxidative stress through reactive oxygen species (ROS), resulting in tissue damage and inflammation and immune effects, is a plausible mechanism for the underlying cause of respiratory damage. Increased

Table 2-5. Summary of Epidemiological Studies Evaluating Respiratory Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Decreased lung function			
Chung et al. 2015 Cross-sectional study; n=870 adults	• Mean: 2.50 • Tertiles: o T1: <2.03 o T2: 2.03–2.81 o T3: >2.81	FVC%	Correlation coefficient: 0.070
		FEV_1%	Correlation coefficient: 0.00
		FEV_1/FVC ratio	**Correlation coefficient: -0.115; p<0.01***
			OR T3: 0.006 (0, 0.286)*
			p-trend: 0.03*
Increased bronchial responsiveness			
Min et al. 2008a Cross-sectional study; n=523 adults	Mean (SD): 2.96 (1.59)	BR	**A 1 µg/dL increase in PbB was associated with a higher BR; β (SE): 0.018 (0.007).***
Asthma			
Joseph et al. 2005 Prospective study; n=4,634 children (ages 3 months to 3 years)	Mean • White: 3.2 • Black: 5.5	Asthma	All compared to PbB <5 µg/dL in white children
			HR white (PbB ≥5): 2.3 (0.8, 6.7); p=0.12
			HR black (PbB <5): 1.8 (1.3, 2.4); p<0.01*
			HR black (PbB ≥5): 1.5 (1.2, 1.8); p<0.01*
			HR black (PbB ≥10): 3.0 (1.2, 7.1); p=0.01*
Rokadia and Agarwal 2013[c] Pooled cross-sectional study; n=9,575 adults (8,411 without OLD; 1,164 with OLD)	Mean • Non-OLD: 1.18 • OLD: 1.73	OLD	**OR for all OLD: 1.94 (1.10, 3.42)***
			OR for mild OLD: 1.21 (0.55, 2.65)
			OR for moderate-severe OLD: 3.49 (1.70, 7.15)*

Table 2-5. Summary of Epidemiological Studies Evaluating Respiratory Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Wells et al. 2014[c] Cross-sectional study; NHANES 2005–2006; n=1,430 children (ages 4–12 years)	Geometric mean: 1.07	Asthma	OR for asthma with atopy: 0.97 (0.61, 1.55) OR for asthma with no atopy: 1.07 (0.86, 1.33)

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 2 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[c]Study population was from NHANES.

BR = bronchial responsiveness; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second (L/s); FEV_1% = percent of predicted FEV_1; FVC = forced vital capacity (L); FVC% = percent of predicted FVC; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OLD = obstructive lung disease; OR = odds ratio; SD = standard deviation; SE = standard error

ROS, along with depletion of antioxidants, results in inflammation and production and release of metabolites and cytokines. Immune-mediated inflammation is observed with asthma and bronchial hyperreactivity.

2.6 CARDIOVASCULAR

Overview. A large number of epidemiological studies showing adverse effects on the cardiovascular system associated with Pb exposure have been published. Most studies evaluated effects in adults, although a few studies in children have been conducted. The effect of Pb exposure on blood pressure is the most studied cardiovascular outcome, with results providing consistent evidence of positive associations between lead exposure and blood pressure. Other cardiovascular endpoints (atherosclerosis, cardiac conduction, cardiovascular disease, and mortality due to cardiovascular disease) also show positive and negative associations with PbB, although the majority of studies had positive associations. In some cases, although no associations between PbB and cardiovascular outcomes were observed, associations were observed for bone Pb, a biomarker of cumulative lead exposure that, among individuals with high historical lead exposures, typically remains elevated for many years after the PbB declines to ≤10 μg/dL; these cases are noted in the discussions below.

The following cardiovascular effects have been associated with PbB:

- ≤10 μg/dL:
    - Greater systolic and diastolic blood pressure:
        - In adults; corroborated in multiple studies.
        - In children; evaluated in a few studies.
        - During pregnancy; evaluated in a few studies.
    - Greater risk of hypertension:
        - In adults, including during pregnancy; evaluated in a numerous studies.
    - Greater risk of atherosclerosis; evaluated in a few studies.
    - Altered cardiac conduction; evaluated in a few studies.
    - Greater risk of mortality due to cardiovascular diseases; evaluated in a few studies with mixed results.

- >10 µg/dL:
    - Increased systolic and diastolic blood pressure:
        - In adults; corroborated in multiple studies and meta-analyses.
        - In children; evaluated in a few studies.
    - Increased risk of hypertension; corroborated in multiple studies.
    - Atherosclerosis; evaluated in a few studies.
    - Increased risk or prevalence of heart disease; evaluated in a few studies.
    - Increased mortality due to cardiovascular diseases; corroborated in multiple studies.

Measures of Exposure. PbB and bone Pb concentrations have been used as biomarkers to evaluate cardiovascular effects of Pb exposure. However, PbB may not provide the ideal biomarker for long-term exposure to target tissues that contribute a hypertensive effect of Pb. Because the development of cardiovascular effects has a long latency period, associations between PbB and cardiovascular disease at concurrent PbB ≤10 µg/dL may be related to higher past Pb exposures. Bone Pb, a metric of cumulative or long-term exposure to Pb, appears to be a better predictor of Pb-induced elevations in blood pressure and alterations in cardiac conduction than PbB.

Confounding Factors and Effect Modifiers. Numerous factors affect blood pressure, including age, body mass, race, smoking, alcohol consumption, ongoing or family history of cardiovascular/renal disease, LDL cholesterol levels, and various dietary factors (e.g., dietary calcium). In addition, renal disease, as well as Pb-induced renal damage, can lead to cardiovascular effects, including increased blood pressure (EPA 2014c; NTP 2012); thus, interpretation of studies examining cardiovascular outcomes is complicated by the link between cardiovascular and renal function. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome (e.g., Møller and Kristensen 1992). For example, adjusting for alcohol consumption will decrease the apparent association between PbB and blood pressure, if alcohol consumption contributes to Pb intake and, thereby, PbB (Bost et al. 1999; Hense et al. 1993; Hertz-Picciotto and Croft 1993; Wolf et al. 1995). Varying approaches and breadth of inclusion of these may account for the disparity of results that have been reported. Measurement error may also be an important factor. Blood pressure estimates based on multiple measurements or, preferably, 24-hour ambulatory measurements, are more reproducible than single measurements (Staessen et al. 2000).

Characterization of Effects. General trends between studies showing a relationship between PbB and cardiovascular effects are shown in Table 2-6. Over the PbB range of ≤10–>50 µg/dL, results of epidemiological studies provide evidence for increased blood pressure and hypertension, atherosclerosis (increased intimal medial thickening and peripheral artery disease), heart disease (myocardial infarction, ischemic heart disease, left ventricular hypertrophy, cardiac arrhythmias, and angina), and increased risk of mortality due to cardiovascular diseases. The effect of Pb exposure on blood pressure is the most studied cardiovascular outcome. A review by Navas-Acien et al. (2007) concluded that that available literature provides evidence that "is sufficient to infer a causal relationship of lead exposure and hypertension" and evidence that "is suggestive but not sufficient to infer a causal relationship of lead exposure with clinical cardiovascular outcomes" (cardiovascular, coronary heart disease, and stroke mortality; and peripheral arterial disease). Well-controlled studies in laboratory animals provide additional support regarding effects of Pb on blood pressure; see EPA (2014c) for additional information.

Table 2-6. Overview of Cardiovascular Effects in Adults and Children Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Increased blood pressure and hypertension	Al-Saleh et al. 2005; Bost et al. 1999; Bushnik et al. 2014; Cheng et al. 2001; Chu et al. 1999; Den Hond et al. 2002; Elmarsafawy et al. 2006; Faramawi et al. 2015; Gerr et al. 2002; Glenn et al. 2003; Gump et al. 2005, 2011; Hense et al. 1993; Hu et al. 1996a; Korrick et al. 1999; Martin et al. 2006; Muntner et al. 2005; Nash et al. 2003; Park et al. 2009b; Perlstein et al. 2007; Proctor et al. 1996; Rothenberg et al. 2002b; Schwartz 1995; Scinicariello et al. 2010, 2011; Vupputuri et al. 2003; Wells et al. 2011; Yazbeck et al. 2009; Zhang et al. 2011; Zota et al. 2013
	Atherosclerosis[a]	Ari et al. 2011; Muntner et al. 2005; Navas-Acien et al. 2004;
	Heart disease[b]	Cheng et al. 1998; Eum et al. 2011; Jain et al. 2007; Park et al. 2009a
	Mortality due to cardiovascular disease	Aoki et al. 2016; Khalil et al. 2009; Lanphear et al. 2018; Menke et al. 2006; Schober et al. 2006; Weisskopf et al. 2009

Table 2-6. Overview of Cardiovascular Effects in Adults and Children Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
>10–30	Increased blood pressure and hypertension	Coate and Fowles 1989; Factor-Litvak et al. 1999; Grandjean et al. 1989; Harlan et al. 1985; Møller and Kristensen 1992; Pirkle et al. 1985; Rabinowitz et al. 1987
	Atherosclerosis[a]	Pocock et al. 1988; Poreba et al. 2011, 2012
	Heart disease[b]	Poreba et al. 2013
	Mortality due to cardiovascular disease	Lustberg and Silbergeld 2002; Schober et al. 2006
>30–50	Increased blood pressure and hypertension	Aiba et al. 1999; Al-Saleh et al. 2005; Factor-Litvak et al. 1996, 1999; Ghiasvand et al. 2013; Glenn et al. 2006; Rapisarda et al. 2016; Weaver et al. 2008; Weiss et al. 1986, 1988
	Heart disease[b]	Bockelmann et al. 2002; Jain et al. 2007
	Mortality due to cardiovascular disease	Gerhardsson et al. 1995a
>50	Increased blood pressure and hypertension	Kirby and Gyntelberg 1985; Were et al. 2014
	Atherosclerosis[a]	Kirby and Gyntelberg 1985
	Mortality due to cardiovascular disease	Cooper 1988; Cooper et al. 1985; Fanning 1988; Gerhardsson et al. 1995a; McDonald and Potter 1996

[a]Atherosclerosis includes increased intimal medial thickening and peripheral artery disease.
[b]Heart disease includes myocardial infarction, ischemic heart disease, left ventricular hypertrophy, cardiac arrhythmias, and angina.

Numerous studies provide a weight of evidence for associations between PbB and increased blood pressure over a wide PbB range in adults (Table 2-6). Results of meta-analyses estimate small but consistent increases in blood pressure per doubling of PbB. The largest meta-analysis of 31 studies published between 1980 and 2001 included a total of 58,518 subjects (Nawrot et al. 2002); blood pressure data from studies included in the analysis are shown in Table 2-7 and Figures 2-2 and 2-3. Nawrot et al. (2002), in an update of an earlier meta-analysis by Staessen et al. (1994), estimated the increase in systolic pressure per doubling of PbB to be 1 mmHg (95% CI 0.5, 1.4) and the increase in diastolic pressure to be 0.6 mmHg (95% CI 0.4, 0.8). The range of mean (or median) PbBs for studies included in the analysis was 2.28–63.82 µg/dL. Although a PbB mean was not estimated for the entire study population, only nine studies had a mean PbB <10 µg/dL; therefore, it is likely that the overall PbB mean for the entire study population was >10 µg/dL. Similar outcomes were observed in two other meta-analyses (Schwartz 1995; Staessen et al. 1994). A meta-analysis reported by Staessen et al. (1994)

included 23 studies (published between 1984 and 1993; 33,141 subjects) and found a 1 mmHg (95% CI 0.4, 1.6) increase in systolic blood pressure and 0.6 mmHg (95% CI 0.2, 1.0) increase in diastolic pressure per doubling of PbB. Schwartz (1995) conducted a meta-analysis that encompassed a similar time frame (15 studies published between 1985 and 1993) and found a 1.25 mmHg (95% CI 0.87, 1.63) increase in systolic blood pressure per doubling of PbB (diastolic not reported). The latter analysis included only those studies that reported a standard error (SE) on effect measurement (e.g., increase in blood pressure per doubling of PbB). Of the 15 studies included in the Schwartz (1995) analysis, 8 were also included in the Staessen et al. (1994) analysis. The estimated increase in blood pressure per doubling of PbB in these meta-analyses is small; however, on a population basis, the consequences of increased blood pressure includes increased risks of serious and potentially fatal effects, including atherosclerosis, stroke, and myocardial infarction. Increased blood pressure during pregnancy has been associated with PbB and bone Pb (Rothenberg et al. 2002b; Wells et al. 2011; Yazbeck et al. 2009); these studies are discussed in more detail below (*Effect at Blood Pb Levels ≤10 µg/dL*).

Table 2-7. Characteristics of the Study Population in Meta-Analyses of Effects of Lead (Pb) on Blood Pressure

	Reference	Number[a]	Population[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (µg/dL)[g]
1[h]	Pocock et al. 1984[i,j]; Shaper et al. 1981	7,379	GP	100	Y	49 (40–59)	145	82	15.13 (2.07–66.3)[Ae]
2	Kromhout 1988[i,j]; Kromhout et al. 1985[i]	152	GP	100	Y	67 (57–76)	154	92	18.23 (10.77–27.97)[Ac]
3	Moreau et al. 1982[j], 1988; Orssaud et al. 1985[i,j]	431	WC	100	Y	41 (24–55)	131	75	18.23 (8.91–49.94)[Ae]
4	Weiss et al. 1986[i], 1988[i]	89	WC	100	Y	47 (30–64)	122	83	24.45 (18.65–29.01)[Mx]
5	de Kort and Zwennis 1988[i,j]; de Kort et al. 1987[i]	105	BC	100	N	40 (25–80)	136	83	29.22 (4.35–83.29)[Ae]
6	Lockett and Arbuckle 1987[i]	116	BC	100	Y	32 (?–?)	119	80	37.5 (14.92–95.52)[Ae]
7	Parkinson et al. 1987[i]	428	BC	100	Y	36 (18–60)	127	80	27.97 (6.01–49.52)[Ac]
8	Rabinowitz et al. 1987[i]	3,851	GP	0	Y	28 (18–38)	121	76	7.04 (3.73–10.15)[Ac]
9	Elwood et al. 1988a[i,j], 1988b[k]	1,136	GP	100	Y	56 (49–65)	146	87	12.64 (6.01–26.11)[Gc]

Table 2-7. Characteristics of the Study Population in Meta-Analyses of Effects of Lead (Pb) on Blood Pressure

	Reference	Number[a]	Population[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (µg/dL)[g]
10	Elwood et al. 1988a, 1988b[i,j,l]	1,721	GP	50	Y	41 (18–64)	127	78	10.15 (4.56–23.21)[Gc]
11	Gartside et al. 1988[i]; Harlan 1988; Harlan et al. 1985; Pirkle et al. 1985; Ravnskov 1992[m]	6,289	GP	53	Y	30 (10–74)	127	80	13.47 (2.07–95.93)[Ge]
12	Neri et al. 1988[i,j,n]	288	BC	100	?	? (?–?)	?	?	45.17 (6.01–65.06)[Ae]
13	Neri et al. 1988[i,o]	2,193	GP	?	Y	45 (25–65)	?	?	23.41 (0–47.03)[Me]
14	Grandjean et al. 1989, 1991[i,p]	1,050	GP	48	Y	40 (40–40)	?	?	11.6 (3.94–60.09)[Ae]
15	Reimer and Tittelbach 1989[i]	58	BC	100	?	32 (?–?)	134	81	39.99 (12.85–70.24)[Ac]
16	Apostoli et al. 1990[i]	525	GP	48	Y	45 (21–60)	132	84	13.05 (2.07–28.18)[Ae]
17	Morris et al. 1990[i,j]	251	GP	58	Y	? (23–79)	?	?	7.46 (4.97–38.95)[Ae]
18	Sharp et al. 1988[i,j], 1989[i], 1990[i]	249	WC	100	N	43 (31–65)	128	83	6.63 (2.07–14.92)[Pe]
19	Staessen et al. 1984[i,q]	531	WC	75	Y	48 (37–58)	126	78	11.4 (4.14–35.22)[Ge]
20	Møller and Kristensen 1992[i,j,r]	439	GP	100	Y	40 (40–40)	?	?	13.68 (4.97–60.09)[Ae]
21	Hense et al. 1993[i,j]	3,364	GP	51	Y	48 (28–67)	129	80	7.87 (1.24–37.09)[Ae]
22	Maheswaran et al. 1993[i]	809	BC	100	Y	43 (20–65)	129	84	31.7 (0–98.01)[Ae]
23	Menditto et al. 1994	1,319	GP	100	Y	63 (55–75)	140	84	11.19 (6.22–24.66)
24	Hu et al. 1996a; Proctor et al. 1996[s]	798	GP	100	Y	66 (43–93)	134	80	5.59 (0.41–35.02)[Pe]
25	Staessen et al. 1996a[j], 1996b[i,t]	728	GP	49.3	Y	46 (20–82)	130	77	9.12 (1.66–72.52)[Ge]
26	Sokas et al. 1997[u]	186	BC	99	Y	43 (18–79)	130	85	7.46 (2.07–30.04)[Pe]
27	Bost et al. 1999	5,326	GP	48	Y	48 (16–?)	135	75	63.82 (?–?)[G]
28	Chu et al. 1999	2,800	GP	53	Y	44 (15–85)	123	78	6.42 (0.41–69)[Ae]
29	Rothenberg et al. 1999a, 1999b	1,627	GP	0	Y	27 (?–?)	110	59	2.28 (?–?)[G]

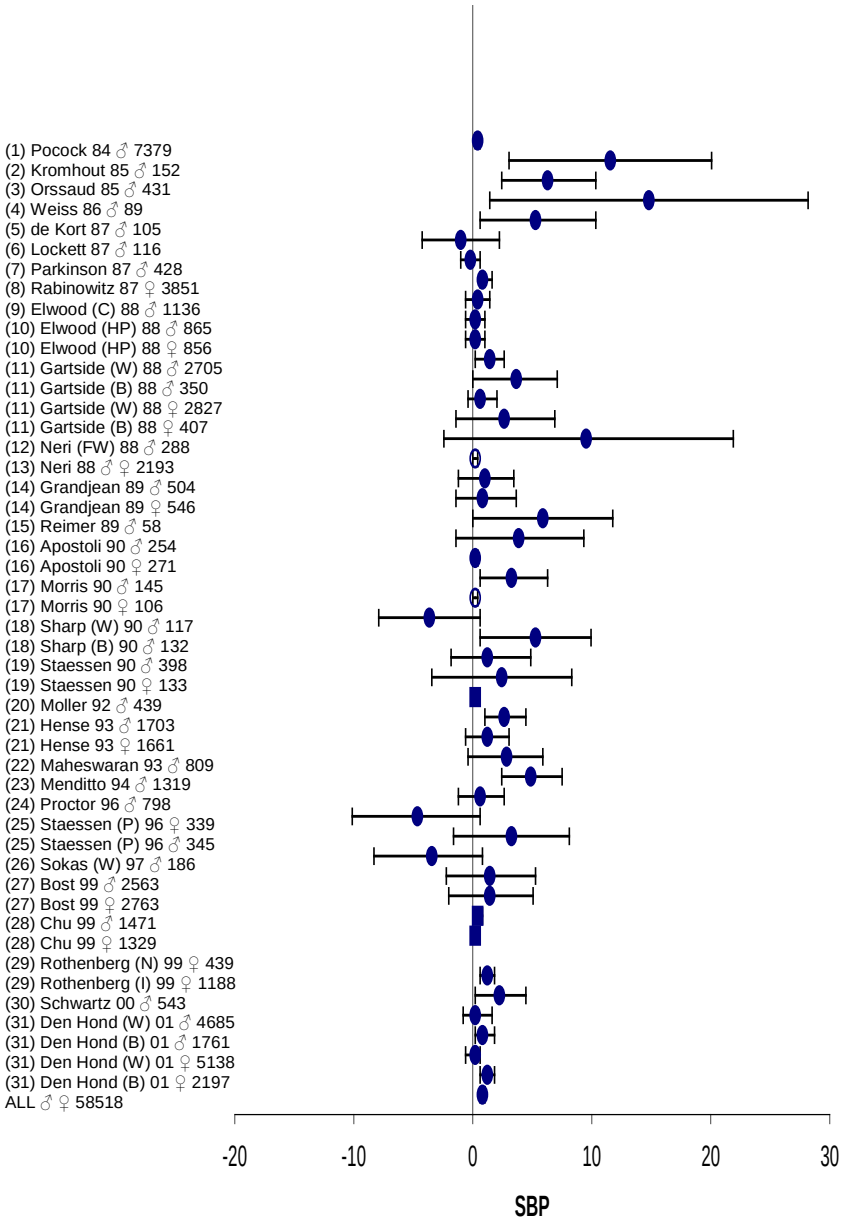
Table 2-7. Characteristics of the Study Population in Meta-Analyses of Effects of Lead (Pb) on Blood Pressure

	Reference	Number[a]	Population[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (µg/dL)[g]
30	Schwartz et al. 2000c	543	BC	100	Y	58 (41–73)	128	77	4.56 (1.04–20.1)[Ae]
31	Den Hond et al. 2001[v]	13,781	GP	53.2	Y	48 (20–90)	125	73	3.11 (0.62–55.94)[Ge]

[a]Number of persons in whom relevant data were available.
[b]Study population: BC = blue collar workers; GP = sample from general population; WC = white collar employees.
[c]Men: Percentage of men.
[d]HT: Indicates whether the sample included (Y = yes) or did not include (N = no) hypertensive patients.
[e]Age: Mean age or midpoint of age span (range or approximate range given between parentheses).
[f]SBP, DBP: Mean systolic and diastolic blood pressures.
[g]Lead: Measure of central tendency: A = arithmetic mean; G = geometric mean; M = midpoint of range; P = P_{50} (median). The spread of blood lead is given between parentheses: c = P_5–P_{05} interval; P_{10}–P_{90} interval, or interval equal to 4 times the standard deviation; e = extremes; x = approximate limits of distribution.
[h]Number refers to reference in Figures 2-2 and 2-3.
[i]Included in the Staessen et al. (1994) meta-analysis.
[j]Included in the Schwartz (1995) meta-analysis.
[k]Caerphilly Study.
[l]Welsh Heart Program.
[m]NHANES (National Health and Nutrition Examination Survey).
[n]Foundry workers.
[o]Canadian Health Survey.
[p]Glostrup Population Study, cross-sectional analysis (1976).
[q]London Civil Servants.
[r]Glostrup Population Study, longitudinal analysis (1976–1987).
[s]Normative Aging Study.
[t]PheeCad (Public Health and Environmental Exposure to Cadmium) Study.
[u]Because of missing information, only the effect in whites is included.
[v]NHANES III Survey.

Source: Nawrot et al. 2002

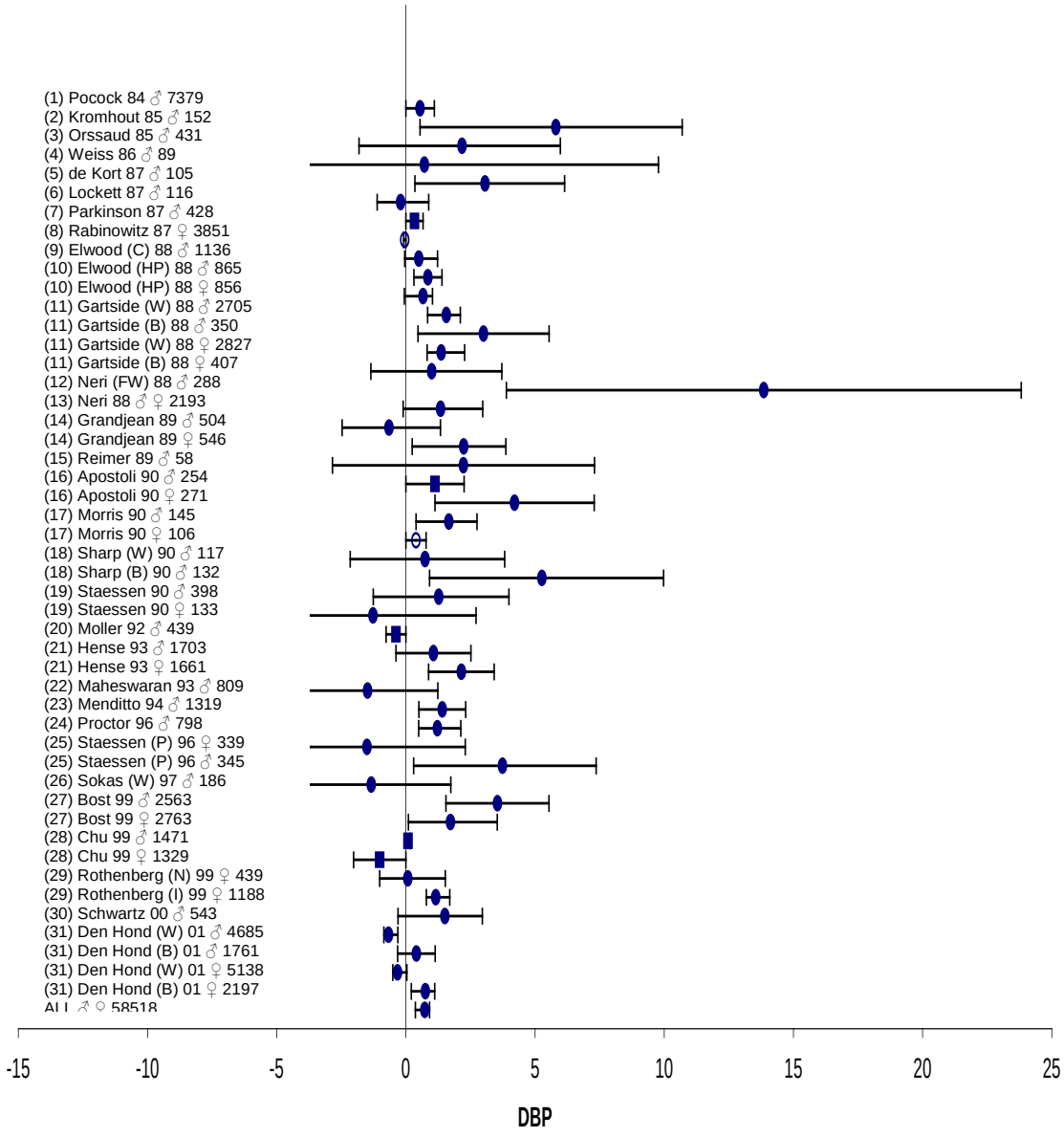
Figure 2-2. Change in the Systolic Pressure Associated with a Doubling of the Blood Lead Concentration (PbB)*



*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 2-7 for more details on study groups.

B = blacks; C = Caerphilly Study; CS = civil servants; FW = foundry workers; HP = Welsh Heart Program; I = immigrants; NI = non-immigrants; P = Public Health and Environmental Exposure to Cadmium Study; W = whites

Figure 2-3. Change in the Diastolic Pressure Associated with a Doubling of the Blood Lead Concentration (PbB)*



*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 2-7 for more details on study groups.

B = blacks; C = Caerphilly Study; CS = civil servants; FW = foundry workers; HP = Welsh Heart Program; I = immigrants; N = non-immigrants; P = Public Health and Environmental Exposure to Cadmium Study; W = whites

Within individual studies, dose-effect relationships are evident at PbB ≤10 µg/dL. A positive dose-effect was observed for PbB and diastolic blood pressure (Zota et al. 2013). An observed positive dose-effect was observed for tibia Pb concentration and hypertension (Hu et al. 1996a). No dose-effect was observed for PbB and pulse pressure (PP), although a positive dose-effect was observed for tibia Pb and PP (Perlstein et al. 2007). In a cross-sectional study of women, diastolic hypertension was observed to have a positive dose-effect when pre- and postmenopausal women were analyzed together and when postmenopausal women were analyzed alone. In contrast, a dose-effect relationship was not observed for PbB and hypertension in a cross-sectional study of men and women (Muntner et al. 2005). A positive dose-effect relationship was observed for PbB and peripheral artery disease (PAD) (Muntner et al. 2005). In men, tibia blood levels had a positive dose-effect relationship with QT interval, but a negative dose-effect relationship with atrioventricular conduction defect (Eum et al. 2011). Studies have also found positive dose-effect relationships between mortality due to cardiovascular disease, myocardial infraction, and stroke and PbB (Menke et al. 2006; Schober et al. 2006).

Several studies have evaluated associations between PbB and cardiovascular function in children (Factor-Litvak et al. 1999, 1996; Gump et al. 2005, 2011; Kapuku et al. 2006; Khalil et al. 2009, 2010; Lustberg and Silbergeld 2002; Menke et al. 2006; Schober et al. 2006; Zhang et al. 2011). Results show alterations in cardiovascular function, including increases in blood pressure and altered cardiovascular function under stress (decreased stroke volume and cardiac output) over a PbB range from <10 to approximately 40 µg/dL.

Effect at Blood Pb Levels ≤10 µg/dL. Studies investigating relationships between PbB ≤10 µg/dL and cardiovascular effects have evaluated effects on blood pressure (including hypertension), atherosclerosis, heart disease (alterations in cardiac conduction and ischemic heart disease), and death due to cardiovascular disease.

Increased blood pressure and hypertension. Numerous studies of large populations show associations between PbB ≤10 µg/dL and increased systolic and/or diastolic blood pressure and increased risk of hypertension (see Table 2-8). The lowest PbB range positively associated with systolic and diastolic blood pressure is 1.41–1.75 µg/dL (Scinicariello et al. 2011). A few studies did not show associations between PbB and blood pressure parameters; however, positive associations between bone Pb concentrations and blood pressure at concomitant PbB ≤10 µg/dL were observed (Gerr et al. 2002; Hu et al. 1996a; Korrick et al. 1999; Zhang et al. 2011). Studies are briefly summarized in Table 2-8, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3.

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Women and men combined (not stratified by sex)[c]			
Faramawi et al. 2015[d] Cross-sectional study; n=13,757	Mean: 3.44	SBP	**β (SE), mmHg for change in blood pressure SD per µg/dL: 0.07 (0.02); p<0.01***
		DBP	β (SE), for change in blood pressure SD per µg/dL: 0.04 (0.03); p=0.08
Martin et al. 2006 Cross-sectional study; n=964 (ages 50–70 years)	Mean: 3.5	SBP	**β, mmHg per 1 µg/dL: 0.99 (0.47,1.51); p<0.01***
		DBP	**β, mmHg per 1 µg/dL: 0.51 (0.24, 0.79); p<0.01***
Zota et al. 2013[d] Cross-sectional study; n=8,194 (ages 40–65 years)	Mean: 1.69 Quintiles: • Q1: ≤1.05 • Q2: 1.06–1.44 • Q3: 1.45–1.90 • Q4: 1.91–2.69 • Q5: >2.70	Elevated SBP (≥140 mmHg)	OR (Q5): 1.23 (0.92, 1.65); p-trend: 0.06
		Elevated DBP (≥90 mmHg)	**OR (Q3): 1.56 (1.11, 2.19)*** **OR (Q4): 1.80 (1.24, 2.60)*** **OR (Q5): 1.77 (1.25, 2.50)*** **p-trend 0.0002**
Women and men (stratified by sex)[c]			
Bost et al. 1999 Cross-sectional study; n=2,563 males and 2,763 females	Mean • M: 3.7 • F: 2.6	SBP	M: no association with PbB (regression coefficient not reported)
			F: no association with PbB (regression coefficient not reported)
		DBP	**M: β, per doubling of PbB: 0.78 (0.01, 1.55)***
			F: regression coefficients not reported

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Bushnik et al. 2014 Population-based survey; n=2,214 males and 2,336 females	Mean • All: 1.64 • Non-hypertensive: 1.59 • Hypertensive: 1.74	SBP	All β, mmHg per 1 µg/dL: 1.85 (-0.20, 3.90); p=0.075
			M β, mmHg per 1 µg/dL: 2.17 (-0.08, 4.42); p=0.058
			F β, mmHg per 1 µg/dL: 0.76 (-2.72, 4.24); p=0.656
		DBP	**All β, mmHg per 1 µg/dL: 1.91 (0.75, 3.08); p=0.002***
			M β, mmHg per 1 µg/dL: 2.36 (0.94, 3.79); p=0.002*
			F β, mmHg per 1 µg/dL: 1.43 (-0.51, 3.38); p=0.142
		Hypertension	**All β, mmHg per 1 µg/dL: -3.87 (-7.46, -0.29); p=0.035***
			M β, mmHg per 1 µg/dL: -6.37 (-15.02, 2.29); p=0.142
			F β, mmHg per 1 µg/dL: -4.18 (-8.78, 0.42); p=0.073
Chu et al. 1999 Population-based survey study; n=1,471 males and 1,329 females	Mean • M: 7.3 • F: 5.7	SBP	**M β (SE), mmHg per 1 $\log_{10}$ µg/dL: 0.185 (0.076); p=0.015***
			F β (SE), mmHg per 1 $\log_{10}$ µg/dL: -0.057 (0.109); p=0.603
		DBP	M β (SE), mmHg per 1 $\log_{10}$ µg/dL: 0.075 (0.053); p=0.159
			F β (SE), mmHg per 1 $\log_{10}$ µg/dL: -0.083 (0.072); p=0.250

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Hense et al. 1993 Population-based survey study; n=1,703 males and 1,661 females	Mean • M: 8.3 • F: 6.0	SBP	**M β, mmHg per 1 µg/dL: 0.29 (0.08, 0.49)***
			F β, mmHg per 1 µg/dL: 0.17 (-0.14, 0.48)
		DBP	M β, mmHg per 1 µg/dL: 0.08 (-0.06, 0.23)
			F β, mmHg per 1 µg/dL: 0.29 (0.09, 0.49)*
Men only[c]			
Cheng et al. 2001[e] Longitudinal study; n=833 men Analysis for hypertension limited to 474 participants who had no history of definite hypertension; analysis for SBP limited to 519 participants who were free from definite hypertension at baseline	PbB mean (all): 6.09 Tibia Pb (µg/g) • Borderline: 23.46 • Definite: 22.69 Patella Pb (µg/g) • Borderline: 33.73 • Definite: 32.72	Hypertension (borderline and definite)	RR, per 1 SD increase in PbB: 1.00 (0.76, 1.33)
			RR, per 1 SD increase in tibia Pb: 1.22 (0.95, 1.57)
			RR, per 1 SD increased in patella Pb: 1.29 (1.04, 1.61); p<0.05*
		SBP	RR, per 1 SD increase in PbB: -0.13 (-1.35, 1.09)
			RR, per 1 SD increase in tibia Pb: 1.37 (0.02, 2.73); p<0.05*
			RR, per 1 SD increased in patella Pb: 0.57 (-0.71, 1.84)
Elmarsafawy et al. 2006[e] Cross-sectional study; n=471	Mean • Low Ca^{2+} intake: 6.6 • High Ca^{2+} intake: 6.6	Hypertension	**Low Ca^{2+}: OR: 1.07 (1.00, 1.15)***
			High Ca^{2+}: OR: 1.03 (0.97, 1.11)
Glenn et al. 2003 Occupational longitudinal study; n=496	Mean: 4.6	SBP	**β (SE; 95% CI), per 1 SD increased in PbB: 0.64 (0.25; 0.14, 1.14)***
		DBP	β (SE; 95% CI); per 1 SD increased in PbB: 0.09 (0.17; -0.24, 0.43)

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Hu et al. 1996a[e] Case-control study of men (n=146) with hypertension and controls (n=444)	Mean • Cases: 6.9 • Controls: 6.1	Hypertension	**Risk of hypertension based on tibia Pb: logistic β (SE): 0.19 (0.0078); p=0.01*** PbB was not associated with hypertension
			OR (95% CL) for 1 µg/g change in tibia Pb: 1.019 (1.004, 1.035)*
			OR (95% CL) for quintile range (8–37 µg/g): 1.5 (1.1, 1.8)*
Perlstein et al. 2007[e] Cross-sectional study; n=593	Mean: 6.12	PP	PbB: no trend over quintiles (p=0.82)
			Bone Pb: p-trend=0.02*
Proctor et al. 1996[e] Cross-sectional study; ≤74 years (n=681); >74 years (n=117)	Mean (SD) • All: 6.5 • ≤74 years: 6.5 • >74 years: 6.3	SBP	All β, mmHg per 1 ln µg/dL PbB: 0.85 (-1.1, 2.7); p>0.05
			≤74 β, mmHg per 1 ln µg/dL PbB: 1.2 (-0.86, 3.2); p>0.05
		DBP	**All β, mmHg per 1 ln µg/dL PbB: 1.2 (0.11, 2.2); p≤0.05***
			≤74 β, mmHg per 1 ln µg/dL PbB: 1.6 (0.42, 2.7); p≤0.01*
Women only[c]			
Al-Saleh et al. 2005 Case-control study of women with hypertension (n=100) and control subjects (n=85)	Mean • Hypertension: 4.75 • Controls: 4.56	Hypertension	OR for PbB ≥3.85 compared to PbB <3.85: 5.27 (0.93, 29.86); p=0.06

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Korrick et al. 1999 Case-control study of women with hypertension (n=89) and control subjects (n=195)	Mean (all): 3	Hypertension	PbB: no increased risk (ORs not reported)
			Patella Pb OR per 1 µg/g increase in PbB: 1.03 (1.00, 1.05); p=0.02*
Nash et al. 2003 Cross-sectional study; n=2,165 all; 1,084 premenopausal, and 663 postmenopausal	Mean (all): 2.9 Quartiles; mean (range) • Q1: 1.0 (0.5–1.6) • Q2: 2.1 (1.7–2.5) • Q3: 3.2 (2.6–3.9) • Q4: 6.4 (4.0–31.1)	SBP	**All β (SE), mmHg per 1 ln µg/dL PbB: 0.32 (0.16); p=0.03***
			Premenopausal β (SE), mmHg per 1 ln µg/dL PbB: 0.14 (0.26); p=0.59
			Postmenopausal β (SE), mmHg per 1 ln µg/dL PbB: 0.42 (0.21); p=0.29
		DBP	**All β (SE): 0.25 (0.09), mmHg per 1 ln µg/dL PbB; p=0.009***
			Premenopausal β (SE), mmHg per 1 ln µg/dL PbB: 0.38 (0.25); p=0.12
			Postmenopausal β (SE) mmHg per 1 ln µg/dL PbB: 0.14 (0.13); p=0.04*
		Hypertension	**Percent of total population with hypertension: p-trend<0.001** (Q1: 19.4; Q2: 20.6; Q3: 25.5 Q4: 28.3)

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Women and men stratified by race[c]			
Den Hond et al. 2002[d] Cross-sectional study n=4,685 MW; 5,138 FW; 1,761 MB; and 2,197 FB	Mean • MW: 3.6 • FW: 2.1 • MB: 4.2 • FB: 2.3	SBP	MW β, per doubling of PbB: 0.3 (-0.2, 0.7); p=0.29
			FW β, per doubling of PbB: 0.1 (-0.4, 0.5); p=0.80
			MB β, per doubling of PbB: 0.9 (0.04,1.8); p=0.04*
			FB β, per doubling of PbB: 1.2 (0.4,2.0); p=0.004*
		DBP	**MW β, per doubling of PbB: -0.6 (-0.9, -0.3); p=0.0003***
			FW β, per doubling of PbB: -0.2 (-0.5, 0.1); p=0.13
			MB β, per doubling of PbB: 0.3 (-0.3, 1.0); p=0.28
			FB β, per doubling of PbB: 0.5 (0.01, 1.1); p=0.047*
Muntner et al. 2005[d] Cross-sectional study of 9,961 (men and women), stratified by race (W, B, MA)	Mean: 1.64 Quartiles: • Q1: <1.06 • Q2: 1.06–1.63 • Q3: 1.63–2.47 • Q4: ≥2.47	Hypertension	W (Q4) OR: 1.10 (0.87, 1.41); p-trend=0.61
			B (Q4) OR: 1.44 (0.89, 2.32); p-trend=0.06
			MA (Q4) OR: 1.54 (0.99, 2.39); p-trend=0.04*

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Park et al. 2009b[d] Cross-sectional study; n=12,500 all, 2,130 MW (<50 years old); 2,152 MW (≥50 years old); 1,048 MB (<50 years old); 540 MB (≥50 years old); 2,429 FW (<50 years old); 2,180 FW (≥50 years old); 1,409 FB (<50 years old); and 612 FB (≥50 years old)	Mean • MW (<50 years old) 4.02 • MW (≥50 years old) 4.92 • MB (<50 years old) 4.55 • MB (≥50 years old) 7.57 • FW (<50 years old) 2.09 • FW (≥50 years old) 3.53 • FB (<50 years old) 2.52 • FB (≥50 years old) 4.49	Hypertension	MW OR: 1.06 (0.92, 1.22)
			FW OR: 1.16 (1.04, 1.29)*
			MB OR: 1.17 (0.98, 1.38)
			FB OR: 1.19 (1.04, 1.38)*
			M (<50 years old) OR: 0.98 (0.80, 1.22)
			M (>50 years old) OR: 1.20 (1.02, 1.41)*
			F (<50 years old) OR: 1.23 (1.04, 1.46)*
			F (>50 years old) OR: 1.09 (0.94, 1.26)
Scinicariello et al. 2010[d] Cross-sectional study; n=6,016 (stratified by race)	Mean • W 2.87 • B 3.59 • MA 3.33	SBP	**W β (SE), mmHg per ln µg/dL PbB: 1.05 (0.37); p=0.01***
			B β (SE), mmHg per ln µg/dL PbB: 2.55 (0.49); p=0.001*
			MA β (SE), **mmHg per ln µg/dL PbB**: 0.84 0.46); p=0.08
		DBP	W β (SE), **mmHg per ln µg/dL PbB**: -0.14 0.49); p=0.77
			B β (SE), mmHg per ln µg/dL PbB: 1.99 (0.44); p=0.0002*
			MA β (SE), **mmHg per ln µg/dL PbB**: 0.74 0.74); p=0.06

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Scinicariello et al. 2011[d] Cross-sectional study; n=16,222 all; 4,538 MW; 4,319 FW; 1,767 MB; 1,854 FB; 1,925 MMA; and 1,819 FMA	Mean • All 1.41 • MW 2.20 • FW 1.55 • MB 2.44 • FB 1.81 • MMA 2.47 • FMA 1.56	SBP	**All β (SE), per ln µg/dL PbB: 1.07 (0.35); p<0.05***
			MW β (SE), per ln µg/dL PbB: 0.87 (0.53); p>0.05
			FW β (SE), per ln µg/dL PbB: 0.89 (0.55); p>0.05
			MB β (SE), per ln µg/dL PbB: 2.30 (0.71); p<0.05*
			FB β (SE), per ln µg/dL PbB: 2.40 (1.14); p<0.05*
			MMA β (SE), per ln µg/dL PbB: 0.10 (0.70); p>0.05
			FMA β (SE), per ln µg/dL PbB: -0.03 (0.64); p>0.05
		DBP	**All β (SE): 0.71 (0.27): p<0.05***
			MW β (SE): 0.90 (0.45): p<0.05*
			FW β (SE): 0.95 (0.38): p<0.05*
			MB β (SE): 2.75 (0.82); p<0.05*
			FB β (SE), per ln µg/dL PbB: 0.30 (0.81); p>0.05
			MMA β (SE), per ln µg/dL PbB: -1.34 (0.66); p<0.05*
			FMA β (SE), per ln µg/dL PbB: -0.74 (0.44); p>0.05

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Vupputuri et al. 2003[d] Cross-sectional study; n=14,952 total; n=5,360 MW; 5,188 FW; 2,104 MB; and 2,300 FB	Mean • MW 4.4 • FW 3.0 • MB 5.4 • FB 3.4	SBP	MW β, per 1 SD (3.3 µg/dL) increase of PbB: 0.29 (-0.24, 0.83)
			FW β, per 1 SD (3.3 µg/dL) increase of PbB: 0.34 (-0.49, 1.17)
			MB β, per 1 SD (3.3 µg/dL) increase of PbB: 0.82 (0.19, 1.44); p<0.05*
			FB β, per 1 SD (3.3 µg/dL) increase of PbB: 1.55 (0.47, 2.64); p<0.01*
		DBP	MW β, per 1 SD (3.3 µg/dL) increase of PbB: 0.01 (-0.38, 0.40); p≥0.05
			FW β, per 1 SD (3.3 µg/dL) increase of PbB: -0.04 (-0.56, 0.47) p≥0.05
			MB β, per 1 SD (3.3 µg/dL) increase of PbB: 0.64 (0.08, 1.20); p<0.05*
			FB β, per 1 SD (3.3 µg/dL) increase of PbB: 1.07 (0.37, 1.77); p<0.01*
		Hypertension	MW OR: 1.04 (0.93, 1.16); p=0.47
			FW OR: 1.32 (1.14, 1.52) p<0.001*
			MB OR: 1.08 (0.99, 1.19); p=0.08
			FB OR: 1.39 (1.21, 1.61); p<0.001)*

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Children and young adults[c]			
Gerr et al. 2002 Cross-sectional study; n=508 young adults (ages 19–29 years)	PbB mean associated with the following bone Pb concentrations: • <1 µg/g: 1.91 (1.58) • 1–5 µg/g: 2.31 (2.06) • 6–10 µg/g: 2.43 (2.36) • >10 µg/g: 3.15 (2.28)	SBP	**Increase (mmHg) associated with bone Pb >10 µg/g (SE): 4.26 (1.48); p=0.004***
		DBP	**Increase (mmHg) associated with bone Pb >10 µg/g (SE): 2.80 (1.25); p=0.03***
Gump et al. 2005 Prospective study; n=122 children assessed at 9 years of age	Cord PbB mean: 2.97	SBP	**β (SE), mmHg log µg/dL: 12.16 (4.96); p=0.016***
		DBP	β (SE), mmHg per log µg/dL: 8.45 (4.54); p=0.066
Gump et al. 2011 Cross-sectional study; n=140 children (ages 9–11 years)	Mean: 1.01 Quartiles: • Q1: 0.14–0.68 • Q2: 0.69–0.93 • Q3: 0.94–1.20 • Q4: 1.21–3.76	SBP	Under acute stress, p-trend over quartiles: 0.31
		DBP	Under acute stress, p-trend over quartiles: 0.29
		TPR	**Under acute stress, p-trend over quartiles: 0.03***

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Zhang et al. 2011 Prospective longitudinal study; n=457 mother-child pairs; children evaluated at ages 7–15 years	• Mean umbilical cord: 5.51 • Mean child concurrent: 2.96 • Median maternal postnatal tibia Pb (µg/g): 9.3	SBP	Maternal tibia Pb, boys, β, mmHg increased per maternal tibia Pb (13 µg/g): –0.34 (–1.98, 1.30)
			Maternal tibia Pb, girls, β mmHg increased per maternal tibia Pb (13 µg/g): 2.11 (0.69, 3.52); p=0.025*
		DBP	Maternal tibia Pb, boys, β, mmHg increased per maternal tibia Pb (13 µg/g): -0.83 (-2.05, 0.38)
			Maternal tibia Pb, girls, β, mmHg increased per maternal tibia Pb (13 µg/g): 1.60 (0.28, 2.91); p=0.007*
Blood pressure during pregnancy[c]			
Rothenberg et al. 2002b Longitudinal study; n=667 pregnant women	Mean: 1.9 Bone (calcaneous) Pb (µg/g) mean:10.7	SBP	Ln-PbB, β: -0.04 (-1.26, 1.18)
			Bone Pb, β: 0.70 (0.04, 1.36)*
		DBP	Ln-PbB, β: 0.20 (-0.78, 1.18)
			Bone Pb, β: 0.54 (0.01, 1.08)*
Wells et al. 2011 Cross-sectional study; n=285 pregnant women during labor	Umbilical cord PbB • mean: 0.66 • Quartiles: o Q1: <0.46 o Q2: 0.47–0.65 o Q3: 0.66–0.95 o Q4: 0.96–6.47	SBP	**Q4 versus Q1 increase in SBP in mmHg at admission: 6.87 (1.51, 12.21); p<0.05***
			Q4 versus Q4 maximum increase in SBP in mmHg: 7.72 (1.83, 13.60); p<0.05*
		DBP	**Q4 versus Q1 increase in DBP in mmHg at admission: 4.40 (0.21, 8.59); p<0.05***
			Q4 versus Q4 maximum increase in DBP in mmHg: Q4: 8.33 (1.14, 15.53); p<0.05*

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Yazbeck et al. 2009 Cross-sectional study; n=971 pregnant women	Mean • Participants with PIH: 2.2 • Participants without PIH: 1.9	PIH	**OR for PIH for an increase of 1 log_{10} µg/dL in PbB; 3.29 (1.11, 9.74); p=0.03***

[a]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[b]If bone Pb is noted under results, study did not show associations between PbB and blood pressure parameters; however, results showed associations between bone Pb concentrations and increased blood pressure at concomitant PbB ≤10 µg/dL.
[c]See the *Supporting Document for Epidemiological Studies for Lead,* Table 3 for more detailed descriptions of studies.
[d]Study population was from NHANES.
[e]Study population was from the Normative Aging Study.

B = black; CI = confidence interval; CL = confidence limit; DBP = diastolic blood pressure; F = female(s); M = male(s); MA = Mexican American; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PIH = pregnancy-induced hypertension; PP = pulse pressure; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; TPR = total peripheral resistance; W = white

The magnitude of effect on blood pressure observed in individual large-scale, cross-sectional studies is consistent with results of meta-analyses (see discussion above on *Characterization of Effects*). For example, Martin et al. (2006) reported that systolic and diastolic blood pressure increased by 0.99 (95% CI 0.47, 1.51; p<0.01) mmHg and 0.51 (95% CI 0.24, 0.79; p<0.01) mmHg, respectively, per 1 µg/dL increase in PbB.

Several studies have examined the relationship between PbB and blood pressure with study populations stratified according to gender, race, and/or age. For example, within study populations, positive associations were observed between PbB and systolic and diastolic blood pressure in men but not in women (Bushnik et al. 2014; Chu et al. 1999; Hense et al. 1993). However, other studies did not find differences between men and women (Bost et al. 1999; Scinicariello et al. 2011). Stratification by sex and age indicates additional differences between men and women. For example, Park et al. (2009b) reported a greater risk of hypertension in men >50 years of age (odds ratio [OR] 1.20; 95% CI 1.02, 1.41), but not in men <50 years of age (OR 0.98; 95% CI 0.80, 1.22), whereas in women, the opposite effect of age was observed, with a greater risk of hypertension in women <50 years of age (OR 1.23; 95% CI 1.04, 1.46) but not >50 years of age (OR 1.09; 95% CI 0.94, 1.26). Studies that stratify populations by race have found race differences in effect sizes on blood pressure. Large-scale cross-sectional studies based on data from NHANES have found larger effect sizes in non-Hispanic blacks and Mexican-Americans than in whites (Den Hond et al. 2002; Muntner et al. 2005; Scinicariello et al. 2011; Vupputuri et al. 2003). Cross-sectional studies based on data from NHANES have consistently shown elevations of systolic blood pressure in association with increasing PbB among black males and females, with less consistency in findings for other demographic groups or for diastolic blood pressure (Den Hond et al. 2002; Nash et al. 2003; Scinicariello et al. 2010, 2011; Vupputuri et al. 2003). Scinicariello et al. (2011) estimated increases in systolic blood pressure ranging from 1.07 to 2.4 per 1 ln increase in PbB (equivalent to approximately 0.7–1.66 per doubling of PbB). The largest effects sizes were observed in black males (2.3; SE 0.71 per ln PbB) and black females (2.4; SE 1.14). Den Hond et al. (2002) estimated the effect size for systolic blood pressure in black males and females to be 0.9 mmHg (95% CI 0.04, 1.8) and 1.2 mmHg (95% CI 0.4, 2.0) per doubling of PbB, respectively. Vupputuri et al. (2003) estimated the effect size for systolic blood pressure in black males and females to be 0.82 mmHg (95% CI 0.19, 1.44) and 1.55 mmHg (95% CI 0.47, 2.64) per 1 standard deviation (SD) increase (3.3 µg/dL) of PbB, respectively. As discussed above (see *Confounding Factors and Effect Modifiers*), numerous co-variables and confounders affect studies of associations between PbB and blood pressure, complicating comparisons between studies.

Few studies have evaluated effects of chronic Pb exposure in children or young adults on blood pressure parameters at PbB at ≤10 μg/dL (Gerr et al. 2002; Gump et al. 2005, 2011; Zhang et al. 2011). Studies are briefly summarized in Table 2-8, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3. Population sizes in these studies are small (n=122–508) compared to studies in adults. Positive associations were observed between concurrent PbB and increased systolic and diastolic blood pressure in young adults (Gerr et al. 2002). Two prospective studies suggest that prenatal exposure to Pb is associated with increased blood pressure in childhood (Gump et al. 2005; Zhang et al. 2011). Umbilical cord PbB was positively associated with increased systolic, but not diastolic, blood pressure in children (Gump et al. 2005). Maternal postnatal bone Pb concentration was associated with increased systolic and diastolic blood pressure in girls, but not boys; however, no association was observed between umbilical cord PbB or patella Pb concentration and increased blood pressure (Zhang et al. 2011).

Effects of Pb on blood pressure and hypertension at PbB at ≤10 μg/dL have also been evaluated during pregnancy (Rothenberg et al. 2002b; Wells et al. 2011; Yazbeck et al. 2009). Studies are briefly summarized in Table 2-8, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3. Increases in systolic and diastolic blood pressure during pregnancy and labor were associated with PbB ≤10 μg/dL umbilical cord PbB, or bone Pb concentrations with concomitant PbB ≤10 μg/dL (Rothenberg et al. 2002b; Wells et al. 2011; Yazbeck et al. 2009). Pregnancy-induced hypertension has been positively associated with PbB ≤10 μg/dL (Yazbeck et al. 2009).

Atherosclerosis. Few studies have evaluated associations between PbB ≤10 μg/dL and atherosclerosis (Ari et al. 2011; Muntner et al. 2005; Navas-Acien et al. 2004). Studies are briefly summarized in Table 2-9, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3. Ari et al. (2011) reported a positive correlation between PbB and intimal medial thickening of the greater carotid artery in non-diabetic hemodialysis patients at a concurrent PbB of 0.41 μg/dL. Peripheral artery disease was positively associated with PbB levels ≥2.47 μg/dL, with a positive trend across quartiles, in a study of a large NHANES 1999–2002 (age 18 years or older) population (Muntner et al. 2005), whereas analyses restricted to adult (≥40 years old) participants of NHANES 1999–2000 reported a positive trend for the risk of peripheral artery disease, although ORs for PbB quartiles (highest PbB quartile >2.90 μg/dL) were not associated with peripheral artery disease (Navas-Acien et al. 2004).

Table 2-9. Summary of Epidemiological Studies Evaluating Atherosclerosis at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Ari et al. 2011 Clinical study; n=50 adult male and female hemodialysis patients and 48 age- and sex-matched controls	Mean • Hemodialysis patients: 0.41 • Controls: 0.10	Greater carotid artery intima-media thickness	**β (SE), mm per µg/dL PbB: 0.101 (0.040); p=0.013***
Muntner et al. 2005[c] Cross-sectional study; n=9,961participants	Mean: 1.64 Quartiles: • Q1: <1.06 • Q2: 1.06–1.63 • Q3: 1.63–2.47 • Q4: ≥2.47	PAD	**OR for prevalence in Q4: 1.92 (1.02–3.61)*** **p-trend (across quartiles): <0.001**
Navas-Acien et al. 2004[c] Cross-sectional study; n=2,125 participants	Mean: 2.07 Quartiles: • Q1: <1.45 • Q2: 1.45–2.07 • Q3: 2.07–2.90 • Q4: >2.90	PAD	OR for prevalence in Q4: 2.88 (0.87, 9.47) **p-trend (across quartiles) for risk: 0.02***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 3 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[c]Study population was from NHANES.

CI = confidence interval; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; PAD = peripheral artery disease; SE = standard error

Heart disease. A series of studies conducted in men from the Normative Aging Study in the greater Boston, Massachusetts area evaluated associations between PbB ≤10 μg/dL and alterations in cardiac conduction and ischemic heart disease (Cheng et al. 1998; Eum et al. 2011; Jain et al. 2007; Park et al. 2009a). Studies are briefly summarized in Table 2-10, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 2. Studies show positive associations between bone Pb concentrations (at concomitant PbB ≤10 μg/dL) and changes to electrocardiograms (prolonged QT and QRS intervals) and atrioventricular conduction defect; however, no associations were observed between PbB and conduction abnormalities (Cheng et al. 1998; Eum et al. 2011; Park et al. 2009a). For ischemic heart disease, increased risks were associated with PbB and with tibia and patella Pb concentrations (Jain et al. 2007). A 1 SD increase in PbB was associated with a 1.27-fold increase in risk for ischemic heart disease.

Mortality due to cardiovascular disease. Mortality due to cardiovascular disease at PbB ≤10 μg/dL has been examined in large prospective and longitudinal studies, which provide mixed results. Studies are briefly summarized in Table 2-11, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3. Three of these were conducted in large studies of men and women participating in NHANES (Aoki et al. 2016; Lanphear et al. 2018; Menke et al. 2006; Schober et al. 2006). Aoki et al. (2016), Lanphear et al. (2018), and Menke et al. (2006) observed positive associations of mortality due to cardiovascular disease, including ischemic heart disease, myocardial infarction, and stroke and at PbB ≤10 μg/dL, including positive trends for mortality with increasing PbB. In contrast, Schober et al. (2006) did not find increased cardiovascular mortality risk at PbB <10 μg/dL, although risk was increased at PbB ≥10 μg/dL and a positive trend for mortality was observed with increasing PbB. For PbB, no increased risk or positive trend for morality due to cardiovascular was observed in men from the Normative Aging Study (Weisskopf et al. 2009). In women, the risk of mortality due to coronary heart disease was increased at PbB ≥8 μg/dL compared to PbB <8 μg/dL (Khalil et al. 2009).

Table 2-10. Summary of Epidemiological Studies Evaluating Heart Disease at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Cheng et al. 1998[d] Longitudinal study; n=775 men (n=277 for men <65 years of age)	PbB mean: 5.8 Bone Pb, µg/g, mean (SD) • Tibia: 22.2 (13.4) • Patella: 30.8 (19.2)	QT interval	β, msec per 10-fold increase in PbB: -0.65 (-10.40, 9.10); p=0.90
			β, msec per 10-fold increase in tibia Pb: 5.03 (0.83, 9.22); p=0.02*
			β, msec per 10-fold increase in patella Pb: 3.00 (0.16, 5.84); p=0.04*
		QRS interval	β, msec per 1 unit increase in PbB: -3.49 (-10.72, 3.75); p=0.35
			β, msec per 1-fold increase in tibia Pb: 4.83 (1.83, 7.83); p<0.01*
			β, msec per 1-fold increase in patella Pb: 2.23 (0.10, 4.36); p=0.04*
		IVCD	**OR for a 10-fold increase in tibia Pb: 2.23 (1.28, 3.90); p<0.01***
Eum et al. 2011[d] Prospective longitudinal study; n=600 men	PbB baseline mean: 5.8 PbB Tertiles: • T1: <4 • T2: 4–6 • T3: >6 Tibia Pb (µg/g) baseline mean: 21.6 Tertiles: • T1: <16 • T2: 16–23 • T3: >23	QT interval	PbB OR for T3: 1.31 (0.69, 2.48); p-trend: 0.41
			Tibia OR for T3: 2.53 (1.22, 5.25)*; p-trend: 0.003*
		Atrioventricular conduction defect	PbB OR for T3: 0.52 (0.19, 1.45); p-trend: 0.16
			Tibia OR for T3: 0.23 (0.06, 0.87); **p-trend: 0.03**

Table 2-10. Summary of Epidemiological Studies Evaluating Heart Disease at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Jain et al. 2007[d] Longitudinal prospective study; n=837 men	PbB Baseline mean • Non-cases 6.2 • Cases 7.0 Patella Pb (µg/g) baseline mean • Non-cases 30.6 • Cases 36.8	Ischemic heart disease	**PbB β per 1 SD increase in PbB: 1.27 (1.01, 1.59)***
			PbB HR per 1 log increased in PbB: 1.45 (1.01, 2.06); p=0.05*
			Patella Pb HR per 1 log increased in bone Pb: 2.64 (1.09, 6.37); p=0.05*
Park et al. 2009a[d] Longitudinal prospective study; n=613 men	• PbB median (IQR): 5 (4–7) • Patella Pb (µg/dL), median (IQR): 26 (18–37) • Tibia Pb (µg/dL), median (IQR): 19 (14–27)	QT interval	PbB β for msec increase per IQR: 1.3 (-0.76, 3.36)
			Patella β for msec increase per IQR: 2.64 (0.13, 5.15)*
			Tibia β for msec increase per IQR: 2.85 (0.29, 5.40)*

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 3 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[c]If bone Pb is noted under results, study did not show associations between PbB and blood pressure parameters; however, results showed associations between bone Pb concentrations and increased blood pressure at concomitant PbB ≤10 µg/dL.
[d]Study population was from the Normative Aging Study.

CI = confidence interval; HR = hazard ratio; IQR = intraquartile range; IVCD = intraventricular conduction defect; OR = odds ratio; Pb = lead; SD = standard deviation

Table 2-11. Summary of Epidemiological Studies Evaluating Mortality due to Cardiovascular Disease at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Aoki et al. 2016[c] Prospective study; n=18,602	Mean: 1.73	Mortality due to cardiovascular disease	**RR, per 10-fold increase in PbB: 1.44 (1.05, 1.98)***
Khalil et al. 2009 Prospective study; n=533 women	Mean: 5.3	Mortality due to coronary heart disease	**PbB ≥8.0 compared to women with PbB <8.0. HR: 3.08 (1.23, 7.70); p=0.016***
Menke et al. 2006[c] Longitudinal study; n=13,946	Baseline mean: 2.58 Tertiles: • T1: <1.93 • T2: 1.94–3.62 • T3: ≥3.63	Mortality due to cardiovascular disease	**HR for T3 versus T1: 1.55 (1.08, 2.24)*; p-trend: 0.003***
		Mortality due to myocardial infarction	**HR for T3 versus T1: 1.89 (1.04, 3.43)*; p-trend: 0.007***
		Mortality due to stroke	**HR for T3 versus T1: 2.51 (1.20, 5.26)*; p-trend: 0.017***
			RR for T3 versus T1: 1.55 (1.16, 2.07)*; p-trend: <0.01*
Lanphear et al. 2018[c] Longitudinal study; n=14,289	Mean: 2.71	Mortality due to cardiovascular disease	**HR for PbB increase from 1.0 to 6.7 µg/dL: 1.70 (1.30, 2.22)***
		Mortality due to ischemic heart disease	**HR for PbB increase from 1.0 to 6.7 µg/dL: 2.08 (1.52, 2.85)***

Table 2-11. Summary of Epidemiological Studies Evaluating Mortality due to Cardiovascular Disease at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Weisskopf et al. 2009[d] Longitudinal study; n=868 men	Mean: 5.6 Tertiles • T1: <4 • T2: 4–6 • T3: >6	Mortality due to cardiovascular disease	HR for T3 versus T1: 1.10 (0.67, 1.80); p-trend: 0.72

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 3 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[c]Study population was from NHANES.
[d]Study population was from the Normative Aging Study.

CI = confidence interval; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; Pb = lead; RR = risk ratio

Associations Between Bone Pb and Cardiovascular Effects. Several studies have evaluated associations between bone Pb concentration and blood pressure and cardiac outcomes. Results provide evidence that long-term exposure to Pb produces adverse effects on the cardiovascular system.

Increased blood pressure and hypertension. Numerous studies show associations between bone Pb concentration and increased blood pressure and increased risk of hypertension (see Table 2-12). The most studied population is older men participating in the Normative Aging Study. Results consistently show positive associations between tibia Pb and systolic blood pressure (Cheng et al. 2001), pulse pressure (Jhun et al. 2015; Perlstein et al. 2007; Zhang et al. 2010), and risk of hypertension (Cheng et al. 2001; Elmarsafawy et al. 2006; Hu et al. 1996a; Peters et al. 2007). The association between bone Pb and elevated pulse pressure suggests that Pb may alter cardiovascular function through loss of arterial elasticity (Jhun et al. 2015; Perlstein et al. 2007; Zhang et al. 2010). Associations between patella Pb and blood pressure outcomes have been somewhat less consistent, with some studies showing positive associations (Hu et al. 1997; Jhun et al. 2015; Perlstein et al. 2007; Peters et al. 2007; Zhang et al. 2010) and other studies showing no associations (Cheng et al. 2001; Elmarsafawy et al. 2006). Other study populations examined include adults (Martin et al. 2006), young adults (Gerr et al. 2002), current and former Pb workers (Glenn et al. 2003; Lee et al. 2001), women (Korrick et al. 1999), pregnant women (Rothenberg et al. 2002b), and mother-child pairs (Zhang et al. 2001). Although study results are not consistent, positive associations between bone Pb and blood pressure and risk of hypertension have been reported. Navas-Acien et al. (2008) conducted a meta-analysis of 10 studies (see Table 2-12 for studies included in the analysis) to evaluate associations between tibia and patella Pb and blood pressure outcomes. Positive associations were observed between tibia Pb and systolic blood pressure and hypertension risk, but no associations were observed between tibia Pb and diastolic blood pressure or between patella Pb and systolic blood pressure, diastolic blood pressure, or hypertension risk.

Table 2-12. Associations Between Bone Pb and Blood Pressure Outcomes

		Blood pressure outcome			
Reference	Population	Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
Cheng et al. 2001[a]	833 men[b]	↑ T 0 P	–	–	↑ T 0 P

Table 2-12. Associations Between Bone Pb and Blood Pressure Outcomes

Reference	Population	Blood pressure outcome			
		Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
Elmarsafawy et al. 2006	471 men[b]	–	–	–	↑ T (at low dietary calcium) 0 P (at high dietary calcium)
Gerr et al. 2002[a]	508 young adults[c]	↑ T	↑ T	–	–
Glenn et al. 2003[a]	496 male Pb workers[d]	↑ T ↑ P	0 T 0 P	–	–
Glenn et al. 2006[a]	575 adult Pb workers[e]	↓ T	0 T	–	–
Hu et al. 1996a[a]	590	–	–	–	↑ T ↑ P
Jhun et al. 2015	727 men[b]	–	–	↑ T ↑ P	–
Korrick et al. 1999[a]	689 women (214 cases; 475 controls)[f]	–	–	–	0 T ↑ P
Lee et al. 2001[a]	924 adult Pb workers (789 cases; 135 controls[e]	↑ T	0 T	–	↑ T
Martin et al. 2006[a]	964 adults	0 T	0 T	–	↑ T
Perlstein et al. 2007	593 men[b]	–	–	↑ T ↑ P	–
Peters et al. 2007	512 men[b]	–	–	–	↑ T (with high stress) ↑ P (with high stress)
Rothenberg et al. 2002b[a]	1,006 pregnant women	–	–	–	↑ C (3rd trimester) 0 T (3rd trimester)
Schwartz et al. 2000c[a]	543 male Pb workers[d]	0 T	0 T	–	0 T
Weaver et al. 2008	652 Pb workers[e]	0 P	0 P	–	0 P
Zhang et al. 2010	612 men[b]	–	–	↑ T ↑ P	–

Table 2-12. Associations Between Bone Pb and Blood Pressure Outcomes

Reference	Population	Blood pressure outcome			
		Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
Zhang et al. 2011	457 mother-child pairs[g]	↑ T (girls) 0 T (boys)	↑ T (girls) 0 T (boys)	–	–

[a]Included in the Navas-Acien et al. (2008) meta-analysis.
[b]Participants in the Normative Aging Study.
[c]19–29 years of age.
[d]Current and former Pb workers in the United States.
[e]Current and former Pb workers in South Korea.
[f]Nurses Health Study.
[g]Based on maternal bone Pb measurement.

↑ = positive association; ↓ = negative association; 0 = no association; – = not reported; C = calcaneous bone; P = patella; Pb = lead; T = tibia

Cardiac function. Several studies evaluating associations between bone Pb and cardiac function, disease, and mortality were conducted in participants of the Normative Aging Study (see Table 2-13). For tibia Pb, positive associations have been observed for QT and QRS intervals (Cheng et al. 1998; Eum et al. 2011; Park et al. 2009a), atrioventricular and intraventricular block (Cheng et al. 1998), and ischemic heart disease (Jain et al. 2007). For patella Pb, positive associations were observed for QT and QRS intervals (Cheng et al. 1998; Park et al. 2009a). Both tibia Pb and patella Pb were positively associated with ischemic heart disease (Jain et al. 2007). However, no association was observed between tibia or patella Pb and all cardiovascular mortality or mortality due to ischemic heart disease (Weisskopf et al. 2009).

Table 2-13. Associations Between Bone Pb and Cardiac Function, Disease, and Mortality

Reference	Population	Outcome		
		Function	Disease	Mortality
Cheng et al. 1998	775 men[a]	↑ T (QT and QRS intervals; AV block; IV block) ↑ P (QT and QRS intervals) 0 P (AV block; IV block)	–	–
Eum et al. 2011	600 men[a]	↑ T (QT and QRS	–	–

Table 2-13. Associations Between Bone Pb and Cardiac Function, Disease, and Mortality

		Outcome		
Reference	Population	Function	Disease	Mortality
		intervals) 0 P (QT and QRS intervals)		
Jain et al. 2007	837 men[a]	–	↑ T (IHD) ↑ P (IHD)	–
Park et al. 2006	413 men[a]	0 T (HRV with MetS) 0 T (HRV without MetS) ↑ P (HRV with MetS) 0 P (HRV without MetS)	–	–
Park et al. 2009a	613 men[a]	↑ T (QT interval) ↑ P (QT interval)	–	–
Weisskopf et al. 2009	868 men[a]	–	–	0 T (all cardiovascular or IHD deaths) 0 P (all cardiovascular or IHD deaths)

[a]Participants in the Normative Aging Study.

↑ = positive association; ↓ = negative association; 0 = no association; – = not reported; AV = atrioventricular; HRV = heart rate variability; IHD = ischemic heart disease (defined as myocardial infarction or angina pectoris); IV = intraventricular; MetS = metabolic syndrome (three or more of the following: obesity, diabetes, hypertension, and dyslipidemia); P = patella; Pb = lead; T = tibia

Mechanisms of Action. Several studies and recent reviews include discussions of mechanisms that may be involved in Pb-induced effects on cardiovascular function (Faramawai et al. 2015; Ghiasvand et al. 2013; Nawrot et al. 2002; Shiue et al. 2014; Weisskopf et al. 2009; Xu et al. 2015; Zota et al. 2013). Control of cardiovascular function is multi-factorial; therefore, numerous mechanisms are likely involved in Pb-induced cardiovascular effects. Specific mechanisms for cardiovascular effects include: impairment of renal function; effects on vascular smooth muscle, including constrictive effects and disruption of NO-induced vasodilatory actions; increase of sympathetic nervous system activity; and altered regulation of the renin-angiotensin-aldosterone axis and the renal kallikrein system. In addition, general mechanisms of toxicity of Pb, including oxidative stress, inflammation, and altered transport of ions across cellular membranes, also are likely to be involved (see Section 2.21).

2.7 GASTROINTESTINAL

Overview. Few epidemiological studies have evaluated gastrointestinal effects associated with chronic exposure to Pb. Almost all available studies were conducted in small numbers of workers with PbB >10 µg/dL, although one study included a group of workers with PbB ≤10 µg/dL. Study results consistently show gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea, and/or constipation) associated with PbB ranging from 8.04 µg/dL to approximately 100 µg/dL. As reviewed in Section 2.2 (Acute Lead Toxicity), acute exposure to Pb is associated with gastrointestinal symptoms and intestinal paralysis.

The following gastrointestinal effects have been associated with PbB:

- ≤10 µg/dL:
    - Gastrointestinal symptoms (abdominal colic/discomfort).
- >10 µg/dL:
    - Gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea and/or constipation); corroborated in a few studies.

Measures of Exposure. Studies examining the association between gastrointestinal effects of Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. Most epidemiological studies on gastrointestinal effects of Pb are survey or cross-sectional studies of small populations of workers. In general, studies did not consider factors, such as age, diet, nutritional factors, alcohol use, and potential exposure to other occupational chemicals or limitations such as study design (cross-sectional and survey). Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. In contrast to the large number of epidemiological studies evaluating effects of Pb on other organ systems (e.g., neurological and cardiovascular outcomes), few epidemiological studies have investigated the gastrointestinal effects of chronic exposure to Pb (see Table 2-14). With the exception of a survey study conducted in 497 workers (Rosenman et al. 2003), studies were conducted in small worker populations (n=69–155). Increased gastrointestinal symptoms (abdominal colic/pain,

Table 2-14. Summary of Studies Evaluating Gastrointestinal Symptoms Associated with Chronic Exposure to Lead (Pb)

Reference and study population	PbB (µg/dL)	Outcomes evaluated[a]	Effects[b]
Awad el Karin 1986 Cross-sectional study; n=92 exposed; 40 controls	Range of means (by job category): 48.1–80.7 Controls mean: 21.2	Abdominal colic	• Exposed (% reporting symptom) 41.3; **exposed versus control p=0.01*** • Control (% reporting symptom): 7.5
		Constipation	• Exposed (% reporting symptom) 41.4; **exposed versus control p=0.01*** • Control (% reporting symptom): 10.0
Baker et al. 1979 Survey study; n=160 Pb workers	Range of means (by job category): 41.8–87.2	Gastrointestinal symptoms	• **Mean PbB at which symptoms are present: 101.24 µg/dL (p<0.01)*** • PbB, symptom absent: 65.98 µg/dL
		Abdominal pain	• **PbB, symptoms present: 100.77 µg/dL (p<0.01)*** • PbB, symptom absent: 68.25 µg/dL
Kuruvilla et al. 2006 Cross-sectional study; n=155; exposed workers: n=105 (52 battery workers; 53 painters); controls: n=50	Mean • Battery workers:42.40 • Painters: 8.04 • Controls: 5.76	Abdominal colic	• **Battery workers (% reporting symptom): 17.3; p<0.01** • **Painters (% reporting symptom):18.9; p<0.01*** • Controls (% reporting symptom): 0
		Abdominal discomfort	• **Battery workers (% reporting symptom): 19.2; p<0.01*** • **Painters (% reporting symptom): 26.4; p<0.001*** • Controls (% reporting symptom): 2
		Vomiting	• Battery workers (% reporting symptom): 1.9 • Painters (% reporting symptom): 1.9 • Controls (% reporting symptom): 0
		Constipation	• Battery workers (% reporting symptom): 0 • Painters (% reporting symptom): 1.9 • Controls (% reporting symptom): 2

Table 2-14. Summary of Studies Evaluating Gastrointestinal Symptoms Associated with Chronic Exposure to Lead (Pb)

Reference and study population	PbB (µg/dL)	Outcomes evaluated[a]	Effects[b]
Matte et al. 1989 Survey study; n=69 (46 manufacturing and 23 battery repair workers)	• Mean: not reported • Workers stratified by PbB <60 and ≥60	Nausea	• PbB <60 (% reporting symptom): 7 • PbB ≥60 (% reporting symptom): 14 • PR (95% CI): 2.0 (0.5, 7.9)
		Abdominal pain	• PbB <60 (% reporting symptom): 12 • PbB ≥60 (% reporting symptom): 18 • PR (95% CI): 1.5 (0.5, 4.6)
Rosenman et al. 2003 Survey study; n=497 workers	• Range 10–70 • Stratification by PbB: o 10–24 (n=139) o 25–29 (n=98) o 30–39 (n=171) o 40–49 (n=58) o 50–59 (n=22) o ≥60 (n=9)	Abdominal pain	AdjOR (95% CI) for PbB: • 10–24: 1 (reference) • 25–29: 0.62 (0.28, 1,37) • 30–39: 0.98 (0.53, 1.82) • **40–49: 2.15 (1.03, 4.49)*** • 50–59: 1.54 (0.52, 5.23) • ≥60: NR

[a]Gastrointestinal symptoms include abdominal colic, nausea, vomiting, diarrhea, and/or constipation.
[b]Asterisk and **bold** indicate association with Pb.

AdjOR = adjusted odds ratio (adjusted by age, ethnicity group, company screening, and smoking status); CI = confidence interval; NR = not reported; PbB = blood lead concentration; PR: prevalence ratio

nausea, vomiting, diarrhea, and/or constipation) were observed in all studies. The lowest PbB associated with increased gastrointestinal symptoms showed an increased percentage of workers reporting abdominal colic and discomfort at a mean PbB of 8.04 µg/dL, compared to controls (PbB 5.76 µg/dL) (Kuruvilla et al. 2006). For example, 18.9% of painters reported abdominal colic compared to 0 in the control group.

Effect at Blood Pb Levels ≤10 µg/dL. See discussion above on Kuruvilla et al. (2006).

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of gastrointestinal toxicity. EPA (2014c) specifically noted that oxidative stress through ROS could result in gastrointestinal toxicity; as a result, damage to the intestinal mucosa epithelium is possible.

2.8 HEMATOLOGICAL

Overview. Pb-induced toxicity to the hematological system has long been established. Pb inhibits heme synthesis, leading to the development of microcytic, hypochromic anemia. Numerous epidemiological studies have evaluated hematological effects associated with exposure to Pb in adults and children. Most studies were cross-sectional in design and evaluated effects on heme synthesis and subsequent changes in erythrocyte hemoglobin parameters and anemia. Studies in adults (general populations and workers) and children consistently show inhibition of heme synthesis enzymes, particularly δ-ALAD, and subsequent decreases in blood hemoglobin, red blood cell parameters (e.g., mean cell hemoglobin, mean cell volume), and development of anemia. Other hematological effects observed in epidemiological studies include alterations in erythrocyte function (decreased activities of pyrimidine 5'-nucleotidase and membrane Ca^{2+}/Mg^{2+}ATPase), changes in serum EPO concentration, and decreased platelet count.

The following hematological effects have been associated with PbB:

- ≤10 µg/dL:
    - Inhibition of δ-ALAD; demonstrated in a few studies.
    - Decreased blood hemoglobin; evaluated in several studies with mixed results.
    - Decreased platelet count.
    - Decreased plasma EPO in adult males.

- >10 µg/dL:
    - Dose-dependent decreased heme synthesis due to inhibition of δ-ALAD and other heme metabolism enzymes; demonstrated in numerous studies.
    - Anemia and decreased blood hemoglobin; demonstrated in numerous studies.
    - Decreased activity of other erythrocyte enzymes (pyrimidine 5'-nucleotidase or red blood cell membrane Ca^{2+}/Mg^{2+}ATPase); demonstrated in a few studies.
    - Altered plasma EPO concentration:
        - Decreased in adult males; evaluated in a few studies with mixed results.
        - Decreased in pregnant females; demonstrated in one study, but findings not corroborated.
        - Mixed results (both increases and decreases observed) in children; evaluated in a few studies.

Measures of Exposure. Studies evaluating the association between hematological effects and Pb exposure most commonly evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. In general, available epidemiological studies on hematological effects do not control for factors, including concomitant exposure to other chemicals, that may affect the hematological system. In addition, dietary insufficiency of iron is the primary cause of microcytic, hypochromic anemia; however, few studies evaluated this as an effect modifier. Age and renal function are also confounding factors, as impairment of renal function can affect renal EPO synthesis and PbB. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. General trends for studies showing a relationship between PbB and hematological effects are shown in Table 2-15. Most epidemiological studies of hematological effects have examined effects on heme metabolism and its consequences, with fewer studies examining other hematological endpoints (altered serum levels of EPO, altered erythrocyte function, and decreased platelet count). As noted above, Pb-induced toxicity to the hematological system, specifically inhibition of heme synthesis enzymes and resulting anemia and decreased erythrocyte hemoglobin, have long been established. Numerous epidemiological studies in adults and children provide consistent evidence that δ-ALAD activity is inversely correlated with PbB over a PbB range of <10–>50 µg/dL (see Table 2-15) with δ-ALAD inhibition and subsequent effects of inhibition showing concentration-dependence for PbB

(Murata et al. 2009; Schwartz et al. 1990). A few studies have reported other hematological effects, including decreased platelet count in Pb workers at PbB of 5.4 µg/dL (Conterato et al. 2013) and >41 µg/dL (Barman et al. 2014). Inhibition of non-heme metabolism enzymes in erythrocytes was also associated with PbB. In Pb workers, membrane Ca^{2+}/Mg^{2+}ATPase was inhibited at a PbB range of approximately 29–42 µg/dL (Abam et al. 2008), and pyrimidine 5'-nucleotidase was inhibited at a PbB of >50 µg/dL (Buc and Kaplan 1978). Pyrimidine 5'-nucleotidase also was inhibited in children (aged 1–5 years) with a PbB range of 30–72 µg/dL (Angle et al. 1982).

Table 2-15. Overview of Hematological Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Altered heme synthesis[a]	Ahamed et al. 2006; Ergurhan-Ilhan et al. 2008; Wang et al. 2010
	Anemia and/or decreased measures of RBC hemoglobin[b]	Ahamed et al. 2006; Conterato et al. 2013; Olivero-Verbel et al. 2007; Queirolo et al. 2010; Riddell et al. 2007; Ukaejiofo et al. 2009
	Decreased platelet count	Conterato et al. 2013
	Decreased EPO	Sakata et al. 2007
>10–30	Altered heme synthesis[a]	Ahamed et al. 2005, 2006; Counter et al. 2008, 2009; Grandjean and Lintrup 1978; Lauwerys et al.1978; Mohammad et al. 2008; Murata et al. 2009; Piomelli et al. 1982 Rabinowitz et al. 1985; Roels et al. 1975, 1976; Roels and Lauwerys 1987; Schumacher et al. 1997; Stuik 1974
	Anemia and/or decreased measures of RBC hemoglobin[b]	Adebonojo 1974; Ahamed et al. 2007; Karita et al. 2005; Schwartz et al. 1990; Shah et al. 2010
	Altered RBC function[c]	Abam et al. 2008; Huel et al. 2008
	Decreased platelet count	Barman et al. 2014
	Decreased EPO	Graziano et al. 1991, Liebelt et al. 1999
	Increased EPO	Factor-Litvak et al. 1999;
>30–50	Altered heme synthesis[a]	Ademuyiwa et al. 2005; Alessio et al. 1976; Conterato et al. 2013; Fukumoto et al. 1983; Griffin et al. 1975; Murata et al. 2009; Roels et al. 1976; Secchi et al. 1974; Solliway et al. 1996
	Anemia and/or decreased measures of RBC hemoglobin[b]	Conterato et al. 2013; Schwartz et al. 1990; Solliway et al. 1996
	Altered RBC function	Abam et al. 2008; Angle et al. 1982; Buc and Kaplan 1978

Table 2-15. Overview of Hematological Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
	Decreased EPO	Romeo et al. 1996
	Increased EPO	Factor-Litvak et al. 1998; Graziano et al. 2004;
>50	Altered heme synthesis[a]	Cools et al. 1976; Gurer-Orhan et al. 2004; Jin et al. 2006; Meredith et al.1978; Murata et al. 2009; Pagliuca et al.1990; Schwartz et al. 1990
	Anemia and/or decreased measures of RBC hemoglobin[b]	Baker et al. 1979; Lilis et al. 1978; Malekirad et al. 2013; Grandjean1979; Patil et al. 2006; Roels et al.1979
	Decreased EPO	Romeo et al. 1996
	Altered RBC function[c]	Buc and Kaplan 1978

[a]Inhibition of heme synthesis measured by decreased δ-ALAD activity, elevated RBC levels or urinary levels of heme precursors (e.g., protoporphyrin, erythrocyte protoporphyrin, free erythrocyte protoporphyrin), and/or increased RBC zinc protoporphyrin/heme ratio.
[b]Decreased blood hemoglobin, hematocrit, erythrocyte count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and/or mean cell volume.
[c]Altered erythrocyte function includes inhibition of pyrimidine 5'-nucleotidase or decreased RBC membrane Ca^{2+}/Mg^{2+}ATPase.

ALAD = aminolevulinic acid dehydratase; EPO = serum erythropoietin; RBC = red blood cell

Several studies have evaluated the relationship between PbB and serum EPO levels in adults (Graziano et al. 1991; Osterode et al. 1999; Romeo 1991; Sakata et al. 2007) and children (Factor-Livak 1998, 1999; Graziano et al. 2004; Liebelt et al. 1999). Erythropoietin is a glycoprotein hormone produced in renal proximal tubules that regulates steady-state and accelerated erythrocyte production. As a compensatory response to conditions producing low blood oxygen (e.g., anemia), proximal tubular cells release EPO, resulting in stimulated erythrocyte production. However, if renal function is compromised due to disease or toxicity (e.g., Pb-induced renal damage), the compensatory increases in serum EPO may be diminished or absent. Results of three cross-sectional studies in adult male workers are inconsistent, showing decreased serum EPO levels at PbB 6.4–65.1 µg/dL (Romeo et al. 1996; Sakata et al. 2007), but no effect on EPO at a PbB of 45.5 µg/dL (Osterode et al. 1999). Study populations in these cross-sectional studies were small (n for exposed groups=10–27). In a subgroup of 48 pregnant women (selected from a larger cohort of 1,502 pregnant women), serum EPO was decreased; the range of PbB means based on hemoglobin stratifications was 23.1–36.2 µg/dL (Graziano et al. 1991). Studies in children have yielded mixed results on associations between PbB and serum EPO. Results of a series of prospective studies of children (n=280) in former Yugoslavia indicate that serum EPO levels in Pb-exposed children exhibit age-dependence (Factor-Litvak et al. 1998, 1999; Graziano et al. 2004). Serum EPO was increased in

children 4.5 (mean PbB: 39.3 µg/dL) and 6.5 years of age (mean PbB: 36.2 µg/dL), but not in children 9.5 (mean PbB: 28.1 µg/dL) or 12 years of age (mean PbB: 30.6 µg/dL) (Factor-Litvak et al. 1998, 1999; Graziano et al. 2004). The study authors suggested that the capacity for compensatory increases in EPO in response to Pb-induced anemia declines over time, possibly due to Pb-induced damage to the renal proximal tubule. In contrast to increases in EPO levels observed in the Yugoslavian cohort, Liebelt et al. (1999) showed decreased EPO levels in a group of children ages 1–6 years (n=95) who had a mean PbB of 18 µg/dL.

Effect at Blood Pb Levels ≤10 µg/dL. Epidemiological studies evaluating hematological effects of PbB ≤10 µg/dL are summarized in Table 2-16, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 4. Studies were conducted in small populations (n for exposed groups=25–391), except for two larger (n=855–2,861) cross-sectional studies in children (Liu et al. 2015a; Riddell et al. 2007). In general, studies show negative associations between PbB ≤10 µg/dL and δ-ALAD activity and blood hemoglobin in adults and children, although results are mixed. Negative correlations between PbB and δ-ALAD activity (measured by plasma δ-ALAD activity or zinc protoporphyrin:heme ratio) have been observed in children (Wang et al. 2010), adolescent males (Ahamed et al. 2006), and adults (Wang et al. 2010) at mean PbB of 5.95–9.96 µg/dL; however, no effect on δ-ALAD activity was observed in children with a mean PbB of 7.11 µg/dL (Ahamed et al. 2005). Differences in δ-ALAD activity were observed for male automotive repair workers (mean PbB: 7.9 µg/dL) and male controls (mean PbB: 2.6 µg/dL). Additionally, two studies in adults showed that blood hemoglobin concentration was lower in Pb workers (mean PbB: 5.4–7.0 µg/dL) compared to controls (mean PbB: 1.5–3.0 µg/dL) (Conterato et al. 2013; Ukaejiofo et al. 2009). In children with mean PbB of 6.9–9.0 µg/dL, there was a negative association between blood hemoglobin concentrations and PbB (Queirolo et al. 2010; Riddell et al. 2007) and erythrocyte Pb concentration (Liu et al. 2015a). At lower PbB in newborns (PbB 3.9 µg/dL) and children (PbB 5.5 µg/dL), no correlation was found; however, these study population were small (n=50–189) (Olivero-Verbel et al. 2007; Zentner et al. 2006). Thus, data are not adequate to establish an exposure-response relationship for decreased hemoglobin at PbB ≤10 µg/dL. Studies in small groups of workers (n=27–50) showed lower platelet count (PbB 5.4 µg/dL) and serum EPO concentrations (PbB 6.4 µg/dL) compared to controls (Conterato et al. 2013; Sakata et al. 2007). Although these findings have not been evaluated in other studies with PbB ≤10 µg/dL, similar effects have been observed at PbB >10 µg/dL.

Table 2-16. Summary of Epidemiological Studies Evaluating Hematological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Heme metabolism			
Ahamed et al. 2005 Cross-sectional study; n=62 children (ages 4–12 years)	Mean (SD) • Group 1: 3.93 (0.61) • Group 2: 7.11 (1.25)	δ-ALAD activity	No difference between groups: • Group 1: 4.82 (1.25) • Group 2: 4.56 (1.20)
Ahamed et al. 2006 Cross-sectional study: n=39 adolescent males (ages 15–18 years)	Mean (SD): 9.96 (3.63) Range: 4.62–18.64	δ-ALAD activity	**A negative correlation between PbB and blood δ-ALAD activity: r= -0.592; p<0.001***
Ergurhan-Ilhan et al. 2008 Cross-sectional study; n=25 male automotive repair workers (mean age 16.8 years): 24 male controls (mean age 16.3 years)	Mean (SD) • Controls: 2.6 (2.0) • Workers: 7.9 (5.2)	ALAD index	• Controls: 0.40 (0.34) • **Workers: 0.73 (0.47); p=0.048***
		ZPP:heme ratio	• Controls: 26.4 (7) • **Workers: 37.2 (15.9); p=0.045***
Wang et al. 2010 Cross-sectional study of 307 children and 391 adults from China	Median • Children: 6.83 • Adults: 5.95	δ-ALAD activity	Pearson correlation coefficients: • **Children: -0.256; p<0.05*** • **Adults: -0.213; p<0.05***
		ZPP	Pearson correlation coefficients: • **Children: 0.135; p<0.05*** • **Adults: 0.083; p<0.05***
Blood hemoglobin			
Conterato et al. 2013 Cross-sectional; n=50 painters; 36 controls	Mean (SE) • Control: 1.5 (0.1) • Painters: 5.4 (0.4)	Hb	Mean (SE), µg/dL • Control: 15.4 (0.2) • **Painters: 15.0 (0.1); p<0.05***

Table 2-16. Summary of Epidemiological Studies Evaluating Hematological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Liu et al. 2015a Cross-sectional study; n=855 children (age range: 3–7 years)	PbB quartiles: • Q1: 2.20–5.16 • Q2: 5.16–7.33 • Q3: 7.33–10.62 • Q4: 10.62–37.78 Erythrocyte Pb quartiles: • Q1: 5.98–13.52 • Q2: 13.52–19.35 • Q3: 19.35–28.42 • Q4: 28.42–101.01	Hb	Change in Hb compared to Q1: • PbB Q3: 1.45 (-0.28, 3.18) • Erythrocyte Pb o **Q3: -3.01 (-4.71,1.31); p<0.05*,[c]** o **Q4: -3.97 (-5.68, -2.27); p<0.05***
Olivero-Verbel et al. 2007 Cross-sectional study: n=189 children (age range 5–9 years)	Mean (SE): 5.49 (0.23)	Hb	Spearman correlation coefficient: 0.069; p=0.348
Queirolo et al. 2010 Cross-sectional study; n=222 children (age: 5–45 months)	Mean (SD): 9.0 (6.0)	Hb	**Blood Hb <10.5 g/L was a predictor of PbB. β (95% CI): 2.40 (0.77, 4.03); p<0.01***
Riddell et al. 2007 Cross-sectional study; n=2,861 children (age 6 months–5 years)	Mean: 6.9	Hb	**A 1 g/dL increase in Hb was associated with a 3% decrease in PbB (p=0.043)***
Ukaejiofo et al. 2009 Cross-sectional study; n=81 Pb workers; 30 controls	Mean (SD) • Controls: 3.00 (0.19) • Workers: 7.00 (0.07)	Hb	Mean (SE), g/dL • Controls: 12.96 (0.089) • **Workers: 12.05 (1.62); p<0.001***
Zentner et al. 2006 Cross-sectional study; n=55 newborns	Umbilical mean (SD): 3.9 (3.6)	Hb	Pearson correlation coefficient: -0.04; p=0.721

Table 2-16. Summary of Epidemiological Studies Evaluating Hematological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

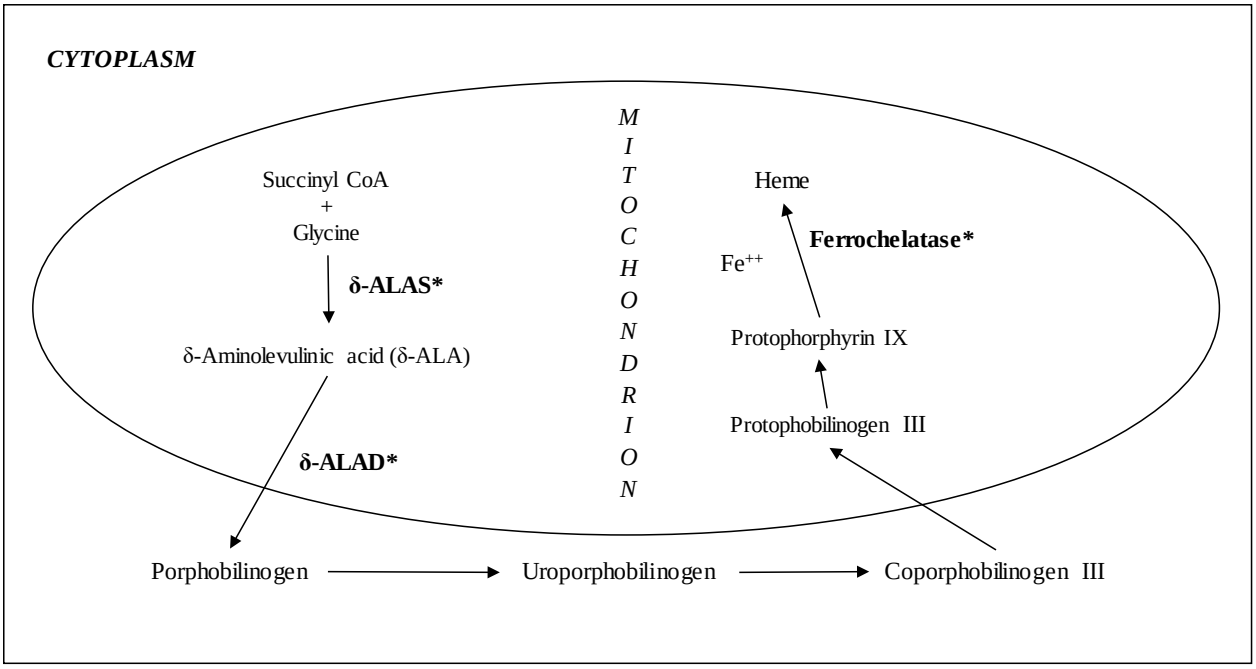
Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Other hematological effects			
Conterato et al. 2013 Cross-sectional; n=50 painters; 36 controls	Mean (SE) • Control: 1.5 (0.1) • Painters: 5.4 (0.4)	Platelet count	Mean (SE), % • Control: 244.3 (8.3) • **Painters: 203.7 (6.5); p<0.05***
Sakata et al. 2007 Cross-sectional studies: n=27 exposed workers; 9 controls	Mean (SD); range • Controls: 2.4 (1.1) • Workers: 6.4 (2.2)	EPO	Mean (SD), mU/mL: • Controls:18.8 (4.6) • **Workers: 12.7 (3.5); p<0.01***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 4 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb.
[c]The discrepancy between the 95% confidence limits and the p-value appears to be caused by an error in the reporting of the upper confidence limit (i.e., -1.31, rather than 1.31).

ALAD index = log(active δ-ALAD/non-activated δ-ALAD); δ-ALAD = δ-aminolevulinic acid dehydratase; EPO = serum erythropoietin; Hb = hemoglobin; Pb = lead; SD = standard deviation; SE = standard error; ZPP = zinc-protoporphyrin

Mechanisms of Action. Pb inhibits heme synthesis by inhibiting δ-ALAD and ferrochelatase (see Figure 2-4). As a consequence, the activity of the rate-limiting enzyme of the pathway, δ-aminolevulinic synthetase (δ-ALAS), which is feedback inhibited by heme, is subsequently increased. The end results of these changes in enzyme activities are increased urinary porphyrins, coproporphyrin, and δ-amino-levulinic acid (δ-ALA), increased blood and plasma δ-ALA, increased erythrocyte protoporphyrin (EP), and decreased hemoglobin. The impairment of heme synthesis by Pb may have a far-ranging impact not limited to the hematopoietic system. EPA (1986) provided an overview of the known and potential consequences of the reduction of heme synthesis as shown in Figure 2-5. Solid arrows indicate well-documented effects, whereas dashed arrows indicate effects considered to be plausible further consequences of the impairment of heme synthesis.

Figure 2-4. Pb Interactions in the Heme Synthesis Pathway

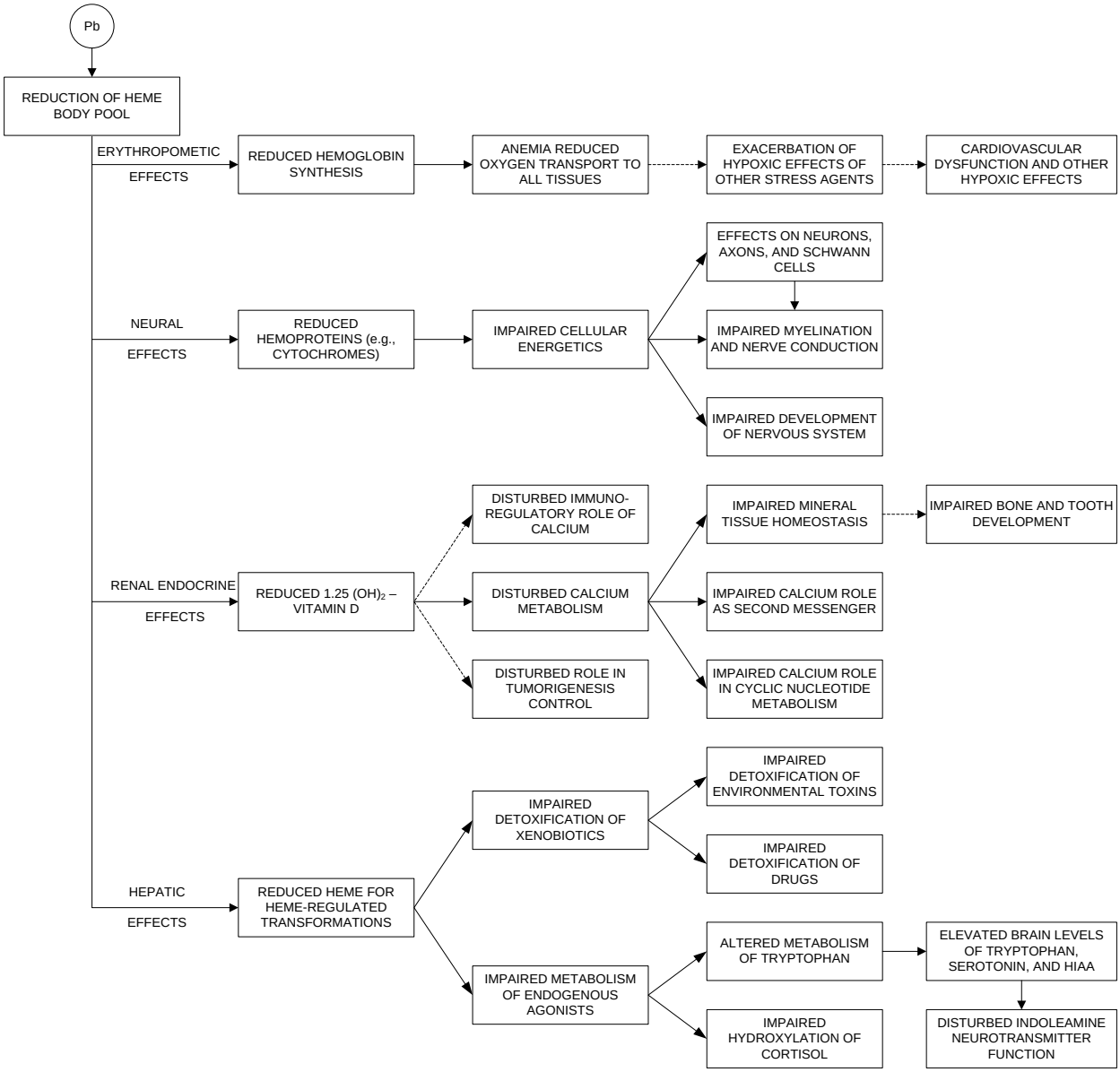


Abbreviations as noted in Ahamed and Siddiqui (2007): δ-ALAS = delta-aminolevulinic acid synthetase; δ-ALAD = delta-aminolevulinic dehydratase; CoA = coenzyme A

*Activity of enzymes inhibited by lead.

Source: Reprinted from Ahamed and Siddiqui (2007) with permission from Elsevier.

Figure 2-5. Multiorgan Impact of Reduction of Heme Body Pool by Lead



Source: EPA 1986

In addition to decreased hemoglobin synthesis, general mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of adverse effects to the hematological system. EPA (2014c) specifically noted effects of oxidative stress (altered antioxidant enzymes, decreased cellular glutathione, and lipid peroxidation) as an important mechanism for hematological effects. As reviewed in Section 3.2.3 (Toxicokinetics, Distribution), 99% of Pb in blood is distributed to erythrocytes, providing a toxicokinetic mechanism for hematological effects (Bergdahl et al. 1997a, 1998, 1999; Hernandez-Avila et al. 1998; Manton et al. 2001; Schutz et al. 1996; Smith et al. 2002).

2.9 MUSCULOSKELETAL

Overview. Few epidemiological studies have evaluated musculoskeletal effects associated with Pb exposure; thus, limited data are available to fully describe the exposure-response relationship or evaluate the weight-of-evidence for certain effects. Studies provide evidence of bone loss, increased markers of bone metabolism/turnover, and adverse periodontal and dental effects (periodontal bone loss, tooth loss, periodontal disease, dental caries). However, within dose ranges (≤10, 10–30, 30–50, and >50 µg/dL), few studies examined the same endpoints. Available studies include a prospective study in women and cross-sectional studies in adults and children, with some studies in large populations.

The following musculoskeletal effects have been associated with PbB:

- ≤10 µg/dL:
    - Bone loss or markers of increased bone or joint tissue metabolism.
    - Periodontal bone loss.
    - Tooth loss.
    - Dental caries.
    - Periodontitis.
- >10 µg/dL:
    - Muscle soreness/weakness.
    - Osteoporosis/decreased bone mineral density (BMD) in adults.
    - Increased BMD in children.
    - Periodontal disease.
    - Dental caries.

Measures of Exposure. Most studies examining the association between musculoskeletal effects and Pb exposure have evaluated exposure by measurement of PbB, although some studies also evaluated exposure by bone Pb concentration.

Confounding Factors and Effect Modifiers. A complicating factor in the interpretation of studies examining associations between PbB and bone loss or measures of bone metabolism is that increased bone metabolism (bone turnover or loss) can result in higher PbB due to Pb released from bone into the blood (reverse causality). This contributes to confounding from other factors that are associated with

bone loss, including nutrition, age, pregnancy and menopause, and activity. Results of studies examining Pb-induced periodontal or dental effects need to account for dental hygiene, diet/nutrition, and previous dental interventions. For example, interpretation of results on associations between dental caries and PbB would be uncertain if daily fluoride intake or prophylactic dental treatments (e.g., fluoride treatments or coating of molars during childhood) were not considered as confounding factors. Studies that rely on *in vivo* estimates of bone Pb (e.g., XRF) as the exposure metric for changes in BMD should also consider the potential for changes in BMD affecting the measurement of the concentration of Pb in bone mineral (Hu et al. 2007).

Characterization of Effects. Studies evaluating musculoskeletal effects associated with PbB provide evidence of bone loss, altered bone or joint tissue metabolism, and adverse periodontal and dental effects (periodontal bone loss, tooth loss, periodontal disease, dental caries). Due to the small number of studies, it is difficult to establish exposure-response relationships; in addition, within specific dose-ranges (≤10, 10–30, 30–50, and >50 µg/dL), few studies examined the same endpoints. Effects associated with chronic Pb exposure are shown in Table 2-17. In adults, decreased BMD has been observed over a PbB range of ≤10–>50 µg/dL (Campbell and Auinger 2007; Dongre et al. 2013; Khalil et al. 2008), although BMD was not deceased in women at PbB ≤10 µg/dL (Pollack et al. 2013). BMD was increased in a single study in children with a mean PbB of 23.6 µg/dL (Campbell et al. 2004). The study authors suggested that the effect may represent accelerated bone maturation due to Pb-induced inhibition of parathyroid hormone-related peptide and transforming growth factor β-1. The study authors also noted that the accelerated bone maturation may be a predisposing factor for osteoporosis later in life. Sun et al. (2008a, 2008b) showed that PbB was associated with increased prevalence of osteoporosis (mean PbB men: 20.22 µg/dL; women 15.50 µg/dL). Periodontal disease (including periodontitis), periodontal bone loss, tooth loss, and dental caries have been reported over a PbB range of ≤10–30 µg/dL (Arora et al. 2009; Campbell et al. 2000a; Dye et al. 2002; Gemmel et al. 2002; Kim and Lee 2013; Moss et al. 1999; Youravong and Teanpaisan 2015). Most studies examining periodontal and dental effects of Pb are conducted in populations with PbB ≤10 µg/dL. Muscle soreness and weakness has also been reported, although at higher PbB (40–49 µg/dL) (Rosenman et al. 2003).

Table 2-17. Overview of Musculoskeletal Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Bone loss/increased bone metabolism	Khalil et al. 2008; Machida et al. 2009; Nelson et al. 2009
	Tooth loss	Arora et al. 2009
	Periodontal bone loss	Dye et al. 2002
	Periodontitis	Kim and Lee 2013
	Dental caries	Gemmel et al. 2002; Moss et al. 1999
>10–30	Osteoporosis	Sun et al. 2008a, 2008b
	Decreased bone mineral density (adults)	Campbell and Auinger 2007
	Increased bone mineral density (children)	Campbell et al. 2004
	Periodontal disease	Youravong and Teanpaisan 2015
	Dental caries	Campbell et al. 2000a
>30–50	Muscle soreness/weakness	Rosenman et al. 2003
	Decreased bone mineral density	Campbell and Auinger 2007
>50	Decreased bone mineral density	Dongre et al. 2013

Effects at Blood Pb Levels ≤10 µg/dL. Epidemiological studies of musculoskeletal effects associated with PbB ≤10 µg/dL have examined effects on bone and periodontal and dental health; studies are briefly summarized in Table 2-18, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 5. A prospective study in women reported an increased rate of bone loss at PbB ranges of 4–7 and 8–21 µg/dL and an increased risk of non-spine fractures at a PbB range of 8–21 µg/dL (Khalil et al. 2008). In cross-sectional studies, markers of bone metabolism were positively associated with PbB in women at mean PbBs of <2 and 2.9 µg/dL, although no relationship was observed for these markers and PbB in men (mean PbB 1.2 µg/dL) (Machida et al. 2009; Nelson et al. 2011). No associations between PbB and BMD have been observed in cross-sectional studies in women (Machida et al. 2009; Pollack et al. 2013). Studies examining periodontal and dental effects include large (n=3,966–10,033) cross-sectional studies in adults and children (Dye et al. 2002; Kim and Lee 2013; Moss et al. 1999). Positive associations have been observed between PbB and presence of dental furcations in male and female adults (mean PbB 1.9–3.3 µg/dL) (Dye et al. 2002), periodontitis in adult males (PbB mean 3.1 µg/dL), but not females (mean PbB 2.2) (Kim and Lee 2013), and dental

Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Bone metabolism			
Khalil et al. 2008 Prospective cohort study; n=533 women (age range: 65–87 years).	**PbB:** Mean (SD): 5.3 (2.3) Tertiles: • T1 (n=122): ≤3 (reference) • T2 (n=332): 4–7 • T3 (n=79): 8–21	Bone loss	Percentage rate of calcaneous bone loss • **T1: -1.01 (-1.27, -0.74)*** • **T2: -1.41 (-1.57, -1.24)*** • **T3: -1.49 (-1.86, -1.10)*; p=trend: 0.03***
		Non-spine fractures	**HR T3: 2.50 (1.25, 5.03)*; p-trend: 0.016**
Machida et al. 2009 Cross-sectional study; n=1,225 female Japanese farmers (age range: 35–75 years)	**PbB:** Median • Premenopausal (n=261): 1.6 • Perimenopausal (n=319): 2.0 • Younger postmenopausal (n=397): 1.8 • Older postmenopausal (n=248): 1.7	BALP	Spearman's correlation coefficients • **All women: 0.143; p=0.000*** • **Perimenopausal women: 0.234; p=0.000***
		OC	Spearman's correlation coefficients • **All women: 0.191; p=0.000*** • **Perimenopausal women: 0.391; p=0.000***
		NTx	Spearman's correlation coefficients • **All women: 0.181; p=0.000*** • **Perimenopausal women: 0.261; p=0.000***
		BMD	Spearman's correlation coefficients • All women: -0.016; p=0.570 • Perimenopausal women: -0.101; p=0.071

Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Nelson et al. 2011 Cross-sectional study of 329 males (mean age: 65 years and 342 females (mean age: 62 years)	Median (range) • Males: 2.2 (0.5–25.1) • Females: 1.9 (0.5–25.4)	uNTX-I	β, change in biomarker per 5 µg/dL increase in ln-PbB • Males: 1.06 (0.95, 1.18) • **Females: 1.45 (1.21, 1.74)***
		uCTX-II	β, change in biomarker per 5 µg/dL increase in ln-PbB • Males: 1.07 (0.97, 1.18) • **Females: 1.28 (1.04, 1.58)***
		C2C (65 years)	β, change in biomarker per 5 µg/dL increase in ln-PbB • Males: 1.00 (0.94, 1.04) • Females: 1.00 (0.92, 1.08)
		CPII	β, change in biomarker per 5 µg/dL increase in ln-PbB • Males: 0.99 (0.93, 1.05) • Females: 1.09 (0.97, 1.22)
		HA	β, change in biomarker per 5 µg/dL increase in ln-PbB • Males: 1.01 (0.88, 1.05) • Females: 0.96 (0.71, 1.29)
		COMP	β, change in biomarker per 5 µg/dL increase in ln-PbB • **Males: 1.08 (1.00, 1.18)*** • Females: 0.96 (0.87, 1.06)
Pollack et al. 2013 Cross-sectional study of 249 premenopausal women (ages 18–44 years)	Mean (SD): 1.03 (0.64)	BMD	β per log-unit increase in PbB: 0.004 (-0.029, 0.020).

Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Periodontal and dental effects			
Arora et al. 2009 Cross-sectional study of 333 men (age range: 50–94 years)	PbB Tertiles • T1: ≤4.0 (reference) • T2: 4.2–6.4 • T3: 7.0–35.0 Bone Pb (µg/g) Tertiles for tibia • T1: ≤15.0 (reference) • T2: 16.0–23.0 • T3: 24.0–96.0 Tertiles for patella • T1: ≤22.0 (reference) • T2: 23.0–36.0 • T3: 37.0–126.0	Tooth loss	OR PbB (compared to T1) • T3: 0.88 (0.52, 1.50); p-trend=0.57 OR Tibia Pb (compared to T1) • **T2: 1.81 (1.02, 3.18)*** • **T3: 3.03 (1.60, 5.76)*; p-trend=0.001*** OR Patella Pb (compared to T1) • **T3: 2.41 (1.30, 4.49)*; p-trend 0.005***
Dye et al. 2002 Cross-sectional study in 10,033 participants in NHANES III (ages 20–69 years)	Mean (SE) • Males: 3.3 (0.12) • Females: 1.9 (0.05)	Presence of dental furcations	**β (SE), for presence of dental furcations (combined men and women): 0.13 (0.05); p=0.005***
Gemmel et al. 2002 Cross-sectional study in 498 children (age range: 6–10 years) from rural (n=239) and urban (n=259) settings.	Mean (SD) • Rural: 1.7 (1.0) • Urban: 2.9 (2.0)	Dental caries	Regression coefficient (SE): • Rural: -0.15 (0.09); p=0.09 • **Urban: -0.22 (0.08); p=0.005***

Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Kim and Lee 2013 Cross-sectional of 3,966 adults (≥20 years of age)	**PbB:** Mean (SE): • Men o no periodontitis: 2.625 (0.028) o periodontitis: 3.118 (0.057); p<0.001 • Women, o no periodontitis: 1.906 (0.025) o periodontitis: 2.222 (0.052); p<0.001	Periodontitis	OR (95% CI), per doubling of PbB: • **Men: 1.699 (1.154, 2.503)*** • Women: 1.242 (0.833, 1.850)
Moss et al. 1999 Cross-sectional study of 24,901 participants (2–5 years old: n=3,547; 6–11 years old: n=2,894; ≥12 years: n=18,460) in NHANES III	Mean (SE): • Age 2–5 years: 2.9 (0.12) • Age 6–11 years: 2.1 (0.08) • Age 12–17 years: 2.5 (0.06)	Dental caries in children (ages 5–17 years)	**OR per 5 µg/dL increased in PbB: 1.8 (95% CI 1.3, 2.5)***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 5 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb.
[c]If bone Pb is noted under results, study did not show associations between PbB and musculoskeletal effects; however, results showed associations between bone Pb concentrations and musculoskeletal effects at concomitant PbB ≤10 µg/dL.

BALP = bone-specific alkaline phosphatase (marker of bone metabolism); BMD = bone mineral density; C2C = serum cleavage neoepitope of type II collagen (marker of joint tissue metabolism); COMP = serum cartilage oligomeric matrix protein (marker of joint tissue metabolism); CPII = serum type II procollagen synthesis C-propeptide (marker of joint tissue metabolism); HA = serum hyaluronic acid (marker of joint tissue metabolism); HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; NTx = N-telopetide cross-linked collagen type I (marker of bone metabolism); OC = osteocalcin (marker of bone metabolism); OR = odds ratio; Pb = lead; SD = standard deviation; SE = standard error; uCTX-II = C-telopeptide urine fragments of type II collagen (marker of joint tissue metabolism); uNTX-I = urine cross-linked N telopeptide of type I collagen (marker of joint tissue metabolism)

caries in children ages 6–17 years (PbB 2.1–2.4 µg/dL) (Moss et al. 1999). One study in adult males showed an association between bone Pb and tooth loss, but not PbB and tooth loss (Arora et al. 2009).

Mechanisms of Action. In bone and teeth, Pb substitutes for calcium (see Section 3.1.2, Toxicokinetics, Distribution). As reviewed by EPA (2014c), several mechanisms may be involved in the development of bone and periodontal/dental effects. Possible mechanisms include the following:

- Alterations in plasma growth hormones and calcitropic hormones (e.g., 1,25-[OH]2D3) leading to altered bone cell differentiation and function.
- Suppression in bone cell proliferation due to altered growth factors and hormones, including growth hormone, epidermal growth factor, transforming growth factor-beta 1 (TGF-β), and parathyroid hormone-related protein.
- Alterations in vitamin D-stimulated production of osteocalcin production, with inhibition of secreted bone-related proteins (e.g., osteonectin and collagen).
- Increased chondrogenesis through alterations of multiple signaling pathways, including TGF-β, bone morphogenic protein, activator protein-1, and nuclear factor kappa B.
- Inhibition of the posteruptive enamel proteinases.
- Decreased microhardness of tooth surface enamel.

2.10 HEPATIC

Overview. Few epidemiological studies have evaluated hepatic effects associated with exposure to Pb, with most available studies comparing hepatic effects in small numbers of workers with PbB >10 µg/dL to controls with PbB lower than workers. Results of studies evaluating effects of Pb on liver function tests are inconsistent and do not demonstrate exposure-response relationships. Liver enlargement and increased gall bladder wall thickness was observed in workers with mean PbB of ≥28.66 µg/dL. Observed effects are consistent with oxidative stress. Histopathological effects of the liver associated with Pb have not been established.

The following hepatic effects have been associated with PbB >10 µg/dL:

- Greater plasma liver enzymes; evaluated in a few studies with mixed results.
- Greater total cholesterol.
- Enlarged liver and increased thickness of gall bladder wall.

Measures of Exposure. Studies examining the association between hepatic effects Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. Most epidemiological studies on hepatic effects of Pb were of small populations of workers using cross-sectional designs. In general, studies did not consider factors, such as age, diet, concurrent diseases, and potential exposure to other workplace chemicals that could affect hepatic function in association with, or independent of, Pb exposure. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. In contrast to the large number of epidemiological studies evaluating effects of Pb on other organ systems (e.g., neurological and cardiovascular outcomes), few studies have investigated the hepatic effects of Pb. Brief study descriptions are provided in Table 2-19. Available studies were conducted in small populations (n=23–100) of workers with mean PbB of 5.4–77.5 µg/dL. The most serious effects reported for Pb-induced hepatic damage are liver enlargement and greater gall bladder wall thickness observed in workers with low PbB (28.66 µg/dL) and high PbB (40.58 µg/dL), respectively, compared to the control group (PbB 8.34 µg/dL) (Kasperczyk et al. 2013). However, these findings have not been corroborated in other studies. The study authors stated that no signs consistent with liver necrosis were observed. Most studies evaluated hepatic toxicity by liver function tests measuring plasma levels of liver enzymes. As shown in Table 2-20, results on effects of Pb on liver function tests are inconsistent and do not demonstrate exposure-response relationships. For example, Patil et al. (2007) reported greater alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in spray painters with a mean PbB of 22.32 µg/dL, but no change in ALT or AST in battery workers or silver jewelry workers with higher mean PbB (53.64 and 48.56 µg/dL, respectively), compared to controls (mean PbB: 12.52 µg/dL). Similarly, AST was elevated in painters with a mean PbB of 5.4 µg/dL, but no change in AST was observed in battery workers with a mean PbB of 49.9, compared to controls with a mean PBB of 1.5 µg/dL (Conterato et al. 2013). Effects in painters with lower PbB compared to other workers with higher PbB may be due to co-exposure to other occupational chemicals. In addition to liver enzymes, total serum cholesterol and high-density lipoprotein (HDL)-cholesterol were greater in workers with a mean PbB of 26.99–42.3 µg/dL, compared to controls with a mean PbB 2.7–14.81 µg/dL (Can et al. 2008; Kristal-Boneh et al. 1999).

Effect at Blood Pb Levels ≤10 µg/dL. See discussion above on Conterato et al. (2013).

Table 2-19. Summary of Epidemiological Studies Evaluating Hepatic Effects Associated with Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Outcomes evaluated	Effects[b]
Al-Neamy et al. 2001 Cross-sectional study; n=100 workers; 100 controls	Mean (SD) • Workers: 77.5 (42.8) • Controls: 19.8 (12.3)	LFTs	• Greater: LDH, AP • No difference: ALT, AST, GGT, bilirubin, albumin
Can et al. 2008 Cross-sectional study; n=22 battery workers; 38 muffler repair workers; 24 controls	Mean (SD) • Battery workers: 36.83 (8.13) • Muffler workers: 26.99 (9.42) • Controls: 14.81 (3.01)	LFTs	Battery workers" • Greater LDH, AP, TC Muffler workers: • Greater" LDH, AP
Conterato et al. 2013 Cross-sectional study; n=50 painters; 23 battery workers; and 36 controls	Mean (SE) • Painters: 5.4 (0.4) • Battery workers 49.8 (4.0) • Controls: 1.5 (0.1)	LFTs	Painters: • Greater: AST • No difference: GGT Battery workers: • No difference: AST, GGT
Hsiao et al. 2001 Longitudinal study (baseline 1989; follow-up 1999); n=30 battery workers	Baseline: 60 Follow-up: 30	LFTs	No correlation of PbB to ALT
Kasperczyk et al. 2013 Cross-sectional study; n (from Pb-Zn processing facility): 57 low Pb exposure; 88 high Pb exposure; and 36 controls	Mean (SD); range • Low Pb: 28.66 (6.60); 20–35 • High Pb: 40.58 (6.74); 35–60 • Control: 8.34 (2.91)	Liver size	• Low PbB: Greater • High Pb: Greater
		Gall bladder wall thickness	• Low PbB: Greater • High PbB: Greater
		LFTs	• Low PbB: o No difference: ALT, AST, LDH, GGT, bilirubin
			• High PbB: o No difference: ALT, LDH, AST, bilirubin o Greater AST, GGT

Table 2-19. Summary of Epidemiological Studies Evaluating Hepatic Effects Associated with Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Outcomes evaluated	Effects[b]
Khan et al. 2008 Cross-sectional study; n=87 workers; 61 controls	Median (range) • Workers: 29.1 (9.0–61.1) • Controls: 8.3 (1.0–21.7)	LFTs	• Greater ALT, GGT, albumin • No change: AP, bilirubin
Kristal-Boneh et al. 1999 Cross-sectional study; n=56 exposed; 87 controls	Mean (SD) • Workers: 42.3 (14.9) • Controls: 2.7 (3.6)	Cholesterol and lipoproteins	• Greater: TC, HDL • No change: LDL, TG, HDL:TC ratio
Patil et al. 2007 Cross-sectional study; n=30 battery workers; 30 silver jewelry workers; 30 spray painters[a]; 35 controls	Mean (SD) • Battery workers: 53.63 (16.98) • Silver jewelry workers: 48.56 (7.39) • Spray painters: 22.32 (8.87) • Controls: 12.52 (4.08)	LFTs	Battery workers: • Greater percentage change: albumin, bilirubin • No change: ALT, AST Silver jewelry workers: • Lesser percentage change: albumin compared to controls • No change: ALT, AST, bilirubin compared to controls Spray painters: • Greater percentage change: ALT, AST • Decreased: albumin • No change: bilirubin

[a]Reporting inconsistencies regarding number of spray painters evaluated; reported as 30 and 35.
[b]All comparisons are to control groups.

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transpeptidase; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LFT = liver function test (plasma activity of hepatic enzymes); Pb = lead; SD = standard deviation; SE = standard error; TC = total cholesterol; TG = triglycerides; Zn = zinc

Table 2-20. Effects on Liver Function Tests Associated with Chronic Exposure to Lead (Pb)[a]

Mean PbB (µg/dL)	Population (n)[b]	ALT	AST	GGT	LDH	AP	Reference
5.4	P (50)	–	↑	0	–	–	Conterato et al. 2013
22.32	P (35)[c]	↑	↑	–	–	–	Patil et al. 2007
26.99	Pb-A (38)	0	0	0	↑	↑	Can et al. 2008
28.66	Pb-Zn (57)	0	0	0	0	0	Kasperczyk et al. 2013
29.1	Pb (87)	↑	–	↑	–	0	Khan et al. 2008
30	B (30)	0	–	–	–	–	Hsiao et al. 2001
36.83	B (22)	0	0	0	↑	0	Can et al. 2008
40.58	Pb-Zn (88)	0	↑	↑	0	↑	Kasperczyk et al. 2013
48.56	J (30)	0	0	–	–	–	Patil et al. 2007
9.8	B (23)	0	0	0	–	–	Conterato et al. 2013
53.63	B (30)	0	0	–	–	–	Patil et al. 2007
77.5	Pb (100)	0	0	0	↑	↑	Al-Neamy et al. 2001

[a]Reporting inconsistencies regarding number of spray painters evaluated; reported as 30 and 35.

↑ = increased; 0 = no change; – = not assessed; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; B = battery workers; G = general population; GGT = gamma-glutamyl transpeptidase; J = silver jewelry workers; LDH = lactate dehydrogenase; MDA: malondialdehyde; P = painters; Pb = Pb-exposed industrial workers; Pb-A = Pb-exposed auto workers; Pb-Zn = Pb-zinc processers

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of hepatic toxicity. EPA (2014c) specifically noted that oxidative stress through ROS can result in damaged function and histopathological damage to the liver, including peroxidation of lipid membranes.

2.11 RENAL

Overview. Numerous epidemiologic studies in adults show that exposure to Pb can cause altered kidney function and contribute to the development of chronic kidney disease (CKD). A few studies in children also show decreases in renal function. Pb-induced nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, and interstitial fibrosis (Diamond 2005; Goyer 1989; Loghman-Adham 1997). Functional deficits in humans that have been associated with excessive Pb exposure include enzymuria, low- and high-molecular weight proteinuria, impaired transport of organic anions and glucose, and depressed GFR. A few studies have revealed histopathological features of renal injury in humans, including intranuclear inclusion bodies and cellular necrosis in the proximal tubule and interstitial fibrosis (Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979). Studies show consistent evidence of renal damage and reduced renal function associated over a wide range of PbB

(≤10–>50 µg/dL), with the overall dose-effect pattern suggesting an increasing severity of nephrotoxicity associated with increasing PbB.

The following renal effects have been associated with PbB:

- ≤10 µg/dL:
  - Decreased GFR; corroborated in numerous studies.
  - Proteinuria; demonstrated in a few studies.
- >10 µg/dL:
  - Decreased GFR; corroborated in numerous studies.
  - Enzymuria; corroborated in numerous studies.
  - Proteinuria; corroborated in numerous studies.
  - Impaired tubular transport; demonstrated in a few studies.
  - Histopathological damage; demonstrated in a few studies.

Measures of Effect. Endpoints demonstrating renal damage include various measures of glomerular and tubular dysfunction. Effects on GFR typically are assessed from measurements of creatinine clearance, serum creatinine concentration, or blood urea nitrogen (BUN). Increased excretion of albumin (albuminuria) is an indication of damage to the glomerular endothelium or basement membrane, resulting in increased filtration of albumin, or impaired function of the proximal tubule, resulting in decreased reabsorption of filtered albumin. Increased excretion of low molecular weight serum proteins (e.g., 2µG or retinol-binding protein) are an indication of impaired reabsorption of protein in the proximal tubule. Increased excretion of enzymes associated with the renal tubule (renal tubular enzymuria) is an indication of injury to renal tubular cells resulting in release of membrane or intracellular enzymes into the tubular fluid. Pb-induced renal tubular enzymuria is most commonly evaluated from measurements of urinary N-acetyl-D-glucosaminidase (NAG). Increased excretion of NAG has been found in Pb-exposed workers in the absence of increased excretion of other proximal tubule enzymes (e.g., alanine aminopeptidase, alkaline phosphatase, glutamyltransferase) (Pergande et al. 1994). Indices of impaired transport include altered clearance or transport maxima for organic anions (e.g., p-aminohippurate, urate) or glucose (Biagini et al. 1977; Hong et al. 1980; Wedeen et al. 1975). Proximal tubular injury can also be confirmed through histopathological examination of renal tissue, although few studies provide this information (Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979).

Measures of Exposure. Most studies evaluating renal damage use PbB as the biomarker for exposure, although more recent epidemiological studies have explored associations between toxicity and bone Pb concentrations. These studies provide a basis for establishing PbB, and, in some cases, bone Pb concentration ranges associated with specific nephrotoxicity outcomes.

Confounding Factors and Effect Modifiers. Inconsistencies in the reported outcomes for renal effects across studies may derive from several causes, including failure to account for confounding factors and effect modifiers. Various factors can affect kidney function, including age, underlying diseases (e.g., hypertension), and concomitant exposure to other nephrotoxicants (e.g., cadmium). Results of epidemiological studies of general populations have shown an effect of age on the relationship between GFR (assessed from creatinine clearance of serum creatinine concentration or cystatin C) and PbB (Kim et al. 1996a; Muntner et al. 2003; Payton et al. 1994; Staessen et al. 1990, 1992). Pb-induced decrements in renal function can lead to higher Pb body burden due to decreased excretion of Pb (i.e., reverse causality) (Bellinger 2011; Evans and Elinder 2011; Marsden 2003). Thus, reverse causality potentially confounds interpretation of the dose-response relationship between PbB and decreased renal function. Pb exposure has also been associated with increases in GFR (Hsiao et al. 2001; Roels et al. 1994). This may represent a benign outcome or a potentially adverse hyperfiltration, which may contribute to subsequent adverse renal effects. Hypertension can be both a confounder in studies of associations between Pb exposure and creatinine clearance (Perneger et al. 1993) and a covariable with Pb exposure (Harlan et al. 1985; Muntner et al. 2003; Payton et al. 1994; Pirkle et al. 1985; Pocock et al. 1984, 1988; Tsaih et al. 2004; Weiss et al. 1986). Renal damage can cause increased blood pressure, which in turn can result in further damage to the kidneys. In addition, varying uncertainty also exists across studies in exposure history of subjects and in the biomarkers assessed.

Characterization of Effects. A large number of studies showing decrements in renal function associated with Pb exposure in humans have been published (Table 2-21). Most of these studies are of adults whose exposures were of occupational origin; however, a few environmental, mixed, and/or unknown exposures are represented, and a few studies of children are also included. Although these studies demonstrate adverse renal effects across the PbB range, some studies did not find associations (Buchet et al. 1980; de Kort et al. 1987; Fadrowski et al. 2010; Gennart et al. 1992; Huang et al. 2002; Karimooy et al. 2010; Omae et al. 1990). However, collectively, the body of evidence demonstrates that long-term exposure to Pb is nephrotoxic. General trends regarding the relationship between PbB and qualitative aspects of the kidney response are shown in Table 2-21. Decreased GFR and proteinuria have been observed in association with PbB $\leq$10 μg/dL; the significance of these studies is discussed in greater detail below.

Enzymuria and proteinuria have been observed in association with PbB >10–≤50 µg/dL. Functional deficits, including enzymuria, proteinuria, impaired transport, and depressed GFR have been observed at PbB >50 µg/dL. Histopathological findings, including tubular atrophy, focal sclerosis of glomeruli, and periglomerular and interstitial fibrosis have also been observed at PbB >50 µg/dL. The overall dose-effect pattern suggests an increasing severity of nephrotoxicity associated with increasing PbB, with effects on glomerular filtration evident at PbBs <10 µg/dL, enzymuria and proteinuria becoming evident >10 µg/dL, and severe deficits in function and pathological changes occurring in association with PbBs >50 µg/dL.

Table 2-21. Overview of Renal Effect Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Increased GFR	de Burbure et al. 2006
	Decreased GFR	Akesson et al. 2005; Fadrowski et al. 2010; Lin et al. 2001; Khan et al. 2010a; Kim et al. 1996a; Lin et al. 2003; Lin-Tan et al. 2006a, 2006b; Muntner et al. 2003; Navas-Acien et al. 2009; Payton et al. 1994; Pollack et al. 2015; Spector et al. 2011; Staessen et al. 1992, 2001; Yu et al. 2004
	Proteinuria	Navas-Acien et al. 2009; Pollack et al. 2015
>10–≤30	Decreased GFR	Kim et al. 1996a; Staessen et al. 1990
	Enzymuria	Bernard et al. 1995; Chia et al. 1994; Sonmez et al. 2002; Sun et al. 2008b
	Proteinuria	Bernard et al. 1995; Chia et al. 1995a, 1995b
>30–≤50	Increased GFR	Hsiao et al. 2001; Roels et al. 1994
	Decreased GFR	Orisakwe et al. 2007; Weaver et al. 2003a, 2003b, 2005a; Wedeen et al. 1975
	Enzymuria	Cardenas et al. 1993; Cardozo dos Santos et al. 1994; Fels et al. 1994; Garcon et al. 2007; Gerhardsson et al. 1992; Kim et al. 1996a; Kumar and Krishnaswamy 1995; Lin and Tai-yi 2007; Mortada et al. 2001; Pergande et al. 1994; Roels et al. 1994; Verberk et al. 1996; Verschoor et al. 1987; Weaver et al. 2003a, 2003b, 2005a
	Proteinuria	Factor-Litvak et al. 1999; Fels et al. 1998; Garcon et al. 2007; Gerhardsson et al. 1992; Kumar and Krishnaswamy 1995; Mortada et al. 2001; Pergande et al. 1994; Verschoor et al. 1987
	Impaired tubular transport	Pinto de Almeida et al. 1987

Table 2-21. Overview of Renal Effect Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
>50	Decreased GFR	Baker et al. 1979; Biagini et al. 1977; Cramer et al. 1974; Ehrlich et al. 1998; Hong et al. 1980; Lilis et al. 1968, 1980; Onuegbu et al. 2011; Wedeen et al. 1975, 1979
	Enzymuria	Cabral et al. 2012; Gao et al. 2010; Garcon et al. 2007
	Proteinuria	Cabral et al. 2012; Gao et al. 2010; Garcon et al. 2007
	Impaired tubular transport	Biagini et al. 1977; Ehrlich et al. 1998; Hong et al. 1980; Wedeen et al. 1975
	Histopathological changes	Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979

GFR = glomerular filtration rate

Effects at Blood Pb Levels ≤10 µg/dL. Studies of renal function in populations with PbB ≤10 µg/dL provide evidence for effects of Pb on GFR in children and adults. Results are summarized in Table 2-22, with study details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 6. Most studies found that increasing PbB was associated with decreased GFR; however, one study found evidence for increasing GFR in children (de Burbure et al. 2006).

A few studies have examined associations between low PbB and GFR in children and adolescents (de Burbure et al. 2006; Fadrowski et al. 2010; Khan et al. 2010a; Staessen et al. 2001). de Burbure et al. (2006) examined serum creatinine in a cross-sectional study of approximately 800 children (age range 8.5–12.3 years) who resided near nonferrous smelters. Serum creatinine and cystatin C decreased (indicating an increase in GFR) by approximately 7% in the upper quartile PbB group (mean 7.8 µg/dL) compared to the lowest quartile (<2.84 µg/dL). Fadrowski et al. (2010) examined adolescents (12–20 years, n=769). GFR (estimated from serum cystatin C) decreased with increasing PbB. In the upper quartile PbB group (>2.9 µg/dL), the decrease was 6.6 mL/minute/1.73 m^2, which represented approximately a 6% decrease in GFR. In a smaller study of younger children of Pb-exposed workers (ages 1–6 years; n=123; PbB: 8.1 µg/dL), serum creatinine was higher compared to controls (ages 1–6 years; n=123; PbB: 6.7 µg/dL) (Khan et al. 2010), indicating decreased GFR. Several factors may have contributed to the different outcomes in these studies (decrease or increase in GFR), including a different age range of the study groups, different approaches to adjusting outcome metrics for confounders, and different exposures (e.g., co-exposure to Pb, cadmium, and mercury in the de Burbure et al. 2006 study).

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Akesson et al. 2005 Cross-sectional study; n=820 adult women	Median: 2.2	CCr	**Linear regression β coefficient (mL/minute per µg/dL): -0.018 (95% CI -0.03, -0.006)***
		GFR	**Linear regression β coefficient (mL/minute per µg/dL): -0.02 (95% CI -0.03, -0.009)***
		UPHC	Linear regression β coefficient (µg/L per µg/dL): reported as NS
		UNAG	Linear regression β coefficient (U/g creatinine per µg/dL): reported as NS
de Burbure et al. 2006 Cross-sectional study; n>800 children (ages 8.5–12.3 years)	Mean range (three locations) Control: 2.81–3.81 Exposure: 3.64–6.51	SCr	**Decreased 7% (p<0.01) in Q4 (PbB >5.59 µg/dL), compared to Q1 (PbB <2.85 µg/dL)***
		Sβ2M	**Decreased 9% (p<0.01) in Q4 (PbB >5.86 µg/dL), compared to Q1 (PbB <3.10 µg/dL)***
Fadrowski et al. 2010 Cross-sectional study; n=769 adolescents (ages 12–20 years)	Median: 1.5 Quartiles: • Q1: <1.0 • Q2: 1.0–1.5 • Q3: 1.6–2.9 • Q4: >2.9	GFR	• **Change in GFR (mL/minute/1.73 m^2) Q4 compared to Q1: -6.6 (-12.6, -0.7)*** • **p-Trend across Q1-Q4=0.009*** • **Mean difference in GFR associated with a 2-fold increase in blood lead level: -2.9 (-5.0, -0.7)***
Kim et al. 1996a Retrospective cohort study; n=459 men	Mean: 9.9	SCr	• **Regression coefficient (SE) for all participants (µmol/L per µg/dL): 0.033 (0.012); p=0.005*** • **Regression coefficient (SE) for PbB ≤10 (µmol/L per µg/dL): 0.060 (0.019); p=0.002***

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Khan et al. 2010 Cross sectional study children (ages 1–6 years) of Pb workers (n=123) and controls (n=123)	Median • Control: 6.7 • Exposed: 8.10	SCr	• **Serum creatinine (µmol/L): control: 52; exposed: 56; p≤0.01*** • **Spearman's correlation coefficient: r=0.13; p≤0.05***
Lin et al. 2001 Prospective, longitudinal study; n=110 patients with chronic renal insufficiency	Low PbB mean: 3.9 High PbB mean: 6.6	CCr	• **18 Months CCr (mL/second) mean±SD: low Pb: 0.72±0.25; high Pb: 0.59±0.22 µg/dL (p=0.007)*** • **21 Months CCr (mL/second) mean±SD: low Pb: 0.70±0.24; High Pb: 0.57±0.22 µg/dL (p=0.006)*** • **24 Months CCr (mL/second) mean±SD: low Pb: 0.70±0.24; High Pb: 0.55±0.22 µg/dL (p=0.001)***
Lin et al. 2003 Prospective, longitudinal study; n=202 patients with chronic renal insufficiency	Baseline: 5.3 After 24-month observation, prior to chelation[e] • Placebo: 5.9 • Chelation: 6.1	GFR	• **GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo 25.5±12.3; chelation 34.4±14.7 (p=0.01)*** • **Change in GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo -6.0±5.8; chelation 2.1±5.7 (p>0.001)***
Lin et al. 2006a Prospective, longitudinal study; n=124 patients with chronic renal insufficiency	After 24-month observation, prior to chelation[e] • Placebo: 3.0 • Chelation: 2.6	GFR	• **GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo 38.0±8.9; chelation 47.9±17.0 (p=0.0493)*** • **Change in GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo -4.6±4.3; chelation 6.6±10.7 (p>0.0005)***
		UP (24-hour)	• Urine protein (g) following chelation: placebo 1.11±1.63; chelation: 0.92±1.16 (p=0.6236)

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Lin et al. 2006b Prospective, longitudinal study; n=238 patients with type II diabetes and progressive diabetic neuropathy	End of 12-month observation, prior to chelation[e] • Placebo: 5.9 • Chelation: 7.5	GFR	• **GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo 13.1±4.5; chelation 18.0±7.3 (p=0.0352)*** • **Decrements in GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo 13.2±7.6; chelation 4.4±6.8 (p>0.0045)***
Lin-Tan et al. 2007 Placebo-controlled clinical study; n=116 non-diabetic patients with chronic kidney disease	Mean after 51-month chelation • Placebo: 6.0 • Chelation: 3.5	GFR	• **GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo 23.7±10.8; Chelation 35.4±17.0 (p<0.0001)*** • **Change in GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo -12.7±8.4; chelation -1.8±8.8 (p>0.0001)***
		UP (24-hour)	UP (mean±SD): placebo 0.96±1.04; chelation: 0.81±0.86 (p=0.3369)
Muntner et al. 2003 Cross-sectional study; n=4,813 hypertensive; n=10,398 normotensive adults[g]	Normotensive Mean: 3.30±0.10 Quartiles • Q1 (reference): 0.7–1.6 • Q2: 1.7–2.8 • Q3: 2.9–4.6 • Q4: 4.7–52.9 Hypertensive Mean: 4.21±0.14 Quartiles: • Q1 (reference): 0.7–2.4 • Q2: 2.5–3.8 • Q3: 3.9–5.9 • Q4: 6.9–56.0	GFR	Estimated GFR, mL/minute (mean±SD) • Normotensive: 115±0.7 • **Hypertensive: 95±0.7 (p<0.001)***
		SCr	OR for elevated SCr in hypertensive patients: **Q2: 1.47 (1.03, 2.10)*** **Q3: 1.80 (1.34, 2.42)*** **Q4: 2.41 (1.46, 3.97)*** **p-trend: <0.001***
		CKD	OR for elevated CKD in hypertensive patients: Q2: 1.44 (1.00, 2.09) **Q3: 1.85 (1.32, 2.59)*** **Q4: 2.60 (1.52, 4.45)*** **p-trend: <0.001***

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Navas-Acien et al. 2009[f] Cross-sectional study; n=14,778 adults	Mean: 1.58 Quartiles: • Q1 (reference): ≤1.1 • Q2: >1.1–1.6 • Q3: >1.6–2.4 • Q4: >2.4	GFR	ORs for reduced GFR • Q2: 1.10 (0.80, 1.51) • Q3: 1.36 (0.99, 1.85) • **Q4: 1.56 (1.17, 2.08)*** • **p-trend: <0.001***
		Albuminuria	ORs for albuminuria • Q2: 0.83 (0.66, 1.04) • Q3: 0.92 (0.76, 1.12) • Q4: 1.19 (0.96, 1.47) • **p-trend: <0.001***
Payton et al.1994 Cross-sectional study; n=744 men	Mean: 8.1	CCr	**Regression coefficient, β (SE), mL/minute per µg/dL: -0.0403 (0.0198); p=0.0426***

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Pollack et al. 2015 Prospective cohort study; n=257 premenopausal women	Median: 0.88 Tertiles: • T1 (reference): <0.72 • T2: 0.72–1.10 • T3: >1.10	GFR	• **Regression β coefficient (% change per twofold increase in PbB): -3.73 (-6.55, -0.83)*** • **Regression β coefficient (% change per 2-fold increase in PbB) by tertile:** o **T2: -8.28 (-14.07, -2.5); p<0.05*** o **T3: -6.79 (-13.10, -0.49); p<0.05***
		SCr	Regression β coefficient (% change per 2-fold increase in PbB): 3.47 (0.86, 6.16)
		BUN	Regression β coefficient (% change per 2-fold increase in PbB): -0.13 (-4.97, 4.96)
		Blood albumin	Regression β coefficient (% change per 2-fold increase in PbB): -0.38 (-1.28, 0.52)
		Blood glucose	Regression β coefficient (% change per 2-fold increase in PbB): 0.93 (-0.28, 2.15)
		Blood protein	Regression β coefficient (% change per 2-fold increase in PbB): -0.76 (-1.61, 0.09)
Spector et al. 2011[f] Cross-sectional study; n=3,941 adults	Mean (all): 1.7 Mean (≥60 years) Tertiles (all): • T1 (reference): ≤1.3 • T2: >1.3–2.2 • T3: >2.2	GFR	• **All participants: change in GFR (mL/minute/1.73 m^2) per 2-fold increase in PbB: -1.9 (-3.2, -0.7)*** • **All participants: OR for reduced GFR by tertiles** o T2: -1.6 (-4.2, 1.0) o **T3: -3.3 (-5.3, -1.4)*** o **p-trend: 0.001*** • **Participants ≥60 years: change in GFR (mL/minute/1.73 m^2) per 2-fold increase in PbB: -4.5 (-5.6, -3.3)**

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Staessen et al. 1992 Cross-sectional study; n=1,981 adults (965 men; 1,016 women)	Mean men: 11.4 Mean women: 7.5	CCr	**Partial regression coefficient (SE) for CCr (mL/minute per log µg Pb/L):** • **Men: -13.1 (4.0); p≤0.001*** • **Women: -30.1 (3.4); p≤0.001***
Staessen et al. 2001 Cross-sectional study; n=200 17-year-old adolescents girls	Mean control: 1.4 Mean exposed area 1: 1.8 Mean exposed area 2: 2.7	Serum cystatin C	**Change in per 2-fold increase in PbB: +3.6% (1.5, 5.7)***
		Urine β_2-migroblobulin	**Change per 2-fold increase in PbB: +16.0% (2.7, 31)***
Tsaih et al. 2004 Prospective study; n=448 (66–72 years of age); n=26 participants with diabetes, and n=115 participants with hypertension	Mean at baseline: 6.5 Mean at follow-up: 4.5	SCr	Baseline regression β coefficients (mg/dL per ln µg/dL): • All participants: 0.009 (SE 0.006) • **Participants with diabetes: 0.076 (SE 0.023); p<0.05*** • Participants with hypertension: 0.008 (0.010); Follow-up (4–8 years) regression β coefficients (mg/dL per ln µg/dL): • Participants with diabetes: 0.223 (SE 0.183); **Participants with hypertension: 0.352 (0.097); p<0.05***

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Yu et al. 2004 Prospective longitudinal study; n=121 patients with chronic renal insufficiency; progression of renal insufficiency was evaluated for 48 months	Mean: 4.2	GFR	**Change in GFR (mL/minute/1.73 m^2 per 1 µg/dL): -4.0 (p=0.0148)***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 6 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]A variety of methods are used to estimate GFR (Chao et al. 2015). Each has limitations for application to both clinical evaluations and epidemiology. The preferred method is to measure the clearance of substance from plasma that is known to be eliminated solely by glomerular filtration and is not reabsorbed in the renal tubule. Typically, in the clinical setting, this is accomplished with intravenous administration of GFR markers, such as ^{125}I-iothalmate, for the radiocontrast agent (e.g., iohexol). These procedures are feasible in the clinical setting, but not in epidemiology studies in which invasive procedures and administration of such agents is not practical or possible. Clearance of endogenous creatinine is an alternative that has had wide use in epidemiology. However, it requires concurrent measurements of serum creatinine and the rate of urinary excretion of creatinine, which can be accurately determined only with a carefully timed urine sample that can represent the amount of glomerular filtrate formed over a given time interval. Achieving accurately timed urine samples requires a rigidly implemented and supervised collection protocol, which is not always feasible, particularly in large-scale epidemiology studies. Alternatives to clearance methods are measurement of endogenous metabolites in plasma whose clearance approximates GFR. Typically, this is achieved with endogenous creatinine or cystatin C. The serum concentration of these two metabolites strongly correlates with GFR; however, the relationship between concentration and GFR is also affected by other variables, including age, sex, race, and creatinine muscle mass. Several approaches have been developed to improve estimates of GFR from serum creatinine that attempt to account for these co-variables. These methods rely on multiple variable regression models that relate GFR to serum creatinine and other significant determinants of GFR (Cockcroft and Gault 1976; Levey et al. 1999, 2009). An evaluation of two of the more commonly used methods for estimating GFR from serum creatinine, the CKD-EPI and MDRDS equations, found that both achieved a median difference between calculated and measured GFR (from clearance measurements) that range from 2 to 6 mL/minute per 1.73 m^2 (Levey et al. 2009). The interquartile range in the difference was approximately 18 mL/minute per 1.73 m^2 in a validation dataset consisting of data for 3,986 study subjects. This suggests that approximately 25% of the GFR estimates from these methods are expected to be in error of the true GFR by >18 mL/minute (or approximately 15% of the GFR in a healthy adult, 120 mL/minute).
[d]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[e]Blood lead estimated by EDTA mobilization.
[f]Population from NHANES.

BUN = blood urea nitrogen; CCr = creatinine clearance; CI = confidence interval; CKD = chronic kidney disease; EDTA = ethylenediaminetetraacetic acid; GFR = glomerular filtration rate; NHANES = National Health and Nutrition Examination Survey; NR = not reported; NS = not statistically significant; OR = odds ratio; Pb = lead; Sβ2M = serum β_2-microglobulin; SCr = serum creatinine concentration; SD = standard deviation; SE = standard error; UP = urine protein; UPHC = urine human complex-forming protein (α1-microglobulin); UNAG = urine *N*-acetyl-β-D-glucosaminidase

A smaller study of adolescents (17 years of age, n=200) also found evidence for higher serum cystatin C (indicating lower GFR) in a group with a mean PbB of 2.7 µg/dL compared to a group with a mean PbB of 1.4 µg/dL (Staessen et al. 2001).

A larger number of studies have been conducted in adult populations (Table 2-22). These include several prospective studies (Lin et al. 2001, 2003, 2006a, 2006b; Lin-Tan et al. 2007; Pollack et al. 2015; Tsaih et al. 2004; Yu et al. 2004). Most of these studies have examined changes in GFR in patients who had ongoing renal disease and depressed GFR (Lin et al. 2001, 2003, 2006a, 2006b; Lin-Tan et al. 2007; Yu et al. 2004). In adult patients who had indications of renal insufficiency (e.g., serum creatinine concentration >1.5 mg/dL), GFR increased following repeated chelation therapy with calcium disodium ethylenediaminetetraacetic acid (EDTA) (Lin et al. 2003, 2006b). Yu et al. (2004) estimated the decline in GFR in patients with renal insufficiency to be approximately 4 mL/minute/1.73 m^2 per 1 µg/dL increase in PbB. A prospective study of premenopausal women estimated the decline in GFR to be approximately 3.73% per doubling of PbB (Pollack et al. 2015). The median PbB in the cohort was 0.88 µg/dL. A prospective study of older males found an association between increased serum creatinine (indicative in decreasing GFR) and PbB in subjects diagnosed with hypertension or diabetes. Mean PbBs were 6.5 µg/dL at baseline and 4.5 µg/dL at follow-up (Tsaih et al. 2004).

Several large cross-sectional studies have examined associations between PbB and GFR in adults (Table 2-22). Three large studies relied on data collected in the NHANES (Munter et al. 2003; Navas-Acien et al. 2009; Spector et al. 2011). The Munter et al. (2003) study, which included 4,813 hypertensive subjects and 10,938 normotensive subjects, found an association between increasing PbB and decreasing GFR in the hypertensive group. Navas-Acien et al. (2009) included 14,788 adult subjects and reported decreased GFR (<60 mL/minute/1.73 m^2) among participants in the highest PbB quartile (mean >2.4 µg/dL). Spector et al. (2011) included 3,941 adults. In the age group ≥60 years, the estimate for the decline in GFR was 4.5 mL/minute/1.73 m^2 per doubling of PbB. The mean PbB in this group was 2.2 µg/dL. Several smaller cross-sectional studies have also found associations between increasing PbB and decreasing GFR in adult populations in which mean or median PbBs were <10 µg/dL (Akesson et al. 2005; Payton et al. 1994; Staessen et al. 1992). Collectively, these studies indicate that Pb exposure is associated with decreasing GFR, and effects on GFR are evident in populations with PbB <10 µg/dL. People with on-going renal disease or hypertension may be more vulnerable to the effects of Pb. Estimates of the decline in GFR associated with increasing PbB vary across studies, with some studies indicating declines of 3–6 mL/minute/1.73 m^2 at PbB <10 µg/dL (Pollack et al. 2015; Spector et

al. 2011; Yu et al. 2004). However, as noted above, the estimates may be inflated by reverse causality for associations between deceasing GFR and increasing Pb body burden.

Associations Between Bone Pb and Renal Effects. Studies evaluating associations between bone Pb and renal function are summarized in Table 2-23. Weaver et al. (2003a, 2005a, 2005c, 2006, 2009) conducted a series of studies evaluating associations between bone Pb and metrics of renal GFR (e.g., serum creatinine concentration, creatinine clearance calculated from serum creatinine concentration, BUN) and renal tubular injury (urinary NAG) in current and former Pb workers in South Korea. These studies provide evidence that tibia Pb is positively associated with serum creatinine concentration in older workers (Weaver et al. 2003a, 2005a, 2005c) and in male, but not female, workers (Weaver et al. 2009); and negatively associated with tibia Pb and creatinine clearance in male workers (Weaver et al. 2009) and in workers with vitamin D receptor (VDR) genotypes BB and Bb (Weaver et al. 2006). Tibia Pb was also positively associated with urinary NAG in older workers (Weaver et al. 2005a). Studies of participants of the longitudinal Normative Aging Study have found positive associations between tibia Pb and serum creatinine concentration in participants with diabetes (Tsaih et al. 2004) and with ALAD genotypes 1-2 and 2-2 (Wu et al. 2003a). A small case-control study did not find an association between tibia Pb and end-stage renal disease. Taken together, the results suggest that long-term exposure to Pb is associated with diminished renal function.

Table 2-23. Associations Between Bone Pb and Renal Function

		Effect					
Reference	Population	SCr	CCr	NAG	RBP	BUN	ESRD
Muntner et al. 2007	55 adult ESRD patients; 53 controls	–	–	–	–	–	0 T
Tsaih et al. 2004	448 men[a]	0 T ↑ T (diabetics) 0 P 0 P (diabetics)	–	–	–	–	–
Weaver et al. 2003a	803 adult Pb workers; 135 controls[b]	0 T (all workers) ↑ T (>46 years[c])	0 T[c]	0 T[c]	0 T[c]	0 T[c]	–
Weaver et al. 2005a	803 adult Pb workers[b]	↑ T (>46 years[c])	–	↑ T (>46 years)[c]	–	–	–
Weaver et al. 2005c	795 adult Pb workers[b]	↑ T (>40.6 years)	–	–	–	–	–

Table 2-23. Associations Between Bone Pb and Renal Function

		Effect					
Reference	Population	SCr	CCr	NAG	RBP	BUN	ESRD
Weaver et al. 2006	647 adult Pb workers[b]	0 T (VDR[d]) 0 T (VDR[e]) 0 P (VDR[d]) 0 P (VDR[e])	0 T (VDR[d]) ↓ T (VDR[e]) 0 P (VDR[d]) 0 P (VDR[e])	–	–	–	–
Weaver et al. 2009	398 adult male and 139 female Pb workers[b]	↑ T (M) 0 T (F)	↓ T (M) 0 T (F)	–	–	0 T (M) ↑ T (F)	–
Wu et al. 2003a	709 men[a]	↑ T (ALAD[f]) 0 P	0 T ↓ P	–	–	–	–

[a]Participants in the Normative Aging Study.
[b]Current and former Pb workers in South Korea.
[c]Data were analyzed for all study participants and by age tertiles (Tertile 1: ≤36 years old; Tertile 2: 36.1–46 years old; Tertile 3: >46 years old). Any association observed in a specific age tertile are noted. If no association was observed for all participants and for all age tertiles, this is noted with a single entry of 0.
[d]Vitamin D receptor genotype bb.
[e]Vitamin D receptor genotypes BB and Bb.
[f]Interaction between ALAD genotype (ALAD 1-2/2-2 versus ALAD 1-1).
↑ = positive association; ↓ = negative association; 0 = no association; – = not reported; ALAD = aminolevulinic acid dehydratase; BUN = blood urea nitrogen; CCr = creatinine clearance; ESRD = end-stage renal disease; F = female; M = male; NAG = N-acetyl-D-glucosaminidase; P = patella; Pb = lead; RBP = retinol binding protein; SCr = serum creatinine concentration; T = tibia; VDR = vitamin D receptor

Mechanisms of Action. Several mechanisms have been established or proposed as mechanisms for kidney damage associated with exposure to Pb, including general mechanisms of Pb-induced toxicity (reviewed in Section 2.21). Mechanisms of renal damage associated with Pb exposure were recently reviewed in detail by EPA (2014c), including oxidative stress, inflammation, apoptosis of glomerular and tubular cells, alterations in renal gangliosides (plasma membrane lipids that play a role in the control of GFR), changes in renal vascular tone, and alterations in the renin-angiotensin-aldosterone system. As discussed in Pb Section 3.1.2 (Toxicokinetics, Distribution), Pb is distributed to the kidney, providing a toxicokinetic mechanism for direct effects to the kidney.

2.12 DERMAL

No epidemiological studies evaluating adverse dermal effects of chronic exposure to Pb were identified.

2.13 OCULAR

Few epidemiological studies have evaluated non-neurological ocular effects of Pb exposure, with studies examining associations with macular degeneration (Erie et al. 2009; Park et al. 2015) and cataract development (Schaumberg et al. 2004). In a cross-sectional study of 3,865 participants with a mean PbB of 2.69 µg/dL participating in the Korea National Health and Nutrition Examination study (2008–2011), the risks of age-related early (adjusted OR 1.12; 95% CI 1.02, 1.23; p=0.009) and late (adjusted OR 1.25; 95% CI 1.05, 1.50; p=0.015) macular degeneration were increased (Park et al. 2015). A cross-sectional study of human donor eyes with (n=25) and without (n=36) age-related macular degeneration found no association between Pb concentration in the retinal pigment epithelium-choroid complex and subjects with age-related macular degeneration and normal subjects (Erie et al. 2009). A prospective study of 642 men participating in the Normative Aging Study found no association between PbB (range: 1.0–35.0 µg/dL) and risk of cataracts, although the risk of cataracts was increased in association with tibia Pb levels (Schaumberg et al. 2004).

2.14 ENDOCRINE

Effects of chronic exposure to Pb on reproductive hormones are reviewed in Section 2.16 (Reproductive).

Overview. Effects on endocrine systems have been evaluated in several epidemiological studies in adults (general populations and workers), adolescents, and children. Investigations have focused on effects on thyroid function, cortisol levels, vitamin D levels, serum levels of other growth factors, and diabetes. Associations between PbB and thyroid function, assessed by measurement of serum thyroid hormone levels, is the most investigated endocrine outcome, although results do not demonstrate a consistent pattern of effect or dose-response relationships. Other endocrine endpoints have been evaluated in only a few studies.

The following endocrine effects have been associated with PbB:

- ≤10 µg/dL:
    - Altered serum levels of thyroid hormones (thyroxine [T4], triiodothyronine [T3], thyroid-stimulating hormone [TSH]); evaluated in multiple studies. Few effects were observed and results do not demonstrate consistent patterns of effects or exposure-response relationships.
    - Altered salivary cortisol awakening response in pregnant women.

  - Increased stress-induced salivary cortisol response in children.
  - Decreased serum levels of insulin-like growth factor-1 (IGF-1) in children.
- >10 µg/dL:
  - Altered serum levels of thyroid hormones (T4, T3, TSH); evaluated in a few studies; results do not demonstrate consistent patterns of effects or exposure-response relationships.
  - Increased thyroid peroxidase antibodies.
  - Decreased serum levels of vitamin D; evaluated in a few studies in children with consistent results.

Measures of Exposure. Studies evaluating the association between endocrine effects and Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. Results of epidemiological studies on endocrine effects have not been consistent. In general, statistical analyses were not rigorous and potential confounding factors and effect modifiers were not fully considered. Exposure to other metals and other chemical with endocrine effects is an important confounding factor to consider when interpreting study results. Although a few studies were of large populations (e.g., NHANES participants); most studies examined relatively small populations and used cross-sectional designs.

Characterization of Effects. General trends for studies showing a relationship between PbB and endocrine effects are shown in Table 2-24. Several studies have evaluated associations between PbB and effects on serum levels of thyroid hormones (T4, T3, and TSH) at mean PbB ranging from <1 to 71 µg/dL; an overview of study results is presented in Table 2-25. Based on evaluation of thyroid hormones, it is unclear if PbB is associated with altered thyroid function. At PbB ≤10 µg/dL, results of epidemiological studies, including cross-sectional studies of large NHANES populations, show associations between PbB and some alterations in serum levels of thyroid hormones; however, results do not demonstrate apparent patterns or exposure response relationships (see discussion below on *Effect at Blood Pb Levels ≤10 µg/dL*). Epidemiological studies at PbB >10 µg/dL, conducted in smaller populations (n=25–309), show more effects on thyroid hormones than observed at PbB ≤10 µg/dL. However, similar to studies at lower PbB, results are inconsistent. Khan et al. (2014) found decreased T4 ($p<0.0001$) and increased thyroid peroxidase antibodies (TPO; $p=0.0002$) during the second trimester of pregnancy in women (n=144) with mean PbB 20.00 µg/dL compared to women (n=147) with PbB of 5.57 µg/dL; no increase in TSH was observed. The adjusted OR (95% CI) for testing positive for TPO

antibodies was 2.41 (1.563, 3.82). Results indicate that autoimmunity is a potential mechanism for altered thyroid function. This finding has not been corroborated in other studies.

Table 2-24. Overview of Endocrine Effects Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Altered levels of thyroid hormones[a]	Abdelouahab et al. 2008; Dundar et al. 2006; Luo and Hendryx 2014; Mendy et al. 2013; Yorita Christensen 2013
	Altered salivary cortisol levels	Braun et al. 2014; Gump et al. 2008
	Decreased serum IGF-1	Fleisch et al. 2013
>10–30	Altered levels of thyroid hormones[a] and increased TPO antibodies	Gustafson et al. 1989; Khan et al. 2014; Lamb et al. 2008; Lopez et al. 2000
>30–50	Decreased serum vitamin D level	Mahaffey et al. 1982; Rosen et al. 1980
>50	Altered levels of thyroid hormones[a]	Pekcici et al. 2010; Robins et al. 1983; Singh et al. 2000; Tuppurainen et al. 1988
	Decreased serum vitamin D level	Rosen et al. 1980

[a]Thyroid hormones: T4, T3, and/or TSH.

IGF-1 = insulin-like growth factor-1; PbB = blood lead concentration; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TPO = thyroid peroxidase

Table 2-25. Effects on Thyroid Hormones Associated with Blood Lead Concentration (PbB) ≤10 µg/dL

Mean PbB (µg/dL)	Number of participants	T4		T3		TSH	Reference
		Total	Free	Total	Free		
PbB ≤10 µg/dL							
0.93	1,109 adolescents[a]	0	0	0	0	0	Chen et al. 2013
1.3	1,587 adults[a]	↓	0	0	0	0	Yorita Christensen 2013
1.52	4,652 adults[a]	↓	0	0	0	0	Mendy et al. 2013
1.74	87 women	0	–	0	–	↓	Abdelouahab et al. 2008
1.75	4,409 adults[a]	0	0	0	0	0	Chen et al. 2013
1.82	6,231 adults[a]	-	0	–	↑	0	Luo and Hendryx 2014
6.3[b]	24 infants[b]	–	0	–	–	0	Iijama et al. 2007
7.3	42 adolescents	–	↓	–	0	0	Dundar et al. 2006
PbB >10 µg/dL							
20.00	291 adults	–	↓	–	–	0	Khan et al. 2014
20.56	309 pregnancy[c]	–	↓	–	–	–	Lamb et al. 2008
24.1	151 adults	0	0	–	–	0	Schumacher et al. 1998

Table 2-25. Effects on Thyroid Hormones Associated with Blood Lead Concentration (PbB) ≤10 µg/dL

Mean PbB	Number of		T4		T3	TSH	Reference
25	68 children	0	0	–	–	–	Siegel et al. 1989
31	77 adults	–	0	–	0	0	Erfurth et al. 2001
<33.19[c]	6,231 adults[a]	0	–	–	↑	0	Luo and Hendryx 2014
39.5	25 adults	↑	–	–	–	↑	Gustafson et al. 1989
50.9	75 adults	↑	↓	0	–	0	Lopez et al. 2000
51.9	47 adults	↓	↓	–	–	0	Robins et al. 1983
51.9	58 adults	0	–	↓	–	↑	Singh et al. 2000
56.1	176 adults	↓	↓	0	–	0	Tuppurainen et al. 1988
71.1	65 adults	–	↑	–	↑	↑	Pekcici et al. 2010

[a]NHANES population.
[b]Umbilical cord PbB; assessments in infants.
[c]Mean not reported.

↑ = Increased; ↓ = decreased; 0 = no change; – = not assessed; NHANES = National Health and Nutrition Examination Survey; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

Studies also have investigated alterations in serum levels of vitamin D at PbB >30 µg/dL (Mahaffey et al. 1982). In children and adolescents, serum levels of 1,25-dihydroxycholecaliciferol were negatively associated with PbB over a range of 30–120 µg/dL (Mahaffey et al. 1982). Similar results were observed for vitamin D in children with PbB >50 µg/dL (Rosen et al. 1980). However, in children with PbB <10 µg/dL, no associations between PbB and vitamin D levels were observed (Kemp et al. 2007) (see discussion below on *Effect at Blood Pb Levels ≤10 µg/dL*). Studies investigating associations between PbB and other endocrine outcomes (salivary cortisol levels, serum levels of growth factors and diabetes) were conducted in populations with PbB ≤10 µg/dL (see discussion below on *Effect at Blood Pb Levels ≤10 µg/dL*).

Effect at Blood Pb Levels ≤10 µg/dL. Epidemiological studies of endocrine effects associated with PbB ≤10 µg/dL have examined thyroid function, as assessed by serum levels of thyroid hormones (Abdelouahab et al. 2008; Chen et al. 2013; Dundar et al. 2006; Iijama et al. 2007; Luo and Hendryx 2014; Mendy et al. 2013; Yorita Christensen 2013), cortisol levels and cortisol responses to stress (Braun et al. 2014; Gump et al. 2008), vitamin D levels (Kemp et al. 2007), IGF-1 levels (Fleisch et al. 2013), and diabetes (Moon 2013); study details are summarized in *Supporting Document for Epidemiological Studies for Lead,* Table 7. Studies examining thyroid function, including several large cross-sectional studies of NHANES populations (Chen et al. 2013; Mendy et al. 2013; Luo and Hendryx 2014; Yorita Christensen 2013), report inconsistent results; see Table 2-25. Results of NHANES studies at low PbB

(range of means: 0.93–1.82) are mixed, showing decreased total T4 and no change for free T4 (Mendy et al. 2013; Yorita Christensen 2013), and no change for total or free T4 (Chen et al. 2013; Luo and Hendryx 2014). The NHANES studies did not show associations between PbB and T3 or TSH levels, except for an increase in FT3 (Luo and Hendryx 2014). In smaller studies, decreased TSH and increased free T4 were observed at PbB of 3.10 and 7.3 µg/dL, respectively (Abdelouahab et al. 2008; Dundar et al. 2006). Thus, few effects on measures of thyroid function have been observed at PbB 10 µg/dL, and results do not demonstrate consistent patterns of effects or exposure-response relationships. Results of studies examining other endocrine effects associated with PbB have not been corroborated. Study findings include: associations between PbB and decreased cortisol awakening response during pregnancy at PbB ≥5.1 µg/dL (Braun et al. 2014); enhanced salivary cortisol response to cold stress in children at PbB 1.1–6.2 µg/dL (Gump et al. 2008); no association between PbB and serum vitamin D in children at PbB means 4.94–4.94 µg/dL (Kemp et al. 2007); decreased serum IGF-1 in children at PbB 5–9 µg/dL (Fleisch et al. 2013); and no association between PbB and diabetes in children at mean PbB 4.08 µg/dL (Moon 2013).

Mechanisms of Action. Adverse effects on the endocrine system (non-reproductive effects) associated with chronic Pb exposure have not been established; therefore, mechanisms of toxicity have not been identified. Thyroid function could be decreased through stimulation of autoimmunity to the thyroid gland, as shown by increased thyroid peroxidase antibodies (Kahn et al. 2014). In addition, general mechanisms of toxicity (reviewed in Section 2.21) of Pb would likely be involved in any endocrine toxicity.

2.15 IMMUNOLOGICAL

Overview. This section of the profile summarizes the immunological effects of Pb, exclusive of asthma, which is summarized in Section 2.5. Studies conducted in animal models have shown that Pb can perturb the humoral and cell-mediated immune systems, leading to decreased resistance to disease, sensitization, autoimmunity, and inflammation (EPA 2014c). These studies support epidemiological evidence of associations between Pb exposures (as indexed to PbB) and changes in biomarkers of humoral and cell-mediated immunity.

The following immunological effects have been associated with PbB:

- ≤10 µg/dL:
  - Increases in susceptibility to infections.
  - Sensitization to allergens.
  - Changes in indicators of humoral immunity (immunoglobulins, B-cells); demonstrated in several studies.
  - Changes in indicators of cell-mediated immunity (T-cells, eosinophils, neutrophils); demonstrated in several studies.
  - Changes in indicators of inflammatory response (circulating inflammation cytokines).
- >10 µg/dL:
  - Changes in indicators of humoral immunity (immunoglobulins, B-cells).
  - Changes in indicators of cell-mediated immunity (T-cells, natural killer [NK]-cells, neutrophils).
  - Changes in indicators of inflammatory response (inflammatory response of activated monocytes).
  - Decreases in circulating complement.

Measures of Exposure. Studies of associations between Pb exposure and immunological outcomes have relied on PbB as a biomarker of exposure. Most studies have been cross-sectional in design, which increases uncertainty in the interpretation of the results since the exposure history of the subjects is not necessarily indicated by the cross-sectional PbB measurement.

Confounding Factors and Effect Modifiers. The immune system is responsive to a multitude of environmental and physiological factors, which can be confounding factors or effect modifiers in studies of associations between Pb exposure and immunological outcomes. Factors that have been considered in some studies, but not consistently across studies, include age, sex, smoking, physical activity, allergen exposures, history of inflammatory disease, SES factors, recreational activities, and co-exposures to other chemicals.

Characterization of Effects. Table 2-26 lists epidemiological studies that have found associations between PbB and immunological outcomes, grouped by population PbB (typically mean or geometric mean). Several studies have found alterations in immunological endpoints in association with PbB over the range <10–>50 µg/dL.

Table 2-26. Overview of Immunological Effects Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Increased susceptibility to infections	Kruger and Wade 2016
	Sensitization to allergens	Jedrychowski et al. 2011; Pizent et al. 2008
	Changes in indicators of humoral immunity[a]	Hon et al. 2009, 2010; Karmaus et al. 2005; Min and Min 2015; Pizent et al. 2008; Sarasua et al. 2000; Wells et al. 2014; Xu et al. 2015
	Changes in indicators of cell-mediated immunity[b]	Boscolo et al. 2000; Conterato et al. 2013; Hsiao et al. 2011; Karmaus et al. 2005; Sarasua et al. 2000; Wells et al. 2014
	Changes in indicators of inflammatory response[c]	Kim et al. 2007, Sirivarasai et al. 2013; Songdej et al. 2010
>10–30	Changes in indicators of humoral immunity[a]	Heo et al. 2004, Lutz et al. 1999; Sun et al. 2003
	Changes in indicators of cell-mediated immunity[b]	Alomran and Shleamoon 1988; Bergeret et al. 1990; Boscolo et al. 1999; Di Lorenzo et al. 2006; Fischbein et al. 1993; Kimber et al. 1986; Mishra et al. 2003; Queiroz et al. 1993, 1994; Sata et al. 1998; Valentino et al. 1991, 2007; Zhao et al. 2004
	Changes indicators of inflammatory response[c]	Valentino et al. 2007
>30–50	Changes in indicators of humoral immunity[a]	Ewers et al. 1982; Heo et al. 2004; Pinkerton et al. 1998
	Changes in indicators of cell-mediated immunity[b]	Fischbein et al. 1993; Conterato et al. 2013; Garcia-Leston et al. 2012; Niu et al. 2015; Pinkerton et al. 1998
>50	Changes in indicators of humoral immunity[a]	Basaran and Undeger 2000
	Changes in indicators of cell-mediated immunity[b]	Basaran and Undeger 2000; Mishra et al. 2010; Undeger et al. 1996
	Decreases in circulating complement levels	Ewers et al. 1982; Undeger et al. 1996

[a]Immunoglobulins, B-cells.
[b]T-cells, natural killer (NK) cells, eosinophils, neutrophils and related receptors and cytokines.
[c]Circulating cytokines (e.g., C-reactive protein [CRP], interleukin-6 [IL-6], tumor necrosis factor-alpha [TNFα]).

Humoral immunity. Numerous epidemiological studies have examined associations between Pb exposure and circulating levels of immunoglobulins. These studies provide evidence that exposure to Pb is associated with increases in circulating IgE in children (Hon et al. 2009, 2010; Karmaus et al. 2005; Lutz et al. 1999; Sun et al. 2003) and in adults (Heo et al. 2004; Sarasua et al. 2000). IgE is an important mediator of hypersensitivity reactions and inflammation and Pb-induced perturbations in IgE may

contribute to associations between Pb exposure and sensitization and inflammation. Although some studies have found changes in levels of other immunoglobins, the evidence for these effects is not as strong as for IgE (Alomran and Shleamoon 1988; Anetor and Adeniyi 1998; Ewers et al. 1982; Kimber et al. 1986; Pinkerton et al. 1998; Queiroz et al. 1994b; Ündeger et al. 1996). The association between circulating IgE levels and PbB appears to extend to PbB levels <10 µg/dL (Karmaus et al. 2005; Min and Min 2015; Pizent et al. 2008; Sarasua et al. 2000; Wells et al. 2014).

T-cells. T-cells are important mediators of immunity to self-cells (e.g., cancer cells and cells infected with virus) and for activation of B-cells and humoral immunity. Epidemiological studies provide evidence that exposure to Pb is associated with decreases in T-cell abundance in children (Karmaus et al. 2005; Lutz et al. 1999; Sarasua et al. 2000; Zhao et al. 2004) and increases in abundance in adults (Boscolo et al. 1999, 2000; Sarasua et al. 2000). Several studies in adults found no consistent effect on T-cell abundance (Fischbein et al. 1993; Mishra et al. 2010; Pinkerton et al. 1998; Ündeger et al. 1996; Yücesoy et al. 1997b). Most of the studies on T-cell abundance did not differentiate specific classes of T-cell population affected; however, evidence is stronger for effects on CD3+ cells (Karmaus et al. 2005; Lutz et al. 1999; Sarasua et al. 2000; Zhao et al. 2004), with some studies finding effects on abundances of CD4+ (T helper) or CD8+ (T cytotoxic) cells (Boscolo et al. 1999, 2000; Karmaus et al. 2005; Sarasua et al. 2000). The association between circulating T-cell abundance and PbB appears to extend to PbB levels ≤10 µg/dL (Boscolo et al. 2000; Karmaus et al. 2005; Sarasua et al. 2000).

Neutrophils. Neutrophils are phagocytic cells that function in the immune defense against bacterial infections. Epidemiological studies have found associations between Pb exposure and neutrophil function. The effects on cultured human PMNs in populations that had mean PbB >10 µg/dL includes suppression of chemotaxis, phagocytosis, respiratory oxidative burst, and antigen killing (Alomran and Shleamon 1988; Bergeret et al. 1990; Fischbein et al. 1993; Kimber et al. 1986; Queiroz et al. 1993, 1994; Valentino et al. 1991). In a worker population having mean PbB ≤10 µg/dL, increasing PbB was associated with decreases in circulating neutrophil abundance (Conterato et al. 2013), whereas in a worker population having mean PbB >10 µg/dL, PbB was associated with increases in neutrophil abundance (DiLoenzo et al. 2006) and decreases in circulating complement levels (Ewers et al. 1982; Undeger et al. 1996).

NK cells. NK cells contribute to the immune defense (cytotoxicity) against tumor cells and viral infected cells. Although a few studies have found associations between PbB and NK cell abundance (Boscolo et al. 1999, 2000), most studies have found no associations (Fischbein et al. 1993; Garcia-Leston et al. 2011;

Karmaus et al. 2005; Kimber et al. 1986; Mishra et al. 2003; Pinkerton et al. 1998; Sarasua et al. 2000; Undeger et al. 1996; Yucesoy et al. 1997) at population mean PbBs ≤10 or >10 µg/dL.

Lymphocyte activation. A few epidemiological studies have found associations between exposure to Pb and increased lymphocyte activation (HLA-DR expression) and proliferation in children (Lutz et al. 1999) and adults (Alomran and Shleamon 1988; Boscolo et al. 1999; Cohen et al. 1989; Fischbein et al. 1993; Kimber et al. 1986; Mishra et al. 2003). These studies found effects in populations that had PbB >10 µg/dL.

Sensitization. Epidemiological studies provided evidence for associations between exposure to Pb and sensitization. This evidence includes increased risk of atopy to airborne allergens in children (Jedrychowski et al. 2011) and adults (Pizent et al. 2008). Consistent with findings in animal studies which found that Pb exposure suppresses delayed type hypersensitivity (DTH), Hsiao et al. (2011) found that higher PbB was associated with decreases in circulating levels of IFN-γ γa T-helper cytokine known to be important in DTH). The above effects related to sensitization have been observed in populations that had mean PbB ≤10 µg/dL.

Inflammation. A few epidemiological studies have examined possible associations between Pb exposure and biomarkers of inflammation. Results for these studies suggests that Pb exposure can modify the control of inflammatory responses, including modifying macrophage NO release and ROS production in macrophages harvested from exposed children (Pineda-Zavaleta et al. 2004), and in adults, decreases in abundance of circulating monocytes (Conterato et al. 2013; Pinkerton et al. 1998), and lower circulating levels of HLA-DR+ (Fischbein et al. 1993) in adults. Three studies found evidence for effects indicative of enhancement or stimulation of inflammation in adults at mean PbB ≤10 µg/dL. Outcomes include increases in circulating tumor necrosis factor-alpha (TNFα) (Kim et al. 2007) and C-reactive protein (CRP) in men (Songdej et al. 2010; Sirivarasai et al. 2013).

Effect at Blood Pb Levels ≤10 µg/dL. Epidemiological studies that have evaluated immunological effects associated with exposures to Pb that resulted in PbB ≤10 µg/dL are summarized in Table 2-27, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 8. Outcomes that have been observed in populations with PbB ≤10 µg/dL include susceptibility to infections, sensitization in children and adults, humoral and cell-mediated immunity in children and adults, and inflammation in children and adults.

Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Sensitization			
Jedrychowski et al. 2011 Prospective study, n=244 children of women recruited in the 2nd trimester of pregnancy	Gmean (95% CL): Cord: 1.16 (1.12, 1.22) Maternal: 1.60 (1.52, 1.67)	Atopy	Adjusted RR: • **Cord PbB: 2.28 (1.12, 4.62)*** • Maternal PbB: 1.72 (0.98, 3.00)
Pizent et al. 2008 Cross-sectional study, n=216 adults (age range 19–67 years)	Gmean (95% CL): • Male: 3.17 (0.99, 7.23) • Female: 2.16 (0.56, 7.35)	SPT	**Adjusted OR for positive SPT: 0.92 (0.86, 0.98)***
Humoral immunity			
Karmaus et al. 2005 Cross-sectional study, n=671 children (age 7–10 years)	Gmean (95% CL): • Males: 2.78 (1.48, 4.82) • Females: 2.54 (1.10, 4.38)	IgE	**Mean serum IgE levels were higher (p≤0.05) in PbB strata >2.84 and >3.41 µg/dL.***
		B-cells	**B-cell abundance was lower (p≤0.05) in PbB stratum 2.21–2.83 compared to <2.2 µg/dL.***
Min and Min 2015 Cross-sectional study, n=4,287 adults (age ≥22 years)[c]	Gmean (95% CL): • 1.46 (1.44, 1.50)	IgE	β for 1 $\log_{10}$ increase in IgE per 1 $\log_{10}$ increase in PbB (95% CL): • **Q2 (1.1–1.69 µg/dL): 0.20 (0.05, 0.34)*** • **Q3 (1.7–2.6 µg/dL): 0.26 (0.10, 0.42)*** • **Q4 (2.61–26.4 µg/dL): 0.35 (0.20, 0.51)***
Pizent et al. 2008 Cross-sectional study, n=216 adults (age range 19–67 years)	Gmean (95% CL): • Male: 3.17 (0.99, 7.23) • Female: 2.16 (0.56, 7.35)	IgE	**β log increase in IgE per log increase in PbB µg/L (SE), females not taking oral contraceptives or hormone replacement therapy: 0.600 (0.298); p=0.046***

Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Sarasua et al. 2000 Cross-sectional study, n=1,561 residents of communities with elevated levels of Cd or Pb in soil (age range 6 months–75 years) (1991)	Gmean (95% CL): • Age 6–35 months: 7.0 (1.7, 16.1) • Age 36–71 months: 6.0 (1.6, 14.1) • Age 6–15 years: 4.0 (1.1, 9.2)	IgA	**β per 1 µg/dL PbB, age 6–35 months: 0.8, p<0.01***
		IgG	• **β per 1 µg/dL PbB, age 6–35 months: 0.8; p<0.01*** • **β per 1 µg/dL PbB, age 6–15 years: 7.5; p=0.02***
		IgM	**β per 1 µg/dL PbB, age 6–35 months: 1.0; p=0.03***
		B-cell count	**β per 1 µg/dL PbB, age 6–35 months: 16.9; p<0.01***
		B-cell%	**β per 1 µg/dL PbB, age 6–35 months: 0.19; p=0.02***
Wells et al. 2014 Cross-sectional study, n=1,788 children (age 2–12 years)[c]	Gmean (95% CL): • 1.13 (1.04, 1.22)	IgE	**β per 1 µg/dL PbB for % increase per 1 µg/dL: 10.27 (3.52, 17.47)***
Xu et al. 2015 Cross-sectional study, n=590 children (age 3–7 years)	Gmean (SD of log PbB): • Male: 6.61 (0.19) • Female: 6.16 (0.18)	Hepatitis B virus	Antibody titers deceased with increasing PbB β signal to cut-off ratio per 1 µg/dL (SE) at two assessment dates: • **2011: -0.4467 (0.0225); p<0.001*** • **2012: 0.3661 (0.0193); p<0.001***

Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Cell-mediated immunity			
Boscolo et al. 2000 Cross-sectional study, n=30 atopic women (age range 19–49 years) and 30 non-atopic women	Median: • Atopic: 6.4 (4.9, 7.9) • Control: 5.5 (4.4, 6.7)	T-cell abundance	Positive correlation between PbB and T-cell abundances in non-atopic subjects (r for cell count): • **CD4+CD45RO-: 0.464; p<0.05*** • **CD3+ CD8+: 0.430; p<0.05*** • **CD3- HLA-DR+>: 0.435; p<0.05***
Conterato et al. 2013 Cross-section study of battery manufacture workers (n=59), and automobile painters (n=23); ages 15–61 years	Median: • Battery workers: 49.8 (4.0) • Painters: 5.4 (0.4) • Controls: 1.5 (0.1)	Neutrophil abundance	Mean (SE), $10^3/mm^3$: • **Battery workers: 2.87 (0.27); p<0.05*** • **Painters: 3.07 (0.13); p<0.05)*** • Controls: 3.75 (2.49)
Hsiao et al. 2011 Cross-sectional study, n=214 children (primary school grades 5–6)	Mean (SD): • Allergic and residing near oil refinery: 8.80 (0.45) • Non-allergic and residing near oil refinery: 5.23 (0.36) • Other rural or urban groups, allergic or not: 3.16–3.83		Compared to all other groups, allergic group residing near the refinery had:
		IFN-γ	**>96% decrease in serum IFN-γ; p<0.05***
		IL-12	**>96% decrease; p<0.05***
		IL-4	**>500% increase; p<0.05***
		IL-25	**>500% increase; p<0.05***
Karmaus et al. 2005 Cross-sectional study, n=67 children (age 7–10 years)	Gmean (95% CL): • Males: 2.78 (1.48, 4.82) • Females: 2.54 (1.10, 4.38)	T-cell and T_C	**Lower (p≤0.05) in PbB stratum 2.21–2.83 compared to <2.2 µg/dL***

Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Sarasua et al. 2000 Cross-sectional study, n=1,561; age range 6 months–75 years)	Gmean (95% CL): Age • 6–35 months: 7.0 (1.7, 16.1) • 36–71 months: 6.0 (1.6, 14.1) • Age 6–15 years: 4.0 (1.1, 9.2)	T-cell%	**β per 1 µg/dL PbB: -0.18; p=0.03***
		T-cell count	β per 1 µg/dL PbB: 7.2; p=0.59
		NK-cell%	β per 1 µg/dL PbB: 0.00; p=0.99
		NK-cell count	β per 1 µg/dL PbB: 1.3; p=0.60
Wells et al. 2014 Cross-sectional study, n=1,788 children (age 2–12 years)[c]	Gmean (95% CL): 1.13 (1.04, 1.22)	Eosinophils %	**β for % increase per 1 µg/dL (95% CL): 4.61 (2.44, 6.83)***
Inflammation			
Kim et al. 2007 Cross-sectional study, n=300 adults (mean age 24±2 years)	Mean (range): • Q1: 1.46 (0.337,1.885) • Q2: 2.22 (1.886, 2.511) • Q3: 2.77 (2.513, 3.103) • Q4: 3.93 (3.110, 10.470)		In males for PbB stratum >2.51 relative to lower PbB stratum. % per 1 µg/dL increase in PbB:
		TNFα	**23% (4, 55); p=0.015***
		WBC	**15% (0, 35); p=0.004***
		IL-6	26% (0, 55%); p=0.082
Sirivarasai et al. 2013 Cross-sectional study, n=924 male adults (mean age 43 years)	Mean: 5.45 Quartiles, mean (range): • Q1: 2.44 (1.23, 3.47) • Q2: 3.95 (3.48, 4.55) • Q3: 5.77 (4.56, 6.47) • Q4: 9.21 (6.48, 24.62)	CRP	CRP was higher in upper quartile PbB stratum compared to Q1 and Q2 (p<0.001). In Q4 stratum, adjusted OR was elevated for GSTM1 and GSTT1 null genotypes (95% CL): • **-GSTM1-/- and GSTT1-/-: 1.98 (1.47, 2.55)*** • **-GSTM1-/-: 1.32 (1.03, 1.69)*** • **-GSTT1-/-: 1.65 (1.17, 2.35)***

Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Songdej et al. 2010 Cross-sectional study, n=9,145 adults (age >40 years)[c]	Gmean: 1.89		OR for <1.16 versus >3.09 µg/dL:
		CRP	• **Males: 2.85 (1.49, 5.45)*** • Females: 0.57 (0.43, 0.76)
		Fibrinogen	• Males: 1.15 (0.61, 2.16) • Females: 0.87 (0.57, 1.33)
		WBC	• Males: 1.55 (0.96, 2.49) • Females: 0.84 (0.62, 1.13)

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 8 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[c]Study of NHANES participants.

Cd = cadmium; CI = confidence interval; CL = confidence limit; CRP = C-reactive protein; Gmean = geometric mean; GPx = glutathione peroxidase; GSTM1 = glutathione S-transferase Mu 1; GSTT1 = glutathione S-transferase theta 1; Ig = immunoglobulin antibody; IL = interleukin; IFN-γ = interferon gamma; NHANES = National Health and Nutrition Examination Survey; NK = natural killer; OR = odds ratio; Pb = lead; SD = standard deviation; SE = standard error; SPT = skin prick test; TNFα = tumor necrosis factor-alpha; WBC = white blood cell

Susceptibility to infections. A cross-sectional study of data from NHANES (1999–2012) found a trend for increasing OR for being seropositive for *H. pylori*, *T. gondii*, and *Hepatitis B* virus in a population that has a geometric mean PbB of 1.5 µg/dL (Krueger and Wade 2016).

Humoral immunity. Several studies have found associations between circulating IgE levels and PbB in populations in which mean or geometric mean PbB levels ≤10 µg/dL (Karmaus et al. 2005; Min and Min 2015; Pizent et al. 2008; Sarasua et al. 2000; Wells et al. 2014). In general, these studies found increases in serum IgE levels in association with increasing PbB in children (Karmaus et al. 2005; Sarasua et al. 2000; Wells et al. 2014) and adults (Min and Min 2015; Pizent et al. 2008). A cross-sectional study of children (3–7 years of age) found an association between increasing PbB and decreasing *Hepatitis B* virus antibody titers (Xu et al. 2015).

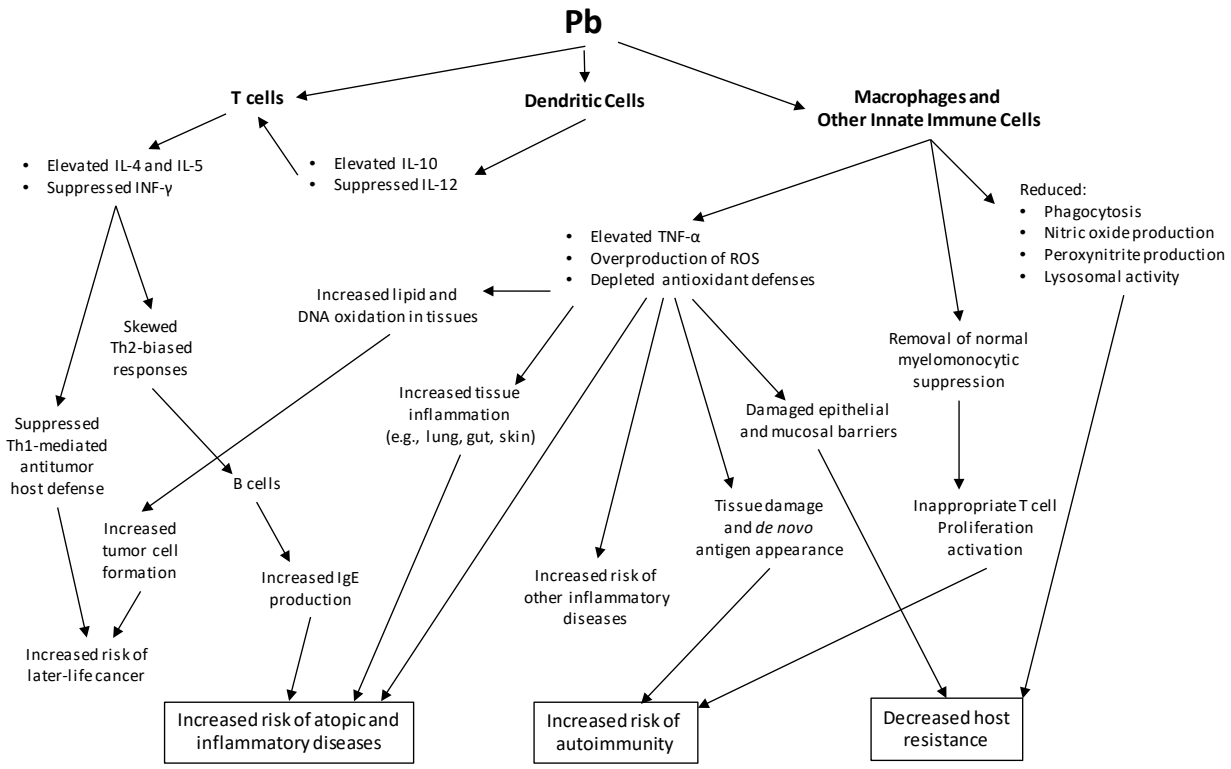
T-cells, neutrophils, and NK cells. Several studies have found associations between T-cell abundance and PbB in populations in which mean or geometric mean PbB levels ≤10 µg/dL. In studies of children, T-cell abundances decreased (Karmaus et al. 2005), whereas in a study of adults, T-cell abundance increased (Boscolo et al. 2000). In a study of Pb workers, neutrophil abundance was lower in Pb workers compared to controls (Contertato et al. 2013). The worker populations included a group of painters in which the mean PbB was 5.4±0.4 (SE) µg/dL, compared to the control group (1.5±0.1, SE). A study of a population of atopic adult women with median PbB 6.6 µg/dL (25^{th}–75^{th} percentile range: 4.9–7.9), found an association between increasing PbB and increasing abundance of NK cells (CD4+CD45RO+; Boscolo et al. 2000).

Sensitization. Exposures to Pb that resulted in population geometric mean PbB ≤10 µg/dL was associated increased risk of atopy to airborne allergens in children (Jedrychowski et al. 2011) and adults (Pizent et al. 2008). Higher PbB was associated decreases in circulating levels of IFN-γ (a T-helper cytokine known to be important in DTH) in a population of children with a mean PbB 8.8±0.45 (SD) µg/dL (Hsaio et al. 2011).

Inflammation. A few studies have found evidence for increases in circulating TNFα (Kim et al. 2007) and CRP (Songdej et al. 2010; Sirivarasai et al. 2013) in adults at mean PbB <10 µg/dL. These outcomes are indicative of enhancement or stimulation of inflammation.

Mechanisms of Action. Studies conducted in animal models and cell cultures have shown that Pb can disrupt the immune response through diverse mechanisms (EPA 2014c). Figure 2-6 shows the various potential pathways by which Pb may perturb the immune system and increase risk of atopy and inflammation, autoimmunity, and host resistance. In addition to its effects on T-cells, dendritic cells, and macrophages, Pb may also alter immune function at many other processes in the pathways shown in Figure 2-6.

Figure 2-6. Immunological Pathways by which Pb Exposure Potentially may Increase Risk of Immune-Related Diseases



Note: As shown in the figure, immunological pathways may increase risk of diseases such as cancer and inflammatory diseases in the cardiovascular, renal, and hepatic systems.

Source: EPA 2014c

2.16 NEUROLOGICAL

Overview. The literature on the neurobehavioral effects of Pb is extensive. With the improvement in analytical methods to detect Pb in the various biological media and in study designs, the concentrations of Pb, particularly in blood, associated with alterations in neurobehavioral outcomes continue to decrease, suggesting that there may be no threshold for the effects of Pb on intellectual function (CDC 2012d). Due

to the enormous size of the database on neurobehavioral effects of Pb, this discussion has been limited to representative and/or major studies published on specific topics crucial to understanding dose-response relationships in the lower exposure ranges (e.g., PbB ≤10 μg/dL). For additional information, the reader is referred to a recent review of this topic (EPA 2014c).

Numerous epidemiological studies have evaluated effects of Pb on neurological function in children and adults. These studies show consistent evidence of associations between decrements in cognitive and neuromotor/neurosensory function with PbBs that range from ≤10 to >50 μg/dL. The PbB-effect relationship for cognitive effects in children extends well below 10 μg/dL, with no evidence for a threshold. In several PbB-effect models, the slope for decrements in cognitive function in children show greater increases at lower PbB concentration ranges. These models predict that larger decrements in cognitive function would occur when PbB increases from 1 to 10 μg/dL, than when PbB increases to levels >10 μg/dL. All of the cognitive and neurobehavioral effects of Pb observed in children have also been observed in adults; however, it is not certain what life-stage exposures contribute most to outcomes in adults. A few studies that have followed children to early adulthood provide evidence of associations between childhood Pb exposure (e.g., PbB) and behavioral and neuroanatomical changes in adults, suggesting a possible role of exposures in childhood to adult outcomes. Other studies have found evidence of associations between cumulative Pb exposures (e.g., bone Pb) and neurological outcomes in adults.

The following neurobehavioral effects in children have been associated with PbB:

- ≤10 μg/dL:
    - Decreased cognitive function including full scale IQ (FSIQ).
    - Altered mood and behaviors that may contribute to learning deficits, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency.
    - Altered neuromotor and neurosensory function, including gross and fine motor skills, visual-motor integration, and hearing threshold.
- >10 μg/dL:
    - Decreased cognitive function including FSIQ.
    - Altered mood and behaviors, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency.
    - Altered neuromotor and neurosensory function, including gross and fine motor skills, visual-motor integration, hearing threshold, and visual evoked potentials.

  - Peripheral neuropathy.
  - Encephalopathy.

The following neurobehavioral effects in adults have been associated with increasing PbB:

- ≤10 µg/dL:
  - Decreased cognitive function including attention, memory, and learning.
  - Altered neuromotor and neurosensory function including decreased reaction time and walking speed, tremor, and increased risk of amyotrophic lateral sclerosis (ALS).
  - Altered mood and behavior including risk of various psychiatric symptoms including anxiety, depression, and schizophrenia.
- >10 µg/dL:
  - Reduced brain volume and altered brain neurochemistry.
  - Decreased cognitive function.
  - Altered neuromotor and neurosensory function.
  - Decreased peripheral nerve conduction velocity.

Measures of Exposure. Studies conducted in children have relied heavily on PbB as an exposure metric. Although bone or tooth Pb measurements may be informative, few studies have been conducted in children (Bellinger et al. 1994; Campbell et al. 2000b; Fergusson et al. 1993; Kim et al. 1995; Needleman et al. 1979, 1990, 1996, 2002; Wasserman et al. 2003). Maternal bone Pb has been used as an exposure metric for evaluating outcomes in children (Gomaa et al. 2002; Xu et al. 2015). Bone Pb has been used as metric of cumulative exposure in a growing number of epidemiological studies of adults (see Section 3.3.1, Biomarkers of Exposure). An association between a health outcome and bone Pb does not necessarily infer an association between the outcome and PbB (or *vice versa*) as indicated by studies in which associations are not consistent for the two metrics. These differences may reflect the relative importance of cumulative exposure on the given outcome, or differences in error associated with measurements of blood and bone Pb concentrations. A review by Shih et al. (2007) concluded that negative associations between Pb and cognitive function are stronger for bone Pb (specifically tibia Pb) for environmental exposures and for PbB for occupational exposures.

Confounding Factors and Effect Modifiers. Various factors have the potential to contribute to bias in estimates of associations between PbB and neurobehavioral outcomes. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome,

depending on the direction of the effect of the variable on the outcome. Neurological function can be influenced by numerous factors that may also correlate with lead exposure in the population studied. A contributor to these correlations is the influence of SES-related factors on Pb exposure. Confounding factors that are typically evaluated in all high-quality studies include maternal education and IQ, SES, and HOME score (parental care). However, other factors have also been explored in some studies, including maternal substance abuse (including prenatal alcohol) and psychopathology, birth weight, exposure to tobacco smoke, nutritional status, and ALAD allele type. The relatively strong correlation between SES and PbB can result in overcontrol in studies of populations that have wide SES variability. Overcontrol will tend to attenuate the estimated association between PbB and the outcome (Bellinger 2004). However, SES may also modify the effect of Pb on neurological function (Bellinger et al. 1990; Ris et al. 2004; Tong et al. 2000). If this were to occur, then SES would also be an effect-modifier.

Characterization of Effects in Children. A large number of studies showing decrements in neurological function in children have been published (Table 2-28). Collectively, these studies support the concept that Pb affects cognitive function in children prenatally exposed to PbB ≤10 μg/dL, with numerous studies providing evidence for effects at PbB ≤5 μg/dL. Neurobehavioral functions that have been associated with PbB ≤10 μg/dL include decrements in cognitive function (learning and memory), altered behavior and mood (e.g., attention, hyperactivity, impulsivity, irritability, delinquency), and altered neuromotor and neurosensory function (visual-motor integration, dexterity, postural sway, changes in hearing and visual thresholds). These outcomes also have been observed in association with PbB >10 μg/dL. In children who have been followed to early adulthood, mean childhood PbBs of 13 μg/dL were associated with altered brain volume and neurochemistry (Brubaker et al. 2010; Cecil et al. 2008, 2011). PbBs >30 μg/dL are associated with a variety of decrements in cognitive function, behavior (e.g., depression, aggression), and nerve function (e.g., decrements in fine and gross motor skills, peripheral neuropathy). Encephalopathy has been observed in children who have experienced severe Pb poisoning typical of PbB >80 μg/dL (NAS 1972b).

Table 2-28. Overview of Neurological Effects in Children Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Intellectual deficits[a]	Baghurst et al. 1992; Bellinger and Needleman 2003; Bellinger et al. 1992; Boucher et al. 2014; Braun et al. 2012; Canfield et al. 2003; Chandramouli et al. 2009; Chiodo et al. 2004; Dietrich et al. 1986, 1987, 1989, 1991, 1992, 1993a; Emory et al. 2003; Evens et al. 2015; Gomaa et al. 2002; Hong et al. 2015; Hu et al. 2006; Jedrychowski et al. 2009; Jusko et al. 2008; Kordas et al. 2011; Krieg et al. 2010; Lanphear et al. 2000a, 2005; Lin et al. 2013; Liu et al. 2014b; Mazumdar et al. 2011; McLaine et al. 2013; Min et al. 2009; Miranda et al. 2009; Schnaas et al. 2006; Sobin et al. 2015; Tellez-Rojo et al. 2006; Vigeh et al. 2014; Wang et al. 2008; Wasserman et al. 1994, 1997, 2003; Zhang et al. 2013
	Altered mood and behavior[b]	Boucher et al. 2012; Braun et al. 2006, 2008; Choi et al. 2016; Dietrich et al. 2001; Froehlich et al. 2009; Hong et al. 2015; Kim et al. 2013a, 2016; Liu et al. 2014a, 2015b; Sioen et al. 2013; Wang et al. 2008
	Altered neuromotor neurosensory function[c]	Chiodo et al. 2004; Dietrich et al. 1987, 1989, 1993b; Ethier et al. 2012; Fraser et al. 2006; Kim et al. 2013b; Osman et al. 1999 Tellez-Rojo et al. 2006;
	Altered brain anatomical development and activity	Cecil et al. 2008, 2011
>10–30	Intellectual deficits[a]	Baghurst et al. 1992; Bellinger et al. 1987, 1990, 1991; Chen et al. 2005, 2007; Dietrich et al. 1992, 1993a; Factor-Litvak et al. 1999; Hornung et al. 2009; Kordas et al. 2006; Magzamen et al. 2013, 2015; Marques et al. 2014; McMichael et al. 1988; Roy et al. 2011; Schnaas et al. 2000; Shen et al. 1998; Tong et al. 1996; Wasserman et al. 1994, 1997, 2000, 2003
	Altered mood and behavior[b]	Amato et al. 2013; Chen et al. 2007; Dietrich et al. 1993b, 2001; McFarlane et al. 2013; Neugebauer et al. 2015; Rothenberg et al. 1989; Roy et al. 2009
	Altered neuromotor neurosensory function[c]	Baghurst et al. 1995; Bhattacharya et al. 2006; Otto et al. 1985; Palaniappan et al. 2011; Parajuli et al. 2013, Ris et al. 2004; Robinson et al. 1985; Schwartz and Otto 1987, 1991
>30–50	Intellectual deficits[a]	do Nascimento et al. 2016; Royal et al. 2013

Table 2-28. Overview of Neurological Effects in Children Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
>50	Intellectual deficits[a]	Hou et al. 2013
	Altered mood and behavior[b]	Hou et al. 2013
	Altered neuromotor neurosensory function[c]	Hou et al. 2013;
	Peripheral neuropathy[d]	Erenberg et al. 1974; Landrigan et al. 1976; Schwartz et al. 1988; Seto and Freeman 1964
>80	Encephalopathy	NAS 1972b

[a]Intellectual deficits include decreased IQ, cognitive function, verbal comprehension, language development, perceptual organization, processing speed, decreased math and reading aptitude, educational attainment, school performance, and memory.
[b]Altered mood and behavior includes hyperactivity, ADHD, decreased adaptive skills and emotional functioning, externalizing behaviors, internalizing behaviors, social problems, delinquent behavior, impulsive behavior, irritability, autistic behavior, altered sleep, and associations between child PbB and adult behavior (see McFarlane et al. (2013).
[c]Altered neuromotor neurosensory function includes decreased integrated motor activities, gross motor skills; fine motor speed and dexterity, and visual-motor integration.
[d]Peripheral neuropathy includes decreased motor and sensory nerve conduction velocity.

ADHD = attention-deficit/hyperactivity disorder; IQ = intelligence quotient; PbB = blood lead concentration

Characterization of Effects in Adults. A large number of studies showing decrements in neurological function in adults have been published (Table 2-29). These studies have found neurobehavioral effects in populations whose PbBs were ≤10 µg/dL. Neurobehavioral functions that have been associated with PbB ≤10 µg/dL include decreased cognitive function, altered behavior and mood, and altered neuromotor and neurosensory function. These outcomes also have been observed in association with PbB >10 µg/dL. PbBs in the range of 10–20 µg/dL, measured either during childhood or in adulthood, have been associated with decreased brain volume and changes in brain neurochemistry (Brubaker et al. 2010; Cecil et al. 2008; 2011; Hsieh et al. 2009). PbBs >30 µg/dL are associated with a variety of decrements in cognitive function, behavior and nerve function, including postural sway and stability; decreased walking speed; decreased visuospatial function and visual-motor performance; decrements in hearing; peripheral neuropathy; psychiatric symptoms (depression, panic disorders, anxiety, hostility, confusion, anger, and schizophrenia); and changes in regional brain volumes and neurochemistry.

Table 2-29. Overview of Neurological Effects in Adults Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Intellectual deficits[a]	Muldoon et al. 1996; Payton et al. 1998; Power et al. 2014; Seo et al. 2014; Shih et al. 2006; Weisskopf et al. 2007; Weuve et al. 2006a, 2006b; Wright et al. 2003b
	Altered mood and behavior[b]	Bouchard et al. 2009; Buser and Scinicariello 2017; Golub et al. 2010; Opler et al. 2004; Rajan et al. 2007, 2008; Rhodes et al. 2003
	Altered neuromotor neurosensory function[c]	Hwang et al. 2009; Ji et al. 2013; Krieg et al. 2005
	Neurological diseases (ALS)	Fang et al. 2010
>10–30	Intellectual deficits[a]	Mantere et al. 1982; Reuben et al. 2017
	Altered mood and behavior[b]	Beckley et al. 2018; Yoon and Ahn et al. 2016
	Altered neuromotor neurosensory function[c]	Chuang et al. 2007; Yokoyama et al. 1997
	Altered brain architecture and metabolism	Brubaker et al. 2010; Cecil et al. 2008, 2011; Hsieh et al. 2009
>30–50	Intellectual deficits[a]	Baker et al. 1983; Barth et al. 2002; Campara et al. 1984; Fazli et al. 2014; Goodman et al. 2002; Hogstedt et al. 1983; Meyer-Baron and Seeber 2000; Schwartz et al. 2005
	Altered mood and behavior[b]	Baker et al. 1983; Lucchini et al. 2000; Maizlish et al. 1995; Malekirad et al. 2013; Parkinson et al. 1986
	Altered neuromotor neurosensory function[c]	Baker et al. 1983; Barth et al. 2002; Chia et al. 1996b; Choi et al. 2012; Haenninen et al. 1978; Iwata et al. 2005
	Altered nerve conduction	Araki et al. 1980, 1987, 2000; Chia et al. 1996b; Hirata and Kosaka et al. 1993; Pasternak et al. 1989; Stollery et al. 1989, 1991
>50	Intellectual deficits[a]	Arnvig et al. 1980; Campara et al. 1984; Matte et al. 1989; Valciukas et al. 1978
	Altered mood and behavior[b]	Awad el Karin et al. 1986; Zimmerman-Tansella et al. 1983
	Altered neuromotor neurosensory function[c]	Hanninen et al. 1998
	Altered nerve conduction	Triebig et al. 1984
	Altered brain architecture	Jiang et al. 2008

[a]Intellectual deficits include decreased IQ, cognitive function, learning ability, verbal reasoning, logic, memory, and concentration.
[b]Altered mood and behavior include depression, panic disorders, anxiety, hostility, confusion, anger, and schizophrenia.
[c]Altered neuromotor neurosensory function includes postural sway; postural stability, decreased walking speed, decreased visuospatial function and visual-motor performance, hearing loss, and altered hearing threshold.

ALS = amyotrophic lateral sclerosis; PbB = blood lead concentration

***Effects at Blood Pb Levels ≤10 µg/dL in Children*.** Numerous prospective and large cross-sectional studies provide a weight of evidence for decreased cognitive function, altered mood and behavior, and altered neuromotor and neurosensory function in children in association with exposures that result in PbB <10 µg/dL, with some studies showing effects at PbB ≤5 µg/dL. Study details are reviewed in the *Supporting Document for Epidemiological Studies for Lead*, Table 9. The cognitive outcome metric that has been most extensively studied and compared across studies is FSIQ. Tests of memory, learning, and executive function have also been used to assess cognitive function. Studies that attempt to identify associations between PbB and cognitive function must control for major factors known to influence or correlate with cognitive development and function, including SES, parental education and IQ, quality of caregiving, nutrition, and birth weight. Many of these same factors correlate with PbB and can confound associations between PbB and outcomes. Relationships between PbB and outcomes appear to be nonlinear. Greater decrements in cognitive function per unit change in PbB are seen with PbB increases within lower PbB concentration ranges than increases within higher PbB concentration ranges. Decrements in cognitive function in children have been associated with increasing PbB measured at various life stages, including prenatal and various metrics of child PbB including peak, concurrent, and cumulative. No specific life stage has been conclusively identified as the critical time period for exposure.

*Cognitive function in infanc*y. Several prospective studies have evaluated cognitive function in infancy and early child cohorts having mean PbB <10 µg/dL (Table 2-30). In general, these studies provide evidence for decrements in cognitive function in association with increasing PbB. Several studies used the Mental Development Index (MDI) score from the Bayley Scales of Infant Development (BSID), allowing comparison of results across studies (Dietrich et al. 1986, 1987, 1989; Gomaa et al. 2002; Hu et al. 2006; Jedyrychowski et al. 2009; Liu et al. 2014b). Each study found decreases in MDI scores measured from 6 to 36 months in association with increasing prenatal (e.g., maternal) or neonatal PbB. Cohort mean PbB ranged from 1.2 to 7.1 µg/dL. In a cohort that had a mean PbB of 1.23 µg/dL (range 0.44–6.9 µg/dL), the change in MDI score measured at 24 months of age was -7.6 (95% confidence limit [CL] -14.7, -0.62) points per 1 $\log_{10}$ increase in cord PbB (Jedrychowski et al. 2009). The largest effect size was reported for a cohort that had a mean PbB of 8±3.8 (SD) µg/dL; the change in MDI score measured at age 6 months was -15±5.1 (SE, $p<0.03$) points per cord lnPbB (Dietrich et al. 1986). Studies that repeatedly measured MDI scores longitudinally within the same birth cohorts found that the associations observed at 6 months persisted to later ages (Dietrich et al. 1986, 1987, 1989, 1991; Jedyrychowski et al. 2009; Liu et al. 2014b).

Cognitive function in early childhood - FSIQ. Prospective studies initiated at time of pregnancy or birth have consistently found decrements in child FSIQ in association with increasing cohort mean PbB <10 µg/dL measured at various stages of development (Table 2-30). Collectively, these studies provide evidence for effect sizes ranging from -1 to -6 FSIQ points in association with a 10-fold increase in PbB and larger effect sizes in cohorts or cohort strata having a lower mean PbB. These studies do not consistently point to a specific life stage as being more or less vulnerable, as negative associations with FSIQ have been observed with PbB measured during pregnancy, infancy, and childhood, and measured previous to or concurrently with the FSIQ evaluation. Results of an adult follow-up of a birth cohort suggest that FSIQ decrements observed in childhood may persist to adulthood (Mazumdar et al. 2011). FSIQ was assessed at age 28–30 years in 43 members of the Boston prospective study cohort (Bellinger et al. 1992). The change in FSIQ was -1.89 points (95% CL -3.00, -047) per µg/dL increase in late child PbB (mean 6.7±3.6 at age 4 years, 3.0±2.7 at age 10 years). After adjustment for maternal IQ, the change in FSIQ was -1.11 (95% CL -2.29, 0.06).

The largest study was a pooled analysis from seven individual prospective studies that evaluated FSIQ (Baghurst et al. 1992; Bellinger et al. 1992; Canfield et al. 2003; Dietrich et al. 1993a; Ernhart et al. 1989; Schnaas et al. 2000; Wasserman et al. 1997). The pooled cohort consisted for 1,333 children who were evaluated for FSIQ between ages 4.8 and 6 years (Lanphear et al. 2005). Co-variates considered in the analysis included study, maternal IQ, HOME score (Home Observation for Measurement of the Environment Inventory score), maternal education, marital status, birth weight, birth order, maternal age, race, and prenatal tobacco exposure. Of these, maternal IQ, HOME, and birth weight were included in the final models. When the full cohort was considered (PbB range 0.1–72 µg/dL), the adjusted change in FSIQ was loglinear, with greater changes in IQ per unit change in PbB a lower PbB. Several blood Pb metrics were explored in regression modeling, and slopes were significant for childhood, peak, lifetime average, or concurrent (with IQ testing) PbB. The model that used concurrent PbB had the highest r^2 (not reported). The covariate adjusted regression β for this model was -2.70 (95% CL -3.74, -1.66) IQ points per 1 lnPbB. The unadjusted β was -4.66 (-5.72, -3.60). The concurrent PbB model predicts a decrease of 6.2 points in FSIQ when PbB increased from 1 to 10 µg/dL and a decrease of 4.4 points when PbB increases from 1 to 5 µg/dL. In a PbB stratum 0.9 to 7.4 µg/dL, the mean change in FSIQ was -2.9 (95% CI -5.2, -0.71) per 1 µg/dL change in PbB measured at the age of IQ testing. Re-analyses of the pooled cohort reported in Lanphear et al. (2005) have been conducted (Crump et al. 2013; EPA 2014e). EPA (2014e) made several corrections to the dataset and obtained β coefficients that were similar to those reported in Lanphear et al. (2005). The results of the EPA (2014e) reanalysis are presented in Table 2-30.

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Intellectual deficits			
Baghurst et al. 1992 Prospective cohort, n=494 children followed from birth to age 7 years	Quartile range: • Birth: 4.3, 15.0 • Mean 0–2 years: 11.6, 27.1 • Mean 0–3 years: 12.2, 28.2 • Mean 0–4 years: 12.2, 27.7 • Lifetime average (7 years):10.8, 24.8	FSIQ	β (SE) for PbB metrics per each ln PbB increase: • Prenatal: 0.6 (1.4), p=0.68 • **Mean 0–2 years: -4.6 (2.1), p=0.03*** • **Mean 0–3 years: -4.8 (2.3), p=0.04*** • **Mean 0–4 years: -4.6 (2.4), p=0.05*** • Lifetime average: -3.7 (2.5), p=0.14
Bellinger et al. 1992; Bellinger and Needleman 2003 Prospective cohort, n=148 children followed from birth to age 10 years	Mean (SE): • 6 months: 6.7 (7.0) • 1 years: 7.7 (6.5) • 2 years: 6.5 (4.9)	FSIQ	β (SE) for PbB metrics per each 1 µg/dL increase in PbB: • Prenatal: -2.55 (2.56), p=0.57 • 6 months: -0.13 (0.15), p=0.39 • **2 years: -0.58 (0.21), p<0.007*** • **Peak <10 µg/dL: -1.56 (p=0.03)*** • Peak >10 µg/dL: -0.58 (p=NA)
Boucher et al. 2014 Prospective cohort, n=93 infants	Umbilical cord PbB: • Mean (SD): 4.8 (3.5) • Range: 0.5–17.8	FT-II-Fixed duration	**β 0.21 (0.07, 0.35); p≤0.01***
Braun et al. 2012 Prospective cohort, n=1,035 mother-infant pairs	Median (5th, 95th percentile) at age: • 1 years: 4.2 (1.3, 10.6) • 2 years: 4.6 (1.5, 13.4) • 3 years: 5.5 (2.3, 13.8) • 4 years: 5.9 (2.5, 12.8)	GCI	Coefficient for change in GCI (measured at year 4) per 10 µg/dL increase in PbB for PbB measured at each year: • PbB at 1 year: -2.5 (-5.6, 0.5) • **PbB at 2 years: -3.8 (-6.3, -1.4)*** • PbB at 3 years: -0.7 (-3.1, 1.6) • PbB at 4 years: -2.5 (-5.1, 0.1)

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Canfield et al. 2003 Prospective cohort, n=172 children, followed from age 24–40 months to 5 years	Mean (SD): Lifetime average at age 5: 7.4 (4.3) Peak: 11.1 (7.1) Concurrent with FSIQ: 5.8 (4.1)	FSIQ	β per IQ for each 1 µg/dL increase in PbB at 5 years of age: Full cohort (n=172): • **Lifetime average: -0.57 (-0.93, -0.20); p=0.003*** • **Peak: -0.26 (-0.47, -0.05); p=0.02*** • **Concurrent: -0.61 (-0.99, -0.24); p <0.001** Peak PbB <10 (n=101) • **Lifetime average: -1.52 (-2.94, -0.09); p=0.04*** • **Peak: -1.44 (-2.55, -0.33); p=0.01*** • **Concurrent: -1.79 (-3.00, -0.60); p=0.004***
Chandramouli et al. 2009 Prospective study, n=488 children followed from age 4–30 months (born 1992) to age 7–8 years	Mean (SD) at age 30 months: 4.22 (3.12)	Reading	• PbB 2–5 µg/dL OR: 0.88 (0.54, 1.43); p=0.608 • **PbB 5–10 µg/dL OR: 0.51 (0.32, 0.82); p=0.006***
		Writing	• PbB 2–5 µg/dL OR: 1.08 (0.69, 1.71); p=0.729 • **PbB 5–10 µg/dL OR:0.49 (0.31, 0.78); p=0.003***
		Standard assessment test scores	A 2-fold increase in PbB was associated with a 0.3-point (95% CI -0.5, -0.1) decrease in scores.
Chiodo et al. 2004 Prospective study, n=237 children, age 7.5 years	Mean (SD, range): 5.4 (3.3, 1–25)	FSIQ	β (SE): • **<3 µg/dL: -0.10; p≤0.1*** • **<5 µg/dL: -0.12; p≤0.1*** • **<7.5 µg/dL: -0.14; p≤0.05*** • **<10 µg/dL: -0.18; p≤0.01*** • **Cohort: -0.20; p≤0.01***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Dietrich et al. 1986 Prospective study, n=280 mother-infant pairs	Prenatal (maternal): • Mean (SD): 8.0 (3.8) • Range: 1–27 Neonatal (age 10 days): • Mean (SD): 4.5 (2.9) • Range: 1–22	MDI	Associations with maternal PbB (n=245), β per lnPbB (SE): **-14.978 (6.114); p<0.02*** Associations with neonatal PbB (n=280), β per lnPbB (SE): **-15.110 (5.083); p<0.003*** In males: **F (1,122): 4.95; p=0.03***
Dietrich et al. 1987 Prospective study, n=185 mother-infant pairs	Mean (SD, range): • Prenatal (maternal): 8.3 (3.8, 1–27) • Neonatal (10 days): 4.9 (3.3, 1–24) • Neonatal (3 months): 6.3 (3.8, 1–22) • Neonatal (6 months): 8.1 (5.2, 1–36)	MDI	β per lnPbB (SE): • **3-month: -12.113 (4.727); p=0.01*** • **6-month: -2.117 (0.916); p=0.02***
		PDI	• **β (SE): -13.248 (4.250); p=0.002***
		Motor maturity	• **β (SE): -0.570 (0.260); p=0.03***
Dietrich et al. 1989 Prospective study, n=192 mother-infant pairs	Mean (SD, range): • Prenatal (maternal): 8.2 (3.6, 1–27) • Neonatal (10 days): 4.8 (3.1, 1–23) • Neonatal (3 months): 6.0 (3.5, 1–20) • Neonatal (6 months): 7.9 (4.8, 1–35) • Neonatal (9 months): 11.5 (6.9, 2–57) • Neonatal (12 months): 14.2 (7.3<4–47)	MDI	Structural Equation Model indicated associations (p≤0.05) between increasing prenatal PbB and 12-month MDI through deceasing birth weight. Standardized regression coefficients: • **Prenatal PbB --> birth weight: -0.15, p≤0.05*** • **Birth weight ---> 12-month MDI: 0.18, p≤0.05***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Dietrich et al. 1991 Prospective study, n=258 4-year-old children	Mean (SD, range): (based on Dietrich et al. 1992) • Maternal (6–7 months): 8.2 (3.8, 1–27) • Neonatal (10 days): 4.8 (3.3, 1–26)	K-ABC scores	Coefficients per µg/dL neonatal PbB: • **Mental processing composite: -0.63; p<0.01*** • **Sequential processing: -0.68, p<0.01*** • **Simultaneous processing: -0.50; p<0.05*** • **Nonverbal: -0.63; p<0.01*** • **Achievement: -0.28; p<0.05***
Dietrich et al. 1992 Prospective study, n=259 5-year-old children	Mean (SD, range): • Maternal (6–7 months): 8.2 (3.8, 1–27) • Neonatal (10 days): 4.8 (3.3, 1–26) • Postnatal (5 years): 11.9 (6.4, 3–38)	FWS scores	Coefficients per µg/dL neonatal PbB: • **FWS(T): -0.26 p<0.1*** • **FWS(L): -0.20, p<0.01*** • **FWS(R) -0.13, p<0.1*** Coefficients per µg/dL concurrent PbB: • **FWS(T): -0.11 p<0.1*** • **FWS(L): -0.06, p<0.1*** • **FWS(R) -0.08, p<0.05***
Dietrich et al. 1993a Prospective study, n=253 6–7-year-old children	Mean (SD): • Maternal: 8.3 (3.7) • Birth: 5 (3.4) • 4–5 years: 11.8 (6.3)	FSIQ	Adjusted β (SE) in IQ per each 1 µg/dL: • Prenatal: 0.15 (0.21), • Lifetime average: -0.13 (0.11); • **Concurrent: -0.33 (0.14); p≤0.05***
Emory et al. 2003 Retrospective study, n=79 African-American mother-infant pairs	Mean (SD, 5th–95th percentile): • Maternal: 0.72 (0.86, 0.28–1.18)	FTII, Scaled Novelty Risk (risk of mental retardation later in life)	Score: PbB (SD): • Low risk: 0.65 µg/dL (0.80) • Medium risk: 0.89 µg/dL (0.88) • High risk: 1.01 µg/dL (0.126)

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
EPA 2014e (re-analysis of pooled cohort from Lanphear et al. 2005 with corrections to the database) Prospective; pooled-analysis; n=1,333 children from seven prospective studies	Mean (95% CL): • Lifetime average: 12.4 (4.1, 34.8) • Peak: 18.0 (6.2, 47.0) • Concurrent with FSIQ: 9.7 (2.5, 33.2)	FSIQ	β in IQ for per each 1 µg/dL increase in PbB (95% CL): • **6–24 months: -2.21 (-3.38, -1304)*** • **Lifetime average: -3.14 (-4.39, -1.88)*** • **Peak: -2.86 (-4.10, -1.61)*** • **Concurrent: -2.65 (-3.69, -1.61)*** FSIQ change for concurrent PbB range: • **2.4–10 µg/dL: -3.8 points (-2.3, -5.3)*** • **10–20 µg/dL: -1.8 points (-1.1, -2.6)*** • **20–30 µg/dL: -1.1 (-0.7, -1.5)***
Evens et al. 2015 Population-based retrospective cohort study, n=47,168 children	Mean (SD): 4.81 (2.22): Participants with PbB <10: 100%	ISAT reading scores	**Regression coefficient (SE): -0.60 (0.03); p<0.0001*** **Adjusted RR:** • **1 µg/dL: 1.06 (1.05, 1.07)*** • **5 µg/dL: 1.32 (1.26, 1.39)***
		Math	**Regression coefficient (SE): -0.50 (0.03); p<0.0001*** **Adjusted RR:** • **1 µg/dL: 1.06 (1.05, 1.07)*** • **5 µg/dL: 1.32 (1.26, 1.39)***
Gomaa et al. 2002 Prospective study, n=197 children followed from birth to age 2 years	Umbilical cord mean (SD): 6.7 (3.4) Participants with PbB ≥10: 15.7%	MDI	**β (SE): -4.48 (2.04); p=0.03***
Hong et al. 2015 Cross-sectional study, n=1,001 children (ages 8–11 years)	Gmean (GSD): 1.80 (1.40) 5th–95th percentile range: 0.53–6.16	IQ	Regression coefficients per 10-fold increase in PbB: • **Verbal IQ: -2.64 (-4.98, -0.30); p=0.027*** • **Full-scale IQ: -7.23 (-13.39, -1.07); p=0.021***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Hu et al. 2006 Prospective study, n=146 mother-child pairs	Mean±SD (range): • Umbilical cord: 6.20±3.88 (0.9–20.0) • Child 12-month: 5.22±3.41 (0.9–20.4) • Child 24-month: 4.79±3.71 (0.8–36.8) • Maternal 1st trimester: 7.07±5.10 (1.49–43.6) • Maternal 2nd trimester: 6.08±3.15 (1.58–22.4) • Maternal 3rd trimester: 6.86±4.23 (1.53–33.1)	MDI	β per 1 SD change in ln PbB: • Umbilical cord: -0.35 (-4.72, 4.03); p=0.88 • Child 12-month: -2.38 (-6.24, 1.49); p=0.23 • Child 24-month: -1.00 (-3.93, 1.94); p=0.50 • **Maternal 1st trimester: -4.13 (-8.10, -0.17); p=0.04*** • Maternal 2nd trimester: -4.08 (-8.29, 0.12); p=0.06 • Maternal 3rd trimester: -2.42 (-6.38, 1.54); p=0.23
Jedrychowski et al. 2009 Prospective study, n=444 children followed prenatally to age 3 years	Umbilical cord PbB • Gmean: 1.29 • Median: 1.23 • Range: 0.44–6.90	MDI	β per lg cord PbB±SE: • 12 months: -5.419±2.935 (-11.188, 0.3495); p=0.066 • **24 months: -7.653±3.577 (-14.684,-0.623); p=0.033*** • **36 months: -6.717±2.964 (-12.546, -0.889); p=0.024*** • **All participants with PbB <5 (combination of all testing times): -6.618±2.499 (-11.517, -1.719); p=0.008***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Jusko et al. 2008 Prospective study, n=174 children recruited at age 24–30 months and evaluated for FSIQ at 6 years	Lifetime average: • Mean (SD): 7.2 (4.1) • Range: 1.4–27.1 • Participants <10: 77%	FSIQ	• **Associations between increasing PbB and decreasing FSIQ measured at age 6 years (p=0.003)*** • **Comparison of children with PbB of 5–9.9 (high) to those with PbB <5 (low) showed a 4.9-point decrease in FSIQ score (low: 91.3; high 86.4; p=0.04)*** • Adjusted changes in IQ for each 1 µg/dL increase in peak lifetime PbB (p not reported): o 2.1–10 µg/dL: -1.2 o 10–20 µg/dL: -0.32 o 20–30 µg/dL: -0.15
Kim et al. 2013b Prospective birth cohort; n=884 mother infant pairs	Gmean (GSD): Early pregnancy: 1.4 (1.5) Late pregnancy: 1.3 (1.5)	MDI	**β per 1 µg/dL change in late pregnancy PbB: -1.94 (-3.60, -0.29); p=0.02***
Kordas et al. 2011 Prospective study, n=186 children followed prenatally (to age 4 years)	Mean (SD): • Umbilical cord: 6.6 (3.3) • 24 months: 8.1 (4.4) • 48 months: 8.1 (3.6)	MDI (24 months)	• **β (SE) Cord PbB: -0.7 (0.3); p<0.05*** • β (SE) Concurrent PbB: -0.1 (0.2)
		PDI (24 months)	• β (SE) Cord PbB: -0.4 (0.2) • β (SE) Concurrent PbB: -0.2 (0.2)
		GCI (48 months)	• β (SE) Cord PbB: -0.2 (0.3) • **β (SE) Concurrent PbB: -0.6 (0.2); p<0.05***
		Memory score	• β (SE) Cord PbB: 0.1 (0.1) • β (SE) Concurrent PbB: -0.3 (0.1)

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Lanphear et al. 2000a Cross-sectional study, n=4,853 children (ages 6–16 years)	Gmean: 1.9 Participants with PbB • ≥5: 9.7% • ≥10: 2.1%	Arithmetic	Regression coefficients (SE): • PbB <2.5: -1.28 (0.98), p=0.20 • **PbB <5.0: -1.06 (0.48); p=0.03*** • **PbB <7.5: -1.06 (0.39); p=0.01*** • **PbB <10: -0.89 (0.32); p=0.008***
		Reading	Regression coefficients (SE): • PbB <2.5: -1.71 (0.93); p=0.07 • **PbB <5.0: -1.66 (0.36); p<0.001*** • **PbB <7.5: -1.53 (0.31); p<0.001*** • **PbB <10: -1.44 (0.30); p<0.001***
		Block design	Regression coefficients (SE): • PbB <2.5: -0.08 (0.22); p=0.72 • PbB <5.0: -0.05 (0.07); p-0.45 • **PbB <7.5: -0.11 (0.06); p=0.04*** • **PbB <10: -0.13 (0.06); p=0.03***
		Digit span	Regression coefficients (SE): • PbB <2.5: -0.25 (0.17); p=0.17 • PbB <5.0: -0.09 (0.07), p=0.20 • PbB <7.5: -0.09 (0.05); p=0.11 • **PbB <10: -0.08 (0.04); p=0.03***
Lanphear et al. 2005 (same cohorts used for Budtz-Jorgensen et al. 2013) Prospective; pooled-analysis; n=1,333 children from seven prospective studies	Mean (96% CL): • Lifetime average: 12.4 (4.1, 34.8) • Peak: 18.0 (6.2, 47.0) • Concurrent with FSIQ: 9.7 (2.5, 33.2)	FSIQ	β in IQ for per each 1 µg/dL increase in PbB: • **6–24 months: -2.04 (-3.27, -0.81)*** • **Lifetime average: -3.04 (-4.33, -1.75)** • **Peak: -2.85 (-4.10, -1.60)*** • **Concurrent: -2.70 (-3.74, -1.66)*** FSIQ change for lifetime average PbB: • **2.4–10 µg/dL: -3.9 points (-2.4, -5.3)*** • **10–20 µg/dL: -1.9 points (-1.2, -2.6)*** • **20–30 µg/dL: -1.1 (-0.7, -1.5)***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Lin et al. 2013 Prospective (Taiwan Birth Panel Study; birth dates: April 2004–January 2005) of 230 mother-infant pairs from Taipei, Taiwan, followed until age 2	Umbilical cord • Mean (SD): 1.30 (0.75) • Range: 0.016–4.32	Cognitive score	Regression analysis comparing PbB ≥1.645 (75th percentile) and PbB <1.645. Adjusted β (SE): • **Total score: −4.23 (1.82); p<0.05*** • **Cognitive: −5.35 (2.19); p<0.05*** • Language: −2.53 (1.89); p≥0.05
Liu et al. 2014b Prospective study; n=243 infants followed from birth to age 3 years	Umbilical cord (mean±SD): • Low PbB group: 1.35±0.26 • High PbB group: 5.63±0.32	MDI	Regression coefficients: • **6 months: -1.647 (-2.094, -1.200); p=0.016*** • **12 months: -1.458 (-1.832, -1.084); p=0.023*** • **24 months: -1.385 (-1.683, -1.087) p=0.033*** • **36 months: -1.291 (-1.550, -1.032); p=0.036*** Increasing PbB at ages 24 and 36 months was associated with decreasing MDI scores measured at 24 and 36 months, respectively; β: • **24 months: -1.403; p=0.026*** • **36 months: -1.298; p=0.036***
		PDI	**Regression coefficients at 36 months: -1.302 (-1.572, -1.031); p=0.041***
Mazumdar et al. 2011 A prospective of 43 adults followed from birth (1979–1981) to age 28–30 years	Mean (SD): • Cord: 6.5 (5.3) • 6 months: 8.0 (5.3) • 12 months: 10.0 (6.7) • Age 2 years: 7.7 (4.0) • Age 4 years: 6.7 (3.6) • Age 10 years: 3.0 (2.7)	FSIQ	Change in FSIQ per 1 µg/dL increase in PbB. β (95% CL) for average late childhood PbB (mean of 4- and 10-year PbB): • **Unadjusted: -1.89 (-3.30, -0.47), p<0.01*** • Adjusted for maternal IQ: -1.11 (-2.29, 0.06) • Other adjustments: 95% UCLs <0

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
McLaine et al. 2013 Population-based retrospective cohort study, n=3,406 children	Median: 4.2 Interquartile range: 2.6, 6.0	PALS-K scores	Mean differences (95% CI) in PALS-K scores (85% CL), compared to PbB <5: • PbB 5–9: -4.51 (-6.61, -2.85); p>0.182 • PbB ≥10: -10.13 (-13.30, -6.96); p>0.182 PR for falling below the PALS-K benchmark, compared to PbB <4: • **PbB 5–9: 1.21 (1.19, 1.23); p<0.001*** • **PbB ≥10: 1.56 (1.51, 1.60); p<0.001***
Min et al. 2009 Prospective study, n=267 children followed prenatally age 11 years	Mean (SD): • 4 years: 7.0 µg/dL (4.1)	FSIQ	Regression coefficient (SE): • **4 years: -0.50 (0.20), p<0.05*** • **9 years: -0.41 (0.19), p<0.05*** • **11 years: -0.54 (0.19); p<0.01***
Miranda et al. 2009 Population-based retrospective cohort study, n=57,678 4th grade children	Mean: 4.8 Median: 4 Range: 1–16	EOG scores	Multivariate regression coefficients for PbB (µg/dL) of: • **PbB 2: -0.30 (-0.58, -0.01); p<0.0001*** • **PbB 3: -0.46 (-0.73, -0.19); p<0.0001*** • **PbB 4: -0.52 (-0.79, -0.24); p<0.0001*** • **PbB 5: -0.80 (-1.08, -0.51); p<0.0001*** • **PbB 6: -0.99 (-1.29, -0.68); p<0.0001*** • **PbB 7: -1.07 (-1.40, -0.74); p<0.0001*** • **PbB 8: -1.35 (-1.73, -0.97); p<0.0001*** • **PbB 9: -1.20 (-1.64, -0.75); p<0.0001*** • **PbB ≥10: -1.75 (-2.09, -1.41); p<0.0001***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Schnaas et al. 2006 Prospective study, n=150 followed from birth to age 10 years	Maternal during full pregnancy • Gmean (range): 8.0 (1–33) Maternal PbB during pregnancy weeks 28–36 • Gmean (95% CI): 7.3 (1.5–17.4) Child 1–5 years • Gmean (range): 9.8 (2.8–36.4) Child 6–10 years • Gmean (range): 6.2 (2.2–18.6)	FSIQ	β assessed at age 6–10 years: • **Ln maternal PbB (28 weeks pregnancy): -4.00 (-6.37, -1.65); p= 0.001*** • **Ln child PbB (6–10 years): -2.45 (-4.09, -0.81); p= 0.003***
Sobin et al. 2015 Cross-sectional; n=252 children (age 5.1–11.8 years)	Mean (SD): • Females: 2.7 (1.5) • Males: 2.4 (1.0) • 96% <5.0 µg/dL	Working memory	**β (SE): 0.11 (0.03), p<0.01***
Tellez-Rojo et al. 2006 Prospective study, n=294 children followed from birth to age 2 years	Mean (SD): • Cord: 4.85 (3.0) • 12 months: 4.27 (2.14) • 24 months: 4.28 (2.25)	MDI	β per ln PbB 12 months: • <10 µg/dL: -0.15, p=0.57 • ≥10 µg/dL: -0.71, p=0.17 β per lnPbB 24 mo: • **<10 µg/dL: -1.04, p<0.01*** • ≥10 µg/dL: 0.07, p=0.84

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Vigeh et al. 2014 Prospective study, n=174 mother-child pairs, birth to 36 months	Mean±SD (range): • 1st trimester: 4.15±2.43 (1.6–20.5) • 2nd trimester: 3.44±1.28 (1.1–7.5) • 3rd trimester: 3.78±1.40 (1.5–8.0) • Umbilical cord: 2.86±1.09 (1.2–6.9).	ECDI score	**OR 1st trimester: 1.74 (1.18–2.57); p=0.005***
Wasserman et al. 1994, 1997, 2003 Prospective study, n=332 children age 4 years, 261 children age 7 years, 167 children age 10–12 years	Mean (SD): • Age 4 years: 9.6, Pristina 39.9, K. Mitrovica • Age 10–12 years: 6.1 (1.9), Pristina 30.9 (9.6), K. Mitrovica	FSIQ	β (SE) for each ln PbB increase: • **4 years: -9.43 (2.44); p=0.000*** • **Lifetime AUC 7 years: -8.59 (1.89); p<0.05*** • **Lifetime average 10–12 years: -5.31 (1.98); p<0.05***
Zhang et al. 2013 Population-based retrospective cohort study, n=8,831, 7,708, and 4,742 students in grades 3, 5, and 8, respectively	Mean (SD): 7.12 (7.26) **Analysis:** academic achievement	Math	• **OR 1–5 PbB (µg/dL): 1.42 (1.24, 1.63)*** • **OR 6–10 PbB (µg/dL): 2.00 (1.74, 2.30)*** • **OR >10 PbB (µg/dL): 2.40 (2.07, 2.77)***
		Science	• **OR 1–5 PbB (µg/dL): 1.33 (1.10, 1.62)*** • **OR 6–10 PbB (µg/dL): 2.22 (1.82, 2.72)*** • **OR >10 PbB (µg/dL): 2.26 (1.84, 2.78)***
		Reading	• **OR 1–5 PbB (µg/dL): 1.45 (1.27, 1.67)*** • **OR 6–10 PbB (µg/dL): 2.21 (1.92, 2.55)*** • **OR >10 PbB (µg/dL): 2.69 (2.31, 3.12)***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Mood and behavior			
Boucher et al. 2012 Prospective study, n=272 children (mean age 11.3 years)	Mean±SD (range): • Umbilical cord: 4.7±3.3 (0.8–20.9) • Current: 2.7±2.2 (0.4–12.8)	ADHD-inattentive type	Adjusted ORs: • T2 (n=94): 1.06 (0.42, 2.66) • T3 (n=91): 1.01 (0.38, 2.64)
		ADHD-hyperactive-impulsive type	• **T2(n=94): 4.01 (1.06, 15.23)*** • **T3(n=91): 5.52 (1.38, 22.12)***
		ODD and/or CD	• T2 (n=94): 1.90 (0.88, 4.11) • T3 (n=91): 1.53 (0.67, 3.49)
		Behavior problem scores	Umbilical cord PbB was not associated with associated with behavior problem scores (data not reported).
Braun et al. 2006 Cross-sectional study, n=4,704 children (ages 4–15 years)	Quintiles: • Q1 (reference): ND–0.7 • Q2: 0.8–1.0 • Q3: 1.1–1.3 • Q4: 1.4–2.0 • Q5: ≥2.0	ADHD	Adjusted ORs: • Q2: 1.1 (0.4, 3.4); p=0.804 • Q3: 2.1 (0.7, 6.8); p= 0.195 • Q4: 2.7 (0.9, 8.4);p=0.086 • **Q5: 4.1 (1.2, 14.0); p= 0.026*** • **p-trend: 0.012***
Braun et al. 2008 Cross-sectional study, n=3,082 children (ages 8–15 years)	Quartiles: • Q1 (reference): 0.2–0.7 • Q2: 0.8–1.0 • Q3: 1.1–1.4 • Q4: >2.0	Conduct disorder	Adjusted ORs: • **Q2: 7.24 (1.06, 49.47)*** • **Q3: 12.37 (2.37, 64.56*)** • **Q4: 8.64 (1.87, 40.04)***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Choi et al. 2016 Longitudinal study, n=2,159 children (ages 7–9 years)	Gmean (GSD): • All participants >7 years: 1.62 (1.52) • Boys: 1.65 (1.75) • Girls: 1.47 (1.76); p<0.001, compared to boys	ADHD	• **RR for PbB ≥2.17 (compared to PbB <2.17): 1.552 (1.002, 2.403)***
Dietrich et al. 2001 Prospective study, n=195 subjects (age 15–17 years)	Categories: Lowest: <10 Low: 10–15 Medium: 16–20 High: >20	SRDBS scores	β (SE): • **Prenatal PbB: 0.192 (0.076); p=0.002*** • **78-month PbB: 0.193 (0.061); p=0.002*** • **Average child PbB: 0.101 (0.047); p=0.036***
Froehlich et al. 2009 Cross-sectional study, n=2,588 children (ages 8–15 years)	Tertiles T1: 0.2–0.8 T2: 0.9–1.3 T3: >1.3	ADHD	Adjusted ORs: • T2: 1.7 (0.97, 2.9); p=0.06 • **T3: 2.3 (1.5, 3.8); p=0.001***
Hong et al. 2015 A cross-sectional study, n=1,001 children (age 8–11 years)	Gmean (GSD): 1.80 (1.40) Range: 0.53–6.16	ADHD-hyperactive-impulsive type	PbB (log-transformed) OR: **3.66 (1.18, 6.13); p=0.004***
		ADHD-inattentive type	• OR: 2.72 (-0.12, 5.56); p=0.060
		Total score	• **OR: 6.38 (1.36, 11.40); p=0.013***
Kim et al. 2016 Prospective study, n=2,473 children (age 7–8 years)	Mean (95% CI): • Ages 7–8 years: 1.64 (1.60, 1.68) • Ages 9–10 years: 1.58 (1.55, 1.61) • Ages 11–12 years: 1.58 (1.55, 1.61)	ASSQ	PbB (log transformed) β (SE): • **7–8 years: 0.151 (0.061, 0.242)*** • 9–10 years: -0.023 (-0.143, 0.097 • 11–12 years: 0.054 (-0.061, 0.170)
		SRS	• **PbB at 7–8 years: 2.489 (1.378, 3.600)*** • PbB at 9–10 years: 1.295 (-0.235, 2.825) • PbB at 11–12 years: β (SE): 0.724 (-0.727, 2.176)

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Liu et al. 2014a Prospective study, n=332 mother-infant pairs	Mean (SD): • Low PbB group o 1st trimester: 1.22 (0.28) o 2nd trimester: 1.01 (0.19) o 3rd trimester: 1.19 (0.23) o Delivery: 1.26 (0.25) • High PbB group o 1st trimester: 6.49 (0.62) o 2nd trimester: 5.63 (0.43) o 3rd trimester: 6.31 (0.51) o Delivery: 6.65 (0.55)	NBNA score	β: • **1st trimester: -4.86 (-8.831, -0.889); p=0.03*** • **2nd trimester: -3.98 (-8.180, 0.220); p=0.07*** • 3rd trimester: -3.65 (-6.609, 1.309); p=0.21 • Delivery: -3.39 (-7.531, 0.751); p=0.11
Liu et al. 2015b Prospective study, n=665 children (ages 3–13 years)	Mean (SD): 6.26 (2.54)	Sleep onset delay	**β: 0.033 (0.009, 0.056); p= 0.006***
Sioen et al. 2013 Prospective study, n=270 children, followed newborn to 8 years	Umbilical cord mean (25th–75th percentiles): 1.43 (0.73–2.53)	Hyperactivity	**OR: 2.940 (1.172, 7.380); p=0.022***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Wang et al. 2008 Case-control study, n=630 children (ages 4–12 years)	Means (SE): • ADHD cases: 8.77 (3.89) • Controls: 5.76 (3.36) • Cases versus control: p<0.05 Tertiles: • T1 (reference): ≤5 • T2: 5–10 • T3: ≥10	ADHD	OR: • **T2: 4.92 (3.47, 6.98); p<0.01*** • **T3: 6.00 (4.11, 8.77); p<0.01***
Neuromotor neurosensory function			
Chiodo et al. 2004 Prospective study, n=237 children (age 7.5 years)	Mean (SD, range): 5.4 (3.3, 1–25)	Battery test performance	Tests with declines (β) at <3, <5, <7.5, or <10 µg/dL: • **Block design: <10, <5; p≤0.05*** • **Digit span backwards: <7.5; p≤0.05*** • **Beery visual-motor integration: <10, <5; p≤0.05*** • **MFF (number correct): <5; p≤0.05*** • **Attention-TRF: <3; p≤0.05*** • **Barkley-inattention: <5 <3; p≤0.05*** • **Withdrawn-TRF: <7.5, <3; p≤0.05*** • **Barkley off-task: <10, <5; p≤0.05*** • **Sternberg RT "Yes: <5, <3; p≤0.05*** • **Color naming: <5; p≤0.05*** • **CPT visual (number correct): none** • **Seashore rhythm: <3; p≤0.05*** • **Mental rotation RT "forward": <10, <7.5; p≤0.05***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Dietrich et al. 1987 Prospective study, n=185 mother-infant pairs	Mean (SD, range): • Prenatal (maternal): 8.3 (3.8, 1–27) • Neonatal (10 days): 4.9 (3.3, 1–24) • Neonatal (3 months): 6.3 (3.8, 1–22) • Neonatal (6 months): 8.1 (5.2, 1–36)	Motor maturity	Associations with 3-month ln PbB, β (SE): • **PDI: -13.248 (4.250); p=0.002*** • **Motor maturity: -0.570 (0.260); p=0.03*** Associations with 6-month ln PbB, β (SE): • **PDI: -2.117 (0.916); p=0.02*** • Motor maturity: -0.092 (0.056); p=0.11
		PDI	Associations with 3-month ln PbB, β (SE): • **PDI: -13.248 (4.250); p=0.002*** Associations with 6-month ln PbB, β (SE): • **PDI: -2.117 (0.916); p=0.02***
Dietrich et al. 1989 Prospective study, n=192 mother-infant pairs	Mean (SD, range): • Prenatal (maternal): 8.2 (3.6, 1–27) • Neonatal (10 days): 4.8 (3.1, 1–23) • Neonatal (3 months): 6.0 (3.5, 1–20) • Neonatal (6 months): 7.9 (4.8, 1–35) • Neonatal (9 months): 11.5 (6.9, 2–57) • Neonatal (12 months): 14.2 (7.3<4–47)	PDI	β (SE), 12 months: -14.09 (7.26); p=0.054 SEM indicated associations between increasing prenatal PbB and race and 12-month PDI. • **Prenatal PbB --> 12-month PDI: -0.47, p≤0.05*** • **Prenatal PbB x race --> birth weight: 0.97, p≤0.05*** • **Race --> 12-month MDI: -0.72, p≤0.05***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Dietrich et al. 1993b Prospective study, n=245 children (age 6 years)	Mean (SD): • Prenatal (maternal: 8.4 (3.8) • Neonatal: 4.8 (3.1) • Life average • 6 years: 10.1 (5.6) • Lifetime average quartile range: 7–22	Motor performance	Tests with (p≤0.05) declines (β) associated with neonatal (N), mean lifetime (L) or concurrent (C) PbB: • Bilateral coordination: N, M • Visual motor control: C • Upper limb speed and dexterity: C, M, N • Fine motor composite: C, M, N
Ethier et al. 2012 Prospective longitudinal, n=149 children (age 10–13 years)	Mean (SD, range): • Cord: 4.6 (3.1, 0.8–19.5) • 11 years: 2.6 (2.3, 0.4–12.8)	Delay of N150 latency of VEP	Association between increasing cord PbB and delay of N150 latency of VEP at multiple contracts. Mean latency (estimated from reported bar plot): • **≥4.15 µg/dL: ~160 ms, p<0.05*** • <4.15 µg/dL: ~153 ms (reference)
Fraser et al. 2006 Prospective study, n=101 children (age 5 years)	Mean (SD): Cord: 4.9 (3.7) Child: 5.3 (4.9)	Hand movements	**β -0.30, p≤0.01***
		Sway velocity	**β -0.28, p≤0.01***
		Transversal sway	**β 0.24, p≤0.05***
Kim et al. 2013b Prospective birth cohort, n=884 mother infant pairs	Gmean (GSD): Early pregnancy: 1.4 (1.5) Late pregnancy: 1.3 (1.5)	PDI	β per 1 µg/dL change in PbB (95% CL): -1.69 (-3.65, -0.27); p=0.09

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Osman et al. 1999 Retrospective study, n=155 children (age 4–14 years)	Median (range): • 7.2 (1.9–28.1)	Hearing threshold	β per 1 change in PbB for right ear (95% CL) for full cohort: • **0.5 kHz: 0.054 (0.035, 0.074)*** • **1 kHz: 0.044 9 (0.026, 0.062)*** • **2 kHz: 0.048 (0.029, 0.066)*** • **4 kHz: 0.060 (0.039, 0.081)*** • **6 kHz: 0.068 (0.044, 0.092)*** • **8kHz: 0.072 (0.050, 0.094)*** β per 1 change in PbB for left ear (95% CL): • **0.5 kHz: 0.051 (0.026, 0.075)*** • **1 kHz: 0.032 (0.014, 0.050)*** • **2 kHz: 0.036 (0.019, 0.053)*** • **4 kHz: 0.039 (0.020, 0.059)*** • **6 kHz: 0.004 (0.044, 0.049)*** • **8kHz: 0.047 (0.024, 0.080)*** **Association (p<0.05) between increasing PbB and increasing hearing threshold at all frequencies in PbB stratum <10 µg/dL (thresholds not reported)***
Tellez-Rojo et al. 2006 Prospective study, n=294 children (followed from birth to age 2 years)	Mean (SD): • Cord: 4.85 (3.0) • 12 months: 4.27 (2.14) • 24 months: 4.28 (2.25)	PDI	β per 1 ln change in PbB: 12 months: • <10 µg/dL: -0.01, p=0.98 • **≥10 µg/dL: -1.19, p=0.01*** 24 months: • **<10 µg/dL: -1.18, p<0.01*** • ≥10 µg/dL: 0.04, p=0.89

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Altered brain structure and chemistry			
Cecil et al. 2008 Prospective study, n=157 adults, age 19–24 years from a birth cohort born 1979–1984 from Cincinnati, Ohio	Mean (SD, range): • 6 month–6.5 years: 13.3 (5.9, 4.6–37.2)	Brain volume	Association (p≤0.001) between increasing childhood mean PbB and decreasing brain volume affecting 1.2% of the total gray matter. Effects were greater in males than females. Largest effects were in the anterior cingulate cortex.
Cecil et al. 2011 Prospective study, n=159 adults, age 19–24 years from a birth cohort born 1979–1984 from Cincinnati, Ohio	Mean (SD, range): • 6 months–6.5 years: 13.3 (6.1, 4.7–37.2)	Brain metabolism	Association (p<0.05) between increasing childhood mean PbB and decreasing regional levels of gray matter N-acetyl aspartate, glutamate-glutamine, creatine and phoshocreatine, and white matter cholines. Areas affected include the basal ganglia, cerebellum vermis, parietal white matter, and frontal white matter.

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 9 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Asterick indicates association with PB; unless otherwise specified, values in parenthesis are 95% CIs.

ADHD = attention-deficit/hyperactivity disorder; ASSQ = Autism Spectrum Screening Development Questionnaire; AUC = area under the curve; CD = Conduct Disorder; CI = confidence interval; CL = confidence limit; CPT = Continuous Performance Test; EOG = End of Grade; FSIQ = full-scale IQ; FSIQ = Full-Scale intelligence quotient; FTII = Fagan Test of Infant Intelligence; FWS = Filtered Word Subtest; Gmean = geometric mean; GSD = geometric standard deviation; IQ = intelligence quotient; ISAT = Illinois Standard Achievement Test; GCI = General Cognitive Index; K-ABC = Kaufman Assessment Battery for Children; MDI = Mental Development Index; MFF = Matching Familiar Figures; NBNA = Neonatal Behavioral Neurological Assessment; ND = not detected; ODD = Oppositional Defiant Disorder; OR = odds ratio; PALS-K = Phonological Awareness Literacy Screening-Kindergarten; PDI = Psychomotor Development Index; PR = prevalence ratio; RR = relative risk; SD = standard deviation; SE = standard error; SRDBS = Self-Reported Delinquent Behavior Survey; SRS = Social Responsiveness Scale; TRF = Teacher Report Form from the Child Behavior Checklist; UCL = upper confidence limit; VEP = visual evoked potential

The model that used early childhood PbB (6–24 months) had the highest r^2 (0.6433), although the r^2 was similar to concurrent PbB (0.6414). A benchmark dose (BMD) analysis of the pooled data from Lanphear et al. (2005) estimated BMDLs (95% lower one-sided confidence limit on BMD) ranging from 0.1 to 1 µg/dL for a 1% decrease in FSIQ for the best-fitting models (Budtz-Jorgensen et al. 2013). This BMD analysis provides supporting evidence that exposures to Pb may produce effects on cognitive function in populations whose PbBs are well below 5 µg/dL, and may extend to levels below 1 µg/dL.

In addition to the seven prospective studies included in the Lanphear et al. (2005) pooled analysis, more recent prospective studies have evaluated associations between PbB and FSIQ in children (Braun et al. 2012; Chiodo et al. 2004; Jusko et al. 2008; Kordas et al. 2011; Min et al. 2009; Schnaas et al. 2006; Table 2-30). Each of these studies found significant associations between increasing PbB <10 µg/dL and decreasing measures of FSIQ. The largest of these studies combined four Mexico City birth cohorts for a total of 1,035 mother-infant pairs (Braun et al. 2012). Cognitive function assessed at age 4 years (McCarthy General Cognitive Index [GCI]) decreased with increasing PbB measured at age 2 years. The adjusted effect of concurrent PbB was estimated as -3.8 (95% CI -6.3, -1.4) points when PbB increased by 10 µg/dL. Similar to the findings of the Lanphear et al. (2005) study, covariate adjustment decreased the regression β by approximately 40% (from -6.4 to -3.8). The cohort mean PbB was 4.6 µg/dL (5^{th}–95^{th} percentile range 1.3–13.4). Studies of smaller cohorts from Mexico City found similar associations (Kordas et al. 2011; Schnaas et al. 2006). Schnaas et al. (2006) estimated the effect size to be a -4.0 (95% CL -6.37, -1.65) point change in FSIQ measured at ages 6–10 years in association with a natural log increase in maternal PbB; the cohort geometric mean was 7.3 µg/dL (95% CL 1.5, 17.4). Kordas et al. (2011) estimated the effect size to be -0.6 (SE 0.2) for a 1 µg/dL increase in concurrent PbB (mean 8.1 µg/dL ±4.4 SE). Prospective studies conducted in Cleveland, Ohio (Min et al. 2009) and Rochester, New York (Jusko et al. 2008) also found similar effect sizes for the associations between increasing PbB and decreasing IQ. In the Rochester study, the changes in FSIQ were larger at lower PbB, consistent with the outcomes of the Lanphear et al. (2005) study (Jusko et al. 2008). For the PbB range 2.1–10 µg/dL, the change in FSIQ measured at age 6 years was -1.2 per 1 µg/dL increase in PbB. This decreased to -0.32 and -0.15 for the ranges 10–20 and 20–30 µg/dL, respectively. In the Cleveland study, the change was -0.50±0.20 (SE) in FSIQ measured at age 4 years per 1 µg/dL increase in concurrent PbB (Min et al. 2009). A study conducted in Detroit, Michigan estimated the change in FSIQ to be -0.20 per 1 SD change in PbB (Chiodo et al. 2004). The decrement was significant ($p \leq 0.05$) in PbB strata <7.5 and <10 µg/dL.

A cross-sectional study conducted in South Korea evaluated PbB and FSIQ in 1,001 children 8–11 years of age (Hong et al. 2015). The estimated effect of PbB on FSIQ was -7.23 points (95% CL -13.39, -1.07) per 10-fold increase in PbB. The 5^{th}–95^{th} percentile range for the cohort PbB was 0.53–6.16 µg/dL.

Cognitive function in early childhood–other than FSIQ. Several studies have examined outcomes other than IQ and have found associations between PbB and changes in cognitive function in children whose PbBs were <10 µg/dL (Table 2-30). These include prospective studies that used the same outcome metric, the BSID MDI, allowing comparison of outcomes across studies (Dietrich et al. 1986, 1987, 1989; Kim et al. 2013b, Tellez-Rojo et al. 2006). A prospective study of 884 children conducted in South Korea found negative associations between PbB in late pregnancy (geometric mean 1.3±1.5, geometric standard deviation [GSD]) and MDI scores measured at age 6 months (Kim et al. 2103b). A prospective study of 294 children conducted in Mexico City found negative associations between concurrent PbB (mean 4.27±2.14, SD) and MDI measured at 24 months in a PbB stratum <10 µg/dL (Tellez-Rojo et al. 2006). A prospective study conducted in Cincinnati, Ohio (approximately 190 infants) also found declines in MDI scores at age 6 and 12 months in association with increasing maternal, neonatal, or infant PbB (Dietrich et al. 1986, 1987, 1989).

Several large-scale retrospective studies linked academic performance for individual children with their corresponding blood Pb data recorded in state or local blood Pb registries (Evens et al. 2015; Miranda et al. 2009; Zhang et al. 2013; Table 2-30). Evens et al. (2015) linked individual 3^{rd} grade Illinois Standard Achievement Test (ISAT) scores and PbB data (birth–72 months) for a population of 47,158 children in Chicago, Illinois. All children had PbB <10 µg/dL and the population mean was 4.8±2.2 µg/dL (SD). Increasing PbB was negatively associated with decreasing covariate adjusted scores in math and reading. The adjusted relative risks (RRs) for failing scores was also significant for a 1 or 5 µg/dL increase in PbB. Miranda et al. (2009) linked 4^{th} grade reading End of Grade (EOG) scores and PbB data collected (birth–36 months) for a population of 57,678 children in North Carolina. The population mean PbB was 4.8 µg/dL (range 1–16 µg/dL); 94% of children had PbB <10 µg/dL. Increasing PbB was associated with decreasing covariate adjusted scores in all PbB strata, the lowest of which was 2 µg/dL. The effect size (change in score/µg/dL PbB) increased with increasing PbB. Zhang et al. (2013) linked Michigan Educational Assessment Program (MEAP) scores and PbB data (birth–72 months) of age for a population of approximately 21,000 children in Detroit, Michigan. Covariate adjusted ORs for failing scores in mathematics, science, and reading were significant for PbB strata 1–5, 6–10, and >10 µg/dL. A cross-sectional study of data from NHANES III examined associations between PbB and scores on tests of cognitive function (Wide Range Achievement Test-Revised [WRAT-R], Wechsler Intelligence Scales for

Children-Revised [WISC-R]) in approximately 5,000 children 6–16 years of age (Lanphear et al. 2000a). Increasing PbB was significantly associated with decreasing scores in reading in blood strata <5.0, <7.5, and <10 µg/dL. McLaine et al. (2013) examined associations between PbB (9–72 months) and kindergarten readiness assessed from Phonological Awareness Literacy Screening-Kindergarten (PALS-K) scores in approximately 3,400 children in Providence, Rhode Island. The population median PbB was 4.2 µg/dL (interquartile range 2.9–6.0); 93% of children had PbB <10 µg/dL. Mean difference in covariate adjusted scores in blood strata 5–9 and ≥10 µg/dL compared to <4 µg/dL were in the negative direction and adjusted prevalence ratios for test failure was significant in both strata.

Altered mood and behavior. Numerous studies have examined possible associations between neonatal and child PbB risk of behaviors that may contribute to learning deficits, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency (Table 2-30).

Several studies have examined attention-deficit/hyperactivity disorder (ADHD) as an outcome, allowing comparisons of outcomes across studies (Boucher et al. 2012; Braun et al. 2006; Choi et al. 2016; Froehlich et al. 2009; Hong et al. 2015; Wang et al. 2008). Collectively, the ADHD studies indicate that risk of childhood ADHD increases in association with increasing PbB <10 µg/dL (Table 2-30). In a case-control study conducted in China (630 cases), covariate adjusted ORs for ADHD in children 4–14 years of age were 4.92 (95% CL 3.47, 6.98) for the PbB range 5–10 µg/dL and 6.00 (4.11, 8.77) for PbB ≥10 µg/dL compared to <5 µg/dL (Wang et al. 2008). A prospective study of 272 children (mean age 11 years) conducted in Nunavik, Canada found elevated covariate adjusted ORs of 4.01 (95% CL 1.06, 15.23) for a PbB stratum 1.6–2.7 µg/dL and 5.52 (95% CL 1.38, 22.12) for the stratum 2.7–12.8 µg/dL (Boucher et al. 2012). A longitudinal study examined ADHD outcomes of 2,159 South Korean children (ages 7–9 years) who did not exhibit ADHD symptoms at recruitment (Choi et al. 2016). Two years following baseline assessment, the covariate adjusted relative risk of ADHD was estimated to be 1.552 (95% CL 1.002, 2.403) for children having PbB ≥2.17 µg/dL compared to ≤2.17 µg/dL. The geometric mean PbB for the cohort was 1.62 µg/dL ±1.52 (GSD). Several cross-sectional studies have also found associations between concurrent PbB and risk of ADHD (Braun et al. 2006; Froehlich et al. 2009; Hong et al. 2014). A study of data on approximately 4,700 children (age 4–15 years) reported in the 1999–2002 NHANES found elevated risk of ADHD in association with concurrent PbB >2 µg/dL and a significant trend in risk with increasing PbB (Braun et al. 2006). Froehlich et al. (2009) examined data for children 8–15 years of age from the 2001–2004 NHANES. Covariate adjusted ORs of ADHD were elevated for the PbB stratum >1.3 µg/dL (compared to ≥0.8 µg/dL). A cross-sectional study conducted in South Korea examined associations between PbB and ADHD rating scores of 1,001 children of age 8–

11 years (Hong et al. 2015). One log_{10} increase of PbB was associated with increases in teacher-rated ADHD hyperactivity (OR 3.66; 95% CI 1.18, 6.13) and total ADHD score (OR 6.38; 95% CI 1.36, 11.40). The cohort geometric mean PbB was 1.8±1.4 µg/dL (SD).

Prospective studies have also provided evidence for associations between neonatal or early childhood PbB and other neurobehavioral outcomes, including neonatal behavior, sleep disorders, hyperactivity, autistic behavior, and delinquency (Dietrich et al. 2001; Kim et al. 2016; Liu et al. 2014b, 2015b; Sioen et al. 2013).

Altered neuromotor-neurosensory function. Numerous studies have examined possible associations between neonatal and child PbB and neuromotor or neurosensory function (Table 2-30). Several studies used the Psychomotor Development Index (PDI) score from the BSID, allowing comparison of results across studies (Dietrich et al. 1987, 1989; Kim et al. 2013b; Tellez-Rojo et al. 2006). Each study found negative associations for PDI scores measured from 6 to 12 months in association with increasing prenatal (e.g., maternal) or neonatal PbB. Studies that repeatedly measured PDI scores longitudinally within the same birth cohorts found that associations observed at 6 months persisted to later ages (Dietrich et al. 1987, 1989, 1991; Tellez-Rojo et al. 2006). A prospective study conducted in China administered a neurobehavioral test battery to a birth cohort of 237 children at age 7 years (Chiodo at al. 2004). Significant declines in performance ($p \leq 0.05$) were observed in PbB strata that ranged from <3 µg/dL at the lowest to <10 µg/dL; most tests that showed significant declines at <10 µg/dL, also showed declines at <5 µg/dL ($p \leq 0.05$). A prospective study conducted in Nunavik, Canada evaluated fine motor control in a birth cohort at 5 years (Fraser et al. 2006). Significant changes in motor control assessed from sway and reaction times were associated with increasing concurrent PbB ($p \leq 0.01$). The cohort PbB mean was 5.3 µg/dL ±4.9 (SD). This birth cohort also exhibited changes in visual evoked potentials that were associated in increasing cord PbB (Ethier et al. 2012). The cohort cord PbB mean was 4.6±3.1 (SD).

Altered brain structure and neurochemistry. A follow-up to the Cincinnati prospective study (Dietrich et al. 1986) estimated whole brain volumes and imaged brain metabolites in 157–159 adults at age 19–24 years (Brubaker et al. 2010; Cecil et al. 2008, 2011; Table 2-30). Decreasing covariate adjusted brain volume was associated with increased childhood mean PbB (measured between ages 6 months and 6 years). Brain volume reductions that were associated with childhood PbB compromised approximately 1.2% of the total gray matter and were more severe in males compared to females. The largest effects were observed in the anterior cingulate cortex. This region of the brain is involved in controlling

executive function, mood, and decision-making. Increasing childhood PbB was also associated with decreasing concentrations of various metabolites in brain known to be important in supporting metabolic structural integrity of neurons (e.g., lipid metabolism and myelin production). These included decreased N-acetyl aspartate (NAA) in the basal ganglia and cerebellar hemisphere, decreased glutamate-glutamine in the vermis and parietal white matter, decreased creatine and phosphocreatine in the basal ganglia, and decreased cholines in the cerebellum, parietal white matter, and frontal white matter. These changes in association with childhood PbB suggest that childhood Pb exposure may be indicators of longer-term changes in brain glutamate-associated lipid metabolism or neuronal architecture (Cecil et al. 2011).

Associations Between Bone Pb and Neurological Effects in Children. Few studies have been conducted to assess possible associations between bone Pb and neurological function in children (Table 2-31). Prospective studies of outcomes in children of mother-infant pairs have found associations between maternal or child bone Pb cognitive function (Campbell et al. 2000b; Gomaa et al. 2002; Needleman et al. 1996; Wasserman et al. 2003; Xu et al. 2015). Increasing bone Pb measured at age 24 months was associated with decrements in cognitive development (Gomaa et al. 2002) and behaviors indicative of attention deficit hyperactivity disorder assessed at age 7–15 years (Xu et al. 2015). Increasing child bone Pb measured later in childhood (ages 11–14 years) was associated with decrements in language processing (Campbell et al. 2000b); full scale, verbal, and performance IQ (Wasserman et al. 2003); and delinquent, aggressive, internalizing, externalizing behaviors (Needleman et al. 1996). A case-control study of adjudicated delinquency at age 12–18 years found associations between increasing bone Pb and delinquency (Needleman et al. 2002).

Table 2-31. Associations Between Bone Pb and Neurological Outcomes in Children

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Campbell et al. 2000b	156 males, age: 11–14 years	↑ T	–	–	Language processing
Gomaa et al. 2002	197 mother-infant pairs	↑ P[a] 0 T[a]	–	–	24-month MDI[b]

Table 2-31. Associations Between Bone Pb and Neurological Outcomes in Children

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Needleman et al. 1996	301 males, age: 9–13 years	–	–	↑ T	Delinquent, aggressive, internalizing, externalizing behaviors
Needleman et al. 2002	194 male cases, 145 controls, age: 12–18 years	–	–	↑ T	Adjudicated delinquency
Wasserman et al. 2003	167 children, age: 10–12 years	↑ T	–	–	IQ (full scale, verbal, performance)[c]
Xu et al. 2015	197 mother-infant pairs	–	–	↑ P[a]	Attenuation of effect of maternal self-esteem on ADHD assessed at age 7–15 years[d]

[a]Maternal bone lead measured within 1 month of birth.
[b]Bayley Scale.
[c]Wechsler Intelligence Scale for Children-III.
[d]Maternal self-esteem was evaluated with Coopersmith Self-Esteem Inventory. ADHD was evaluated with Conners' Parent Rating Scale-Revised and Behavior Rating Inventory of Executive Function.

↑ = positive association; ↓ = negative association; 0 = no association; – = not reported; ADHD = Attention deficit hyperactivity disorder; C = calcaneous bone; MDI = Mental Developmental Index; P = patella; Pb = lead; T = tibia; O = other

Effects at Blood Pb Levels ≤10 µg/dL in Adults. Numerous longitudinal and large cross-sectional studies in adults provide a weight of evidence for decreased cognitive function, altered mood and behavior, and altered neuromotor and neurosensory function in association with exposures that result in PbB <10 µg/dL, with some studies showing effects in the 3–5 µg/dL range. Study details are reviewed in the *Supporting Document for Epidemiological Studies for Lead*, Table 10. Cognitive, neuromotor, and neurosensory outcomes have been evaluated with tests of memory, learning, executive function, reaction time, walking speed, and tremor. Pb exposure has been associated with risk of various psychiatric symptoms including anxiety, depression, and schizophrenia, and with risk of ALS. In some studies, associations were found between outcomes and PbB and/or bone Pb. Several studies have examined cohorts of people who had mean ages within the range 50–70 years. Studies of cognitive function in elderly populations must

control for factors that contribute to age-related decrements in function, including confounding from the relationship between age and bone Pb, which increases with age. Longitudinal studies offer advantages over cross-sectional studies in that they can provide measurement changes in function of individual subjects with age.

Cognitive function. Numerous studies have examined possible associations between Pb exposure and cognitive function in adults (Table 2-32). Most of these studies have found associations between increasing Pb exposure, indicated by blood or bone Pb, and indications of decreased cognitive function (Muldoon et al. 1996; Payton et al. 1998; Power et al. 2014; Seegal et al. 2013; Seo et al. 2014; Shih et al. 2006; Weisskopf et al. 2007; Weuve et al. 2006, 2009; Wright et al. 2003b). However, one of the largest cross-sectional studies analyzed data from NHANES III (1988–1994) and found no associations between PbB and performance neurobehavioral tests (Krieg et al. 2005). This study compared scores from several tests from the Neurobehavioral Evaluation System (NBES) and concurrent PbB in approximately 5,700 adults (age 20–50 years). Implemented tests measured processing speed, attention, learning, and memory (reaction time, symbol-digit substitution, serial digit learning). The geometric mean PbB was 2.51 µg/dL (range 0.7–42) and 96% of the cohort was <10 µg/dL. No significant associations (defined as $p \leq 0.05$) between PbB and cognitive outcomes were found. Several studies have examined smaller cohorts from longitudinal studies designed to evaluate health in aging populations. Studies of male cohorts of from the Normative Aging Study have found significant ($p \leq 0.05$) associations between increasing blood and/or bone Pb and decreasing scores on cognitive tests, including short-term memory, verbal memory, and visuoconstruction (Payton et al. 1998; Weisskopf et al. 2007; Weuve et al. 2006). Cohort sizes in these studies ranged from approximately 600 to 1,100 and the mean PbB ranged from 2.9±1.9 to 5.5±3.5 µg/dL. Weuve et al. (2006) found that decreases in cognitive performance were associated with PbB in a cohort of ALAD-2 carriers, but not in a cohort that carried the wildtype ALAD allele. Studies of female cohorts (approximately 600 subjects) from the longitudinal Nurses' Health Study have found mixed outcomes (Power et al. 2014; Weuve et al. 2009). Weuve et al. (2009) found significant association between increasing tibia Pb, but not PbB, and scores on a telephone survey of cognitive function (the Telephone Interview for Cognitive Status, TIC). The TIC has been used to assess memory and executive function and has been used to evaluate dementia. The effect size was -0.051 (95% CL -0.099, -0.003) points per 1 SD of tibia Pb. Power et al. (2014) used the same telephone survey instrument and found no associations between blood or bone Pb and cognitive function; the effect size for PbB was -0.013 (95% CL -0.044, 0.017) and the cohort mean PbB was 2.9±1.9 (SD) µg/dL. A cross-sectional study of approximately 1,000 adults from the Boston Memory Study found negative

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Cognitive abilities			
Krieg et al. 2005 Cross-sectional study, n=5,662 adults, age 20–59 years	Gmean (range): 2.51 (0.7, 41.8)	Simple visual reaction time	No associations between PbB and performance scores • Mean reaction time: p=0.24
		Symbol-digit substitution	• Mean total latency: p=0.27 • Number of errors: p=0.82
		Serial digit learning	• Trials to criterion: p=0.26 • Total score: p=0.24
Muldoon et al. 1996 Cross-sectional study, n=530 adult women, mean age 70 years	Mean (SD): • All: 4.8 (0.4) • Rural: 4.5 (0.4) • Urban: 5.4 (0.4) • Low: 4 • Medium: 4–7 • High: >7	Trailmaking B	• **Urban** o Medium PbB OR: 0.97 (0.40, 2.40) o High PbB OR: 0.79 (0.20, 3.04) • **Rural** o **Medium PbB OR: 2.05 (1.05, 4.02)*** o **High PbB OR: 2.60 (1.04, 6.49)***
		Digit symbol (correct)	• **Urban** o Medium PbB OR: 0.61 (0.25, 1.50) o High PbB OR: 0.64 (0.16, 2.47) • **Rural** o **Medium PbB OR: 2.03 (1.06, 3.88)*** o **High PbB OR: 3.73 (1.57, 8.84)***
		Incidental memory	• **Urban** o Medium PbB OR: 0.50 (0.22, 1.16) o High PbB OR:0.99 (0.28, 1.16) • **Rural** o Medium PbB: OR: 1.37 (0.77, 2.41) o High PbB: OR: 1.89 (0.83, 3.41)

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Payton et al. 1998 Longitudinal study, n=141 males, mean age 67 years	Mean (SD): • 5.5 (3.5) • Q1: 1.4 • Q2: 3.5 • Q3: 5.4 • Q4: 9.8	Pattern recognition	• **β (95% CL): 0.074 (0.032), p=0.02***
		Vocabulary	• **β (95% CL): -0.841 (0.20), p=0.0001***
		Word list memory	• **β (95% CL): -0.182 (0.086), p=0.036***
		Boston naming test	• **β (95% CL): -0.036 (0.016), p=0.028***
		Verbal fluency	• β (95% CL): -0.230 (0.120), p=0.09
Power et al. 2014 Longitudinal study, n=584 adults females, mean age 61 years	Mean (SD): • 2.9 (1.9) Tibia Pb (µg/g): Mean (SD): • 10.5 (9.7) Patella Pb (µg/g) mean (SD): • 12.6 (11.7)	Overall cognition	β for 1-age year change in score per 1 SD PbB: -0.013 (-0.044, 0.017)
		Verbal memory	β for 1-age year change in score per 1 SD PbB: 0.006 (-0.037, 0.050)
Seo et al. 2014 Cross-sectional study, n=31 retired female Pb workers, mean age 60.4 years, and 34 controls	Gmean (range): Exposed: 4.07 (0.88–13.5) Controls: 2.00 (1.24–6.47)	Verbal memory	Accuracy % (SD), exposed versus control: • 1-back test: 55.9 (19.8) versus 65.4 (19.4), p=0.056 • **2-back test: 61.4 (20.1) versus 77.2 (15.6), p=0.001***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Shih et al. 2006 Cross-sectional study, n=985 adults, mean age 59.4 years	Mean (SD): • 3.46 (2.23) Tibia Pb (µg/g) mean (SD): • 18.72 (11.24)	Language	• **B per 1 µg/g tibia Pb: -0.0083 (0.0023), p≤0.01***
		Processing speed	• **β per 1 µg/g tibia Pb: -0.0042 (0.0021), p<0.01***
		Eye-hand	• **β per 1 µg/g tibia Pb: -0.0079 (0.0020), p≤0.01***
		Executive function	• **β per 1 µg/g tibia Pb: -0.0075 (0.0019), p≤0.01***
		Verbal memory and learning	• **β per 1 µg/g tibia Pb: -0.0078 (0.0024), p≤0.01***
		Visual memory	• **β per 1 µg/g tibia Pb: -0.0067 (0.0023), p≤0.01***
		Visuoconstruction	• **β per 1 µg/g tibia Pb: -0.0122 (0.0027), p≤0.01***
Weisskopf et al. 2007 Longitudinal study cohort, n=1,089 males, mean age 68.7 years	Median (IQ range): • 5 (3–6) Tibia Pb (µg/g) median (IQ range): • 20 (13–28) Patella Pb (µg/g) median (IQ range): • 25 (17–37)	Vocabulary	**β per 3 µg/dL increase in PbB: -1.26 (-2.08, -0.44), p=0.003***
		Visuoconstruction (patella Pb)	**β per IQR: -0.067 (-0.11, -0.02), p=0.0041***
		Pattern comparison latency (tibia Pb)	**β: 0.079 (0.04, 0.12), p=0.0004***
Weuve et al. 2006 Longitudinal study cohort, n=915 males, mean age 68.7 years	Median (IQ range): • 5.2 (2.9) • 94% <10	Cognitive function	Change in MMSE score per IQR in PbB, 3 µg/dL: • **ALAD-2: IQR (95% CL): -0.29 (-0.56, -0.02)*** • ALAD wildtype: IQR (95% CL): -0.05 (-0.16, 0.06)

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Weuve et al. 2009 Longitudinal study cohort, n=587 females, mean age 61 years	Mean (SD): • 2.9 (1.9) Tibia Pb (µg/g) median (SD): • 10.5 (9.7) Patella Pb (µg/g) median (SD): • 12.6 (11.6)	Cognitive function	Change in score per 1 SD in PbB or bone Pb: • PbB: -0.016 (-0.071, 0.039), p=0.57 • **Tibia: -0.051 (-0.099, -0.003), p=0.04*** • Patella Pb: -0.033 (-0.080, 0.014), p=0.17
Wright et al. 2003b Longitudinal study cohort, n=736 males, mean age 68.2 years	Mean (SD): • All: 4.5 (2.5) • Q1: 2.5 • Q2: 4.0 • Q3: 5.9 • Q4: 8.9 Tibia Pb (µg/g) median (SD): • 22.4 (15.3) Patella Pb (µg/g) median (SD): • 29.5 (21.2)	MMSE score	Adjusted OR with 1 µg/dL increase in PbB or 1 µg/g increase in bone Pb: • **PbB: 1.21 (1.07, 1.36)*** • **Patella Pb: 1.02 (1.00, 1.03)*** • **Tibia Pb: 1.02 (1.00, 1.04)*** Effect of age increased with increasing PbB. β for age with increasing Pb for PbB quartile (95% CL): • **Q1 -0.04 (-0.07, -0.02)*** • **Q2 -0.04 (-0.08, -0.01)*** • **Q3 -0.09 (-0.13, -0.06)*** • **Q4 -0.12 (-0.17, -0.02)***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Mood and behavior			
Bouchard et al. 2009 Cross-sectional study, n=1,987 adults (age 20–39 years)	Gmean±GSD (range): • 1.24 (1.96) • 99%≤10 • Q1: 0.6 • Q2: 0.9 • Q3: 1.2 • Q4: 1.3 • Q5: 3.0	Major depressive disorder	• **Adjusted ORs for PbB for Q5 relative to Q1: 2.32 (1.13, 4.75); p-trend=0.05*** • **Eliminating current smokers, adjusted ORs for PbB for Q5 relative to Q1: 2.93 (1.24, 6.92); p-trend=0.03***
		Panic disorder	• **Adjusted ORs for PbB for Q5 relative to Q1: 4.94 (1.32, 18.48); p-trend=0.02*** • **Eliminating current smokers, adjusted ORs for PbB for Q5 relative to Q1: 9.57 (1.28, 71.43); p-trend=0.01***
		Generalized anxiety disorder	• Adjusted ORs for PbB for Q5 relative to Q1**:** 1.53 (0.39, 5.96); p-trend=0.78 • Eliminating current smokers, adjusted ORs for PbB for Q5 relative to Q1: 1.59 (0.19, 13.31); p-trend=0.44
Buser and Scinicariello 2017 Cross-sectional study of 3,905 adults (age ≥20 years) from NHANES 2011–2012	Cohort stratified into PbB quartiles: • Q1: <0.7 • Q2: 0.70–1.06 • Q3: 1.07–1.67 • Q4: >1.67	Depression	Adjusted OR for depression symptoms in adult females (age 20–47 years) associated with increasing PbB: • **Q3: 1.86 (1.01, 3.41, p<0.05*** • **Q4: 2.97 (1.01, 8.74), p<0.05***
Golub et al. 2010 Cross-sectional study of 4,195 adults (age ≥20 years) from NHANES 2005–2006	Cohort stratified into PbB quartiles: • Q1: <0.88 • Q2: 0.89–1.40 • Q3: 1.41–2.17 • Q4: 2.18–26.4		Adjusted OR for depression symptoms was elevated in PbB quartile 3 (95% CI): • **Q3: 1.25 (1.07, 1.47)***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Opler et al. 2004 Case-control study, n=44 schizophrenia cases and 75 matched controls from birth cohorts	Cohort stratified into <15 or ≥15 µg/dL based on 2nd trimester ALA measurements	Schizophrenia	Adjusted OR for schizophrenia associated with high (≥15 µg/dL) prenatal PbB: 2.43 (0.99, 5.96), p=0.051
Opler et al. 2008 Case-control study, n=71 schizophrenia cases and 129 matched controls	Cohort stratified into <15 or ≥15 µg/dL based on 2nd trimester ALA measurements	Schizophrenia	Adjusted OR for schizophrenia associated with high (≥15 µg/dL) prenatal PbB: **1.92 (1.05, 3.87), p=0.03***
Rajan et al. 2007 Longitudinal study cohort, n=1,075 males, mean age 67.1 years	Mean (SD): • All: 6.2 (4.1) Tibia Pb (µg/g) median (SD): • 22.1 (13.8) Patella Pb (µg/g) median (SD): • 31.4 (19.6)	Somatization, tibia Pb	Adjusted OR for inter quartile increases in tibia Pb (14 µg/g) or patella Pb (20 µg/g): **1.21 (1.01, 1.46)***
		Global severity index, patella Pb	**OR: 1.23 (1.02, 1.47)***
Rhodes et al. 2003 Longitudinal study cohort, n=526 males, mean age 67.1 years	Mean (SD): • 6.3 (4.2) Tibia Pb (µg/g) median (SD): • 21.9 (13.5) Patella Pb (µg/g) median (SD): • 32.1 (19.8)	Phobic anxiety	**Adjusted OR (95% CL) for inter quintile increases in patella Pb (8.9 µg/dL: 1.91 (1.01, 3.61)***
		Combined symptoms	**Adjusted OR (95% CL) for inter quintile increases** • **PbB OR: 2.91 (1.39, 6.09)*** • **Tibia Pb OR: 2.08 (1.06, 4.07)*** • **Patella Pb OR: 3.62 (1.62, 8.08)***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Scinicariello and Buser 2015 Cross-sectional study of 2,892 adults (age 20–39 years) from NHANES 2007–2010	**PbB:** Gmean (GSD) • 0.96 (0.02).	Depression	Adjusted OR for depression symptoms was not associated with increasing PbB (ORs were not reported).
Neuromotor neurosensory function			
Hwang et al. 2009 Cross-sectional study, n=259 male steel workers, mean age 36.0 years	Mean (SD): 5.43 (3.46)	Hearing loss	Adjusted OR for hearing loss (>25 dB) at 3,000–8,000 Hz in PbB categories relative to ≤4 µg/dL: Loss at 3000 Hz • 4–7 µg/dL: 0.75 (0.17, 3.29) • **≥7 µg/dL: 4.49 (1.28, 15.8); p<0.005*** Loss at 4000 Hz: • **4–7 µg/dL: 3.54 (1.40, 8.97)*** (p-value not reported) • **≥7 µg/dL: 6.26 (2.35, 16.6); p<0.005*** Loss at 6000 Hz: • 4–7 µg/dL: 2.11 (0.94, 4.47) • **≥7 µg/dL: 3.06 (1.27, 7.39); p<0.05***
Ji et al. 2013 Cross-sectional study, n=1,795 males and 1,798 females, age >50 years (median 61.2)	Mean (SD): • Females: 2.17 (0.06) • Males: 3.18 (0.12)	Walking speed	Mean change in walking speed (ft/sec) for PbB quintile relative to Q1 (≤1.2 µg/dL): • PbB 1.3–≤1.6. β: -0.024 (-0.112, 0.064), p=0.58 • PbB 1.7–≤2.1, β: -0.027 (-0.118, 0.063), p=0.54 • **PbB 2.2–≤2.9, β: -0.104 (-0.187, -0.021), p=0.02*** • **PbB 3.3–≤53.0, β: -0.114 (-0.191, -0.038), p=0.01*** • **P-trend=0.005***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Ji et al. 2015 Longitudinal study cohort, n=807 males, mean age 69 years	Mean (SD): 5.0 (2.7) • % <10: 96% Bone Pb, µg/g (SD) • Patella: 28.0 (18.4) Tibia: 21.2 (13.3)	Tremor	OR for tremor by PbB quintile (95% CL): • Q5 (8–28), PbB: 0.84 (0.38, 1.86), p=0.72 • Q5 (40–165), patella Pb: 0.83 (0.31, 2.19), p=0.41 • Q5 (30–126): tibia Pb: 1.08 (0.46, 2.53), p=0.60
Muldoon et al. 1996 Cross-sectional study, n=530 adult women, mean age 70 years	Mean (SD): • All: 4.8 (0.4) • Rural: 4.5 (0.4) • Urban: 5.4 (0.4) • Low: <4 • Medium: 4–7 • High: >7	Pegboard	OR for poor performance (low PbB reference) in the rural cohort: ANOVA, p=0.98 • Medium PbB: OR (95% CL): 1.37 (0.71, 2.65) • High PbB: OR (95% CL): 1.16 (0.45, 3.01)
		Upper extremity	ANOVA, p<0.01, in the rural cohort • Medium PbB: OR (95% CL): 1.39 (0.73, 2.65) • **High PbB: OR (95% CL): 2.43 (1.01, 5.83)***
		Lower extremity	ANOVA, p<0.01, in the rural cohort • Medium PbB: OR (95% CL): 1.29 (0.68, 2.47 • **High PbB: OR (95% CL): 2.84 (1.19, 6.74)***
Neurological disease			
Fang et al. 2010 Case-control study, n=184 male ALS cases and 194 matched controls, mean age 63 years	Mean (range): • Controls: 1.76 (0.32–6.90) • Cases: 2.41 (0.72–7.58)	ALS	**Adjusted OR for ALS for doubling of PbB:** • **All cases (n=184): 1.9 (1.3, 2.7)*** • **Excluding progressive muscular atrophy and primary lateral sclerosis (n=151): 1.8 (1.2, 2.5)***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Kamel et al. 2002 Case-control study, n=109 ALS cases and 256 matched controls, age 30–80 years	Mean (range): • Cases: 3 of 194 had PbB >10 • Controls: <10 µg/dL	ALS	• Adjusted OR for ALS (for a 1 µg/dL increase in PbB: **1.9 (1.4, 2.6)*** • Adjusted OR for ALS relative to <2 µg/dL: o **3–4 µg/dL: 14.3 (3.0, 69.3)*** o **5–14 µg/dL: 24.5 (4.3, 139.3)***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 10 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Asterick indicates association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.

ALA = aminolevulinic acid; ALAD-2 = delta-aminolevulinic acid dehydratase allele; ALS = amyotrophic lateral sclerosis; ANOVA = analysis of variance; CI = confidence interval; CL = confidence limit; Gmean = geometric mean; GSD = geometric standard deviation; IQ = intelligence quotient; IQR = interquartile range; MMSE = Mini-Mental Status Examination; OR = odds ratio; Pb = lead; RR = relative risk; SD = standard deviation; SE = standard error

associations ($p \leq 0.05$) between performance on cognitive tests and increasing tibia Pb, but not for PbB (Shih et al. 2006). The cohort mean blood Pb was 3.46±2.2 (SD) µg/dL. Cognitive function evaluated included language, processing speed, executive function, verbal memory and learning, and visuoconstruction. The effect sizes were substantially attenuated by race/ethnicity and years of educational and were no longer significant ($p<0.05$) when adjusted for these covariates. A cross-sectional study of approximately 500 adult females from the Study of Osteoporotic Fractures found significant associations ($p \leq 0.05$) between performance on cognitive tests and increasing PbB (Muldoon et al. 1996). The odds of performing worse on visual attention and short-term memory tests were significantly decreased ($p \leq 0.05$) in a PbB stratum 4–7 and to >7 µg/dL compared to stratum <4 µg/dL.

Altered mood and behavior. Several studies have examined associations between Pb exposure assessed from blood or bone Pb and symptoms of psychiatric disorders (Table 2-32). Several studies have analyzed cross-sectional data from NHANES to explore associations between depression symptoms and PbB (Bouchard et al. 2009; Buser and Scinicariello 2017; Golub et al. 2010; Scinicariello and Buser 2015). Three studies found associations between PbB and depression in adult populations that had geometric mean PbBs that were 2–3 µg/dL compared to populations that have PbBs <1 (Bouchard et al. 2009; Buser and Scinicariello 2017; Golub et al. 2010). Buser and Scinicariello (2017) found stronger associations in adult women than in men. Associations between psychiatric disorders and Pb exposure metrics have also been studied in longitudinal studies (Rajan et al. 2007; Rhodes et al. 2003). Two studies of cohorts from the Normative Aging Study found significant ORs for blood or bone Pb and various psychiatric symptoms in males (mean age 67±7, SD), including somatization, phobic anxiety, and composite indices of distress. Mean PbBs in these cohorts were 6±4 (SD) µg/dL. Associations between PbB and psychiatric disorders have also been found in case-control studies (Opler et al. 2004, 2008). The largest was a study of 71 schizophrenia cases and 129 matched controls (Opler et al. 2008). The adjusted OR for schizophrenia was 1.92 (95% CI 1.05, 3.87) for the PbB stratum ≥15 µg/dL compared to 15 µg/dL. Because individual PbB data were not available, subjects were categorized into the high (<15 µg/dL) or low (15 µg/dL) PbB categories based on measurements of serum ALA and a regression model relating PbB and ALA derived from a different population (Graziano et al. 1990). Although the accuracy of the method for assigning subjects from Graziano et al. (1990) into low or high categories was, on average, approximately 90%, uncertainty in the actual regression model is likely to have resulted in some misclassification of individuals.

Altered neuromotor neurosensory function. Several studies have examined associations between Pb exposure assessed from blood or bone Pb and performance on tests of neuromotor or neurosensory

function (Table 2-32). The largest study analyzed data from NHANES III (1988–1994) and found no association (p=0.34) between concurrent PbB and simple visual reaction time in a cohort of 5,700 adults (age 20–50 years; Krieg et al. 2005). The geometric mean PbB was 2.51 µg/dL (range 0.7–42) and 96% of the cohort was <10 µg/dL. A more recent analysis of data from NHANES (1999–2002) examined walking speed in cohorts of approximately 1,800 males or females and found a significant association between increasing PbB and decreasing walking speed in females in a PbB stratum 2.2–≤2.9 µg/dL compared to 1.6 µg/dL; there was a significant trend with increasing PbB (Ji et al. 2013). This outcome is consistent with a smaller cross-sectional study of women (mean age 70±4 years) that found significant decreases in upper and lower extremity reaction times in association with increasing PbB (Muldoon et al. 1996). A longitudinal study of a cohort from the Normative Aging Study found no significant associations between bone or blood Pb and hand tremor in males (mean age 60±7 years; Ji et al. 2015). The mean PbB for the cohort was 5.0±2.7 (SD) µg/dL.

Neurological diseases. Possible associations between Pb exposure and risk of ALS have been examined in case-control studies (Fang et al. 2010; Kamel et al. 2002). A case-control study of 184 male ALS cases and 194 matched controls found a significant association between increasing PbB and ALS (Fang et al. 2010). The mean PbB for cases was 2.41 µg/dL (range 0.72–7.58 µg/dL). A case-control study of 109 ALS cases (43 females, 66 males) and 194 matched controls estimated the OR for ALS to be 1.9 (95% CL 1.4, 2.6) for a 1 µg/dL increase in PbB (Kamel et al. 2002).

Associations Between Bone Pb and Neurological Effects in Adults. Decrements in neurological function in adults have also been associated with bone Pb (Table 2-33). In general, these studies provide further support for associations between Pb exposure and neurobehavioral function, including decrements in cognitive function, altered neuromotor and neurosensory function, and altered behavior and mood. Most of these studies are of cohorts from longitudinal health studies: Boston Memory Study (Bandeen-Roche et al. 2009; Glass et al. 2009; Shih et al. 2006), Nurses' Health Study (Power et al. 2014; Weuve et al. 2009), or Normative Aging Study (Eum et al. 2013; Grashow et al. 2013a, 2013b, 2015; Ji et al. 2015; Park et al. 2010; Payton et al. 1998; Power et al. 2014; Rajan et al. 2007, 2008; Rhodes et al. 2003; Schwartz et al. 2005; Wang et al. 2007; Weisskopf et al. 2004, 2007; Wright et al. 2003b). These studies have provided both cross-sectional and longitudinal assessments of associations between bone Pb (and PbB) and neurological function in adult populations. Longitudinal designs are particularly important because they allow age-related declines in cognitive function to be assessed. Longitudinal studies have found that associations between bone Pb and cognitive function (learning, memory) persist when adjustments are made for age (Bandeen-Roche et al. 2009; Dorsey et al. 2006; Eum et al. 2013; Grashow

et al. 2013a; Khalil et al. 2009; Payton et al. 1998; Power et al. 2014; Rajan et al. 2008; Schwartz et al. 2005; Seegal et al. 2013; Shih et al. 2006; Stewart et al. 2002; van Wijngaarden et al. 2009; Weisskopf et al. 2007; Weuve et al. 2009, 2013; Wright et al. 2003b). Rates of decrement in cognitive function with age have been found to be more severe in association with increasing bone Pb (Power et al. 2014; Schwartz et al. 2005; Wang et al. 2007; Weisskopf et al. 2004, 2007; Wright et al. 2003b).

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Bandeen-Roche et al. 2009	965 adults, age: 50–70 years[a]	↑ T	–	–	Learning, memory, executive function, eye-hand coordination
Coon et al. 2006	121 adult cases, 414 controls, age: 50–>80 years	–	↑ 0[d]	–	Parkinson's disease
Dorsey et al. 2006	652 adult lead workers, age: 20–70 years	↑ P ↑ T	↑ P ↑ T	↑ P ↑ T	Reaction time, executive function. manual dexterity, vibration threshold, depression
Eum et al. 2013	789 adult males[b], age: 68 years (median)	↑ P ↑ T	–	–	Memory, verbal and written skills, executive function
Eum et al. 2015	100 adult cases, 194 controls, age: 60 years (mean)	–	↑ P ↑ T	–	Interaction between lead, amyotrophic lateral sclerosis and hemochromatosis gene polymorphisms
Glass et al. 2009	1,001 adults[a], age: 50–70 years	↑ T	↑ T	–	Interaction between lead and psychosocial hazard scale for eye-hand coordination, executive function, language

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Grashow et al. 2013a	51 adult males[b], age: 75 years (mean)	↑ P 0 T	–	–	Fear conditioning
Grashow et al. 2013b	362 adult males[b], age: 69 years (mean)	–	↑ P ↑ T	–	Manual dexterity
Grashow et al. 2015	164 adult males[b], age: 80 years (mean)	–	0 P ↑ T	–	Olfactory function
Ji et al. 2015	672 adult males[b], age: 50–98 years	–	0 P 0 T	–	Tremor (no association in adjusted models)
Kamel et al. 2002	109 adult cases, 256 controls, age: 30–80 years	–	0 P 0 T	–	Amyotrophic lateral sclerosis (no association in adjusted models)
Khalil et al. 2009	83 adult workers and 51 controls, age: >55 years	↑ T	–	–	Learning, memory
Park et al. 2010	448 adult males[b], age: 65 years (mean)	–	↑ P ↑ T	–	Hearing function
Payton et al. 1998	141 adult males[b], age: 67 years (mean)	↑ T	–	–	Memory, visual-spatial performance
Power et al. 2014	584 adult females[c], age: 60–74 years	0 P 0 T	–	–	Learning, memory, executive function
Rajan et al. 2007	1,075 adult males[b], age: 48–94 years	–	–	↑ P ↑ T	Psychiatric symptoms
Rajan et al. 2008	982 adult males[b], age: 49–>72 years	0 P ↑ T	–	–	Visual-spatial performance
Rhodes et al. 2003	536 adult males[b], age: 48–70 years	–	–	↑ P ↑ T	Anxiety
Schwartz et al. 2000b	535 lead workers,	↑ T	↑ T	–	Memory, executive function, manual

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

Reference	Population	Neurological outcome			
		Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
	age: 56 years (mean)				dexterity
Schwartz et al. 2001	803 exposed lead workers and 135 controls, age: 40 years (mean)	0 T	0 T	0 T	Learning, memory, executive function, manual dexterity, grip strength, mood and depression
Schwartz et al. 2005	576 exposed lead workers, age: 41 years (mean)	↑ T	↑ T	↑ T	Executive function, manual dexterity, vibration threshold, depression
Seegal et al. 2013	241 capacitor workers, age: 64 years (mean)	↑ T	↑ T	–	Learning, memory, executive function, manual dexterity
Shih et al. 2006	991 adults[a], age: 50–70 years	↑ T	↑ T	–	Learning, memory, executive function, manual dexterity
Stewart et al. 2002	529 lead workers, age: 40–>70 years	↑ T	↑ T	–	Learning, memory, executive function, reaction time, manual dexterity
van Wijngaarden et al. 2009	47 adults, age: 55–67 years	↑ C	–	–	Learning, memory
Wang et al. 2007	358 adult males[b], age: 67 years (median)	↑ T	–	–	Interaction between lead and hemochromatosis gene polymorphisms on learning, memory, executive function
Weisskopf et al. 2004	466 adult males[b], age: 68 years (mean)	↑ P	–	–	Memory, verbal and written skills, executive function
Weisskopf et al. 2007	761 adult males[b], age: 69 years (mean)	↑ P ↑ T	–	–	Memory, visual-spatial performance
Weisskopf et al. 2010	330 adult cases and 308 controls,	–	↑ T	–	Parkinson's disease

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

Reference	Population	Neurological outcome			
		Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
	age: 67 years (mean)				
Weuve et al. 2009	587 adult females[c], age: 47–74 years	0 P ↑ T	–	–	Learning, memory
Weuve et al. 2013	101 cases and 50 controls, age: 55–80 years	0 P ↑ T	–	–	Learning, memory (stronger association with lead among Parkinson's disease cases)
Wright et al. 2003b	736 adult males[b], age: 68 years (mean)	↑ P ↑ T	–	–	Memory, verbal and written skills, executive function

[a]Boston Memory Study.
[b]Normative Aging Study.
[c]Nurses Health Study.
[d]Whole-body lead predicted from bone lead.

↑ = positive association; ↓ = negative association; 0 = no association; – = not reported; C = calcaneous bone; P = patella; Pb = lead; T = tibia; O = other

Bone Pb has been associated with declines in neuromotor and neurosensory function. Neuromotor outcomes that have been associated with bone Pb include tremor, Parkinson's disease, and ALS (Coon et al. 2006; Eum et al. 2015; Weisskopf et al. 2010; Weuve et al. 2013). Neurosensory outcomes include decrements in olfactory and hearing function, vibration threshold, and manual dexterity (Dorsey et al. 2006; Grashow et al. 2013b, 2015; Park et al. 2010; Schwartz et al. 2000b; 2005; Shih et al. 2006; Stewart et al. 2002). Bone Pb has also been associated with increased risk or odds of psychiatric symptoms such as anxiety and depression (Dorsey et al. 2006; Rajan et al. 2007; Rhodes et al. 2003; Schwartz et al. 2005).

Mechanisms of Action. Numerous cellular mechanisms are likely involved in Pb-induced alterations in neurological function. Pb disrupts cellular function through diverse mechanisms, including displacement of metal ion co-factors from protein, enzyme inhibition, inhibition of ion transport, disruption of cell and

mitochondrial membrane potentials, disruption of intracellular calcium homeostasis oxidative stress, and inflammation and endocrine disruption (see Section 2.21). All of these Pb mechanisms have been demonstrated in neuronal tissues, although there is no consensus on which mechanisms dominate. Evidence for various mechanisms that may participate in Pb neurotoxicity are summarized in this section. The reader is referred to references cited therein for more detailed information (Bouton and Pevsner 2000; Bressler et al. 1999; Cory-Slechta 1995, 2003; EPA 2014c; Gilbert and Lasley 2002; Lasley and Gilbert 2000; Nihei and Guilarte 2002; Suszkiw 2004; Toscano and Guilarte 2005; Zawia et al. 2000; Zhang et al. 2015).

Pb can affect the nervous system by multiple mechanisms, one of the most important of which is by mimicking calcium action and/or disruption of calcium homeostasis. Because calcium is involved as a cofactor in many cellular processes, it is not surprising that many cell-signaling pathways are affected by Pb. One pathway that has been studied in more detail is the activation of protein kinase C (PKC). PKC is a serine/threonine protein kinase involved in many processes important for synaptic transmission such as the synthesis of neurotransmitters, ligand-receptor interactions, conductance of ionic channels, and dendritic branching. The PKC family is made up of 12 isozymes, each with different enzymatic cofactor requirements, tissue expression, and cellular distributions. The γ-isoform is one of several calcium-dependent forms of PKC and is a likely target for Pb neurotoxicity; it is neuron-specific and is involved in long-term potentiation (see below), spatial learning, and memory processes. Pb has the capacity to both activate and inhibit PKCs. Studies have shown that micromolar concentrations of Pb can activate PKC-dependent phosphorylation in cultured brain microvessels, whereas picomolar concentrations of Pb activate preparations of PKC *in vitro*. Interestingly, studies in rats exposed to low Pb levels have shown few significant changes in PKC activity or expression, suggesting that the whole animal may be able to compensate for Pb PKC-mediated effects compared to a system *in vitro*. PKC induces the formation of the AP-1 transcriptional regulatory complex, which regulates the expression of a large number of target genes via AP-1 promoter elements. A gene regulated by Pb via AP-1 promoters is the glial fibrillary acidic protein (GFAP), an astrocytic intermediate filament protein that is induced during periods of reactive astrocytic gliosis. Astrocytes, along with endothelial cells, make up the blood-brain barrier. Studies in rats exposed chronically to low Pb levels have reported alterations in the normal pattern of GFAP gene expression in the brain, and the most marked long-lasting effects occurred when the rats were exposed during the developmental period. In immature brain microvessels, most of the protein kinase C is in the cytosol, whereas in mature brain microvessels, this enzyme is membrane-bound. Activation of protein kinase C in other systems is known to result in a change in distribution from cytosol to membrane, and has been observed with exposure of immature brain microvessels to Pb. An inhibition of

microvascular formation has been observed with Pb concentrations that are effective in activating PKC. Thus, it appears that premature activation of PKC by Pb may impair brain microvascular formation and function, and at high levels of Pb exposure, may account for gross defects in the blood-brain barrier that contribute to acute Pb encephalopathy. The blood-brain barrier normally excludes plasma proteins and many organic molecules, and limits the passage of ions. With disruption of this barrier, molecules such as albumin freely enter the brain, and ions and water follow. Because the brain lacks a well-developed lymphatic system, clearance of plasma constituents is slow, edema occurs, and intracranial pressure rises. The particular vulnerability of the fetus and infant to the neurotoxicity of Pb may be due in part to immature brain microvessels, which affect the blood brain barrier, and to the lack of the high-affinity Pb-binding protein in astroglia, which sequester Pb.

Another enzyme altered by Pb is calmodulin, a major intracellular receptor for calcium in eukaryotes. Normally, calcium induces a conformational change in calmodulin that converts the protein to an active form; Pb improperly activates the enzyme. Some studies suggest that activation of calmodulin by Pb results in protein phosphorylation in the rat brain and brain membrane preparations and can alter proper functioning of cAMP messenger pathways. It has been shown that calmodulin can mediate gene expression via calmodulin-dependent kinases. The effects of Pb on gene expression via activation of calmodulin are not as marked as those via PKC because activation of calmodulin requires 100-fold more Pb than activation of PKC.

Pb also can substitute for zinc in some enzymes and in zinc-finger proteins, which coordinate one or more zinc cations as cofactors. The substitution of Pb for zinc in zinc-finger proteins can have significant effects on *de novo* expression of the bound proteins and in any genes transcriptionally-regulated by a particular protein. Pb has been found to alter the binding of zinc-finger transcriptional regulator Sp1 to its specific DNA sequences. This is accompanied by aberrant expression of Sp1 target genes such as myelin basic protein and proteolipid protein. Another gene regulated by Sp1 is the β-amyloid precursor protein (APP) gene. Recently, it was shown that Pb exposure in neonatal rats transiently induces APP mRNA, which is overexpressed with a delay of 20 months after exposure to Pb has ceased. In contrast, APP expression, and Sp1 activity, as well as APP and β-amyloid protein levels, were unresponsive to Pb during old age, suggesting that exposures occurring during brain development may predetermine the expression and regulation of APP later in life. It has been suggested that the multiple responses to Pb exposure are due to Pb specifically targeting zinc-finger proteins found in enzymes, channels, and receptors.

Pb affects virtually every neurotransmitter system in the brain, but most information on changes is available on the glutamatergic, dopaminergic, cholinergic, and gamma-aminobutyric acid (GABA). Of these, special attention has been paid to the glutamatergic system and its role in hippocampal long-term potentiation (LTP). Hippocampal LTP is a cellular model of learning and memory characterized by a persistent increase in synaptic efficacy following delivery of brief tetanic stimulation (high-frequency stimulation). LTP provides a neurophysiological substrate for learning and storing information and is thought to utilize the same synaptic mechanisms as the learning process. LTP is established only with complex patterns of stimulation but not with single pulse stimulation. While it has been studied primarily in the hippocampal subregions CA1 and dentate gyrus, it can also be evoked in cortical areas. Exposure of intact animals or tissue slices to Pb diminishes LTP by a combination of three actions: increasing the threshold for induction, reducing the magnitude of potentiation, and shortening its duration by accelerating its rate of decay. This effect on LTP involves actions of Pb on glutamate release (presynaptic effects) and on the N-methyl-D-aspartate (NMDA) receptor function. Pb exposure inhibits release of glutamine from pre-synaptic endings, which may be mediated, in part, by altered pre-synaptic vesicle formation or activation. Studies have shown that the effects of Pb vary as a function of the developmental exposure period and that Pb exposure early in life is critical for production of impaired LTP in adult animals. LTP is more readily affected by Pb during early development, but exposure initiated after weaning also affects synaptic plasticity. Studies also have shown that both LTP magnitude and threshold exhibit a U-shape type response with increasing Pb doses. While LTP is primarily a glutamatergic phenomenon, it can be modulated through input from extrahippocampal sources including noradrenergic, dopaminergic, and cholinergic sources.

Studies in animals treated with Pb (PbB 30–40 μg/dL) have shown that induction of pair-pulse facilitation in the dentate gyrus is impaired. Since the phenomenon is mediated primarily by increased glutamate release, the reasonable assumption is that Pb reduces glutamate release. Support for this assumption is also derived from studies in which depolarization-induced hippocampal glutamate release was reduced in awake animals with similar PbB. This inhibition of glutamate release was shown to be due to Pb-related decrements in a calcium-dependent component. The exact mechanism for the inhibition of glutamate release by Pb is not known, but is consistent with Pb at nanomolar concentrations preventing maximal activation of PKC, rather than Pb blocking calcium influx into the presynaptic terminal through voltage-gated calcium channels. Reduced glutamate release can be observed in rats exposed from conception through weaning and tested as adults, when Pb was no longer present, suggesting that a direct action of Pb is not necessary and that other mechanisms, such as reductions in synaptogenesis, also may be involved. As with LTP, depolarization-evoked hippocampal glutamate release in rats treated chronically

with several dose levels of Pb exhibited a U-shaped response. That is, glutamate release was inhibited in rats treated with the lower Pb doses, but not in those exposed to the higher concentrations of Pb. Although speculative, this was interpreted as Pb at the higher doses mimicking calcium in promoting transmitter release and overriding the inhibitory effects of Pb that occur at lower Pb levels.

The findings regarding the effects of Pb on postsynaptic glutamatergic function have been inconsistent across laboratories, but a direct inhibitory action of Pb on the NMDA receptor is unlikely at environmentally relevant exposure levels. Some studies have shown that continuous exposure of rats from gestation to adulthood results in a significant increase in NMDA receptor numbers in cortical areas, hippocampus, and forebrain. This was observed in the forebrain at PbB of 14 μg/dL. Other studies, however, have reported changes in the opposite direction and the reason for the discrepancy in results may be due to the different exposure protocols used. From a functional point of view, it seems plausible that a Pb-induced reduction in presynaptic transmitter release be compensated by a postsynaptic increase in number or density of receptors in order to maintain a viable function.

The dopaminergic system also has a role in aspects of cognitive function since lesions of dopaminergic neurons impair behavior in various types of learning and cognitive tasks. Also, individuals who suffer from Parkinson's disease, a disease associated with dopamine depletion in the striatum, sometimes show difficulties in cognitive functions. Most of the evidence available suggests that Pb may impair regulation of dopamine synthesis and release, indicating a presynaptic site of action. Studies in animals often report opposing effects of Pb on nigrostriatal and mesolimbic dopamine systems regarding receptor binding, dopamine synthesis, turnover, and uptake. Postweaning exposure of rats to Pb resulted in supersensitivity of D1 and D2 dopamine receptors, which can be interpreted as a compensatory response to decreased synthesis and/or release of dopamine. Lesions to the nucleus accumbens (a terminal dopamine projection area) and the frontal cortex result in perseverative deficits, suggesting that the mesolimbic system is preferentially involved in the effects of Pb. Results of studies using dopaminergic compounds seem to indicate that changes in dopamine systems do not play a role in the effects of Pb on learning. Instead, it has been suggested that changes in dopaminergic systems may play a role in the altered response rates on Fixed-Interval (FI) schedules of reinforcement that have been observed in animals exposed to Pb. This type of change has been thought to represent a failure to inhibit inappropriate responding.

It is widely accepted that the cholinergic system plays a role in learning and memory processes. Some cognitive deficits observed in patients with Alzheimer's disease have been attributed to impaired cholinergic function in the cortex and hippocampus. Exposure to Pb induces numerous changes in

cholinergic system function, but the results, in general, have been inconsistently detected, or are of opposite direction in different studies, which may be attributed to the different exposure protocols used in the different studies. However, it is clear that Pb blocks evoked release of acetylcholine and diminishes cholinergic function. This has been demonstrated in central and peripheral synapses. Studies with the neuromuscular junction showed that Pb reduces acetylcholine release by blocking calcium entry into the terminal. At the same time, Pb prevents sequestration of intracellular calcium by organelles, which results in increased spontaneous release of the neurotransmitter. Studies *in vitro* show that Pb can block nicotinic cholinergic receptors, but it is unclear whether such effects occur *in vivo* or whether Pb alters the expression of nicotinic cholinergic receptors in the developing brain. Evidence for an involvement in Pb-induced behavioral deficits has been presented based on the observation that intrahippocampal transplants of cholinergic-rich septal and nucleus basalis tissue improve the deficits and that treatment with nicotinic agonists can improve learning and memory impairments following perinatal Pb treatment of rats. Chronic exposure of rats to Pb has resulted in decreased muscarinic-receptor expression in the hippocampus. Whether or not Pb exposure during development alters muscarinic receptor sensitivity is unclear as there are reports with opposite results. The preponderance of the binding data suggests that Pb does not directly affect muscarinic receptors with the exception of the visual cortex, where Pb may have a direct inhibitory effect on muscarinic receptors from rods and bipolar cells of the retina.

Pb exposure decreases spontaneous and evoked release of GABA in rats and in hippocampal cultures and brain slices. In general, GABA functions in the brain as a post-synaptic inhibitory transmitter. The role of changes in GABA release in the neurotoxicity of Pb has not been firmly established.

Various other mechanisms may also contribute to Pb neurotoxicity. Exposure to Pb has also been shown to stimulate inflammation in a variety of tissues, including neuronal tissue (see Section 2.21). Contributing mechanisms include alterations in levels of ROS, activation of nuclear activation factor NFκβ, cytokine release, and alterations in prostaglandin metabolism. Pb exposure has been shown to alter neuronal nitric oxide signaling (NOS) and the hormone levels regulated by the hypothalamic-pituitary-thyroid axis.

2.17 REPRODUCTIVE

Overview. Numerous epidemiological studies have evaluated effects of Pb on male and female reproductive function. In males, most exposures were occupational, with mean PbB >10 µg/dL. In general, studies in males show consistent evidence of reproductive effects on sperm (production, motility,

viability, and morphology), semen quantity and composition, serum reproductive hormone levels, and fertility, with severity of effects increasing with increasing PbB. In contrast to exposure of males, most exposures of females were non-occupational, with mean PbB ≤10 µg/dL. Studies investigating effects on serum reproductive hormone levels, fertility, spontaneous abortion, and preterm birth provide mixed results; thus, dose-dependence of effects in females is difficult to assess.

The following reproductive effects in males have been associated with PbB:

- ≤10 µg/dL:
    - Increased serum testosterone; evaluated in a few studies with mixed results.
    - Effects on sperm (decreased sperm count, concentration, motility, and viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm); evaluated in a few studies with mixed results.
- >10 µg/dL:
    - Altered serum concentrations of reproductive hormones (testosterone, FSH, LH); evaluated in a several studies with mixed results.
    - Effects on sperm (decreased sperm count, concentration, motility, and viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm); corroborated in several studies.
    - Alterations in semen quality (decreased semen volume and altered composition of seminal fluid); evaluated in a few studies.
    - Decreased fertility; evaluated in a few studies.
    - Histopathological changes to the testes (peritubular fibrosis, oligospermia, and vacuolization of Sertoli cells); evaluated in a few studies.

The following reproductive effects in females have been associated with PbB:

- ≤10 µg/dL:
    - Increased serum levels of estradiol, FSH, and LH; studies have mixed results.
    - Decreased fertility; studies have mixed results.
    - Increased spontaneous abortion; studies have mixed results.
    - Increased preterm birth; studies have mixed results.
    - Decreased age at onset of menopause; demonstrated in a few studies.

- >10 µg/dL:
    - Decreased fertility; studies have mixed results.
    - Increased preterm birth; studies have mixed results.

Measures of Exposure. Most studies evaluating effects on male and female reproductive systems used PbB as the biomarker for exposure. More recent studies in men have explored the relationship between the concentration of Pb in semen or spermatozoa and adverse effects (Table 2-34). It has been suggested that semen levels of Pb may be a better biomarker for assessment of male reproductive effects, particularly at low PbB, because no relationship between PbB and Pb levels in semen or spermatozoa has been observed (Hernandez-Ochoa et al. 2005; Mendiola et al. 2011). In women, other biomarkers of exposure include concentration of Pb in plasma (Lamadrid-Figueroa et al. 2007), red blood cells (Perkins et al. 2014), and placenta (Gundacker et al. 2010), and plasma/blood ratio (Lamadrid-Figueroa et al. 2007).

Confounding Factors and Effect Modifiers. Numerous factors may add uncertainty in the interpretation of studies examining associations between PbB and reproductive effects, including overall health, body weight, nutrition, and SES. Exposures to other substances, including recreational drugs, alcohol, therapeutic agents, industrial chemicals, insecticides, and pesticides, also may affect fertility (Foster and Gray 2008). Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome. Some studies examining effects on sperm (discussed below) were conducted on samples obtained at fertility clinics; therefore, other causes for sperm effects could be effect modifiers (additional details are provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 11). In addition, because sperm counts can vary by geographical location, it is important that control and exposed groups are matched for geographic location.

Characterization of Effects in Males. General trends regarding the relationship between PbB and male reproductive effects are shown in Table 2-34. Overall, the dose-effect pattern suggests an increasing severity of toxicity associated with increasing PbB, with effects on sperm at ≤10 µg/dL (discussed in more detail below). At increasing PbB, effects become more severe, with decreased fertility observed at PbB >10 µg/dL and histopathological changes of the testes at PbB of approximately 30 µg/dL. Effects on sperm, including decreased sperm count, concentration, motility, and viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm, have been observed at PbB of ≤10–>50 µg/dL (Alexander et al. 1998; Assennato et al. 1987; Bonde et al. 2002; Cullen et al. 1984;

Hernández-Ochoa et al. 2005; Kasperczyk et al. 2008; Lancranjan et al. 1975; Lerda 1992; Li et al. 2015; Meeker et al. 2008; Moran-Martinez et al. 2013; Telisman et al. 2007; Wildt et al. 1983). However, a few studies showed no association between PbB and adverse effects on sperm (Lancranjan et al. 1975; Mendiola et al. 2011). Decreased semen volume and altered composition of seminal fluid have been observed at PbB >10 µg/dL (Bonde et al. 2002; Naha and Chowdhury 2006; Telisman et al. 2000; Wildt et al. 1983). Decreased fertility has been reported in association with PbB >10–>50 µg/dL (Sallmén et al. 2000b; Shiau et al. 2004), although no effect on fertility was observed in one study of workers with PbB >40 µg/dL (Coste et al. 1991). Histopathological assessment of biopsied testicular tissue from Pb workers (mean PbB 29.0 µg/dL) showed peritubular fibrosis, oligospermia, and vacuolization of Sertoli cells (Braunstein et al. 1978). Evaluations of associations between PbB and serum levels of reproductive hormones show inconsistent results (Table 2-35). At PbB ≤10 µg/dL, positive associations between PbB and serum testosterone levels have been observed (Kresovich et al. 2015; Lewis and Meeker 2015; Meeker et al. 2010; Telisman et al. 2007), whereas negative associations or no effects were reported at PbB >10 µg/dL. No effects on FSH or LH were reported at PbB ≤10 µg/dL, and inconsistent results were observed at PbB >10 µg/dL. Changes in serum levels of reproductive hormones may indicate disruption of the hypothalamic-pituitary-gonadal axis; however, due to inconsistent findings, an association between PbB and endocrine disruption in males has not been firmly established.

Table 2-34. Overview of Effects on the Male Reproductive System Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Effects on sperm (decreased sperm concentration, motility, and viability; increased morphologic abnormalities)	Hernández-Ochoa et al. 2005; Li et al. 2015; Meeker et al. 2008; Telisman et al. 2007
	Effects on hormones (increased serum levels of testosterone and estradiol; decreased serum prolactin and sex-hormone binding globulin)	Kresovich et al. 2015; Lewis and Meeker 2015; Meeker et al. 2010; Telisman et al. 2007
>10–30	Effects on sperm (decreased sperm count, concentration, density, motility, and viability; morphologic abnormalities)	Alexander et al. 1998; Bonde et al. 2002; Moran-Martinez et al. 2013
	Effects on semen (decreased volume)	Bonde et al. 2002
	Decreased fertility	Sallmén et al. 2000b

Table 2-34. Overview of Effects on the Male Reproductive System Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
>30–50	Effects on sperm (decreased count, concentration, motility, viability; morphologic abnormalities)	Hsu et al. 2009; Lancranjan et al. 1975; Lerda 1992; Telisman et al. 2000
	Effects on composition of seminal fluid	Telisman et al. 2000
	Effects on hormones (increased estradiol, LH, FSH; decreased testosterone)	Braunstein et al. 1978; Ng et al. 1991; Telisman et al. 2000
	Histopathological changes to testes (peritubular fibrosis, oligospermia, vacuolization of Sertoli cells)	Braunstein et al. 1978
	Decreased fertility	Sallmén et al. 2000b; Shiau et al. 2004
>50	Effects on sperm (decreased count, concentration, motility, viability; morphologic abnormalities)	Assennato et al. 1987; Cullen et al. 1984; Kasperczyk et al. 2008; Lancranjan et al. 1975; Lerda 1992; Naha and Chowdhury 2006; Wildt et al. 1983
	Effects on semen (decreased volume; altered composition)	Naha and Chowdhury 2006; Wildt et al. 1983
	Effects on hormones (altered serum levels of testosterone, FSH, LH, prolactin)	Assennato et al. 1987; Rodamilans et al. 1988
	Decreased fertility	Sallmén et al. 2000b

FSH = follicle-stimulating hormone; LH = luteinizing hormone

Table 2-35. Effects on Reproductive Hormones Associated with Chronic Exposure to Lead (Pb) in Males

PbB	Hormone							
(µg/dL)	T	FSH	LH	E	P	A	SHBG	Reference
≤10	↑	0	–	–	–	0	0	Kresovich et al. 2015
	↑	0	0	–	–	–	0	Meeker et al. 2010
	↑	–	–	↑	0	–	–	Telisman et al. 2007
	↑	–	–	–	–	–	–	Lewis and Meeker 2015
	0	0	0	–	–	–	–	Mendiola e al. 2011
10–30	0	0	0	–	–	–	–	Hsieh et al. 2009a
	0	0	0	–		–	–	Alexander et al. 1998

Table 2-35. Effects on Reproductive Hormones Associated with Chronic Exposure to Lead (Pb) in Males

PbB (µg/dL)	Hormone							Reference
	T	FSH	LH	E	P	A	SHBG	
30–50	↓	0	0	–	0	–	–	Braunstein et al. 1978
	0	0	0	–	0	–	–	Erfurth et al. 2001
	0	↓	↓	–	–	–	–	Gustafson et al. 1989
	0	↑	↑	–	–	–	–	McGregor and Mason 1990
	↓	↑	↑		0	–	–	Ng et al. 1991
				↑	–	–	–	Telisman et al. 2000
	0	0	0	0	–	–	–	Sadeghnaiit Haghighi et al. 2013
	↓	–	–	–	–	–	–	Rodamilans et al. 1988

0 = no effect; ↑ = increased serum level; ↓ = decreased serum level; – = not evaluated; A = androstenedione; E = estradiol; FSH = follicle stimulating hormone; LH = luteinizing hormone; P = prolactin; SHGB = sex hormone binding globulin; T = testosterone

Effects in Males at Blood Pb Levels ≤10 µg/dL. Cross-sectional studies evaluating adverse effects of non-occupational exposures to Pb on the male reproductive system show that damage to sperm, decreased semen volume, and increased serum testosterone are associated with mean PbB ≤10 µg/dL or with Pb concentrations in semen or spermatozoa when PbBs are ≤10 µg/dL. Results are summarized in Table 2-36, with study details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 11. None of the studies evaluated associations between PbB and male fertility parameters (i.e., pregnancy). In general, study populations were small (n=61–240), although two studies using NHANES data were of larger populations (Kresovich et al. 2015; Lewis and Meeker 2015). In addition, for a few studies, participants were selected from infertility clinics and it is unclear how this may have biased study results (Meeker et al. 2008, 2010; Mendiola et al. 2011). Despite these limitations, taken together, results of non-occupational exposure studies support that adverse effects to the male reproductive system occur at PbB ≤10 µg/L.

Sperm and semen. A significant association between an increase in PbB ≤10 µg/dL and increasing percentages of morphologically abnormal sperm, wide sperm, and round sperm was observed in a population of Croatian men (Telisman et al. 2007). The mean PbB was 4.92 µg/dL; although the maximum PbB value in this study was 14.9 µg/dL, over 90% of participants had PbB <10 µg/dL. Li et al. (2015) found small, but significant negative associations between PbB and sperm count, sperm

Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Effects on serum hormone levels			
Kresovich et al. 2015 Cross-sectional study; n=869	Median:2.0 Quartiles: • Q1: ≤1.4 (reference) • Q2: 1.4–2.1 • Q3: 2.10–3.20 • Q4: >3.20	Testosterone	• **β coefficient ng/mL per µg/dL (SE)** • **Q3: 0.54 (0.21); p<0.05*** • **Q4: 0.79 (0.22); p<0.05*; p-trend=0.00268***
Lewis and Meeker 2015 Cross-sectional study; n=484	Gmean:1.06 Quartiles: • Q1: <0.71 • Q2: 0.71–1.00 • Q3: 1.00–1.59 • Q4: 1.59–33.67	Testosterone	• Percent change in serum testosterone concentration associated with a doubling (100% increase) in PbB: **6.65% (2.09, 11.41); p<0.004)*; p-trend across quartiles=0.003***
Meeker et al. 2010 Cross-sectional study; n=219	Median:1.5 Quartiles • Q1: 1.1 (reference) • Q2: 1.1–1.5 • Q3: 1.5–2.0 • Q4: 2.0–16.2	Testosterone	**Regression coefficient Q4 (ng/dL per µg/dL): 39.9 (3.32, 76.4)***
		FSH	Regression coefficient Q4 (mIU/mL per µg/dL): 0.07 (-0.18, 0.31)
		LH	Regression coefficient Q4 (mIU/m per µg/dL): 0.08 (-0.14, 0.29)
		Inhibin B	Regression coefficient Q4 (pg/mL per µg/dL): -7.79 (-29.0, 13.4)
		SHBG	Regression coefficient Q4 (nmol/L per µg/dL): 0.07 (-0.10, 0.23)
		FAI	Regression coefficient Q4 (per µg/dL): 0.08 (-0.05, 0.21)

Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Mendiola et al. 2011 Case-control study; n=61	Gmean: 2.8	Testosterone	β coefficient (ng/mL per µg/L): -0.12 (-0.40, 0.14)
		FSH	β coefficient (IU/L per µg/L): -0.20 (-0.64, 0.25)
		LH	β coefficient (IU/L per µg/L): -0.07 (-0.49, 0.31)
Telisman et al. 2007 Cross-sectional study; n=240	Median: 4.92	Testosterone	**β coefficient (nmol/L per µg/L): 0.21; p<0.003***
		Estradiol	**β coefficient (nmol/L per µg/L): 0.22; p<0.0008***
		Prolactin	β coefficient (µg per µg/L): -0.18; p<0.007
Sperm and semen quality			
Herandez-Ochoa et al. 2005 Cross-sectional study; n=68	Mean: 9.3 SPZ Pb: 0.047 ng/10^6 cells SF Pb: 2.02 µg/L	Log sperm concentration	**β coefficient SPZ Pb (10^6 cells/mL per ng/10^6 cells): -17.17 (p<0.05)***
		Sperm motility	β coefficient PbB (% per µg/dL): -0.006 **β coefficient SPZ Pb: (% per ng/10^6 cells): -2.12 (p<0.05)***
		Sperm morphology (abnormal)	β coefficient PbB (% per µg/dL): -0.001 **β coefficient SPZ Pb (% per ng/10^6 cells): -1.42 (p<0.05)***
		Sperm viability	β coefficient PbB (% per µg/dL): -0.095 **β coefficient SPZ Pb (% per ng/10^6 cells): -0.130 (p<0.05)***
		Semen volume	β coefficient PbB (mL per µg/dL): -0.043 **β coefficient SF Pb (mL per µg/L): -0.183 mL; p<0.05***

Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Li et al. 2015 Cross-sectional study; n=154	Mean: All participants: 2.78 Low-quality semen group: 3.43 High-quality semen group: 2.38	Low quality sperm	**OR: 1.040 (1.011, 1.069); p=0.0061***
		Decreased sperm concentration	**OR: 1.046 (1.015, 1.078); p=0.0032***
		Decreased sperm number	**OR: 1.041 (1.012, 1.071); p=0.0048***
		Decreased motile sperm	**OR: 1.057 (1.026, 1.089; p=0.0003***
		Decreased morphologically normal sperm	**OR: 1.071 (1.025, 1.118; p=0.0021***
Meeker et al. 2008 Cross-sectional study; n=219	Median:1.50 • Quartiles (Q): o Q1: <1.10 o Q2: 1.10–1.50 o Q3: 1.50–2.00 o Q4: 2.00–16.2	Sperm concentration	Regression coefficient (10^6/mL per µg/dL) Q4: 0.02 (-0.39, 0.43)
		Sperm motility	Regression coefficient (% per µg/dL) Q4: 1.10 (-4.56, 6.75)
		Sperm morphology	Regression coefficient (% per µg/dL) Q4: -0.16 (-1.58, 1.26)
		Semen volume	Regression coefficient (mL per µg/dL) Q4: 0.17 (-0.41, 0.74)
Mendiola et al. 2011 Case-control study; n=61	Gmean: 2.8 Median: 2.9	Sperm concentration	β coefficient (10^6/mL per µg/L): 0.08 (-4.1, 5.2)
		Immobile sperm	β coefficient (% per µg/L): -0.49 (-1.8, 0.62)
		morphologically normal sperm	β coefficient(% per µg/L): -0.8 (-3.5, 3.4)

Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Telisman et al. 2007 Cross-sectional study; n=240	Median: 4.92	Immature sperm	β coefficient (10^6/mL per µg/L): 0.13 (p<0.07)
		Pathologic sperm	**β coefficient (% per µg/L): 0.31 (p<0.0002)***
		Wide sperm	**β coefficient (% per µg/L): 0.32 (p<0.0001)***
		Round sperm	**β coefficient (% per µ: 0.16 (p<0.03)***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 11 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Asterick indicates association with PB; unless otherwise specified, values in parenthesis are 95% CIs.

CI = confidence interval; FAI = free androgen index; FSH = follicle-stimulating hormone; Gmean = geometric mean; Inhibin B = gonadal dimeric polypeptide hormone; LH = luteinizing hormone; OR = odds ratio; Pb = lead; SF = seminal fluid; SE = standard error; SHBG = sex hormone-binding globulin; SPZ = spermatozoa

concentration, motile sperm, and morphologically normal sperm in 154 men from a reproductive clinic in Taiwan. The median PbB was 2.78 µg/dL (SD 1.85); range and percentiles were not reported. Other studies have shown associations between Pb levels in semen and/or spermatozoa and increased percentages of morphologically abnormal sperm and decreased sperm motility and viability, although no associations were observed between PbB and these outcomes (Hernandez-Ochoa et al. 2005; Mendiola et al. 2011); mean PbB levels were 9.3 µg/dL in the Hernandez-Ochoa et al. (2005) study and 2.8 µg/dL in the Mendiola et al. (2011) study. No associations were observed between PbB and sperm concentration, motility, or morphologic abnormalities in men at a median PbB of 1.5 µg/dL (Meeker et al. 2008). Semen volume (mL) was negatively associated with PbB at a mean PbB of 9.3 µg/dL; however, 48% of participants had PbB >10 µg/dL (Herandez-Ochoa et al. 2005).

Serum testosterone levels. Significant associations have also been observed between PbB ≤10 µg/dL and increased serum testosterone levels (Table 2-34). Studies using NHANES data found significant positive associations between PbB and serum testosterone levels (Kresovich et al. 2015; Lewis and Meeker 2015). Examined by PbB quartiles, Kresovich et al. (2015) observed significant positive associations between PbB and serum testosterone (ng/L) for PbBs of 2.10–3.20 and >3.2 µg/dL; the median PbB of the study population was 2.0 µg/dL. A doubling of PbB was positively associated with a 6.65% change in serum testosterone; the mean PbB of the study population was 1.06 µg/dL (Lewis and Meeker 2015). The toxicological significance of the observed associations between PbB and serum testosterone has not been established.

Characterization of Effects in Females. As noted above, most epidemiological studies evaluated effects at PbB ≤10 µg/dL, with few studies of PbB >10 µg/dL. Studies of PbB ≤10 µg/dL are discussed in detail in the section below. General trends for studies showing a relationship between PbB ≤10–50 µg/dL and female reproductive effects are shown in Table 2-37. Effects associated with PbB include increased serum levels of estradiol, FSH, and LH at PbB ≤10 µg/dL (Chang et al. 2006; Krieg et al. 2007), decreased fertility at PbB ≤10 µg/dL (Chang et al. 2006), increased time to pregnancy at PbB >30–40 µg/dL (Sallmén et al. 1995), increased spontaneous abortion at PbB ≤10–30 µg/dL (Borja-Aburto et al. 1999; Yin et al. 2008), decreased number of gestational days at PbB >10–40 µg/dL (Jelliffe-Pawlowski et al. 2006), and increased preterm birth at PbB ≤10–50 µg/dL (McMichael et al. 1986; Jelliffe-Pawlowski et al. 2006; Rabito et al. 2014). Although epidemiological studies demonstrate effects on reproductive function, results are inconsistent, with several studies reporting no association between PbB and female reproductive effects (Baghurst et al. 1987; Bloom et al. 2010, 2011, 2015; Garcia-Esquinas et al. 2014; Jackson et al. 2007; Murphy et al. 1990; Perkins et al. 2014; Pollack et al. 2011; Sallmén et al. 1995;

Taylor et al. 2015; Vigeh et al. 2010). Dose-dependence has not been firmly established within the relatively narrow range of PbB (≤10 µg/dL) in most studies.

Table 2-37. Overview of Effects on the Female Reproductive System and Pregnancy Outcomes Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Increased serum hormones (estradiol, FSH, LH)	Chang et al. 2006; Krieg et al. 2007
	Decreased fertility	Chang et al. 2006
	Increased spontaneous abortion	Yin et al. 2008
	Increased preterm birth	Rabito et al. 2014
	Decreased age at menopause	Eum et al. 2014; Popovic et al. 2005
>10–30	Increased spontaneous abortion	Borja-Aburto et al. 1999
	Decreased number of gestational days	Jelliffe-Pawlowski et al. 2006
	Increased preterm birth	McMichael et al. 1986
>30–40	Increased time to pregnancy	Sallmén et al. 1995
	Decreased number of gestational days	Jelliffe-Pawlowski et al. 2006
	Increased preterm birth	Jelliffe-Pawlowski et al. 2006
>40–50	Increased preterm birth	Jelliffe-Pawlowski et al. 2006

FSH = follicle-stimulating hormone; LH = luteinizing hormone

Effects in Females at Blood Pb Levels ≤10 µg/dL. As discussed above, most epidemiology studies evaluating adverse effects of Pb on female reproductive function reported mean PbB ≤10 µg/dL. Although some studies provide evidence showing associations between PbB ≤10 µg/dL and effects on serum reproductive hormones (Chang et al. 2006; Krieg 2007), fertility (Chang et al. 2006), spontaneous abortion (Lamadrid-Figueroa et al. 2007; Yin et al. 2008), and preterm birth (Rabito et al. 2014; Taylor et al. 2015; Vigeh et al. 2011), many studies show no associations between PbB and these outcomes. In general, most studies are limited by small sample sizes, although, as discussed below, some studies were of larger populations. The basis for differences in study outcomes in not readily apparent, although several factors may contribute, including low samples size, timing of evaluations in menstrual and life cycles, and inclusion of study participants identified from fertility clinics. Results are summarized in Table 2-38, with study details provided in the *Supporting Document for Epidemiological Studies for Lead* Table 12.

Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Effects on serum hormone levels			
Chang et al. 2006 Case control study; n=147	Mean: 3.55	Estradiol	**β coefficient pg/mL per µg/dL (SE): 1.18 (0.60); p=0.049***
Jackson et al. 2011 Longitudinal cohort study; n=252	Mean: 0.87	FSH	β coefficient (IU/L per µg/dL): -2.5 (-11.2, 7.0)
		LH	β coefficient (mg/L per µg/dL): 2.5 (-12.3, 19.9)
		Estradiol	β coefficient (pg/mL per µg/dL): 4.9 (-5.0, 15.9)
		Progesterone	β coefficient (ng/mL per µg/dL): 4.6 (-12.2, 24.6)
Krieg 2007 Cross-sectional study; n=3,375	Gmean: 2.2	FSH	• **Slope pre-menopausal (IU/L per µg/dL): 8.3 (2.2); 95% CI 3.8, 12.7; p=0.0006*** • **Slope post-menopausal (IU/L per µg/dL): 22.2 (4.3); 95% CI 13.5, 30.8; p=0.0000*** • **Slope both ovaries removed (IU/L per µg/dL): 32.6 (11.2); 95% CI 10.1, 55.1; p=0.0054***
		LH	• Slope pre-menopausal (IU/L per µg/dL): 1.7 (1.2); 95% CI -0.6, 4.1; p=0.1486 • **Slope post-menopausal (IU/L per µg/dL): 6.2 (1.6); 95% C: 3.0, 9.5; p=0.0003*** • **Slope both ovaries removed (IU/L per µg/dL): 10.0 (4.4); 95% CI 1.1, 18.9; p=0.0279***

Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Pollack et al. 2011 Longitudinal cohort study; n=252	Mean: 0.93	Estradiol	β coefficient (pg/mL per µg/dL): 0.03 (-0.05, 0.11)
		FSH	β coefficient (mIU/mL per µg/dL): -0.01 (-0.07, 0.06)
		LH	β coefficient (ng/mL per µg/dL): 0.02 (-0.06, 0.10)
		Progesterone	β coefficient (ng/mL per µg/dL): 0.06 (-0.04, 0.17)
Fertility			
Bloom et al. 2010 Longitudinal cohort study; n=15	Mean: 0.82	Oocyte fertilization (*in vitro*)	RR: 1.09 (0.72, 1.65).
Bloom et al. 2011 Longitudinal cohort study; n=80	Mean: 1.54	Achieving pregnancy over 12 menstrual cycles	β coefficient (probability of pregnancy per µg/dL): -0.031 (95% CI -1.066, 1.004); p=0.954
Chang et al. 2006 Case control study of 147	Mean: • All: 3.12 • Controls: 2.78 • Cases: 3.55	Infertility	**OR for PbB >2.5 versus ≤2.5 µg/dL: 2.94 (95% CI 1.18, 7.34); p=0.021***
Pregnancy outcome			
Bloom et al. 2015 Case control study of 235	Mean: 0.71 Tertiles (mean): • T1: not reported • T2: 0.55 • T3: 0.73	Duration of gestation	Regression coefficient gestational age per µg/dL) T3: 0.14 (-0.81, 1.09)

Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Garcia-Esquinas et al. 2014 Birth cohort study; n=100	Gmean: 1.83	Duration of gestation	Mean difference in gestational age (weeks) per 2-fold increase in PbB: 0.02 (95% CI -0.44, 0.47)
Gundacker et al. 2010 Cross-sectional study; n=30	Median PbB: 2.5 Median PbPl: 25.8	Spontaneous abortion	**PbPl in women with a history of miscarriage was higher (n=8; p=0.039) than in women with no history of miscarriage (n=22)***
Lamadrid-Figueroa et al. 2007 Cross-sectional study; n=207	Mean PbB: 6.24 (4.48) Mean plasma Pb: 0.014 Mean plasma/blood Pb ratio: 0.22% (tertile values not reported)	Spontaneous abortion	IRR PbB: 0.93; p=0.56 IRR Plasma Pb: 1.12; p=0.22 **Plasma/blood Pb ratio: 1.18; p=0.02*** IRR for T2 plasma/blood Pb ratio: 1.161; p=0.612 **IRR for T3 plasma/blood Pb ratio: 1.903; p=0.015***
Perkins et al. 2014 Birth cohort; n=949	Estimated mean PbB: 0.4 Mean RBC: 1.22 µg/dL Quartile RBC (µg/dL): • Q1: 0.65 • Q2: 0.96 • Q3: 1.27 • Q4: 2.02	Duration of gestation	β coefficient Q4 gestational age (weeks) per µg/dL: -0.17 (-0.51, 0.16)
Rabito et al. 2014 Birth cohort; n=98	Second trimester mean: 0.42 Third trimester mean: 0.45	Preterm birth	**OR second trimester: 1.66 (1.23, 2.23); p<0.01*** **OR third trimester: 1.24 (1.01, 1.52); p=0.04***
Taylor et al. 2013, 2015 Longitudinal cohort study; n=3,870	Mean: 3.67 Median: 3.42	Preterm birth	**OR for PbB ≥5.0: 2.0 (1.35, 3.00); p=0.001***

Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Vigeh et al. 2010 Longitudinal cohort study; n=351	Mean: 3.8	Spontaneous abortion	OR (log PbB): 0.331 (0.011, 10.096); p=0.53
Vigeh et al. 2011 Longitudinal cohort study; n=44 women with preterm birth; n=304 women with term birth	Mean: • Term birth: 3.72 • Preterm birth: 4.52	Preterm birth	**OR: 1.41 (1.08, 1.84)***
Yin et al. 2008 Case-control study; n=80	Control (term birth): 4.5 Spontaneous abortion: 5.3	Spontaneous abortion	**PbB was higher in cases of anembryonic pregnancy during gestational weeks 8–13 compared to controls with term births (p=0.03).***
Zhu et al. 2010 Retrospective cohort; n=43,288 mother-infant pairs (n=3,519 preterm birth; n=39,769 term birth)	**PbB** Mean: 2.1 Quartiles: • Q1: ≤1.0 • Q2: 1.1–2.0 • Q3: 2.1–3.0 • Q4: 3.1–9.9	Preterm birth	Adjusted ORs did not show an increased risk of preterm birth for any quartile. Q4: 1.04 (0.89, 1.22)

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 12 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Asterick indicates association with PB; unless otherwise specified, values in parenthesis are 95% CIs.

CI = confidence interval; FSH = follicle-stimulating hormone; Gmean = geometric mean; IRR = incidence rate ratio; LH = luteinizing hormone; OR = odds ratio; Pb = lead; PbPl = Pb concentration in placenta (µg/kg); RBC = red blood cell; RR = relative risk; SE = standard error

Serum hormone levels and estrus cycle. Results of epidemiological studies on associations between PbB ≤10 μg/dL and serum hormone levels show conflicting results (Table 2-38). The strongest evidence showing that chronic Pb exposure alters serum hormone levels is from a large cross-sectional study (mean PbB 2.2 μg/dL) participating in the NHANES III study (Krieg 2007). Serum levels of FSH (IU/L) increased with PbB in both pre-menopausal and post-menopausal women. Serum levels of LH increased with PbB in post-menopausal women, but not pre-menopausal women. The lowest PbBs associated with a significant increase in FSH in pre- and post-menopausal women were 4.1 μg/dL and 2.4 μg/dL, respectively. The lowest PbB associated with a significant increase in FSH in post-menopausal women was 2.8 μg/dL (slope±SE 8.6±3.3; 95% CI 2.1, 15.2; p=0.0109). Increases in serum FSH and LH were also observed in women who had total ovariectomy, indicating that increased hormone levels may be related to effects on the hypothalamus or pituitary (Krieg 2007). No associations were observed between Pb and serum levels of FSH, LH, estradiol, or progesterone or menstrual cycle length in a smaller study of pre-menopausal women with a mean PbB of 0.87 μg/dL (Jackson et al. 2011). In this same study population, when PbB was examined by tertiles, increased serum progesterone levels were observed in the second PbB tertile (0.73–1.10 μg/dL) compared to the lowest tertile (0.30–0.72 μg/dL), but no effects were observed in the highest PbB tertile (1.11–6.20 μg/dL) compared to the lowest (Pollack et al. 2011). In this study population, no association was observed between PbB and anovulation. In a case-control study of women attending a fertility clinic, a significant association was observed between PbB and serum estradiol concentrations (Chang et al. 2006).

Fertility. Little epidemiological information is available on the effects of PbB ≤10 μg/dL on female fertility. A prospective cohort study with a mean Pb of 1.5 μg/dL showed no effect on achieving pregnancy over 12 menstrual cycles (Bloom et al. 2011). A case-control study of women from a fertility clinic showed a 2.9-fold risk of infertility for PbB >2.5 μg/dL compared to PbB ≤2.5 μg/dL (Chang et al. 2006). In a study of women undergoing *in vitro* fertilization, no association was observed between PbB and oocyte fertilization; however, only 15 women were included in this study. Available epidemiological studies on the effects of PbB ≤10 μg/dL on fertility are limited due to small numbers of participants and study populations of women undergoing fertility treatment; thus, data are not sufficient to determine if fertility in women is affected at PbB ≤10 μg/dL.

Spontaneous abortion. Few epidemiological studies have evaluated associations between PbB ≤10 μg/dL and spontaneous abortion (Table 2-38). Although studies provide some evidence suggesting associations between PbB ≤10 μg/dL or plasma/blood Pb ratio and spontaneous abortion, results are inconsistent. In a case-control study, PbB was significantly higher in cases of spontaneous abortion (PbB 5.3 μg/dL;

p=0.03) during weeks 8–13, compared to women with term birth (PbB 4.5 μg/dL) (Yin et al. 2008). A cross-sectional study reported that the risk of miscarriage per 1 SD increase of plasma/blood Pb ratio [mean plasma/blood Pb ratio±SD (%): 0.22±0.14] was associated with an 18% greater incidence of spontaneous abortion, although the association between risk of spontaneous abortion and PbB (mean 6.24) was not significant (Lamadrid-Figueroa et al. 2007). In contrast, results of a longitudinal cohort study showed no association between PbB and spontaneous abortion during gestational weeks 13–19 (Vigeh et al. 2010).

Preterm birth. Several studies have evaluated associations between PbB ≤10 μg/dL and preterm birth (<37 weeks of gestation), including two studies of larger study populations (n=705–3,870) (Perkins et al. 2014; Taylor et al. 2015). Results of these studies are mixed (Table 2-38). The strongest evidence showing that chronic Pb exposure is associated with preterm birth is from a large, longitudinal cohort study (Taylor et al. 2013, 2015). When stratified into groups of PbB <5 and ≥5.0 μg/dL, there was a 2-fold increase in the risk of preterm birth for PbB ≥5.0 μg/dL compared to PbB <5 μg/dL. In the PbB ≥5.0 μg/dL group, the maximum PbB was 19.14 μg/dL, although very few PbBs were >10 μg/dL; however, the group mean PbB was not reported. The risk of preterm birth also was increased in a longitudinal cohort study (Vigeh et al. 2011). Mean PbB in women with preterm birth was significantly higher than in women with term birth (preterm PbB: 4.52 μg/dL; term birth PbB: 3.72 μg/dL). A cohort study showed increased odds of preterm birth associated with PbB measured in the 2nd (mean: 0.42 μg/dL) and 3rd (mean: 0.45 μg/dL) trimesters (Rabito et al. 2014). ORs for risks of preterm birth were 1.66 (p<0.01) and 1.24 (p=0.04) for 2nd and 3rd trimester PbB, respectively. Other studies reported no associations between PbB and preterm birth at mean PbB of 0.71–1.22 μg/dL (Bloom et al. 2015; Perkins et al. 2014; Zhu et al. 2010), including a large retrospective cohort study (Zhu et al. 2010) and a large case-control study (Perkins et al. 2014).

Age at menopause. A few studies had evaluated associations between Pb exposure and age at menopause (Eum et al. 2014; Popovic et al. 2005). Eum et al. (2014) found a negative association between tibia Pb and age at onset of natural menopause (e.g., non-surgical) in a population of 434 participants in the Nurses Health Study cohort. In the highest tibia Pb tertile, the age at onset of menopause was 1.21 years earlier than controls. However, no associations were observed between PbB (mean PbB: <5 μg/dL) or patella Pb. In a study of 108 former smelters (mean PbB: 2.73 μg/dL), the age at onset of combined natural and surgical menopause was lower by 7 years (p=0.001) compared to controls (n=99; PbB: 1.25 μg/dL) (Popovic et al. 2005). No difference was observed between the age at onset and natural menopause between the exposed and control groups.

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of toxicity to male and female reproductive systems. Oxidative stress through ROS is a plausible mechanism for reproductive effects, as is the disruption of calcium homeostasis. Mechanisms for alterations in circulating hormone levels have been not been established. However, EPA (2014c) and NRC (2012) noted several possible mechanisms that may be involved in alterations of serum hormones, including direct inhibition of LH secretion; reduced expression of steroidogenic acute regulatory protein (a protein required in maintaining gonadotropin-stimulated steroidogenesis); altered release of pituitary hormones due to interference with cation-dependent second messenger systems; and altered binding of hormones to receptors. Pb is distributed to, and has been measured in, semen, spermatozoa, the fetus, umbilical cord blood, placenta, and follicular fluid (see Section 3.1.2, Toxicokinetics, Distribution), providing a toxicokinetic mechanism for direct effects to reproductive tissues.

2.18 DEVELOPMENTAL

This section discusses developmental effects of Pb other than neurodevelopmental defects. Neurodevelopmental effects are discussed in Section 2.16 (Neurological Effects). The term "developmental" used in the discussion that follows refers to effects other than neurodevelopmental.

Overview. Numerous epidemiological studies have evaluated developmental effects (birth outcomes, birth defect, neural tube defects, decreased anthropometric measures in children, and delayed puberty) associated with Pb exposure, with the database for developmental effects dominated by environmental exposure studies with PbB ≤10 µg/dL. In general, studies provide mixed evidence for effects on birth outcomes (e.g., infant size) and anthropometric measures in children, but more consistent evidence for delayed puberty. Although studies provide evidence of associations between PbB and developmental outcomes, results are inconsistent, and several studies, including prospective studies, with PbB ≤10 µg/dL show no associations with developmental outcomes.

The following developmental effects have been associated with PbB:

- ≤10 µg/dL:
    - Effects on birth outcomes (decreased birth weight, head circumference, and crown-heel length); results are mixed when compared across studies.

  - Decreased anthropometric measures in children (weight, height, head circumference, trunk length, leg length, arm length, BMI); results are mixed when compared across studies.
  - Delayed puberty in females (breast development, pubic hair development, onset of menarche); corroborated in multiple studies.
  - Delayed puberty in males (testicular volume, genitalia development, pubic hair development); a few studies with equivocal results.
- >10 µg/dL (based on few studies):
  - Effects on birth outcomes (low birth weight).
  - Decreased anthropometric measures in children (decreased weight, height, head circumference, chest circumference).
  - Delayed puberty in females (breast development).
  - Delayed puberty in males (decreased testicular size, delayed pubic hair development, delayed penile development).

Measures of Exposure. Most studies evaluating developmental effects used maternal PbB and/or cord, infant, or child PbB as the biomarker for exposure. In some studies, Pb concentrations in red blood cells (Perkins et al. 2014), maternal bone (Afeiche et al. 2011; Cantonwine et al. 2010b; Hernandez-Avila et al. 2002; Kordas et al. 2009), or hair (Sanín et al. 2001; Sanna and Vallascas 2011) were used as biomarkers.

Confounding Factors and Effect Modifiers. Numerous complicating factors may add uncertainty in the interpretation of studies examining associations between PbB and developmental effects. These factors include nutrition during pregnancy, prenatal care, adequate nutrition during infancy and childhood, SES, intercurrent diseases, alcohol consumption, smoking status, and potential exposure to other chemicals. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. As noted above, most epidemiological studies evaluated developmental effects at PbB ≤10 µg/dL, with few studies of PbB >10 µg/dL. Studies of PbB ≤10 µg/dL are discussed in detail in the section below. General trends for studies showing a relationship between PbB ≤10–50 µg/dL and developmental effects are shown in Table 2-39. Effects on birth outcomes, including decreased birth weight, head circumference, and crown-heel length have been observed at maternal PbBs of ≤10–50 µg/dL. Decreased anthropometric measures in infants and children, including decreased weight, height, head circumference, trunk length, leg length, arm length, and BMI, have been observed

over the PbB range of ≤10–30 µg/dL. Delayed onset of puberty in males and females was observed over the PbB range of ≤10–30 µg/dL. Very little data are available regarding *in utero* exposure to Pb and birth defects. Two studies that examined neural tube defects did not find associations with Pb exposure at mean blood levels over for PbB means ranging from 2.4 to 24 µg/dL (Brender et al. 2006; Zeyrek et al. 2009). As discussed below, although epidemiological studies demonstrate developmental effects of Pb, results across studies are inconsistent, with several studies reporting no association between PbB and developmental effects. For example, results of effects on birth outcomes in study populations with maternal PbB ≤10 µg/dL are equivocal (see Tables 2-40 and 2-41). For studies with maternal PbB >10 µg/dL, equivocal results also were observed for associations between PbB and birth weight and length (Factor-Litvak et al. 1991; Hernandez-Avila et al. 2002; McMichael et al. 1986; Murphy et al. 1990). Dose-dependence has not been firmly established within the relatively narrow range of PbB (≤10 µg/dL) in most studies.

Table 2-39. Overview of Developmental Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Effects on birth outcome (decreased birth weight, crown-heel length, head circumference)	Bornschein et al. 1989; Gonzales-Cossio et al. 1997; Nishioka et al. 2014; Odland et al. 1999; Taylor et al. 2013, 2015; Xie et al. 2013; Zhu et al. 2010
	Minor congenital anomalies	Needleman et al. 1984
	Decreased anthropometric measures in children (decreased weight, height, head circumference, trunk length, leg length, arm length, body mass index)	Afeiche et al. 2011; Dallaire et al. 2014; Hauser et al. 2008; Hong et al. 2014; Ignasiak et al. 2006; Little et al. 2009; Min et al. 2008b; Olivero-Verbel et al. 2007; Schell et al. 2009; Yang et al. 2013a
	Delayed puberty in females (breast development, pubic hair development, onset of menarche)	Denham et al. 2005; Den Hond et al. 2011; Gollenberg et al. 2010; Naicker et al. 2010; Selevan et al. 2003; Wu et al. 2003b
	Delayed puberty in males (testicular volume, genitalia development, pubic hair development)	Hauser et al. 2008; Williams et al. 2010

Table 2-39. Overview of Developmental Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
>10–30	Effects on birth outcome (decreased birth weight)	Chen et al. 2006; Hernandez-Avila et al. 2002
	Decreased anthropometric measures in children (decreased weight, height, head circumference, chest circumference)	Frisancho and Ryan 1991; Tomoum et al. 2010
	Delayed puberty in females (breast development)	Tomoum et al. 2010
	Delayed puberty in males (decreased testicular size, delayed pubic hair development; delayed penile development)	Tomoum et al. 2010
>30–50	Effects on birth outcome (low birth weight)	Jelliffe-Pawlowski et al. 2006

Table 2-40. Effects on Birth Outcomes at Blood Lead Concentration (PbB) ≤10 µg/dL

	Birth outcome			
Reference (population size)	Birth weight	Height or C-H length	SGA	Head circumference
Al-Saleh et al. 2014 (n=1,577)	0[a]	0	0	0
Bloom et al. 2015 (n=235)	0[a]	0	−	0
Bornschein et al. 1989 (n=202)	↓[a]	↓	−	0
Garcia-Esquinas et al. 2014 (n=97)	0[a]	0	−	−
Gonzalez-Cossio et al. 1997 (n=272)	0[b]	−	−	−
Nishioka et al. 2014 (n=386)	↓[b]	−	−	−
Odland et al. 1999 (n=50)	↓[a,b]	−	−	−
Perkins et al. 2014 (n=949)	0[a,b]	0	−	0
Rabito et al. 2014 (n=98)	0[a]	−	−	−
Taylor et al. 2015 (n=4,285)	↓[b]	↓	−	↓
Thomas et al. 2015 (n=1,835)	−	−	0	−
Xie et al. 2013 (n=252)	↓[b]	0	−	0
Zhu et al. 2010 (n=43,288)	↓[b]	−	0	−

[a]Birth weight not adjusted for gestational age
[b]Birth weight adjusted for gestational age
↓ = decrease in outcome measure; 0 = no effect on outcome measure; − = not assessed; C-H = crown-heel; SGA = small for gestational age

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Al-Saleh et al. 2014 Cross-sectional study; n=1578 mother-infant pairs	Maternal PbB mean: 2.897	Birth weight	OR: 1.107 (0.797, 1.538); p=0.545
		Birth height	OR: 1.299 (0.945, 1.786); p=0.107
		Crown-heel length	OR: 1.061 (0.795, 1.415); p=0.689
		SGA	OR: 1.168 (0.837, 1.631); p=0.362
		Head circumference	OR: 1.007 (0.724,1.400); p=0.968
		Apgar	OR: 1.027 (0.787, 1.341); p=0.842
Bloom et al. 2015 Case-control study; n=235 mother-infant pairs	Maternal PbB mean: 0.71 Tertiles: • T1: <0.55 (reference) • T2: 0.55-<0.73 • T3: 0.73–2.23	Birth weight	Linear regression coefficient (g per µg/dL) T3: -34.85 (-97.76, 128.06); p-trend=0.202
		Birth length	Linear regression coefficient (cm per µg/dL) T3: 0.14 (-0.81, 1.09); p-trend:0.671
		Head circumference	Linear regression coefficient (cm per µg/dL) T3: -0.33 (-1.07, 0.41); p-trend: 0.132
Bornschein et al. 1989 Prospective study; n=202 mother-infant pairs	**PbB:** Mean (SD): 7.5	Birth weight	**Regression coefficient (g per ln µg/dL) for all births: -114; p<0.001*.** **Regression coefficient (g per ln µg/dL) with significant interaction with maternal age (p=0.0073)*:** **maternal age 18 years: -58*** **maternal age 30 years: -601***
		Birth length	**Regression coefficient (cm per ln µg/dL): -2.5; p=0.019***
		Head circumference	Regression coefficient (cm per ln PbB µg/dL): 0.0 p=0.97

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Garcia-Esquinas et al. 2014 Birth cohort study; n=100 mother-infant pairs	Maternal PbB Gmean: 1.83	Birth weight	Adjusted mean difference in grams for a 2-fold increase in PbB (µg/L): 62.4 (-73.1, 197.8)
		Birth length	Adjusted mean difference in cm for a 2-fold increase in PbB (µg/L): 0.17 (-0.56, 0.91)
		Abdominal diameter	Adjusted mean difference in cm for a 2-fold increase in PbB (µg/d): 0.31 (-0.52, 1.15)
		Cephalic diameter	Adjusted mean difference in cm for a 2-fold increase in PbB (µg/L): 0.15 (-0.21, 0.51)
Gonzalez-Cossio et al. 1997 Birth cohort study; n=272 mother-infant pairs	**PbB:** • Maternal o Mean (SD): 8.9 (4.1) o Quartiles: ▪ Q1: ≤5.8 ▪ Q2: 5.9–8.0 ▪ Q3: 8.1–11.0 ▪ Q4: ≥11.1 • Umbilical cord o Mean (SD): 7.1 (3.5) o Quartiles ▪ Q1: ≤4.6 ▪ Q2: 4.7–6.1 ▪ Q3: 6.2–8.5 ▪ Q4: ≥8.6	Birth weight	Regression coefficient: • Maternal PbB for Q4: -98.30 (59.55); p=0.100 • Umbilical cord PbB for Q4: -41.74 (64.04); p=0.514
Nishioka et al. 2014 Cohort study; n=386 mother-infant pairs	Maternal PbB mean at gestational weeks: • 12 weeks: 0.98 • 25 weeks: 0.92 • 36 weeks: 0.99	Birth weight	Regression coefficient based on log µg/dL: • **Infant males: -0.151 (p<0.05)*** • Infant females: -0.098 (p>0.05)

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Odland et al. 1999 Cohort study; n=262 mother-infant pairs	Maternal, mean (range); p-values compare Russian and Norwegian cohorts • Russian cohort: 2.9 (0.83–13.5) • Norwegian cohort: 2.3 (0.41–3.9); p<0.001	Birth weight	Regression coefficient, combined Russian and Norwegian cohorts [g per µmol/L (g per 20.7 µg/dL)]: **-1,068 (95% CI -2,134, -2); p<0.05***
Perkins et al. 2014 Birth cohort study; n=829 mother-infant pairs	Maternal RBC Pb concentration (µg/dL) mean: 1.22 Quartiles for RBC Pb; mean: • Q1: 0.65 • Q2: 0.96 • Q3: 1.27 • Q4: 2.02 Estimated maternal PbB mean: 0.4	Birth weight	Linear regression β coefficient for RBC (µg/dL) Q4: -47 (-128, 35); p-trend: 0.27
		Birth length	Linear regression β coefficient for RBC (µg/dL) Q4: -0.15 (-0.54, 0.23); p-trend: 0.37
		Head circumference	Linear regression β coefficient for RBC (µg/dL) Q4: -0.08 (-0.33, 0.16); p-trend: 0.56
Rabito et al. 2014 Birth cohort study; n=98 mother-infant pairs	Maternal 2nd trimester PbB mean: 0.42 Maternal 3rd trimester PbB mean: 0.45	Birth weight	Linear regression β coefficient, g per µg/dL maternal: • 2nd trimester: -43.21 (-88.6, 2.18); p=0.06 • 3rd trimester: β not reported; p=0.68 • Delivery: β not reported; p=0.83

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Taylor et al. 2013, 2015 Longitudinal cohort study; n= 4,285 mother-infant pairs	Maternal PbB mean: 3.67 Population stratified by PbB <5.0 and ≥5.0	Birth weight	**β coefficient (g per µg/dL): -13.23 (-23.75, -2.70); p=0.014***
		Head circumference	**β coefficient (cm per µg/dL): -0.04 (-0.07, -0.06)[e]; p=0.021***
		Crown-heel length	**β coefficient (cm per µg/dL): -0.05 (-0.10, -0.00); p=0.034***
Thomas et al. 2015 Prospective cohort; n=1,835 mother-infant pairs	Maternal PbB median: 0.59 Tertiles: • T1: <0.52 • T2: 0.52–1.04 • T3: >1.04–4.04	SGA	Adjusted RR for T3 (95% CI): 1.19 (0.65, 2.18)
Xie et al. 2013 Birth cohort study; n=252 mother-infant pairs	Maternal PbB mean: 3.53	Birth weight	**β coefficient (g per square root µg/dL): -148.99 (-286.33, -11.66); p=0.03***
		Birth length	β coefficient (cm per square root µg/dL): -0.46 (-1.25, 0.34); p=0.26
		Head circumference	β coefficients (cm per square root µg/dL): -0.37 (-0.78, 0.19); p=0.24

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Zhu et al. 2010 Retrospective cohort study; n=43,288 mother-infant pairs	Maternal PbB mean: 2.1	Birth weight	**β coefficient g per µg/dL (95% CI):** 0: reference **1: -27.4 (-17.1, -37.8)*** **2: -38.8 (-24.1, -53.4)*** **3: -47.5 (-29.6, -65.4)*** **4: -54.8 (-34.2, -75.5)*** **5: -61.3 (-38.2, -84.4)*** **6: -67.2 (-41.8, -92.5)*** **7: -72.5 (-45.2, -99.9)*** **8: -77.6 (-48.3, -106.8)*** **9: -82.3 (-51.2, -113.3)*** **10: -86.7 (-54.0, -119.4)***
		SGA	Adjusted OR for Q4: 1.07 (0.93, 1.23)

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 13 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Values are for maternal PbB, unless otherwise specified.
[d]Asterick indicates association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[e]Values are reported; the value for the β coefficient is outside of the 95% CI.

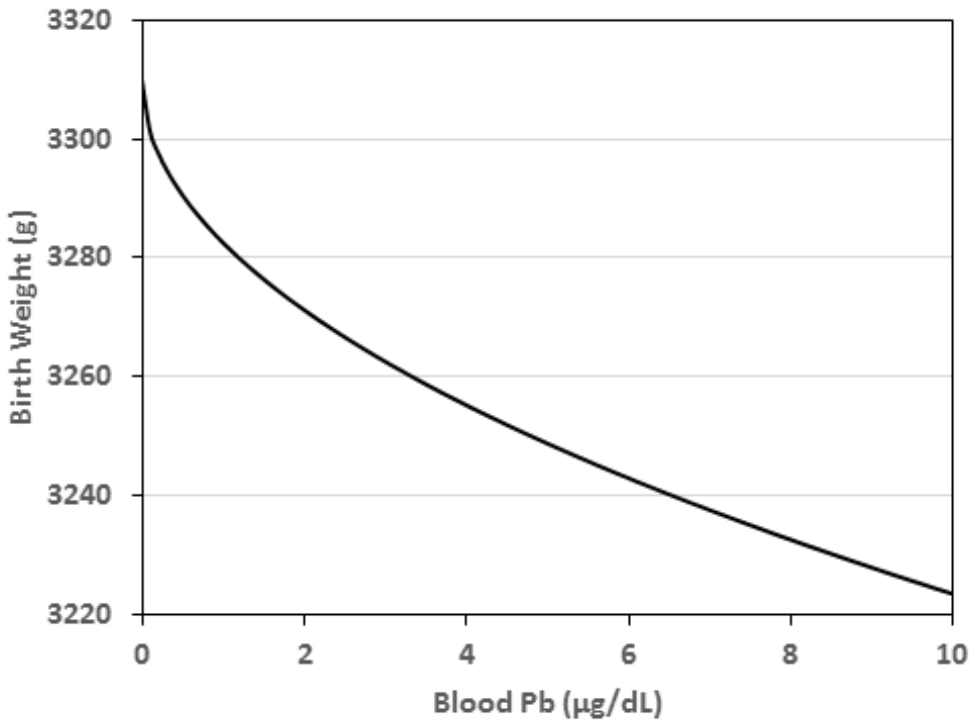
CI = confidence interval; NS = not statistically significant; OR = odds ratio; Pb = lead; RBC = red blood cell; RR = relative risk; SGA = small for gestational age

Effect at Blood Pb Levels ≤10 μg/dL. Epidemiology studies have reported developmental effects, including birth outcomes, birth defects, anthropometric measures in children, and delayed onset of puberty, at mean PbB ≤10 μg/dL. Study details are provided in *Supporting Document for Epidemiological Studies for Lead*, Table 13. Results of studies on associations between PbB and adverse effects on birth outcomes and anthropometric measures are mixed when compared across studies. Delayed onset of puberty in females has been corroborated in several studies. Fewer studies are available regarding effects of Pb on onset of puberty in males, with equivocal results. Exposure to Pb has not been shown to cause birth defects in humans. Neural tube defects have not been associated with Pb exposure and findings of a single study showing minor anomalies have not been corroborated.

Birth outcomes. An overview of results of studies that evaluated associations between Pb exposure and birth outcomes (infant weight, height or crown-heel length, small for gestation age [SGA], and head circumference) at maternal PbB ≤10 μg/dL is shown in Table 2-40, with more detailed results in Table 2-41. Studies include two prospective studies (Bornschein et al. 1989; Thomas et al. 2015), several studies of large populations (n=829–43,288) (Al-Saleh et al. 2014; Perkins et al. 2014; Taylor et al. 2015; Thomas et al. 2015; Zhu et al. 2010), and cohort and case-control studies of smaller (n=98–386) populations (Bloom et al. 2015; Garcia-Esquinas et al. 2014; Gonzalez-Cossio et al. 1997; Nishioka et al. 2014; Rabito et al. 2014). As shown in Table 2-41, results of these studies show either decreases or no change in birth outcomes. In a small (n=202) prospective study, Bornschein et al. (1989) reported associations between maternal PbB (mean 7.5 μg/dL) and decreased birth weight and length. The size of the effect of PbB varied with maternal age ($p<0.007$), with a 58 g per lnPbB decrease for pregnancies at age 18 years and a 601 g decrease per ln PbB (μg/dL) for pregnancies at age 30 years. In the complete birth cohort from this study, which included mothers who declined participation in the infant follow-up (n=861), the decline in birth weight was -114 g per ln PbB. Results of the largest cohort study, a retrospective study of >43,000 participants (mean PbB 2.1 μg/dL), showed a negative association between PbB and birth weight (Zhu et al. 2010). The best fitting model was a linear change in birth weight with square root of PbB (Figure 2-7). The model predicts a 34 g decrease in birth weight for an increase in PbB from 1 to 5 μg/dL and a 59 g decrease for an increase in PbB from 1 to 10 μg/dL (adjusted for confounders). Results of a longitudinal cohort study of 4,285 mother-infant pairs (maternal PbB mean: 2.1 μg/dL; range 0.42–19.14) showed negative associations between birth weight, crown-heel length, and head circumference for participants with PbB ≥5 μg/dL compared to PbB <5 μg/dL (Taylor et al. 2015). Other smaller cohort studies also showed associations between maternal PbB ≤10 μg/dL and decreased birth weight (Nisioka et al. 2014; Odland et al. 1999). In contrast, other studies, including a prospective study and cohort studies of large populations, did not find associations between PbB and birth outcome

measures. A prospective study of 1,835 mother-infant pairs did not find an association between PbB and SGA, with PbB data stratified by tertiles (range for highest tertile: 1.04–4.04 μg/dL) (Thomas et al. 2015). Similarly, no associations between maternal PbB and decreased birth weight, length, or head circumference were observed in a cohort study of 829 participants (estimated PbB mean of 0.4 μg/dL) (Perkins et al. 2014), or in a cross-sectional study of 1,578 participants (Al-Saleh et al. 2014). Smaller cohort studies also report no associations between PbB and adverse birth outcome measures (Bloom et al. 2015; Garcia-Esquinas et al. 2014; Gonzalez-Cossio et al. 1997; Rabito et al. 2014). Equivocal findings for birth outcomes in studies examining effects at maternal PbB ≤10 μg/dL are not surprising, given that prospective studies at maternal PbB >10 μg/dL also have reported conflicting results for adverse effects on birth outcomes (Factor-Litvak et al. 1991; Hernandez-Avila et al. 2002; McMichael et al. 1986; Murphy et al. 1990). For example, two prospective studies found no associations between PbB and birth weight in birth cohorts that had mean maternal PbBs >10 μg/dL (Factor-Litvak et al. 1991; McMichael et al. 1986).

Figure 2-7. Relationship Between Blood Lead Concentration (PbB) and Birth Weight at PbB ≤10 μg/dL



Source: Zhu et al. 2010

Birth defects. Few studies have evaluated associations between *in utero* exposure to Pb and birth defects. Details of studies evaluating PbB ≤10 μg/dL are provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 13. No association was observed between PbB and neural tube defects in a case-control study (n=409) with mean maternal PbB of 2.5 μg/dL (Brender et al. 2006). Other epidemiological studies that have reported associations between Pb in exposure media (e.g., water, soil) and neural tube defects are limited by the lack of PbB measurement (Bound et al. 1997; Huang et al. 2011; Irgens et al. 1998). An early cross-sectional study of birth outcomes examined associations between PbB and congenital anomalies using hospital records on 5,183 deliveries in Boston, Massachusetts (Needleman et al. 1984). The RR of an anomaly increased with increasing cord PbB; the RR (relative to PbB 0.7 μg/dL) was 1.87 (95% CI 1.44, 2.42) for PbB of 6.3 μg/dL and increased to 2.39 (95% CI 1.66, 3.43) at 15 μg/dL and 2.73 (95% CI 1.80, 4.16) at 24 μg/dL. The anomalies were considered to be minor (hemangiomas, lymphangiomas, hydrocele, minor skin anomalies, undescended testicle) and no specific anomaly was associated with PbB. Limitations of this study are that it was a cross-sectional study of a convenience sample with outcomes obtained from hospital records. Associations between PbB and congenital anomalies have not been corroborated.

Anthropometric measures in children. An overview of results of studies evaluating associations between Pb exposure and growth of infants and children (aged 0.5–15 years) at maternal and/or offspring PbB ≤10 μg/dL is shown in Table 2-42, with more detailed results in Table 2-43. Studies include two prospective studies (Dallaire et al. 2014; Lamb et al. 2008), cross-sectional studies of large (n=899–1,050) populations (Afeiche et al. 2011; Hong et al. 2014; Ignakiak et al. 2006), and several smaller (n=108–489) cohort and cross-sectional studies (Hauser et al. 2008; Little et al. 2009; Min et al. 2008b; Olivero-Verbel et al. 2007; Schell et al. 2009; Yang et al. 2013a). Most studies report negative associations between Pb exposure and height, with mixed results for weight and BMI (Table 2-42). A small (n=290) prospective study showed an association between cord PbB (mean 4.8 μg/dL) and small decreases in height and head circumference, but not for weight or BMI (Dellaire et al. 2014). Similarly, Lamb et al. (2008) did not find an association between maternal PbB and height or BMI at maternal PbB means of 5.60–20.56 μg/dL (means for different geographic locations). In contrast, results of large case-control studies showed negative associations between maternal bone Pb and weight (Afeiche et al. 2011), maternal PbB and weight and height (Hong et al. 2014), and child PbB and several growth measures, including weight, height, and BMI (Ignasiak et al. 2006). The largest negative association for decreased weight was observed for maternal bone Pb in females assessed at 2–5 years of age; the mean PbB in children was 3.8 μg/dL (Afeiche et al. 2011). At the 5-year assessment, body weight in females was decreased by approximately 172 g for each 1-SD increase in maternal bone Pb. Smaller case-control and

cohort studies reported consistent negative associations between PbB and height, with equivocal findings for weight, and no associations for BMI.

Table 2-42. Overview of Decreased Anthropometric Measures in Children at Blood Lead Concentration (PbB) ≤10 µg/dL

Reference	Age at time of assessment (years)	Anthropometric measurements		
		Weight	Height	BMI
Afeiche et al. 2011	1–5	↓ (F); 0 (M)	−	−
Dallaire et al. 2014	8–14	0	↓	0
Hauser et al. 2008	8–9	0	↓	0
Hong et al. 2014	0.5–2	↓	↓	−
Ignasiak et al. 2006	7–15	↓ (F); 0 (M)	↓ (F); 0 (M)	↓
Lamb et al. 2008	1–10	0	0	0
Little et al. 2008	2–12	↓	−	−
Min et al. 2008b	5–13	0	↓	−
Olivero-Verbel et al. 2007	5–9	0	↓	−
Schell et al. 2009	0.5−1	0	↓	−
Yang et al. 2013a	3–9	↓	↓	0

↓ = decrease in outcome measure; 0 = no effect on outcome measure; − = not assessed; BMI = body mass index; F = females; M = males

Delayed puberty. Results of studies that evaluated associations between Pb exposure and sexual maturation in boys and girls at child PbB ≤10 µg/dL are summarized in Table 2-44. In girls, delayed onset of puberty, as measured by breast development, pubic hair development, and attainment of menarche, has been corroborated in multiple cross-sectional studies (Den Hond et al. 2011; Denham et al. 2005; Gollenberg et al. 2010; Naicker et al. 2010; Selevan et al. 2003; Wu et al. 2003b). Mean PbB in these studies ranged from 0.49 to 4.9 µg/dL. Delays in the predicted attainment of menarche ranged from 3.6 to 10.6 months (Denham et al. 2005; Selevan et al. 2003). Fewer studies examining associations between Pb exposure and sexual maturation in boys at child PbB ≤10 µg/dL are available. Results of these studies are equivocal. Delayed sexual maturation, measured by genitalia development, testicular volume, and pubic hair development, was observed in two cross-sectional studies of the same study population of 489 boys; the median child PbB was 3 µg/dL (Hauser et al. 2008; Williams et al. 2010). However, no association between PbB and the onset of puberty was observed in a cross-sectional study of 887 boys with a median PbB of 2.5 µg/dL (Den Hond et al. 2011).

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Afeiche et al. 2011 Cross-sectional study; n=999 mother-child pairs	• Child PbB mean: 3.8 • Maternal bone Pb (patella) mean (µg/g): 10.4	Weight (females)	Associations between a 1-SD increase in maternal bone Pb (µg/g) and child weight (g) for children aged: • 12 months: -70.9 (-147.9, 6.0) • **24 months: -96.1 (-170.4, -21.8)*** • **36 months: -121.3 (-200.0, -42.6)*** • **48 months: -146.4 (-235.5, -57.4)*** • **60 months: -171.6 (-275.2, -68.0)***
		Weight (males)	Associations between a 1-SD increase in maternal bone Pb (µg/g) and child weight (g) for children aged: • 12 months: 29.4 (-42.1, 100.8) • 24 months: 27.8 (-43.5, 99.1) • 36 months: 7.9 (-67.3, 83.1) • 48 months: -13.6 (-97.9, 70.8) • 60 months: -35.0 (-132.4, 62.3)
Dallaire et al. 2014 Prospective cohort study; n=290 children (aged 8–14 years)	• Cord PbB mean: 4.8 • Child PbB mean: 2.7	Height	**β coefficients (cm per µg/dL cord): -1.57; p=0.004***
		Head circumference	**β coefficients (cm per µg/dL cord): -0.005; p=0.04***
		Weight	β coefficients (kg per µg/dL cord): β not reported; p=0.70
		BMI	β coefficients (kg/m^2 per µg/dL cord): 0.07; p=0.23

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Hauser et al. 2008 Cross-sectional study n=489children (aged 8–9 years)	Child PbB, mean: 3	Height	**Regression coefficient (cm per µg/dL): -1.439 (-2.25, -0.63); p<0.001***
		Weight	Regression coefficient (kg per µg/dL): -0.761 (-1.54, 0.02); p=0.067
		BMI	Regression coefficient (kg/m^2 per µg/dL): -0.107 (-0.44, 0.23); p=0.53
Hong et al. 2014 Cross-sectional study; n=1,150 infants (aged 6–24 months)	Maternal PbB mean: 1.25	Weight	**Weight z score: -0.28 (-0.48, -0.09); p<0.05***
		Height	**Height z score: -0.28 (-0.49, -0.06); p<0.05***
Ignasiak et al. 2006 Cross-section study; n=899 children (aged 7–15 years)	Child PbB mean: 7.7	Weight	• Slope boys(kg per $\log_{10}$ µg/dL): 4.00 (2.45); p=0.10 • **Slope girls (kg per $\log_{10}$ µg/dL): -6.59 (2.09); p=0.001***
		Height	• Slope boys (cm per $\log_{10}$ µg/dL): -6.26 (1.40); p=0.002 • **Slope girls (cm per $\log_{10}$ µg/dL): -5.54 (2.05); p=0.007***
		BMI	• Slope boys (kg/m^2 per $\log_{10}$ µg/dL): -0.39 (0.82); p=NS • **Slope girls (kg/m^2 per log µg/dL): -1.86 (0.75); p=0.01***
		Trunk length	• **Slope(boys (cm per $\log_{10}$ µg/dL): -2.21 (0.97); p=0.02*** • Slope girls (cm per log µg/dL): -1.47 (1.00); p=NS

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
		Leg length	• **Slope boys (cm per log_{10} µg/dL): -4.05 (1.27); p=0.002*** • **Slope girls (cm per log_{10} µg/dL): -4.08 (1.27) p=0.0001***
		Arm length	• **Slope boys (cm per µg/dL): -3.20 (0.97); p=0.0001*** • **Slope girls (cm per log_{10} µg/dL): -2.61 (0.98); p=0.008***
		Trunk-length ratio	• **Slope boys (per log_{10} µg/dL): 0.71 (0.34): p=0.04*** • **Slope girls (per log_{10} µg/dL): 1.03 (0.34); p=0.003***
Lamb et al. 2008 Population-based prospective cohort; n=309 children (aged 1–10) years	Maternal PbB mean for towns of: • Pristina: 5.60 • Mitrovica: 20.56	Height/BMI	Pristina (β coefficients per log µg/dL): • Age 1 year: -0.61 (-2.24, 1.03) • Age 10 years: -0.09 (-3.69, 3.52) Mitrovica (β coefficients per log µg/dL): • Age 1 year: -0.30 (-2.55, 1.96) • Age 10 years: -2.87 (-6.21, 0.47)
Little et al. 2009 Cross-sectional study; n=360 children (aged 2–12 years)	Child PbB mean • 1980 cohort: 23.6 • 2002 cohort: 1.6 • Pooled cohort PbB mean not reported	Height	**β coefficient (cm per10 µg/dL PbB decrease): 2.1 (1.9, 2.3); p<0.0001***
		Weight	**β coefficient (kg per 10 µg/dL PbB decrease): 1.9 (1.7, 2.1); p<0.0001***
		BMI	**β coefficient (kg/m^2 per 10 µg/dL PbB decrease): 0.5 (0.4, 0.7); p<0.0001***

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Min et al. 2008b Cross-sectional study; n=108 children (aged 5–13 years)	Child PbB mean: 2.4	Height	**Regression coefficient cm per µg/dL (SE): -1.449 (0.639); p=0.026***
		Weight	Regression coefficient kg per µg/dL (SE): -0.646 (0.718); 0.370
		BMI	Regression coefficient kg/m^2 per µg/dL (SE): -0.006 (0.272); p=0.982
		Arm length	**Regression coefficient cm per µg/dL (SE): -1.804 (0.702); p=0.012***
Olivero-Verbel et al. 2007 Cross-sectional study; n=189 children (aged 5–9 years)	Child PbB mean: 5.53	Height	**Correlation coefficient: -0.224; p=0.002***
		Weight	Correlation coefficient: -0.126; p=0.087
Schell et al. 2009 Longitudinal cohort study; n=244 children (aged 3–12 months)	Maternal PbB mean: 2.8	Length	Regression coefficients (SE): • **6 months (cm per log µg/dL): 0.149 (0.076); p=0.05*** • 12 months (cm per log µg/dL): 0.073 (0.083); p=0.38
		Weight-for-age	Regression coefficients (SE): • 6 months (kg per µg/dL): 0.013 (0.098); p=0.89 • 12 months (kg per µg/dL): 0.124 (0.107); p=0.25
		Weight for length	Regression coefficients (SE): • 6 months(per µg/dL): -0.158 (0.111); p=0.16 • 12 months (per µg/dL): 0.084 (0.111); p=0.45

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
		Head circumference	Regression coefficients (SE): • **6 months (cm per µg/dL): -0.242 (0.094); p=0.01*** • **12 months (cm per µg/dL): -0.220 (0.109); p=0.05***
		Upper arm circumference	Regression coefficients (SE): • 12 months (cm per µg/dL):-0.132 (0.114); p=0.25
Yang et al. 2013a Cross sectional study; n=246 children (aged 3–8 years)	Child PbB mean: 7.30	Height	**β coefficient(cm per µg/dL): -0.10; p=0.02***
		Weight	**β coefficient (kg per µg/dL): -0.14; p=0.01***
		BMI	β coefficient (kg/m^2 per µg/dL): -0.08;p=0.24

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 13 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Values are for maternal PbB, unless otherwise specified.
[d]Asterick indicates association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.

BMI = body mass index; CI = confidence interval; NS = not statistically significant; OR = odds ratio; Pb = lead; SD = standard deviation; SE = standard error

Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty at Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Onset of puberty in females			
Den Hond et al. 2011 Cross-sectional study; n=792 girls (aged 14–15 years)	Median: 1.81	Pubic hair development	**OR: 0.65 (0.45, 0.93); p=0.020***
Denham et al. 2005 Cross-sectional study; n=138 girls (aged 10–16.9 years)	Mean: 0.49	Attainment of menarche	**β coefficient (SE) predicting likelihood of attaining menarche (per ln µg/dL): -1.29 (0.494); p=0.01***
Gollenberg et al. 2010 Cross-sectional study; n=705 girls (aged 6–11 years)	Median: 2.5 Tertiles • T1: <1.0 • T2: 1–4.99 • T3: ≥5.00	Inhibin B pubertal cutoff value	**OR for exceeding pubertal cutoff value:** • **T2 (OR): 0.38 (0.12, 1.15)*** • **T3 (OR): 0.26 (0.11, 0.60)***
Naicker et al. 2010 Cross-sectional, longitudinal study; n=682 girls (aged 13 years)	Mean: 4.9	Breast development	**Trend analysis over ages 8–16 years: p<0.001***
		Pubic hair development	**Trend analysis over ages 8–16 years: p<0.001***
		Attainment of menarche	**Trend analysis over ages 8–16 years: p<0.001***

Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty at Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Selevan et al. 2003 Cross-sectional study; n=2,186 girls (aged 8–18 years)	Gmean • NHW: 1.4 • NHAA: 2.1 • MA: 1.7	Breast development	• NHW OR: 0.82 (0.47, 1.42) • **NHAA OR: 0.64 (0.42, 0.97); p<0.05*** • **MA OR**: **0.76 (0.63, 0.91); p<0.05***
		Pubic hair development	• NHW OR: 0.75 (0.37, 1.51) • **NHAA OR: 0.62 (0.41, 0.96); P<0.05** • **MA OR: 0.70 (0.54, 0.91); p<0.05**
		Age of menarche	• NHW HR: 0.74 (0.55, 1.002) • **NHAA HR: 0.78 (0.63, 0.98); p<0.05 (age at menarche delayed 3.6 months)*** • MA HR: 0.90 (0.73, 1.11)
Wolff et al. 2008 Cross-sectional study; n=192 girls (aged 9 years)	Median: 2.4	Breast development	PR for breast stage ≥2 versus stage 1: 1.01 (0.79,1.30)
		Pubic hair development	PR for pubic hair stage ≥2 versus stage 1: 1.25 (0.83, 1.88)
Wu et al. 2003b Cross-sectional study; n=1,706 girls (aged 8–16 years)	Mean: 2.5 Tertiles: • T1: 0.7–2.0 (reference) • T2: 2.1–4.9 • T3: 5.0–21.7	Breast development	• OR for T2: 1.51 (0.90, 2.53) • OR for T3: 1.20 (0.51, 2.85)
		Pubic hair development	• **OR for T2: 0.48 (0.25, 0.92)*** • **OR for T3: 0.27 (0.08, 0.93)***
		Attainment of menarche	• **OR for T2: 0.42 (0.18, 0.97)*** • **OR for T3: 0.19 (0.08, 0.43)***
Onset of puberty in males			
Den Hond et al. 2011 Cross-sectional study; n=887 boys (aged 12–15 years)	Median: 2.50	Onset of puberty	No association between PbB and the onset of puberty (specific data not reported)

Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty at Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Hauser et al. 2008 Cross-sectional study; n=489 peripubertal boys (aged 8–9 years)	Median: 3	Genitalia development	**OR for having entered genitalia stage G2 for PbB ≥5 compared to PbB <5: 0.57 (0.34, 0.95); p=0.03***
Williams et al. 2010 Longitudinal cohort; n=489 peripubertal boys (aged 8–9 years)	Median: 3	Testicular volume	**HR for testicular volume <3 mL for PbB ≥5 µg/dL compared to PbB <5 µg/dL: 0.73 (0.55, 0.97); p=0.03***
		Genitalia stage	**HR for having entered genitalia stage G2 for PbB ≥5 µg/dL compared to PbB <5 µg/dL: 0.76 (0.59, 0.98); p=0.04***
		Pubic hair stage	HR for having entered pubic hair stage G2 for PbB ≥5 µg/dL compared to PbB <5 µg/dL: 0.69 (0.44, 1.07); p=0.10

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 13 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Values are for maternal PbB, unless otherwise specified.
[d]Asterick indicates association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.

CI = confidence interval; MA = Mexican Americans; NHW = Non-Hispanic whites; NHAA = Non-Hispanic African Americans; NS = not statistically significant; OR = odds ratio; Pb = lead; PR = prevalence ratio; SE = standard error

Associations Between Bone Pb and Birth Outcome and Post-Natal Growth. Studies evaluating associations between maternal bone Pb and birth outcome (birth weight and length, head circumference) and postnatal growth (infant and child weight gain) are summarized in Table 2-45. Studies were conducted in mother-infant/child pairs residing in Mexico City. Maternal tibia Pb was negatively associated with birth weight (Cantonwine et al. 2010b; Gonzalez-Cossio et al. 1997; Kordas et al. 2009), birth length (Hernandez-Avila et al. 2002), and head circumference (Hernandez-Avila et al. 2002; Kordas et al. 2009). Maternal patella Pb was associated with decreased head circumference (Hernandez-Avila et al. 2002), but not birth weight (Afeiche et al. 2011; Gonzalez-Cossio et al. 1997) or birth length (Hernandez-Avila et al. 2002). Infant weight gain measured at 1 month of age was negatively associated with maternal patella Pb, but not maternal tibia Pb (Sanin et al. 2001); no associations between maternal tibia or patella Pb were observed from birth to 12 months of age (Afeiche et al. 2011). Maternal patella Pb was negatively associated with weight gain in girls, but not boys, at 5 years of age; however, no associations were observed for maternal tibia Pb for boys or girls. Taken together, results of these studies provide evidence that long-term maternal Pb exposure is negatively associated with infant size and post-natal growth.

Table 2-45. Associations Between Maternal Bone Pb and Birth Outcome and Postnatal Growth

		Effect				
Reference	Population[a]	Birth weight	Birth length	Head circumference	Infant weight gain	Child weight gain[b]
Afeiche et al. 2011	Mother-infant pairs (522 boys; 477 girls)	0 T (M, F) 0 P (M, F)	–	–	0 T (M, F)[c] 0 P (M, F)[c]	0 T (M, F) 0 P (M) ↓ P (F)
Cantonwine et al. 2010b	538 mother-infant pairs	↓ T	–	–	–	–
Gonzalez-Cossio et al. 1997	272 mother-infant pairs	↓ T 0 P	–	–	–	–
Hernandez-Avila et al. 2002	223 mother-infant pairs	–	↓ T 0 P	↓ T ↓ P	–	–
Kordas et al. 2009	474 mother-infant pairs	↓ T	0 T	↓ T	–	–

Table 2-45. Associations Between Maternal Bone Pb and Birth Outcome and Postnatal Growth

		Effect				
Reference	Population[a]	Birth weight	Birth length	Head circumference	Infant weight gain	Child weight gain[b]
Sanin et al. 2001	329 mother-infant pairs	–	–	–	0 T[d] ↓ P[d]	–

[a]From Mexico City.
[b]Measured at 5 years of age.
[c]Measured from birth to 12 months of age.
[d]Measured at 1 month of age.

↓ = negative association; 0 = no association; – = not reported; F = female; M = male; P = patella; Pb = lead; T = tibia

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in adverse development effects. EPA (2014c) specifically noted that delayed puberty may result from alterations in pulsatile release of sex hormones and that insulin-like growth factor 1 (IGF-1) may play a role in this effect. Pb is distributed to the fetus and has been measured in umbilical cord blood, placenta, and follicular fluid (See Section 3.1.2, Toxicokinetics, Distribution), providing a toxicokinetic mechanism for direct exposure of the fetus.

2.19 CANCER

Overview. Numerous epidemiological studies have investigated associations between Pb exposure and cancer. Studies include exposure of workers and general populations, with many studies reporting PbB. In most studies, mean PbBs in these studies are <10 µg/dL. Although studies provide limited evidence of carcinogenicity of Pb in humans, results are inconsistent and interpretation may be limited due to confounding factors.

Many studies of occupational cohorts and cancer risks do not report PbB data. These studies have reported associations between occupational exposure to Pb and cancer, including overall cancer mortality and cancers of the lung, brain, stomach, kidney, and bladder. However, results are inconsistent and interpretation may be limited due to confounding factors.

The following cancers have been associated with PbB:

- ≤10 µg/dL:
  - Increased risk of all cancer; evaluated in multiple studies with mixed results.
  - Increased risk of lung cancer; evaluated in multiple studies with mixed results.
- >10 µg/dL:
  - Increased risk of all cancer; evaluated in multiple studies with mixed results.
  - Increased risk of respiratory tract cancers (bronchus, trachea, lung); evaluated in multiple studies with mixed results.
  - Increased risk of stomach cancer; evaluated in multiple studies with mixed results.
  - Increased risk of intestinal cancer.
  - Increased risk of cancer of the larynx.
  - Increased risk of glioma.

Carcinogenicity Classifications of Pb and Pb Compounds. IARC has classified inorganic Pb compounds as probably carcinogenic to humans (Group 2A) based on sufficient evidence in animals and limited evidence in humans; evidence for organic Pb compounds was considered to be inadequate in humans and animals (IARC 2006). The National Toxicology Program 14th Report on Carcinogens classified Pb and Pb compounds as reasonably anticipated to be human carcinogens (NTP 2016). As the basis of the Group 2A classification for inorganic Pb compounds, IARC (2006) cited multiple animal studies showing kidney cancer following chronic oral and parenteral exposure (Azar et al. 1973; Balo et al. 1965; Fears et al. 1989; Kasprzak et al. 1985; Koller et al. 1985; Van Esch and Kroes 1969; Zawirska 1981; Zollinger 1953), renal tubular adenoma in offspring of mice exposed during gestation and lactation (Waalkes et al. 1995), and brain gliomas following oral exposure of rats (Zawirska 1981; Zawirska and Medras 1972). For epidemiological studies of occupational cohorts, IARC (2006) noted limited evidence of carcinogenicity of the lung, stomach, kidney, and brain/nervous system, although studies yielded inconsistent results, and interpretation of results was compromised due to potential confounding factors (e.g., smoking, occupational exposure to other carcinogens such as arsenic).

Confounding Factors and Effect Modifiers. Numerous factors can influence results of epidemiological studies evaluating associations between Pb exposure and cancer, including smoking status, family history of cancer, and co-exposure to other carcinogens. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome. For example, many occupational studies include smelters where

exposure to arsenic and other carcinogenic metals (e.g., cadmium) can be correlated with exposure to Pb. Exposures to Pb occur throughout the lifetime and a cross-sectional evaluation of PbB may not adequately represent the exposure history of the individual.

Measures of Exposure. Numerous studies evaluating cancer in general populations and Pb-exposed workers report PbB as a measure of exposure. A few studies measured exposure by bone Pb concentrations, cumulative blood Pb index, or cumulative exposure (Bhatti et al. 2009; Englyst et al. 2001; Ionescu et al. 2007; Rajaraman et al. 2006); however, these studies did not report PbB.

Characterization of Effects. Numerous epidemiological studies have assessed associations between PbB and cancer. Studies of general populations and workers are briefly summarized in Table 2-46. Studies of general populations include large cross-sectional studies (n=5,482–13,946) of NHANES participants (Cheung et al. 2013; Jemal et al. 2002; Menke et al. 2013; Schober et al. 2006). Mean PbBs in most studies are <10 µg/dL, although in some studies that stratify by PbB, the highest exposure categories are >10 µg/dL (Jemal et al. 2002; Kelly et al. 2013; Schober et al. 2006). Results of two studies with PbB <10 µg/dL show increased risks of all cancer and of lung cancer (Cheung et al. 2013; Schober et al. 2006), although other studies show no increases in cancer risk (Jemal et al. 2002; Khalil et al. 2009; Kelly et al. 2013; Menke et al. 2013; Santibanez et al. 2008; Wiesskoph et al. 2009). Results of occupational exposure studies are mixed and do not establish a pattern of effects of exposure-response relationships. PbBs in these studies generally are >40 µg/dL. Studies have reported associations between PbB and all cancer (Anttila et al. 1995; Lundstrom et al. 1997; Lustberg and Silbergeld 2002; McElvenny et al. 2015; Wong and Harris et al. 2000), cancers of the bronchus, trachea, and lung (Anttila et al. 1995; Chowdhury et al. 2014; Kim et al. 2015; Lundstrom et al. 1997; McElvenny et al. 2015; Steenland and Boffetta 2000), cancer of the larynx (Chowdhury et al. 2014), stomach cancer (Cooper et al. 1985; Steenland and Boffetta 2000; Wong and Harris et al. 2000), intestinal cancer (Kim et al. 2015), and gliomas (Anttila et al. 1996).

Many studies of occupational cohorts with high exposure to Pb and cancer risks do not report PbB data (Bertazzi and Zocchetti 1980; Bhatti et al. 2009; Cocco et al. 1994, 1997, 1998a, 1998b, 1999a, 1999b; Davies 1984a, 1984b; Dingwall-Fordyce and Lane 1963; Fayerweather et al. 1997; Hu et al. 1999; Jones et al. 2007; Kauppinen et al. 1992; Lin et al. 2009; McElroy et al. 2008; Michaels et al. 1991; Pan et al. 2011; Partanen et al. 1991; Pesch et al. 2000; Rajaraman et al. 2006; Risch et al. 1988; Rousseau et al. 2007; Sankila et al. 1990; Sheffet et al. 1982; Siemiatycki 1991; Sweeney et al. 1986; van Wijngaarden and Dosemeci 2006; Wingren and Englander 1990). Although results of these studies are mixed and

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
General population			
Cheung et al. 2013 Cross-sectional study; n=3,482 (NHANES III)	Mean (SE): 4.44 (0.14)	All cancer	**OR: 1.071 (1.036, 1.106)***
		Lung cancer	**OR: 1.090 (1.054, 1.127)***
Jemal et al. 2002 Cross-sectional study; n=3,592 (NHANES II, age 6 months–74 years)	Quartiles: • Q1: ≤9.8 • Q2: 9.9–12.9 • Q3: 13.0–16.9 • Q4: ≥17.0	All cancer	Adjusted RR Q4: 1.50 (0.75, 3.01)
Khalil et al. 2009 Prospective cohort study; n=532 women (age 65–87 years)	Mean: 5.3 <8 (n=453) ≥8 (n=79)	All cancer	Adjusted HR PbB ≥8 (versus <8): 1.64 (0.73, 3.71)
Kelly et al. 2013 Nested case-control study; n=194 cases NHL; 76 cases MM; and 270 controls (mean age 53.08 years)	Mean (range) • Males: 6.18 (1.54, 67.2) • Females: 5.27 (1.1, 40.1) Quartiles • Q1: 1.54–3.93 • Q2: 3.93–5.88 • Q3: 5.88–8.72 • Q4: 8.75–40.1	NHL	OR Q4: 0.93 (0.43, 2.02) p-trend=0.849
		MM	OR Q4: 1.63 (0.45, 5.94) p-trend=0.533
Menke et al. 2006 Cross-sectional study; n=13,946 (NHANES 1988–1994; mean age 44.4 years)	Mean: 2.58 Tertiles: • T1: <1.93 • T2: 1.94–3.62 • T3: ≥3.62	All cancer	Adjusted OR • T2: 0.72 (0.46, 1.12); p-trend=0.130 • T3: 1.10 (0.82, 1.47); p-trend=0.101

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
Santibanez et al. 2008 Case-control study; n=185 esophageal cancer patients; 285 controls (age 30–80 years)	Low: ≤4.9 High: >4.9	Esophageal	Adjusted OR • Low: 0.79 (0.43, 1.46) • High: 1.69 (0.57, 5.03)
Schober et al. 2006 Cross-sectional study; n=9,757 (NHANES III; age ≥40 years)	Tertiles • T1: <5 (mean 2.6) • T2: 5–9 (mean 6.3) • T3: >10 (mean 11.8)	All cancer	Adjusted RR • **T2: 1.44 (1.12, 1.86)*** • **T3: 1.69 (1.14, 2.52)*** • **p-trend<0.01***
Weisskopf et al. 2009 Prospective study; n=868 men (Normative Aging Study; age 21–80 years)	Mean (SD): 5.6 (3.4) Tertiles: • T1: <4 • T2: 4–6 • T3: >6	All cancer	**Adjusted HR T3: 0.48 (0.25–0.91)*; p-trend=0.02**
Workers			
Anttila et al. 1995 Cross-sectional study; n=20,700 workers (age 30–74 years)	Tertiles: • T1: 0–18.6 • T2: 20.7–39.4 • T3: 41.1–161.6	All cancer	**SMR T2: 1.4 (1.1, 1.8)*** SMR T3: 1.2 (0.9, 1.8)
		Lung, trachea	**SMR T2: 2.0 (1.2, 3.2)*** SMR T3: 1.5 (0.8, 2.1)
Anttila et al. 1996 Cross-sectional study; n=20,741 workers (age 18–74 years)	Tertiles: • T1: 2.1–14.5 • T2: 16.6–26.9 • T3: 29.0–89.1	All nervous system cancers	Adjusted OR T3: 2.2 (0.7, 6.6) p-trend=0.17
		Glioma	**Adjusted OR T3: 11 (1.0, 626)*** **p-trend: 0.037**

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
Chowdhury et al. 2014 Survey study/cross-sectional; n=58,368 male workers (mean age 38.9 years)	Quartiles • Q1: 0–<5 • Q2: 5–<25 • Q3: 25–<40 • Q4: ≥40	Lung	**SMR Q4: 1.20 (1.03, 1.39)***
		Brain	SMR Q4: 0.83 (0.41, 1.49)
		Kidney	SMR Q4: 0.72 (0.33, 1.37)
		Stomach	SMR Q4: 0.92 (0.44, 1.69)
		Esophagus	SMR Q4: 0.65 (0.32, 1.16)
		Larynx	**SMR Q4: 2.11 (1.05, 3.77)***
		Bladder	SMR Q4: 0.70 (0.28, 1.45)
Cooper et al. 1985 Cohort study; n=4,519 battery workers; 2,300 smelters	Mean • Battery (n=1,326): 62.7 • Smelters (n=537): 79.7	All cancer	Battery PMR: 1.06 (0.96, 1.16) Smelters PMR: 1.02 (0.87, 1.19)
		Stomach	**Battery PMR: 1.54 (1.11, 2.15)*** Smelters PMR: 1.03 (0.75, 1.42)
		Large intestine	Battery PMR: 0.98 (0.69, 1.40) Smelters PMR: 1.19 (0.62, 2.28)
		Larynx	Battery PMR: 1.19 (0.54, 2.65) Smelters PMR (95% CI): 1.06 (0.27, 4.21)
		Bronchus, trachea, lung	Battery PMR: 1.16 (0.97, 1.39) Smelters PMR: 1.13 (0.84, 1.51)
		Brain and other CNS	Battery PMR: 1.09 (0.55, 2.18) Smelters PMR: 0.97 (0.32, 3.01)

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
Kim et al. 2015 Cross-sectional study; n=81,067 inorganic Pb workers (54,788 males; 26,279 females; age 20–≤50 years)	Mean (SD) • Males: 8.8 (8.5) • Females 5.8 (5.4) Tertiles: • T1: <10 • T2: 10–20 • T3: >20	All cancer	Males: RR T3: 0.95 (0.56, 1.61) Females RR T3: 1.68 (0.40, 7.13)
		Stomach	Males: RR T3: 0.80 (0.23, 2.71) Females RR T2: 1.82 (0.20, 16.36) Females T3: No cases
		Colo-rectal	Males: RR T3: 1.86 (0.35, 9.79) **Females RR T2: 13.42 (1.21, 149.4)*; p<0.05** Females T3: No cases
		Liver	Males: RR T3: 1.72 (0.72, 4.14) Females T2 RR: 0.83 (0.10, 6.56) Females T3: No cases
		Bronchus, lung	Males: RR T3: 0.46 (0.10, 2.01) **Females RR T2: 10.45 (1.74, 62.93)*; p<0.05** **Females RR T3: 12.68 (1.69, 147.86)*; p<0.05**
Lundstrom et al. 1997 Cross-sectional; n=3979 workers	Mean: • In 1950: 62.2 • In 1987: 33.2	All cancer	**SMR: 1.2 (1.0, 1.5)***
		Lung	**SMR: 2.8 (2.0, 3.8)***
Lundstrom et al. 2006 Nested case-referent study; 3,979 smelter workers	Peak: Cases (n=40): 49.7 Referents (n=114): 55.9	Lung	OR: 0.93 (0.60, 1.44)
Lustberg and Silbergeld 2002 Cross-sectional study; n=4,292; age 30–74 years (NHANES II)	Tertiles: • T1 (n=818): <10 • T2 (n=2,735): 10–19 • T3 (n=637): 20–29	All cancer (rate ratio)	RR T2: 1.46 (0.87, 2.48) **RR T3: 1.68 (1.02, 2.78)***

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
McElvenny et al. 2015 Cohort study; n=9,122 workers; mean age 29.2 years	Mean (SD): 44.3 (22.7) Range: 2.3–321.5	All cancer	**SMR: 1.13 (1.07, 1.20)***
		Esophagus	SMR: 1.05 (0.78, 13.8)
		Stomach	SMR: 1.11 (0.86, 1.43)
		Colon	SMR: 0.98 (0.77, 1.26)
		Kidney	SMR: 1.30 (0.91, 1.86)
		Bladder	SMR: 0.95 (0.67, 1.35)
		Bronchus, trachea, lung	**SMR: 1.42 (1.29, 1.57)***
		Brain	SMR: 0.92 (0.61, 1.38)
Selevan et al. 1985 Retrospective cohort study; n=1,987 male workers	Mean: 56.3	All cancer	SMR: 0.95 (0.78, 1.14)
		Digestive organs	SMR: 0.77 (0.52, 1.10)
		Respiratory system	SMR: 1.11 (0.80, 1.51)
		Kidney	SMR: 2.04 (0.75, 4.44)
		Bladder	SMR: 1.44 (0.53, 3.14)
Steenland and Boffetta 2000 Meta-analysis; data from eight studies on Pb workers; n=36,027 workers	Range of study means: 26–80	Lung	**RR: 1.14 (1.04, 1.25)***
		Stomach	**RR: 1.34 (1.14, 1.57)***
		Brain	RR: 1.06 (0.81, 1.40)
Steenland et al. 1992 Cohort study (same cohort as Selevan et al. 1985); n=1,990 male smelter workers	Mean: 56.3	All Cancer	SMR: 0.98 (0.84, 1.12)
		Colon	SMR: 0.48 (0.22, 0.90)
		Lung	SMR: 1.18 (0.92, 1.48)
		Kidney	SMR: 1.93 (0.88, 3.67)

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
Wong and Harris et al. 2000 Cohort study; n=4,519 battery workers; 2,300 smelters (same cohort as Cooper et al. 1985)	Mean: • All workers: 64.0 • Battery workers: 62.7 • Smelters: 79.7	All cancer	**SMR: 1.045 (1.012, 1.080)***
		Stomach	**SMR: 1.474 (1.125, 1.898)***
		Large intestine	SMR: 0.994 (0.789, 1.235)
		Bronchus, trachea, lung	SMR: 1.164 (1.039, 1.299)
		Kidney	SMR: 0.636 (0.339, 1.087)
		CNS	SMR: 0.748 (0.419, 1.234)

[a]Asterick indicates association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.

CI = confidence interval; CNS = central nervous system; HR = hazard ratio; MM = multiple myeloma; NHANES = National Health and Nutrition Examination Survey; NHL = non-Hodgkin's lymphoma; OR = odds ratio; Pb = lead; PMR = proportionate mortality ratio; RR = rate ratio or relative ratio; SD = standard deviation; SE = standard error; SMR = standard mortality ratio

interpretation may be limited due to confounding factors, associations have been reported between occupational exposure to Pb and cancer, including overall cancer mortality and cancers of the lung, brain, stomach, kidney, and bladder.

Mechanisms of Action. Numerous mechanisms for Pb-induced carcinogenicity have been proposed (EPA 2014c); however, it is likely that a combination of mechanisms, rather than a single mechanism, is involved. Although Pb is considered to be only weakly mutagenic, it has been shown to produce DNA damage (single and double strand breaks), sister chromatid exchanges (SCEs), chromosome aberrations, micronuclei (MN) formation, and cytogenetic damage. Epigenetic mechanisms (e.g., changes in gene expression in the absence of changes to DNA), post-translational alterations to protein structure, and immune modulation of tumorigenesis in response to Pb-induced ROS oxidative damage and inflammation have also been proposed as possible mechanisms involved in Pb-induced carcinogenesis.

2.20 GENOTOXICITY

The genotoxicity of Pb has been studied in Pb workers and the general population, in *in vivo* animal models, and *in vitro* cultures of microorganisms and mammalian cells. For the following discussions, data from epidemiological studies on genotoxicity were obtained from the primary literature. Information on *in vitro* studies and *in vivo* animal studies was taken from comprehensive reviews of Pb genotoxicity (EPA 2014c; Garcia-Leston et al. 2010; IARC 2006; NTP 2003).

Epidemiological Studies

Overview. Epidemiological studies have examined genotoxic effects associated with Pb exposure in adults (general populations and workers) and children. Most studies were conducted in small populations of workers. Numerous studies with PbB ≥10 μg/dL report positive associations for exposure to Pb and genotoxic endpoints (gene mutation, DNA damage, SCE, MN formation, and DNA methylation); results are generally positive, although some negative associations have been reported. Few epidemiology studies have evaluated genotoxicity at PbB ≤10 μg/dL.

The following genotoxic effects have been associated with PbB:

- ≤10 µg/dL:
  - Gene mutation.
  - DNA damage; evaluated in a few studies with mixed results.
  - DNA methylation; positive results, corroborated in a few studies.
- >10 µg/dL:
  - DNA damage; corroborated in numerous studies.
  - Decreased telomere length.
  - Chromosomal aberrations; evaluated in numerous studies with mainly positive results.
  - Sister chromatid exchange; evaluated in numerous studies with mainly positive results.
  - Micronuclei formation; evaluated in numerous studies with mainly positive results.

Measures of Exposure. Studies evaluating the association between genotoxic effects and Pb exposure typically evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. Most epidemiological studies evaluating genotoxic effects were conducted in worker populations. Therefore, potential co-exposure to other genotoxic compounds (such as arsenic) could occur, complicating interpretation of results. In addition, many studies were conducted in small populations (n<100).

Characterization of Effects. General trends for studies demonstrating associations between PbB and genotoxic effects are shown in Table 2-47. Additional study details are provided in the *Supporting Document for Epidemiological Studies for Lead,* Table 14. Although few studies have evaluated genotoxic effects at PbB ≤10 µg/dL (see discussion below), numerous studies in adult workers with mean PbBs ranging from 20 to >50 µg/dL provide evidence of increased DNA damage, chromosomal aberrations, SCEs, and MN. One study reported decreased telomere length in workers (Pawlas et al. 2016). A few studies in workers reported negative findings for chromosomal aberrations (Anwar and Kamal 1988; Bulsma and DeFrance 1976; Mäki-Paakkanen et al. 1981; Schwanitz et al. 1975) and SCEs (Grandjean et al. 1983; Mäki-Paakkanen et al. 1981); however, positive results for these endpoints were reported in other studies at similar PbBs.

Table 2-47. Overview of Epidemiology Studies Evaluating Genotoxicity Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Gene mutation	Van Larebeke et al. 2004
	DNA damage/repair	Jasso-Pineda et al. 2012
	Decreased telomere length	Pawlas et al. 2015
	DNA methylation	Hanna et al. 2012; Li et al. 2016; Pilsner et al. 2009
	MN	Mielzynska et al. 2006
>10–30	DNA damage/repair	Chinde et al. 2014; Danadevi et al. 2003; Jannuzzi and Alpertunga 2016; Kašuba et al. 2012; Kayaalti et al. 2015b; Méndez-Gómez et al. 2008; Shaik and Jamil 2009
	Chromosomal aberrations	Pinto et al. 2000
	SCE	Anwar and Kamal 1988; Pinto et al. 2000
	MN	Chinde et al. 2014; Khan et al. 2010b; Kašuba et al. 2012;Nordenson et al. 1978; Pinto et al. 2000
>30–50	DNA damage/repair	Fracasso et al. 2002; Grover et al. 2010
	Decreased telomere length	Pawlas et al. 2016
	Chromosomal aberrations	Forni et al. 1976; Grover et al. 2010; Schwanitz et al. 1970
	SCE	Duydu et al. 2001, 2005; Wiwanitkit et al. 2008; Wu et al. 2002
	MN	Grover et al. 2010; Hamurcu et al. 2001; Minozzo et al. 2004
>50	DNA damage/repair	de Restrepo et al. 2000
	Chromosomal aberrations	Al-Hakkak et al. 1986; Forni et al. 1976; Huang et al. 1988; Nordenson et al. 1978; Schwanitz et al. 1970
	SCE	Huang et al. 1988
	MN	Shaik and Jamil 2009; Singh et al. 2013; Vaglenov et al. 1998, 2001

DNA = deoxyribonucleic acid; MN = micronuclei; PbB = blood lead concentration; SCE = sister chromatid exchange

Results of genotoxicity studies conducted in small populations of children (n=12–103) are inconsistent; for study details, see the *Supporting Document for Epidemiological Studies for Lead,* Table 14. Mixed results were observed for studies on DNA damage, with positive associations at mean PbBs of 7.3 and 28.5 µg/dL (Méndez-Gómez et al. 2008; Jasso-Pineda et al. 2012) and no associations at a mean PbB of 19.5 µg/dL (Méndez-Gómez et al. 2008). No associations were observed for chromosome aberrations at a PbB range of 12–33 µg/dL (Bauchinger et al. 1977) and for SCE at mean PbBs of 7.69 and 62.7 µg/dL (Dalpra et al. 1983; Mielzynska et al. 2006). MN formation was positively associated with a mean PbB of 7.69 µg/dL (Mielzynska et al. 2006), and altered DNA methylation was found in newborns at mean umbilical cord PbB of 6.6 µg/dL (Pilsner et al. 2009).

Effect at Blood Pb Levels ≤10 µg/dL. Results of studies evaluating genotoxic effects of PbB ≤10 µg/dL are summarized in Table 2-48, with study details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 14. Few studies have evaluated genotoxicity at PbB ≤10 µg/dL. Some endpoints were only evaluated in a single study; therefore, it is difficult to draw conclusions. With the exception of a large study conducted in NHANES participants (Zota et al. 2015), genotoxic effects were evaluated in small study populations (n=12–103). Gene mutations were observed in a single study of Finnish women at a PbB range of 1.6–5.2 µg/dL (Van Larebeke et al. 2004). Results of studies on DNA damage are mixed, with no associations in adult workers at PbB means of 2.1–4.4 µg/dL (Al Bakheet et al. 2013; Hengstler et al. 2003), and positive associations in a small study of children with a mean PbB of 7.3 µg/dL (Jasso-Pineda et al. 2012). No effect on telomere length was observed in a large NHANES study of adults with a mean PbB of 1.67 µg/dL (Zota et al. 2015). No associations were observed for SCE in a single study in workers with a mean PbB of 9.3 µg/dL and for MN in children with a mean PbB of 7.69 µg/dL (Meilzynska et al. 2006; Wu et al. 2002). Studies on DNA methylation showed positive associations in adult women undergoing *in vitro* fertilization (median PbB 2.88 µg/dL), in children (mean PbB 1.36 µg/dL), and in newborns (mean umbilical cord PbB 6.6 µg/dL) (Hanna et al. 2012; Li et al. 2016; Pilsner et al. 2009).

***In Vivo* Animal Models and I*n Vitro* Cultures of Mammalian Cells and Microorganisms.** Numerous studies have investigated the genotoxicity of Pb using *in vivo* animal models and cultured mammalian cells and microorganisms. Rather than reviewing these numerous studies, an overview of findings is summarized below. This information was taken from the following reviews: EPA 2006, 2014c; IARC 2006; NTP 2016.

In vivo studies in animals. DNA damage has been observed in several *in vivo* exposure studies in rodents. DNA damage (single strand breaks), as measured in comet assays, was observed in various organ systems, bone marrow, leukocytes, and spermatozoa of mice and rats following repeated inhalation or oral exposures to Pb or Pb acetate. Global hypomethylation in hepatic DNA of rats was observed following single intravenous injection of Pb nitrate; hypomethylation was associated with an increase in cell proliferation. Exposure to Pb compounds is correlated with increased DNA synthesis and cell proliferation in the mammalian liver following intravenous injection. Numerous studies have assessed Pb compounds for chromosomal damage. Chromosomal aberrations were observed in bone marrow cells and spermatocytes of mice and rats following single or repeated exposure (intraperitoneal, gavage, dietary); however, the increase in aberrations did not consistently demonstrate dose-dependence.

Table 2-48. Results of Genotoxicity Studies at Blood Lead Concentration (PbB) ≤10 µg/dL

PbB or range (µg/dL)	Population (n)	Gene mutation	DNA damage	Telomere length	SCE	MN	DNA methylation	Reference
1.6–5.2	Women (99)	↑	NA	NA	NA	NA	NA	Van Larebeke et al. 2004
2.1	Men (40)	NA	0	NA	NA	NA	NA	Al Bakheet et al. 2013
3.28	Children (99)	NA	NA	↓	NA	NA	NA	Pawlas et al. 2015
4.4	Workers (78)	NA	0	NA	NA	NA	NA	Hengstler et al. 2003
7.3	Children (12)	NA		NA	NA	NA	NA	Jasso-Pineda et al. 2012
1.67	Adults (6,796)[a]	NA	NA	0	NA	NA	NA	Zota et al. 2015
9.3	Workers (34)	NA	NA	NA	0	NA	NA	Wu et al. 2002
7.69	Children	NA	NA	NA	NA	0	NA	Meilzynsja et al. 2006
>0.73	Women (43)	NA	NA	NA	NA	NA	↓	Hanna et al. 2012
1.45	Adults (78)[b]	NA	NA	NA	NA	NA	↓	Li et al. 2016
6.6[c]	Newborns (103)	NA	NA	NA	NA	NA	↑↓	Pilsner et al. 2009

[a]NHANES participants.
[b]Prospective study; genotoxicity assessed in adults and evaluated against PbB obtained during childhood (birth–78 months).
[c]Umbilical cord PbB.

↑ = increase observed for specific effect; ↓ = decrease observed for specific effect; ↑↓ = decreased DNA methylations at some differentially methylated regions, and increased DNA methylation at other regions; 0 = no effect observed; DNA = deoxyribonucleic acid; MN = micronuclei; NA = not assessed; NHANES = National Health and Nutrition Examination Survey; SCE = sister chromatid exchange

Exposure to Pb compounds has been associated with SCEs in bone marrow of mice and rats following intravenous exposure. Studies assessing Pb compounds for MN formation in bone marrow erythrocytes of rats and mice were positive for multiple exposure routes (gavage, drinking water, intraperitoneal).

In vitro studies in human cell lines. *In vitro* studies in human cells lines have yielded mixed results. Pb acetate was weakly mutagenic in keratinocytes in the presence of 6-thioguanine, but not mutagenic in human foreskin, fibroblasts, or lung carcinoma cells. Results of assays assessing Pb compounds for DNA damage in human cell cultures were inconsistent. Double or single DNA strand breaks have been observed in peripheral blood lymphocytes, endothelial cells, hTERT-immortalized human skin fibroblasts, and HepG2 cells, but not in HeLa cells. DNA-protein crosslinks were observed in lymphoma cells exposed to 100 µM Pb acetate, although cross-links were not observed for Pb nitrate at concentrations up to 10,000 µM. Studies investigating SCEs and MN formation in human lymphocytes were positive following exposure to Pb nitrate and Pb chloride; however, no SCEs were observed in human lung cells or primary lymphocytes exposed to Pb. Interpretation of *in vitro* studies is challenging because concentrations used in these studies typically are very high and are not relevant to environmental or occupational exposures. As discussed in Section 3.1.2 (Toxicokinetics, Distribution), >99% of Pb in blood is bound to erythrocytes, leaving <1% available in plasma. Thus, plasma levels of Pb are far lower (at least two orders of magnitude) than the concentrations examined in *in vitro* studies in human cell lines. This leads to the introduction of considerable bias when interpreting study results (Bannon and Williams 2017).

In vitro studies in prokaryotic and mammalian cells. Mutagenicity tests of Pb compounds in prokaryotic organisms have mostly yielded negative results. Studies assessed gene mutation and DNA damage in *Salmonella typhimurium, Escherichia coli,* and *Bacillus subtilis* and gene conversion and mitotic recombination in *Saccharomyces cerevisiae* in the presence or absence of metabolic activation. The only Pb compound that yielded positive results for gene mutation in *S. typhimurium* and *E. coli* was Pb bromide. Results of *in vitro* studies in mammalian cells for Pb compounds are mixed. Mutagenicity assays (hypoxanthine phosphorybosyl transferase [HPRT] and glutamate pyruvate transaminase [gpt] assays) were mutagenic in Chinese hamster ovary (CHO) and CHV79 cells at higher concentrations (>100 µM) and negative at lower concentrations (<100 µM). Pb chloride was the only Pb compound that was consistently mutagenic (gpt assay) in CHO cells at low concentrations (0.1–1.1 µM; equivalent to 2.3–23 µg/dL). Comet assays assessing Pb acetate for DNA damage (single strand breaks) in undifferentiated PC12 cells and mouse bone marrow mesenchymal stem cells were positive. Concentration-dependent increases in DNA-protein crosslinks were observed in hepatoma cells exposed

to Pb nitrate, although Pb acetate did not induce single or double DNA strand breaks or DNA crosslinks in CHV79 cells. Exposure to Pb nitrate or Pb glutamate did not induce chromosomal aberrations in CHO cells. Assays assessing Pb compounds for SCEs in CHV79 cells were negative when fewer cells per concentrations were utilized (25–30 cells), but were positive when the number of cells per concentration was increased (100 cells). Conflicting results were reported for MN formation in Chinese hamster cells.

Mechanisms of Action. Several mechanisms of action are likely involved in the genotoxic effects of Pb (EPA 2014c; IARC 2006; NTP 2016). Studies in occupationally exposed populations have found significant correlations between DNA breaks, decreased glutathione levels in the lymphocytes, and increased production of ROS, which may indicate oxidative stress as a possible mechanism for this response. The production of ROS after Pb exposure is a multi-pathway process, which results from oxidation of ALA, membrane and lipid oxidation, NAD(P)H oxidase activation, and antioxidant enzyme depletion. Disruption of functional metal ions that form enzymes (superoxide dismutase [SOD], catalase [CAT], and glutathione peroxidase [GPx]) may occur as part of this process.

2.21 GENERAL CELLULAR MECHANISMS OF ACTION

2.21.1 Perturbation of Ion Homeostasis

Pb exerts many of its adverse effects by perturbing ion homeostasis. This perturbation occurs when Pb displaces other metal ions such as iron, calcium, zinc, magnesium, selenium, and manganese, interfering with the critical biological processes mediated by the ions themselves or by enzymes and proteins that require these ions (reviewed by EPA 2014c; Flora et al. 2012). Among the biological processes that Pb has been shown to affect via its impact on ion homeostasis are: calcium homeostasis; transportation of ions across cell membranes; cellular energetics; and the functioning of numerous proteins involved in cell signaling, growth and differentiation, gene expression, energy metabolism, and biosynthetic pathways.

Calcium Homeostasis. Many of Pb's adverse effects can be traced back to its ability to displace calcium, leading to perturbations of numerous calcium-dependent cellular functions, including energy metabolism, apoptosis, cellular motility, signal transduction, and hormonal regulation (reviewed by EPA 2014c). In addition, intracellular migration of Pb has been shown in several cell lines (HEK293, HeLa, and PC12) to occur via calcium channels; higher Pb permeation correlated with lower calcium concentrations, suggesting that Pb competed with calcium for the channel binding sites.

Ion Transport. Pb has been shown to disrupt the transportation of critical cations across the cell membrane by decreasing the activity of ATPases (including Na+/K+-, Ca2+, and Mg2+-ATPases; reviewed by EPA 2014c). Pb-induced inhibition of ATPase activities has been shown in the kidneys, livers, erythrocytes, and brain synaptosomes of rats exposed to Pb in drinking water; in testes of rat pups exposed during lactation and postweaning; in primary cerebellar granule neuronal cultures of rat pups exposed pre- and postnatally; in rabbit kidney membranes and sarcoplasmic reticulum exposed *in vitro*; and in human erythrocyte ghosts. Furthermore, blood or hair Pb levels were inversely correlated with ATPase activities in erythrocytes in several human epidemiological studies.

In addition to ATPases, Pb's action on ion transport includes competitive inhibition of voltage-gated calcium channels (reviewed by EPA 2014c). A number of *in vitro* studies have demonstrated inhibition of calcium transport via voltage gated channels in cultured neurons and neuroblastoma cells, bovine adrenal chromaffin cells, and human embryonic kidney cells. Inhibition of calcium transportation via voltage-gated channels can disrupt release of neurotransmitters, and impaired neurotransmitter release has, in fact, been shown with Pb exposure at low *in vitro* levels. In addition to inhibiting calcium-dependent neurotransmitter release, Pb may mimic calcium, thereby increasing neurotransmitter release in some circumstances. For example, Pb exposure *in vitro* has been shown to induce the spontaneous release of norepinephrine from bovine adrenal chromaffin cells and increase the release of catecholamine from PC12 cells. It has been suggested that Pb may trigger spontaneous neurotransmitter release via activation of calcium/calmodulin-dependent protein kinase II-dependent phosphorylation of synapsin I, or by directly activating synaptotagmin I (a calcium-sensing protein that regulates neurotransmitter release). Intracellular migration of Pb has been shown to occur via calcium channels; higher Pb permeation in several cell lines (HEK293, HeLa, and PC12) correlated with lower calcium concentrations, suggesting that Pb competed with calcium for the channel binding sites.

Pb also disrupts the activity of calcium-dependent potassium channels, as shown by increased efflux of potassium from inverted erythrocyte vesicles, and alterations in potassium channel activation in erythrocytes exposed to Pb (reviewed by EPA 2014c). The nature of the effect on potassium channels is dose-dependent; at low Pb concentrations (<10 µM), potassium channels are activated, while inhibition of the channels is seen at higher Pb concentrations. As with calcium channels, alterations in potassium channel activity may also disrupt neurotransmitter release. In rats exposed to Pb *in utero* and postnatally, potassium-stimulated release of hippocampal GABA was decreased at low exposure levels, but enhanced GABA release was observed at higher exposures (in the absence of calcium).

Cellular Energetics. Evidence indicating that Pb exposure perturbs mitochondrial function and cellular energy metabolism is abundant (as reviewed by EPA 2014c). In rats exposed to Pb via diet or drinking water, renal tubular and epididymal mitochondria exhibited swelling, rupture of the outer membrane, distorted cristae or loss of cristae, vacuolization, inclusion bodies, and fusion with nearby mitochondria. As discussed further in Section 2.21.6, Apoptosis, Pb exposure has been shown to open the mitochondrial transmembrane pore, initiating the apoptotic caspase cascade. Evidence for Pb's effect on energy metabolism includes decreased ATP levels and/or adenylate energy charge (AEC) (along with increased ADP, AMP, and/or adenosine levels) in forebrain synaptosomes from rats exposed via drinking water, in cerebellar granule neuronal cultures from rats exposed by drinking water, in PC-12 cells exposed *in vitro*, and in isolated mitochondria exposed *in vitro*. In osteoblasts exposed *in vitro*, Pb inhibited both coupled and uncoupled respiratory oxygen use in mitochondria. Pb has been proposed to behave as a classic chemical uncoupler of respiration, abolishing the proton gradient necessary for oxidative phosphorylation. In the muscles of rats exposed to Pb in drinking water, decreased activities of the enzymes of complex I and IV of the respiratory chain were observed. However, in forebrain synaptosomes from rats exposed to Pb *in vivo*, oxidative phosphorylation was not inhibited, despite the fact that ATP levels were decreased.

Pb may affect cellular energetics via perturbation of the glycolysis pathway. Decreased glycolysis was observed in osteoblasts and erythrocytes exposed to Pb *in vitro* (reviewed by EPA 2014c). However, increased levels of glycolytic enzymes were noted in workers with higher blood Pb levels, when compared with workers with lower blood Pb, suggesting that Pb may activate anaerobic glycolysis.

Depletion of cellular nucleotide pools required for ATP synthesis has also been observed after Pb exposure of human erythrocytes *in vitro* and in rats exposed via drinking water (reviewed by EPA 2014c). This effect may be mediated by Pb-induced inhibition of enzymes involved in nucleotide biosynthesis in erythrocytes, including adenine phosphoribosyltransferase (see Impaired Protein Function below) and NAD synthetase (which depends on magnesium for activity). In support of the latter mechanism, in humans exposed to Pb, PbB levels were inversely correlated with NAD synthetase activity.

Impaired Protein Function. Pb impairs the functions of numerous proteins, with concomitant effects on signaling, growth and differentiation, gene expression, energy metabolism, and biosynthetic pathways. The mechanisms by which Pb alters protein activity are by displacing metal cofactors or binding to sulfhydryl groups (reviewed by EPA 2014c). Table 2-49 shows proteins known to be bound to or

Table 2-49. Effects of Lead (Pb) on Function of Various Proteins

Protein	General function	Effect of Pb; summary of evidence
Calcium-dependent proteins		
Calcium binding proteins (CABPs I and II)	Regulation of calcium signaling, especially in neuronal cells	No data -Ca^{2+} displacement shown *in vitro*.
Ca^{2+}-dependent K^+ channel	Ion transport; activation of channels regulates neuron firing and neurotransmitter release	Activates or inhibits channel -Pb promoted efflux of K^+ from inverted red blood cell vesicles. -Pb induced activation of K^+ channel in erythrocytes at low Pb concentrations and inhibited activity at high concentrations.
Calmodulin	Cell signaling, including structural integrity, gene expression, and maintenance of membrane potential	Amplifies calmodulin activity -Pb activated calmodulin-dependent phosphodiesterase and cyclic nucleotide phosphodiesterase activities. -Pb stimulated brain membrane phosphorylation. -Pb increased binding of calmodulin to brain membranes.
Mitochondrial transmembrane pore (MTMP)	Triggers mitochondrial apoptosis cascade when open	Opens MTMP, triggering apoptosis -Pb increased mitochondria-regulated apoptotic indicators (cytochrome c, caspases) in rat retinal rod cells and hepatic oval cells *in vitro*.
NAD(P)H oxidase	Inflammatory mediator; triggers oxidative burst (via production of superoxide) in response to infection	Increases activity, leading to ROS generation -Pb increased protein levels of glycosylated subunit of NAD(P)H oxidase in brain, heart, and renal cortex of rats exposed via drinking water and in human coronary artery endothelial cells *in vitro*.
Osteocalcin	Bone resorption, osteoclast differentiation, and bone growth	Alters binding of osteocalcin to hydroxyapatite -Pb exposure has been shown to both increase and decrease binding of osteocalcin to hydroxyapatite.
Parvalbumin	Unclear; may buffer Ca^{2+} levels; expressed at high levels in interneurons	No data -Ca^{2+} displacement shown *in vitro*.
Phospholipase A_2	Hydrolyze fatty acids from membrane phospholipids; released fatty acids are metabolized to bioactive lipid mediators	No data -Ca^{2+} displacement shown *in vitro*.

Table 2-49. Effects of Lead (Pb) on Function of Various Proteins

Protein	General function	Effect of Pb; summary of evidence
Protein kinase C (PKC)	Cell signaling, especially growth and differentiation	Increases or decreases activity -Pb shown to activate PKC *in vitro* in bovine adrenal chromaffin cells, rat brain microvessels, human erythrocytes, and rabbit mesenteric arteries. -Pb decreased PKC activity in mouse macrophages and rat brain cortex.
Synaptotagmin I	Ca^{2+} sensor regulating neurotransmitter release	No data -Ca^{2+} displacement shown *in vitro*.
Troponin C	Ca^{2+} sensor regulating muscle contraction	No data -Ca^{2+} displacement shown *in vitro*.
Heme-dependent proteins		
Catalase	Antioxidant; scavenger of hydrogen peroxide	Increases or decreases activity -Pb shown to increase activity in some studies and decrease activity in others, possibly due to differences in species, exposure duration, dose, or other study design variations.
Guanylate cyclase	Catalyzes synthesis of cGMP, which stimulates vasorelaxation in vascular tissues	Impairs production of cGMP -Pb reduced cGMP in plasma and urine of rats exposed by drinking water. -Pb decreased protein levels of soluble guanylate cyclase in vascular tissue.
Hemoglobin	Oxygen transportation	Impairs heme production needed for synthesis of hemoglobin -Pb binding to hemoglobin demonstrated in human blood.
Magnesium-dependent proteins		
Adenine and hypoxanthine/guanine phosphoribosyltransferases	Recycling of nucleotides	Inhibits activity -Pb inhibited phosphoribosyltransferase activities in erythrocytes of rats exposed via drinking water and in human erythrocytes in vitro.
NAD synthetase (Mg)	Nucleotide biosynthesis	Decreases activity -Blood Pb was inversely correlated with NAD synthetase activity in humans.
Pyrimidine 5'-nucleotidase	Dephosphorylates pyrimidine nucleotides in erythrocytes, preserving purine nucleotides (e.g., ATP, ADP) necessary for energy	Alters protein conformation and amino acid positioning at active site, possibly by occupying active site -Pb binding and protein conformation changes observed *in vitro*. -Pyrimidine nucleotide accumulation in erythrocytes is seen in lead poisoning.

Table 2-49. Effects of Lead (Pb) on Function of Various Proteins

Protein	General function	Effect of Pb; summary of evidence
Zinc-dependent proteins		
δ-ALA (δ-ALAD or porphobilinogen synthase)	Heme biosynthesis (converts δ-ALA to porphobilinogen)	Depletes δ-ALAD, preventing heme biosynthesis and leading to accumulation of δ-ALA. - δ-ALAD shown to be major binding target of Pb in erythrocytes.
GATA zinc finger proteins	Activation/suppression of DNA transcription	Decreases ability of GATA proteins to bind to DNA and regulate transcription -Pb binding to cysteine residues and displacement of Zn from GATA proteins observed *in vitro*. -Pb-bound GATA proteins exhibited reduced DNA binding.
Transcription factors TFIIIA, Sp1, and Erg-1	Activation/suppression of DNA transcription	Decreases ability of TFIIIA, Sp1, and Erg-1 to bind to DNA and regulate transcription -Pb exposure caused dissociation of TFIIIA-DNA adducts. -Pb exposure altered DNA binding profile of Sp-1 and Erg-1 in rat pups exposed via lactation, leading to changes in gene expression.
Proteins altered by lead interaction with via other cations or sulfhydryl groups		
ATPases (Ca^{2+}-, Mg^{2+}-, and Na^{+}/K^{+}-)	Ion transport	Decreases activity -Pb decreased ATPase activities in brain, kidneys, liver, testes, and erythrocytes (cells or tissues).
cGMP phosphodiesterase (Zn, Mg)	Hydrolysis of cGMP	Inhibits activity -Decreased activity observed in homogenized bovine retinas exposed to Pb *in vitro*.
Ferrochelatase (Fe)	Heme biosynthesis; incorporates Fe^{2+} into protoporphyrin IX to form heme	Inhibits insertion of Fe into protoporphyrin ring, leading to substitution by Zn -Zn-protoporphyrin levels correlated with blood Pb levels in humans.
Glutathione peroxidase and glutathione S-transferase (Se)	Antioxidants	Reduces uptake of Se and depletes cellular GSH and protein thiols, resulting in altered GST and GPx enzyme activities -Decreased activity, often with compensatory upregulation of the enzymes, seen in Pb-exposed animals and humans.

Table 2-49. Effects of Lead (Pb) on Function of Various Proteins

Protein	General function	Effect of Pb; summary of evidence
Metallothionein (Zn, Cu)	Trace element homeostasis; free radical scavenging	Sequestered by metallothionein, providing protective effect -Pb toxicity is seen at lower blood Pb levels in humans with low expression of metallothionein or low Pb binding to metallothionein. -Pb induced production of metallothionein in mice exposed via intraperitoneal or intravenous injection and in rats exposed via intraperitoneal injection, but not in rats exposed via drinking water. -Presence of zinc metallothionein reduced effect of Pb on membrane integrity in hepatocytes exposed *in vitro*. -Pb nephrotoxicity and preneoplastic and neoplastic lesions in the testes, bladder, and kidneys were more severe or seen at increased incidences in metallothionein-null mice compared with wild-type.
Superoxide dismutase	Antioxidant; catalyzes conversion of superoxide to hydrogen peroxide; inhibits oxidative inactivation of nitric oxide	Increased or decreased activity -Pb shown to increase activity in several studies and decrease activity in others, possibly due to differences in species, exposure duration, dose, or other study design variations.
Thymosin β-4	Actin regulation; exerts angiogenic, anti-inflammatory, and cardioprotective effects on the heart	No data -Pb binding observed *in vitro.*

ADP = adenosine diphosphate; δ-ALA = aminolevulinic acid; δ-ALAD = aminolevulinic acid dehydratase; ATP = adenosine triphosphate; ATPase = family of phosphatase enzymes that breakdown ATP and ADP; cGMP = cyclic guanosine monophosphate; DNA = deoxyribonucleic acid; Erg-1 = early growth response protein 1; GST = glutathione S-transferase; GSH = glutathione; GPx = glutathione peroxidase; NAD = nicotinamide adenine dinucleotide; NAD(P)H = the reduced form of nicotinamide adenine dinucleotide phosphate; ROS = reactive oxygen species; Sp1 = Transcription factor specificity protein 1; TFIIIA = transcription factor IIIA

Sources: EPA 2014c; Ahamed and Siddiqui 2007; Flora et al. 2012; Gonick 2011

otherwise altered by Pb, along with their functions and brief summaries of the evidence for Pb-induced alterations. As the table suggests, Pb-induced alterations in proteins may play a role in its adverse effects on the neurological, hematological, cardiovascular, and skeletal systems.

Through its displacement of calcium, Pb perturbs the function of several calcium-dependent proteins, including protein kinase C, calmodulin, osteocalcin, the mitochondrial transmembrane pore, and NAD(P)H oxidase (reviewed by EPA 2014c). The protein kinase C family of enzymes is important to cell signaling, growth, and differentiation. Pb exposure has been shown to activate PKC in a number of cell types tested *in vitro* (see table), and to decrease its activity in mouse macrophages and rat brain cortex. Pb stimulates calmodulin activity, as shown by increased activity of several calmodulin-dependent enzymes, and increased binding of calmodulin to brain membranes. In experiments testing the affinity of metal cations to bind calmodulin, Pb was more potent than mercury, cadmium, iron, and even calcium. Pb binding to calmodulin has been postulated as a mechanism for it stimulatory effect on Ca^{2+}/Mg^{2+} ATPase. Calmodulin plays an essential role in maintaining calcium homeostasis and regulating calcium-dependent cell signaling important to structural integrity, gene expression, and maintaining membrane potential (reviewed by EPA 2014c).

Skeletal effects of Pb may be mediated in part by Pb's interference with another calcium-dependent protein: osteocalcin (reviewed by EPA 2014c). The binding of Pb to osteocalcin is much stronger than binding of calcium, and Pb binding alters the structure of osteocalcin. The conformational change in osteocalcin induced by Pb has been postulated as the mechanism by which Pb exposure diminishes the adsorption of osteocalcin to hydroxyapatite.

Other calcium-dependent proteins bound to or impaired by Pb include parvalbumin, phospholipase A2, synaptotagmin I (see *Ion Transport* above), troponin C, the mitochondrial transmembrane pore (see Section 2.21.6, Apoptosis), and NAD(P)H oxidase (see Section 2.21.3, Oxidative Stress) (reviewed by EPA 2014c).

Pb also displaces zinc in a number of critical proteins, including ALAD, GATA proteins, and several zinc-binding transcription factors (TFIIIA, Sp1, and Erg-1) (reviewed by EPA 2014c). Section 2.8 provides a detailed discussion of Pb's effects on ALAD and heme biosynthesis. Binding of Pb to zinc-binding domains in GATA proteins and transcription factors inhibits their binding to DNA and impairs their ability to regulate gene expression (see Section 2.21.5, *Epigenetic Effects*, below for further detail).

Through competitive inhibition of magnesium-dependent proteins, Pb also affects the activities of adenine and hypoxanthine/guanine phosphoribosyltransferases, cyclic guanosine monophosphate (cGMP) phosphodiesterase, and pyrimidine 5'-nucleotidase (reviewed by EPA 2014c). In erythrocytes, adenine phosphoribosyltransferase catalyzes the synthesis of nucleotides via the adenine salvage pathway; Pb exposure has been shown to decrease nucleotide pools in human erythrocytes *in vitro* and in erythrocytes from rats exposed via drinking water. Inhibition of cGMP phosphodiesterase, a magnesium-dependent enzyme regulating cGMP signaling in smooth muscle contraction and relaxation, has been observed in homogenized bovine retinas cultured with Pb. Pb inhibits magnesium binding in pyrimidine 5'-nucleotidase, inhibiting its activity by changing its active site conformation. Pyrimidine 5'-nucleotidase occurs at high levels in erythrocytes, where it dephosphorylates pyrimidine nucleotides while leaving purine nucleotides (used as an energy source in erythrocytes, as they lack mitochondria), intact. Basophilic stippling of erythrocytes, a common feature of Pb poisoning, is also seen in individuals with inherited pyrimidine-5'-nucleotidase deficiency (Rees et al. 2003), providing supporting evidence that Pb inactivates the enzyme.

2.21.2 Protein Binding/Sequestration

A number of low molecular-weight proteins, including metallothionein, have been shown to bind (through thiol residues) to Pb, forming inclusion bodies in the kidney, liver, lung, and glial cells (reviewed by EPA 2014c; Gonick 2011). In the case of metallothionein, the effect of the binding is to sequester Pb, protecting the exposed cells and tissues. The strongest evidence for the protective effect of metallothionein comes from studies of metallothionein-null mice, which exhibit more severe Pb-induced renal toxicity, as well as increased incidences of neoplastic and nonneoplastic lesions in the testes, bladder, and kidneys, compared with wild-type mice. Supporting this finding is the observation that higher blood Pb levels, as well as more pronounced Pb-induced effects on systolic blood pressure and kidney function, were observed in exposed workers with a metallothionein mutation (compared with those exhibiting normal metallothionein genotype). Metallothionein levels have been shown to be induced by Pb exposure in mice and in rats pretreated with zinc.

In erythrocytes, the major Pb-binding protein is ALAD; hemoglobin also binds Pb (reviewed by EPA 2014c; Gonick 2011). In exposed humans, polymorphisms in the ALAD gene that increase the Pb-binding capacity of its protein product (e.g., ALAD-2) were observed to decrease blood Pb levels and biomarkers for Pb toxicity, including plasma levulinic acid, zinc protoporphyrin, cortical bone Pb levels,

and dimercaptosuccinic acid-chelatable Pb levels. Other proteins that bind Pb in erythrocytes include pyrimidine 5'-nucleotidase and acyl-coenzyme A binding protein.

In rat kidneys, inclusion bodies consisting of Pb-bound proteins have been observed in a number of studies (reviewed by EPA 2014c; Gonick 2011). These inclusion bodies are initially observed in the cytosol, but appear to translocate to the nucleus, as they disappear concomitantly with the appearance of intranuclear inclusion bodies. The primary Pb-bound protein in the kidney (a 32 kDa protein with an isoelectric point of 6.3, named p32/6.3) has not been identified, but has been shown to be enriched in the brain and is highly conserved across species (rats, mice, dogs, chickens, and humans). Studies in rats exposed by food or drinking water showed that p32/6.3 is not found in the kidneys of untreated rats but rather is induced by Pb exposure. Other Pb-binding proteins identified in the kidneys of rats or humans include acyl-CoA binding protein and thymosin β-4 (the latter is involved in actin regulation).

2.21.3 Oxidative Stress

Pb exposure has resulted in oxidative damage in several tissues in humans and rats, including the brain, kidneys, reproductive organs, heart, and erythrocytes (reviewed by EPA 2014c; Ahamed and Siddiqui 2007). Oxidative damage may play a role in Pb-induced toxicity in these tissues, including neurological effects, hypertension and other cardiovascular effects, and diminished fertility. Pb induces oxidative stress through several mechanisms, including increased production of ROS via inhibition of heme biosynthesis and activation of NAD(P)H oxidase; stimulation of lipid peroxidation and alteration of lipids enhancing their susceptibility to lipid peroxidation; and inactivation and/or depletion of antioxidant enzymes. Through the increased production of ROS, which sequesters nitric oxide, Pb exposure also leads to perturbation of nitric oxide signaling that is critical to vasodilation.

Exposure to Pb triggers increased production of ROS via its effects on heme biosynthesis. In erythrocytes, Pb has been shown to bind to δ-ALAD as well as to inhibit its activity by interfering with the zinc ions the enzyme requires for heme biosynthesis; in fact, inhibition of δ-ALAD activity is inversely correlated with PbB levels in humans (reviewed by EPA 2014c; Ahamed and Siddiqui 2007). δ-ALAD catalyzes the conversion of δ-ALA to porphobilinogen; thus, its inhibition results in accumulation of δ-ALA in blood and in urine. In these environments, δ-ALA undergoes autoxidation, yielding superoxide and hydroxyl radicals, as well as hydrogen peroxide and an ALA radical. In addition, through subsequent reduction of ferricytochrome c and transfer of electrons from oxyhemoglobin, methemoglobin, and ferric and ferrous iron complexes, oxidized δ-ALA also produces ROS.

Pb may also increase intracellular ROS by upregulating expression of NAD(P)H oxidase, an enzyme that produces superoxide anion via reaction of NAD(P)H and molecular oxygen, but data are limited (reviewed by EPA 2014c). Increased protein expression of the glycosylated subunit of NAD(P)H oxidase was observed in tissues of rats exposed to Pb in drinking water, and in human endothelial cells *in vitro*.

ROS produced via Pb effects on δ-ALA and/or NAD(P)H oxidase can damage membrane lipids through peroxidation. In addition, however, Pb has been shown to catalyze ferrous ion-initiated lipid peroxidation (reviewed by EPA 2014c). Furthermore, there is evidence that Pb exerts effects on membrane lipids that render them more vulnerable to peroxidation (reviewed by EPA 2014c; Ahamed and Siddiqui 2007). For example, Pb has been shown to alter the composition of fatty acids in chicks exposed by drinking water, such that a higher fraction of longer fatty acids (such as arachidonic acid) and lower fraction of shorter fatty acids (compared with controls) were observed. Oxidative potential of fatty acids is correlated with both length and desaturation (i.e., the number of double bonds; the hydrogen on a double bond is easier to remove). It has been proposed that Pb may stimulate both elongation and desaturation of fatty acids, increasing their susceptibility to peroxidation. Alterations in lipid composition may also affect membrane permeability and functions, including the activity of membrane-associated enzymes, solute transport functions, endo- and exocytosis, and signal transduction.

Increased circulating ROS (specifically, superoxide anion) can inactivate nitric oxide, an endogenously produced molecule that plays an important role in vasodilation (reviewed by EPA 2014c). Depletion of nitric oxide has been observed in animals exposed to Pb, as well as in human and animal immune cells treated *in vitro*. In addition, nitric oxide depletion is believed to be the mechanism behind Pb-induced upregulation of nitric oxide synthases seen in vascular tissues after Pb exposure. Nitric oxide depletion occurs when it reacts with superoxide anion to form the highly reactive peroxynitrite anion, which itself damages DNA and proteins. Levels of nitrotyrosine, which results from peroxynitrite-induced nitration of tyrosine residues in proteins, were increased in plasma and other tissues after *in vivo* exposure to Pb. In vascular tissues, nitric oxide induces vasorelaxation via cGMP signaling (reviewed by EPA 2014c). Exposure of rats to Pb in drinking water for 1–3 months markedly reduced cGMP levels in both blood and urine. Synthesis of cGMP is catalyzed by soluble guanylate cyclase, a heme-dependent enzyme. Pb exposure has been shown to reduce protein levels of soluble guanylate cyclase in vascular tissues; alleviation of this effect by antioxidant treatment (ascorbic acid) demonstrated that this finding was mediated, at least in part, by increased oxidative stress.

In human epidemiological studies, the ratio of oxidized glutathione (glutathione disulfide or GSSG) to reduced glutathione (GSH), a measure of oxidative stress, was positively correlated with blood Pb levels (reviewed by EPA 2014c; Ahamed and Siddiqui 2007; Flora et al. 2012). The effects of Pb on oxidative stress levels may occur through depletion of antioxidant levels in addition to stimulation of ROS, as oxidative stress occurs when the antioxidant capacity of the body is exceeded. Pb forms covalent bonds with sulfhydryl groups in antioxidant enzymes such as GSH, glutathione reductase (GR), and glutathione S-transferase (GST) (reviewed by EPA 2014c; Ahamed and Siddiqui 2007; Flora et al. 2012). In humans, animals, and *in vitro* studies, decreased GSH in blood and organs has been associated with Pb exposure. After long-term exposure to Pb, increased GSH levels, attributed to compensatory upregulation of GSH biosynthesis, have been reported. Like GSH, GR (which reduces GSSG back to GSH) and GST also have disulfides at their active site that could be bound by Pb. Studies examining GR and GST activity after Pb exposure used varying study designs and showed both increases and decreases; it is not clear whether the differences in results reflect species, strain, dose, or duration differences.

Pb's capacity to compete with cations and its interference with heme biosynthesis have also been suggested as potential mechanisms for its ability to alter levels of SOD, CAT, GPx, and GST (reviewed by EPA 2014c; Flora et al. 2012; Ahamed and Siddiqui 2007). SOD forms require copper, zinc, or manganese, cations that Pb may displace, while catalase is a heme-dependent enzyme. Several studies in humans and animals have shown alterations in SOD and CAT activity, with some evidence for a nonlinear dose-response relationship. EPA (2014c) suggested that increased SOD and CAT may occur at low doses as a result of ROS generation by Pb, while at higher doses, Pb may inactivate the enzymes. Pb exposure also alters activities of GPx and GST, potentially by reducing the uptake of selenium (required by GPx) and/or disrupting protein thiols (necessary for GST function). Decreased GPx and GST activities have been observed, along with compensatory upregulation of these enzymes, in Pb-exposed humans and animals.

2.21.4 Inflammation

Increasing oxidative stress through ROS generation and depletion of antioxidant enzymes may be one mechanism by which Pb induces an inflammatory response (reviewed by EPA 2014c). Inflammation, considered a hallmark of Pb exposure (EPA 2014c), may also be triggered by pro-inflammatory signaling and cytokine production. Inflammation has been seen after Pb exposure in many different cell types, as well as in the kidneys of rats exposed to Pb in drinking water.

Oxidative stress is known to activate the pro-inflammatory nuclear transcription factor kappa B (NFκB) In the rat kidney, Pb-induced inflammation was accompanied by activation of NFκB as well as lymphocyte and macrophage infiltration (reviewed by EPA 2014c). Pb has been shown to stimulate the expression of pro-inflammatory signal mediators including NFκB, activator protein-1 (AP-1), and c-Jun, and to stimulate phosphorylation of the Erk/MAPK pathway. In addition, exposure to Pb is associated with increased production of prostaglandins, which also mediate pro-inflammatory messaging. Increases in arachidonic acid production, leading to increases in prostaglandins E2 and F2 and thromboxane levels, have been seen in Pb-exposed workers as well as in animals and in cultured cells systems exposed to Pb. In vascular smooth muscle cells, Pb has been shown to activate phospholipase A2, which may explain its ability to stimulate the release of arachidonic acid.

In both human epidemiological and laboratory animal studies, Pb exposure has been demonstrated to increase cytokine production (reviewed by EPA 2014c). In these studies, a fairly consistent picture of decreasing Th-1 cytokines and increasing Th-2 cytokines has emerged. EPA (2014c) outlined three modes by which Pb influences cytokine production: (1) direct action on macrophages to increase pro-inflammatory cytokines such as TNF-α and interleukin 6 (IL-6); (2) skew the ratio of IL-12 to IL-10, leading to suppression of Th-1 cell responses and stimulate Th-2 cell responses; and (3) during acquired immune response occurring after Pb exposure, production of cytokines by Th-1 lymphocytes is suppressed, and Th-2 cytokines are increased. The net result of these changes is consistent with the pro-inflammatory picture seen with Pb exposure.

Human epidemiological studies have provided evidence that Pb exposure skews immune responses toward Th-2 pro-inflammatory responses (reviewed by EPA 2014c). Higher blood Pb levels in children were associated with increased serum levels of Il-4 (which induces differentiation of Th0 cells to the Th-2 phenotype) and lower levels of interferon gamma (IFN-γ). In adult students in Korea, higher blood Pb levels were positively associated with increased TNF-α and IL-6; a 1 µg/dL increase in blood Pb was associated with a 23% increase in log TNF-α and a 26% increase in IL-6. Finally, in occupationally-exposed workers, higher blood Pb levels were associated with increases in IL-2, IL-10, IL-6, TNF-α, and granulocyte colony stimulating factor (G-CSF), and, in one study, lower levels of Th1 cytokines IL-1β and IFN-γ. Similar effects were seen in mice exposed to Pb in feed; blood levels of Th-1 cytokines (IL-2 and IFN-γ) were decreased at low dietary doses, while increases in IL-4 were seen as the Pb dose increased. Based on these data, EPA (2014c) suggested that the immune system response to Pb may exhibit nonlinearities at low doses. In rats exposed to Pb via intraperitoneal injection, increased levels of

TNF-α were seen in the hippocampus, and increased IL-6 was noted in the forebrain. *In vitro* data have also shown alterations in cytokine production after exposure to Pb.

2.21.5 Epigenetic Effects

In a small number of studies, Pb has been shown to induce epigenetic effects, including perturbations in DNA methylation as well as alterations in mitogenesis (reviewed by EPA 2014c; Bakulski et al. 2013). In human studies, maternal blood Pb was correlated with decreased DNA methylation of Alu retrotransposable elements in umbilical cord blood, and bone Pb levels were correlated with decreased DNA methylation of LINE-1 retrotransposons in elderly men, while higher blood Pb was associated with increased methylation of p16 tumor suppressor gene promoters in occupationally exposed individuals. Other evidence for effects of Pb on DNA methylation include a study in primates in which the activity of DNA methyltransferase 1 was decreased by early life Pb exposure, and *in vitro* data showing decreased global DNA methylation in rat pheochromocytoma cells. Hypomethylation of DNA has been shown to trigger changes in gene expression that may lead to alterations in tissue differentiation.

Pb exposure also induces effects on mitogenesis, including both increases in cell proliferation and decreases in some systems (reviewed by EPA 2014c). Increased cell proliferation and/or DNA synthesis have been reported in workers exposed to Pb, in hepatocytes of rats exposed by intravenous injection of Pb nitrate, and in mouse lung after exposure to Pb acetate via inhalation. In *in vitro* studies, results were mixed: in some cases cell proliferation was decreased, as Pb exposure resulted in cell cycle arrest. Effects of Pb exposure on gene expression have been demonstrated in several studies (reviewed by EPA 2014c). Although the exact mechanisms by which Pb alters gene expression have not been elucidated, Pb is known to interfere with GATA proteins and several transcription factors (TFIIIA, Sp1, and Erg-1) through its interaction with zinc-binding domains, reducing the ability of these proteins to bind to DNA and exert their transcriptional regulation functions. *In vivo* and *in vitro* studies have shown that Pb alters the transcription of genes for metabolic enzymes including GST-P and GST-Ya, CYPs 1A1 and 1A2, and NAD(P)H:quinone oxidoreductase, as well as genes involved in the pentose phosphate pathway and amino acid metabolism.

2.21.6 Apoptosis

As discussed earlier, Pb is capable of opening the mitochondrial transmembrane pore (MTMP, the first step in the mitochondrial apoptosis cascade), possibly by displacing calcium on the matrix side of the pore (reviewed by EPA 2014c). Evidence for this effect includes observations of mitochondrial swelling

and decreased membrane potential in rat primary cerebellar granule neuronal cultures, astroglia, proximal tubule cells, and retinal rod photoreceptor cells. In addition, release of cytochrome c and activation of caspases 3 and 9 were observed in rat retinal rod cells and hepatic oval cells exposed to Pb *in vitro*. In lymphocytes of Pb-exposed humans, increased apoptosis, karyorrhexis, and karyolysis (early indicators of apoptosis) were observed. Other tissues have also exhibited increased apoptosis after Pb exposure, including liver, fibroblasts, and alveolar macrophages.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Overview. The toxicokinetics of Pb in humans has been extensively studied and several models have been published that simulate the absorption and complex distribution and elimination of Pb from blood, soft tissues, and bone.

- Absorption:
    - Respiratory tract: Inorganic Pb in submicron size particles can be almost completely absorbed through the respiratory tract, whereas larger particles may be moved after deposition in the respiratory tract by mucociliary clearance toward the oropharynx and swallowed.
    - Gastrointestinal tract: The fraction of ingested Pb absorbed from the gastrointestinal tract depends on many factors, including age, diet, nutrition, and physiological characteristics of Pb in the medium ingested.
    - Children can absorb 40–50% of an oral dose of water-soluble Pb compared to 3–10% for adults.
    - Gastrointestinal absorption of inorganic Pb occurs primarily in the duodenum by saturable mechanisms.
    - Dermal: Inorganic Pb can be absorbed following inhalation, oral, and dermal exposure, but the latter route is much less efficient than the former two, with the exception of hand-to-mouth behavior. Studies in animals have shown that organic Pb is absorbed through the skin.

- Distribution:
    - The distribution of Pb in the body is route-independent and, in adults, approximately 94% of the total body burden of Pb is in the bones compared to approximately 73% in children.
    - Pb in blood is primarily in red blood cells. Conditions such as pregnancy, lactation, menopause, and osteoporosis increase bone resorption and consequently also increase Pb in blood.

  - Pb can be transferred from the mother to the fetus and also from the mother to infants via maternal milk.

- Metabolism:
  - Metabolism of inorganic Pb consists of formation of complexes with a variety of protein and nonprotein ligands.
  - Organic Pb compounds are actively metabolized in the liver by oxidative dealkylation by P-450 enzymes.

- Excretion:
  - Pb is excreted primarily in urine and feces regardless of the route of exposure. Minor routes of excretion include sweat, saliva, hair, nails, breast milk, and seminal fluid.
  - Elimination of Pb is multiphasic, reflecting pools of Pb in the body that have varying retention times. The apparent elimination half-time in blood varies with age and exposure history and ranges from 1 week to 2 years. Elimination of Pb from bone occurs with an apparent half-time of 1–2 decades.

- Toxicokinetics models:
  - Several models of Pb pharmacokinetics have been proposed to characterize such parameters as intercompartmental Pb exchange rates, retention of Pb in various tissues, and relative rates of distribution among the tissue groups.
  - Some models are currently being used or are being considered for broad application in Pb risk assessment.

3.1.1 Absorption

Inhalation Exposure

Inorganic Pb. Inorganic Pb in ambient air consists of aerosols of particulates that can be deposited in the respiratory tract when the aerosols are inhaled. Amounts and patterns of deposition of particulate aerosols in the respiratory tract are affected by the size of the inhaled particles, age-related factors that determine breathing patterns (e.g., nose versus mouth breathing), airway geometry, and air-stream velocity within the respiratory tract (James et al. 1994). Absorption of deposited Pb is influenced by particle size and solubility as well as the pattern of regional deposition within the respiratory tract. Larger particles

(>2.5 μm) that are deposited in the ciliated airways (nasopharyngeal and tracheobronchial regions) can be transferred by mucociliary transport into the esophagus and swallowed. Smaller particles (2.5 to <1 μm), which can be deposited in the alveolar region, can be absorbed after extracellular dissolution or ingestion by phagocytic cells (Bailey and Roy 1994).

Deposition in, and clearance from, the respiratory tract have been measured in adult humans (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). In these studies, exposures were to Pb-bearing particles having mass median aerodynamic diameters (MMADs) below 1 μm and, therefore, deposition of the inhaled Pb particles can be assumed to have been primarily in the bronchiolar and alveolar regions of the respiratory tract (James et al. 1994) where transport of deposited Pb to the gastrointestinal tract is likely to have been only a minor component of particle clearance (Hursh et al. 1969). Approximately 25% of inhaled Pb chloride or Pb hydroxide (MMAD 0.26 and 0.24 μm, respectively) was deposited in the respiratory tract in adult subjects who inhaled an inorganic Pb aerosol through a standard respiratory mouthpiece for 5 minutes (Morrow et al. 1980). Approximately 95% of deposited inorganic Pb that was inhaled as submicron particles was absorbed (Hursh et al. 1969; Wells et al. 1975). Rates of clearance from the respiratory tract of inorganic Pb inhaled as submicron particles of Pb oxide, or Pb nitrate, were described with half-times ($t_{1/2}$) of 0.8 hours (22%), 2.5 hours (34%), 9 hours (33%), and 44 hours (12%) (Chamberlain et al. 1978). These rates are thought to represent, primarily, absorption from the bronchiolar and alveolar regions of the respiratory tract. Absorption half-times have been estimated in adults who inhaled aerosols of Pb and bismuth isotopes generated from decay of ^{220}Rn or ^{222}Rn (Butterweck et al. 2002; Marsh and Birchall 1999). The absorption half-time was approximately 10 hours in subjects who inhaled aerosols having an activity median particle diameter of approximately 160 nm (range 50–500 nm), and approximately 68 minutes for aerosols having diameters of approximately 0.3–3 nm.

Rates and amounts of absorption of inhaled Pb particles >2.5 μm will be determined, primarily by rates of transport to and absorption from the gastrointestinal tract. Absorption of Pb from the gastrointestinal tract varies with the chemical form ingested, age, meal status (e.g., fed versus fasted), and nutritional factors (see Section 3.1.1 *Oral Exposure*).

Organic Pb. Following a single exposure to vapors of radioactive (^{203}Pb) tetraethyl Pb (approximately 1 mg/m^3 breathed through a mouthpiece for 1–2 minutes) in four male subjects, 37% of inhaled ^{203}Pb was initially deposited in the respiratory tract, of which approximately 20% was exhaled in the subsequent 48 hours (Heard et al. 1979). One hour after the exposure, approximately 50% of the ^{203}Pb burden was

associated with liver, 5% was associated with kidney, and the remaining burden was widely distributed throughout the body (determined by external gamma counting), suggesting near complete absorption of the Pb that was not exhaled. In a similar experiment conducted with (^{203}Pb) tetramethyl Pb, 51% of the inhaled ^{203}Pb dose was initially deposited in the respiratory tract, of which approximately 40% was exhaled in 48 hours. The distribution of ^{203}Pb 1 hour after the exposure was similar to that observed following exposure to tetraethyl Pb.

The relatively rapid and near complete absorption of tetraalkyl Pb that is inhaled and deposited in the respiratory tract is also supported by studies conducted in animal models (Boudene et al. 1977; Morgan and Holmes 1978).

Oral Exposure

Inorganic Pb. The extent and rate of gastrointestinal absorption of ingested inorganic Pb are influenced by physiology (e.g., age, fasting, nutritional calcium and iron status, pregnancy), physicochemical characteristics of the medium ingested (e.g., particle size, mineralogy, solubility, and Pb species) and the ingested Pb dose.

Mechanisms of Absorption. Gastrointestinal absorption of inorganic Pb occurs primarily in the duodenum (Mushak 1991). The exact mechanisms of absorption are unknown and may involve active transport and/or diffusion through intestinal epithelial cells (transcellular) or between cells (paracellular), and may involve ionized Pb (Pb^{+2}) and/or inorganic or organic complexes of Pb. *In vitro* studies of Pb speciation in simulated human intestinal chyme indicate that the concentration of ionized Pb is negligible at Pb concentrations below 10^{-3} M (207 mg/L) and that Pb phosphate and bile acid complexes are the dominant forms when inorganic Pb salts (e.g., Pb nitrate) are added to chyme (Oomen et al. 2003a). However, these complexes may be sufficiently labile to provide ionized Pb for transport across cell membranes (Oomen et al. 2003b). Saturable mechanisms of absorption have been inferred from measurements of net flux kinetics of Pb in *in situ* perfused mouse intestine, *in situ* ligated chicken intestine, and *in vitro* isolated segments of rat intestine (Aungst and Fung 1981; Barton 1984; Flanagan et al. 1979; Mykkänen and Wasserman 1981). By analogy to other divalent cations, saturable transport mechanisms for Pb^{+2} may exist within the mucosal and serosal membranes and within the intestinal epithelial cell. For calcium and iron, these are thought to represent membrane carriers (e.g., Ca^{2+}-Mg^{2+}-ATPase, Ca^{2+}/Na^{+} exchange, DMT1) or facilitated diffusion pathways (e.g., Ca^{2+} channel) and

intracellular binding proteins for Ca^{2+} (Bronner et al. 1986; Fleming et al. 1998b; Gross and Kumar 1990; Teichmann and Stremmel 1990).

Effect of Age. Gastrointestinal absorption of water-soluble Pb appears to be higher in children than in adults. Estimates derived from dietary balance studies conducted in infants and children (ages 2 weeks to 8 years) indicate that approximately 40–50% of ingested Pb is absorbed (Alexander et al. 1974; Ziegler et al. 1978). In adults, estimates of absorption of ingested water-soluble Pb compounds (e.g., Pb chloride, Pb nitrate, Pb acetate) ranged from 3 to 10% in fed subjects (Heard and Chamberlain 1982; James et al. 1985; Rabinowitz et al. 1980; Watson et al. 1986). Data available on Pb absorption between childhood and adulthood ages are very limited. While no absorption studies have been conducted on subjects in this age range, the kinetics of the change in stable isotope signatures of blood Pb in mothers and their children, as both come into equilibrium with a novel environmental Pb isotope profile, suggest that children ages 6–11 years and their mothers may absorb a similar percentage of ingested Pb (Gulson et al. 1997b).

Studies in experimental animals provide additional evidence for an age-dependency of gastrointestinal absorption of Pb. Absorption of Pb, administered as Pb acetate (6.37 mg Pb/kg, gavage), was higher in juvenile Rhesus monkeys (38% of dose) compared to adult female monkeys (26% of the dose) (Pounds et al. 1978). Rat pups absorb approximately 40–50 times more Pb from the diet than do adult rats (Aungst et al. 1981; Forbes and Reina 1972; Kostial et al. 1978). This age difference in absorption may be due, in part, to the shift from the neonatal to adult diet, and to postnatal physiological development (enzymes, transporters, gastric pH) of the gastrointestinal tract (Weis and LaVelle 1991).

Effect of Fasting. The presence of food in the gastrointestinal tract decreases absorption of water-soluble Pb (Blake and Mann 1983; Blake et al. 1983; Heard and Chamberlain 1982; James et al. 1985; Maddaloni et al. 1998; Rabinowitz et al. 1980). In adults, absorption of a tracer dose of Pb acetate in water was approximately 63% when ingested by fasted subjects and 3% when ingested with a meal (James et al. 1985). Heard and Chamberlain (1982) reported nearly identical results. The arithmetic mean of reported estimates of absorption in fasted adults was 57% (calculated by ATSDR based on Blake et al. 1983; Heard and Chamberlain 1982; James et al. 1985; Rabinowitz et al. 1980). Reported fed/fasted ratios for absorption in adults range from 0.04 to 0.2 (Blake et al. 1983; Heard and Chamberlain 1983; James et al. 1985; Rabinowitz et al. 1980). Mineral content is one contributing factor to the lower absorption of Pb when Pb is ingested with a meal; in particular, the presence of calcium and phosphate in a meal will depress the absorption of ingested Pb (Blake and Mann 1983; Blake et al. 1983; Heard and Chamberlain

1982). Suppression of absorption by meals may explain the observation of lower PbB in children (age 3–5 years) who ate breakfast compared to children who went without breakfast, after controlling for nutritional variables (Liu et al. 2011).

Effect of Nutrition. Pb absorption in children is affected by nutritional iron status. Children who are iron deficient have higher PbBs than similarly exposed children who are iron replete, which would suggest that iron deficiency may result in higher absorption of Pb or, possibly, other changes in Pb biokinetics that would contribute to lower PbBs (Mahaffey and Annest 1986; Marcus and Schwartz 1987). Genetic variation in genes involved in iron metabolism appear to affect PbBs; however, it is not certain if these associations are caused by changes in Pb absorption. These include variants in the hemochromatosis (HFE) and transferrin genes, which have been associated with higher PbBs in children (Hopkins et al. 2008), and with lower PbBs and bone Pb levels in elderly men (Wright et al. 2004).

Evidence for the effect for iron deficiency on Pb absorption has been provided from animal studies. In rats, iron deficiency increases the gastrointestinal absorption of Pb, possibly by enhancing binding of Pb to iron binding proteins in the intestine (Bannon et al. 2003; Barton et al. 1978b; Morrison and Quaterman 1987). Interactions between iron and Pb appear to involve either intracellular transfer or basolateral transfer mechanisms. Iron ($FeCl_2$) added to the mucosal fluid of the everted rat duodenal sac decreases serosal transfer, but not mucosal uptake of Pb (Barton 1984). When mRNA for DMT1, a mucosal membrane carrier for iron (which also transports other divalent metal cations), was suppressed in Caco 2 cells (a human gastrointestinal cell line), the rate of iron and cadmium uptake decreased by 50% compared to cells in which DMT1 mRNA was not suppressed; however, DMT1 mRNA suppression did not alter the rate of Pb uptake by Caco 2 cells, indicating that Pb may enter Caco 2 cells through a mechanism that is independent of DMT1 (Bannon et al. 2003). The above observations suggest that rate-limiting saturable mechanisms for Pb absorption are associated with transfer of Pb from cell to blood rather than with mucosal transfer. Similar mechanisms may contribute to Pb-iron and Pb-calcium absorption interactions in humans, and possibly interactions between Pb and other divalent cations such as cadmium, copper, magnesium, and zinc.

Dietary calcium intake affects Pb absorption. An inverse relationship has been observed between dietary calcium intake and PbBs in children, suggesting that children who are calcium-deficient may absorb more Pb than calcium-replete children (Elias et al. 2007; Mahaffey et al. 1986; Schell et al. 2004; Ziegler et al. 1978). An effect of calcium on Pb absorption is also evident in adults. In experimental studies of adults, absorption of a single dose of Pb (100–300 μg Pb chloride) was lower when the Pb was ingested together

with calcium carbonate (0.2–1 g calcium carbonate) than when the Pb was ingested without additional calcium (Blake and Mann 1983; Heard and Chamberlain 1982). A similar effect of calcium occurs in rats (Barton et al. 1978a). Complexation with calcium (and phosphate) in the gastrointestinal tract and competition for a common transport protein have been proposed as possible mechanisms for this interaction (Barton et al. 1978a; Heard and Chamberlain 1982). Absorption of Pb from the gastrointestinal tract is enhanced by dietary calcium depletion or administration of cholecalciferol (Mykkänen and Wasserman 1981, 1982). This "cholecalciferol-dependent" component of Pb absorption appears to involve a stimulation of the serosal transfer of Pb from the epithelium, not stimulation of mucosal uptake of Pb (Mykkänen and Wasserman 1981, 1982). This is similar to the effects of cholecalciferol on calcium absorption (Bronner et al. 1986; Fullmer and Rosen 1990).

In a study of young children (ages 6–12 months), PbBs increased in association with lower dietary Zn levels (Schell et al. 2004); however, it is not certain if these associations were caused by changes in Pb absorption.

Effect of Pregnancy. Absorption of Pb may increase during pregnancy. Although there is no direct evidence for this in humans, an increase in Pb absorption may contribute, along with other mechanisms (e.g., increased mobilization of bone Pb), to the increase in PbBs that has been observed during the latter half of pregnancy (see Section 3.1.2, *Pb Distribution during Pregnancy and Maternal-Fetal-Infant Transfer*).

Effect of Dose. Pb absorption in humans may be a capacity-limited process, in which case, the percentage of ingested Pb that is absorbed may decrease with increasing rate of Pb intake. Studies, to date, do not provide a firm basis for discerning if the gastrointestinal absorption of Pb is limited by dose. Numerous observations of nonlinear relationships between PbB and Pb intake in humans provide support for the existence of a saturable absorption mechanism or some other capacity-limited process in the distribution of Pb in humans (Pocock et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1984) (see Section 3.1.2, *Pb in Blood* and *Pb in Plasma* for discussion of saturable uptake of Pb in red blood cells). However, in immature swine that received oral doses of Pb in soil, Pb dose-blood Pb relationships were curvilinear, whereas dose-tissue Pb relationships for bone, kidney, and liver were linear. The same pattern (nonlinearity for PbB and linearity for tissues) was observed in swine administered Pb acetate intravenously (Casteel et al. 1997, 2006). These results suggest that the nonlinearity in the Pb dose-blood Pb relationship may derive from an effect of Pb dose on some aspect of the biokinetics of Pb other than absorption. In fasted rats, absorption was estimated at 42 and 2% following single oral administration of

1 and 100 mg Pb/kg, respectively, as Pb acetate, suggesting a limitation on absorption imposed by dose (Aungst et al. 1981). Evidence for capacity-limited processes at the level of the intestinal epithelium (Aungst and Fung 1981; Barton 1984; Flanagan et al. 1979; Mykkänen and Wasserman 1981) suggests that the intake-uptake relationship for Pb is likely to be nonlinear; however, the dose at which absorption becomes appreciably limited in humans is not known.

Effect of Particle Size. Particle size influences the degree of gastrointestinal absorption (Ruby et al. 1999). In rats, an inverse relationship was found between absorption and particle size of Pb in diets containing metallic Pb particles that were ≤250 μm in diameter (Barltrop and Meek 1979). Tissue Pb concentration was a 2.3-fold higher when rats ingested an acute dose (37.5 mg Pb/kg) of Pb particles that were <38 μm in diameter than when rats ingested particles having diameters in the range of 150–250 μm (Barltrop and Meek 1979). Dissolution kinetics experiments with Pb-bearing mine waste soil suggest that surface area effects control dissolution rates for particles sizes of <90 μm diameter; however, dissolution of 90–250 μm particle size fractions appeared to be controlled more by surface morphology (Davis et al. 1994). Similarly, Healy et al. (1982) found that the solubility of Pb sulfide in gastric acid *in vitro* was much greater for particles that were 30 μm in diameter than for particles that were 100 μm in diameter.

Absorption from Soil. Absorption of Pb from the gastrointestinal tract involves absorptive transport of soluble Pb species (e.g., Pb^{2+}) across the gastrointestinal tract epithelium. In order for Pb to be absorbed from soil, it must first be made bioaccessible in the gastrointestinal tract. The process of rendering soil Pb bioaccessible may involve: (1) physical and/or chemical digestion of the soil particles to expose Pb deposits to gastrointestinal tract fluids; (2) transfer of Pb minerals from exposed surfaces on soil particles to the aqueous environment of the gastrointestinal tract; and (3) chemical transformation of Pb minerals to soluble Pb species (e.g., Pb^{2+}) that are substrates for absorptive transport. Although absorptive transport of Pb occurs predominantly, if not solely, in the upper small intestine, bioaccessibility processes occurring in the stomach appear to be major determinants of Pb absorption.

Adult subjects who ingested soil (particle size <250 μm) collected from the Bunker Hill National Priorities List (NPL) site absorbed 26% of the resulting 250 μg/70 kg body weight Pb dose when the soil was ingested in the fasted state, and 2.5% when the same soil Pb dose was ingested with a meal (Maddaloni et al. 1998). The value reported for fasted subjects (26%) was approximately half that reported for soluble Pb ingested by fasting adults, or approximately 60% (Blake et al. 1983; Heard and Chamberlain 1983; James et al. 1985; Rabinowitz et al. 1980). Measurements of the absorption of soil Pb in infants or children have not been reported.

Absorption of Pb from ingested soils and surface dust has been studied more extensively in animals (Bannon et al. 2009; Barltrop and Meek 1979; Bradham et al. 2016; Brown et al. 2004; Casteel et al. 1997, 2006; Freeman et al. 1992, 1994, 1996; Healy et al. 1982; Hettiearachchi et al. 2003; Juhasz et al. 2009; Ryan et al. 2004; Weis and Lavelle 1991). These studies have shown that absorption of soil Pb varies depending upon the Pb mineralogy and physical characteristics of the Pb in the soil (e.g., encapsulated or exposed, particle size). Studies conducted in swine and other animal models have provided estimates of relative bioavailability (RBA) of Pb in soils collected from sites impacted by a variety of sources of Pb contamination including ore and ore processing, shooting of Pb munitions, and Pb-based paint (Bannon et al. 2009; Barltrop and Meek 1979; Bradham et al. 2016; Brown et al. 2004; Casteel et al. 1997, 2006; Freeman et al. 1992, 1994, 1996; Healy et al. 1982; Hettiearachchi et al. 2003; Juhasz et al. 2009; Ryan et al. 2004; Weis and Lavelle 1991). RBA is the ratio of the absolute bioavailability (or absorption fraction) of Pb in soil to that of a water-soluble reference (Pb acetate). RBA has been measured in animals models using various approaches, including measurement of blood and tissue Pb in animals following dosing with soil or Pb acetate. RBA estimates from these studies ranged from 1 to 100% (mean 60%, n=33, calculated by ATSDR). RBA for soils from firing ranges where the predominant form of Pb was Pb carbonate were approximately 100% (Bannon et al. 2009). A soil amended with NIST paint standard (a mixture of Pb carbonate and Pb oxide) had an RBA of 92%. Smelter slag and soils in which the dominant source of Pb was smelter slag had relatively low RBA (14–40%). Galena (lead sulfide) in soil also had relatively low RBA (1–6%).

Casteel et al. (2006) estimated Pb RBA of 19 soils in swine and categorized the RBA according to Pb mineral associations. Electron microprobe analyses of Pb-bearing grains in the various soils revealed that the grains ranged from as small as 1–2 μm up to a maximum of 250 μm (the sieve size used in preparation of the samples) and that Pb was present in a wide range of different mineral associations (phases), including various oxides, sulfides, sulfates, and phosphates. These variations in size and mineral content of the Pb-bearing grains are the suspected cause of variations in the gastrointestinal absorption of Pb from different samples of soil. Based on these very limited data, the RBA of Pb mineral phases were rank-ordered (Table 3-1).

Table 3-1. Ranking of Relative Bioavailability of Lead (Pb) Mineral Phases in Soil[a]

Low bioavailability (RBA<0.25)	Medium bioavailability (RBA=0.25–0.75)	High bioavailability (RBA>0.75)
Angelsite	Pb oxide	Cerussite
Fe(M) oxide	Pb phosphate	Mn(M) oxide
Fe(M) sulfate		
Galena		
Pb(M) oxide		

[a]Estimates are based on studies of immature swine.

Fe = iron; M = metal; Mn = manganese; RBA = relative bioavailability (compared to Pb acetate)

Source: Casteel et al. 2006

Several studies have shown that elevating the phosphate concentration of soil can decrease soil Pb RBA (Brown et al. 2004; Hettiarachichi et al. 2003; Ryan et al. 2004). The mechanism for the effect is thought to be the formation of a relatively insoluble form of Pb in soil, pyromorphite, which has a low RBA (Scheckel et al. 2013).

Bioaccessibility in Soil and its Relationship to Relative Bioavailability. Empirical evidence supporting the importance of gastric bioaccessibility in Pb absorption comes from studies of relationships between extractability of Pb from soil measured *in vitro* and Pb RBA measured in animals. *In vitro* extractability of Pb from soil (*in vitro* bioaccessibility, IVBA) strongly correlates with RBA measured swine assays when the extraction is performed at gastric pH (r^2=0.92, n=18; Drexler and Brattin 2007). Bioaccessibility estimates obtained from IVBA assays are sensitive to assay conditions such as pH, liquid:soil ratios, inclusion or absence of food material, and differences in methods used to separate dissolved and particle-bound Pb (e.g., centrifugation versus filtration); as a result, different assays can yield different results when applied to the same soils or surface dusts (Dong et al. 2016; Juhasz et al. 2011; Lu et al. 2011; Roussel et al. 2010; Saikat et al. 2007; Smith et al. 2011; Van de Wiele et al. 2007). For this reason, application of IVBA assays for predicting RBA must be supported by demonstration of a strong correlation between IVBA and RBA (Drexler and Brattin 2007). Even in the absence of validation of RBA predictions, IVBA assays may be useful for predicting relative differences in RBA between soils. For example, the relative change in Pb RBA resulting from treatment of soils with phosphate amendments was predicted from IVBA measurements even though the IVBA assay performed poorly at predicting the actual RBA of the soils (Juhasz et al. 2016). Bioaccessibility measured with IVBA assays has been shown to increase with decreasing particle size (varied from <2,000 to <50 μm) (Juhasz et al. 2011) and increase with increasing soil acidity and organic matter content (Jin et al. 2005).

Dermal Exposure

Inorganic Pb. Dermal absorption of inorganic Pb compounds is generally considered to be much less than absorption by inhalation or oral routes of exposure; however, few studies have provided quantitative estimates of dermal absorption of inorganic Pb in humans, and the quantitative significance of the dermal absorption pathway as a contributor to Pb body burden in humans remains an uncertainty. Pb was detected in the upper layers of the stratum corneum of Pb-battery workers, prior to their shifts and after cleaning of the skin surface (Sun et al. 2002), suggesting adherence and/or possible dermal penetration of Pb. Following skin application of ^{203}Pb-labeled Pb acetate in cosmetic preparations (0.12 mg Pb in 0.1 mL or 0.18 mg Pb in 0.1 g of a cream) to eight male volunteers for 12 hours, absorption was ≤0.3%, based on whole-body, urine, and blood ^{203}Pb measurements, and was predicted to be 0.06% during normal use of such preparations (Moore et al. 1980). Most of the absorption took place within 12 hours of exposure. Pb also appears to be absorbed across human skin when applied to the skin as Pb nitrate; however, quantitative estimates of absorption have not been reported. Pb (4.4 mg, as Pb nitrate) was applied (vehicle or solvent not reported) to an occluded filter placed on the forearm of an adult subject for 24 hours, after which, the patch was removed, the site cover and the forearm were rinsed with water, and total Pb was quantified in the cover material and rinse (Stauber et al. 1994). The amount of Pb recovered from the cover material and rinse was 3.1 mg (70% of the applied dose). Based on this recovery measurement, 1.3 mg (30%) of the applied dose remained either in the skin or had been absorbed in 24 hours; the amount that remained in or on the skin and the fate of this Pb (e.g., exfoliation) was not determined. Exfoliation has been implicated as an important pathway of elimination of other metals from skin (e.g., inorganic mercury; Hursh et al. 1989). Pb concentrations in sweat collected from the right arm increased 4-fold following the application of Pb to the left arm, indicating that some Pb had been absorbed (amounts of sweat collected or total Pb recovered in sweat were not reported; Stauber et al. 1994). In similar experiments with three subjects, measurements of ^{203}Pb in blood, sweat, and urine, made over a 24-hour period following dermal exposures to 5 mg Pb as ^{203}Pb nitrate or acetate, accounted for <1% of the applied (or adsorbed) dose (Stauber et al. 1994). This study also reported that absorption of Pb could not be detected from measurements of Pb in sweat following dermal exposure to Pb as Pb carbonate.

Information on relative dermal permeability of inorganic and organic Pb salts of Pb comes from studies of *in vitro* preparations of excised skin; the rank ordering of penetration rates through excised human skin

was: Pb nuolate (Pb linoleic and oleic acid complex) > Pb naphthanate > Pb acetate > Pb oxide (nondetectable) (Bress and Bidanset 1991).

Studies conducted in animals provide additional evidence that dermal absorption of inorganic Pb is substantially lower than absorption from the inhalation or oral route. In a comparative study of dermal absorption of inorganic and organic salts of Pb conducted in rats, approximately 100 mg of Pb was applied in an occluded patch to the shaved backs of rats. Based on urinary Pb measurements made prior to and for 12 days following exposure, Pb compounds could be ranked according to the relative amounts absorbed (i.e., percent of dose recovered in urine; calculated by ATSDR): Pb naphthalene (0.17%), Pb nitrate (0.03%), Pb stearate (0.006%), Pb sulfate (0.006%), Pb oxide (0.005%), and metal Pb powder (0.002%). This rank order (i.e., Pb naphthalene > Pb oxide) is consistent with a rank ordering of penetration rates of inorganic and organic Pb salts through excised skin from humans and guinea pigs: Pb nuolate (Pb linoleic and oleic acid complex) > Pb naphthanate > Pb acetate > Pb oxide (nondetectable) (Bress and Bidanset 1991). The estimates for percent of dose excreted underestimate actual absorption as these estimates do not account for the Pb retained in bone and other tissues.

Following application of Pb acetate to the shaved clipped skin of rats, the concentration of Pb in the kidneys was found to be higher relative to controls, suggesting that absorption of Pb had occurred (Laug and Kunze 1948). This study also observed that dermal absorption of Pb from Pb arsenate was significantly less than from Pb acetate, and that mechanical injury to the skin significantly increased the dermal penetration of Pb.

Organic Pb. Relative to inorganic Pb and organic Pb salts, tetraalkyl Pb compounds have been shown to be rapidly and extensively absorbed through the skin of rabbits and rats (Kehoe and Thamann 1931; Laug and Kunze 1948). A 0.75-mL amount of tetraethyl Pb, which was allowed to spread uniformly over an area of 25 cm^2 on the abdominal skin of rabbits, resulted in 10.6 mg of Pb in the carcass at 0.5 hours and 4.41 mg at 6 hours (Kehoe and Thamann 1931). Tetraethyl Pb was reported to be absorbed by the skin of rats to a much greater extent than Pb acetate, Pb oleate, and Pb arsenate (Laug and Kunze 1948). Evidence for higher dermal permeability of organic Pb compounds compared to inorganic organic salts of Pb also comes from *in vitro* studies conducted with excised skin. The rank order of absorption rates through excised skin from humans and guinea pigs was as follows: tetrabutyl Pb > Pb nuolate (Pb linoleic and oleic acid complex) > Pb naphthanate > Pb acetate > Pb oxide (nondetectable) (Bress and Bidanset 1991).

3.1.2 Distribution

Inorganic Pb. Absorbed inorganic Pb appears to be distributed in essentially the same manner regardless of the route of absorption (Chamberlain et al. 1978; Kehoe 1987); therefore, the distribution of absorbed Pb (i.e., by any route) is discussed in this section, rather than in separate sections devoted to specific routes of exposure. The expression "body burden" is used here to refer to the total amount of Pb in the body. Most of the available information about the distribution of Pb to major organ systems (e.g., bone, soft tissues) derives from autopsy studies conducted in the 1960s and 1970s and reflect body burdens accrued during periods when ambient and occupational exposure levels were much higher than current levels (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). A more recent autopsy study found lower Pb concentrations in autopsies performed during the period 2004–2013 (Mari et al. 2014). In general, these studies indicate that the distribution of Pb appears to be similar in children and adults, although a larger fraction of the Pb body burden of adults resides in bone. Several models of Pb pharmacokinetics have been proposed to characterize such parameters as intercompartmental Pb exchange rates, retention of Pb in various tissues, and relative rates of distribution among the tissue groups (see Section 3.1.5 for further discussion of models).

Pb in Blood. Concentrations of Pb in blood vary considerably with age, physiology/life stage (e.g., pregnancy, lactation, menopause), and numerous factors that affect exposure to Pb. PbBs in various demographic strata of the U.S. population are periodically estimated from the NHANES. Based on data from NHANES (2015–2016, CDC 2018a), the geometric mean PbB of U.S. adults, age ≥20 years, was 0.920 μg/dL (95% CI 0.862, 0.982). The geometric mean PbB of U.S. children, age 1–5 years, was 0.758 (95% CI 0.675, 0.850). PbBs in the United States have decreased considerably in the last several decades as a result of removal of Pb from gasoline and restrictions placed on the use of Pb in residential paints (Brody et al. 1994; CDC 2011, 2018a; Pirkle et al. 1994, 1998; Schwartz and Pitcher 1989). While historically, the geometric mean PbB in U.S. children has been higher than that of the adult population, recent estimates indicate that geometric means in children have fallen below that of adults.

Pb in Red Blood Cells. Pb in blood is primarily in the red blood cells (99%) (Bergdahl et al. 1997a, 1998, 1999; Hernandez-Avila et al. 1998; Manton et al. 2001; Schutz et al. 1996; Smith et al. 2002). Although the mechanisms by which Pb crosses cell membranes have not been fully elucidated, results of studies in intact red blood cells and red blood cell ghosts indicate that there are two, and possibly three, pathways for facilitated transfer of Pb across the red cell membrane. The major proposed pathway is an anion exchanger that is dependent upon HCO_3^- and is blocked by anion exchange inhibitors (Bannon et al.

2000, Simons 1985, 1986a, 1986b, 1993). A second minor pathway, which does not exhibit HCO_3^- dependence and is not sensitive to anion exchange inhibitors, may also exist (Simons 1986b). Pb and calcium may also share a permeability pathway, which may be a Ca^{2+}-channel (Calderon-Salinas et al. 1999). Pb is transferred out of the erythrocyte by an active transport pathway, most likely a (Ca^{2+}, Mg^{2+})-ATPase (Simons 1988).

Pb in erythrocytes binds to several intracellular proteins. ALAD is the primary binding ligand for Pb in erythrocytes (Bergdahl et al. 1997a, 1998; Sakai et al. 1982; Xie et al. 1998). Pb binding to ALAD is saturable; the binding capacity has been estimated to be approximately 85 μg/dL red blood cells (or approximately 40 μg/dL whole blood) and the apparent dissociation constant has been estimated to be approximately 1.5 μg/L (Bergdahl et al. 1998). Two other Pb-binding proteins have been identified in erythrocytes, a 45 kDa protein (Kd 5.5 μg/L) and a smaller protein(s) having a molecular weight <10 kDa (Bergdahl et al. 1996, 1997a, 1998). Of the three principal Pb-binding proteins identified in erythrocytes, ALAD has the strongest affinity for Pb (Bergdahl et al. 1998) and appears to dominate the ligand distribution of Pb (35–84% of total erythrocyte Pb) at blood Pb levels below 40 μg/dL (Bergdahl et al. 1996, 1998; Sakai et al. 1982). The decrease in hematocrit that occurs in early infancy (51% at birth to 35% at 6 months) may decrease the total binding capacity of blood and PbBs over the first postnatal 6 months (Simon et al. 2007).

Pb binds to and inhibits the activity of ALAD (Gercken and Barnes 1991; Gibbs et al. 1985; Jaffe et al. 2000; Sakai et al. 1982, 1983). Binding of zinc is essential for ALAD activity, and Pb inhibits activity of ALAD by displacing zinc (Jaffe et al. 2000). Synthesis of ALAD appears to be induced in response to inhibition of ALAD and, therefore, in response to binding of Pb to ALAD (Boudene et al. 1984; Fujita et al. 1982). Several mechanisms may participate in the induction of ALAD, including (1) inhibition of ALAD directly by Pb; (2) inhibition by protoporphyrin, secondary to accumulation of protoporphyrin as a result of Pb inhibition of ferrochelatase; and (3) accumulation of ALA (a substrate of ASAD), secondary to inhibition of ALAD, which may stimulate ALAD synthesis in bone marrow cells (Boudene et al. 1984; Fujita et al. 1982).

ALAD is a polymorphic enzyme with two alleles (ALAD 1 and ALAD 2) and three genotypes (ALAD 1,1, ALAD 1,2, and ALAD 2,2) (Battistuzzi et al. 1981, Scinicariello et al. 2007). Numerous studies have examined the relationship between ALAD genotype and PbBs and the results of these studies are mixed with some studies finding higher PbBs in association with the ALAD 2 allele and other studies finding no associations or lower PbBs associated with the ALAD 2 allele (see Section 3.2). One possible

mechanism by which ALAD polymorphism could affect PbBs is by allelic variation in Pb binding to ALAD (Bergdahl et al. 1997b). However, competitive displacement studies with recombinant human ALAD 1 and ALAD 2 did not indicate differences in affinity for Pb relative to zinc (Jaffe et al. 2000).

Pb in Blood Plasma. Pb binds to several constituents in plasma and it has been proposed that Pb in plasma exists in four states: loosely bound to serum albumin or other proteins with relatively low affinity for Pb, complexed to low molecular weight ligands such as amino acids and carboxylic acids, tightly bound to a circulating metalloprotein, and as free Pb^{2+} (Al-Modhefer et al. 1991). Free ionized Pb (i.e., Pb^{2+}) in plasma represents an extremely small percentage of total plasma Pb. The concentration of Pb^{2+} in fresh serum, as measured by an ion-selective Pb electrode, was reported to be 1/5,000 of the total serum Pb (Al-Modhefer et al. 1991). Approximately 40–75% of Pb in the plasma is bound to plasma proteins, of which albumin appears to be the dominant ligand (Al-Modhefer et al. 1991; Ong and Lee 1980). Pb also binds to transferrins and γ-globulins (Guo et al. 2014; Ong and Lee 1980). Pb in serum that is not bound to protein exists largely as complexes with low molecular weight sulfhydryl compounds (e.g., cysteine, homocysteine). Other potential low molecular weight Pb-binding ligands in serum may include citrate, cysteamine, ergothioneine, glutathione, histidine, and oxylate (Al-Modhefer et al. 1991).

Saturable binding to red blood cell proteins contributes to curvature to the blood Pb-plasma Pb relationship with an increase in the plasma/blood Pb ratio with increasing PbB (Barbosa et al. 2006a; Bergdahl et al. 1997b, 1998, 1999; DeSilva 1981; Jin et al. 2008; Kang et al. 2009; Manton et al. 2001; Rentschler et al. 2012; Smith et al. 2002; Tian et al. 2013). The curvature becomes evident at PbBs well above 10 µg/dL. As binding sites for Pb in red blood cells become saturated, a larger fraction of the blood Pb is available in plasma to distribute to brain and other Pb-responsive tissues. This contributes to a curvature in the relationship between Pb intake and PbB, with the blood Pb/intake slope decreasing with increasing Pb intake, which has been observed in children (Sherlock and Quinn 1986) and immature swine (Casteel et al. 2006). Saturable binding of Pb to red blood cell proteins also contributes to a curvilinear relationship between blood Pb and urinary Pb, whereas the relationship between plasma Pb concentration and urine Pb is linear (Bergdahl et al. 1997b).

Pb in Bone. In human adults, approximately >90% of the total body burden of Pb is found in the bones. Based on analyses of post-mortem tissues, bone accounted for 94% of the total Pb body burden of adults and 73% of the body burden in children (Barry 1975). Pb concentrations in bone increase with age, indicative of a relatively slow turnover of Pb in adult bone (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968; Wilker et al. 2011). A portion of Pb in bone readily exchanges with the

plasma Pb pool and, as a result, bone Pb is a reservoir for replenishment of Pb eliminated from blood by excretion (Alessio 1988; Behinaein et al. 2012, 2014; Chettle et al. 1991; Hryhorczuk et al. 1985; Nie et al. 2005; Nilsson et al. 1991; Rabinowitz et al. 1976). Pb in adult bone can serve to maintain blood Pb levels long after exposure has ended (Fleming et al. 1997; Inskip et al. 1996; Kehoe 1987; O'Flaherty et al. 1982; Smith et al. 1996). It can also serve as a source of Pb transfer to the fetus when maternal bone is resorbed for the production of the fetal skeleton (Franklin et al. 1997; Gulson et al. 1997b, 1999b, 2003).

Pb forms highly stable complexes with phosphate and can replace calcium in the calcium-phosphate salt, hydroxyapatite, which comprises the primary crystalline matrix of bone (Bres et al. 1986; Lloyd et al. 1975; Meirer et al. 2011; Miyake 1986; Verbeek et al. 1981). As a result, Pb deposits in bone during the normal mineralization process that occurs during bone growth and remodeling and is released to the blood during the process of bone resorption (Aufderheide and Wittmers 1992; O'Flaherty 1991b, 1993). During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in cortical and trabecular bone. This suggests that Pb accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). The association of Pb uptake and release from bone with the normal physiological processes of bone formation and resorption renders Pb biokinetics sensitive to these processes. Physiological states (e.g., pregnancy, menopause, advanced age) or disease-related states (e.g., osteoporosis, prolonged immobilization) that are associated with increased bone resorption will tend to promote the release of Pb from bone, which, in turn, may contribute to an increase in the concentration of Pb in blood (Berkowtiz et al. 2004; Bonithon-Kopp et al. 1985; Garrido Latorre et al. 2003; Hernandez-Avila et al. 2000; Jackson et al. 2010; Markowitz and Weinberger 1990; Mendola et al. 2013; Nash et al. 2004; Nie et al. 2009; Popovic et al. 2005; Silbergeld et al. 1988; Symanski and Hertz-Picciotto 1995; Thompson et al. 1985).

Two physiological compartments appear to exist for Pb in cortical and trabecular bone, to varying degrees. In one compartment, bone Pb is essentially inert, having an elimination half-time of several decades. A labile compartment exists as well that allows for maintenance of an equilibrium of Pb between bone and soft tissue or blood (Rabinowitz et al. 1976). Although a high bone formation rate in early childhood results in the rapid uptake of circulating Pb into mineralizing bone, bone Pb is also recycled to other tissue compartments or excreted in accordance with a high bone resorption rate (O'Flaherty 1995a). Thus, most of the Pb acquired early in life is not permanently fixed in the bone (O'Flaherty 1995a). In general, bone turnover rates decrease as a function of age, resulting in slowly increasing bone Pb levels among adults (Barry 1975; Gross et al. 1975; Schroeder and Tipton 1968).

Bone Pb burdens in adults are slowly lost by diffusion (heteroionic exchange) as well as by resorption (O'Flaherty 1995a, 1995b). An XRF study of tibia Pb concentrations in individuals >10 years old showed a gradual increase in bone Pb after age 20 (Kosnett et al. 1994). In 60–70-year-old men, the total bone Pb burden may be ≥200 mg, while children <16 years old have been shown to have a total bone Pb burden of 8 mg (Barry 1975). However, in some bones (i.e., mid femur and pelvic bone), the increase in Pb content plateaus at middle age and then decreases at higher ages; the decrease with age was more pronounced in females (Drasch et al. 1987). Osteoporosis and release of Pb from resorbed bone to blood may contribute to decreasing bone Pb content in females (Gulson et al. 2002).

Evidence for the exchange of bone Pb and soft tissue Pb stores comes from analyses of stable Pb isotope signatures of Pb in bone and blood. A comparison of blood and bone Pb stable isotope signatures in five adults indicated that bone Pb stores contributed to approximately 40–70% of the Pb in blood (Smith et al. 1996). During pregnancy, the mobilization of bone Pb increases, as the bone is resorbed to produce the fetal skeleton. Analysis for kinetics of changes in the stable isotope signatures of blood Pb in pregnant women as they came into equilibrium with a novel environmental Pb isotope signature indicated that 10–88% of the Pb in blood may derive from the mobilization of bone Pb store and approximately 80% of cord blood may be contributed from maternal bone Pb (Gulson 2000; Gulson et al. 1997b, 1999c, 2003). The mobilization of bone Pb during pregnancy may contribute, along with other mechanisms (e.g., increased absorption), to the increase in Pb concentration that has been observed during the later stages of pregnancy (Gulson et al. 1997b, 2016; Lagerkvist et al. 1996; Schuhmacher et al. 1996). Bone resorption during pregnancy can be reduced by ingestion of calcium supplements (Janakiraman et al. 2003). Additional evidence for increased mobilization of bone Pb into blood during pregnancy is provided from studies in nonhuman primates and rats (Franklin et al. 1997; Maldonado-Vega et al. 1996). Direct evidence for transfer of maternal bone Pb to the fetus has been provided from stable Pb isotope studies in Cynomolgus monkeys (*Macaca fascicularis*) that were dosed with Pb having a different stable isotope ratio than the Pb to which the monkeys were exposed at an earlier age; approximately 7–39% of the maternal Pb burden that was transferred to the fetus appeared to have been derived from the maternal skeleton (Franklin et al. 1997).

In addition to pregnancy, other states of increased bone resorption appear to result in release of bone Pb to blood; these include lactation, osteoporosis, and severe weight loss. Analysis of kinetics of changes in the stable isotope signatures of blood Pb in postpartum women as they came into equilibrium with a novel environmental Pb isotope signature indicated that the release of maternal bone Pb to blood appears to accelerate during lactation (Gulson et al. 2002, 2003, 2004). This is consistent with declines in patella

bone Pb (measured by XRF) during lactation without calcium supplementation (Henandez-Avila et al. 1996). Similar approaches have detected increased release of bone Pb to blood in women, in association with menopause (Gulson et al. 2002). These observations are consistent with epidemiological studies that have shown increases in PbB after menopause and in association with decreasing bone density in postmenopausal women (Berkowitz et al. 2004; Garrido Latorre et al. 2003; Hernandez-Avila et al. 2000; Korrick et al. 2002; Nash et al. 2004; Popovic et al. 2005; Symanski and Hertz-Picciotto 1995). In a prospective study of women who were scheduled to undergo bilateral oophorectomy for benign conditions, blood and tibia bone Pb (measured by XRF and adjusted for bone mineral density) did not change 6–18 months post-surgery, regardless of whether patients were given estrogen replacement therapy (Berkowitz et al. 2004). Severe weight loss (28% of BMI in 6 months) in women, which increased bone turnover, increased PbB (Riedt et al. 2009).

Pb in Soft Tissues. Several studies have compared soft tissue concentrations of Pb in autopsy samples of soft tissues (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). These studies were conducted in the 1960s and 1970s and, therefore, reflect burdens accrued during periods when ambient and occupational exposure levels were much higher than current levels. A more recent autopsy study found lower Pb concentrations in autopsies performed during the period 2004–2013 (Mari et al. 2014). Average PbBs reported in the adult subjects were approximately 20 μg/dL in the Barry (1975) and Gross et al. (1975) studies, whereas more current estimates of the average for adults in the United States are <5 μg/dL (CDC 2018a). Levels in other soft tissues also appear to have decreased substantially since these studies were reported (Barregård et al. 1999; Mari et al. 2014). For example, average Pb concentrations in kidney cortex of male adults were 0.78 μg/g wet tissue and 0.79 μg/g, as reported by Barry (1975) and Gross et al. (1975), respectively (samples in the Barry study were from subjects who had no known occupational exposures). An analysis of kidney biopsy samples collected in Sweden found that the mean level of lead in kidney cortex among subjects not occupationally exposed to Pb was 0.18 μg/g (maximum, 0.56 μg/g) (Barregård et al. 1999). Mari et al. (2014) reported a value of 0.18 μg/g for mean kidney Pb concentration in 20 autopsies performed in Spain. In spite of the downward trends in soft tissue Pb levels, the autopsy studies provide a basis for describing the relative soft tissue distribution of Pb in adults and children. Most of the Pb in soft tissue is in liver. Relative amounts of Pb in soft tissues as reported by Schroeder and Tipton (1968), expressed as percent of total soft tissue Pb, were: liver, 33%; skeletal muscle, 18%; skin, 16%; dense connective tissue, 11%; fat, 6.4%; kidney, 4%; lung, 4%; aorta, 2%; and brain, 2% (other tissues were <1%). The highest soft tissue concentrations in adults also occur in liver and kidney cortex (Barry 1975; Gerhardsson et al. 1986a, 1995b; Gross et al. 1975; Mari et al. 2014; Oldereid et al. 1993). The relative distribution of Pb in soft tissues, in males and

females, expressed in terms of tissue:liver concentration ratios, were: liver, 1.0 (approximately 1 μg/g wet weight); kidney cortex, 0.8; kidney medulla, 0.5; pancreas, 0.4; ovary, 0.4; spleen, 0.3; prostate, 0.2; adrenal gland, 0.2; brain, 0.1; fat, 0.1; testis, 0.08; heart, 0.07; and skeletal muscle, 0.05 (Barry 1975; Gross et al. 1975). In contrast to Pb in bone, which accumulates Pb with continued exposure in adulthood, concentrations in soft tissues (e.g., liver and kidney) are relatively constant in adults (Barry 1975; Treble and Thompson 1997), reflecting a faster turnover of Pb in soft tissue, relative to bone.

Mechanisms by which Pb enters soft tissues have not been fully characterized (Bressler et al. 2005). Studies conducted in preparations of mammalian small intestine support the existence of saturable and nonsaturable pathways of Pb transfer and suggest that Pb can interact with transport mechanisms for calcium and iron (see Section 3.1.1). Pb can enter cells through voltage-gated L-type Ca^{2+} channels in bovine adrenal medullary cells (Legare et al. 1998; Simons and Pocock 1987; Tomsig and Suszkiw 1991) and through store-operated Ca^{2+} channels in pituitary GH3, glial C3, human embryonic kidney, and bovine brain capillary endothelial cells (Kerper and Hinkle 1997a, 1997b). Anion exchangers may also participate in Pb transport in astrocytes (Bressler et al. 2005). In addition to the small intestine, DMT1 is expressed in the kidney (Canonne-Hergaux et al. 1999); however, little information is available regarding the transport of Pb across the renal tubular epithelium. In Madin-Darby canine kidney cells (MDCK), Pb has been shown to undergo transepithelial transport by a mechanism distinct from the anion exchanger that has been identified in red blood cells (Bannon et al. 2000). The uptake of Pb into MDCK cells was both time and temperature dependent. Overexpression of DMT1 in the human embryonic kidney fibroblast cells (HEK293) resulted in increased Pb uptake compared to HEK293 cells in which DMT1 was not overexpressed (Bannon et al. 2002). Based on this limited information, it appears that DMT1 may play a role in the renal transport of Pb.

Pb in other soft tissues such as kidney, liver, and brain exists predominantly bound to protein. High affinity cytosolic Pb binding proteins have been identified in rat kidney and brain (DuVal and Fowler 1989; Fowler 1989; Gonick et al. 2011). The Pb binding proteins of rat are cleavage products of α2μ-globulin, a member of the protein superfamily known as retinol-binding proteins (Fowler and DuVal 1991). α2μ-Globulin is synthesized in the liver under androgen control and has been implicated in the mechanism of male rat hyaline droplet nephropathy produced by certain hydrocarbons (EPA 1991; Swenberg et al. 1989); however, there is no evidence that Pb induces male-specific nephropathy or hyaline droplet nephropathy. The precise role for Pb binding proteins in the toxicokinetics and toxicity of Pb has not been firmly established; however, it has been proposed that binding proteins may serve as a cytosolic Pb "receptor" that, when transported into the nucleus, binds to chromatin and modulates gene

expression (Fowler and DuVal 1991; Mistry et al. 1985, 1986). Other high-affinity Pb binding proteins (Kd approximately 14 nM) have been isolated in human kidney, two of which have been identified as a 5 kD peptide, thymosin 4, and a 9 kD peptide, acyl-CoA binding protein (Smith et al. 1998b). Pb also binds to metallothionein, but does not appear to be a significant inducer of the protein in comparison with the inducers of cadmium and zinc (Eaton et al. 1980; Waalkes and Klaassen 1985). *In vivo*, only a small fraction of the Pb in the kidney is bound to metallothionein, and appears to have a binding affinity that is less than Cd^{2+}, but higher than Zn^{2+} (Ulmer and Vallee 1969); thus, Pb will more readily displace zinc from metallothionein than cadmium (Goering and Fowler 1987; Nielson et al. 1985; Waalkes et al. 1984).

Pb Distribution during Pregnancy and Maternal-Fetal-Infant Transfer. PbBs tend to be lower in pregnant women compared to non-pregnant women of similar age, BMI, iron status, and smoking status (Jain 2013a; Liu et al. 2013). This difference may reflect increased elimination of Pb from the maternal system (Jain 2013b). Maternal PbB changes during and following pregnancy. A U-shaped temporal pattern has been observed in which maternal PbBs decrease during the second trimester and increase during the third trimester and postpartum period (Gulson et al. 2004, 1997, 2016; Hertz-Picciotto et al. 2000; Lagerkvist et al. 1996; Lamadrid-Figueroa et al. 2006; Rothenberg et al. 1994a). Several factors appear to contribute to these changes. During the second trimester, increased plasma volume contributes to hemodilution of maternal blood Pb and a lowering in the PbB (Hytten 1985; Rothenberg et al. 1994b). During the third trimester, growth of the fetal skeleton accelerates, which results in increased mobilization of calcium and Pb from the maternal skeleton, increasing maternal PbB (Gulson et al. 1998b, 2003). Postpartum calcium demand increases further during lactation and breastfeeding, which promotes further mobilization of calcium and Pb from bone and sustains or increases maternal PbBs (Gulson et al. 1998b; Hansen 2011; Tellez-Rojo et al. 2002). Increased demand for calcium in the third trimester and postpartum (to supply calcium for breast milk) is also evident from studies of the effects of dietary calcium supplementation during pregnancy. Calcium supplementation of the maternal diet decreased or delayed the onset of the increase in maternal PbB during the third trimester and postpartum period and delayed mobilization of maternal bone Pb in the third trimester (Ettinger et al. 2009; Gulson et al. 2004, 2016; Manton et al. 2003). The increase in PbB associated with late pregnancy was greater in older women who had a longer history of Pb exposure and, presumably, higher bone Pb levels (Miranda et al. 2010). Pb has been detected in follicular fluid at concentrations similar to that in blood plasma (Silberstein et al. 2006).

A portion of the maternal Pb burden is transferred to the placenta and fetus during pregnancy (Esteban-Vasaloo et al. 2012; Franklin et al. 1997; Gulson et al. 2003, 2016; Kayaalti et al. 2016; Kazi et al. 2014;

O'Flaherty 1998; Reddy et al. 2014). Measurements of stable Pb isotope ratios in pregnant women and cord blood, as they came into equilibrium with a novel environmental Pb isotope signature, indicated that approximately 80% of Pb in fetal cord blood appears to derive from maternal bone stores (Gulson et al. 1997b, 1999c, 2000, 2003, 2016). Stable isotope studies have also demonstrated transfer of Pb from the maternal skeleton to fetus in nonhuman primates (Franklin et al. 1997; O'Flaherty 1998). Transplacental transfer of Pb may be facilitated by an increase in the plasma/PbB ratio during pregnancy (Lamadrid-Figueroa et al. 2006; Montenegro et al. 2008).

Fetal and maternal PbBs and placental Pb concentrations are correlated (Amaral et al. 2010; Baeyens et al. 2014; Baranowska-Boisiacka et al. 2016; Carbone et al. 1998; Chen et al. 2014; Goyer 1990; Graziano et al. 1990; Gulson et al. 2016; Kayaalti et al. 2015b; Kazi et al. 2014; Kim et al. 2015; Kordas et al. 2009; Patel and Prabhu 2009; Reddy et al. 2014). Estimates of the maternal/fetal PbB ratio, based on cord blood Pb measurements at the time of delivery, range from 0.7 to 1.0 at mean maternal PbBs ranging from 1 to 9 μg/dL. In one of the larger studies of fetal PbB, maternal and cord PbB were measured at delivery in 888 mother-infant pairs; the cord/maternal ratio was relatively constant, 0.93, over a blood Pb range of approximately 3–40 μg/dL (Graziano et al. 1990). An analysis of data from 159 mother-infant pairs revealed that higher blood pressure and alcohol consumption late in pregnancy were associated with higher concentrations of Pb in cord blood relative to maternal blood, while higher hemoglobin and sickle cell trait were associated with lower cord blood Pb relative to maternal blood Pb (Harville et al. 2005). No associations were found for calcium intake, physical activity, or smoking. Placental Pb concentrations were found to correlate with ALAD polymorphisms, with higher concentrations observed in association with ALAD2 (Kayaalti et al. 2015b).

Maternal Pb is transferred to infants during breastfeeding. Stable Pb isotope dilution studies suggested that Pb in breast milk can contribute substantially to the isotope profile of infant blood (approximately 40–80%; Gulson et al. 1998b). Numerous studies have reported Pb concentrations in maternal blood and breast milk. In general, these studies indicate that Pb concentrations in breast milk are correlated with Pb concentrations in maternal blood or plasma. Milk/maternal concentration ratios are <0.1, although values of 0.9 have been reported (Baranowska-Boisiacka et al. 2016; Counter et al. 2014; Ettinger et al. 2006, 2014; Gulson et al. 1998a; Koyashiki et al. 2010). Ettinger et al. (2004, 2006) assessed factors influencing breast milk Pb concentration in a group of 367 women and found that PbB (mean 8–9 μg/dL; range 2–30) was a stronger predictor of breast milk Pb (mean 0.9–1.4 μg/dL; range 0.2–8 μg/dL) than bone Pb, and that tibia Pb (mean 9.5 μg/g; range <1–76.5 μg/dL) was a stronger predictor of breast milk Pb than patella bone Pb (mean 14.6 μg/dL; range <1–67.2 μg/dL). Dietary intake of polyunsaturated fatty

acids (PUFA) may decrease transfer of Pb from bone to breast milk (Arora et al. 2008). Pb concentrations in maternal blood and breast milk have been shown to correlate with PbBs in breastfeeding infants (Ettinger et al. 2014; Farhat et al. 2013). Breast milk Pb concentrations explained 37% of the variation in infant blood Pb of breastfeeding infants (Ettinger et al. 2014).

Organic Pb. Information on the distribution of Pb in humans following exposures to organic Pb is extremely limited. One hour following 1–2-minute inhalation exposures to ^{203}Pb tetraethyl or tetramethyl Pb (1 mg/m^3), approximately 50% of the ^{203}Pb body burden was associated with liver and 5% was associated with kidney; the remaining ^{203}Pb was widely distributed throughout the body (Heard et al. 1979). The kinetics of ^{203}Pb in blood of these subjects showed an initial declining phase during the first 4 hours (tetramethyl Pb) or 10 hours (tetraethyl Pb) after the exposure, followed by a phase of gradual increase in PbB that lasted for up to 500 hours after the exposure. Radioactive Pb in blood was highly volatile immediately after the exposure and transitioned to a nonvolatile state thereafter. These observations may reflect an early distribution of organic Pb from the respiratory tract, followed by a redistribution of de-alkylated Pb compounds (see Section 3.1.3 for further discussion of alkyl Pb metabolism).

In a man and woman who accidentally inhaled a solvent containing 31% tetraethyl Pb (17.6% Pb by weight), Pb concentrations in the tissues, from highest to lowest, were liver, kidney, brain, pancreas, muscle, and heart (Bolanowska et al. 1967). In another incident, a man ingested a chemical containing 59% tetraethyl Pb (38% Pb w/w); Pb concentration was highest in the liver followed by kidney, pancreas, brain, and heart (Bolanowska et al. 1967).

3.1.3 Metabolism

Inorganic Pb. Metabolism of inorganic Pb consists of formation of complexes with a variety of protein and nonprotein ligands (see Section 3.1.2 for further discussion). Major extracellular ligands include albumen and nonprotein sulfhydryls. The major intracellular ligand in red blood cells is ALAD. Pb also forms complexes with proteins in the cell nucleus and cytosol.

Organic Pb. Alkyl Pb compounds are actively metabolized in the liver by oxidative dealkylation catalyzed by cytochrome P-450. Relatively few studies that address the metabolism of alkyl Pb compounds in humans have been reported. Studies of workers who were exposed to tetraethyl Pb have shown that tetraethyl Pb is excreted in the urine as diethyl Pb, ethyl Pb, and inorganic Pb (Turlakiewicz

and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994). Trialkyl Pb metabolites were found in the liver, kidney, and brain following exposure to the tetraalkyl compounds in workers; these metabolites have also been detected in brain tissue of nonoccupational subjects (Bolanowska et al. 1967; Nielsen et al. 1978). In volunteers exposed by inhalation to 0.64 and 0.78 mg Pb/m^3 of ^{203}Pb-labeled tetraethyl and tetramethyl Pb, respectively, Pb was cleared from the blood within 10 hours, followed by a re-appearance of radioactivity back into the blood after approximately 20 hours (Heard et al. 1979). The high level of radioactivity initially in the plasma indicates the presence of tetraalkyl/trialkyl Pb. The subsequent rise in blood radioactivity, however, probably represents water-soluble inorganic Pb and trialkyl and dialkyl Pb compounds that were formed from the metabolic conversion of the volatile parent compounds (Heard et al. 1979).

3.1.4 Excretion

Independent of the route of exposure, absorbed Pb is excreted primarily in urine and feces; sweat, saliva, hair and nails, breast milk, and seminal fluids are minor routes of excretion (Chamberlain et al. 1978; Griffin et al. 1975; Hernandez-Ochoa et al. 2005; Hursh and Suomela 1968; Hursh et al. 1969; Kehoe 1987; Rabinowitz et al. 1976; Sears et al. 2012; Stauber et al. 1994). Fecal excretion accounts for approximately one-third of total excretion of absorbed Pb (fecal/urinary excretion ratio of approximately 0.5), based on intravenous injection studies conducted in humans (Chamberlain et al. 1978). A similar value for fecal/urinary excretion ratio, approximately 0.5, has been observed following inhalation of submicron Pb particles (Chamberlain et al. 1978; Hursh et al. 1969). Contributors to fecal excretion may include secretion into the bile, gastric fluid, and saliva (Rabinowitz et al. 1976). Biliary excretion of Pb has been observed in the dog, rat, and rabbit (Klaassen and Shoeman 1974; O'Flaherty 1993).

Mechanisms by which inorganic Pb is excreted in urine have not been fully characterized. Such studies have been hampered by the difficulties associated with measuring ultrafilterable Pb in plasma and thereby in measuring the GFR of Pb. Renal plasma clearance was approximately 20–30 mL/minute in a subject who received a single intravenous injection of a ^{203}Pb chloride tracer (Chamberlain et al. 1978). Urinary Pb excretion is strongly correlated with the GFR of Pb (Araki et al. 1986) and plasma Pb concentration (Bergdahl et al. 1997b; Rentschler et al. 2012) (i.e., urinary excretion is proportional to GFR x plasma Pb concentration). Estimates of plasma-to-urine clearance of Pb range from 13 to 22 L/day, with a mean of 18 L/day (Araki et al. 1986; Manton and Cook 1984; Manton and Malloy 1983; Chamberlain et al. 1978). The rate of urinary excretion of Pb was less than the GFR of ultrafilterable Pb, suggesting renal tubular reabsorption of Pb from the glomerular filtrate (Araki et al. 1986, 1990). Measurement of the renal

clearance of ultrafilterable Pb in plasma indicates that in dogs, Pb undergoes glomerular filtration and net tubular reabsorption (Araki et al. 1986, 1990; Vander et al. 1977; Victery et al. 1979). Net tubular secretion of Pb has been demonstrated in dogs made alkalotic by infusions of bicarbonate (Victery et al. 1979). Renal clearance of blood Pb increases with increasing PbBs >25 μg/dL (Chamberlain 1983). The mechanism for this has not been elucidated and could involve a shift in the distribution of Pb in blood towards a fraction having a higher GFR (e.g., lower molecular weight complex), a capacity-limited mechanism in the tubular reabsorption of Pb, or the effects of Pb-induced nephrotoxicity on Pb reabsorption.

Excretion and Routes of Exposure

Inhalation Exposure

Inorganic Pb. Inorganic Pb inhaled as submicron particles is deposited primarily in the bronchiolar and alveolar regions of the respiratory tract, from where it is absorbed and excreted primarily in urine and feces (Chamberlain et al. 1978; Hursh et al. 1969; Kehoe 1987). Fecal/urinary excretion ratios were approximately 0.5 following inhalation of submicron Pb-bearing particles (Chamberlain et al. 1978; Hursh et al. 1969). Higher fecal-urinary ratios would be expected following inhalation of larger particle sizes (e.g., >1 μm) as these particles would be cleared to the gastrointestinal tract from where a smaller percentage would be absorbed (Kehoe 1987; see Section 3.1.1).

Organic Pb. Pb derived from inhaled tetraethyl and tetramethyl Pb is excreted in exhaled air, urine, and feces (Heard et al. 1979). Following 1–2-minute inhalation exposures to ^{203}Pb tetraethyl (1 mg/m^3), in four male subjects, 37% of inhaled ^{203}Pb was initially deposited in the respiratory tract, of which approximately 20% was exhaled in the subsequent 48 hours (Heard et al. 1979). In a similar experiment conducted with (^{203}Pb) tetramethyl Pb, 51% of the inhaled ^{203}Pb dose was initially deposited in the respiratory tract, of which approximately 40% was exhaled in 48 hours. Pb that was not exhaled was excreted in urine and feces. Fecal/urinary excretion ratios were 1.8 following exposure to tetraethyl Pb and 1.0 following exposure to tetramethyl Pb (Heard et al. 1979). Occupational monitoring studies of workers who were exposed to tetraethyl Pb have shown that tetraethyl Pb is excreted in the urine as diethyl Pb, ethyl Pb, and inorganic Pb (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994).

Oral Exposure

Inorganic Pb. Much of the available information on the excretion of ingested Pb in adults derives from studies conducted on five male adults who received daily doses of ^{207}Pb nitrate for periods up to 210 days (Rabinowitz et al. 1976). The dietary intakes of the subjects were reduced to accommodate the tracer doses of ^{207}Pb without increasing daily intake, thus preserving a steady state with respect to total Pb intake and excretion. Total Pb intakes (diet plus tracer) ranged from approximately 210 to 360 μg/day. Urinary excretion accounted for approximately 12% of the daily intake (range for five subjects: 7–17%) and fecal excretion, approximately 90% of the daily intake (range, 87–94%). Based on measurements of tracer and total Pb in saliva, gastric secretions, bile, and pancreatic secretions (samples collected from three subjects by intubation), gastrointestinal secretion of Pb was estimated to be approximately 2.4% of intake (range, 1.9–3.3%). In studies conducted at higher ingestion intakes, 1–3 mg/day for up to 208 weeks, urinary Pb excretion accounted for approximately 5% of the ingested dose (Kehoe 1987). Elimination of Pb is multiphasic, reflecting pools of Pb in the body that have varying retention times. Elimination from blood and soft tissues is faster than bone (Nilsson et al. 1991; Rabinowitz et al. 1976). As a result, after an abrupt decrease in exposure, PbB declines at an apparent rate that reflects excretion of Pb from blood and replenishment of Pb in blood from bone stores. The elimination half-time of Pb in blood in retired lead workers was tri-exponential, with approximately 22% of elimination occurring at a half-time of 34 days (95% CL 29, 41), 28% at a half-time of 1.2 years (95% CL 0.85, 1.8), and 50% at a half-time of 13 years (95% CL 10, 18) (Nilsson et al. 1991). The corresponding mono-exponential half-time for finger bone (XRF) in these same subjects was 16 years (85% CL 12, 23). Apparent elimination half-times for blood Pb in children also vary considerably, dependent in part on age and exposure history of the child that establishes levels of Pb in bone (Manton et al. 2000; Specht et al. 2018). Manton et al. (2000) estimated apparent elimination half-times for PbB in children (ages 2–3 years at time of exposure) that ranged from 8 to 38 months. However, these estimates reflect both excretion of Pb from blood as well as transfer of Pb from bone to blood; the latter would tend to increase the apparent blood elimination half-time. Specht et al. (2018) estimated blood Pb elimination half-times for Pb transferred from bone to blood (estimated with XRF measurements and biokinetics modeling). Estimated blood Pb half-times were 6.9±4 (SD) in children 1–3 years old and 19.3±14.1 days in children >3 years old (Specht et al. 2018).

Dermal Exposure. Inorganic Pb is excreted in sweat and urine following dermal exposure to Pb nitrate or Pb acetate (Moore et al. 1980; Stauber et al. 1994).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

Early Pb modeling applications relied on classical pharmacokinetics. Compartments representing individual organs or groups of organs that share a common characteristic were defined as volumes, or pools, that are kinetically homogeneous. For example, the body could be represented by a central compartment (e.g., blood plasma), and one or two peripheral compartments, which might be "shallow" or "deep" (i.e., they may exchange relatively rapidly or relatively slowly with blood plasma) (O'Flaherty 1987). One of the first of such models was proposed by Rabinowitz et al. (1976) based on a study of the kinetics of ingested stable Pb isotope tracers and Pb balance data in five healthy adult males. The Rabinowitz model included three compartments: a central compartment representing blood and other tissues and spaces in rapid equilibrium with blood (e.g., interstitial fluid); a shallow tissue compartment, representing soft tissues and rapidly exchanging pools within the skeleton; and a deep tissue compartment, representing, primarily, slowly exchanging pools of Pb within bone. Excretion pathways represented in the model included urinary, from the central compartment, and bile, sweat, hair, and nails, from the shallow tissue compartment. The model predicted pseudo-first-order half-times for Pb of approximately 25, 28, and 10^4 days in the central, shallow tissue, and deep compartments, respectively. The slow kinetics of the deep tissue compartment leads to the prediction that it would contain most of the Pb burden after lengthy exposures (e.g., years), consistent with Pb measurements made in human autopsy samples (see Section 3.1.2 Distribution). Note that this model did not simulate the distribution of Pb within blood (e.g., erythrocytes and plasma), nor did it simulate subcompartments within bone or physiological processes of bone turnover that might affect kinetics of the deep tissue compartment.

Marcus (1985b) reanalyzed the data from stable isotope tracer studies of Rabinowitz et al. (1976) and derived an expanded multicompartment kinetic model for Pb that included separate compartments for cortical (slow, $t_{1/2}$ $1.2x10^4$–$3.5x10^4$ days) and trabecular (fast, $t_{1/2}$ 100–700 days), an approach

subsequently adopted in several models (Bert et al. 1989; EPA 1994a, 1994b; Leggett 1993; O'Flaherty 1993, 1995a). A more complex representation of the Pb disposition in bone included explicit simulation of diffusion of Pb within the bone volume of the osteon and exchange with blood at the canaliculus (Marcus 1985a). The bone diffusion model was based on Pb kinetics data from studies conducted in dogs. Marcus (1985c) also introduced nonlinear kinetics of exchange of Pb between plasma and erythrocytes. The blood model included four blood subcompartments: diffusible Pb in plasma, protein-bound Pb in plasma, a "shallow" erythrocyte pool, and a "deep" erythrocyte pool. This model predicted the curvilinear relationship between plasma and PbBs observed in humans (see Section 3.1.2 Distribution for further discussion of plasma-erythrocyte Pb concentrations).

Additional information on Pb biokinetics, bone mineral metabolism, and Pb exposures has led to further refinements and expansions of these earlier modeling efforts. Four pharmacokinetic models, in particular, are currently being used or are being considered for broad application in Pb risk assessment: (1) the O'Flaherty Model, which simulates Pb kinetics from birth through adulthood (O'Flaherty 1993, 1995a); (2) the EPA Integrated Exposure Uptake BioKinetic (IEUBK) Model for Lead in Children developed by EPA (1994a, 1994b); (3) the Leggett Model, which simulates Pb kinetics from birth through adulthood (Leggett 1993); and (4) the EPA All Ages Lead Model (AALM, EPA 2014a). The structure and parameterization of the O'Flaherty Model is distinct from both the IEUBK Model and Leggett Model. The AALM is an update of the O'Flaherty and Leggett models, extended to include a multi-media exposure model.

The IEUBK Model simulates multimedia exposures, uptake, and kinetics of Pb in children ages 0–7 years for predicting pseudo-steady state relationships between Pb exposure and PbB; the model is not intended for use in predicting short-term kinetics of blood Pb or Pb concentrations in tissues other than whole blood. The O'Flaherty Model, Leggett Model, and AALM are lifetime models, and include parameters that simulate uptake and kinetics of Pb during infancy, childhood, adolescence, and adulthood. Pb exposure (e.g., residence-specific environmental Pb concentrations, childhood activity patterns) is not readily described by current versions of the O'Flaherty and Leggett models. The IEUBK Model and AALM include parameters for simulating exposures and uptake to estimate average daily uptake of Pb (μg/day) among populations potentially exposed via soil and dust ingestion, air inhalation, tap water ingestion, diet, and miscellaneous (other) intakes. All four models have been calibrated, to varying degrees, against empirical physiological data on animals and humans, and data on PbBs in individuals and/or populations (Beck et al. 2001; Bowers and Mattuck 2001; Cal EPA 2013; EPA 1994a, 1994c, 2014a, 2014b, 2016; Griffin et al. 1999; Hogan et al. 1998; Leggett 1993; Li et al. 2016; MacMillan et al.

2015; O'Flaherty 1993, 1995, 1998, 2000; Pounds and Leggett 1998; White et al. 1998; Von Lindern et al. 2003, 2016).

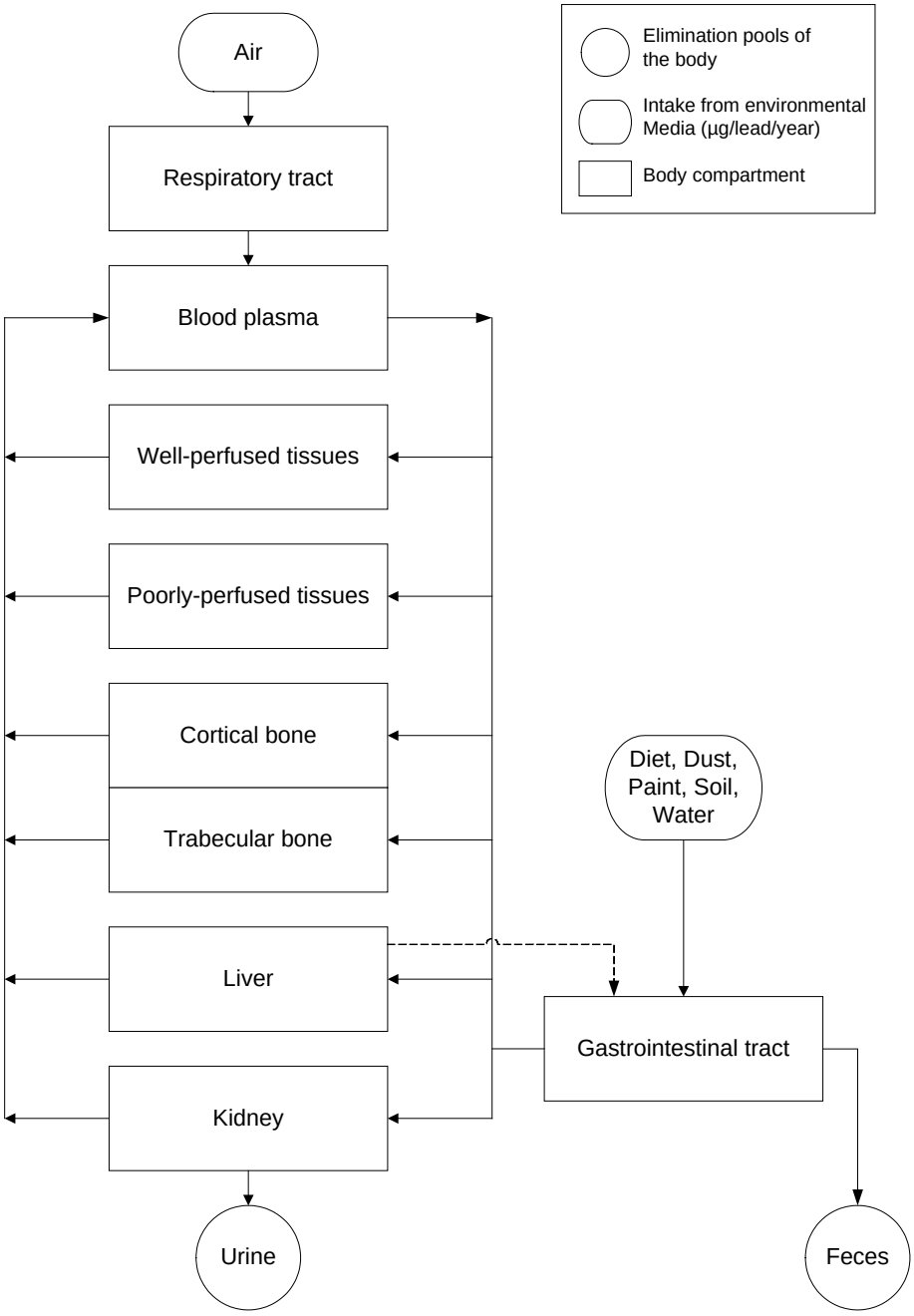
The focus on relying on PbBs for model evaluation and calibration derives from several concerns. The empirical basis for a relationship between low levels of Pb exposure and behavioral dysfunction largely consists of prospective epidemiological studies relating various indices of dysfunction with PbB (see Section 3.3). In this context, PbB has been related to health effects of Pb, and this is the main reason that the focus of interest in the models has been on estimating PbBs. Also, the most available data with which to calibrate and validate the models have been data relating exposure and/or Pb intake to blood concentration. Thus, there is greater confidence in the validity of the models for estimating blood concentrations, rather than Pb levels in other physiologic compartments. Although the principal adverse health effects of Pb have been related to concentrations of Pb in blood, other biomarkers of Pb exposure, such as bone Pb concentrations, are also of value in assessing associations between Pb exposure and health; hence, there is a need for models that predict concentrations of Pb in tissues other than blood (see Section 3.3).

The following four pharmacokinetic models are discussed in great detail below: (1) the O'Flaherty Model (O'Flaherty 1993, 1995a); (2) the IEUBK Model for Lead in Children (EPA 1994a, 1994b); (3) the Leggett Model (Leggett 1993); and (4) AALM (EPA 2014a).

3.1.5.1 O'Flaherty Model

The O'Flaherty Model simulates Pb exposure, uptake, and disposition in humans, from birth through adulthood (O'Flaherty 1993, 1995a). Figure 3-1 shows a conceptualized representation of the O'Flaherty Model, including the movement of Pb from exposure media (i.e., intake via inhalation or ingestion) to the lungs and gastrointestinal tract, followed by the subsequent exchanges between blood plasma, liver, kidney, richly-perfused tissues, poorly-perfused tissues, bone compartments, and excretion from liver and/or kidney. The model simulates both age- and media-specific absorption. Because many of the pharmacokinetic functions are based on body weight and age, the model can be used to estimate PbBs across a broad age range, including infants, children, adolescents, and adults. The model uses physiologically based parameters to describe the volume, composition, and metabolic activity of blood, soft tissues, and bone that determine the disposition of Pb in the human body.

Figure 3-1. Compartments and Pathways of Lead (Pb) Exchange in the O'Flaherty Model*



*Schematic model for Pb kinetics in which Pb distribution is represented by flows from blood plasma to liver, kidney, richly-perfused tissues, poorly-perfused tissues, and cortical and trabecular bone. The model simulates tissue growth with age, including growth and resorption of bone mineral.

Sources: O'Flaherty 1991b, 1993, 1995a

A central feature of the model is the growth curve, a logistic expression relating body weight to age. The full expression relating weight to age has five parameters (constants), so that it can readily be adapted to fit a range of standardized growth curves for men and women. Tissue growth and volumes are linked to body weight; this provides explicit modeling of concentrations of Pb in tissues. Other physiologic functions (e.g., bone formation) are linked to body weight, age, or both.

Pb exchange between blood plasma and bone is simulated as parallel processes occurring in cortical (80% of bone volume) and trabecular bone (20% of bone volume). Uptake and release of Pb from trabecular bone and metabolically active cortical bone are functions of bone formation and resorption rates, respectively. Rates of bone formation and resorption are simulated as age-dependent functions, which gives rise to an age-dependence of Pb kinetics in bone. The model simulates an age-related transition from immature bone, in which bone turnover (formation and resorption) rates are relatively high, to mature bone, in which turnover is relatively slow. Changes in bone mineral turnover associated with senescence (e.g., postmenopausal osteoporosis) are not represented in the model. In addition to metabolically active regions of bone, in which Pb uptake and loss is dominated by bone formation and loss, a region of slow kinetics in mature cortical bone is also simulated, in which Pb uptake and release to blood occur by heteroionic exchange with other minerals (e.g., calcium). Heteroionic exchange is simulated as a radial diffusion in bone volume of the osteon. All three processes are linked to body weight, or the rate of change of weight with age. This approach allows for explicit simulation of the effects of bone formation (e.g., growth) and loss, changes in bone volume, and bone maturation on Pb uptake and release from bone. Exchanges of Pb between blood plasma and soft tissues (e.g., kidney and liver) are represented as flow-limited processes. The model simulates saturable binding of Pb in erythrocytes; this replicates the curvilinear relationship between plasma and erythrocyte Pb concentrations observed in humans (see Section 3.1.2). Excretory routes include kidney to urine and liver to bile. Total excretion (clearance from plasma attributable to bile and urine) is simulated as a function of GFR. Biliary and urinary excretory rates are proportioned as 70 and 30% of the total plasma clearance, respectively.

The O'Flaherty Model simulates Pb intake from inhalation and ingestion. Inhalation rates are age-dependent. Absorption of inhaled Pb is simulated as a fraction (0.5) of the amount inhaled, and is independent of age. The model simulates ingestion exposures from infant formula, soil and dust ingestion, and drinking water ingestion. Rates of soil and dust ingestion are age-dependent, increasing to approximately 130 mg/day at age 2 years, and declining to <1 mg/day after age 10 years. Gastrointestinal absorption of Pb in diet and drinking water is simulated as an age-dependent fraction, declining from

0.58 of the ingestion rate at birth to 0.08 after age 8 years. These values can be factored to account for relative bioavailability when applied to absorption of Pb ingested in dust or soil.

The O'Flaherty Model, as described in O'Flaherty (1993, 1995a), utilizes point estimates for parameter values and yields point estimates as output; however, a subsequent elaboration of the model has been developed that utilizes a Monte Carlo approach to simulate variability in exposure, absorption, and erythrocyte Pb binding capacity (Beck et al. 2001). This extension of the model can be used to predict the probability that children exposed to Pb in environmental media will have PbBs exceeding a health-based reference value (e.g., 5 μg/dL).

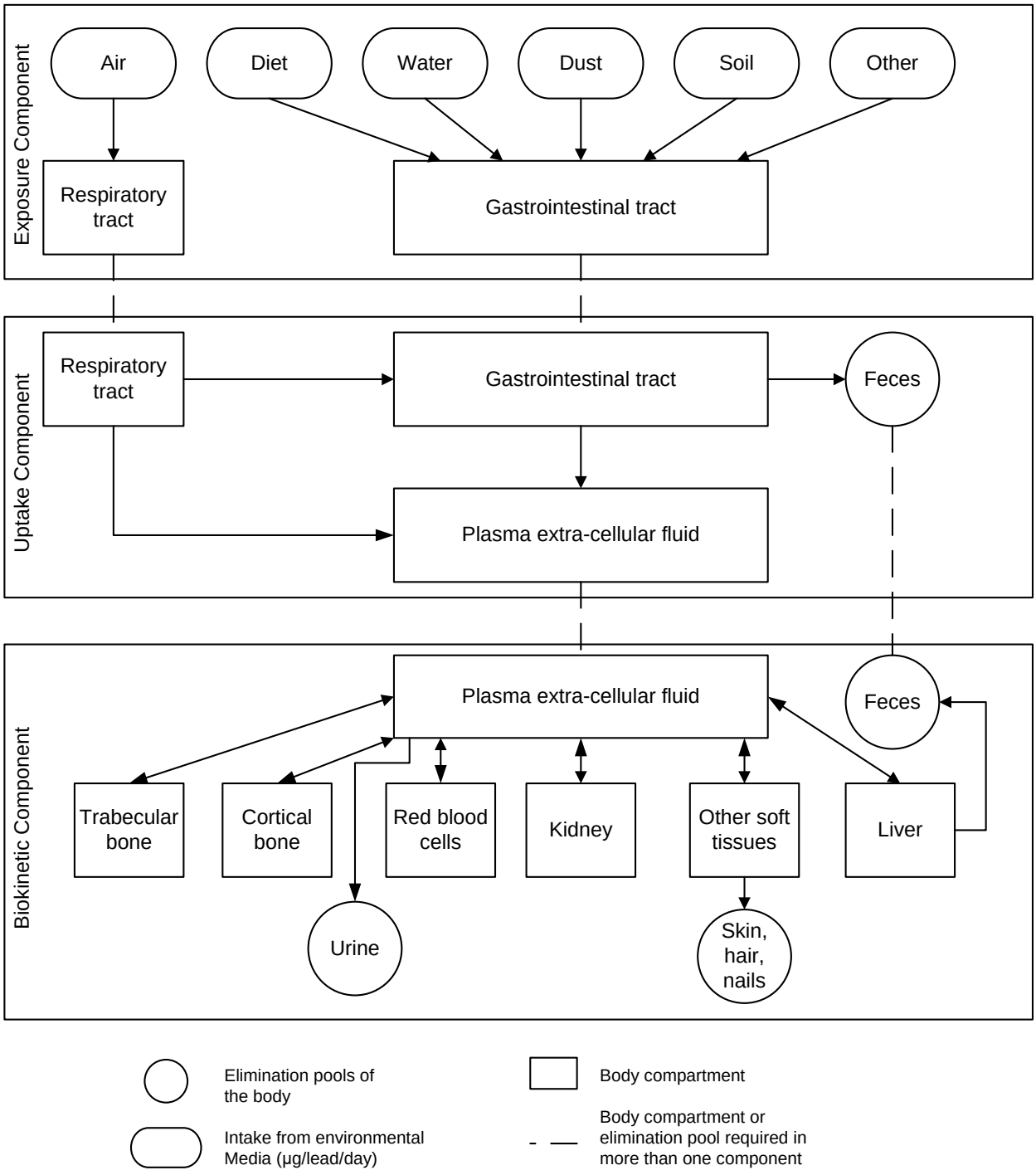
The model was designed to operate with an exposure time step on 1 year (the smallest time interval for a single exposure event). However, the implementation code allows constructions of simulations with an exposure time step as small as 1 day, which would allow simulation of rapidly changing intermittent exposures (e.g., an acute exposure event).

The O'Flaherty Model was initially calibrated to predict blood, bone, and tissue Pb concentrations in rats (O'Flaherty 1991a), and subsequently modified to reflect anatomical and physiological characteristics in children (O'Flaherty 1995a), adults (O'Flaherty 1993), and Cynomolgus monkeys (*M. fasicularis*) (O'Flaherty et al. 1998). Model parameters were modified to correspond with available information on species- and age-specific anatomy and physiological processes described above. Comparisons of predicted and observed PbB in children and adults are reported in O'Flaherty (1993, 1995a). MacMillan et al. (2015) evaluated performance of the model for predicting population blood and bone Pb levels in a convenience sample of 263 individuals (age range 1–83 years) who experienced low chronic exposure. Based on this evaluation, model performance for predicting general trends in population PbBs and cortical bone Pb concentrations was improved by revising parameters that determine binding of Pb in red blood cells. Revisions included decreasing the maximum and affinity constants (*BIND* and *KBIND*, respectively) and increasing clearance of Pb from blood to bone by increasing the permeability constant for Pb diffusion across the canaliculi-bone interface from canaliculi to bone (P_0).

3.1.5.2 EPA IEUBK Model

The EPA IEUBK Model for Lead in Children simulates Pb exposure, uptake, and disposition in human children from birth to age 7 years (EPA 1994a, 1994b, 2002a; White et al. 1998). Figure 3-2 shows a conceptualized representation of the IEUBK Model. The model has four major submodels: (1) exposure

Figure 3-2. Structure of the IEUBK Model for Lead (Pb) in Children*



*Schematic for integrated Pb exposure-kinetics model in which simulated multi-media exposures are linked to simulations of lead uptake (i.e., absorption into the plasma-extracellular fluid), tissue distribution, and excretion).

Sources: EPA 1994a, 1994b

model, in which average daily intakes of Pb (μg/day) are calculated for each inputted exposure concentration (or rates) of Pb in air, diet, dust, soil, and water; (2) uptake model, which converts environmental media-specific Pb intake rates calculated from the exposure model into a media-specific time-averaged uptake rate (μg/day) of Pb to the central compartment (blood plasma); (3) biokinetic model, which simulates the transfer of absorbed Pb between blood and other body tissues, elimination of Pb from the body (via urine, feces, skin, hair, and nails), and predicts an average PbB for the exposure time period of interest; and (4) blood Pb probability model, which applies a log-normal distribution (using geometric mean and geometric standard deviation for parameters) to predict probabilities for the occurrence of a specified given PbB in a population of similarly exposed children.

Exposure Model. The exposure model simulates intake of Pb (μg/day) for inputted exposures to Pb in air (μg/m^3), drinking water (μg/L), soil-derived dust (μg/g), or diet (μg/day). The exposure model operates on a 1-year time step, the smallest time interval for a single exposure event. The model accepts inputs for media intake rates (e.g., air volumes, breathing rates, drinking water consumption rate, soil and dust ingestion rate). The air exposure pathway is partitioned in exposures to outdoor air and indoor air, with age-dependent values for time spent outdoors and indoors (hours/day). Exposure to Pb to soil-derived dust is also partitioned into outdoor and indoor contributions. The intakes from all ingested exposure media (diet, drinking water, soil-derived dust) are summed to calculate a total intake to the gastrointestinal tract, for estimating capacity-limited absorption (see description of the uptake model).

Uptake Model. The uptake model simulates Pb absorption for the gastrointestinal tract as the sum of capacity-limited (represented by a Michaelis-Menten type relationship) and unlimited processes (represented by a first-order, linear relationship). These two terms are intended to represent two different mechanisms of Pb absorption, an approach that is in accord with limited available data in humans and animals that suggest a capacity limitation to Pb absorption (see Section 3.2.1). One of the parameters for the capacity-limited absorption process (that represents that maximum rate of absorption) is age-dependent. The above representation gives rise to a decrease in the fractional absorption of ingested Pb as a function of total Pb intake as well as an age-dependence of fractional Pb absorption. Absorption fractions are also medium-specific. At 30 months of age, at low intakes (<200 μg/day), below the rates at which capacity-limitation has a significant impact on absorption, the fraction of ingested Pb in food or drinking water that is absorbed is 0.5 and decreases to approximately 0.11 (intake, >5,000 μg/day). For Pb ingested in soil or dust, fractional absorption is 0.35 at low intakes (<200 μg/day) and decreases to 0.09 (intake, >5,000 μg/day).

The uptake model assumes that 32% of inhaled Pb is absorbed. This value was originally assigned based on a scenario of exposure to active smelter emissions, which assumed the particle size distribution in the vicinity of an active Pb smelter (<1 μm, 12.5%; 1–2.5 μm, 12.5%; 2–15 μm, 20%; 15–30 μm, 40%; >30 μm, 15%); size-specific deposition fractions for the nasopharyngeal, tracheobronchial, and alveolar regions of the respiratory tract; and region-specific absorption fractions. Pb deposited in the alveolar region is assumed to be completely absorbed from the respiratory tract, whereas Pb deposited in the nasopharyngeal and tracheobronchial regions (30–80% of the Pb particles in the size range 1–15 μm) is assumed to be transported to the gastrointestinal tract.

Biokinetics Model. The biokinetics model includes a central compartment, six peripheral body compartments, and three elimination pools (urine, feces, lumped pool representing skin, hair, and nails). The body compartments include plasma and extracellular fluid (central compartment), red blood cells, kidney, liver, trabecular bone, cortical bone, and other soft tissue (EPA 1994a). The model simulates growth of the body and tissues, compartment volumes, and Pb masses and concentrations in each compartment. PbB at birth (neonatal) is assumed to be 0.85 of the maternal blood Pb. Neonatal Pb masses and concentrations are assigned to other compartments based on a weighted distribution of the neonatal PbB. Exchanges between the central compartment and tissue compartments are simulated as first-order processes, which are parameterized with unidirectional, first-order rate constants. Bone is simulated as two compartments: a relatively fast trabecular bone compartment (representing 20% of bone volume) and a relatively slow cortical bone compartment (representing 80% of the bone volume). Saturable uptake of Pb into erythrocytes is simulated, with a maximum erythrocyte Pb concentration of 12 μg/dL. Excretory routes simulated include urine, from the central compartment; bile-feces, from the liver; and a lumped excretory pathway representing losses from skin, hair and nail, from the other soft tissue compartment.

Blood Pb Probability Model. Inputs to the IEUBK Model are exposure point estimates that are intended to represent time-averaged central tendency exposures. The output of the model is a central tendency estimate of PbB for children who might experience the inputted exposures. However, within a group of similarly exposed children, PbBs would be expected to vary among children as a result of inter-individual variability in media intakes, absorption, and biokinetics. The model simulates the combined impact of these sources of variability as a lognormal distribution of PbB for which the geometric mean is given by the central tendency PbB outputted from the biokinetics model and the GSD is an input parameter. The resulting lognormal distribution also provides the basis for predicting the probability of occurrence of given PbB within a population of similarly exposed children. The model can be iterated for varying

exposure concentrations (e.g., a series of increasing soil Pb concentrations) to predict the media concentration that would be associated with a probability of 0.05 for the occurrence of a PbB exceeding 10 μg/dL. A subsequent elaboration of the model has been developed that utilizes a Monte Carlo approach to simulate variability and uncertainty in exposure and absorption (Goodrum et al. 1996; Griffin et al. 1999). This extension of the model provides an alternative to the blood Pb probability model for incorporating, explicitly, estimates of variability (and uncertainty in variability) in exposure and absorption into predictions of an expected probability distribution of PbBs. More recently, Zartarian et al. (2017) provided an analysis coupling the IEUBK model with EPA's Stochastic Human Exposure and Dose Simulation (SHEDS)-Multimedia Model that considered general U.S. childhood exposures probabilistically and assessed primary sources of Pb exposure across the distribution of PbB.

Performance of the IEUBK Model has been evaluated for predicting observed PbBs in children (Hogan et al. 1998; Li et al. 2016; Von Lindern et al. 2003, 2016). The largest evaluation utilized longitudinal exposure and blood Pb data for approximately 2,200 children who resided near a former smelter in northern Idaho (Bunker Hill site) during a 14-year period of remediation activities (Von Lindern et al. 2003, 2016). The observed annual blood Pb geometric means ranged from 2.5 to 10.6 μg/dL. The model predicted the time course of the observed PbBs as the remediation progressed when the gastrointestinal absorption fraction was calibrated to agree with blood Pb observations (Von Lindern et al. 2003). A similar outcome was obtained in a subsequent analysis in which the gastrointestinal absorption fraction was adjusted to agree with site measurements of soil Pb RBA, and soil and dust ingestion rates were calibrated to the blood Pb observations (Von Lindern et al. 2016). The mean difference between predicted and observed annual geometric mean PbBs (predicted - observed) was -0.31 μg/dL (range: -1.07, 1.93) and the mean relative percent difference was -8.4% (range: -23–21%). Applications of the IEUBK Model to the Bunker Hill site were reviewed by the National Research Council (NRC 2005). Hogan et al. (1998) evaluated the IEUBK Model performance based on residential exposure and blood data for approximately 478 children who resided near three Pb mining and smelting sites. The observed geometric means for the three sites ranged from 5.2 to 6.8 μg/dL. The IEUBK Model predictions agreed reasonably well with observations for children whose exposures were predominantly from their residence (e.g., who spent no more than 10 hours/week away from home). The mean difference between predicted and observed site geometric mean PbBs (predicted-observed) was 0.03 μg/dL (range -0.6–0.7) and the mean relative percent difference was -0.4% (range -12–10%). The predicted geometric mean PbBs were within 0.7 μg/dL of the observed geometric means at each site. The prediction of the percentage of children expected to have PbBs exceeding 10 μg/dL were within 4% of the observed percentage at each site. Li et al. (2016) compared predictions of PbB to observations in a cohort

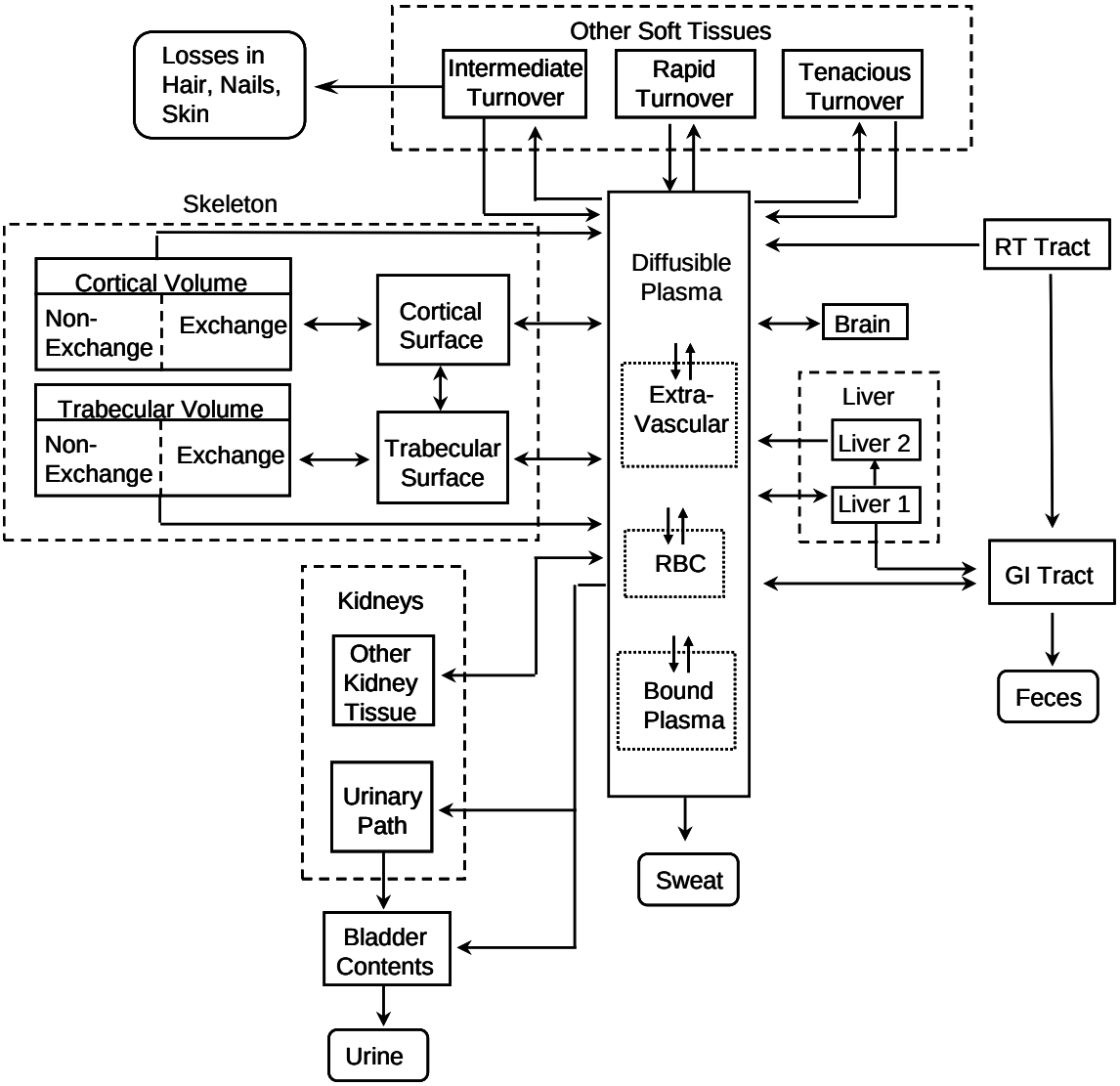
of 760 children in Central China. The observed residence area geometric means ranged from 5 to 14 µg/dL. When exposure parameters for set to the study population (e.g., exposure media Pb concentration and intakes), predicted and observed PbBs were not significantly different. The mean difference between predicted and observed geometric mean PbBs for 21 residence areas (predicted-observed) was 0.55 µg/dL (range -2.0–3.2) and the mean relative percent difference was 3.5% (range -32–28%). These evaluations provide support for the validity of the IEUBK Model for estimating PbBs in children at sites where their exposures can be adequately characterized. Similar empirical comparisons of the IEUBK Model have shown that agreement between model predictions and observed PbBs at specific locations is influenced by numerous factors, including the extent to which the exposure and blood Pb measurements are adequately matched, and site-specific factors (e.g., soil characteristics, behavior patterns, bioavailability) that may affect Pb intake or uptake in children (Bowers and Mattuck 2001; Von Lindern et al. 2003, 2016). In addition to the above empirical comparisons, the computer code used to implement the IEUBK Model (IEUBK version 0.99d) has undergone an independent validation and verification and has been shown to accurately implement the conceptual IEUBK Model (Zaragoza and Hogan 1998).

3.1.5.3 Leggett Model

The Leggett Model simulates Pb intake, absorption, and disposition in humans, from birth through adulthood (Leggett 1993). Figure 3-3 shows a conceptualized representation of the model, including the movement of Pb from exposure media (i.e., intake via inhalation or ingestion) to the lungs and gastrointestinal tract, followed by the subsequent exchanges between diffusible blood plasma, soft tissues, bone compartments, and excretion from liver, kidneys, and sweat. A detailed exposure module is not linked to the Leggett Model; rather, Pb exposure estimates are incorporated into the model as age-specific point estimates of average daily intake (µg/day) from inhalation and ingestion. A description of the model and its potential application to risk assessment are provided below.

The Leggett Model includes a central compartment, 15 peripheral body compartments, and 4 elimination pools (urine, feces, sweat, and lumped pool representing skin, hair, and nails), as illustrated in Figure 3-3. Transport of Pb from blood plasma to tissues is assumed to follow first-order kinetics. Transfer rate constants vary with age and PbB. Above a nonlinear threshold concentration in red blood cells (assumed to be 60 µg/dL), the rate constant for transfer to red blood cells declines and constants to all other tissues increase proportionally (Leggett 1993). This replicates the nonlinear relationship between plasma and red blood cells observed in humans (see Section 3.1.2). The model simulates blood volume as an age-

Figure 3-3. Compartments and Pathways of Lead (Pb) Exchange in the Leggett Model*



*Schematic model for Pb kinetics in which Pb distribution is represented by exchanges between the central plasma-extracellular fluid and tissue compartments. Bone is represented as having surface (which rapidly exchanges with plasma-extracellular fluid) and volume compartments; the latter simulates slow exchange with the surface and slow return of Pb to the plasma-extracellular fluid from bone resorption.

GI = gastrointestinal; RBC = red blood cell; RT = respiratory

Source: Leggett 1993

dependent function, which allows simulation of plasma and PbBs. Pb masses are simulated in all other tissues (tissue volumes are not simulated).

Unidirectional, first-order transfer rates (day^{-1}) between compartments were developed for six age groups, and intermediate age-specific values are obtained by linear interpolation. The total transfer rate from diffusible plasma to all destinations combined is assumed to be 2,000 day^{-1}, based on isotope tracer studies in humans receiving Pb via injection or inhalation. Values for transfer rates in various tissues and tissue compartments are based on measured deposition fractions or instantaneous fractional outflows of Pb between tissue compartments (Leggett 1993).

The Leggett Model was developed from a biokinetic model originally developed for the International Commission on Radiological Protection (ICRP) for calculating radiation doses from environmentally important radionuclides, including radioisotopes of Pb (Leggett 1993). The Leggett Model simulates age-dependent bone physiology using a model structure developed for application to the alkaline earth elements, but parameterized using data specific to Pb where possible. The model simulates both rapid exchange of Pb with plasma via bone surface and slow loss by bone resorption. Cortical bone volume (80% of bone volume) and trabecular bone volume (20% of bone volume) are simulated as bone surface compartments, which rapidly exchange Pb with the blood plasma, and bone volume, within which are *exchangeable* and *nonexchangeable* pools. Pb enters the exchangeable pool of bone volume via the bone surface and can return to the bone surface, or move to the nonexchangeable pool, from where it can return to the blood only when bone is resorbed. Rate constants for transfer of Pb from the nonexchangeable pools and blood plasma vary with age to reflect the age-dependence of bone turnover.

The liver is simulated as two compartments: one compartment has a relatively rapid uptake of Pb from plasma and a relatively short removal half-time (days) for transfers to plasma and to the small intestine by biliary secretion, and a second compartment simulates a more gradual transfer to plasma of approximately 10% of Pb uptake in liver. The kidney is simulated as two compartments: one that exchanges slowly with blood plasma and accounts for Pb accumulation in kidney tissue, and a second compartment that receives Pb from blood plasma and rapidly transfers Pb to urine, with essentially no accumulation (urinary pathway). Other soft tissues are simulated as three compartments representing rapid, intermediate, and slow turnover rates (without specific physiologic correlates). Other excretory pathways (hair, nails, and skin) are represented as a lumped pathway from the intermediate turnover rate soft tissue compartment.

The Leggett Model simulates Pb intakes from inhalation, ingestion, or intravenous injection. The latter was included to accommodate model evaluations based on intravenous injection studies in humans and animal models. The respiratory tract is simulated as four compartments into which inhaled Pb is deposited and absorbed with half-times of 1, 3, 10, and 48 hours. Four percent of the inhaled Pb is assumed to be transferred to the gastrointestinal tract. These parameter values reflect the data on which the model was based, which were derived from studies in which human subjects inhaled submicron Pb-bearing particles (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). These assumptions would not necessarily apply to exposures to large airborne particles (see Section 3.1.1). Absorption of ingested Pb is simulated as an age-dependent fraction of the ingestion rate, declining from 0.45 at birth to 0.3 at age 1 year (to age 15 years), and to 0.15 after age 25 years.

Output from the Leggett Model has been compared with data in children and adult subjects exposed to Pb in order to calibrate model parameters (Leggett et al. 1993; Pounds and Leggett 1998). Nie et al. (2005) evaluated performance of the Leggett Model for predicting bone Pb concentrations in 539 Pb workers. The data included periodic monitoring of PbBs and XRF bone Pb measurements made in 1994 and 1999. Pb intakes of each individual were calibrated to agree with measured PbBs. The Leggett Model underpredicted observed cortical bone Pb concentrations by a factor of 3–4, and underpredicted trabecular bone Pb concentration by a factor of 12–18. EPA (2014a) evaluated performance of the Leggett Model for predicting PbBs in children and blood and bone Pb concentrations in adults. The evaluation of predictions for children used data on blood lead concentrations reported in the NHANES for the years 2007–2008, and required making assumptions about Pb exposures in this population. The Leggett Model overpredicted observed PbBs in children 1–7 years of age by a factor of 2–3. Cal EPA (2013) evaluated the Leggett Model for predicting PbBs in smelter workers whose occupational exposures were interrupted during a workers strike. Pre-hire background Pb intakes and pre-strike intakes were calibrated to agree with measured PbBs and the predicted rate of decline in blood Pb that occurred during the strike period was compared to observations. Cal EPA (2013) reported "the average difference between the measured and predicted post-strike BLL was unacceptably large and indicated significant under-prediction of BLLs". The average difference was >4 µg/dL in a cohort that had a mean post-strike PbB of 31 µg/dL (no further details were provided). Performance was substantially improved when various parameters were calibrated to the observations. These included parameters that control transfers between plasma and bone and red blood cell saturation (see Cal EPA [2013] for details of parameter values changes). The mean difference between predicted and observed annual geometric mean PbBs (predicted-observed) was -0.9 µg/dL (range -26–32) and the mean relative percent difference was -8.8% (range: -55–320%).

Cal EPA (2013) reported several other evaluations of their recalibrated model, including observed and predicted relationships between plasma and whole PbBs in adults, and predicted distribution of Pb in bone and soft tissues compared to estimates from human autopsy studies.

3.1.5.4 EPA All Ages Lead Model (AALM)

The AALM simulates blood and tissue Pb masses (µg) and concentrations (µg/g) resulting from exposures to Pb in air, drinking water, surface dust (e.g., indoor dust, soil dust), food, or miscellaneous Pb ingestion pathways. The AALM exposure module allows the user to simulate multi-pathway exposures that are constant or that vary in time increments as small as 1 day and that occur at any age from birth to 90 years. The user can select to run a systemic biokinetics simulation based on either the Leggett (AALM-LG) or O'Flaherty (AALM-OF) biokinetics models. Parameters in both systemic models were re-calibrated with observations of blood, bone, and soft tissue Pb concentrations in children and adults (EPA 2014a). The version of the AALM described in EPA (2014a) was implemented in Advanced Continuous Simulation Language (acslX, ver. 3.1.4.2). The ICRP Human Respiratory Tract Model (HRTM) deposition and absorption parameters are used in both the AALM-LG and AALM-OF, which allows simulation of inhaled Pb particles of specified size ranges and absorption kinetics (ICRP 1994). The gastrointestinal tract model includes age-dependent absorption fractions and parameters for RBA of Pb from all ingestion pathways.

The structures of the two systemic biokinetics models in AALM-OF and AALM-LG are based on the O'Flaherty and Leggett models, respectively, with the following modifications. Growth parameters from the O'Flaherty Model are used in both models to simulate age-dependent body weight tissue weights. This provides a means for calculating tissue concentrations as the Pb mass (µg) divided by the tissue weight (g). Concentrations of Pb in bone wet weight are converted to concentration per g bone mineral by dividing the wet weight concentration by the ash fraction of bone. This conversion provides a means for comparing model predictions of bone Pb concentration with bone XRF data, which is typically reported in units of Pb per g bone mineral. Parameters for RBA of Pb in each intake medium include the gastrointestinal tract model. This provides a means for independently adjusting the absorption fraction for each of the intake pathways (including respiratory tract-to-gastrointestinal tract) and maintains mass balance for fecal excretion of unabsorbed Pb. Inhalation, deposition, mucociliary clearance, and absorptive clearance of airborne Pb is simulated with a simplified implementation of the ICRP HRTM.

The AALM systemic biokinetic models were recalibrated from the original Leggett and O'Flaherty Models (EPA 2014b). The sequential recalibration utilized several sources of data on blood and bone Pb concentrations in humans. Parameters that control the uptake and retention of Pb in red blood cells were recalibrated using paired data on whole blood and plasma Pb concentrations in children and adults (Bergdahl et al. 1997c, 1998, 1999; Hernández-Avila et al. 1998; Manton et al. 2001; Schütz et al. 1996; Smith et al. 2002). Parameters that control plasma-to-urine clearance were recalibrated based on clearance estimates from studies that measured paired plasma concentration and urinary Pb excretion in adults (Araki et al. 1986; Chamberlain et al. 1978; Manton and Cook 1984; Manton and Malloy 1983). Autopsy data from children and adults were used to evaluate parameters that control the relationship between of tissue Pb concentrations and bone Pb concentrations (Barry 1975). The relationship between bone and plasma Pb concentrations was evaluated with paired data for plasma Pb concentration and XRF bone Pb in adults (Cake et al. 1996; Hernández-Avila et al. 1998). The long-term rate elimination of Pb from blood and bone was evaluated with data on blood and XRF bone Pb in retired Pb workers (Nilsson et al. 1991).

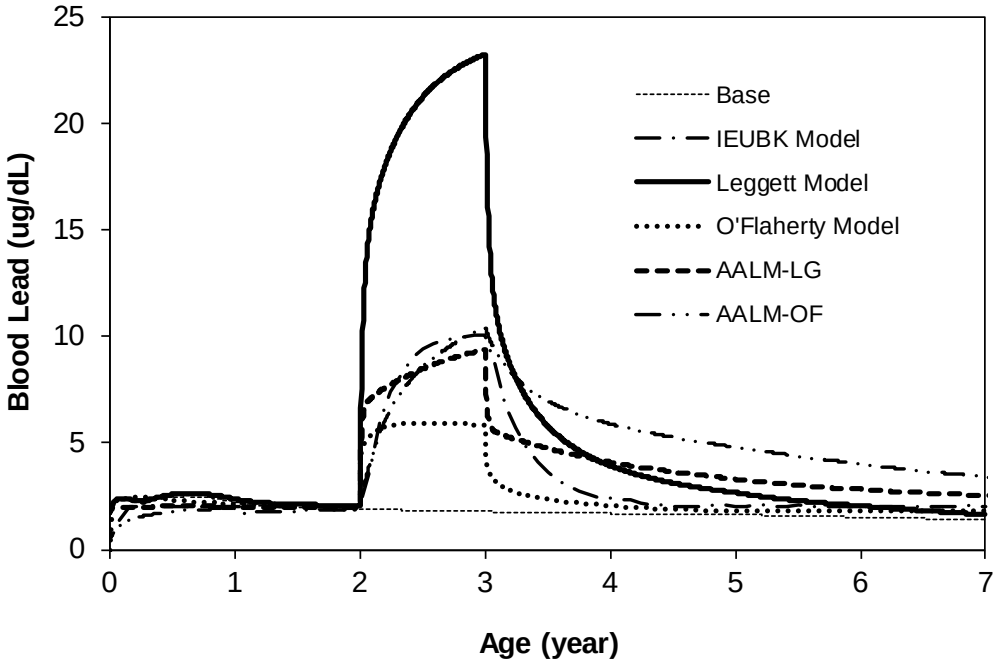
The calibrated AALM was evaluated with data on PbBs measured in infants (Ryu et al. 1983; Sherlock and Quinn 1986) or adults (Rabinowitz et al. 1976) who consumed known quantities of Pb. In the Ryu et al. (1983) study, PbBs were monitored in formula-fed infants who were fed measured quantiles of formula. PbBs predicted from the AALM-LG were within 1 SD of the group means and the r^2 for predictions was 0.85. Predictions from the AALM-OF were uniformly higher than observations and the r^2 for predictions was 0.76. Sherlock and Quinn (1986) measured PbB in infants at age 13 weeks and estimated dietary intake of Pb for each infant based on Pb measurements made in duplicate diet samples collected daily during week 13. The observed dose-blood Pb relationship was predicted with r^2 values of 0.95 for AALM-LG and 0.98 for AALM-OF. Rabinowitz et al. (1976) conducted a pharmacokinetics study in which four adults ingested daily doses of [^{207}Pb] nitrate for periods up to 124 days. Concentrations of ^{207}Pb in blood, urine, and feces were then monitored during and following cessation of exposure, and data on daily intakes and blood concentrations for each subject were reported. Absorption fractions for Pb were estimated for each individual based on mass balance in feces. AALM-LG predictions are closer to the observations; r^2 values ranged from 0.92 to 0.98 for four subjects in the study. The AALM-OF predicted a slower accrual and decline of blood Pb, and lower peak PbBs (r^2 <0.25).

3.1.5.5 Model Comparisons

The O'Flaherty, IEUBK, and Leggett Model differ considerably in the way each represents tissues, exchanges of Pb between tissues, and Pb exposure. The AALM includes biokinetics models based on, but updated from, the O'Flaherty and Leggett models.

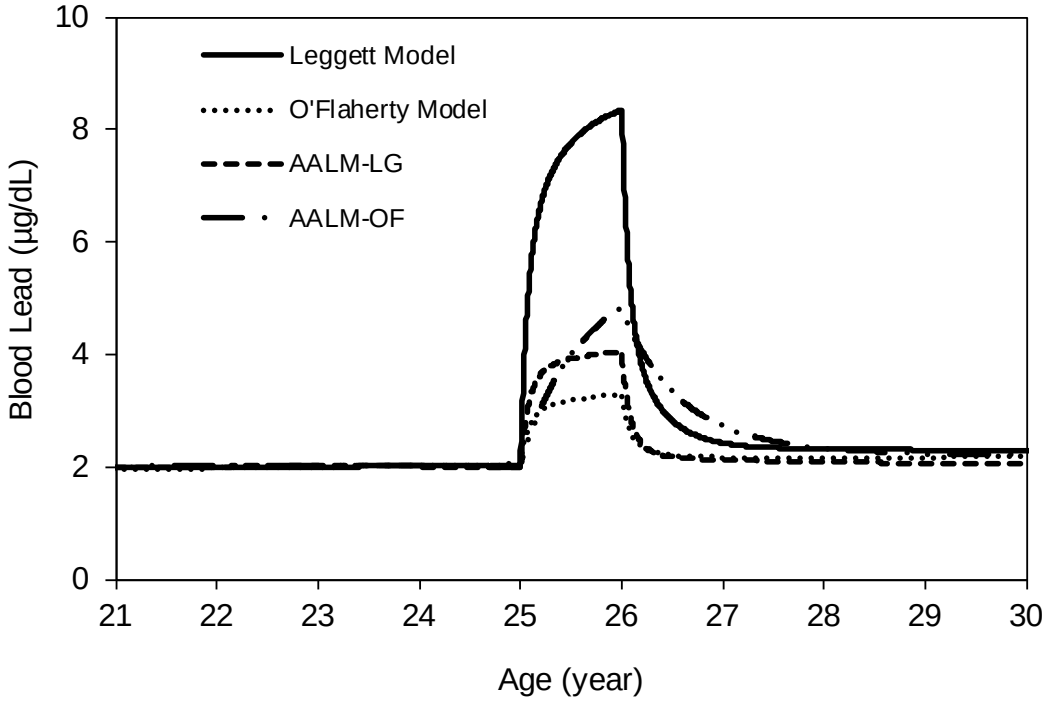
Figure 3-4 compares the PbBs predicted by each model for a hypothetical child who ingests 100 μg Pb/day in soil for a period of 1 year beginning at the age of 2 years (e.g., equivalent to ingestion of 100 μg soil/day at a soil Pb concentration of 1,000 mg Pb/g soil). The 100-μg/day exposure is superimposed on a baseline exposure that yields a PbB of approximately 2 μg/dL at 2 years of age. All five models predict an increase in PbB towards a quasi-steady state during the exposure period, followed by a decline towards the pre-exposure baseline PbB with an apparent half-time of approximately 1 month. Predicted PbBs at the end of the 12-month soil exposure period were 10, 23, 5.9, 23, 9.4, and 10.4 μg/dL for the IEUBK Model, Leggett Model, O'Flaherty Model, AALM-LG, and AALM-OF, respectively. Differences in the magnitude of the predicted impact of the soil exposure on PbB reflect differences in assumptions about Pb biokinetics and cannot be attributed solely to different assumptions about Pb bioavailability. Bioavailability assumptions in the models for the age range 2–3 years are: O'Flaherty Model, 45% (50% at age 2 years, decreasing to 40% at age 3 years); IEUBK Model, 30% (soil Pb at low intakes); Leggett Model, 30%; and AALM-LG and AALM-OF 34% (38% at age 2 years and decreasing to 30% at age 3 years). A comparison of model predictions for a similar exposure during adulthood (100 μg Pb/day for 1 year, beginning at age 25) is shown in Figure 3-5. Predicted PbBs at the end of the 12-month soil exposure period were 8.4, 3.3, 4.0, and 4.8 μg/dL for the Leggett Model, O'Flaherty Model, AALM-LG, and AALM-OF, respectively. All four models predict a smaller change in PbB in adults, compared to children, for a similar increment in exposure. This is attributed, in part, to assumptions of lower Pb bioavailability in adults (i.e., O'Flaherty, 8%; Leggett, 15%; AALM-LG and AALM-OF, 8%).

Figure 3-4. Blood Lead Concentrations (PbBs) in Children Predicted by the IEUBK, Leggett, and O'Flaherty Models and AALM*



*The simulations are of a hypothetical child who has a PbB of 2 µg/dL at age 2 years, and then experiences a 1-year exposure to 100 µg Pb/day. The 100 µg/day exposure was simulated as an exposure to lead in soil in the IEUBK Model. Default bioavailability assumptions were applied in all three models.

Figure 3-5. Blood Lead Concentrations (PbBs) in Adults Predicted by the Leggett and O'Flaherty Models and AALM*



*The simulations are of a hypothetical adult who has a PbB of 2 µg/dL at age 25 years, and then experiences a 1-year exposure to 100 µg Pb/day. Default bioavailability assumptions were applied in all three models.

3.1.5.6 Slope Factor Models

Slope factor models have been used as simpler alternatives to compartmental models for predicting PbBs, or the change in PbB, associated with a given exposure (Abadin et al. 1997; Bowers et al. 1994; Carlisle and Wade 1992; EPA 2017d; Maddaloni et al. 2005; Stern 1994, 1996). In slope factor models, Pb biokinetics is represented with a simple linear relationship between the PbB and either Pb uptake (biokinetic slope factor, BSF) or Pb intake (intake slope factor, ISF). The models take the general mathematical forms:

$$PbB = E \cdot ISF$$

$$PbB = E \cdot AF \cdot BSF$$

where E is an expression for exposure (e.g., soil intake x soil Pb concentration) and AF is the absorption fraction for Pb in the specific exposure medium of interest. Intake slope factors are based on ingested Pb, rather than absorbed Pb and, therefore, integrate both absorption and biokinetics into a single slope factor,

whereas models that utilize a biokinetic slope factor (BSF) to account for absorption in the relationship include an absorption parameter. Slope factors used in various models are presented in Table 3-2. Of the various models presented in Table 3-2, the Bowers et al. (1994) and EPA (2003b) models implement BSFs. The slope factors used in both models (approximately 0.4 μg/dL per μg Pb/day) are similar to BSFs predicted from the O'Flaherty Model (0.65 μg/dL per μg Pb uptake/day) and Leggett Model (0.43 μg/dL per μg Pb uptake/day) for simulations of adult exposures (Maddaloni et al. 2005).

Table 3-2. Comparison of Slope Factors in Selected Slope Factor Models

Model	Receptor	Intake route	Slope factor		Absorption fraction
			Intake	Biokinetics	
Bowers et al. 1994	Adult	Ingestion of soil/dust	ND	0.375	0.08
Carisle and Wade 1992	Child	Ingestion of soil/dust Ingestion of water	0.07 0.04	ND	ND
Carisle and Wade 1992	Adult	Ingestion of soil/dust Ingestion of water	0.018 0.04	ND	ND
Cal EPA 2017	Child	Ingestion of soil/dust Inhalation of respirable dust Dermal contact	ND 0.192 0.0001	0.16 ND ND	0.44 ND ND
EPA 2017d; Maddaloni et al. 2005	Adult	Ingestion of soil/dust	ND	0.4	0.12
Stern 1994	Child	Ingestion of soil/dust	T (0.056, 0.16, 0.18)	ND	ND
Stern 1996	Adult	Ingestion of soil dust	U (0.014, 0.034)	ND	ND

ND = no data; T = triangular probability distribution function (PDF); U = uniform PDF

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic

makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to Pb are discussed in Section 5.7, Populations with Potentially High Exposures.

Age. Children and the elderly are likely to have increased susceptibility to Pb compared to non-elderly adults. As reviewed in Section 3.1.2 (Distribution), Pb crosses the placenta and is distributed to the fetus; neonates are also exposed to Pb in breast milk. Epidemiological studies show that umbilical cord PbB (reflective of neonatal PbB) and PbB in infants are associated with adverse health outcomes during childhood, including decrements in neurological function (reviewed in Chapter 2). Results of a few studies that have followed children to early adulthood show an association between child PbB and behavioral and neuroanatomical changes in adults, suggesting a possible role of exposures in childhood to adult outcomes. Children are likely to be more susceptible than adults to Pb for the following reasons: (1) it is generally accepted that developing systems are more susceptible than mature systems; (2) absorption of Pb is higher in children compared to adults (see Section 3.1.1, Absorption); and (3) children exhibit behaviors that increase ingestion of Pb surface dusts (e.g., hand-to-mouth activity, pica behavior [the compulsive, habitual consumption of nonfood items]), proximity of breathing zone to entrained surface dust).

Regarding the elderly, it is well-established that physiological functions (e.g., renal, neurological, cardiovascular) decline with age. Thus, populations with age-related compromises in physiological function would be anticipated to be more susceptible to Pb than younger populations. Furthermore, because aging is associated with bone loss, Pb is mobilized into blood, resulting in potential increases in PbB.

Sex. As reviewed in Chapter 2, some epidemiological studies examined health outcomes in populations stratified by sex. However, studies have not demonstrated clear sex-related susceptibilities to Pb-induced toxicity for any health effect outcome. In women, pregnancy, lactation, and post-menopausal status may increase bone demineralization, mobilizing bone Pb into the blood and potentially redistributing Pb to other tissues.

Nutritional Status. As discussed in Sections 3.1 (Toxicokinetics) and 3.4 (Interactions with other Chemicals), dietary calcium and nutritional status of iron and zinc can affect absorption of Pb, potentially leading to alterations in PbB and health effects. See Sections 3.1 and 3.4 for additional details.

Pre-existing Conditions, Diseases, and Exposure to Other Substances. Because health effects associated with Pb are observed in every organ system, it is assumed that any condition or disease that compromises physiological functions could cause increased susceptibility to Pb. Examples of underlying conditions include diseases of the kidney (e.g., glomerular nephritis), neurological system (e.g., autism), hematological system (e.g., anemia, thalassemia), and cardiovascular system (e.g., hypertension, cardiac conduction disorders). Similarly, increased susceptibility to Pb would be anticipated due to use of alcohol, tobacco, or any other substance that causes deficits in physiological function.

Genetic Polymorphisms. Numerous genetic polymorphisms that may alter susceptibility to Pb through altered toxicokinetics (i.e., absorption, distribution, and retention of Pb) or toxicodynamics (e.g., effects) have been identified. The most well-studied polymorphisms are δ-ALAD and the VDR. Several other polymorphisms that may alter susceptibility to Pb have been identified, although little data are available. In addition to the references listed below, information also was obtained from a recent review by Broberg et al. 2015.

ALAD. As reviewed in Section 2.8 (Heath Effects, Hematological), Pb binds to and inhibits δ-ALAD, causing decreased hemoglobin formation, measurable decreases in blood hemoglobin concentration, and anemia. δ-ALAD is the major binding site for Pb in the blood (see Section 3.1.2). As such, polymorphisms of ALAD have the potential to alter Pb toxicokinetics, and thereby alter health effects. Many studies have evaluated the potential effects of ALAD polymorphisms on Pb distribution and toxicity. Information reviewed below was obtained from the following publications: Åkesson et al. (2000); Alexander et al. (1998); Astrin et al. (1987); Battistuzzi et al. (1981); Bellinger et al. (1994); Bergdahl et al. (1997a, 1997b); Chia et al. (2005); Chiu et al. (2013); Fang et al. (2010); Fleming et al. (1998a); Gao et al. (2010); Hsieh et al. (2000); Hu et al. (2001); Huo et al. (2014); Jaffe et al. (2000, 2001); Kim et al. (2004); Krieg et al. (2009); Lee et al. (2001); Ong et al. (1990); Pagliuca et al. (1990); Pawlas et al. (2012); Petrucci et al. (1982); Sakai et al. (2000); Schwartz (1995); Schwartz et al. (1995, 1997a, 1997b, 2000a, 2000b); Scinicariello et al. (2007, 2010); Shen et al. (2001); Sithisarankul et al. (1997); Smith (1995); Suzen et al. (2003); Szymanska-Chaowska et al. (2015); Tasmin et al. (2015); Warrington et al. (2015); Weaver et al. (2008); Wetmur et al. (1991a, 1991b); Wu et al. (2003a); and Zheng et al. (2011).

The ALAD gene encodes for the heme metabolism enzyme δ-ALAD. ALAD is a polymorphic enzyme with two alleles (ALAD-1 and ALAD-2) and three genotypes (ALAD 1,1; ALAD 1,2; and ALAD 2,2). The ALAD 2,2 genotype is rare, and is found in 1% of Caucasians; in contrast, the ALAD 1,1 and ALAD 1,2 genotypes occur in 80 and 19%, respectively, of Caucasians. The ALAD 2,2 genotype occurs in <1% of Asian and African populations. A study using NHANES III data (1988–1994) reported that 15.6% of non-Hispanic whites, 2.6% non-Hispanic blacks, and 8.8% Mexican Americans carried the ALAD-2 allele (Scinicariello et al. 2010). The ALAD-2 protein has a higher binding affinity than the ALAD-1 protein for Pb. Due to this higher binding affinity, it has been proposed that ALAD-2 sequesters Pb in erythrocytes, limiting distribution of Pb to other tissues. Numerous studies have shown that ALAD-2 carriers have higher PbB than ALAD-1 carriers. Although it has been demonstrated that ALAD genotype affects the toxicokinetics of Pb, the association between adverse effects of Pb and ALAD genotype have not been definitively established.

VDR. Several studies have evaluated the potential effects of VDR polymorphisms on Pb uptake and distribution. Information reviewed below was obtained from the following publications: Ames et al. (1999); Cooper and Umbach (1996); Gundacker et al. (2009, 2010); Haynes et al. (2003); Krieg et al. (2010); Morrison et al. (1992); Onalaja and Claudio (2000); Rezende et al. (2008); Schwartz et al. (2000a, 2000b); Szymanska-Chaowska et al. (2015); Theppeang et al. (2004); and Weaver et al. (2003b).

The VDR is located in the nucleus of intestinal, renal, and bone cells. It is involved in maintaining calcium and phosphate homeostasis and regulating bone metabolism. Binding of vitamin D3 (the active form of vitamin D) to the VDR activates genes that encode for various calcium-binding proteins involved in intestinal absorption and accumulation of calcium in bone. The VDR regulates the production of calcium-binding proteins, and accounts for up to 75% of the total genetic effect on bone density. Because Pb can replace and mimic calcium, the VDR plays a critical role in the accumulation of Pb in bone. The VDR has several polymorphic forms that are defined based on restriction enzyme digestion; these include FokI with three genotypes (FF, Ff, and ff) and BsmI with three genotypes (BB, Bb, bb). The FF genotype has been associated with higher PbB and increased bone mineral density and calcium uptake. The BB genotype has been associated with higher PbB and bone Pb. However, the role of VDR polymorphisms in the Pb uptake into bone remains to be fully elucidated.

Hemochromatosis gene (HFE). Information on HFE polymorphisms was taken from the following publications: Åkesson et al. (2000); Barton et al. (1994); Fan et al. (2014); Hopkins et al. (2008); Onalaja and Claudio (2000); Park et al. (2009a); Wang et al. (2007); Wright et al. (2004); and Zhang et al. (2010).

Hemochromatosis is an autosomal, recessive disease characterized by the excessive accumulation of iron in the body. In individuals with hemochromatosis, excess iron accumulates in various organs of the body and causes damage to the liver and compromises cardiovascular function. Hemochromatosis is caused by mutations of the HFE gene, which result in defects to the HFE protein. In individuals with normal HFE, HFE binds to transferrin, decreasing the gastrointestinal absorption of iron; however, in individuals with hemochromatosis, the HFE protein is not functional, leading to an increased accumulation of iron. The absorption of Pb is linked to iron status such that Pb absorption increases when iron is limited. HFE polymorphisms have been shown to enhance Pb-induced cognitive impairment (Wang et al. 2007) and the HFE H63D polymorphism appears to enhance positive associations between bone Pb and pulse pressure (Zhang et al. 2010). However, the influence of HFE variants on absorption and health effects of Pb is still being defined.

Other polymorphisms. Several other polymorphisms have been examined to evaluate potential alterations in susceptibility to adverse effects of Pb; however, little data are available. These include:

- *Apoprotein E (APOE).* APOE is an intracellular transporter of cholesterol and fatty acids that is synthesized by astrocytes in the brain and plays a key role in the structure of cell membranes and myelin. There are three alleles of the APOE gene: E2, E3, and E4. It has been proposed that APOE gene variants may alter susceptibility to Pb-induced changes in neurodevelopment and neurological deficits (Stewart et al. 2002; Wright et al. 2003a).
- *Dopamine receptor D4 (DRD4), Dopamine Receptor D2 (DRD2), and Dopamine Transporter (DAT1).* Pb is associated with alterations in the dopaminergic system, which is involved in cognition and behavior. Thus, polymorphisms of DRD4, DRD2, and DAT1 may alter susceptibility to Pb-induced neurocognitive impairment (Froehlich et al. 2007; Kordas et al. 2011; Roy et al. 2011).
- *Glutathione S-transferase mu 1 (GSTM1).* Glutathione is an intracellular scavenger of oxidants and electrophiles. It is encoded by the polymorphic gene GSTM1. Genetic alterations causing a decrease in functional glutathione could result in increased oxidative damage or inflammation (Kim et al. 2007).

- *Endothelial nitric oxide synthase (eNOS).* Nitric oxide, an endogenous signaling molecule involved in vasodilation, is produced by a family of nitric oxide synthase enzymes, including eNOS. Polymorphisms of eNOS could increase susceptibility to Pb (Barbosa et al. 2006b).
- *Metallothionein (MT).* MT binds to and sequesters Pb. It has been proposed that polymorphisms of MT (MT1 and MT2) may affect binding of Pb to MT and lead to an increased PbB (Chen et al. 2010; Fernandes et al. 2016; Yang et al. 2013b).
- *Peptide transporter 2 (PEPT2).* Polymorphisms of PEPT2 have been associated with increased PbB in children (Sobin et al. 2009).
- *Tumor necrosis factor-alpha (TNF-α)*: TNF-α is a cell signaling protein involved in the development of inflammation. Genetic variants in TNF-α have the potential to alter susceptibility to Pb (Kim et al. 2007).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to Pb are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for Pb from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly

adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by Pb are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Biomarkers of exposure in practical use today are measurements of total Pb levels in body fluids or tissues, such as blood, bone, or urine. Tetraalkyl Pb compounds may also be measured in the breath. Of these, PbB is the most widely used and is considered to be the most reliable biomarker for general clinical use and public health surveillance. Currently, PbB measurement is the screening test of choice to identify children with elevated PbBs (CDC 2012d). Venous sampling of blood is preferable to finger prick sampling, which has a considerable risk of surface Pb contamination from the finger if proper finger cleaning is not carried out. In children, PbBs greater than the blood lead reference value identify high-risk childhood populations and geographic areas most in need of primary prevention (CDC 2012d). In 2012, the reference value was defined as 5 μg/dL (CDC 2012d).

PbB. Measurement of PbB is the most widely used biomarker of Pb exposure. CDC considers PbB to be elevated in children when it exceeds a reference value defined as the 97.5th percentile for the U.S. population. The current CDC reference value, based on data from NHANES 2007–2009 and 2009–2010, is 5 μg/dL (CDC 2012d). Elevated PbB (e.g., >5 μg/dL) is an indication of excessive exposure in infants and children. The biological exposure index (BEI) for Pb in blood of exposed workers is 20 μg/dL (ACGIH 2018). The BEI also notes to advise "female workers of child-bearing age about the risk of delivering a child with a PbB over the current CDC reference value." The Occupational Safety and Health Administration's (OSHA) permissible exposure limit (PEL) for lead (50 μg/m^3 air, 8-hour time-weighted average [TWA]) was established to keep a majority of worker PbBs below 40 μg/dL (OSHA 2016a). The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) for workers (50 μg/m^3 air, 8-hour TWA) is established to ensure that the PbB does not exceed 60 μg/dL (NIOSH 2016b).

The extensive use of PbB as a dose metric reflects mainly the greater feasibility of incorporating PbB measurements into clinical or epidemiological studies, compared to other potential dose indicators, such as Pb in kidney, plasma, or bone. PbB measurements have several limitations as measures of total Pb body burden. Blood comprises <2% of the total Pb burden; most of the Pb burden resides in bone (Barry 1975). Pb is eliminated from blood more rapidly than from bone (Behinaein et al. 2014; Brito et al. 2005; Chamberlain et al. 1978; Griffin et al. 1975; Manton et al. 2001; Nie et al. 2005; Nilsson et al. 1991; Rabinowitz et al. 1976; Rentschler et al. 2012); therefore, the Pb concentration in blood reflects mainly the exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of Pb in bone (Graziano 1994; Lyngbye et al. 1990b). Slow release of Pb from bone can contribute to blood Pb levels long after external exposure has ceased (Fleming et al. 1997; Inskip et al. 1996; Kehoe 1987; McNeill et al. 2000; O'Flaherty et al. 1982; Smith et al. 1996). The relationship between Pb intake and PbB is curvilinear; the increment in PbB per unit of intake decreases with increasing PbB (Ryu et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1982, 1984). Pb intake-PbB relationships also vary with age as a result of age-dependency of gastrointestinal absorption of Pb, and vary with diet and nutritional status (Mushak 1991). A practical outcome of the above characteristics of PbB is that PbB can change relatively rapidly (e.g., days to weeks) in response to changes in exposure; thus, PbB can be influenced by short-term variability in exposure that may have only minor effects on total Pb body burden. A single PbB determination cannot distinguish between lower-level intermediate or chronic exposure and higher-level acute exposure. Similarly, a single measurement may fail to detect a higher exposure that occurred (or ended) several months earlier. Time-integrated measurements of PbB (CBLI) may provide a means for accounting for some of these factors and thereby provide a better measure of long-term exposure (Armstrong et al. 1992; Behinaein et al. 2014; Chuang et al. 2000; Fleming et al. 1997; Gerhardsson et al. 1993; Healey et al. 2008; Hu et al. 2007; McNeill et al. 2000; Nie et al. 2011a; Roels et al. 1995). The correlation observed between CBLI and tibia bone Pb concentrations provides supporting evidence for this (Hu et al. 2007).

Bone and Tooth Pb Measurements. The development of noninvasive XRF techniques for measuring Pb concentrations in bone has enabled the exploration of bone Pb as a biomarker of Pb exposure in children and in adults (Behinaein et al. 2011; Chettle et al. 2003; Hu et al. 2007; Ji et al. 2014; Nie et al. 2011b; Specht et al. 2016; Todd et al. 2000). Pb in bone is considered a biomarker of cumulative exposure to Pb because Pb accumulates in bone over the lifetime and most of the Pb body burden resides in bone. Pb is not distributed uniformly in bone. Pb will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in both cortical

and trabecular bone. This suggests that Pb accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Patella, calcaneus, and sternum XRF measurements primarily reflect Pb in trabecular bone, whereas XRF measurements of midtibia, phalanx, or ulna primarily reflect primarily Pb in cortical bone. Pb levels in cortical bone may be a better indicator of long-term cumulative exposure than Pb in trabecular bone, possibly because Pb in trabecular bone may exchange more actively with Pb in blood than does cortical bone. This is consistent with estimates of a longer elimination half-time of Pb in cortical bone, compared to trabecular bone (Behinaein et al. 2014; Borjesson et al. 1997; Brito et al. 2005; Nie et al. 2005; Nilsson et al. 1991; Schutz et al. 1987). Longitudinal studies that have repeatedly measured bone Pb (by XRF) over many years have shown more rapid declines in trabecular bone compared to cortical bone (Kim et al. 1997; Wilker et al. 2011). Estimates of cortical bone Pb elimination half-times (5–50 years) show a dependence on Pb burden, with longer half-times in people who have higher total body burdens (estimated from CBLI) and bone Pb burdens (Behinaein et al. 2014; Brito et al. 2005; Nie et al. 2005). Further evidence that cortical bone Pb measurements may provide a better reflection of long-term exposure than do measurements of trabecular bone comes from studies in which cortical and trabecular bone Pb measurements have been compared to PbB. Pb levels in trabecular bone (in adults) correlate more highly with contemporary PbB than do levels of Pb in cortical bone (Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Cortical bone Pb measurements correlate well with time-integrated PbB measurements, which would be expected to be a better reflection of cumulative exposure than contemporary PbB measurements (Behinaein et al. 2012; Borjesson et al. 1997; Hu et al. 2007; Roels et al. 1994). Bone Pb levels tend to increase with age (Hu et al. 1996b; Kosnett et al. 1994; Roy et al. 1997), although the relationship between age and bone Pb may be stronger after adolescence (Hoppin et al. 1997). These observations are consistent with cortical bone reflecting cumulative exposures over the lifetime.

Standard methods for bone Pb XRF measurements have not been universally accepted, in part, because the technology continues to be improved, and this needs to be considered in comparisons of measurements reported by different laboratories and at different times in development of the methodology used. Historically, two XRF methods have seen the most use in bone Pb epidemiology: K-shell and L-shell methods. The K-shell method is the more widely used, although, improvements in L-shell technology continue to be reported (Nie et al. 2011a). One study reported a correlation of 0.65 between bone Pb measurements made with a portable L-shell device and a K-shell method (Nie et al. 2011a). In general, recent advances in K-shell technology have yielded higher sensitivities (approximately 3 µg/g tibia mineral; Behinaein et al. 2011) than L-shell technology (approximately 8 µg/g tibia bone mineral;

Nie et al. 2011a). Precision of K-shell XRF bone Pb measurements have been extensively discussed (Aro et al. 2000; Behinaein et al. 2014; Todd et al. 2000, 2001, 2002). Methodological factors can contribute substantially to observed variability in bone Pb measurements in populations (Behinaein et al. 2014). These factors include bone Pb target, radioactive source, measurement time, and data reduction methods (e.g., approach to handling negative values). Measurement uncertainty also appears to contribute by biological factors, such as BMI and bone mineral content (Behinaein et al. 2014; Berkowitz et al. 2004; Hu et al. 2007; Theppeang et al. 2008). The association between BMI and measurement uncertainty may reflect the effect attenuation of the XRF signal by tissue overlaying the target bone site (Behinaein et al. 2014). Bone mineral can be a factor because XRF measures bone Pb fluorescence in relation to fluorescence from bone calcium and the result is expressed in units of μg Pb per g bone mineral. As a result, variability in bone mineral content can contribute to variability in measured bone Pb. Typically, potential associations between bone density and bone Pb concentration are not evaluated in epidemiologic studies (Berkowitz et al. 2004; Hu et al. 2007; Theppeang et al. 2008). An important consequence of expressing bone Pb measures relative to bone mineral content is that lower bone mineral density is associated with greater measurement uncertainty in bone Pb. This uncertainty can have important implications for studies in older women for whom low bone mineral density is more common than in other populations including men and younger adults.

Tooth Pb has been considered a potential biomarker for measuring long-term exposure to Pb (e.g., years) because Pb that accumulates in tooth dentin and enamel appears to be retained until the tooth is shed or extracted (Costa de Almeida et al. 2007; Ericson 2001; Fosse et al. 1995; Gomes et al. 2004; Gulson and Wilson 1994: Gulson et al. 1996; Omar et al. 2001; Rabinowitz 1995; Rabinowitz et al. 1989, 1993; Robbins et al. 2010; Steenhout and Pourtois 1987; Tvinnereim et al. 1997). Formation of enamel and primary dentin of deciduous teeth begins *in utero* and is complete prior to the time children begin to crawl. Formation of secondary dentin begins after completion of the tooth root and continues through childhood until the tooth is lost, or otherwise loses vitality. Pb in shed deciduous teeth is not uniformly distributed. Differences in Pb levels and stable isotope signatures of the enamel and dentin suggest that Pb uptake occurs differentially in enamel and dentin (Gulson 1996; Gulson and Wilson 1994). Pb in enamel is thought to reflect primarily Pb exposure that occurs *in utero* and early infancy, prior to tooth eruption. Dentin appears to continue to accumulate Pb after eruption of the tooth; therefore, dentin Pb is thought to reflect exposure that occurs up to the time the teeth are shed or extracted (Gulson 1996; Gulson and Wilson 1994; Rabinowitz 1995; Rabinowitz et al. 1993). The technique of laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) allows measurement of Pb levels in regions of dentin formed at various times during deciduous tooth formation *in utero* and after birth (Arora et al. 2014;

Shepherd et al. 2016). Accumulation of Pb in dentin of permanent teeth may continue for the life of the tooth (Steenhout 1982; Steenhout and Pourtois 1981). Because enamel is in direct contact with the external environment, enamel Pb levels may be more influenced than dentin Pb by external Pb levels and tooth wear (Purchase and Fergusson 1986).

An analysis of eight cross-sectional and/or prospective studies that reported tooth Pb and PbBs of the same children found considerable consistency among the studies (Rabinowitz 1995). The mean tooth Pb levels ranged from <3 to >12 μg/g. Dentin Pb was found to be predictive of Pb in tibia, patella, and mean bone Pb in 32 of 63 subjects at follow-up of ≤13 years (Kim et al. 1996b). The authors estimated that a 10 μg/g increase in dentin Pb levels in childhood was predictive of a 1 μg/g increase in tibia Pb levels, a 5 μg/g in patella Pb levels, and a 3 μg/g increase in mean bone Pb among the young adults. Arora et al. (2014) found that Pb levels in primary (prenatal) dentin were more strongly correlated with PbBs at birth (correlation coefficient, r=0.69, n=27), whereas Pb levels in secondary (postnatal) dentin were more strongly correlated with CBLI (r=0.38, n=75). Shepherd et al. (2016) combined LA-ICP-MS with histological determinations of dentin age to reconstruct the history of incorporation of environmental Pb from various sources.

Plasma Pb Concentration. The concentration of Pb in plasma is extremely difficult to measure accurately because levels in plasma are near the quantitation limits of most analytical techniques (e.g., approximately 0.04 μg/dL at PbB of 10 μg/dL) (Bergdahl and Skerfving 1997; Bergdahl et al. 1997a) and because hemolysis that occurs with typical analytical practices can contribute to substantial measurement error (Bergdahl et al. 1998, 2006; Cavalleri et al. 1978; Smith et al. 1998a). ICP-MS offers sensitivity sufficient for measurements of Pb in plasma (Schütz et al. 1996). The technique has been applied to assessing Pb exposures in adults (Barbosa et al. 2006a; Cake et al. 1996; Hernandez-Avila et al. 1998; Manton et al. 2001; Smith et al. 2002; Tellez-Rojo et al. 2004; Tian et al. 2013). A direct comparison of Pb concentrations in plasma and serum yielded similar results (Bergdahl et al. 2006); however, the interchangeability of plasma and serum Pb measurements for biomonitoring of Pb exposure or body burden had not been thoroughly evaluated in large numbers of subjects (Bergdahl et al. 2006; Manton et al. 2001; Smith et al. 2002).

Urinary Pb. Measurements of urinary Pb levels have been used to assess Pb exposure (e.g., Chiang et al. 2008; Fels et al. 1998; Fukui et al. 1999; Gerhardsson et al. 1992; Lilis et al. 1968; Lin et al. 2001; Mendy et al. 2012; Mortada et al. 2001; Navas-Acien et al. 2005; Rentschler et al. 2012; Roels et al. 1994; Sun et al. 2008b). However, like PbB, urinary Pb excretion mainly reflects recent exposure and thus shares

many of the same limitations for assessing Pb body burden or long-term exposure (Sakai 2000; Skerfving 1988). Although collection of urine is noninvasive, urine Pb levels exhibit variability with PbB, and interpretation of urine Pb levels requires estimates of GFR and measurement of urine volume (NTP 2012). A significant, but relatively weak correlation between urinary Pb levels (μg/dg creatinine) and individual Pb intakes (μg/day) was observed in a study of 10–12-year-old children (β: 0.053, R=0.320, p=0.02, N=57; Chiang et al. 2008). In this study, urine sampling and measurements used to estimate intake were separated by as long as 6 months for some children, which may have contributed to the relatively weak correlation. The measurement is further complicated by variability in urine volume, which can affect concentrations independent of excretion rate (Diamond 1988) and the potential effects of decrements in kidney function on excretion, in association with high, nephrotoxic Pb exposures or kidney disease (Lilis et al. 1968; Wedeen et al. 1975). Urinary Pb concentration increases exponentially with PbB and can exhibit relatively high intra-individual variability, even at similar PbBs (Gulson et al. 1998a; Skerfving et al. 1985). However, the relationship between plasma Pb and urinary Pb (μg Pb/g creatinine) was linear in a small group of children (Rentschler et al. 2012). The linear relationship between plasma and urinary Pb may reflect the importance of plasma Pb in determining the rate of glomerular filtration and renal tubular transport of Pb (see Section 3.1.4). Urinary diethyl Pb has been proposed as a qualitative marker of exposure to tetraethyl Pb (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994).

The measurement of Pb excreted in urine following an injection (intravenous or intramuscular) of the chelating agent, calcium disodium EDTA (*EDTA provocation*), or oral dosing with dimercaptosuccinic acid (DMSA) has been used to detect elevated body burden of Pb in adults (Biagini et al. 1977; Lee et al. 2009; Lilis et al. 1968; Lin et al. 2003, 2006a, 2006b; Schwartz et al. 2000a, 2000c; Wedeen 1992; Wedeen et al. 1975)and children (Chisolm et al. 1976; Markowitz and Rosen 1981). However, the American College of Medical Toxicology (ACMT 2010) position statement on post-chelator challenge urinary metal testing states that "post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning." The assay is not a substitute for PbB measurements in the clinical setting. Note that children whose PbBs are ≥45 μg/dL should not receive a provocative chelation test; they should be immediately referred for appropriate chelation therapy (CDC 2002a, 2012f). For additional information on recommended actions based on PbB level in children and adults, see Section 3.5 (Methods for Reducing Toxic Effects). Further limitations for routine use of the test are that EDTA must be given parenterally and requires timed urine collections. A study conducted in rats found that intraperitoneal administration of a single dose of EDTA following 3–4-month exposures to

Pb in drinking water increased levels of Pb in the liver and brain (Cory-Slechta et al. 1987) raising concern for similar effects in humans who undergo the EDTA provocation test. The use of EDTA to assess bone stores of Pb (Wedeen 1992) is largely being supplanted by more direct, noninvasive procedures for measuring Pb in bone. DMSA is a Pb chelating agent that can be administered orally. DMSA-chelatable Pb has been used as marker of Pb body burden in adults (Schwartz et al. 1997, 2000a, 2000c; Scinicariello et al. 2007; Weaver et al. 2003a, 2003b).

Pb in Saliva and Sweat. Pb is excreted in human saliva and sweat (Genuis et al. 2011; Lilley et al. 1988; Omokhodion and Crockford 1991; Rabinowitz et al. 1976; Stauber and Florence 1988; Sears et al. 2012; Stauber et al. 1994). Sweat has not been widely adopted for monitoring Pb exposures. Lilley et al. (1988) found that Pb concentrations in sweat were elevated in Pb workers; however, sweat and PbBs were poorly correlated. This may reflect excretion of Pb in or on the skin that had not been absorbed into blood. Studies conducted in rats have found relatively strong correlations between Pb concentrations in plasma and saliva (e.g., $r^2>0.9$), compared to blood Pb and saliva; therefore, saliva may serve as a better predictor of plasma Pb than PbB (Timchalk et al. 2006). However, studies of saliva Pb conducted in humans have had mixed results, with some studies showing relatively strong correlations between salivary Pb concentration and PbB (Brodeur et al. 1983; Omokhodion and Crockford 1991; P'an 1981), and other studies showing weak or inconsistent relationships (Barbosa et al. 2006c; Costa de Almeida et al. 2009, 2010, 2011; Nriagu et al. 2006). Variable outcomes from these studies may reflect differences in PbBs, exposure history and/or dental health (i.e., transfer of Pb between dentin and saliva), and methods used for determining Pb in saliva. Other complicating factors reported in the literature include uncontrolled variation in salivary flow rates (Barbosa et al. 2005; Esteban and Castano 2009) and potential blood contamination of saliva (Koh and Koh 2007).

Hair and Nail Pb. Pb is incorporated into human hair and hair roots (Bos et al. 1985; Rabinowitz et al. 1976) and has been explored as a possibly noninvasive approach for estimating Pb body burden (Gerhardsson et al. 1995b; Wilhelm et al. 1989). The method is subject to error from contamination of the surface with environmental Pb and contaminants in artificial hair treatments (i.e., dyeing, bleaching, permanents) and is a relatively poor predictor of PbB, particularly at low concentrations (<12 μg/dL) (Campbell and Toribara 2001; Drasch et al. 1997; Esteban et al. 1999; Rodrigues et al. 2008). Nevertheless, levels of Pb in hair were positively correlated with children's classroom attention deficit behavior in a study (Tuthill 1996). Pb in hair was correlated with liver and kidney Pb in a study of deceased smelter workers (Gerhardsson et al. 1995b). Correlations between maternal and infant hair Pb concentrations have been observed (Kordas et al. 2010). Although hair Pb measurements have been used

in some epidemiologic studies (Bao et al. 2009; Huel et al. 2008; Marcus et al. 2010; Shah et al. 2011), an empirical basis for interpreting hair Pb measurements in terms of body burden or exposure has not been firmly established. Nail Pb has also been utilized as a marker of Pb exposure, although nails may be contaminated with Pb from external sources (Barbosa et al. 2005; Gerhardsson et al. 1995b).

Semen Pb. Pb concentrations in semen have been explored as an internal exposure biomarker for adverse effects of Pb on the testes (Hernandez-Ochoa et al. 2005; Kasperczyk et al. 2015; Slivkova et al. 2009; Taha et al. 2013; Wu et al. 2012). Correlations between concentrations of Pb in semen and blood have been reported and vary in strength across studies (Alexander et al. 1998a, 1998b; Farias et al. 2005; Hernandez-Ochoa et al. 2005; Mendiola et al. 2011; Telisman et al. 2000). This variation may relate, in part, to analytical challenges in the measurement of the relatively low concentrations of Pb in semen. Using ICP-MS and rigorous collection methods to avoid contamination, Farias et al. (2005) reported a detection limit of 0.2 μg/L semen. Mean semen Pb concentration in a group of 160 men (age range 19–48 years) who were not exposed to Pb occupationally was 2.66 μg/L (range 0.08–19.42) and was significantly correlated with PbB (mean 10.8 μg/dL, range 4.5–40.2) and tibia bone Pb (mean 14.51 μg/g, range not-detected–44.71 μg/g).

Stable Pb Isotopes. Analysis of the relative abundance of stable isotopes of Pb in blood and other accessible body fluids (e.g., breast milk, urine) has been used to differentiate exposures from multiple sources (Flegal and Smith 1995). Relative abundances of stable isotopes of Pb (^{204}Pb, ^{206}Pb, ^{207}Pb, and ^{208}Pb) in Pb ores vary with the age of the ore (which determines the extent to which the parent isotopes have undergone radioactive decay to stable Pb). Humans have Pb isotope abundance profiles that reflect the profiles of Pb deposits to which they have been exposed. Pb isotope studies can be used to identify sources of Pb contributing to exposure. Similarly, if exposure abruptly changes to a Pb source having a different isotope abundance profile, the kinetics of the change in profile in the person can be measured, reflecting the kinetics of uptake and distribution of Pb from the new source (Gulson et al. 2003; Maddaloni et al. 1998; Manton et al. 2003). Numerous examples of the application of stable isotope abundance measurements for studying sources of Pb exposures have been reported (Angle et al. 1995; Graziano et al. 1996; Gulson and Wilson 1994; Gulson et al. 1996, 1997b, 1999c, 2016; Manton 1977, 1998).

Effect Biomarkers Used to Assess Exposure to Pb. Certain physiological changes that are associated with Pb exposure have been used as biomarkers of exposure (see Section 3.3.2). These include measurements of biomarkers of impaired heme biosynthesis (blood zinc protoporphyrin, urinary

coproporphyrin, erythrocyte ALAD activity, serum ALA). These types of measurements have largely been supplanted with measurement of PbB for the purpose of assessing Pb exposure due to the higher sensitivity of PbB measurements in quantifying lower level Pb exposures.

3.3.2 Biomarkers of Effect

Certain effects of Pb have been used in diagnosing Pb poisoning to support measurements of PbB; however, none of these diagnostic aids are considered preferable to measurement of PbB. A multisite study of populations living near four NPL sites was conducted to assess the relationship between exposure (PbB and area of residence) and biomarkers of four organ systems: immune system dysfunction, kidney dysfunction, liver dysfunction, and hematopoietic dysfunction (ATSDR 1995). The geometric mean PbB in those living in the target areas was 4.26 μg/dL (n=1,645) compared with 3.45 μg/dL for a group living in comparison areas (n=493). In children <6 years old, the corresponding means were 5.37 versus 3.96 μg/dL. In subjects ≥15 years old, the target and comparison values were 3.06 and 3.63 μg/dL, respectively. Ninety percent of target and 93% of comparison area participants had PbBs <10 μg/dL. Pb in soil and water was found to be higher in comparison areas than in the target areas, but Pb in house dust and in interior paint was higher in the target areas. PbB correlated with Pb in soil and dust, but not with Pb in paint and water. Multivariate regression analyses showed that of all the biomarkers analyzed, PbB was significantly associated with, and predictive of, hematocrit in adults ≥15 years of age and with increased mean serum IgA in children 6–71 months of age. The biological significance of these associations is unclear since both hematocrit and IgA levels were well within normal ranges and were hardly different than levels in subjects from the comparison areas.

Pb inhibits heme biosynthesis, which is necessary for production of red blood cells. Hematologic tests such as hemoglobin concentration may suggest toxicity, but this is not specific for Pb (Bernard and Becker 1988). However, inhibition of ferrochelatase in the heme pathway causes accumulation of protoporphyrin in erythrocytes (CDC 1985). Most protoporphyrin in erythrocytes (about 90%) exists as zinc-protoporphyrin (ZPP). This fraction is preferentially measured by hematofluorometers. Extraction methods measure all of the protoporphyrin present, but strip the zinc from the ZPP during the extraction process. For this reason, extraction results are sometimes referred to as (zinc) free erythrocyte protoporphyrin (FEP). Although the chemical forms measured by the two methods differ slightly, on a weight basis, they are roughly equivalent; thus, results reported as EP, ZPP, or FEP all reflect essentially the same analyte. An elevated EP level is one of the earliest and most reliable indicators of impairment of heme biosynthesis and reflects average Pb levels at the site of erythropoiesis over the previous 4 months

(Janin et al. 1985). The concentration of EP rises above background at PbBs of 25–30 μg/dL, above which, there is a positive correlation between PbB and EP (CDC 1985; Gennart et al. 1992a; Roels and Lauwerys 1987; Soldin et al. 2003; Wildt et al. 1987). Pb toxicity is generally considered to be present when a PbB ≥10 μg/dL is associated with an EP level ≥35 μg/dL (CDC 1991; Somashekaraiah et al. 1990). This effect is detectable in circulating erythrocytes only after a lag time reflecting maturation in which the entire population of red blood cells has turned over (i.e., 120 days) (EPA 1986; Moore and Goldberg 1985). Similarly, elevated EP can reflect iron deficiency, sickle cell anemia, and hyperbilirubinemia (jaundice). Therefore, reliance on EP levels alone for initial screening could result in an appreciable number of false positive cases (CDC 1985; Mahaffey and Annest 1986; Marcus and Schwartz 1987). Conversely, since EP does not go up until the PbB exceeds 25 μg/dL, and the reference value is 5 μg/dL, relying on EP measures would result in many false negative cases. Some have estimated that relying only on ZPP screening to predict future Pb toxicity would miss approximately three cases with toxic PbBs in every 200 workers at risk (Froom et al. 1998). A limitation of measuring porphyrin accumulation is that porphyrin is labile because of photochemical decomposition; thus, assay samples must be protected from light. However, other diseases or conditions such as porphyria, liver cirrhosis, iron deficiency, age, and alcoholism may also produce similar effects on heme synthesis (Somashekaraiah et al. 1990).

ALAD, an enzyme occurring early in the heme pathway, is also considered a sensitive indicator of Pb effect (Graziano 1994; Hernberg et al. 1970; Morris et al. 1988; Somashekaraiah et al. 1990; Tola et al. 1973). ALAD activity is negatively correlated with PbBs of 5–95 μg/dL, with >50% inhibition occurring at PbBs >20 μg/dL (Hernberg et al. 1970; Morita et al. 1997; Roels and Lauwerys 1987). However, ALAD activity may also be decreased with other diseases or conditions such as porphyria, liver cirrhosis, and alcoholism (Somashekaraiah et al. 1990). ALAD was found to be a more sensitive biomarker than urinary ALA and ZPP at PbBs between 21 and 30 μg/dL (Schuhmacher et al. 1997). A marked increase in urinary excretion of ALA, the intermediate that accumulates from decreased ALAD, can be detected when PbB exceeds 35 μg/dL in adults and 25–75 μg/dL in children (NAS 1972b; Roels and Lauwerys 1987; Sakai and Morita 1996; Schuhmacher et al. 1997).

Another potential biomarker for hematologic effects of Pb is the observation of basophilic stippling and premature erythrocyte hemolysis (Paglia et al. 1975, 1977). Pb can impair the activity of pyrimidine 5'-nucleotidase, resulting in a corresponding increase in pyrimidine nucleotides in red blood cells, which leads to a deficiency in maturing erythroid elements and thus, decreased red blood cells. However, this effect is nonspecific; it is encountered with benzene and arsenic poisoning (Smith et al. 1938) and in a

genetically-induced enzyme-deficiency syndrome (Paglia et al. 1975, 1977). Furthermore, since basophilic stippling is not universally found in chronic Pb poisoning, it is relatively insensitive to lesser degrees of Pb toxicity (CDC 1985). The activity of adenine dinucleotide synthetase (NADS) in erythrocytes has also been explored as a biomarker for predicting PbBs >40 μg/dL; NADS activity is negatively correlated with PbB over the range 5–80 μg/dL (Morita et al. 1997).

Reduction in the serum 1,25-dihydroxyvitamin D concentration has been reported as an indicator of increased Pb absorption or Pb concentrations in the blood (Rosen et al. 1980). Pb inhibits the formation of this active metabolite of vitamin D, which occurs in bone mineral metabolism (EPA 1986; Landrigan 1989). Children with PbBs of 12–120 μg/dL showed decreased serum 1,25-dihydroxyvitamin D concentrations comparable to those found in patients with hypoparathyroidism, uremia, and metabolic bone disease (Mahaffey et al. 1982; Rosen et al. 1980). This biomarker is clearly not specific for Pb exposure and several diseases can influence this measurement.

One of the most sensitive systems affected by Pb exposure is the nervous system. Encephalopathy is characterized by symptoms such as coma, seizures, ataxia, apathy, bizarre behavior, and incoordination (CDC 1985). Children are more sensitive to neurological changes than adults. In children, encephalopathy has been associated with PbBs as low as 70 μg/dL (CDC 1985). An early sign of peripheral manifestations of neurotoxicity is gastrointestinal colic, which can occur with PbBs above 50 μg/dL. The most sensitive peripheral index of neurotoxicity of Pb is reported to be slowed conduction velocity in small motor fibers of the ulnar nerve in workers with PbBs of 30–40 μg/dL (Landrigan 1989). Other potential biomarkers of Pb suggested for neurotoxicity in workers are neurological and behavioral tests, as well as cognitive and visual sensory function tests (Williamson and Teo 1986). However, these tests are not specific to elevated Pb exposure.

Functional deficits associated with Pb-induced nephrotoxicity increase in severity with increasing PbB. Effects include decreased glomerular filtration, enzymuria and proteinuria, and impaired transport function. Biomarkers for these changes include elevation of serum creatinine, urinary enzymes (e.g., NAG), or protein (albumin, β2μ-globulin, α1μ-globulin, retinol binding protein). However, none of these markers are specific for Pb-induced nephrotoxicity. A characteristic histologic feature of Pb nephrotoxicity is the formation of intranuclear inclusion bodies in the renal proximal tubule (Choie and Richter 1972; Goyer et al. 1970a, 1970b).

3.4 INTERACTIONS WITH OTHER CHEMICALS

Interactions between Pb and other chemicals can be classified into two categories: interactions with contaminants that are commonly found together with Pb at hazardous waste sites, and interactions with essential elements (ATSDR 2004a, 2004b, 2006; EPA 2014c).

Interactions with Other Contaminants. Several metals and metalloids frequently are found together with Pb at hazardous waste sites, including arsenic (As), cadmium (Cd), manganese (Mn), zinc (Zn), copper (Cu), and inorganic mercury (Hg). ATSDR (2004a, 2004b, 2006) has conducted assessments to predict interactions of these chemicals with Pb; conclusions are presented in Table 3-3. For each co-contaminant, interactions were classified as less than additive (indicating an antagonistic effect with Pb), additive (indicating no effect of combined exposure), or greater than additive (indicating a synergistic effect with Pb). Greater-than-additive effects were observed for neurological effects for As and Cd, male reproductive effects for Cd, and renal effects for Hg. Interactions for other metals were either less than additive or additive for cardiovascular (Cd, Zn), developmental (Zn), hematological (As, Cd, Mn, Zn, Cu), immunological (Cd), neurological effects (Zn), renal (As, Cd, Mn, Zn, Cu), and male reproductive (Zn) effects. Other metals that may interact with Pb include selenium and chromium(VI) (Nordberg et al. 2015). Observed interactions of metals and metalloids with Pb could be the results of alterations to Pb toxicokinetics, toxicodynamics, or a combination of both.

Table 3-3. Influence of Other Metals and Metalloids on Lead (Pb) Toxicity

	Metal					
Organ system	Arsenic[a]	Cadmium[a]	Manganese[b]	Zinc[b]	Copper[b]	Inorganic mercury[c]
Cardiovascular	–	< or 0	–	<	–	–
Developmental	–	–	–	<	–	–
Hematological	< or 0	< or 0	0	< or 0	<	–
Immunological	–	<	–	–	–	–
Neurological	>	>	–	< or 0	<	–
Renal	0	< or 0	0	<	–	>
Male reproductive	–	>	–	<	–	–

[a]ATSDR 2004a.
[b]ATSDR 2004b.
[c]ATSDR 2006.

< = less than additive; 0 = additive (no effect); > = greater than additive; – = not assessed

Interactions with Essential Elements. In physiological systems, Pb mimics divalent cations (calcium, iron, zinc). Substitution of Pb for essential elements in membrane transport systems is the mechanism by which Pb is absorbed from the intestine and crosses cell membranes throughout the body. Thus, numerous interactions between Pb and essential elements have been observed, including the following (additional details on these finding are provided in Section 3.1, Toxicokinetics):

- Dietary calcium intake appears to affect Pb absorption. An inverse relationship has been observed between dietary calcium intake and PbBs in children (Elias et al. 2007; Mahaffey et al. 1986; Schell et al. 2004; Ziegler et al. 1978).
- Nutritional iron status may affect Pb absorption in children. Higher PbBs have been observed in iron-deficient children compared to children who are iron replete. This observation suggests that iron deficiency may result in higher absorption of Pb or, possibly, other changes in Pb biokinetics that would contribute to higher PbBs (Mahaffey and Annest 1986; Marcus and Schwartz 1987).
- In young children (ages 6–12 months), PbB increased in association with lower dietary Zn levels (Schell et al. 2004). It is not clear, however, if these associations were caused by changes in Pb absorption.

3.5 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to lead. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to lead. When specific exposures have occurred, poison control centers, medical toxicologists, or other clinicians with expertise and experience treating and managing lead exposed adults and/or children should be consulted. The following resources provide specific information about treatment and management of patients following exposure to lead:

AAP. 2005. Lead exposure in children: Prevention, detection, and management. Pediatrics 116(4):1036-1046. 10.1542/peds.2005-1947.

AAP. 2016. Council on Environmental Health. Prevention of childhood lead toxicity. Pediatrics 38(1):e20161493

ATSDR. 2017. Case studies in environmental medicine (CSEM). Lead toxicity. https://www.atsdr.cdc.gov/csem/lead/docs/csem-lead_toxicity_508.pdf. August 30, 2018.

Calello DP, Henretig FM. 2014. Lead. In: Goldfrank's toxicologic emergencies. Tenth ed. New York, NY: McGraw-Hill, 1219-1234.

Holland MG, Cawthon D. 2016. ACOEM Position Statement. Workplace lead exposure. J Occup Environ Med 58(12):e371-e374.

Leikin JB, Paloucek FP. 2008. Lead. In: Poisoning and toxicology handbook. Fourth ed. Boca Raton, FL: CRC Press, 807-811.

CDC. 2002a. Managing elevated blood levels among young children. Recommendations from the Advisory Committee on Childhood Lead Poisoning. Centers for Disease Control and Prevention. https://www.cdc.gov/nceh/lead/casemanagement/managingEBLLs.pdf. July 18, 2018.

Kosnett MJ. 2001. Lead. In: Ford M, Delaney KA, Ling L, et al., eds. Clinical toxicology. St. Louis: WB Saunders, 723-736.

Kosnett MJ. 2005. Lead. In: Brent J, Wallace KL, Burkhart KK, et al., eds. Critical care toxicology. Philadelphia, PA: Elsevier Mosby, 821-836.

PEHSU. 2013. Recommendations on medical management of childhood lead exposure and poisoning. Pediatric Environmental Health Specialty Units.

Additional publicly available clinical resources for the health care professional can be found in Appendix D.

3.5.1 Reducing Absorption Following Exposure

No treatment modalities to reduce lead absorption have been developed. Therefore, the most important intervention is to identify and remove the source of exposure (AAP 2005, 2016; ATSDR 2017; CDC 2012f). Lead absorption from the gastrointestinal tract is influenced by nutrition, especially calcium, iron, and vitamin C (AAP 2005; CDC 2012f). It is recommended that a child's diet contain ample amounts of iron and calcium to reduce the likelihood of increased absorption of lead and that children eat regular meals since more lead is absorbed on an empty stomach (AAP 2005; CDC 2002a, 2012f). Good sources of iron include liver, fortified cereal, cooked legumes, and spinach, whereas milk, yogurt, cheese, and cooked greens are good sources of calcium (CDC 1991).

General recommendations to reduce absorption of lead following acute exposure include the following (AAP 2016; ATSDR 2017; Calello and Henretig 2014; Kosnett et al. 2007):

- remove the individual from the source of exposure;
- mitigate source of exposure;
- if suspected that elevated PbB is due to ingestion of a foreign object (e.g., Pb paint chips, toys or jewelry containing Pb, Pb ammunition), radiographic imaging is suggested;
- if elevated PbB is due to ingestion of a foreign object, decontamination of the bowel (surgical or gastric lavage) is indicated; and

- ensure that diet is adequate in calcium, iron, and vitamin C.

For children, specific recommended actions based on PbB levels are summarized in Table 3-4. CDC considers PbB to be elevated in children when it exceeds a reference value defined as the 97.5th percentile for the U.S. population. The current CDC reference value, based on data from NHANES 2007–2009 and 2009–2010, is 5 µg/dL (CDC 2016). Recent NHANES surveys show that the 97.5th percentile PbB in the U.S. population continues to decline (CDC 2018a).

Table 3-4. Recommended Actions Based on Child Blood Lead Level (PbB)

PbB (µg/dL)	Recommended actions
<Reference value[a]	• Education on environmental sources of Pb and sufficient dietary nutrition • Follow-up PbB monitoring

≥Reference value and ≤45	• Follow recommendations for <Reference value
	• Complete history and physical examination
	• Laboratory analysis
	  o Monitor iron status
	  o Consider measurement of hemoglobin or hematocrit
	• Neurodevelopmental monitoring
	• Abdominal radiography and bowel decontamination if ingestion of Pb particulate is suspected
	• Conduct environmental investigation and Pb hazard reduction

≥45 and ≤69	• Follow recommendations for ≥Reference value and ≤45
	• Laboratory analyses
	  o Hemoglobin or hematocrit
	  o Iron status
	  o Zinc protoporphyrin
	• Oral chelation therapy
	• Consider hospitalization if cannot assure mitigation of Pb source

≥70	• Hospitalize • Initiate chelation therapy with consultation with a medical toxicologist or pediatric environmental health expert or unit • Follow recommendations for ≥45 and ≤69

[a]5 µg/dL (CDC 2012d).

Source: CDC 2012f

For occupational exposures, OSHA and NIOSH have developed recommendations to reduce Pb exposure through procedures and surveillance. In 1987, NIOSH created the Adult Blood Lead Epidemiology and Surveillance (ABLES) program to monitor adult PbBs through coordinated efforts with state agencies (NIOSH 2017a). This program was designed to decrease the rate of adults with PbBs ≥10 µg/dL as a result of work-related lead exposure. In 2015, NIOSH designated PbB of 5 µg/dL as the PbB reference value and defined elevated PbB as PbB ≥5 µg/dL (NIOSH 2017a). Several federal and state agencies

work together to reduce the rate of elevated PbBs among workers. The OSHA (1995) mandated rule on lead provides recommendations to reduce occupational Pb exposure for general industry, shipyard employment, and construction through use of respirators, protective clothing, routine biological monitoring of PbB and zinc protoporphyrin, and medical assessments for workers with elevated PbB. More recently, Holland and Cawthon (2016) suggested the actions based on PbB levels, with a baseline PbB <5 µg/dL (Table 3-5).

Table 3-5. Recommended Actions for Workers Based on Blood Lead Level (PbB)

PbB (µg/dL)	Recommended actions
All workers	• PbB monitoring at initial employment • Monitor PbB every 6 months after initial employment monitoring • PbB goal is <5 µg/dL for pregnant workers
≥5–9	• Increase monitoring if indicated • Recommend removal for pregnant workers or workers who are trying to become pregnant; return to work may be considered if two consecutive PbB measurements are <5 µg/dL • Continue PbB monitoring as noted above
10–19	• Monitor PbB every 2 months until two consecutive PbB measurements are <10 µg/dL • Mandatory medical removal for pregnant workers or workers who are trying to become pregnant; return to work may be considered if two consecutive PbB measurements are <5 µg/dL • Continue PbB monitoring as noted above • Evaluate exposure, controls, and work practices
≥20	• Remove from work if repeat PbB measurement in 4 weeks is ≥20 µg/dL or if single PbB measurement is ≥30 µg/dL • Monitor PbB monthly; return to work after two consecutive monthly PbB measurements are <15 µg/dL • Continue PbB monitoring as noted above • Evaluate exposure, controls, and work practices
≥30	• Removed from exposure immediately • Monitor PbB monthly; return to work after two consecutive monthly PbB measurements are <15 µg/dL • Continue PbB monitoring as noted above • Evaluate exposure, controls, and work practices

[a]Source: Holland and Cawthon (2016)

3.5.2 Reducing Body Burden

Lead is initially distributed throughout the body and then redistributed to soft tissues and bone. In human adults and children, approximately 94 and 73% of the total body burden of lead is found in bones,

respectively. Lead may be stored in bone for long periods of time, but may be mobilized, thus achieving a steady state of intercompartmental distribution (see Section 3.3.2).

Currently available methods to obviate the toxic effects of lead are based on their ability to reduce the body burden of lead by chelation. All of the chelating agents bind inorganic lead, enhance its excretion, and facilitate the transfer of lead from soft tissues to the circulation where it can be excreted. Since the success of chelation therapy depends on excretion of chelated lead via the kidney, caution should be used when treating a patient with renal failure. For all cases where chelation therapy is considered or implemented, medical providers should consult with a medical toxicologist or an expert in the medical management of lead toxicity (CDC 2002a, 2012f). Chelation treatment should be administered in conjunction with meticulous supportive therapy (Calello and Henretig 2014). Most of the information below regarding chelators was obtained from Calello and Henretig (2014) and Kosnett (2005, 2007).

Several pharmacological substances are available for chelation therapy for Pb intoxication. Chelating agents currently in use are dimercaprol (British Anti-Lewisite, or BAL), $CaNa_2$-EDTA (or EDTA), and 2,3-dimercaptosuccinic acid (DMSA; Succimer®). Dosages and administration protocols for these agents vary with patient age, PbB level, and symptom types and severity. Specific treatment protocols should be developed in consultation with clinical experts in the management of lead toxicity for the most current chelation therapy procedures for children and adults (CDC 2002a, 2012f).

Dimercaprol (BAL). The mechanism of action of BAL is through formation of stable chelate-metal compounds intra- and extracellularly. BAL is administered parenterally. The onset of action for BAL is 30 minutes. BAL increases fecal excretion of lead as chelated lead is excreted predominantly in bile within 4–6 hours; BAL also increases urinary excretion of chelated lead. A number of adverse reactions have been associated with BAL, including nausea, vomiting, hypertension, tachycardia, headache, increased secretions, anxiety, abdominal pain, and fever.

$CaNa_2$-EDTA (or EDTA). EDTA works by forming a stable metal-chelate complex that is excreted by the kidney. It increases renal excretion of lead 20–50 times. EDTA is administered parenterally. Numerous adverse effects have been described due to treatment with EDTA including rash, fever, fatigue, thirst, myalgias, chills, and cardiac dysrhythmias. Since EDTA chelates zinc, patients with low zinc stores may be adversely affected by EDTA. Since EDTA also chelates other metals, administration of EDTA (or BAL) to persons occupationally exposed to cadmium may result in increased renal excretion of cadmium and renal damage.

2,3-Dimercaptosuccinic acid (DMSA; Succimer®). The mechanism of action of DMSA is similar to BAL. DMSA is administered orally. DMSA has been shown to be as effective as EDTA in increasing the urinary excretion of lead. Minimal adverse effects that have been reported include anorexia, nausea, vomiting, and rashes. DMSA increases the excretion of zinc, but to a much lesser extent than other chelators, and has minimal effects on calcium, iron, magnesium, and copper.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Pb is a naturally occurring element with an abundance of 0.0016% in the earth's crust (Davidson et al. 2014). It is a member of Group 14 (IVA) of the periodic table. Natural Pb is a mixture of four stable isotopes: ^{204}Pb (1.4%), ^{206}Pb (24.1%), ^{207}Pb (22.1%), and ^{208}Pb (52.4%). The Pb isotopes ^{206}Pb, ^{207}Pb, and ^{208}Pb are the stable decay product of the naturally occurring decay series of uranium, actinium, and thorium, respectively (Haynes 2014).

Pb is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world (King et al. 2014). Its properties, such as corrosion resistance, density, and low melting point, make it a familiar metal in pipes, solder, weights, and storage batteries. The chemical identities of Pb and several of its compounds are provided in Table 4-1.

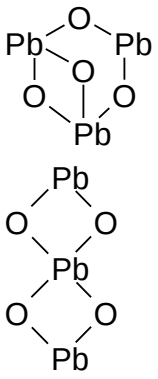
Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead	Lead(II) acetate	Lead(II) azide	Lead(II) bromide
Synonym(s) and registered trade name(s)	C.I. 77575; C.I. Pigment metal 4; Glover; Lead flake; Lead S2; Omaha; Omaha & Grant; SI; SO[a]	Acetic acid lead(2+) salt (2:1); neutral lead acetate; plumbous acetate; normal lead acetate; sugar of lead; salt of Saturn[b]	Lead azide[b]	Lead bromide ($PbBr_2$); plumbous bromide[b]
Chemical formula	Pb[b]	$Pb(CH_3CO_2)_2$[b]	$Pb(N_3)_2$[b]	$PbBr_2$[b]
Chemical structure	Not applicable	Not applicable	Not applicable	Not applicable
CAS Registry Number	7439-92-1[b]	301-04-2[b]	13424-46-9[b]	10031-22-8[b]

Table 4-1. Chemical Identity of Lead and Compounds

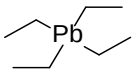
Characteristic	Lead(II) chloride	Lead(II) chromate	Lead(II) tetrafluoroborate[c]	Lead(II) iodide
Synonym(s) and registered trade name(s)	Lead chloride ($PbCl_2$); Lead(2+) chloride; Plumbous chloride[b]	Chromic acid (H_2CrO_4 lead(2+) salt (1:1); Chrome yellow; Cologne yellow; King's yellow; Leipzig yellow; Paris yellow; C.I. Pigment Yellow 34; lead chromium oxide ($PbCrO_4$); plumbous chromate; C.I. 77600[b]	Tetrafluoro borate(1-) Lead(2+)[a]	Lead iodide (PbI_2); Plumbous iodide[b]
Chemical formula	$PbCl_2$[b]	$PbCrO_4$[b]	$Pb(BF_4)_2$[a]	PbI_2[b]
Chemical structure	Not applicable	Not applicable	Not applicable	Not applicable
CAS Registry Number	7758-95-4[b]	7758-97-6[b]	13814-96-5[a]	10101-63-0[b]

Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead molybdenum chromate	Lead(II) nitrate	Lead(II) oxide	Lead(II,II,IV) oxide
Synonym(s) and registered trade name(s)	Chromic acid, lead and molybdenum salt; chromic acid lead salt with lead molybdate; C.I. Pigment Red 104; Lead chromate, Molybdenum-Lead chromate; Molybdenum Orange[a]	Nitric acid lead(2+) salt (2:1); Plumbous nitrate[b]	C.I. 77577; C.I. Pigment Yellow 46; Lead oxide; Lead oxide yellow; Lead protoxide; Litharge; Litharge Yellow L-28; Massicot; Massicotite; Plumbous oxide; Yellow lead ocher[a]	Lead tetraoxide; Lead tetroxide; Lead oxide red; C.I. Pigment Red 105; C.I. 77578; Gold satinobre; Lead orthoplumbate; Lead oxide (3:4); Mineral Orange; Mineral Red; Paris Red; Saturn Red; Minium; Plumboplumbic oxide; Red Lead; Red Lead oxide; Trilead tetraoxide[d,e]
Chemical formula	No data	$Pb(NO_3)_2$[b]	PbO[a]	Pb_3O_4[e]
Chemical structure	Not applicable	Not applicable	Not applicable	
CAS Registry Number	12709-98-7[a]	10099-74-8[b]	1317-36-8[a]	1314-41-6[d]

Characteristic	Lead(II) phosphate	Lead(II) styphnate	Lead(II) sulfate
Synonym(s) and registered trade name(s)	C.I. 77622; Lead orthophosphate; Lead phosphate (3:2); Lead(2+) phosphate; normal lead orthophosphate; Phosphoric acid, lead(2+) salt (2:3); Plumbous phosphate; Trilead phosphate[a]	Lead trinitroresorcinate[f]	Anglesite; C.I. 77630; C.I. Pigment White 3; Fast White; Freemans White Lead; Lead bottoms; Milk white; Mulhouse White; Sulfuric acid, lead(2+) salt (1:1)[a]
Chemical formula	$Pb_3(PO_4)_2$[a]	$Pb(C_6HN_3O_8)_2$[f]	$PbSO_4$[b]
Chemical structure	Not applicable	Not applicable	Not applicable
CAS Registry Number	7446-27-7[a]	15245-44-0[f]	7446-14-2[b]

Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead(II) sulfide	Tetraethyl lead	Lead(II) carbonate
Synonym(s) and registered trade name(s)	C.I. 77640; Galena; Natural lead sulfide; Plumbous sulfide[a]	Tetraethylplumbane; Lead tetraethyl; TEL[b]	Carbonic acid, lead(2+) salt (1:1); Cerussite; Dibasic lead carbonate; Lead(2+) carbonate; White lead[a]
Chemical formula	PbS[a]	$Pb(C_2H_5)_4$[a]	$PbCO_3$[a]
Chemical structure	Not applicable		Not applicable
CAS Registry Number	1314-87-0[a]	78-00-2[b]	598-63-0[a]

[a]Lewis 2012.
[b]O'Neil et al. 2015 2013.
[c]Stable only in aqueous solution (Haynes 2014).
[d]CHEMIDplus 2018.
[e]Haynes 2014.
[f]Boileau et al. 2012.

CAS = Chemical Abstracts Services

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Pb, a blueish-white metal with bright luster, is very soft, highly malleable, ductile, a poor conductor of electricity, and is very resistant to corrosion (Haynes 2014). A clean lead surface will not be attacked by dry air; however, in moist air, the surface will react and become coated with a layer of lead(II) oxide (PbO). This coating may be hydrated and combine with carbon dioxide to form lead(II) carbonate ($PbCO_3$) (Carr et al. 2004). This protective coating of insoluble Pb compounds slows or halts corrosion of the underlying metal. Pb is rarely found in its metallic form in nature and commonly occurs as a mineral with sulfur or oxygen. The most important lead mineral is galena (PbS). Other common Pb-containing minerals include anglesite ($PbSO_4$), cerussite ($PbCO_3$), and minium (Pb_3O_4) (Carr et al. 2004; Davidson et al. 2014; Haynes 2014).

Pb can exist in the 0 oxidation state in metallic Pb and in compounds as the +2 or +4 oxidation states. In the environment, Pb is primarily found in the +2 state in inorganic compounds. The chemistry of inorganic Pb compounds is generally similar to that of the Group 2(II) or alkaline earth metals. There are three common oxides of Pb: lead(II) oxide (PbO); lead(II,IV) oxide or lead tetroxide (Pb_3O_4); and lead(IV) oxide or lead dioxide (PbO_2). The +4 state is only formed under strongly oxidizing conditions. Inorganic Pb(+4) compounds are relatively unstable and would not be expected to be found under

ordinary environmental conditions. Pb is amphoteric, meaning that it can react with acids and bases. In acid, Pb forms Pb(+2) (plumbous) and Pb(+4) (plumbic) salts and in basic solution, it forms plumbites (PbO_2^{2-}) and plumbates ($Pb(OH)_6^{2-}$) (Carr et al. 2004). In organolead compounds, Pb is typically in the tetravalent (+4) oxidation state (Carr et al. 2004; Haynes 2014).

Data on the physical and chemical properties of lead and several of its compounds are provided in Table 4-2.

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead	Lead(II) acetate	Lead(II) azide	Lead(II) bromide
Molecular weight	207.2[a]	325.3[b]	291.24[a]	367.0[b]
Color	Bluish-white, silvery, gray metal[a]	White crystals[b]	Needles or white powder [a]	White orthorhombic crystals[b]
Physical state	Solid	Solid	Solid	Solid
Melting point	327.4°C[a]	280°C[b]	Decomposes at 190°C[c]	371°C[b]
Boiling point	1,740°C[a]	Decomposes[b]	No data	892°C[b]
Density	11.34 g/cm^3 at 20°C[a]	3.25 g/cm^3[b]	4.17 g/cm^3 at 20°C[c]	6.69 g/cm^3[b]
Odor	No data	Slightly acetic odor (trihydrate)[a]	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble[d]	443,000 mg/L at 20°C[b]	230 mg/L at 18°C[a]	9,750 mg/L at 25°C[b]
Acids	Soluble in dilute nitric acid[d]; reacts with sulfuric acid[a]	Soluble in acid[e]	Freely soluble in acetic acid[a]	No data
Bases	No data	Soluble in alkali[e]	No data	No data
Organic solvents	Soluble in glycerin; slightly soluble in alcohol[e]	Slightly soluble in alcohol; freely soluble in glycerol[d]	No data	Insoluble in alcohol[b]
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1.77 mmHg at 1,000°C[a]	No data	No data	0.0075 mmHg at 374°C[b]
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant[f]	Not relevant[f]	Not relevant[f]	Not relevant[f]
Explosive limits	No data	No data	Explodes at 350°C[a]	No data
Valence state	0	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead(II) chloride	Lead(II) chromate	Lead(II) tetrafluoroborate	Lead iodide
Molecular weight	278.1[g]	323.19[a]	380.8[b]	461.05[g]
Color	White, orthorhombic needles[g]	Yellow or orange-yellow powder[a]	No data	Yellow hexagonal crystals[g]
Physical state	Solid	Solid	Stable only in aqueous solution[b]	Solid
Melting point	501°C[g]	844°C[a]	No data	402°C[g]
Boiling point	950°C[g]	No data	No data	954°C[g]
Density	5.85 g/cm^3[g]	6.12 g/cm^3[b]	No data	6.16 g/cm^3[g]
Odor	No data	No data	No data	No data
Odor threshold	No data	No data	No data	No data
Solubility:				
Water	9,900 mg/L at 20°C[g]	0.2 mg/L[a]	Soluble[b]	630 mg/L at 20°C[g]
Acids	Slightly soluble in dilute hydrochloric acid[g]	Soluble in dilute nitric acid; insoluble in acetic acid[a]	No data	No data
Bases	Slightly soluble in dilute ammonia[g]	No data	No data	No data
Organic solvents	Insoluble in alcohol[g]	No data	No data	Insoluble in alcohol[g]
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	7.5 mmHg at 637°C[b]	No data	No data	0.75 mmHg at 470°C[b]
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant[f]	Not relevant[f]	Not relevant[f]	Not relevant[f]
Explosive limits	No data	No data	No data	No data
Valence state	+2	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead molybdenum chromate	Lead(II) nitrate	Lead(II) oxide	Lead(II,II,IV) oxide
Molecular weight	No data	331.23[g]	223.21[g]	685.57[e]
Color	No data	Cubic or monoclinic colorless crystals[g]	Reddish-yellow; yellow (above 489°C)[g]	Bright red heavy powder[a]; red tetrahedral crystals[b]
Physical state	No data	Solid	Solid	Solid
Melting point	No data	Begins to decompose above 205°C[g]	897°C (begins to sublime before melting)[g]	830°C[b]; 500°C[e]
Boiling point	No data	No data	Decomposes at 1,472°C[g]	Decomposes between 500-530°C[d]
Density	No data	4.53 g/cm^3[g]	9.53 g/cm^3 (Litharge)[g]; 9.6 g/cm^3 (Massicot)[g]	8.92 g/cm^3[b]; 9.1 g/cm^3[e]
Odor	No data	No data	No data	No data
Odor threshold:	No data	No data	No data	No data
Solubility:				
Water	No data	56:5 g/100 mL at 20°C[g]	50.4 mg/L at 25°C (Litharge)[g]; 106.5 mg/L at 25°C (Massicot)[g]	Insoluble in water[d]
Acid	No data	Insoluble in concentrated nitric acid[a]	Soluble[g]	Dissolves in acetic acid or hot hydrochloric acid[b,g]
Base	No data	Soluble in alkali and ammonia[g]	Soluble[g]	No data
Organic solvents	No data	87.7 mg/L (43% aqueous ethanol) at 22°C[g]	Insoluble in alcohol[a]	Insoluble in alcohol[g]
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	No data	No data	0.0075 mmHg at 724°C[b]	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant[f]	Not relevant[f]	Not relevant[f]	Not relevant[f]
Explosive limits	No data	No data	No data	No data
Valence state	+2	+2	+2	+2, +2, +4

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead(II) phosphate	Lead(II) styphnate	Lead(II) sulfate
Molecular weight	811.54[a]	450.29[h]	303.25[g]
Color	White powder[a]	Monoclinic orange-yellow crystal (monohydrate)[b]	White, heavy, crystalline powder[a]
Physical state	Solid	Solid	Solid
Melting point	1,014°C[a]	No data	1,170°C[g]
Boiling point	No data	No data	No data
Density	6.9 g/cm^3[a]	3.1 g/cm^3 (monohydrate); 2.9 g/cm^3 (anhydrous)[b]	6.2 g/cm^3[g]
Odor	No data	No data	No data
Odor threshold:	No data	No data	No data
Solubility:			
Water	Insoluble[b]	Insoluble[b]	42.5 mg/L at 25°C[g]
Acid	Soluble in nitric acid[a]	No data	Soluble in concentrated acids[g]
Base	Soluble in fixed alkali hydroxides[a]	No data	Soluble in alkalies[g]
Organic solvents	Insoluble in alcohol[a]	No data	Insoluble in alcohol[a]
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	Not relevant[f]	Not relevant[f]	Not relevant[f]
Explosive limits	No data	Detonates at 260°C[b]	No data
Valence state	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead(II) sulfide	Tetraethyl lead	Lead(II) carbonate
Molecular weight	239.25[g]	323.45[a]	267.22[g]
Color	Metallic black cubic crystals[g]	Colorless[a]	Colorless rhombic crystals[g]
Physical state	Solid	Liquid[a]	Solid
Melting point	1,114°C[d]	No data	315°C (decomposes)[g]
Boiling point	Sublimes at 1,281°C[d]	200 °C; 227.7°C (with decomposition)[a]	No data
Density	7.57–7.59 g/cm^3[g]	1.653 g/cm^3[a]	6.6 g/cm^3[g]
Odor	No data	No data	No data
Odor threshold:	No data	No data	No data
Solubility:			
Water	124.4 mg/L 20°C[g]	0.29 mg/L[i]	1.1 mg/L at 20°C[g]
Acid	Soluble in nitric acid[g]	No data	Soluble[g]
Base	Insoluble in alkalies[d]	No data	Soluble in alkalies; insoluble in ammonia[g]
Organic solvents	Insoluble in alcohol[a]	Soluble in benzene, petroleum ether, gasoline; slightly soluble in alcohol[a]	Insoluble in alcohol[g]
Partition coefficients:			
Log K_{ow}	No data	4.15[j]	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	0.0075 mmHg at 705°C[b]	0.26 mmHg at 25°C[j]	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	200°F (93°C) (closed cup)[k]	No data
Flammability limits	No data	Lower flammable limit: 1.8% by volume[k]	No data
Conversion factors	Not relevant[f]	No data	Not relevant[f]
Explosive limits	No data	No data	No data
Valence state	+2	+4	+2

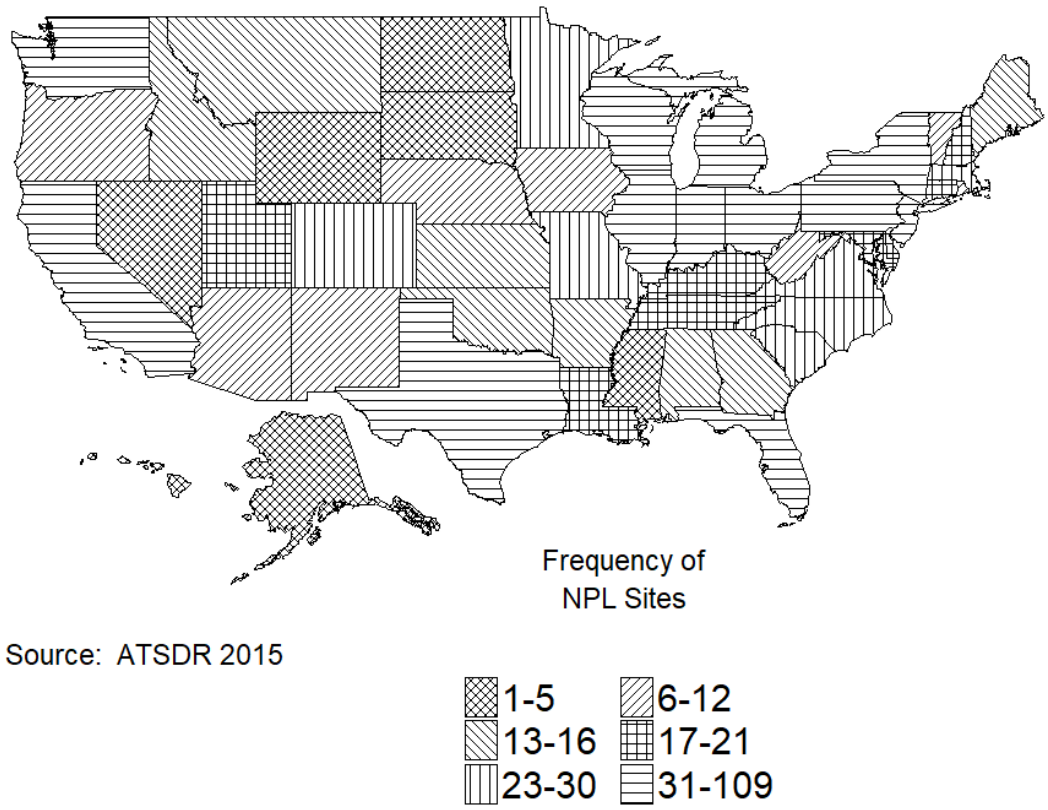
[a]O'Neil et al. 2013.
[b]Haynes 2014.
[c]Akvavan 2004.
[d]Larrañaga et al. 2016.
[e]Jacob 2012.
[f]Since these compounds exist in the atmosphere in the particulate state, their concentrations are expressed as µg/m^3 only.
[g]Carr et al. 2004.
[h]Molecular weight calculated from atomic weights.
[i]Feldhake and Stevens 1963.
[j]Wang et al. 1996.
[k]NFPA 2002.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

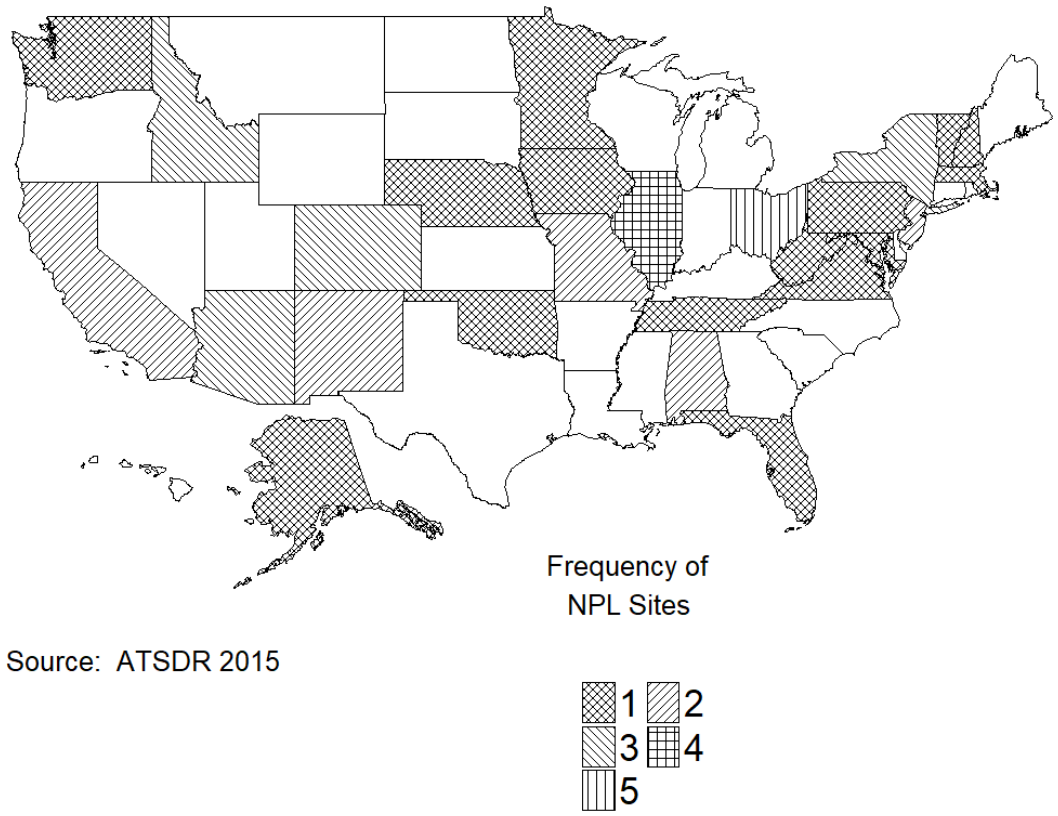
Pb and Pb compounds have been identified in at least 1,274 and 47 sites, respectively, of the 1,832 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2015). However, the number of sites evaluated for Pb is not known. The number of sites in each state is shown in Figures 5-1 and 5-2, respectively. Of these 1,274 sites for Pb, 1,261 are located within the United States, 2 are located in the Virgin Islands, 2 are located in Guam, and 9 are located in Puerto Rico (not shown). All the sites for Pb compounds are only in the United States.

Figure 5-1. Number of NPL Sites with Lead Contamination



Source: ATSDR 2015

Figure 5-2. Number of NPL Sites with Lead Compound Contamination



Source: ATSDR 2015

- Pb is an element found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world.
- The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. For adults, exposure to levels of Pb beyond background are usually associated with occupational exposures.
- For children, exposure to high levels of Pb are associated with living in areas contaminated by Pb (e.g., soil or indoor dust in older homes with Pb paint). Exposure usually occurs by hand-to-mouth activities.
- As an element, Pb does not degrade. However, particulate matter contaminated with Pb can move through air, water, and soil.
- Atmospheric deposition is the largest source of Pb found in soils. Pb is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for Pb.
- Pb adsorbs strongly to most soils, which limits the rate of leaching of Pb from soil. Soil acidity (pH) is the most important factor affecting solubility, mobility, and phytoavailability of Pb in soil.

Other conditions that increase Pb mobility in soils are reducing conditions (low redox potential; for example, anoxia) and high chloride content.

Pb is dispersed throughout the environment primarily as the result of anthropogenic activities. In the air, Pb is in the form of particles and is removed by rain or gravitational settling. The solubility of Pb compounds in water is a function of pH, ionic strength, and the presence of humic material. Solubility is highest in acidic water. Soil and sediment are an important sink for Pb. Because Pb is strongly adsorbed to soil, very little is transported through runoff to surface water or leached to groundwater except under acidic conditions. Anthropogenic sources of Pb include the mining and smelting of ore, manufacture and use of Pb-containing products, combustion of coal and oil, and waste incineration. Many anthropogenic sources of Pb, most notably leaded gasoline, Pb-based paint, Pb solder in food cans, Pb-arsenate pesticides, and shot and sinkers, have been eliminated or are regulated. Pb compounds released to the environment may be transformed to other Pb compounds; however, Pb is an element and cannot be destroyed or degraded. Because Pb does not degrade over time, deposits of Pb in the environment by current and former uses leave their legacy as higher concentrations of Pb in the environment. These deposits can continue to be a source for potential Pb exposure (e.g., soil particles containing Pb also may be resuspended and redeposited). Plants and animals may bioconcentrate Pb, but Pb is not biomagnified in the aquatic or terrestrial food chain.

The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. Segments of the general population at highest risk of health effects from Pb exposure are preschool-age children and pregnant women and their fetuses. Other segments of the general population with an increased exposure include individuals living near sites where Pb was produced or disposed. Some of the more important Pb exposures have occurred as a result of living in urban environments, particularly in areas near stationary emission sources (e.g., smelters); renovation of homes containing Pb-based paint; pica (the compulsive, habitual consumption of nonfood items); contact with interior Pb paint dust; occupational exposure; and secondary occupational exposure (e.g., families of workers in Pb industries). Higher exposures may also occur to residents living in close proximity to NPL sites that contain elevated levels of Pb.

The primary source of Pb in the environment has historically been anthropogenic emissions to the atmosphere. In 1984, combustion of leaded gasoline was responsible for approximately 90% of all anthropogenic Pb emissions. The United States gradually phased out the use of Pb alkyls in gasoline, and by 1990, auto emissions accounted for only 33% of the annual Pb emissions (EPA 1996b). Use of Pb

additives in most motor fuels was totally banned after December 31, 1995 (EPA 1996a). The ban went into effect on February 2, 1996. The ban did not include off-road vehicles, including aircraft, racing cars, farm equipment, and marine engines. Pb additives are still used in fuels for piston driven airplane engines and it continues to be commercially available for other off-road uses. Atmospheric deposition is the largest source of Pb found in soils. Pb is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for Pb. Pb particles are removed from the atmosphere primarily by wet and dry deposition. The average residence time in the atmosphere is 10 days. Over this time, long-distance transport, up to thousands of kilometers, may take place. The speciation of Pb in these media varies widely depending upon such factors as temperature, pH, and the presence of humic materials. Pb is largely associated with suspended solids and sediments in aquatic systems, and it occurs in relatively immobile forms in soil.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

The most important mineable Pb ore is galena (PbS), which is commonly associated with other minerals, typically zinc ores. Anglesite ($PbSO_4$) and cerussite ($PbCO_3$), formed by the weathering of galena, are two other important Pb minerals. Pb is processed from ore to refined metal in four steps: ore dressing; smelting; drossing; and refining. Ore dressing involves crushing, grinding, and beneficiation (concentration) (King et al. 2014).

Since 1998, U.S. production of Pb has shifted to the domestic secondary Pb industry (USGS 2014). Since 2014, primary Pb metal has not been produced in the United States (USGS 2016). The Doe Run Resources Corporation operated the last domestic primary Pb smelter-refinery facility in the United States at Herculaneum, Missouri and it was closed at the end of 2013. Pb-acid batteries are the dominant source of recoverable Pb scrap, accounting for 98% of all secondary Pb (USGS 2016).

Domestic mines produced 368,000 metric tons of recoverable Pb in 2014, a more than 11% increase from 2013. Nearly all of the secondary Pb produced in 2014 was by 7 companies operating 12 plants in Alabama, California, Florida, Indiana, Minnesota, Missouri, New York, Pennsylvania, Tennessee, and Texas (USGS 2016). Secondary (recycled) Pb, derived from mainly scrapped Pb-acid batteries, accounted for all of the domestic refined Pb production in 2014. Due to plant closings, U.S. production

of secondary refined Pb decreased in 2014 by 11% to 1.02 metric tons, from 1.5 metric tons in 2013 (USGS 2016).

World mine production of Pb was 4.91 million metric tons in 2014, a decrease of 9% from 2013. The United States accounted for approximately 8% of global mine production in 2014. The United States ranked third in global mine production behind China and Australia, which accounted for 49 and 15%, respectively. World production of refined Pb (primary and secondary) was 10.6 million metric tons in 2014. China produced about 45% of global refined Pb in 2014 with the United States as the second leading world producer of refined Pb, accounting for 10% (USGS 2016).

Manufacturers and importers of Pb metal and selected Pb compounds are listed in Table 5-1. These data are from EPA's Chemical Data Access Tool, which provides information on chemicals submitted to the EPA under the Toxic Substance Control Act that are manufactured or imported into the United States. Table 5-2 shows the U.S. production volumes for Pb for 2010 through 2013.

Table 5-1. Current U.S. Manufacturers of Lead Metal and Selected Lead Compounds

Company	Location	Domestic manufacturing (pounds/year)
Lead		
5n Plus Inc.	Fairfield, Connecticut	36,671
Colfin Specialty Steel Corp.	New Brighton, Pennsylvania	2,552
Compliance Administrators & Project Services Inc.	Bloomington, California	848,008
Concorde/Interspace Battery	West Covina, California	348,998
Doe Run Co.	Herculaneum, Missouri	280,000,000
East Penn Manufacturing Co. Inc.	Lyon Station, Pennsylvania	194,537,569
Exide Technologies	Bristol, Tennessee	150,000
	Columbus, Georgia	4,200,000
	Forest City, Missouri	84,000,000
	Fort Smith, Arkansas	3,600,000
	Frisco, Texas	140,000,000
	Kansas City, Kansas	9,100,000
	Los Angeles, California	230,000,000
	Manchester, Iowa	16,000,000
	Muncie, Indiana	160,000,000
	Reading, Pennsylvania	130,000,000

Table 5-1. Current U.S. Manufacturers of Lead Metal and Selected Lead Compounds

Company	Location	Domestic manufacturing (pounds/year)
	Salina, Kansas	990,000
Gopher Resource	Eagan, Minnesota	310,000,000
	Tampa, Florida	38,000,000
Horsehead Holding Corp.	Chicago, Illinois	2,444,492
	Palmerton, Pennsylvania	3,867,016
	Rockwood, Tennessee	1,872,054
	Snelling, South Carolina	2,012,236
Johnson Controls	Canby, Oregon	36,832,250
	Geneva, Illinois	47,025,828
	Holland, Ohio	82,721,150
	Kernersville, North Carolina	204,679,893
	Middletown, Delaware	86,732,852
	Tampa, Florida	3,069,380
	Yuma, Arizona	359,977,380
Johnson Controls Distribution Center	Saint Joseph, Missouri	2,550,177
	St. Joseph, Missouri	266,151,342
Renco Group Inc.	Boss, Missouri	310,000,000
Sanders Lead Co., Inc.	Troy, Alabama	471,954,520
Stemar Investments Inc.	Butler, Pennsylvania	40,506
Yuasa Battery Inc.	Laureldale, Pennsylvania	1,492,754
Lead(II) nitrate		
American Pacific Corp.	Cedar City, Utah	42,500
Lead(II) oxide		
C&D Technologies Inc.	Attica, Indiana	18,657,255
	Leola, Pennsylvania	1,348,311
	Milwaukee, Wisconsin	48,491,557
Crown Battery Manufacturing Co.	Fremont, Ohio	25,600,000
Fiamm Energy LLC	Waynesboro, Georgia	4,700,000
Hammond Group Inc.	Hammond, Indiana	3,585,529
	Pottstown, Pennsylvania	8,287,521
Renco Group Inc.	Boss, Missouri	7,700,000
Steel Dust Recycling	Millport, Alabama	2,000,000
Superior Battery Manufacturing	Russell Springs, Kentucky	16,866,793
Trojan Battery Co.	Lithonia, Georgia	38,540,700
	Santa Fe Springs, California	35,241,500

Table 5-1. Current U.S. Manufacturers of Lead Metal and Selected Lead Compounds

Company	Location	Domestic manufacturing (pounds/year)
Lead(II) styphnate		
Alliant Techsystems Inc.	Lewiston, Idaho	78,767
Alliant Techsystems Operations LLC	Independence, Missouri	43,489
Lead(II) sulfate		
Crown Battery Manufacturing Co.	Fremont, Ohio	768,000
East Penn Manufacturing Co., Inc.	Corydon, Iowa	17,006,710
	Lyon Station, Pennsylvania	220,436,420
Johnson Controls	Canby, Oregon	6,098,880
	Geneva, Illinois	11,340,306
	Holland, Ohio	10,714,048
	Middletown, Delaware	5,749,910
	Tampa, Florida	5,506,240
	Yuma, Arizona	86,756
Johnson Controls Distribution Center	Saint Joseph, Missouri	306,021
	St. Joseph, Missouri	29,577,055
Palos Verdes Bldg Corp.	Augusta, Georgia	6,904,629
Superior Battery Manufacturing	Russell Springs, Kentucky	22,905,105
Trojan Battery Co.	Lithonia, Georgia	58,127,100
	Santa Fe Springs, California	53,083,500
Lead(II) chloride		
Horsehead Holding Corp.	Monaca, Pennsylvania	1,891,700
	Palmerton, Pennsylvania	11,484,955

Source: EPA 2014d.

Table 5-2. U.S. Lead Production 2010–2013

Production volumes in metric tons			
2010	2011	2012	2013
356,000	334,000	336,000	331,000
115,000	118,000	111,000	114,000
1,140,000	1,130,000	1,110,000	1,150,000

Source: USGS 2016

Tables 5-3 (Pb) and 5-4 (Pb compounds) list the facilities in each state that manufacture or process Pb or Pb compounds, the intended use, and the range of maximum amounts of Pb that are stored on site. The data listed in Tables 5-3 and 5-4 are derived from the Toxics Release Inventory (TRI) (TRI15 2017). The data presented in Table 5-3 are for Pb metal and the data from Table 5-4 are for all Pb compounds. Facilities with ≥10 full-time employees in certain TRI-covered industry sectors (e.g., manufacturing) must submit data on releases and other waste management for TRI-listed chemicals (Pb and Pb compounds are TRI listed). Therefore, there are sources for Pb and Pb compounds not contained in the TRI database. In comparing TRI data with that of previous years, it is important to note that starting in 2001, the threshold for reporting Pb and all Pb compounds was reduced to 100 pounds, except for lead contained in a stainless steel, brass, or bronze alloy. Previously, reporting was only required of facilities that manufactured or processed >25,000 pounds annually or that used >10,000 pounds annually. Beginning in 1998, additional industries were required to report, including metal mining, coal mining, electrical utilities, and Resource Conservation and Recovery Act (RCRA)/Solvent Recovery.

Table 5-1 lists the producers of primary Pb metal and selected Pb compounds. Companies listed are those producing Pb compounds in commercial quantities >5,000 pounds or $10,000 in value annually.

Table 5-2 shows the U.S. production volumes for Pb for 2010 through 2013. During this time, the primary Pb production declined, while secondary Pb production was relatively constant.

Table 5-3. Facilities that Produce, Process, or Use Lead

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	5	100	99,999	12
AL	105	0	499,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
AR	66	0	999,999	1,2,3,4,6,7,8,9,11,12,13,14
AZ	63	0	9,999,999	1,2,3,5,7,8,9,10,11,12,13,14
CA	214	0	9,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
CO	33	0	99,999	1,2,5,7,8,9,11,12,13,14
CT	53	0	99,999	1,2,3,5,6,7,8,9,10,11,12,13,14
DC	5	0	9,999	1,8,11,12,13,14
DE	5	0	99,999	12,14
FL	188	0	999,999	1,2,3,5,6,7,8,9,10,11,12,13,14
GA	114	0	999,999	1,2,3,5,6,7,8,9,10,11,12,13,14
GU	2	100	9,999	12
HI	4	10,000	999,999	12
IA	108	0	9,999,999	1,2,4,5,7,8,9,10,11,12,13,14
ID	30	0	9,999,999	1,2,3,4,5,8,9,11,12,13,14
IL	242	0	999,999	1,2,3,4,5,7,8,9,11,12,13,14

Table 5-3. Facilities that Produce, Process, or Use Lead

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
IN	169	0	999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
KS	64	0	49,999,999	1,3,5,7,8,9,10,11,12,13,14
KY	83	0	999,999	1,2,3,4,5,6,7,8,9,11,12,13,14
LA	56	0	999,999	1,2,3,5,6,8,9,10,11,12,13,14
MA	62	0	999,999	1,2,3,4,5,7,8,9,11,12,14
MD	35	0	49,999,999	1,5,7,8,9,11,12,14
ME	22	0	999,999	1,2,3,4,5,8,9,11,12,13,14
MI	155	0	999,999	1,2,3,4,5,7,8,9,10,11,12,13,14
MN	140	0	99,999	1,2,3,5,7,8,9,10,11,12,13,14
MO	95	0	499,999,999	2,3,5,6,7,8,9,10,11,12,13,14
MS	46	0	999,999	1,2,3,5,8,9,11,12,13,14
MT	13	0	99,999	1,2,5,12,13,14
NC	167	0	49,999,999	1,2,3,5,6,7,8,9,10,11,12,13,14
ND	19	0	9,999	1,5,8,9,11,12,14
NE	69	0	999,999	1,2,3,5,7,8,9,11,12,13,14
NH	36	0	99,999	1,2,3,4,5,7,8,9,11,12,14
NJ	48	0	99,999	1,2,3,5,7,8,9,11,12,13,14
NM	18	0	999,999	8,11,12
NV	25	0	999,999	1,2,4,5,8,9,11,12,13,14
NY	149	0	9,999,999	1,2,3,5,7,8,9,10,11,12,13,14
OH	266	0	9,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
OK	56	0	99,999,999	1,2,3,5,6,7,8,9,11,12,13,14
OR	54	0	9,999,999	1,2,3,4,5,7,8,10,11,12,13,14
PA	193	0	99,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
PR	8	0	9,999	1,5,7,8,9,11,12
RI	16	0	999,999	1,5,6,7,8,9,10,11,12,13,14
SC	90	0	999,999	1,2,3,4,5,7,8,9,10,11,12,13,14
SD	19	0	99,999	1,5,8,9,12,14
TN	107	0	999,999	1,2,3,4,5,6,7,8,9,11,12,13,14
TX	335	0	9,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
UT	35	0	99,999	1,5,7,8,9,11,12,13,14
VA	114	0	999,999	1,2,3,4,5,7,8,9,10,11,12,13,14
VT	10	0	99,999	1,2,3,5,7,8,9,11,12,13,14
WA	69	0	9,999,999	1,2,3,4,5,7,8,9,10,11,12,13,14
WI	170	0	999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
WV	34	0	999,999	1,2,3,5,7,8,9,11,12,13,14

Table 5-3. Facilities that Produce, Process, or Use Lead

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WY	15	0	99,999	1,2,4,5,6,8,9,10,12,14

[a]Post office state abbreviations used.
[b]Minimum and maximum amounts on site reported for the compilation of all facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI15 2017 (Data are from 2015)

Table 5-4. Facilities that Produce, Process, or Use Lead Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	19	0	499,999,999	1,5,7,9,12,13,14
AL	129	0	499,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
AR	65	0	49,999,999	1,2,3,4,5,6,7,8,9,11,12,13,14
AZ	60	0	9,999,999	1,2,3,4,5,7,8,9,10,11,12,13,14
CA	301	0	49,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
CO	63	0	9,999,999	1,2,3,4,5,7,8,9,11,12,13,14
CT	37	0	49,999,999	1,3,5,6,7,8,9,10,11,12,13,14
DC	1	100,000,000	499,999,999	12
DE	8	100	49,999,999	1,2,3,4,5,7,8,9,12,13,14
FL	157	0	499,999,999	1,2,3,4,5,7,8,9,10,11,12,13,14
GA	100	0	9,999,999	1,2,3,4,5,6,7,8,9,11,12,13,14
GU	3	0	99	1,5,7,9,12,13,14
HI	12	0	99,999	1,2,5,7,9,12,13,14
IA	58	0	49,999,999	1,2,3,4,5,7,8,9,12,13,14
ID	28	0	499,999,999	1,2,3,4,5,7,8,9,11,12,13,14
IL	170	0	49,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
IN	163	0	99,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
KS	38	0	49,999,999	1,2,3,4,5,6,7,8,9,11,12,13,14
KY	74	0	9,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
LA	86	0	99,999,999	1,2,3,4,5,7,8,9,10,11,12,13,14
MA	60	0	49,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
MD	34	0	99,999,999	1,2,3,4,5,7,8,9,11,12,13,14
ME	12	0	999,999	1,5,8,9,12,13,14
MI	121	0	999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14

Table 5-4. Facilities that Produce, Process, or Use Lead Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
MN	56	0	49,999,999	1,2,3,4,5,6,7,8,9,10,12,13,14
MO	73	0	10,000,000,000	1,2,3,4,5,6,7,8,9,11,12,13,14
MP	1	0	99	1,5,12,13,14
MS	72	0	9,999,999	1,2,3,4,5,6,7,8,9,12,13,14
MT	23	0	10,000,000,000	1,2,3,5,6,7,9,12,13,14
NC	130	0	49,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
ND	23	0	99,999	1,2,3,4,5,7,9,10,12,13,14
NE	23	0	999,999	1,3,4,5,6,7,8,9,12,13,14
NH	18	0	999,999	1,2,5,7,8,9,11,12,13,14
NJ	56	0	999,999	1,2,3,4,5,7,8,9,11,12,13,14
NM	16	0	9,999,999	1,2,3,4,5,7,8,9,10,11,12,13,14
NV	52	0	499,999,999	1,2,3,5,6,7,8,9,10,11,12,13,14
NY	84	0	49,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
OH	201	0	49,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
OK	94	0	9,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
OR	50	0	9,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
PA	215	0	99,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
PR	12	0	99,999	1,2,3,4,5,7,8,9,12,13
RI	19	0	99,999	1,2,3,4,5,7,8,9,10,11,12,13,14
SC	99	0	49,999,999	1,2,3,4,5,6,7,8,9,11,12,13,14
SD	13	0	9,999,999	1,3,4,5,6,7,8,9,12,13,14
TN	92	0	9,999,999	1,2,3,4,5,6,7,8,9,11,12,13,14
TX	322	0	499,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
UT	40	0	499,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
VA	82	0	49,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
VI	1	0	99	1,5
VT	5	0	9,999	7,8,14
WA	79	0	9,999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
WI	106	0	999,999	1,2,3,4,5,6,7,8,9,10,11,12,13,14
WV	48	0	999,999	1,2,3,4,5,7,8,9,11,12,13,14
WY	13	0	999,999	1,2,3,4,5,8,9,12,13,14

[a]Post office state abbreviations used.
[b]Minimum and maximum amounts on site reported for the compilation of all facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI15 2017 (Data are from 2015)

5.2.2 Import/Export

In 2014, 1,080 and 593,000 metric tons of Pb as base bullion and pigs and bars, respectively, were imported into the United States. Imports have increased since 2010 when 602 and 271,000 metric tons of Pb as base bullion and pigs and bars, respectively, were imported. In 2014, 65,100 metric tons, Pb content of Pb pigments and compounds were imported in the United States (USGS 2016).

Exports of Pb in ore and concentrates and Pb materials, excluding scrap were 299,000 and 83,500 metric tons, respectively, in 2010 as compared to 365,000 and 61,300 metric tons, respectively, in 2014. In 2013 and 2014, 34,900 and 36,400 metric tons of Pb scrap were exported, respectively (USGS 2016).

5.2.3 Use

Pb may be used in the form of metal, either pure or alloyed with other metals, or as chemical compounds. The main uses of Pb and its compounds are in Pb-acid batteries, with most other applications using Pb alloys. The commercial importance of Pb is based on its physical properties, including its low melting point, ease of casting, high density, softness, malleability, low strength, ease of fabrication, acid resistance, electrochemical reaction with sulfuric acid, and chemical stability in air, water, and soil (King et al. 2014).

In the United States in 2014, Pb was consumed by over 70 companies to manufacture products such as ammunition; building-construction materials; covering for power and communication cable; Pb-acid storage batteries; Pb oxides for ceramics, chemicals, glass, and pigments; Pb sheet; and solder for construction, electronic components and accessories, metal containers, and motor vehicles (USGS 2016). The majority of U.S. Pb consumption (88%) was in the Pb-acid battery industry. Pb-acid batteries were primarily used as starting-lighting-ignition (SLI) batteries for automobiles and trucks and as industrial-type batteries for standby power for computer and telecommunications networks and for motive power. Global consumption of refined Pb was 10.9 million metric tons in 2014, with leading consumers: China (43%); United States (15%); India (5%); Republic of Korea (5%); and Germany (3%) (USGS 2016).

Prior to the EPA beginning to regulate the Pb content in gasoline during the early 1970s, approximately 250,000 tons of organic Pb (e.g., tetraethyl Pb) were added to gasoline on an annual basis in the United States (Giddings 1973). These Pb-based “anti-knock” additives increased the octane rating of the gasoline and, as a result, increased engine efficiency (Giddings 1973). In 1971, the average Pb content

for a gallon of gasoline purchased in the United States was 2.2 g/gallon (Giddings 1973). After determining that Pb additives would impair the performance of emission control systems installed on motor vehicles, and that Pb particle emission from motor vehicles presented a significant health risk to urban populations, EPA, in 1973, initiated a phase-down program designed to minimize the amount of Pb in gasoline over time. By 1988, the phase-down program had reduced the total Pb usage in gasoline to <1% of the amount of Pb used in the peak year of 1970 (EPA 1996a).

In 1990, a Congressional amendment to the Clean Air Act (CAA) banned the use of gasoline containing Pb or Pb additives as fuel in most motor vehicles. On February 2, 1996, the EPA incorporated the statutory ban in a direct final rule, which defined unleaded gasoline as gasoline containing trace amounts of Pb up to 0.05 g/gallon (EPA 1996a). The definition still allowed trace amounts of Pb, but expressly prohibited the use of any Pb additive in the production of unleaded gasoline. The term "lead additive" was defined to include pure Pb as well as Pb compounds (EPA 1996a). Although the regulatory action of Congress banned the use of leaded gasoline as fuel in motor vehicles, it did not restrict other potential uses of gasoline containing Pb or Pb additives (EPA 1996a). Gasoline produced with Pb additives continues to be made and marketed for use as fuels in aircraft, race cars, and non-road engines such as farm equipment engines and marine engines to the extent allowed by law (EPA 1996a), but tetraethyl Pb has not been produced in the United States since March 1991. All gasoline sold for motor vehicle use since January 1, 1996 has been unleaded (EPA 1997a).

Table 5-5 lists the uses of the specific Pb compounds identified in Chapter 4.

Table 5-5. Current and Former Uses of Selected Lead Compounds

Compound	Uses
Lead(II) acetate	Dyeing of textiles, waterproofing, varnishes, lead driers, chrome pigments, gold cyanidation process, insecticide, anti-fouling paints, analytical reagent, hair dye
Lead(II) azide	Primary detonating compound for high explosives, firing of Pb-based ammunition
Lead(II) bromide	Photopolymerization catalyst, inorganic filler in fire-retardant plastics, general purpose welding flux
Lead(II) carbonate	Polymerization catalyst, component of high pressure lubricating greases, coating on vinyl chloride polymers
Lead(II) chloride	Preparation of lead salts, lead chromate pigments, analytical reagent
Lead(II) chromate	Pigment in industrial paints, rubber, plastics, ceramic coatings; organic analysis

Table 5-5. Current and Former Uses of Selected Lead Compounds

Compound	Uses
Lead(II) tetrafluoroborate	Salt for electroplating lead; can be mixed with stannous fluoborate to electroplate any composition of tin and lead as an alloy
Lead(II) iodide	Bronzing, printing, photography, cloud seeding
Lead molybdenum chromate	Analytical chemistry, pigments
Lead(II) nitrate	Lead salts, mordant in dyeing and printing calico, matches, mordant for staining mother of pearl, oxidizer in the dye industry, sensitizer in photography, explosives, tanning, process engraving, and lithography
Lead(II) oxide	Storage batteries, ceramic cements and fluxes, pottery and glazes, glass, chromium pigments, oil refining, varnishes, paints, enamels, assay of precious metal ores, manufacture of red lead, cement (with glycerol), acid-resisting compositions, match-head compositions, other lead compounds, rubber accelerator
Lead(II) phosphate	Stabilizing agent in plastics
Lead(II) styphnate	Primary explosive, firing of Pb-based ammunition
Lead(II) sulfate	Storage batteries, paints, ceramics, pigments, electrical and other vinyl compounds requiring high heat stability
Lead(II) sulfide	Ceramics, infrared radiation detector, semi-conductor, ceramic glaze, source of lead
Tetraethyl lead	Anti-knock agent in aviation gasoline

Sources: Boileau et al. 1987; Carr 1995; Carr et al. 2004; Davidson et al. 2014

Pb arsenate, basic Pb arsenate, and Pb arsenite were formerly used as herbicides, insecticides, or rodenticides. Until the 1960s, they were widely used to control pests in fruit orchards, especially apple orchards (EPA 2002c; PAN Pesticides Database 2004; Peryea 1998; Wisconsin Department of Health and Family Services 2002). All insecticidal use of Pb arsenate was officially banned on August 1, 1988. However, all registrations for its insecticidal use had lapsed before that time.

5.2.4 Disposal

Secondary (recycled) Pb, derived mainly from scrapped Pb-acid batteries, accounted for 100% of refined Pb production in the United States in 2014. Almost all of the Pb recycled in 2014 was recovered by 7 companies operating 12 plants in Alabama, California, Florida, Indiana, Minnesota, Missouri, New York, Pennsylvania, Tennessee, and Texas (USGS 2016). More than 99% of all battery Pb is recycled and new batteries contain between 60 and 80% recycled Pb and plastic, respectively (Battery Council International 2016a). Scrap Pb is also recovered from dross, dust, residue, and sludge generated by smelting of metals, Pb pipe and sheet, printing materials, sheaths from power and telephone cable, and vehicle wheel weights (USGS 2014).

Disposal of wastes containing Pb or Pb compounds is controlled by several federal regulations (see Chapter 7). Pb is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1988). Pb-containing waste products include storage batteries, ammunition waste, ordnance, sheet Pb, solder, pipes, traps, and other metal products; solid waste and tailings from Pb mining; items covered with Pb-based paint; and solid wastes created by mineral ore processing, iron and steel production, copper and zinc smelting, and the production and use of various Pb-containing products (EPA 1982a).

There is currently no federal regulation for battery recycling in the United States (Gies 2015). However, 38 states have adopted battery recycling laws and 5 others have disposal bans (Battery Council International 2016b). The Mercury-Containing and Rechargeable Battery Management Act (the Battery Act) of 1996 removed certain barriers to the recycling of batteries including small, sealed lead acid (SSLA) batteries (EPA 2002b). The intent was to provide the efficient and cost-effective collection and recycling or proper disposal of batteries to keep them out of the waste stream. The Act established uniform national labeling requirements, mandated that batteries under the Act be "easily removable" from consumer products where possible, made the Universal Waste Rule effective in all 50 states for the collection, storage, and transportation of batteries covered by the Battery Act, and required EPA to establish a public education program on battery recycling and the proper handling and disposal of used batteries (EPA 1997a).

According to data from the TRI, total disposal of Pb and Pb compounds varied during the period of 2005–2015 from 387 million pounds in 2009 to 832 million pounds in 2013, with an overall increase of 20% during this time period. The metal mining sector contributes most to the disposal of Pb and Pb compounds, with metal mines reporting 85% of total Pb and Pb compound releases in 2015.

5.3 RELEASES TO THE ENVIRONMENT

Facilities with ≥10 full-time employees in certain industry sectors (e.g., manufacturing) covered by the TRI (e.g., manufacturing) must submit data to TRI on releases and other waste management for TRI-listed chemicals (Pb and Pb compounds are TRI listed). Therefore, TRI data do not reflect all sources of Pb releases (EPA 2005a). TRI-covered facilities are required to report information to the TRI only if they employ the equivalent of ≥10 full-time employees; if their facility is included in Standard Industrial

Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes >25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005a).

Starting in 2001, the threshold to trigger reporting of Pb in most Pb compounds was reduced to 100 pounds. The higher threshold still applies to Pb contained in stainless steel, brass, or bronze alloys. The threshold for Pb is determined using the weight of the metal, whereas the threshold for Pb compounds is determined by the weight of the entire compound. Prior to 1998, only facilities classified within the SIC codes 20–39 (Manufacturing Industries) were required to report. After 1998, the industries required to report were enlarged to include other industrial sectors, such as metal mining, coal mining, electrical utilities, and hazardous waste treatment (EPA 2001).

Pb is a naturally-occurring element that is typically found combined in various minerals. It occurs in the Earth's crust primarily as the mineral galena (PbS), and to a lesser extent as anglesite ($PbSO_4$) and cerussite ($PbCO_3$) (Carr et al. 2004; Davidson et al. 2014; Haynes 2014). Pb minerals are found in association with zinc, copper, and iron sulfides as well as gold, silver, bismuth, and antimony minerals. It also occurs as a trace element in coal, oil, and wood. Typical Pb concentrations in some ores and fuels are: copper ores, 11,000 ppm; Pb and zinc ores, 24,000 ppm; gold ores, 6.60 ppm; bituminous coal, 3–111 ppm; crude oil, 0.31 ppm; No. 6 fuel oil, 1 ppm; and wood, 20 ppm (EPA 2001).

Leaded gasoline remains commercially available for off-road uses, including aircraft, racing cars, farm equipment, and marine engines. Currently, the largest contributor to atmospheric Pb emissions in the United States is piston-engine aircraft emissions (NEI data 2014). Industrial sources of Pb can result from the mining and smelting of Pb ores, as well as other ores in which Pb is a byproduct or contaminant. Fuel combustion also contributes to releases of Pb to the environment. As a result of these processes, Pb may be released to land, water, and air. Many of the anthropogenic sources of Pb have been eliminated or phased out because of Pb's persistence, bioaccumulative nature, and toxicity. These include Pb-based paint in 1978, Pb-containing pesticides in 1988, and Pb in gasoline for use in on-road vehicles in 1996. In

early 2017, the use of Pb ammunition and Pb sinkers was banned on most federal lands; however, this ban was temporarily halted soon after. Because Pb does not degrade and remains in the environment long after its release, these former uses continue to be a potential source for Pb exposure.

5.3.1 Air

According to the TRI, in 2015, a total of 99,738 pounds of Pb were released to air from 4,252 reporting facilities (TRI15 2017). In addition, a total of 290,444 pounds of Pb compounds were released to air from 3,873 reporting facilities (TRI15 2017). Tables 5-6 and 5-7 list amounts of Pb and Pb compounds released from these facilities grouped by state, respectively.

Table 5-6. Releases to the Environment from Facilities that Produce, Process, or Use Lead[a]

	Reported amounts released in pounds per year[b]								
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	5	0	0	0	20,505	0	20,505	0	20,505
AL	105	2,504	908	1	2,014,146	8,978	2,015,775	10,761	2,026,537
AR	66	1,355	120	0	90,130	3,264	91,143	3,726	94,869
AZ	63	307	626	0	116,359	92	94,025	23,359	117,384
CA	204	523	2,044	0	527,218	47,338	523,315	53,808	577,122
CO	33	40	14	0	118,225	2,856	118,057	3,078	121,135
CT	53	86	412	0	2,240	10,650	2,253	11,136	13,389
DC	5	349	1	0	124	300	349	424	774
DE	5	8	3	196	16,110	39	16,121	235	16,356
FL	186	344	161	5	91,265	10,371	53,596	48,549	102,145
GA	114	381	1,139	1	78,152	11,450	77,789	13,333	91,123
GU	2	1	0	0	7,679	0	7,680	No data	7,680
HI	4	0	0	0	104,522	0	104,522	No data	104,522
IA	108	586	75	49	6,405	18,008	4,695	20,428	25,123
ID	30	191	3	0	618,847	15,330	618,421	15,951	634,372
IL	242	2,272	753	0	788,245	33,476	761,987	62,759	824,746
IN	167	2,113	356	102	382,724	1,258,386	5,208	1,638,473	1,643,681
KS	64	785	35	0	48,740	4,208	30,304	23,463	53,768
KY	83	1,974	626	0	29,619	2,654	25,655	9,219	34,873
LA	56	391	719	0	37,749	481	35,790	3,550	39,340
MA	62	54	1,554	73	76,950	23,321	42,215	59,738	101,953
MD	34	44,602	7	0	21,258	314	63,754	2,426	66,181

Table 5-6. Releases to the Environment from Facilities that Produce, Process, or Use Lead[a]

	Reported amounts released in pounds per year[b]								
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
ME	21	5	45	0	8,597	80,670	29	89,288	89,317
MI	152	5,740	641	50	52,619	8,731	34,680	33,102	67,781
MN	140	505	225	22	5,893	2,747	966	8,426	9,392
MO	95	504	65	3	144,956	926	128,775	17,679	146,454
MS	45	1,327	50	0	66,575	1,096	67,096	1,952	69,048
MT	12	19	1	0	49,209	5	48,823	411	49,234
NC	167	409	708	336	113,962	28,503	21,458	122,459	143,917
ND	18	3	66	0	1,370	55	1,412	82	1,494
NE	67	3,805	104	0	150,180	15,920	84,281	85,728	170,009
NH	36	29	11	0	1,649	514	1,136	1,068	2,203
NJ	48	202	31	110	2,706	3,393	1,437	5,004	6,441
NM	18	13	59	0	18,016	1,068	16,735	2,422	19,157
NV	23	257	0	0	743,402	1,263	743,652	1,271	744,922
NY	148	1,168	539	0	38,390	36,515	30,029	46,584	76,613
OH	265	7,419	1,192	1,556	257,007	87,544	230,813	123,905	354,718
OK	56	735	599	2	62,170	2,274	62,818	2,962	65,780
OR	54	95	54	0	1,095,773	1,217	1,093,593	3,545	1,097,138
PA	193	6,806	2,002	246	18,659	533,974	16,014	545,673	561,687
PR	8	4	0	0	5,223	513	5,227	514	5,741
RI	15	7	2	0	10	2,686	7	2,699	2,706
SC	89	1,057	443	838	165,256	2,991	153,116	17,468	170,585
SD	19	6	3	0	3	406	6	412	417
TN	106	1,311	559	1	40,231	5,135	26,058	21,179	47,238
TX	334	2,266	689	69,633	354,930	18,646	401,712	44,452	446,164
UT	34	165	9	0	82,700	47,137	81,008	49,003	130,011
VA	107	1,783	555	76	166,683	38,940	114,534	93,503	208,037
VT	10	1	5	0	12,135	886	12,116	911	13,027
WA	66	117	63	0	3,273,169	137,911	3,246,153	165,107	3,411,260
WI	169	4,756	294	0	42,076	14,652	4,876	56,901	61,777
WV	33	272	2	125	151,600	2,049	147,302	6,745	154,047

Table 5-6. Releases to the Environment from Facilities that Produce, Process, or Use Lead[a]

	Reported amounts released in pounds per year[b]								
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WY	13	86	78	0	42,417	0	39,607	2,974	42,581
Total	**4,252**	**99,738**	**18,648**	**73,425**	**12,364,781**	**2,529,881**	**11,528,626**	**3,557,847**	**15,086,473**

[a]There are sources for release other than those reported to TRI. This chart reflects information provided to TRI. Data are rounded to nearest whole number.
[b]Data in TRI are total amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Underground injection Class I wells and Class II-V wells.
[h]Resource Conservation and Recovery Act (RCRA) Subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI15 2017 (Data are from 2015)

Table 5-7. Releases to the Environment from Facilities that Produce, Process, or Use Lead Compounds[a]

	Reported amounts released in pounds per year[b]								
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	17	10,328	209	0	223,161,561	5	223,165,066	7,037	223,172,103
AL	129	9,457	4,547	0	1,038,358	12,293	922,926	141,730	1,064,656
AR	63	7,901	1,206	0	48,454	71,513	54,177	74,897	129,074
AZ	59	18,709	99	0	20,469,170	2,795	20,482,921	7,852	20,490,773
CA	291	7,559	716	5	4,373,766	14,153	3,879,798	516,401	4,396,199
CO	63	3,278	38	0	8,313,098	8,025	8,294,566	29,874	8,324,440
CT	37	178	722	0	11,910	12,569	201	25,179	25,379
DC	1	0	0	0	23	0	24	0	24
DE	8	218	107	0	18,899	12,731	1,141	30,814	31,955
FL	157	5,896	1,987	0	993,233	12,076	944,643	68,549	1,013,192
GA	100	6,269	2,258	0	388,326	1,066	333,881	64,039	397,920

Table 5-7. Releases to the Environment from Facilities that Produce, Process, or Use Lead Compounds[a]

	Reported amounts released in pounds per year[b]								
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
GU	3	36	2	0	13	0	50	0	50
HI	12	975	23	14	4,664	212	2,237	3,650	5,888
IA	58	7,365	998	11	189,469	31,847	73,657	156,034	229,691
ID	28	1,847	212	0	2,987,992	1,168	2,989,477	1,743	2,991,220
IL	170	13,784	10,450	11,476	1,114,360	583,163	311,897	1,421,336	1,733,233
IN	159	24,115	39,916	1,256	3,998,658	694,360	949,772	3,808,534	4,758,306
KS	38	2,809	244	38	30,739	32,818	30,542	36,106	66,648
KY	73	14,518	574	3,903	889,194	131,680	882,701	157,168	1,039,869
LA	84	5,940	4,456	589	757,684	5,872	595,908	178,633	774,541
MA	60	1,199	270	0	5,266	44,975	2,661	49,049	51,710
MD	34	1,062	326	6	34,647	155,509	14,410	177,140	191,550
ME	12	784	586	0	30,452	4	4,750	27,075	31,825
MI	120	5,708	3,991	59	741,434	107,685	437,412	421,465	858,877
MN	56	2,650	415	0	1,031,992	3,124	113,673	924,508	1,038,182
MO	72	15,169	21,933	2,075	24,880,815	208,477	24,725,309	403,158	25,128,468
MP	1	2	0	0	1	No data	2	No data	2
MS	72	2,050	2,445	309,122	66,528	3,350	338,514	44,980	383,494
MT	23	2,225	2	5,557	6,576,730	1,996	6,578,917	7,592	6,586,510
NC	126	6,064	785	0	713,311	80,430	611,373	189,216	800,589
ND	21	3,836	40	0	113,296	5,254	84,928	37,498	122,425
NE	23	951	108	0	62,568	6,743	56,177	14,193	70,370
NH	18	64	13	0	1,531	5,968	299	7,278	7,576
NJ	55	1,295	1,480,932	0	22,073,190	1,092,177	47,828	24,599,766	24,647,594
NM	16	1,351	103	1	7,619,073	113,027	7,591,784	141,772	7,733,556
NV	51	5,670	0	0	71,295,426	209	71,297,978	3,327	71,301,305
NY	84	2,791	4,992	0	651,466	23,267	74,757	607,759	682,516
OH	200	11,150	3,223	24,123	1,078,489	320,175	457,177	979,985	1,437,161
OK	93	6,165	278	0	485,889	463	401,246	91,549	492,795
OR	50	1,325	2,141	0	44,379	233	12,427	35,650	48,077
PA	215	15,389	8,771	7	1,182,089	288,391	530,697	963,950	1,494,648
PR	12	916	287	6	1,183	2,456	1,207	3,641	4,848
RI	19	54	10	0	989	137	54	1,137	1,191
SC	98	4,238	499	0	2,383,853	32,870	121,907	2,299,555	2,421,462
SD	13	101	2	0	840,669	124	839,746	1,149	840,895
TN	92	4,985	2,886	84	1,301,596	251,629	1,230,147	331,032	1,561,180
TX	317	15,182	4,166	937	2,657,771	14,300	2,381,651	310,704	2,692,356
UT	40	10,399	261	0	126,927,346	3,486	126,882,715	58,778	126,941,493

Table 5-7. Releases to the Environment from Facilities that Produce, Process, or Use Lead Compounds[a]

	Reported amounts released in pounds per year[b]								
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
VA	80	12,727	7,938	0	297,037	14,306	219,221	112,787	332,008
VI	1	11	0	0	0	No data	11	No data	11
VT	5	10	0	0	81	0	10	81	91
WA	79	5,094	1,243	0	254,154	19,721	212,365	67,847	280,212
WI	104	4,410	1,539	4	247,231	34,846	81,033	206,996	288,029
WV	48	3,448	1,171	0	509,721	3,604	371,742	146,202	517,944
WY	13	786	11	0	78,585	320	69,971	9,730	79,701
Total	**3,873**	**290,444**	**1,620,131**	**359,275**	**542,978,361**	**4,467,601**	**509,709,687**	**40,006,124**	**549,715,811**

[a]There are sources for release other than those reported to TRI. This chart reflects information provided to TRI. Data are rounded to nearest whole number.
[b]Data in TRI are total amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Underground injection Class lass I wells and Class II-V wells.
[h]Resource Conservation and Recovery Act (RCRA) Subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI15 2017 (Data are from 2015)

The decrease in national Pb emissions between 1970 to 2011 is estimated to be 99.6% (220,000 tons), which is mostly attributed to the elimination of leaded gasoline for on-road vehicles. Since 2000, nonroad engines and metals industrial processing have accounted for most of the anthropogenic Pb emissions in the United States (EPA 2015). Based on data from the National Emissions Inventory (NEI 2014), the following sectors contribute the largest portions of total Pb emissions in the United States: mobile-aircraft (63%), industrial processes–not elsewhere classified (6.8%), industrial processes–ferrous metals (6.8%), fuel combustion–electric generation–coal (5.5%), and industrial processes–non-ferrous metals (4.1%) (EPA 2016c). Historical trends of Pb emissions in the United States are provided in Table 5-8 (EPA 2015).

Table 5-8. Historic Levels of Lead Emissions to the Atmosphere in the United States (in Thousand Metric Tons)

	1970	1975	1980	1985	1990	1995	1999	2002	2005	2008	2011
On-road vehicles	172	130.2	60.5	18.1	2.17	2.05	1	0	0	0	0
Metals industrial processing	24.22	9.923	3.03	2.1	0.5	0.49	0.96	0.4	0.3	0.16	0.14
Fuel combustion	10.62	10.35	4.3	0.52	0.42	0.02	0	0.39	0.14	0.12	0.09
Nonroad engines	9.737	6.13	4.2	0.92	0.78	0.54	0.55	0.45	0.66	0.56	0.49
Other sources	4.331	3.053	2.12	1.31	1.11	0.83	0.84	0.43	0.25	0.11	0.1

Source: EPA 2015

According to the data from the NEI, the largest portions of total Pb emissions are in the U.S. mobile-aircraft sector. Murphy et al. (2008) studied weekly patterns of metals and other aerosol components using data collected from 2000 to 2006 at Interagency Monitoring of Protected Visual Environments (IMPROVE) sites, and these data suggested that Pb concentrations were impacted by piston aircraft emissions.

As indicated in Table 5-6, by the early 2000s, transportation (i.e., automotive) emissions were no longer the dominant source of Pb emitted to the atmosphere. When such emissions were prevalent, >90% (mass basis) of automotive Pb emissions from leaded gasoline were in the form of inorganic particulate matter (e.g., Pb bromochloride [PbBrCl]) and <10% (mass basis) were in the form of organolead vapors (e.g., Pb alkyls). In 1984, the average Pb content of gasoline was 0.44 g Pb/gallon (EPA 1986); however, as of January 1986, the allowable Pb content of leaded gasoline dropped to 0.1 g Pb/gallon (EPA 1985d). Between January and June of 1990, the actual average Pb concentration in leaded gasoline was 0.085 g Pb/gallon, indicating consumption of approximately 230,000 kg of Pb for the production of 2.74 billion gallons of leaded gasoline. In the early 1980s, EPA allowed up to 0.05 g of Pb in a gallon of unleaded gasoline (EPA 1982b).

According to data from TRI, on-site air releases of Pb and Pb compounds varied over the same period from 431,311 pounds in 2014 to 1,037,265 pounds in 2006, with an overall decrease of 40%. The electric utility and primary metals industry sectors contributed to this overall decrease; both sectors have decreased air Pb and Pb compounds releases by approximately 70% from 2005 to 2015. The primary metal sector, which includes iron and steel manufacturers and smelting operations, contributes the greatest quantity of Pb and Pb compounds to air releases (EPA 2017a, 2017b).

While Pb levels in paints for interior use have been restricted since the 1950s, older houses and furniture may still be covered with leaded paint. Releases from Pb-based paints are frequently confined to the area in the immediate vicinity of painted surfaces, and deterioration or removal of the paint by sanding or sandblasting can result in high localized concentrations of Pb dust in both indoor and outdoor air.

The largest volume of organolead vapors released to the atmosphere results from industrial processes; prior to its phaseout and ban, leaded gasoline containing tetraethyl Pb as an anti-knock additive was also a major contributor. Tetraalkyl Pb vapors are photoreactive, and their presence in local atmospheres is transitory. Halogenated Pb compounds are formed during combustion by reaction of the tetraalkyl Pb compounds with halogenated Pb scavenger compounds. These halogenated Pb compounds ultimately give rise to Pb oxides and carbonates in the environment (EPA 1985b). Tetraalkyl Pb compounds once contributed 5–10% of the total particulate Pb present in the atmosphere. Organolead vapors were most likely to occur in occupational settings (e.g., gasoline transport and handling operations, gas stations, and parking garages) and high-traffic areas (Nielsen 1984).

5.3.2 Water

According to the TRI, in 2015, a total of 18,648 pounds of Pb were released to water from 4,252 reporting facilities (TRI15 2017). In addition, a total of 620,131 pounds of Pb compounds were released to water from, 3,873 reporting facilities (TRI15 2017). Tables 5-6 and 5-7 list amounts of Pb and Pb compounds released from these facilities grouped by state, respectively.

The following industry sectors accounted for the majority of release of Pb to surface water in 2015: chemicals (27%); paper (25%); primary metals (18%); transportation equipment (12%); fabricated metals (7%); and electrical utilities (3%). The following industry sectors accounted for the majority of release of Pb compounds to surface water in 2015: metal mining (32%); paper (31%); electric utilities (15%); primary metals (9%); chemicals (5%); fabricated metals (4%); and petroleum (3%) (TRI15 2017). The trends in discharges of Pb and Pb compounds to surface water from 2001 to 2015 are presented in Table 5-9.

Table 5-9. U.S. Surface Water Discharges of Lead and Lead Compounds (Pounds/Year)

Year	Lead	Lead compounds
2001	45,871	97,479
2002	20,694	92,366
2003	21,314	109,299
2004	14,564	107,386
2005	15,883	100,778
2006	22,985	86,772
2007	16,745	82,815
2008	11,404	153,681
2009	9,886	73,683
2010	7,263	72,556
2011	7,086	77,568
2012	7,307	60,656
2013	6,327	76,053
2014	8,836	79,344
2015	5,264	70,981

Source: EPA 2017c; TRI15 2017

Data reported by Environment and Climate Change Canada (2016) show that other industries, which include the iron and steel industry, oil and gas industry, and cement and concrete industry, contributed 136.9 tonnes of the total Pb released to water in 2014. This release includes 134.1 tonnes of Pb that were released when a dam securing a tailings pond from the Mount Polley mine in central British Columbia breached on August 4, 2014, spilling mining waste into Polley Lake and surrounding waters. Waste, pulp, paper, and paperboard industry, and non-ferrous smelting and refining were the next largest contributors (Table 5-10). In 2013, Pb releases to water were similar for other industries and waste.

Table 5-10. Canada Surface Water Discharges of Lead and Lead Compounds (Tonnes)

Year	Other industries	Waste	Pulp, paper, and paperboard industry	Non-ferrous smelting and refining	Other sources
2003	4.38	15.49	2.55	1.74	0.18
2004	3.97	11.53	2.84	2.26	0.26
2005	6.11	9.47	3.29	1.82	0.58
2006	5	9.9	2.35	1.65	0.24
2007	3.63	6.42	2.37	1.64	0.19
2008	4.76	11.58	2.42	2.04	0.16

Table 5-10. Canada Surface Water Discharges of Lead and Lead Compounds (Tonnes)

Year	Other industries	Waste	Pulp, paper, and paperboard industry	Non-ferrous smelting and refining	Other sources
2009	3.39	8.49	2.25	2.13	0.19
2010	3.21	11.97	2.12	1.45	0.14
2011	3.65	8.97	2.91	1.5	0.16
2012	4.66	4.69	2.8	1.75	0.12
2013	4.17	4.66	2.42	1.48	0.13
2014	136.92	5.11	1.85	1.77	0.13

Source: Environment and Climate Change Canada (2016)

Urban runoff and atmospheric deposition are significant indirect sources of Pb found in the aquatic environment. Pb reaching surface waters is sorbed to suspended solids and sediments (EPA 1982a; EPA 2006, 2014c).

Pb is released into surface water from Pb shot and Pb sinkers. A study of a shooting range in Southwestern Virginia found that the dissolved Pb content of surface water ranged up to 473 ppb, with the highest concentrations closest to the backstop (Craig et al. 1999). Upstream from the site, the Pb concentration was 0.5 ppb. In 1991, the U.S. Fish and Wildlife Service banned the use of Pb shot when hunting waterfowl, such as geese or ducks, in order to avoid releasing Pb directly to surface water.

5.3.3 Soil

According to the TRI, in 2015, a total of 12,364,781 pounds of Pb were released to the land, both on-site and off-site, by 4,252 reporting facilities (TRI15 2017). Table 5-6 lists amounts of Pb released from these facilities grouped by state. In addition, a total of 542,978,361 pounds of Pb compounds were released to land, both on-site and off-site, by 3,873 reporting facilities (TRI15 2017). Table 5-7 lists amounts of Pb compounds released from these facilities grouped by state. In addition, 73,425 and 359,275 pounds of Pb and Pb compounds, respectively, were injected underground. Ninety-five percent of Pb injected underground were by two facilities in Texas. Eighty-six percent of Pb compounds injected underground was by one facility in Mississippi. Facilities with ≥10 full-time employees in certain TRI-covered industry sectors (e.g., manufacturing) must submit data on releases and other waste management for TRI-listed chemicals (Pb and Pb compounds are TRI listed).

Pb-containing material from home and commercial use may be sent to municipal landfills. It is important to note that land is the ultimate repository for Pb, and Pb released to air and water ultimately is deposited in soil or sediment. For example, Pb released to the air from leaded gasoline or in stack gas from smelters and power plants will settle on soil, sediment, foliage, or other surfaces. The heaviest contamination occurs near the highway, in the case of leaded gasoline, or near the facility, in the case of a power plant or smelter. Road dust contributes to Pb in soil. Pb concentrations were higher in surface soils within 1,000 m of roadways (134 kg/ha) as compared to outside the 1,000-m region (38.7 kg/ha) (Yesilonis et al. 2008). Wheel weights can contribute to releases of Pb along roadways. Aucott and Caldarelli (2012) estimated that approximately 12 tons of Pb as wheel weights are deposited on New Jersey roadways; however, they estimated that only a small amount enters the environment as small particulate from grinding. Root (2000) also estimated a rate of Pb deposition in Albuquerque, New Mexico as 50–70 kg/km/year. However, use of Pb wheel weights are on the decline due to legislation, voluntary phase-out, and new wheel technology (Aucott and Caldarelli 2012).

5.3.4 Paint

Although the sale of residential Pb-based paint was banned in the United States in 1978, flaking paint, paint chips, and weathered powdered paint, which are most commonly associated with deteriorated housing stock in urban areas, remain major sources of Pb exposure for young children residing in these houses, particularly for children afflicted with pica (the compulsive, habitual consumption of nonfood items) (Bornschein et al. 1986; EPA 1986). Pb concentrations of 1–5 mg/cm^2 have been found in chips of Pb-based paint (Billick and Gray 1978), suggesting that consumption of a single chip of paint would provide greater short-term exposure than any other source of Pb (EPA 1986). An estimated 40–50% of occupied housing in the United States may contain Pb-based paint on exposed surfaces (Chisolm 1986).

In the late 1980s, the U.S. Department of Housing and Urban Development (HUD) conducted a national survey of Pb-based paint in housing. The EPA subsequently sponsored a comprehensive technical report on the HUD-sponsored survey to provide estimates of the extent of Pb-based paint in housing. In the EPA report, a home is considered to have Pb-based paint if the measured Pb concentration on any painted surface is ≥1.0 mg/cm^2. The EPA report estimates that 64 million (±7 million) homes, or 83% (±9%) of privately-owned housing units built before 1980, have Pb-based paint somewhere in the building. Approximately 12 million (±5 million) of these homes are occupied by families with children under the age of 7 years. Approximately 49 million (±7 million) privately owned homes have Pb-based paint in

their interiors. By contrast, approximately 86% (±8%) of all pre-1980 public housing family units have Pb-based paint somewhere in the building (EPA 1995b).

Damaged Pb-based paint is associated with excessive dust Pb levels. Approximately 14 million homes (19% of pre-1980 housing) have >5 square feet of damaged Pb-based paint, and nearly half (47%) of those homes have excessive dust Pb levels (EPA 1995b).

In the Cincinnati prospective Pb study of public and private low- and moderate-income housing, the Pb concentration ranges were: painted interior walls, 0.1–35 mg/cm^2; interior home surface dust, 0.04–39 mg/m^2 and 72–16,200 μg/g; interior home dustfall, 0.0040–60 mg/m^2/30 days; exterior dust scrapings, 20–108,000 μg/g; and dust on children's hands, 1–191 μg. The Pb levels in older private deteriorating or dilapidated housing were higher than the levels in newer public and rehabilitated housing (Clark et al. 1985).

Releases from Pb-based paints are frequently confined to the area in the immediate vicinity of painted surfaces, and deterioration or removal of the paint can result in high localized concentrations of Pb in dust in air (from sanding and sandblasting) and on exposed surfaces. A study was conducted in New Orleans where power sanding is a common practice during repainting old houses; median, 90th percentile, and maximum Pb concentrations in 31 study houses were 35, 126, and 257 mg/g, respectively (Mielke et al. 2001). Pb concentrations in dust and soil samples from one study of a house where the paint chips contained about 90 mg Pb/g were very high. If the house had been sanded down to bare wood, 7.4 kg of Pb would have been released to the environment. Disturbance of older structures containing Pb-based paints is now a significant contributor to total Pb releases.

The authors of a report of findings from NHANES III, conducted in 1988–1991, commented that of the multiple sources of exposure, Pb-based paint is the principal high-dose source of Pb. Exposure occurs not only through the direct ingestion of flaking and chalking paint, but also through the inhalation of dust and soil contaminated with paint (Brody et al. 1994). According to a study by the New York State Department of Health, renovation and remodeling activities that disturb Pb-based paints in homes can produce significant amounts of Pb dust, which can be inhaled or ingested (CDC 1997a).

5.4 ENVIRONMENTAL FATE

The atmosphere is the main environmental transport media for Pb that is deposited onto surface water and soils (EPA 2006, 2014c). Upon release to the atmosphere, Pb particles are dispersed and ultimately removed from the atmosphere by wet or dry deposition. Pb deposition is typically greatest closer to Pb emission sources. An important factor in determining the atmospheric transport of Pb is particle size distribution. Large particles settle out of the atmosphere more rapidly and are deposited relatively close to emission sources and smaller particles may be transported much farther distances. After deposition, particles may be resuspended and redeposited. The cycling of Pb in aquatic environments is governed by chemical, biological, and mechanical processes. The exchange between sediment and surface water will be affected by pH, ionic strength, formation of organic complexes with Pb ions, and oxidation-reduction potential of the environment (EPA 2006, 2014c).

5.4.1 Transport and Partitioning

Transport and partitioning of Pb in the environment is an interplay of various processes (EPA 2014c). Global atmospheric deposition of Pb peaked in the 1970s and has declined since then; however, these deposits are still in the environment and can be transported and partitioned between environmental compartments. Past and current releases of Pb to the air result in the deposition of Pb on land and in surface water. While soil is a repository for Pb, it is not a passive repository, and resuspension of Pb contaminated soil-derived dust particulates can contribute to Pb exposure (Laidlaw and Filippelli 2008; Laidlaw et al. 2012). Pb in soil can be washed off surfaces into waters, and within water, it can partition between water and sediments (EPA 2006, 2014c).

Air. EPA (2006) summarized that the major pathway for the transport of Pb in the environment is the atmosphere and that airborne Pb tends to be in the form of submicron aerosols, which can travel large distances. After release to the atmosphere, Pb particles are dispersed and ultimately removed from the atmosphere by wet or dry deposition. Dry deposition was the major removal process for Pb in coarse particulate matter and wet deposition was the most important removal process for fine particulate matter. Soil-bound Pb and contaminated road dust can be resuspended and can be a significant source of airborne Pb in areas near major sources of Pb emissions (EPA 2006, 2014c).

In the atmosphere, non-organic compounds of Pb exist primarily in the particulate form. The median particle distribution for Pb emissions from smelters is 1.5 μm, with 86% of the particle sizes under 10 μm (Corrin and Natusch 1977). The smallest Pb-containing particulate matter (<1 μm) is associated with

high-temperature combustion processes. Upon release to the atmosphere, Pb particles are dispersed and ultimately removed from the atmosphere by wet or dry deposition. Approximately 40–70% of the deposition of Pb is by wet fallout; 20–60% of particulate Pb once emitted from automobiles is deposited near the source. An important factor in determining the atmospheric transport of Pb is particle size distribution. Large particles, particularly those with aerodynamic diameters of >2 μm, settle out of the atmosphere more rapidly and are deposited relatively close to emission sources (e.g., 25 m from the roadway for those size particles emitted in motor vehicle exhaust in the past); smaller particles may be transported thousands of kilometers away from the emission source.

The amount of Pb scavenged from the atmosphere by wet deposition varies widely; wet deposition can account for 40–70% of Pb deposition depending on such factors as geographic location and amount of emissions in the area (Nielsen 1984). An annual scavenging ratio (concentration in precipitation, mg/L, to concentration in air, $\mu g/m^3$) of $0.18x10^{-6}$ has been calculated for Pb, making it the lowest value among seven trace metals studied (iron, aluminum, manganese, copper, zinc, cadmium); this indicates that Pb (which initially exists as fine particles in the atmosphere) is removed from the atmosphere by wet deposition relatively inefficiently.

While Pb particles from automobile emissions are quite relatively small (<0.1 μm in diameter), they may coagulate to form larger particulates (Chamberlain et al. 1979). Pb has been found in sediment cores of lakes in Ontario and Quebec, Canada far from any point sources of Pb releases, suggesting that long-range atmospheric transport was occurring (Evans and Rigler 1985). Sabin and Schiff (2008) reported that median dry deposition fluxes along a coastal transect in southern California ranged from 0.52 to 14 $\mu g/m^2$-day in 2006. Pb fluxes ranged from 20 to 330 $\mu g/m^2$-day in 1975. Osterberg et al. (2008) reported elevated concentrations of Pb in a 1970–1998 ice core from the summit of Mt. Logan, Canada, and indicated that elevated levels correspond to increased industrial activity in Asia over the same time period. Mean Pb concentrations in the 1970–1998 portion were 68.9 ng/L, more than 10-fold above the natural background (5.6 ng/L).

Pb in soil in urban areas of older cities may be a source of airborne Pb (Laidlaw and Filippelli 2008). Studies of the Pb species found in airborne particulate matter collected in El Paso, Texas found that Pb-humate was the dominant form of Pb in air samples. Pb-humate, a stable, sorbed complex formed in the humus fraction of Pb contaminated soil, is the major Pb species in soils in El Paso (Pingitore et al. 2009). In a review, Cho et al. (2011) noted that studies over the past 40 years have shown that there has been a shift of airborne particle bound Pb to larger sizes of particulate as concentrations of Pb in urban areas

have decreased. They note that this shift has occurred as the use of leaded gasoline was phased-out and that industrial emissions and resuspension of road dust became more important sources of Pb. In addition to soil-derived dust, re-entrainment of dusts near highways and deteriorating Pb-based paint from elevated steel structures can contribute to airborne Pb (Sabi et al. 2006; Weis et al. 2006). Studies suggest that there is long-range transport of Pb bound to particulate matter from industrial emissions. Dust samples from surface glaciers and in dust traps in remote areas on the west coast of New Zealand's South Island were identified as being both Australian and New Zealand in origin. Samples were enriched in metals, including Pb, and the degree of metal enrichment indicted that they were transported from eastern Australia (Marx et al. 2008).

Water. The amount of soluble Pb in surface waters depends upon the pH and the ionic strength of the water. Equilibrium calculations show that at pH >5.4, the total solubility of Pb is approximately 30 μg/L in hard water and approximately 500 μg/L in soft water. Sulfate ions, if present in soft water, limit the Pb concentration in solution through the formation of Pb sulfate. Above pH 5.4, the Pb carbonates, $PbCO_3$ and $Pb_2(OH)_2CO_3$, limit the amount of soluble Pb. The carbonate concentration is in turn dependent upon the partial pressure of carbon dioxide, pH, and temperature (EPA 1986).

A significant fraction of Pb carried by river water is expected to be in an undissolved form, which can consist of colloidal particles or larger undissolved particles of Pb carbonate, Pb oxide, Pb hydroxide, or other Pb compounds incorporated in other components of surface particulate matters from runoff. Pb may occur either as sorbed ions or surface coatings on sediment mineral particles, or it may be carried as a part of suspended living or nonliving organic matter in water.

Sediment and Soil. EPA (2006, 2014c) reviewed and summarized the factors affecting the behavior of Pb in soil. While Pb is relatively immobile in soil and has a long retention time in most soils, it has some capacity to leach through the soil column and potentially contaminate groundwater. Pb sorbs strongly to soil components and is only weakly soluble in pore water, making the leaching of Pb in soil a slower process as compared to other contaminants. Various soil conditions and characteristics affect the sorbing capacity of the soil and the solubility of contaminants including hydraulic conductivity of the soils, composition of the soil solution, organic matter, clay mineral content of the soil, pH, and microbial activity (EPA 2006). In soil, Pb can be partitioned between the soil water, precipitate forms, secondary iron and manganese oxides, carbonates, organic matter, sulfides, or the surfaces of clay, humus, or silicate particles. Pb adsorbed to the surfaces of colloid soil particles (e.g., organic matter, clay, oxides, and carbonates) are the most labile fraction. High chloride content in soil also enhances Pb solubility. At low

pH, metal species bound to carbonates, hydroxides, and other soil components are more likely to dissolve into solution, increasing rates of Pb migration through the soil. EPA (2014c) reported that soil pH is the most important factor affecting solubility, mobility, and phytoavailability of Pb in soil; however, reducing conditions (e.g., anoxia) in soil also increase Pb mobility. In addition, dissolved organic matter is more important than iron oxyhydroxides in Pb mobility in soil.

The fate of Pb in soil is affected by the adsorption at mineral interfaces, precipitation of sparingly soluble solid forms of the compound, and formation of relatively stable organic-metal complexes or chelates with soil organic matter. These processes are dependent on such factors as soil pH, soil type, particle size, organic matter content of soil, presence of inorganic colloids and iron oxides, cation exchange capacity (CEC), and amount of Pb in soil (NSF 1977; Reddy et al. 1995). Soil samples were extracted from the Powder River Basin in Wyoming to determine the relative distribution and speciation of Pb and other metals in acidic environments (Reddy et al. 1995). At near neutral pH, organic carbon-Pb complexes were the predominant species in the soil water extracts. At low pH, dissolved Pb in ionic form (Pb^{2+}) and ion pairs (e.g., $PbSO_4$) were the predominant species. It was concluded that the mobility of Pb will increase in environments having low pH due to the enhanced solubility of Pb under acidic conditions. The accumulation of Pb in most soils is primarily a function of the rate of deposition from the atmosphere. Most Pb is retained strongly in soil, and very little is transported through runoff to surface water or leached to groundwater except under acidic conditions (EPA 1986; NSF 1977). Clays, silts, iron and manganese oxides, and soil organic matter can bind metals electrostatically (cation exchange) as well as chemically (specific adsorption) (Reed et al. 1995). Although sorption to organic matter in soil limits the rate and extent of leaching, Pb may enter surface waters as a result of erosion of Pb-containing soil particulates. Pb bromochloride, the primary form of Pb emitted from motor vehicles, which once burned leaded gasoline in the presence of organohalogen scavenger compounds, is converted to the less-soluble Pb sulfate either by reactions in the atmosphere or by reactions at the soil surface, thus limiting its mobility in soil. It has been determined that Pb oxides, carbonates, oxycarbonates, sulfates, and oxysulfates become the most prominent constituents of aged automobile exhaust particles (i.e., those collected at locations more remote from traffic sources) (Ter Haar and Bayard 1971). Pb may also be immobilized by ion exchange with hydrous oxides or clays or by chelation with humic or fulvic acids in the soil (Olson and Skogerboe 1975). In soils with pH ≥5 and with at least 5% organic matter content, atmospheric Pb is retained in the upper 2–5 cm of undisturbed soil. Inorganic Pb may be bound into crystalline matrices of rocks and remain essentially immobile; it can also occur in water entrapped in soil macro- and micropores (Reed et al. 1995). In soil with high organic matter content and a pH of 6–8, Pb may form insoluble organic Pb complexes; if the soil has less organic matter at the same pH, hydrous Pb

oxide complexes may form or Pb may precipitate out with carbonate or phosphate ions. At a pH of 4–6, the organic Pb complexes become soluble and leach out or may be taken up by plants (EPA 1986). Entrainment or suspension of soil particles in moving air is another route of Pb transport (EPA 1982c). This process may be important in contributing to the atmospheric burden of Pb around some Pb smelting facilities and NPL sites that contain elevated levels of Pb in soil.

The downward movement of elemental Pb and inorganic Pb compounds from soil to groundwater by leaching is very slow under most natural conditions except for highly acidic situations (NSF 1977). The conditions that induce leaching are the presence of Pb in soil at concentrations that either approach or exceed the CEC of the soil, the presence of materials in soil that are capable of forming soluble chelates with Pb, and a decrease in the pH of the leaching solution (e.g., acid rain) (NSF 1977). Favorable conditions for leaching may be present in some soils near Pb smelting and NPL sites. Tetraalkyl Pb compounds, such as tetraethyl Pb, are insoluble in water and would not be expected to leach in soil. However, they can be transported through a soil column when it is present in a migrating plume of gasoline (USAF 1995). In aqueous media, tetraalkyl Pb compounds are first degraded to their respective ionic trialkyl Pb species and are eventually mineralized to inorganic Pb (Pb^{2+}) by biological and chemical degradation processes (Ou et al. 1995).

In a study of Pb migration in forest soils in Vermont, Miller and Friedland (1994) used Pb deposition time series and measurements of organic soil horizon Pb content made in 1966, 1980, and 1990 to compute dynamic response times for Pb storage in several types of soil. The authors concluded that maximum Pb concentrations in organic soil occurred around 1980, with concentrations of about 85 μg/g in soils of the northern hardwood forests of the study area and about 200 μg/g in soils of the spruce-fir forests. The large surge of atmospheric Pb deposited in these forests during the time when leaded gasoline was routinely used in motor vehicles is being redistributed in the soil profile rather than being retained in the organic horizon. Based on an analysis of Pb transit times through mineral soil horizons, the pulse of Pb may begin to be released to upland streams sometime in the middle of the next century (Miller and Friedland 1994). However, Wang et al. (1995) observed that Pb migration in forest soils is slowed considerably due to a decrease in solubility when Pb moves from the soil surface horizon to streams. Their results suggest that Pb is effectively trapped in the subsurface soil horizons, which may greatly reduce its release to streams.

Lewis et al. (2010) studied the distribution, chemical speciation, and mobility of Pb and antimony from small arms ammunition in a coarse-grained surface sand and reported that the transport of Pb was small in

this soil type. Ninety-three percent of the mass of the bullets was found in the top 30 cm of the sand. Pb was mostly associated with the following grain sizes in decreasing order >5.0 mm (~3.3 g/kg), 1.2–5.0 mm (~1.5 g/kg), and <0.06 mm (~0.25 m/kg). In the 0.06–0.6 mm fractions, Pb concentrations were just above background levels (0.0004 g/kg). Declining concentrations with depth has also been observed in clay/loam shooting range soils (Vantelon et al. 2005). Pb in the fine fraction (<2 mm) shooting range soils also showed a depth distribution, with the highest concentrations in the top 10 cm (Cao et al. 2003a, 2003b; Hui et al. 2002; Lin et al. 1995; Perroy et al. 2014; Selonen et al. 2012). In a study of various contaminant levels in soil at a major training facility used for testing military tanks and munitions, Pb concentrations in the 0–15 cm soil depth ranged from 249.2 to 1,963.7 mg/kg (Berthelot et al. 2008).

Flooding events can change the spatial distribution of Pb in soil and sediments (Lead ISA 2013). Zahran et al. (2010) and Presley et al. (2010) reported variations in Pb concentrations in soil samples from schoolyards in New Orleans, Louisiana before and after Hurricanes Katrina and Rita in 2005, with some sites increasing and others decreasing in Pb concentrations. Forty-six census tracts in New Orleans were sampled before and after Hurricanes Katrina and Rita; 29 of these showed a decline in Pb concentrations, with 6 samples >400 mg/kg. Prior to these hurricanes, 15 of 46 samples had Pb concentrations >400 mg/kg. Across the tracts, the average median Pb concentration deceased from 328.5 to 203.33 mg/kg (Zahran et al. 2010). Presley et al. (2010) reported similar trends. Of the 17 schoolyard sites that were sampled, 7 sites had concentrations exceeding Pb concentrations of 400 mg/kg in June 2005, and in January 2006, Pb concentrations at 3 sites exceeded this concentration. The geometric mean concentration of the sites decreased from 290.0 to 207.4 mg/kg; however, at two sites, Pb concentrations increased from 804.0 to 1,740.0 mg/kg and from 1,090.0 to 2,500.0 mg/kg. During a 4-day storm event, 2,400 tonnes of suspended particulate matter were transported in a historical mining, ore processing, and smelting region in the Czech Republic that contained various metals including 2,954 kg of Pb (Žak et al. 2009).

Other Media. Plants and animals may bioconcentrate Pb, but biomagnification is not expected. In general, the highest Pb concentrations are found in aquatic and terrestrial organisms with habitats near Pb mining, smelting, and refining facilities; storage battery recycling plants; areas affected by high automobile and truck traffic; sewage sludge and spoil disposal areas; sites where dredging has occurred; areas of heavy hunting and fishing (Pb from spent shot or sinkers); and urban and industrialized areas. Pb may be present on plant surfaces as a result of atmospheric deposition; its presence in internal plant tissues indicates biological uptake from the soil and leaf surfaces. Although the bioavailability of Pb in soil to plants is limited because of the strong adsorption of Pb to soil organic matter, bioavailability

increases with increased soil organic matter content and with decreased soil pH (more acidic). Plants grown in Pb-contaminated soils were shown to accumulate low levels of Pb in the edible portions of the plant from adherence of dusts and translocation into the tissues (Finster et al. 2004). Thirty-two different types of fruits or vegetables were grown in urban gardens with soils containing high Pb levels (27–4,580 mg/kg). Samples were harvested and washed with either water or detergents and analyzed for Pb content. Only one fruiting vegetable among 52 samples contained Pb levels greater than the detection limit of 10 μg/g in the edible portion. However, 39% of the leafy vegetables and herbs had Pb levels >10 μg/g in the edible shoot portion following washing of the vegetables with detergent and water (Finster et al. 2004).

Pb may be taken up in edible plants from the soil via the root system, by direct foliar uptake and translocation within the plant, and by surface deposition of particulate matter. The amount of Pb in soil that is bioavailable to a vegetable plant depends on factors such as cation exchange capacity, pH, amount of organic matter present, soil moisture content, and type of amendments added to the soil. Background agricultural soil Pb concentrations for major growing areas of the United States have been determined (Holmgren et al. 1993).

The influence of various combinations of soil amendments on Pb uptake by soybeans was studied for a metal-contaminated alluvial soil (Pierzynski and Schwab 1993). Addition of limestone was found to be most effective in reducing the bioavailability of metals (including Pb) as indicated by the reduction in labile soil metals, increased yields, and decreased soybean tissue metal content. Uptake of metals by lettuce and radishes grown in a loam soil spiked with cadmium chloride and Pb nitrate (from 100 to 1,000 mg/kg) was also studied (Nwosu et al. 1995). Results indicated that the mean uptake of Pb by lettuce increased as the concentration of Pb rose in the soil mixture. However, the uptake was low and this finding is inconsistent with other reports. Pb was not bioaccumulated by either plant regardless of soil Pb concentrations. The response of kidney bean growth to the concentration and chemical form of Pb in soils obtained near a zinc smelter in Japan has been studied (Xian 1989). It was found that the amount of Pb in the total plant (approximately 35–80 μg) correlated strongly with the concentration of Pb in the soil (0–240 mg/kg). The best relationship was found between the amount of metal uptake and the concentration of exchangeable and carbonate forms of Pb in the soil.

Uptake of Pb in animals may occur as a result of inhalation of contaminated ambient air or ingestion of contaminated plants. However, Pb is not biomagnified in aquatic or terrestrial food chains. Older organisms tend to contain the greatest body burdens of Pb. In aquatic organisms, Pb concentrations are

usually highest in benthic organisms and algae, and lowest in upper trophic level predators (e.g., carnivorous fish). Exposure of a fresh water fish to several sublethal concentrations of Pb for a period of 30 days showed significant accumulation of Pb in the blood and tissues. The Pb accumulation in tissues was found to increase with Pb in water up to a concentration of 5 mg/L (μg/mL); at concentrations of 10 and 20 mg/L, the Pb accumulation in the tissues, although indicating an increase, was not proportional to the Pb concentration in water (Tulasi et al. 1992). High bioconcentration factors (BCFs) were determined in studies using oysters (6,600 for *Crassostrea virginica*), fresh water algae (92,000 for *Senenastrum capricornutum*), and rainbow trout (726 for *Salmo gairdneri*). However, most median BCF values for aquatic biota were significantly lower: 42 for fish, 536 for oysters, 500 for insects, 725 for algae, and 2,570 for mussels (Eisler 1988). Pb is toxic to all aquatic biota, and organisms higher up in the food chain may experience Pb poisoning as a result of eating Pb-contaminated food. Organolead compounds, such as trialkyl and tetraalkyl Pb compounds, are more toxic than inorganic forms and have been shown to bioconcentrate in aquatic organisms.

Biomagnification of organolead compounds has not been found to occur. Depuration is relatively rapid, with half-life values of 30–45 hours for rainbow trout exposed to tetramethyl Pb. Tetraalkyl Pb compounds are more toxic than trialkyl Pb compounds, and ethyl forms are more toxic than methyl forms (Eisler 1988). Isolation of a *Pseudomonas aeruginosa* strain designated CHL004, which is able to remove Pb from solidified media and soil, has been reported (Vesper et al. 1996). The rate of uptake of Pb nitrate by CHL004 was very rapid initially and then decreased greatly.

5.4.2 Transformation and Degradation

As an element, Pb cannot be degraded in the environment, but may undergo various precipitation or ligand exchange reactions. Pb will typically be found in compounds with oxygen and sulfur, and may undergo oxidation-reduction reactions under different environmental conditions. Under most environmental conditions, Pb will most likely exist in its Pb(II) oxidation state. Pb can be complexed by various ligands present in the environment (e.g., fulvic and humic acids). Despite forming complexes with organic matter, it is unlikely that it would be incorporated into organic compounds under environmental conditions. Transformations of Pb compounds that occur during their movement through the environment will be between various inorganic compounds.

Air. According to EPA (2014c), Pb accumulated on airborne mineral dusts can be transformed into different compounds during transport. It was also noted that Pb can accumulate on coarse particulate

matter during transport in air and undergo chemical transformations. For example, Pb sulfate ($PbSO_4$), one of the main components of Pb-containing aerosols from coal combustion, can react with calcite ($CaCO_3$) in particulate matter to form various Pb carbonate compounds on the calcite surface. Another study included in the discussion noted that Pb levels in the PM_{10} fraction from dust storms collected in Israel were enriched with Pb at levels higher than those found in their source in the Sahara desert, suggesting that the dust samples accumulated Pb during transit between the Sahara desert and Israel (EPA 2014c).

Before the ban on sales of leaded gasoline, Pb particles were emitted to the atmosphere from automobile exhaust as Pb halides (mostly PbBrCl) and as double salts with ammonium halides (e.g., $2PbBrCl \cdot NH_4Cl$, $Pb_3[PO_4]_2$, and $PbSO_4$) (Biggins and Harrison 1979; Ter Haar and Bayard 1971). After 18 hours, approximately 75% of the bromine and 30–40% of the chlorine was released, and Pb carbonates, oxycarbonates, and oxides were produced. These Pb oxides are subject to further weathering to form additional carbonates and sulfates (Olson and Skogerboe 1975). Pb particles are emitted from mines and smelters primarily in the form of elemental Pb and Pb-sulfur compounds, $PbSO_4$, $PbO \cdot PbSO_4$, and PbS (Corrin and Natusch 1977; EPA 1986; Spear et al. 1998). The Pb emitted from the combustion of waste oil was found to be in the form of $PbCl_2$, PbO, and elemental Pb (Pb^0) (Nerin et al. 1999). In the atmosphere, Pb exists primarily in the form of $PbSO_4$ and $PbCO_3$ (EPA 1986).

While Pb is no longer added to gasoline for on-road use, the inorganic Pb degradation products of these organolead compounds may still be present in the environment. Based on the vapor pressure of tetraethyl Pb (0.26 mmHg at 25 °C) and tetramethyl Pb (26.0 mmHg at 20 °C), these two compounds exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al. 1981). When exposed to sunlight, they decompose rapidly to trialkyl and dialkyl Pb compounds, and eventually to inorganic Pb oxides by a combination of direct photolysis, reaction with hydroxyl radicals, and reaction with ozone. The half-life of tetraethyl Pb in reactions with hydroxyl radicals during summer is approximately 5.7 hours, based on a rate constant of 6.8×10^{-11} cm^3/molecule-second (Nielsen et al. 1991). The half-life for tetramethyl Pb is about 65 hours, based on a rate constant of 5.9×10^{-12} cm^3/molecule-second. In the winter, both compounds have half-lives of up to several days since the concentration of atmospheric hydroxyl radicals is lower than in summer months (DeJonghe and Adams 1986).

Water. The fate of Pb in water will be determined by the conditions of the water, including acidity (pH), ionic strength, oxidation-reductions potential, flow rate, and amount and composition of suspended materials (EPA 2014c). The pH of water is an important factor in determining the fate of Pb in water. At

neutral to more basic pH, Pb will tend to be complexed, precipitated, or sorbed to suspended sediments in water (EPA 2014c). Pb will form compounds of low solubility with the major anions found in natural waters. The maximum solubility of Pb in hard water is about 30 μg/L at pH>5.4 and the maximum solubility of Pb in soft water is approximately 500 μg/L at pH>5.4 (EPA 1977). In the environment, the divalent form (Pb^{2+}) is the stable ionic species of Pb. Hydroxide, carbonate, sulfide, and, more rarely, sulfate may act as solubility controls in precipitating Pb from water. At pH<5.4, the formation of Pb sulfate limits the concentration of soluble Pb in water, while at pH>5.4, the formation of Pb carbonates limits the amount of soluble Pb (EPA 1979). The relatively volatile organolead compound, tetramethyl Pb, may form as a result of biological alkylation of organic and inorganic Pb compounds by microorganisms in anaerobic lake sediments; however, if the water over the sediments is aerobic, volatilization of tetramethyl Pb from the sediments is not considered to be important because the tetramethyl Pb will be oxidized (EPA 1979).

The speciation of Pb was found to differ in fresh water and seawater. In fresh water, Pb may partially exist as the divalent cation (Pb^{2+}) at pHs below 7.5, but complexes with dissolved carbonate to form insoluble $PbCO_3$ under alkaline conditions (Long and Angino 1977). Even small amounts of carbonate ions formed in the dissolution of atmospheric CO_2 are sufficient to keep Pb concentrations in rivers at the 500 μg/L solubility limit (EPA 1979). Pb chloride and Pb carbonate are the primary compounds formed in seawater (Long and Angino 1977). The speciation of Pb in water is also dependent on the presence of other ligands in water. Pb is known to form strong complexes with humic acid and other organic matter (Denaix et al. 2001; Gao et al. 1999; Guibaud et al. 2003). Pb-organic matter complexes are stable to a pH of 3 with the affinity increasing with increasing pH, but decreasing with increased water hardness (EPA 1979). In seawater, there is the presence of Pb complexed to Fe-Mn oxides, which is due to the content of these oxides in seawater (Elbaz-Poulichet et al. 1984). Sorption of Pb to polar particulate matter in fresh water and estuarine environments is an important process for the removal of Pb from these surface waters. The adsorption of Pb to organic matter, clay, and mineral surfaces, and coprecipitation and/or sorption by hydrous iron and manganese oxides increases with increasing pH (EPA 1979).

Sediment and Soil. Pb in its naturally-occurring mineral forms is a component of many soils in the United States. The speciation of Pb in soils is dependent upon the properties of the soil. In a calcareous soil, $PbSO_4$ and $PbCO_3$ were shown to account for <5% of the total Pb content, whereas in roadside dust, $PbSO_4$, elemental Pb, Pb_3O_4, $PbO{\cdot}PbSO_4$, and $2PbCO_3{\cdot}Pb(OH)_2$ were present in significant quantities (Chaney et al. 1988). It was also reported that after adding 3,000–4,000 mg/kg of Pb in the form of

$PbSO_4$, subsequent extractions revealed that the Pb sulfate was rapidly transformed to other Pb compounds in the soil (Chaney et al. 1988).

Nearly all forms of Pb that are released to soil from anthropogenic sources, such as elemental Pb, $PbSO_4$, $PbCO_3$, PbS, $Pb(OH)_2$, $PbCrO_4$, and PbClBr, are transformed by chemical and biotic processes to adsorbed forms in soil (Chaney et al. 1988). The transformation process involves the formation of Pb complexes with binding sites on clay minerals, humic acid and other organic matter, and hydrous iron oxides (Chaney et al. 1988; Chuan et al. 1996; Sauve et al. 1997). The ability of soils to bind Pb is dependent on soil pH and the cation exchange capacity of the soil components (e.g., hydrous iron oxides on clay and organic matter) (Chaney et al. 1988; EPA 1986). Only a small fraction (0.1–1%) of Pb appears to remain water-soluble in soil (Khan and Frankland 1983). The solubility of Pb in soil is dependent on pH, being sparingly soluble at pH 8 and becoming more soluble as the pH approaches 5 (Chuan et al. 1996). Between pH 5 and 3.3, large increases in Pb solubility in soil are observed. These changes in Pb solubility appear to correlate with the pH-dependent adsorption and dissolution of Fe-Mn oxyhydroxides. In addition to pH, other factors that influence Pb solubility in soil are total Pb content and the concentrations of phosphate and carbonate in soils (Bradley and Cox 1988; Ge et al. 2000; Pardo et al. 1990; Sauve et al. 1997).

Large particles of elemental Pb (e.g., shot and bullet fragments) degrade from weathering processes (Cao et al. 2003a, 2003b). Weathering includes physical transformation of larger particles to smaller particles (particle dissolution), as well as oxidation of the particle surface (coating) to PbO_2, with subsequent further oxidation to carbonates, phosphates, and sulfates (Cao et al. 2003a, 2003b; Hardison et al. 2004; Hashimoto 2013; Lewis et al. 2010; Lin et al. 1995; Rooney et al. 2007; Vantenlon et al. 2005). Particle dissolution rates for shotgun pellets in soils have been estimated to range from 1 to 20 mg/g pellet/year, depending on soil type, precipitation, and vegetation cover (Jorgenson and Willems 1987; Takamatsu et al. 2010).

Since the ban on the use of leaded gasoline, atmospheric Pb deposition to soil has decreased considerably. However, the deposited organolead compounds and their transformation products remain in the soil. Limited data indicate that tetraethyl and tetramethyl Pb are converted into water-soluble Pb compounds in soil through microbial metabolism (Ou et al. 1994). Using an Arredondo fine sand from Florida (92% sand, 7% silt, 1% clay, 11.8 g/kg organic carbon, pH 5.5), tetraethyl Pb was shown to degrade sequentially to monoionic triethyl Pb, diionic diethyl Pb, and eventually Pb^{+2} (Ou et al. 1994). Experiments were conducted using non-sterilized and autoclaved soil samples. The presence of

monoionic triethyl Pb and diionic diethyl Pb was generally lower in the autoclaved samples, suggesting that both abiotic and biotic mechanisms are responsible for the degradation of tetraethyl Pb. At the end of a 28-day incubation period, no tetraethyl Pb was present in the soil; however, there were significant quantities of monoionic triethyl Pb and diionic diethyl Pb, which suggest that the degradation products are more persistent than the original species. Although tetraethyl and tetramethyl Pb are not expected to leach significantly through soil, their more water-soluble metabolites may be subject to leaching (EPA 1985a).

Pb content in plants is largely the result of atmospheric deposition. This is due to the strong retention of particulate matter on plant surfaces that is difficult to remove through washing (EPA 1977). Uptake of Pb into plant tissue appears to involve a combination of uptake from the leaf surface and uptake from roots, with the relative contribution of each pathway dependent on species and soil characteristics (Angelova et al. 2010; Bindler et al. 2008; Chrastny et al. 2010; Cui et al. 2007; Guyette et al. 1991; Hu and Ding 2009; Nwosu et al. 1995). Pb taken up by the root systems remains largely associated with root tissues (Comino et al. 2011; Businelli et al. 2011; Deng et al. 2004; Mellem et al. 2009; Murray et al. 2009; Nan and Cheng 2001; Sonmez et al. 2008; Wang et al. 2011). Translocation from roots to stem and leaf tissue has been shown to occur in some species (Peralta-Videa et al. 2009; Shaheen and Tsadilas 2009; Tamura et al. 2005; Wang et al. 2006; Zaprjanova et al. 2010). Eventually, the Pb will be returned to soil when these plants decay unless they are harvested (to possibly enter the food chain) or removed.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to Pb depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of Pb in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on Pb levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-11 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-12.

Table 5-11. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	1.5 ng/cm^2 (XRF)	EPA, 1999, Method IO-3.3
	2.6 µg/sample	NIOSH 2017b, Method 7082
	6 µg/sample	NIOSH 1998, Method 7702
	0.02 µg/sample	NIOSH 1994c, Method 7105
	0.05 µg/sample	NIOSH 2016a, Method 7701
	0.062 µg/filter	NIOSH 2003c, Method 7300
	0.062 µg/filter	NIOSH 2003a, Method 7301
	0.023 µg/mL	NIOSH 2003b, Method 7303
	0.6 µg/sample	NIOSH 2014a, Method 7302
	1 µg/sample	NIOSH 2014b, Method 7304
	0.062 µg/sample	NIOSH 2015, Method 7306
	0.03 µg/mL	OSHA 2002, Method ID-121
	2.1 µg/sample	OSHA 2002, Method ID-125G
Drinking water	1.1 µg/L (ICP-AES) 0.02 µg/L (ICP-MS)	EPA 2003 Method 200.5 EPA 1994 Method 200.8
Surface water and groundwater	0.07 µg/L	EPA 1997b
	2.4 µg/L (GFAA) 0.28 µg/L (GFAA with preconcentration) 0.07 µg/L (ICP-MS)	EPA 1997b
	0.05 µg/L (ICP-MS) 60 µg/L (ICP-OES)	USGS 1998
	1 µg/L (GFAA) 1.1 µg/L (AVICP-AES)	USGS 1993
	10 µg/L (ICP) 100 µg/L (total recoverable, FLAA) 1 µg/L (whole water recoverable, GFAA) 0.5 µg/L (dissolved in water by GFAA) 100µg/L (suspended recoverable, FLAA) 100 µg/L (dissolved, FLAA)	USGS 1989
	0.6 µg/L (ICP-MS) 0.7 µg/L (GFAA) 10 µg/L (ICP-AES)	EPA 1994d
Soil/sediment	0.15 µg/g (ICP-MS) 0.2 µg/g (XRF) 0.2 µg/g (GF-AAS)	NOAA 1998
	10 µg/g (FLAA)	USGS 1989

Table 5-11. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Wipes	0.042 µg/wipe	NIOSH 2003d, Method 9102
	0.02 µg/cm² for 100-cm² area (FLAA or ICP); 0.001 µg/cm² for 100-cm² area (GF-AAS)	NIOSH 1996a, Method 9100
	Range: 5–15 µg/wipe sample	NIOSH 2003e, Method 9105

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

AES = atomic emission spectroscopy; AVICP = axially viewed inductively coupled plasma; FLAA = flame atomic absorption; GFAA = graphite furnace atomic absorption; GF-AAS = graphite furnace-atomic absorption spectrometer; GRAV = gravimetry; ICP = inductively coupled plasma; MS = mass spectrometry; OES = optical emission spectrometry; Pb = lead; XRF = x-ray fluorescence

Table 5-12. Lead Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	0.118	0.0075	13.8	1.451	657
Soil (ppb)	1,110	878	19.8	1.443	655
Air (ppbv)	0.00165	0.0025	32.6	84	50

[a]Concentrations found in ATSDR site documents from 1981 to 2015 for 1,832 NPL sites (ATSDR 2015). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Four national monitoring networks collect data on Pb concentrations in ambient air to report to the Air Quality System (AQS). State and local agencies carry out monitoring at state and local monitoring stations (SLAMS). These data are primarily used to evaluate compliance with the National Ambient Air Quality Standard (NAAQS) for Pb. Pb levels are also monitored in the Chemical Speciation Network (CSN), Interagency Monitoring of Protected Visual Environments (IMPROVE), and National Air Toxics Trends Station (NATTS) networks. Pb concentrations in air are measured in three particulate matter (PM) size fractions: total suspended particles (TSP), PM_{10}, and $PM_{2.5}$. The CNS and IMPROVE networks monitor Pb in $PM_{2.5}$ and the NATTS network monitors Pb in PM_{10}. These networks are designed to meet different objectives than those of the Pb NAAQS monitoring network (EPA 2006, 2014c). EPA (2014c) analyzed data from these monitoring systems and presented data summaries for

source-oriented (defined as near point sources and exceeded a defined emission threshold) and non-source-oriented Pb monitors across the United States for 2008–2010 (EPA 2014c). Maximum 3-month daily average Pb concentrations were calculated for non-source-oriented Pb-TSP monitors for 47 counties across the United States (1.5% of U.S. counties) and for source-oriented Pb-TSP monitors for 50 counties across the United States (1.6% of U.S. counties) during the period 2008–2010. Summaries of these analyses are presented in Table 5-13.

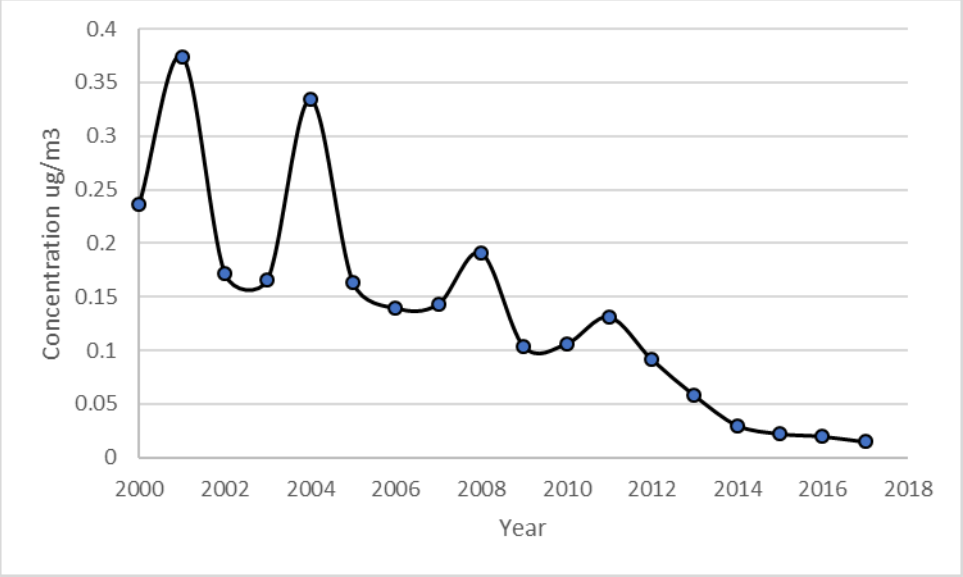
Table 5-13. Summary Data for Lead Monitors Across the United States, 2008–2010 (µg/m^3)

	Mean	Median	95th%	99th%	Maximum
Monthly (source-oriented)	0.20	0.063	0.86	1.6	4.4
Monthly (nonsource-oriented)	0.012	0.010	0.040	0.052	0.14

Source: EPA 2014c

Pb levels have been declining in the ambient air of the United States for several decades and according to the EPA, there has been approximately a 94% decrease since 2000 (EPA 2018a). Figure 5-3 shows the annual maximum 3-month average Pb level in the United States based upon data at 24 monitoring sites.

Figure 5-3. Annual Maximum 3-Month Average Representing the National Trend



Data compiled from the EPA AQS database from 2015 to 2018 were used to calculate the percentile distribution of arithmetic mean 3-month averages at locations across the United States. These data are summarized in Table 5-14.

Table 5-14. Percentile Distribution of Mean Lead (TSP) Concentrations (μg/m^3) Measured in Ambient Air at Locations Across the United States

	Percentile				
Year	25th	50th	75th	95th	Maximum
2015	0.0036	0.0090	0.0216	0.0753	0.1942
2016	0.0038	0.0093	0.0220	0.0782	0.1466
2017	0.0039	0.0080	0.0190	0.0756	0.2087
2018	0.0035	0.0090	0.0313	0.1248	0.5574

TSP = total suspended particles

Source: EPA 2018b

Pb in indoor air is related to Pb in housedust, and predominant sources are outdoor air and degraded Pb-based paint (EPA 2006). Smoking can also contribute to higher concentrations of Pb in indoor air. Pb concentrations in air and dust in the indoor environment were measured in residential homes as part of the National Human Exposure Assessment Survey (NHEXAS) in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin). Mean (±1 SD) and median concentrations of Pb in indoor air from 213 residences were 15.2 ng/m^3 (37.6 ng/m^3) and 6.17 ng/m^3, respectively, with a maximum value of 293.5 ng/m^3 (Bonanno et al. 2001). The median Pb concentration in outdoor air was 8.84 ng/m^3 (Clayton et al. 2002). Pb concentrations were higher in households where one or more residents smoked indoors (mean concentration of 21.8 ng/m^3) as compared to households with nonsmoking residents (mean concentration of 7.79 ng/m^3) (Bonanno et al. 2001). In dust collected from the living areas of 238 residences, the mean (±1 SD) and median Pb concentrations were 467.4 μg/g (2,100 μg/g) and 131.6 μg/g, respectively, with a maximum value of 30,578 μg/g. Dust samples collected from window sills had mean (±1 SD) and median Pb concentrations of 987 μg/g (2,723 μg/g) and 207.5 μg/g, respectively, with a maximum value of 21,120 μg/g. For both indoor air and dust measurements, higher concentrations of Pb were correlated with dilapidated and suburban homes. Dixon et al. (2009) analyzed children's exposures to residential dust Pb using data from the NHANES survey and associated demographics as well as smoking status to exposure levels. Children who resided in homes in which smoking occurred indoors had significantly (p=0.015) higher PbB levels than children who lived in homes of nonsmokers.

In another analysis of the NHEXAS EPA Region V data, Pellizzari et al. (1999) looked at potential differences in Pb concentrations in indoor air and personal air exposures between minorities (e.g., Hispanics and African-Americans) and nonminorities (e.g., Caucasian). Some differences were noted in the mean (±1 SD) Pb concentrations between minorities of 57 ng/m^3 (±24 ng/m^3) and nonminorities of 22 ng/m^3 (±3.4 ng/m^3) in personal air exposures, although the differences were not significant (p=0.147). Similarly, differences were noted between minorities (26±12 ng/m^3) and nonminorities (13±2.6 ng/m^3) in indoor air, although these were also not significantly different (p=0.266). When the age of the home was considered in the analysis, it was found that Pb concentrations were significantly (p=0.036) higher in homes built before 1940 than in homes built between 1960 and 1979, with mean (±1 SD) values of 46 ng/m^3 (±1.6 ng/m^3) and 13 ng/m^3 (±2.1 ng/m^3), respectively. The Pb concentrations measured in indoor air in homes built before 1940 were not significantly different from mean (±1 SD) Pb concentrations of 22 ng/m^3 (±5.1 ng/m^3) and 23 ng/m^3 (±5.1 ng/m^3) measured in indoor air in homes built between 1940 and 1959 and between 1980 and 1995, respectively.

5.5.2 Water

Pb has been monitored in surface water, groundwater, and drinking water throughout the United States and other countries. The concentration of Pb in surface water is highly variable depending upon sources of pollution, Pb content of sediments, and characteristics of the system (pH, temperature, etc.). Pb concentrations in surface water are generally higher in urban areas than in rural areas (EPA 1982c), and Pb measured in natural or "pristine" surface waters may be due to anthropogenic input. Western Airborne Contaminants Assessment Project (WACAP) data collected at five U.S. National Parks showed median Pb levels in surface waters ranging from 0.006 to 0.075 μg/L (EPA 2014c). The median Pb level in natural river water was 5 μg/L, with a range of 0.6–120 μg/L; however, lower Pb levels are to be expected after leaded gasoline was banned in 1985, which resulted in decreased rates of atmospheric deposition (Bown et al. 1966; King et al. 2014). The National Academies of Science reported Pb concentration levels in surface water and groundwater (EPA 1986). The mean Pb concentration level in surface water was 4 μg/L with a range from below the detection limit to 890 μg/L (EPA 2014c); concentrations >100 μg/L were observed near sources of urban runoff or industrial discharge. Mean levels of Pb in surface water measured at 50,000 surface water stations throughout the United States were 3.9 μg/L (based on 39,490 occurrences) (Eckel and Jacob 1988). Using the EPA Storage and Retrieval (STORET) database, from January 1, 2005 to May 16, 2005, Pb had been detected in surface water in Washington, Utah at concentrations of 20.5 and 142 μg/L and surface water from Salt Lake City, Utah at 7.75 μg/L (EPA 2005b). Pb was not detected above the detection limits in 224 other surface water samples obtained

from various locations in Utah and Iowa over the sampling period (EPA 2005b). Pb content in groundwater is driven largely by the surrounding bedrock geochemistry; Pb concentrations are generally low in groundwater and natural springs ranging from below the detection limit to 100 µg/L (EPA 2014c). Pb levels in seawater are estimated as 0.005 µg/L (EPA 1982c).

Urban storm water runoff is an important source of Pb entering receiving waterways. Sources of Pb in runoff can be contributed to substantial direct atmospheric deposition, as well as indirect release from building materials, soil, and road dust, and industrial discharge. Pb is found in building material (brick, concrete, painted and unpainted wood, roofing, and vinyl), and automotive sources (brakes, used oil), which contribute to runoff (Davis et al. 2001). The largest contributing sources were siding and roofing. Soto-Jiménez-Flegal (2009) evaluated the sources of Pb pollution in the Gulf of California, northwest Mexico by sampling urban and rural areas for Pb levels and isotope ratios. Urban street dust (157 µg/g), agricultural soils (29.0 µg/g), and surface estuary sediments (35.6 µg/g) were all higher than natural bedrock (16.0 µg/g). Isotopic ratios in rural and soil runoff samples were comparable to natural Pb containing bedrock. Pb concentrations in the suspended particulate matter were measured in sewage effluent (132 µg/g), agricultural effluent (29.3 µg/g), river runoff (7.3 µg/g), and estuary water (68.3 µg/g). Urban, street dust, and sewage showed contributions from automotive emissions from past leaded gasoline combustion.

Pb in drinking water can derive from source water contamination as described above, but the more common source of Pb in drinking water is from internal corrosion of water distribution system piping and plumbing. Internal corrosion of Pb service lines, Pb-based pipe solder, brass meters and plumbing fixtures, and dissolution of existing protective scales contribute directly to Pb levels in drinking water. The Lead and Copper Rule (LCR) was promulgated in 1991 with the purpose of protecting public health by minimizing Pb and copper levels in drinking water, primarily by reducing water corrosivity (EPA 2004). The LCR established a Pb action level (AL) of 15 µg/L and a maximum contaminant level goal (MCLG) of zero. The Pb action level is based on feasibility of public water systems to control corrosion in their distribution systems and is not a health benchmark for Pb in drinking water. The Pb action level is exceeded if the concentration of the 90th percentile first draw tap sample (collected after a minimum stagnation period of 6 hours from high risk sites) exceeds 15 µg/L (EPA 2016g). If the Pb AL is exceeded, the LCR can require public water systems to take steps to minimize the risk of Pb exposure that may include source water monitoring/treatment, public education, water quality monitoring, implementing corrosion control treatment, and Pb service line replacement.

The amount of Pb contained in pipes and plumbing fittings has been strictly regulated since 1986. Section 1417 of the Safe Drinking Water Act (SDWA) was amended to ban the use of service lines, pipe fittings, pipe solder, and fixtures that are not "Pb free" (not more than 0.2% Pb for pipe solder and flux, and not more than 8% Pb for pipe fittings and service lines) and are connected to a public water system and intended to provide water for human consumption. The 1996 Amendment broadened this ban by limiting the amount of leaching of Pb from new plumbing, and an industry standard was established. In 2011, the Reduction of Lead in Drinking Water Act amended Section 1417, revising the existing SDWA definition of "Pb free" and getting rid of the leaching certification requirement. Implemented in 2014, the act reduced the allowable level of Pb by "not more than a weighted average of 0.25 percent Pb when used with respect to the wetted surfaces of pipes, pipe fittings, plumbing fittings and fixtures."

Analyses done in support of the short-term revisions to the LCR suggest that in 2003, <2% of public water systems serving >3,300 people exceeded the Pb action level of 15 μg/L (EPA 2007a). Additionally, a 2004 study conducted by the EPA on LCR compliance monitoring for public water systems serving >3,300 people indicated that <4% of those systems exceeded the Pb action level (Hill 2011). It is important to note that states were not required until 2002 to report 90th percentile Pb concentrations to the EPA unless those samples exceeded the Pb AL; therefore, it is difficult to accurately compare differences between tap water Pb levels prior to LCR implementation and immediately following LCR implementation with current nationwide Pb concentration levels (Hill 2011). Nevertheless, the EPA evaluated water sample data from 166 large public water systems (systems serving >50,000 people) that exceeded the Pb AL in 1992 and 1993 (Hill 2011). Of the large systems that exceeded the Pb AL in 1992–1993, only 15 of those systems continued to exceed the Pb AL between 2000 and 2004, and their associated average 90th percentile Pb concentration levels significantly decreased from 32 to 8.2 μg/L.

According to EPA's National Public Water Systems Compliance Report for calendar year 2013 (EPA 2013), 73% of public water systems in the United States, serving approximately 77% of the population, had no significant reported violations of any type. Significant violations include all violations of health-based standards, including violations of the maximum contaminant levels, treatment technique requirements, and significant monitoring and reporting requirements. In 2013, 7% of public water systems had no reported violations of health-based standards, and 5% of all health-based standard violations were LCR violations.

5.5.3 Sediment and Soil

Pb is a naturally occurring metal found in the earth's crust at about 15–20 mg/kg (Goyer 2001). However, the concentration of Pb in the top layers of soil varies widely due to deposition and accumulation of atmospheric particulates from anthropogenic sources. The concentration of soil Pb generally decreases as distance from contaminating sources increases. The estimated Pb levels in the upper layer of soil beside roadways are typically 30–2,000 μg/g higher than natural levels, although these levels drop exponentially up to 25 m from the roadway (EPA 1986). Soil adjacent to a smelter in Missouri had Pb levels in excess of 60,000 μg/g (Palmer and Kucera 1980). Soils adjacent to houses with exterior Pb-based paints have reported Pb levels >10,000 μg/g (EPA 1986). As a result of Pb reactions with the soil, extractable Pb in surface soil samples (0–5 cm depth) from an agricultural area near a car battery manufacturing plant (taken at 0.3 km from the source) decreased from 117 to 1 μg/g within 1 year after the plant stopped operating (Schalscha et al. 1987). Soil collected by scraping the top 2.5 cm of soil surface near homes and streetside in Louisiana and Minnesota contained median Pb concentrations of >840 μg/g in New Orleans and 265 μg/g in Minneapolis. In contrast, the small towns of Natchitoches, Louisiana, and Rochester, Minnesota had soil Pb concentrations of <50 and 58 μg/g, respectively. These data suggest that Pb-contaminated soil is a major source of Pb exposure in urban areas (Mielke 1993). As would be expected, soils in elementary school properties were also found to have the same pattern of Pb levels as the soils in the surrounding residences. Pb concentrations in soils collected from inner-city schools in New Orleans were higher (median concentration of 96.5 μg/g) than soils collected from mid-city (30.0 μg/g) and outer-city (16.4 μg/g) elementary schools (Higgs et al. 1999).

The former use of Pb in paints, particularly in older structures, is also a source of Pb in soil and within homes. Meilke and Gonzales (2008) reported median Pb concentrations of 76,603 mg/kg (464–317,151 mg/kg) and 416 mg/kg (24–63,313 mg/kg) for exterior and interior paints, respectively, in 40 paint chip samples collected from homes in metropolitan New Orleans. The authors noted that the age of the house is often used as a surrogate for the amount of Pb in paints; the mid-1920s being the peak use of leaded paint with declines until 1978. Demolition and renovation of buildings where leaded paint was used can result in transport of Pb to soil surrounding the building as well as indoor dust that contains Pb.

Pb concentrations were measured in residential transects through Lubbock, Texas. Pb concentrations through the city showed a trend of decreasing Pb concentrations with increasing distance from the city center, which also paralleled a decrease in the property age. The highest Pb concentration in the city center were 90.0–174.0 mg/kg, with a median of 35.4 mg/kg, and decreased out to the farther part of the

residential transect to 6.0–9.0 mg/kg. The highest concentrations outside city development were 4.9 mg/kg (Brown et al. 2008).

Studies conducted in Maryland and Minnesota indicate that within large, light-industrial, urban settings such as Baltimore, the highest soil Pb levels generally occur near inner-city areas, especially where high traffic flows have long prevailed (Mielke et al. 1983, 1984, 1989) and that the amount of Pb in the soil is correlated with the size of the city (Mielke 1991). In 1981, soil Pb levels in the Minneapolis/St. Paul inner-city area were 60 times higher (423 μg/g) than levels found in rural Minnesota (6.7 μg/g), with almost all the increase (95%) resulting from the combustion of leaded gasoline. A study conducted in Minneapolis, Minnesota, after the Pb content of gasoline had been significantly reduced, found that median soil Pb levels taken from the foundations of homes, in yards, and adjacent to the street were 700, 210, and 160 μg/g, respectively; median soil Pb concentrations in comparable samples from the smaller city of Rochester, Minnesota, did not exceed 100 μg/g at any location tested (Mielke et al. 1989). The Minneapolis data suggested that average Pb levels were elevated in soil samples taken from the foundations of homes, but that Pb levels were low (<50 μg/g) in areas where children could be expected to play, such as parks that were located away from traffic, but were higher in play areas around private residences. Soil samples taken from around the foundations of homes with painted exteriors had the highest Pb levels (mean concentrations of 522 μg/g), but levels around homes composed of brick or stucco were significantly lower (mean concentration 158 μg/g) (Schmitt et al. 1988). Severely contaminated soils (levels as high as 20,136 μg/g) were located near house foundations adjacent to private dwellings with exterior Pb-based paint. Elevated soil Pb concentrations were found in larger urban areas, with 27, 26, 32, and 42% of the soil samples exceeding 300 μg/g Pb in Duluth, inner-city North Minneapolis, inner-city St. Paul, and inner-city South Minneapolis, respectively. Only 5% of the soil samples taken from the smaller urban areas of Rochester and St. Cloud, Minnesota, had Pb levels >150 μg/g. It has been suggested that the higher Pb levels associated with soils taken from around painted homes in the inner city are the result of greater atmospheric Pb content, resulting from the burning of leaded gasoline in cars and the washdown of building surfaces to which the small Pb particles adhere by rain (Mielke et al. 1989). A state-wide Minnesota study concluded that exterior Pb-based paint was the major source of contamination in severely contaminated soils located near the foundations of private residences and that aerosol Pb accounted for virtually all of the contamination found in soils removed from the influence of Pb-based paint. Contamination due to Pb-based paint was found to be “highly concentrated over a limited area, while contamination due to aerosol Pb was found to be less concentrated, but more widespread” (Schmitt et al. 1988).

Pb was analyzed in dust wipes and soil samples from 67 public housing projects containing 487 dwelling units across the United States (Succop et al. 2001). A total of 5,906 dust wipes and 1,222 soil samples were included in the data set. The median soil levels were 194 ppm near the foundation, 177 ppm near the walkways, and 145 ppm elsewhere in the yard. The maximum level, 3,900 ppm, was found in a foundation sample. Median dust Pb loading (μg m^{-2}) from kitchens, living rooms, and two children's bedrooms were 151 (5^{th}–95^{th} percentile range: 22, 674), 936 (86, 10,190), and 8,560 (818, 313,000) for floor window sills and window troughs, respectively. Thirteen percent of the floor samples and 30% of the window sill samples from the rooms exceeded the HUD Interim Dust Lead Standards of 431 and 2,690 μg m^{-2} for floor and window sill samples, respectively.

5.5.4 Paint

Weathering and deterioration of Pb-based paint can contribute to the Pb content of dust and soil (Clark et al. 2004; Hunt et al. 1992; Jaeger et al. 1998; Lucas et al. 2013; Marcus and Elias 1995 <in Beard and Iske 1995>; MPCA 1987). A state-wide Minnesota study concluded that exterior Pb-based paint was the major source of contamination in severely contaminated soils located near the foundations of private residences (MPCA 1987). A soil Pb study in Minneapolis, Minnesota, found that soil samples taken from around the foundations of homes with painted exteriors had a mean concentration of 522 μg/g, while soil samples taken from around the foundations of brick or stucco had a mean concentration of 158 μg/g (Schmitt et al. 1988). Pb-based paint, removed from surfaces by burning (gas torch or hot air gun), scraping, or sanding have been found to result, at least temporarily, in higher levels of exposure for families residing in these homes. A 2006 survey of U.S. housing stock estimated that 35% of 106 million housing units contained Pb-based paint and that approximately 20% of houses contained deteriorating Pb-based pant (HUD 2011).

5.5.5 Other Media

Pb has been detected in a variety of foods and spices (Lin et al. 2010). Pb may be introduced into food through uptake from soil into plants or atmospheric deposition onto plant surfaces, during transport to market, processing, and kitchen preparation (EPA 1986). The ban on leaded gasoline as well as the use of welded (non-soldered) food cans during the 1980s are largely responsible for the decreases in levels of Pb in the U.S. diet beginning in the 1980s (FDA 2006). The FDA analyzed samples of foods commonly eaten by toddlers and infants for Pb and noted that levels of Pb in infant and toddler foods, on average, are relatively low (FDA 2016a). These results are summarized in Table 5-15. Selected data from the 2006–2011 FDA Total Diet Study Market Baskets are presented in Table 5-16 (FDA 2016b). Mean Pb levels in

dairy products (e.g., milk, cheese, ice cream, cream, yogurt) were generally low or below the detection limit. The dairy product category with the highest Pb level was for low-fat fruit-flavored yogurt, with a mean concentration of 0.002 mg/kg for 24 analyses. Mean concentrations of Pb in fruits and vegetable were also generally low, with the highest concentrations in raisins (0.005 mg/kg), spinach (0.004 mg/kg), and lettuce (0.004 mg/kg). Mean concentration of Pb in baby foods ranged from not detected to 0.013 mg/kg. The highest levels reported were found in sweet potatoes (0.013 mg/kg), arrowroot cookies (0.012 mg/kg), grape juice (0.011 mg/kg), teething biscuits (0.008 mg/kg), and apple-cherry juice (0.008 mg/kg). Based on a multimedia Pb exposure modeling analysis for children 1–5 years old, below the 70th percentile of PbB in the general U.S. population, dietary intake was a major background exposure pathway (Zartarian et al. 2017)

Table 5-15. Lead Levels in Foods Commonly Eaten by Toddlers and Infants

Product category	Average[a] (range) (µg/kg)	Number of samples
Cereal, infant/toddler (rice)	15.6 (5.0–82.0)	76
Cereal, infant/toddler (multigrain)	7.2 (6.0–8.0)	6
Cereal, infant/toddler (non-rice)	4.8 (0.4–17.0)	30
Apples[b]	3.3	10
Cereal, oat ring	7.8 (3.3–16.4)	30
Grapes	3.7 (3.3–7.6)	10
Juice, grape	5.6 (0.3–41.3)	30
Juice boxes and pouches	3.3 (0.3–17.0)	40
Peanut butter	5.3 (3.3–45.2)	29
Quinoa	22.2 (0.4–98.0)	30
Raisins	18.1 (1.8–151)	23
Stage 2 toddler foods	5.2 (1.0–22.2)	35
Teething biscuits	12.0 (2.0–131)	27
Toddler puffs	19.1 (3.3-–91.0)	31

[a]The average concentration reported for each product category was calculated using all values. For those samples with results below the detection limit, half of the detection limit was used to calculate the average.
[b]All of the apple samples were below the limit of detection.

Source: FDA 2016a

Table 5-16. Selected Mean Lead Concentrations in Food from the FDA Total Diet Study

Food	Mean (range) (mg/kg)[a]	Number of analyses	Number <LOD	LOD (mg/kg)
Syrup, chocolate	0.016 (0–0.027)	24	1	0.007
Apricots, canned in heavy/light syrup	0.015 (0–0.036)	24	1	0.007
Baby food, sweet potatoes	0.013 (0–0.034)	24	5	0.007
Peach, canned in light/medium syrup	0.013 (0–0.038)	24	2	0.007
Candy bar, milk chocolate, plain	0.013 (0–0.027)	24	5	0.01
Baby food, arrowroot cookies	0.012 (0–0.031)	24	9	0.01
Sweet potatoes, canned	0.012 (0–0.018)	24	2	0.007
Shrimp, boiled	0.012 (0–0.18)	24	18	0.01
Baby food, juice, grape	0.011 (0–0.02)	24	1	0.004
Fruit cocktail, canned in light syrup	0.011 (0–0.025)	24	4	0.007
Brownie	0.01 (0–0.032)	24	5	0.007

[a]Note: 1 mg/kg = 1,000 µg/kg.

FDA = U.S. Food and Drug Administration; LOD = limit of detection

Source: FDA 2016b

The U.S. Fish and Wildlife Service reported the concentrations of metals in a total of 315 composite samples of whole fish sampled from 109 stations nationwide from late 1994 to early 1995. For Pb, the geometric mean, maximum, and 85th percentile concentrations (µg/g wet weight) were 0.11, 4.88, and 0.22, respectively. The mean concentration of Pb was significantly lower than in the 1980–1981 survey. Pb concentrations in fish have declined steadily from 1976 to 1984, suggesting that reductions of leaded gasoline and controls on mining and industrial discharges have reduced Pb in the aquatic environment (Schmitt and Brumbaugh 1990).

In order to reduce Pb exposure from consumption of Pb-contaminated fish and shellfish, consumption advisories are issued by states recommending that individuals restrict their consumption of specific fish and shellfish species from certain water bodies where Pb concentrations in fish and shellfish tissues exceed the human health level of concern. This level of concern is set by individual state agencies and used to issue advisories recommending no consumption, or restricted consumption, of contaminated fish and shellfish from certain waterbody types (e.g., lakes and/or rivers). In 1995, the EPA Office of Water issued guidance to states on sampling and analysis procedures to use in assessing the health risks from consuming locally caught fish and shellfish. The risk assessment method proposed by EPA was specifically designed to assist states in developing fish consumption advisories for recreational and

subsistence fishers (EPA 1995a). These two groups within the general population consume larger quantities of fish and shellfish than the general population and frequently fish the same water bodies routinely. Because of this, these populations are at greater risk of exposure to Pb and other chemical contaminants if the waters they fish are contaminated. In 2007, eight advisories restricting the consumption of Pb-contaminated fish and shellfish were in effect in five states (Hawaii, Idaho, Washington, Kansas, and Missouri) and one territory (American Samoa) (EPA 2007b).

Elevated levels of Pb in the blood of cattle grazing near a Pb smelter have been reported, although no implications regarding Pb in beef were made. The mean Pb levels for the herd were highest near the smelter and decreased with distance. Ingestion of soil along with the forage was thought to be a large source of additional metal (Neuman and Dollhopf 1992). Evidence has also been shown for transfer of Pb to milk and edible tissue in cattle poisoned by licking the remains of storage batteries burned and left in a pasture (Oskarsson et al. 1992). Levels of Pb in muscle of acutely sick cows that were slaughtered ranged from 0.23 to 0.5 mg/kg (wet weight basis). Normal Pb levels in bovine meat from Swedish farms are <0.005 mg/kg. For eight cows that were less exposed, levels of Pb in milk taken 2 weeks after the exposure were 0.08±0.04 mg/kg. The highest Pb level found in the milk of eight cows studied for 18 weeks was 0.22 mg/kg. Pb in most milk samples decreased to values <0.03 mg/kg 6 weeks after exposure. Two affected cows delivered a calf at 35 and 38 weeks after the exposure. There was a high Pb level in the blood of the cows at the time of delivery, which suggests mobilization of Pb in connection with the latter stages of gestation and delivery. Pb levels in colostrum were increased as compared to mature milk samples taken 18 weeks after exposure. The concentration of Pb in milk produced after delivery decreased rapidly with time and was almost down to the limit of detection in mature milk.

In a survey, 324 multivitamin-mineral products were analyzed for Pb content (Mindak et al. 2008). Estimates of Pb exposure from these products were derived for four groups summarized in Table 5-17. The overall median value for Pb exposure was 0.576 µg/day. Five samples would have provided exposures that exceeded 4 µg/day. The authors reported that the estimates of Pb exposures were below the provisional total tolerable intake levels for the four population groups (Mindak et al. 2008). Twenty-one elements, including Pb, were analyzed in various botanical and dietary supplements; Pb concentrations ranged from not detected to 4.21 µg/g. None of the products analyzed would result in a maximum exposure that exceeds a tolerable level of exposure (Avula et al. 2010).

Table 5-17. Estimated Median and Maximum Lead Exposures

Population group	Median (µg/day)	Maximum (µg/day)
Young children (0–6 years)	0.123	2.88
Older children (7+ years)	0.356	1.78
Pregnant or lactating women	0.845	8.97
Adult women	0.842	4.92

Source: Adapted with permission from Mindak et al. (2008), American Chemical Society.

Many non-Western folk remedies used to treat diarrhea or other ailments may contain substantial amounts of Pb. Examples of these include: Alarcon, Ghasard, Alkohl, Greta, Azarcon, Liga, Bali Goli, Pay-loo-ah, Coral, and Rueda. In addition, an adult case of Pb poisoning was attributed to an Asian remedy for menstrual cramps known as Koo Sar. The pills contained Pb at levels as high as 12 ppm (CDC 1998). The source of the Pb was thought to be in the red dye used to color the pills. Pb was the most common heavy metal contaminant/adulterant found in samples (n=54) of Asian traditional remedies available at health food stores and Asian groceries in Florida, New York, and New Jersey (Garvey et al. 2001). Sixty percent of the remedies tested would give a daily dose of Pb in excess of 300 mg when taken according to labeling instructions. Pb poisoning has been caused by ingestion of a Chinese herbal medicine to which metallic Pb was added to increase its weight and sales price (Wu et al. 1996). Ayurveda is a traditional form of medicine practiced in India and other South Asian countries; the medications used often contain herbs, minerals, metals, or animal products and are made in standardized and nonstandardized formulations (CDC 2004). CDC (1998, 2002b) reported cases of elevated PbBs in children after consuming candy from Mexico or using various folk remedies. Elevated PbBs were reported in two 7-year-old children in Rhode Island. A sample of litargirio, which was used as an antiperspirant/deodorant, found in the home contained 79% Pb (CDC 2005).

During 2011–2012, six cases of Pb poisoning were associated with the use of 10 oral Ayurvedic medications made in India. Pb concentrations in these medications were as high as 2.4%. Blood Pb levels of these women ranged from 16 to 64 µg/dL (CDC 2012c). In 2004–2012, the New York City Department of Health and Mental Hygiene identified 22 oral medications, supplements, or remedies containing high levels of heavy metals, including Pb (Table 5-18).

Table 5-18. Lead Content in Ayurvedic Medications and Other Health Remedies

Product	Country where manufactured	Country where purchased	Lead content (ppm)
Calabash Chalk (Nzu)	Unknown	United States	6.6
Emperor's Tea Pill (concentrated)	China	United States	5,400
Garbha Chintamani Ras (Vrihat) (Swarna Yukt)	India	India	120
Garbha Dharak Yog	India	India	110
Garbhapal Ras	India	India	22,000
Garbhapal Ras	India	United States	15,000
Hepatico Extract (concentrated)	China	United States	5,900
Jambrulin	India	United States	243,000
Kankayan Bati (Gulma)	India	United States	12
Lakshmivilash Ras (Nardiya)	India	United States	260
Laxmana Louh	India	India	180
Maha Sudarshan	India	United States	41
Mahashakti Rasayan	India	India	9,400
Mahayogaraj Guggulu (enriched with silver)	India	United States	47,000
Ovarin	India	India	24,000
Pigmento	India	India	7.3
Pregnita	India	India	12,000
Sorin	India	India	46,707
Tierra Santa	Mexico	United States	13
Vasant Kusumakar Ras (with Gold and Pearl)	India	India	29
Vatvidhwansan Ras	India	United States	20,000
Vita Breath	United States	United States	1,100

Source: CDC 2012c

A study was conducted in an urban neighborhood in Chicago in order to gauge the levels of Pb in an array of fruits, vegetables, and herbs (Finster et al. 2004). The soil Pb concentrations where the plants were sampled varied from 27 to 4,580 ppm (median 800 ppm, geometric mean 639 ppm). Detectable Pb levels in the edible fruit, vegetables, and herbs sampled ranged from 11 to 81 ppm. Only one fruiting vegetable (cucumber 81 ppm) among the 52 sampled had detectable levels of Pb in the edible portion. However, 12 of the 31 leafy vegetables and herbs sampled contained Pb in the edible shoot part of the plant (range, 11–60 ppm). The Pb concentrations in the four samples of root vegetables ranged from 10 to 21 ppm. No significant correlation was found between the Pb concentrations in the edible portion of plant and the soil Pb level.

Pb may leach from Pb crystal decanters and glasses into the liquids they contain. Port wine that contained an initial concentration of 89 μg/L Pb was stored for 4 months in crystal decanters containing up to 32% Pb oxide. At the end of 4 months, Pb concentrations in the port were 5,331, 3,061, and 2,162 μg/L in decanters containing 32, 32, and 24% Pb oxide, respectively. Pb was also found to elute from Pb crystal wine glasses within minutes. Mean Pb concentrations in wine contained in 12 glasses rose from 33 μg/L initially to 68, 81, 92, and 99 μg/L after 1, 2, 3, and 4 hours, respectively (Graziano and Blum 1991).

Hair dyes and some cosmetics may contain Pb compounds (Cohen and Roe 1991). Hair dyes formulated with Pb acetate may have Pb concentrations 3–10 times the allowable concentration in paint. Measured Pb concentrations of 2,300–6,000 μg of Pb/gram of product have been reported (Mielke et al. 1997). Pb acetate is soluble in water and easily transferred to hands and other surfaces during and following application of a hair dye product. Measurements of 150–700 μg of Pb on each hand following application have been reported (Mielke et al. 1997). In addition to transfer of Pb to the hand-to-mouth pathway of the person applying the product, Pb can be transferred to any other surface (comb, hair dryer, outside of product container, counter top, etc.) that comes into contact with the product. It is also on the hair that it is applied to and the hands applying it. Objects coming into contact with hair dyed with a Pb-containing product also become contaminated. A dry hand passed through dry hair dyed with a Pb-containing product in cream form was been shown to pick up about 786 μg of Pb. A dry hand passed through dry hair dyed using foam or liquid Pb-containing hair dye products picked up less Pb: 69 μg/hand for foam products and 73 μg/hand for liquid products (Mielke et al. 1997). An elevated PbB (12 μg/dL) in an infant was observed after the use of tiro, a Nigerian eye cosmetic applied to the infant's eyes (CDC 2012a). Elevated PbBs (27.0 and 33.5 μg/dL) were reported in two young children in New Mexico after the use of kajal, a cosmetic imported from Afghanistan, that was applied to the children's eyelids. The kajal was reported to contain 54% Pb (CDC 2013). Sindoor, a cosmetic and cultural/religious powder used Hindu cultures, has been found to contain very high amounts of Pb (Lin et al. 2010).

Cases of Pb poisoning have been related to less common sources of exposure. Illicit "moonshine" whiskey made in stills composed of Pb-soldered parts (e.g., truck radiators) may contain high levels of Pb. Detectable levels of Pb with a maximum concentration of 5.3 mg/L were found in 7 of 12 samples of Georgia moonshine whiskey (Gerhardt et al. 1980). Of the 115 suspected moonshine samples seized by local law enforcement between 1995 and 2001 and analyzed by the Bureau of Alcohol, Tobacco, and Firearms, 33 samples (28.7%) contained Pb levels >300 μg/dL. The median and maximum levels were 44.0 and 53,200 μg/dL, respectively (Parramore et al. 2001).

Firing of Pb ammunition may result in exposure to Pb aerosols and dusts generated during gun or rifle discharge at levels up to 1,000 μg/m^3 (EPA 1985c), from Pb pellets ingested by or imbedded in animals that are used as food sources, and from Pb pellets or fragments imbedded in humans from shooting incidents (see Appendix C, Ingestion of Lead Debris). Exposures to airborne Pb dust from firearm discharge in indoor shooting ranges has been shown to result in increases in PbBs that are 1.5–2 times higher than preexposure concentrations (Greenberg and Hamilton 1999; Gulson et al. 2002). However, the use of copper-jacketed bullets, nonlead primers, and well-ventilated indoor firing ranges lessen the impact of airborne Pb on blood Pb levels (Gulson et al. 2002).

A Pb poisoning hazard for young children exists in imported vinyl miniblinds that had Pb added to stabilize the plastic. Over time, the plastic deteriorates to produce Pb dust that can be ingested when the blinds are touched by children, who then put their hands in their mouths (CPSC 1996). The U.S. Consumer Product Safety Commission (CPSC) has requested that manufacturers change the manufacturing process to eliminate the Pb. As a consequence, vinyl miniblinds should now be Pb-free. The CPSC recommends that consumers with young children remove old vinyl miniblinds from their homes and replace them with new miniblinds made without added Pb or with alternative window coverings.

Inexpensive metallic jewelry items specifically intended for children and teenagers have been shown to contain varying levels of Pb (Maas et al. 2005). A total of 311 chemical assays conducted using 285 jewelry items purchased in 20 different stores in California revealed that a considerable amount of Pb was added to the items, presumably to increase their weight or to impart some type of metallic coating to the surface of the item. The mean weight percentage of Pb for all 311 assays was 30.6%. Of the 311 samples tested, 169 contained at least 3% Pb by weight in at least one portion of the jewelry piece and 123 of the samples were found to contain >50% Pb by weight (Maas et al. 2005). In addition, 62 pieces of the purchased jewelry were tested for surface levels of Pb that could potentially be transferred dermally through the routine handling of these pieces. Using standard laboratory wipes, the surface of the jewelry pieces were wiped for a total of 20 seconds and subsequently analyzed for Pb content. Mean Pb levels in the wipes ranged from 0.06 to 541.97 μg. The authors characterized the potential Pb exposure from these dermal transfer experiments as either low exposure (<1 μg of Pb transferred to the laboratory wipe), moderate exposure (1–10 μg of Pb transferred to the laboratory wipe), high exposure (10–50 μg of Pb transferred to the laboratory wipe), and very high exposure (>50 μg of Pb transferred to the laboratory wipe). Approximately 35% of the 62 pieces tested were characterized as

having low exposure, 48% were characterized as moderate exposure, 11% were characterized as high exposure, and 5% were characterized as very high exposure (Maas et al. 2005).

5.6 GENERAL POPULATION EXPOSURE

Measurements of Pb in blood, urine, and tissues (postmortem) have been used to assess exposures of individuals to Pb. Table 5-19 shows the lowest limit of detections that are achieved by analytical analysis of blood, urine and tissues.

Table 5-19. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Whole blood/urine/tissue	0.05 µg Pb/g blood or mL urine	NIOSH 1994b, Method 8003
	1 µg/100 g blood; 0.2 µg/g tissue	NIOSH 1994a, Method 8005
Animal tissue	0.1 µg/g (ICP-MS or GFAA)	NOAA 1998

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

GFAA = graphite furnace atomic absorption; ICP-MS = inductively coupled plasma-mass spectrometry

Prior to the 1980s, aerolized Pb emissions from the use of leaded gasoline was the main source of Pb exposure for the general U.S. population. Aerolized Pb can be either inhaled or ingested after deposition on surfaces and food crops. Adult Pb exposures tend to be limited to occupational or recreational sources. For children, the primary source of Pb exposure is from surface dusts (on the ground or entrained) that contain Pb from a variety of sources including deteriorated Pb-based paint (Bornschein et al. 1986; CDC 2009; Dixon et al. 2009; Egeghy et al. 2005; EPA 1996c; Garavan et al. 2008; Gulson et al. 2009; Lanphear and Roghmann 1997; Lanphear et al. 1998a; Lewin et al. 1999; Malcoe et al. 2002; Mielke et al. 2007; Succop et al. 1998; Von Lindern et al. 2003, 2016; Zahran et al. 2013). Young children are particularly vulnerable to Pb exposure because of hand-to-mouth activity, which contributes to ingestion of Pb in surface dusts. Pb in the fine particle fraction of surface dusts (<150 µm) readily adheres to the skin surface, from which it can be inadvertently ingested from hand-to-mouth activity (Choate et al. 2006a, 2006b; Clausing et al. 1987; Davis and Mirick 2006; Davis et al. 1990; Siciliano et al. 2009; Yamamoto et al. 2006). Several studies have attempted to quantify soil and dust ingestion in children (Chien et al. 2017; Ozkaynak et al. 2011; Sedman et al. 1994; Stanek et al. 2012; Von Lindern et al. 2016; Wilson et al. 2013) and adults (Calabrese et al. 1990; Doyle et al. 2012; Irvine et al. 2014; Stanek et al. 1997).

Although air Pb can be a direct pathway of exposure in children, it can also be an indirect pathway from its effect on Pb concentration in surface dusts (Brunekreef 1984; Hayes et al. 1994; Hilts 2003; Rabinowitz et al. 1985; Schnaas et al. 2004; Schwartz and Pitcher 1989; Tripanthi et al. 2001). Second-hand smoke may also contribute to increased Pb exposure (Apostolou et al. 2012; Mannino et al. 2003; Richter et al. 2013). Dietary sources of Pb can originate from direct or indirect transfer of atmospheric Pb emissions to secondary media such as water, food crops, game, and fish. Pb in the maternal system can also be transferred to the fetus during gestation and to the nursing infant (EPA 2014c).

Several studies provided data with which dietary intakes of Pb for the general population in the United States have been estimated (FDA 2016 <TDS 2006–2011>; FDA 2016 -< Combination Metals Testing>; FDA 2016 <TDS 2006–2011>). An analysis of individual food intakes and PbB from NHANES (2006–2008) estimated that diet explained approximately 2.9% of the variations of PbB in children and 1.6% in adults (Davis et al. 2014). A randomized survey of 250 individuals (adults and children) from the Midwest United States conducted over the period 1995–1997 estimated average dietary Pb intake to be approximately 10 µg/day (Clayton et al. 1999). The EPA has estimated mean dietary Pb intakes in children ages 6–84 months to be approximately 2 µg/day (EPA 2014c). The ban on the use of welded (non-soldered) food cans during the 1980s has resulted in a decrease in Pb exposure from foods (FDA 2006). In recent surveys, the mean Pb levels in dairy products (e.g., milk, cheese, ice cream, cream, yogurt) were generally low or below the detection limit. Mean concentrations of Pb in fruits and vegetable were also generally low. Mean concentration of Pb in baby foods ranged from not detected to 0.013 mg/kg. Possible sources of Pb in food samples include introduction during processing or preparation with drinking water contaminated with Pb, deposition of Pb onto raw materials for each food, and Pb exposure in livestock that produce dairy or meat ingredients (EPA 2014c). Pb has also been reported in home-prepared reconstituted infant formula. Although, at one time, use of Pb solder in formula containers contributed to PbB from formula consumption (Ryu et al. 1983), this practice was phased out after 1970 in the United States and subsequently banned (FDA 1995). However, tap water remains a potential source of Pb in home-prepared formula at locations where tap water Pb concentrations are elevated. In a study conducted in the Boston area in 1997, 2 of 40 samples of home-prepared formula had Pb concentrations >15 µg/L. In both cases, the reconstituted formula had been prepared using cold tap water run for 5–30 seconds, drawn from the plumbing of houses >20 years old. Pb-containing ceramic ware used in food preparation has also been associated with childhood Pb exposure in children of Hispanic ethnicity in San Diego County, California. One study (Gersberg et al. 1997) used the IEUBK

Model to determine that dietary Pb exposure from beans prepared in Mexican ceramic bean pots may account for a major fraction of blood Pb burden in children whose families use such ceramic ware.

Generally, Pb is unlikely to be found in source water used for drinking water unless there is a specific source of contamination. The main source of Pb in drinking water is from the corrosion of Pb service lines, which are pipes constructed of pure Pb that connect the water distribution main to a building's internal plumbing. Other common sources of Pb in drinking water are exposed leaded solder or corroded fixtures containing Pb (EPA 2016). While Pb was restricted to no more than 8% in plumbing materials in 1986, older homes and neighborhoods may still contain Pb service lines, Pb connections, Pb solder, or other Pb-based plumbing materials that may contaminate drinking water during its delivery from its source to homes. Corrosion of these older plumbing materials can result in leaching of Pb into drinking water (CDC 2012b; Hanna-Attisha et al. 2016). Flint, Michigan is an example of how a water system with Pb sources in drinking water infrastructure resulted in elevated Pb levels in drinking water. For decades, the drinking water for the City of Flint was purchased from the Detroit Water and Sewer Department. This water had optimized corrosion control and was treated with orthophosphate, a corrosion inhibitor that reduces Pb solubility and leaching from leaded plumbing materials by the formation of protective scales on the pipe's interior surface. When the water source was changed to the Flint River in 2014, corrosion control was not implemented, which allowed Pb to leach into the drinking water (EPA 2017). Pb concentration in first-draw tap water tends to be higher than after the plumbing system has been flushed, although with Pb service lines, it is possible to see higher Pb concentrations in flushed water, if flushing is sufficient draw stagnant water from the service line to the tap. Gulson et al. (1997a) measured Pb in household water throughout the day when the plumbing system of an unoccupied test house was not flushed. Water concentration data ranged from 119 μg/L for the initial (first-draw) sample to 35–52 μg/L for hourly samples to 1.7 μg/L for a fully flushed sample. The 1991 LCR was implemented to protect public health by minimizing Pb and copper levels in drinking water, by primarily reducing water corrosivity (EPA 2010). The rule set a Pb action level of 15 μg/L based on 90^{th} percentile levels of tap water samples. The LCR established tap sampling monitoring requirements for public water systems. One-liter samples are taken at the tap where water has stood in the pipes for at least 6 hours (first-draw) in homes and buildings that are considered high-risk of Pb and copper contamination, and the number of samples are based on the system size. Pb action level exceedances can trigger a number of steps that a water system can take to reduce Pb exposure. These requirements include implementing a corrosion control treatment program, monitoring and/or treating source water, public education, and Pb service line replacement (EPA 2004).

Other less common sources of Pb exposure also exist. Exposure may also result from engaging in hobbies that use Pb (e.g., leaded solder is used in making stained glass, molten Pb used in casting, leaded glazes and frits are used in making pottery, and Pb compounds as coloring agents in glassblowing) (Grabo 1997). The use of inadequately glazed or heavily worn earthenware vessels for food storage and cooking may result in Pb exposure (CDC 1985; EPA 1986). Various folk remedies and Ayurvedic medication (CDC 1998, 2004, 2012c; Garvey et al. 2001; Wu et al. 1996) and some cosmetics (Mielke et al. 1997) may also be sources of Pb exposure. Moonshine consumption was strongly associated with elevated PbBs (Morgan and Parramore 2001). A 2000 study found a median PbB of 11 μg/dL among 35 moonshine consumers versus 2.5 μg/dL in 68 randomly-selected nonmoonshine consumers (Parramore et al. 2001). Exposure to infants and children can occur from mouthing of leaded jewelry and toys containing Pb or painted with leaded paint (CDC 2018c).

Plastic food wrappers may be printed with pigments that contain Pb chromates. Plastic wrappers used for 14 different national brands of bread collected in New Jersey contained a mean concentration of 26 mg of Pb for a bag size of 2,000 cm^2. A survey of 106 homemakers who buy such breads indicated that 39% of them reused the bags and 16% of the respondents turned the bags inside out to reuse them, suggesting that the potential exists for Pb leaching from the paint into the stored food (Weisel et al. 1991).

Blood Pb levels measured as a part of the NHANES revealed that between 1976 and 1991, the mean PbBs of the U.S. population aged 1–74 years old dropped 78%, from 12.8 to 2.8 μg/dL. The prevalence of PbBs ≥10 μg/dL also decreased sharply from 77.8 to 4.3%. The major cause of the observed decline in PbBs is most likely the removal of 99.8% of Pb from gasoline and the removal of Pb from soldered cans (Pirkle et al. 1994). Data from the Fourth National Report on Human Exposure to Environmental Chemical are summarized in Tables 5-20 and 5-21, which provide geometric means of Pb levels in the blood and urine in segments of the U.S. population.

Table 5-20. Geometric Mean Blood Lead Levels (μg/dL) and the 95th Percentile Confidence Interval, by Race/Ethnicity, Sex, and Age for the Years for 2011–2016

	Survey years	Geometric mean (95% confidence interval)	Sample size
Total	11–12	0.973 (0.916–1.04)	7,920
	13–14	0.858 (0.813–0.906)	5,215
	15–16	0.820 (0.772–0.872)	4,988
Age group			
1–5 years	11–12	0.970 (0.877–1.07)	713
	13–14	0.782 (0.705–0.869)	818
	15–16	0.758 (0.675–0.850	790

Table 5-20. Geometric Mean Blood Lead Levels (µg/dL) and the 95th Percentile Confidence Interval, by Race/Ethnicity, Sex, and Age for the Years for 2011–2016

	Survey years	Geometric mean (95% confidence interval)	Sample size
6–11 years	11–12	0.681 (0.623–0.744)	1,048
	13–14	0.567 (0.529–0.607)	1,075
	15–16	0.571 (0.523–0.623)	565
12–19 years	11–12	0.554 (0.511–0.601)	1,129
	13–14	0.506 (0.464–0.551)	627
	15–16	0.467 (0.433–0.504	1,023
20 years and older	11–12	1.09 (1.03–1.16)	5,030
	13–14	0.967 (0.921–1.02)	2,695
	15–16	0.920 (0.862–0.982)	2,610
Gender			
Males	11–12	1.13 (1.06–1.21)	3,968
	13–14	0.994 (0.919–1.08)	2,587
	15–16	1.13 (1.06–1.21)	3,968
Females	11–12	0.842 (0.796–0.890)	3,952
	13–14	0.746 (0.715–0.777)	2,628
	15–16	0.735 (0.679–0.795)	2,500
Race/ethnicity			
Mexican Americans	11–12	0.838 (0.767–0.916)	1,077
	13–14	0.746 (0.685–0.813)	969
	15–16	0.704 (0.659–0.759)	994
Non-Hispanic blacks	11–12	0.998 (0.947–1.05)	2,195
	13–14	0.871 (0.787–0.963)	1,119
	15–16	0.856 (0.763–0.962	1,070
Non-Hispanic whites	11–12	0.993 (0.914–1.08)	2,493
	13–14	0.882 (0.820–0.950)	1,848
	15–16	0.835 (0.774–0.900)	1,511
All Hispanics	11–12	0.855 (0.793–0.922)	1,931
	13–14	0.742 (0.695–0.793)	1,481
	15–16	0.703 (0.658–0.750)	1,664
Asians	11–12	1.15 (1.06–1.24)	1,005
	13–14	1.01 (0.923–1.11)	510
	15–16	1.07 (0.976–1.18)	479

Source: CDC 2018a

Table 5-21. Geometric Mean Urine Lead Levels (µg/dL) and the 95th Percentile Confidence Interval, by Race/Ethnicity, Sex, and Age

	Survey years	Geometric mean (95% confidence interval)	Sample size
Total	11–12	0.360 (0.328–0.396)	2,504
	13–14	0.277 (0.257–0.298)	2,664
Age group			
6–11 years	11–12	0.346 (0.292–0.410)	399
	13–14	0.222 (0.192–0.258)	402
12–19 years	11–12	0.259 (0.219–0.305)	390
	13–14	0.201 (0.166–0.245)	451
20 years and older	11–12	0.381 (0.348–0.416)	1,715
	13–14	0.297 (0.280–0.315)	1,811
Gender			
Males	11–12	0.414 (0.367–0.466)	1,262
	13–14	0.315 (0.295–0.337)	1,318
Females	11–12	0.316 (0.282–0.355)	1,242
	13–14	0.245 (0.222–0.269)	1,346
Race/ethnicity			
Mexican Americans	11–12	0.372 (0.320–0.431)	317
	13–14	0.277 (0.240–0.319)	453
Non-Hispanic blacks	11–12	0.431 (0.385–0.483)	669
	13–14	0.371 (0.320–0.429)	581
Non-Hispanic whites	11–12	0.346 (0.311–0.385)	820
	13–14	0.267 (0.245–0.290)	985
All Hispanics	11–12	0.372 (0.327–0.423)	573
	13–14	0.270 (0.239–0.305)	701
Asians	11–12	0.383 (0.341–0.429)	353
	13–14	0.257 (0.230–0.287)	292

Source: CDC 2018a

The Adult Blood Lead Epidemiology and Surveillance (ABLES) program tracks adult (aged ≥16 years) cases with elevated PbBs from workplace exposure. In 2016, 26 states submitted PbB data on 18,093 adults with PbBs ≥10 µg/dL. PbBs ≥10 µg/dL declined from 26.6 adults per 100,000 employed in 2010 to 15.8 per 100,000 employed in 2016 (results for data submitted as of December 2018). In 2016, among adults with known exposures, 90.3% had occupational exposure. The majority of these adults were employed in manufacturing, construction, mining, and services. Table 5-22 presents industries within each sector with the most workers with occupational exposures resulting in PbB ≥25 µg/dL during 2010–2016 (NIOSH 2017a).

Table 5-22. Industries by Sector with Most Workers having Blood Lead Concentrations (PbBs) ≥25 µg/dL, 2010–2016

NORA Sector	Industry NAICS Code
Manufacturing	Storage battery manufacturing (33591)
	Nonferrous metal (except copper and aluminum) rolling, drawing, extruding, and alloying (33149)
	Alumina and aluminum production and processing (33131)
	Nonferrous metal foundries (33152)
	Nonferrous metal (except aluminum) smelting and refining (33141)
	Other basic inorganic chemical manufacturing (32518)
	Motor vehicle electrical and electronic equipment manufacturing (33632)
Construction	Painting and wall covering contractors (23832)
	Highway, street, and bridge construction (23731)
	Residential building construction (23611)
	Plumbing, heating, and air-conditioning contractors (23822)
	Site preparation contractors (23891)
	Commercial and institutional building construction (23622)
Services (except public safety)	All other amusement and recreation industries (71399)
	Remediation services (56291)
	Automotive mechanical and electrical repair and maintenance (81111)
	Other services (except public safety industries) (71394)
Mining	Copper, nickel, lead, and zinc mining (21223)

NAICS = North American Industry Classification System; NORA = National Occupational Research Agenda

Source: NIOSH 2017a

Raymond and Brown (2015a, 2015b, 2017) and analyzed the 2007–2012 and 2009–2014 datasets from the Childhood Blood Lead Surveillance (CBLS) system. In 2007, a total of 38 states identified and reported 37,289 children (<6 years) with PbB ≥10 µg/dL. In 2012, a total of 30 jurisdictions identified and reported approximately 138,000 children (<6 years) with PbB ≥5 µg/dL. In 2012, federal funding ended and several states lost their state-wide Pb poisoning prevention programs and in 2013, the number of states reporting data declined, as did the number of children reported to the CDC with PbB ≥5 µg/dL. In October 2013, federal funding resumed and in 2013, 27 states, the District of Columbia, and New York City reported data. In 2014, 30 states, the District of Columbia, and New York City reported data. Table 5-23 summarizes the number and rate per 100,000 children aged <5 years with blood Pb levels 5–9 µg/dL reported in the 2010–2014 CBLS system. PbBs ≥10 µg/dL continue to be more prevalent among children with known risk factors, such as minority race or ethnicity, urban residence, residing in homes built prior to the 1950s, and low family income (CDC 2009).

Table 5-23. Number and Rate per 100,000 Children Aged <5 Years with Blood Lead Levels 5–9 µg/dL in the Childhood Blood Lead Surveillance System, United States, 2010–2014

	<1 Year		1–4 Years	
Year	Number	Rate	Number	Rate
2010[a]	18,598	448.48	137,887	805.62
2011[b]	13,981	352.69	130,838	810.56
2012[c]	7,876	199.74	95,854	596.58
2013[d]	5,494	138.26	57,293	360.46
2014[e]	5,904	148.51	70,680	444.49

[a]37 jurisdictions reporting.
[b]36 jurisdictions reporting.
[c]30 jurisdictions reporting.
[d]29 jurisdictions reporting.
[e]32 jurisdictions reporting.

Source: Raymond and Brown 2017

Various studies suggest that ingestion of game hunted with Pb shot is associated with increased PbBs. Johansen et al. (2006) collected blood samples from 50 men in Nuuk, Greenland to study the relationship between the consumption of birds hunted with Pb shot and PbBs. Men who regularly ate hunted birds killed with Pb shot had mean PbB ranging from 6.2 µg/dL in the group eating 0.1–5 bird equivalents per month to 12.8 µg/dL in those eating >30 bird equivalents per month. In addition, levels were highest in mid-winter when consumption of hunted birds was highest. Those who did not consume hunted birds had a mean PbB of 1.5 µg/dL. These results are consistent with earlier surveys of Arctic hunting communities. A 1992 survey of 492 Inuit adults from the Arctic region of Quebec, Canada showed that consumption of waterfowl, along with age and smoking, were associated with elevated PbB (Dewailly et al. 2001). The geometric mean PbB was 0.42 µmol/L (8.7 µg/dL), with a range of 0.04–2.28 µmol/L (0.8–47 µg/dL). In a cohort of Inuit newborns from northern Quebec, where the population consumed game killed with Pb shot, the geometric umbilical cord PbB was 3.9 µg/dL (range 0.2–27 µg/dL); 7% of Inuit newborns had cord PbBs >10 µg/dL as compared to 0.16% of the non-Inuit population in southern Quebec (Lévesque et al. 2003).

Second-hand smoke may also contribute to increased Pb exposure (Apostolou et al. 2012; Mannino et al. 2003; Richter et al. 2013). Pb is a component of tobacco and tobacco smoke, and smokers often have higher Pb blood levels than nonsmokers (Bonanno et al. 2001; Mannino et al. 2003). Using data from the NHEXAS EPA Region V study, PbB levels in smokers and nonsmokers were analyzed and a correlation between tobacco smoke and exposure levels was observed (Bonanno et al. 2001). The mean PbBs in

smokers, nonsmokers exposed to environmental tobacco smoke (ETS), and nonsmokers without ETS were 2.85, 2.06, and 1.81 µg/dL, respectively (Bonanno et al. 2001). Recent Pb urine concentrations for the U.S. adult population from the NHANES by smoking status are presented in Table 5-24.

Table 5-24. Geometric Mean Urine Lead Levels (µg/dL) and the 95th Percentile Confidence Interval by Smoking Status

	Survey years	Geometric mean (95% confidence interval)	Sample size
Cigarette smokers			
Total	11–12	2.36 (1.71–4.62)	876
	13–14	1.51 (1.30–1.91)	957
Age group			
20–49 years	11–12	1.78 (1.41–3.07)	522
18–49 years	13–14	1.34 (1.13–1.92)	583
50 years and older	11–12	3.35 (1.62–6.83)	354
	13–14	1.72 (1.40–2.03)	374
Gender			
Males	11–12	3.07 (1.73–5.03)	527
	13–14	1.91 (1.48–2.14)	512
Females	11–12	1.58 (1.14–3.45)	349
	13–14	1.30 (1.12–1.41)	445
Nonsmokers[a]			
Total	11–12	1.38 (1.25–1.58)	1,343
	13–14	1.16 (0.950–1.51)	1,487
Age group			
20–49 years	11–12	1.26 (1.02–1.38)	671
18–49 years	13–14	0.880 (0.720–1.04)	778
50 years and older	11–12	1.63 (1.29–2.16)	672
	13–14	1.48 (1.12–2.52)	709
Gender			
Males	11–12	1.61 (1.18–2.13)	635
	13–14	1.51 (1.04–2.68)	663
Females	11–12	1.32 (1.06–1.38)	708
	13–14	0.238 (0.219–0.258)	824

[a]Cigarette nonsmokers who used other tobacco products were excluded.

Source: CDC 2018a

Studies have been conducted to determine exposure of firearm instructors to Pb at outdoor firing ranges when either nonjacketed (pure Pb) or jacketed (copper-coated) bullets were used. Instructors are likely to have higher exposure than shooters because they spend more time at the range. In studies at an outdoor

range in Virginia, the mean breathing zone Pb level when nonjacketed bullets were fired was 67.1 μg/m^3 for one instructor and 211.1 μg/m^3 for another (Tripathi and Llewellyn 1990). When jacketed bullets were used, breathing zone levels decreased to ≤8.7 μg/m^3. PbBs of the instructors did not exceed the OSHA Pb standard's medical removal level of 2.4 μmol/L (60 μg/dL) in either case (OSHA 2016a). When shooters fired conventional Pb bullets, their mean exposures to airborne Pb were 128 μg/m^3 in the personal breathing zone and 68 μg/m^3 in the general area. When totally copper-jacketed Pb bullets were fired, the mean breathing zone and general area air sample concentrations were 9.53 and 5.80 μg/m^3, respectively (Tripathi and Llewellyn 1990). At an outdoor uncovered range in Los Angeles, instructors who spent an average of 15–20 hours/week behind the firing line were found to be exposed to breathing zone Pb concentrations of 460 and 510 μg/m^3 measured as 3-hour, time-weighted averages. The PbB of one instructor reached 3.38 μmol/L (70 μg/dL). After reassignment to other duties, repeat testing indicated his PbB had dropped to 1.35 μmol/L (28 μg/dL) (Goldberg et al. 1991).

In 1991, NIOSH conducted a survey of the Federal Bureau of Investigations (FBI) Firearms Training Unit firing ranges and related facilities to determine occupational Pb exposures among FBI and Drug Enforcement Agency (DEA) firing range personnel (NIOSH 1996b). Sixty-one personal breathing-zone and 30 area samples for airborne Pb were collected. Exposures ranged up to 51.7 μg/m^3 (mean, 12.4 μg/m^3), 2.7 μg/m^3 (mean, 0.6 μg/m^3), and 4.5 μg/m^3 (mean, 0.6 μg/m^3) for range instructors, technicians, and gunsmiths, respectively. Exposure of custodians ranged from nondetectable to 220 μg/m^3 during short-term cleaning of a large indoor range. Carpet dust sampling of dormitory rooms of students who practiced at the firing ranges revealed higher ($p<0.0005$) dust-Pb concentrations when compared to nonstudent dormitories (dust-Pb concentration range of 116–546 μg/g with a geometric mean of 214 μg/g in the student's rooms versus a dust-Pb concentration range of 50–188 μg/g with a geometric mean of 65 μg/g for the nonstudent rooms). This suggested that the students were contaminating their living quarters with Pb.

The American Academy of Pediatrics (AAP) (1998, 2005) concluded that although monitoring data demonstrate a decline in PbBs, Pb remains a common, preventable, environmental health threat. Most Pb poisoning in children is the result of dust and chips from deteriorating Pb paint on interior surfaces (AAP 2005, 2016; ATSDR 2017). The AAP supported the CDC guidelines endorsing universal screening in certain areas and targeted screening for children at high risk (CDC 1997b, 2005). Many children continue to be at risk for ingestion of Pb-based paint and of soil and dust contaminated through the deterioration of Pb-based paint and the residues from combustion of leaded gasoline. A 1974 study indicated that elevated PbBs in children were most likely a result of ingesting Pb-contaminated soil, and that the most

likely source was Pb-based paint rather than Pb from automotive exhaust (Ter Haar and Aronow 1974). However, more recent studies have shown that children with the highest PbBs live in areas with high traffic flow where Pb particles in the air may fall directly to the soil or adhere to the outer surfaces of building and wash to the soil with rain (Mielke et al. 1989, 2008, 2010). The CDC concluded that a common source of Pb exposure for children who have elevated PbB is Pb-based paint that has deteriorated into paint chips and Pb dusts (CDC 1997c, 2012d).

Pb can readily cross the placenta; therefore, exposure of women to Pb during pregnancy results in uptake by the fetus. Furthermore, since the physiological stress of pregnancy may result in mobilization of Pb from maternal bone, fetal uptake of Pb can occur from a mother who was exposed to Pb before pregnancy, even if no Pb exposure occurs during pregnancy. Maternal Pb can also be transferred to breastfeeding infants.

Malcoe et al. (2002) assessed Pb sources and their effect on blood Pb in rural Native American and white children living in a former mining region. Blood samples, residential environmental samples (soil, dust, paint, water), and caregiver interviews (hand-mouth behaviors, socioeconomic conditions) were obtained from a representative sample of 245 children ages 1–6 years. There were no ethnic differences in the results. However, poor children were especially vulnerable. Regression analysis showed that mean floor dust Pb loading >10.1 μg/ft^2 and yard soil Pb >165.3 mg/kg were independently associated with blood Pb levels ≥10 μg/dL.

The Pb content of dusts can be a significant source of exposure, especially for young children. Baseline estimates of potential human exposure to dusts, including intake due to normal hand-to-mouth activity, are 0.2 g/day for children 1–6 years old versus 0.1 g/day for adults when both indoor and outdoor ingestion of soil including dust is considered (EPA 1989c). For children who engage in pica behavior (the compulsive, habitual consumption of nonfood items), the ingestion rate of soil can be as high as 5 g/day. Although ingestion of Pb-containing paint may lead to elevated PbBs in young children, a major source of elevated PbBs (>10 μg/dL) in children is often contaminated household dust and subsequent hand contamination and repetitive mouthing (Bornschein et al. 1986; Charney et al. 1980; Dixon et al. 2009; Lanphear and Roghmann 1997; Lanphear et al. 1998a; Succop et al. 1998). Weathering of Pb-based paint can contribute to the Pb content of dust and soil. Pb levels of indoor dust and outdoor soil were found to be strongly predictive of PbBs in over 200 urban and suburban infants followed from birth to 2 years of age; however, PbBs were not correlated with indoor air or tap water Pb levels, nor the size of nearby roadways. Indoor dust Pb levels and soil Pb levels in the homes of children with high PbBs

(>8.8 µg/dL) were 72 µg/wipe (window sill dust) and 1,011 µg/g, respectively; children with low PbBs (<3.7 µg/dL) were exposed to 22 µg/wipe and 380 µg/g, respectively. In addition, 79% of the homes of children with high PbBs had been renovated, while only 56% of the homes of children with low PbBs had been renovated, suggesting that renovating the interior of homes previously painted with leaded paint may increase, at least temporarily, a child's exposure to Pb dust (Rabinowitz et al. 1985). Regular use of dust control methods (e.g., wet mopping of floors, damp-sponging of horizontal surfaces, high-efficiency vacuum cleaner) has been shown in some, although not all, cases to reduce indoor dust, Pb dust, and blood Pb levels in some, although not all, older homes containing leaded paints (Lanphear et al. 2000b; Rhoads et al. 1999). Decreases of between 17 and 43% in blood Pb concentrations were observed in children where regular dust control methods had been used to reduce indoor levels of Pb (Rhoads et al. 1999). EPA (2014c) summarized concentrations of Pb in house dust in the United Stated from 2006 to 2011; these data are presented in Table 5-25.

Table 5-25. Measurements of Lead in Indoor Dust in the United States from 2006 to 2011

Location	Sample site	Value reported
New York City, New York	Glass plate next to open window of academic building	Median weekly dust loading: 52 µg/m^2
Eureka, Utah near Eureka Mills Superfund Site	Indoor home site (not specified)	Dust concentrations, range: 160–2,000 mg/kg
Denver, Colorado, near Vasquez Blvd and I-70 Superfund Site	Indoor home site (not specified)	Dust concentrations, range: 11–660 mg/kg
East Helena, Montana, near East Helena Superfund Site	Indoor home site (not specified)	Dust concentrations, range: 68–1,000 mg/kg
Syracuse, New York	Floor	Dust concentrations, range: 209–1,770 mg/kg
United States (nationwide)	Smooth floor	Median dust loading: 1.7 µg/m^2 Average dust loading: 4.4 µg/m^2
	Rough floor	Median dust loading: 5.6 µg/m^2 Average dust loading: 16 µg/m^2
	Smooth windowsill	Median dust loading: 2.5 µg/m^2 Average dust loading: 190 µg/m^2
	Rough windowsill	Median dust loading: 55 µg/m^2 Average dust loading: 480 µg/m^2
Milwaukee, Wisconsin	Central perimeter	Average dust concentration: 107 µg/m^2
	Entry	Average dust concentration: 140 µg/m^2
	Window	Average dust concentration: 151 µg/m^2

Table 5-25. Measurements of Lead in Indoor Dust in the United States from 2006 to 2011

Location	Sample site	Value reported
Rural towns, Idaho	Vacuum	Dust concentration Median: 120 mg/kg Maximum: 830 mg/kg
	Floor	Median dust concentration: 95 mg/kg Maximum dust concentration: 1,300 mg/kg
Bunker Hill, Idaho Superfund Site	Vacuum	Median dust concentration: 470 mg/kg Maximum dust concentration: 2,000 mg/kg
	Floor	Median dust concentration: 290 mg/kg Maximum dust concentration: 4,600 mg/kg

Source: EPA 2014c

Lanphear and Roghmann (1997) and Lanphear et al. (1996a, 1996b, 1998b) studied factors affecting PbBs in urban children and found the following independent predictors of children's PbBs: dust Pb loading in homes (carpets, uncarpeted floors, window sills, and troughs), African-American race/ethnicity, foundation perimeter soil Pb levels, ingestion of soil or dirt, Pb content and condition of interior painted surfaces, and first-flush kitchen drinking water Pb levels (Lanphear et al. 1996a, 1996b). Differences in housing conditions and exposures to Pb-containing house dust appear to contribute to the racial differences in urban children's PbBs. In addition, white children were more likely to put soil in their mouths (outdoor exposure) and suck their fingers, and African-American children were more likely to put their mouths on window sills (indoor exposure) and to use a bottle. Interior Pb exposures were more significant for African American children and exterior Pb exposures were more significant for white children (Lanphear et al. 1996a, 1996b). Mouthing behaviors are an important mechanism of Pb exposure among urban children (Lanphear and Roghmann 1997). Community characteristics such as residence within a city, proportion of African Americans, lower housing value, housing built before 1950, higher population density, higher rates of poverty, lower percent of high school graduates, and lower rates of owner-occupied housing have been used to identify children with elevated blood levels (Lanphear et al. 1998b). An analysis of children's PbBs and multiple measures of Pb concentrations in household dust, tap water, foundation perimeter soil, and interior house paint has been used to predict the effect of changing concentrations of Pb in environmental media on children's PbBs. An increase in dust Pb loading from background to 200 μg/ft^2 was estimated to produce an increase of 23.3% in the percentage of children estimated to have a PbB >10 μg/dL; an increase in tap water Pb concentration from background to 15 μg/L was estimated to produce an increase of 13.7% in the percentage of children estimated to have a PbB level >10 μg/dL; and an increase in soil Pb concentration from background to

400 μg/g was estimated to produce an increase of 11.6% in the percentage of children estimated to have a PbB level >10 μg/dL (Lanphear et al. 1998a).

Outdoor Pb dust was found to be a more potent contaminant of children's hands than indoor dust at daycare centers in New Orleans; boys, in general, had higher hand Pb levels than girls. The conclusions were based on Pb analysis of hand wipe samples taken before and after children played outdoors at four different daycare centers (a private inner-city site, a private outer-city site, a public inner-city site, and a public outer-city site). The private inner-city site had a severely contaminated outdoor play area with measured soil Pb concentrations ranging from 287 to 1,878 mg/kg. The outdoor play area at the public inner-city site, where children exhibited the lowest hand Pb measurements of any site in the study, had been completely paved over with concrete or rubberized asphalt and had well-maintained equipment (Viverette et al. 1996).

EPA conducted the Urban Soil Lead Abatement Demonstration Project (USLADP), also known as the "Three City Lead Study," in Boston, Baltimore, and Cincinnati (EPA 1996c). The purpose was to determine whether abatement of Pb in soil could reduce PbBs of inner-city children. No significant evidence was found that soil abatement had any direct impact on children's PbBs in either the Baltimore or Cincinnati studies. In the Boston study, however, a mean soil Pb reduction of 1,856 ppm resulted in a mean decline of 1.28 μg/dL PbB at 11 months postabatement (Weitzman et al. 1993). Phase II extended the study to 2 years and included soil abatement of the two comparison areas from Phase I (Aschengrau et al. 1994). Combined results from Phase I and II suggested a higher impact of soil remediation on PbBs (2.2–2.7 μg/dL). EPA reanalyzed the data from the USLADP in an integrated report (EPA 1996c). They concluded that when soil is a significant source of Pb in the child's environment, under certain conditions, the abatement of that soil will result in a reduction in exposure and consequently, PbB level. The results of the USLADP suggest that a number of factors are important in determining the influence of soil remediation on PbBs in children. These include the site-specific exposure scenario, the magnitude of the remediation, and the magnitude of additional sources of Pb exposure.

Authors of a study of PbBs in children in Toronto, Canada, before and after abatement of Pb-contaminated soil and house dust found that they could neither strongly support nor refute beneficial effects of abatement. The failure to reach a definite conclusion from the results of the study, which included data from 12 cross-sectional blood-screening surveys that were conducted over an 8-year period, was due, in part, to a low response rate (32–75%) to questionnaires used to determine behavioral,

household, lifestyle, neighborhood, and environmental factors relating to study participants (Langlois et al. 1996).

Seasonal variations in PbBs in children have been observed in a number of studies (Gulson et al. 2008; Haley and Talbot 2004; Havlena et al. 2009; Kemp et al. 2007; Johnson and Bretsch 2002; Johnson et al. 1996; Laidlaw et al. 2005; Yiin et al. 2000). These studies suggest a general trend of increasing PbB during late summer and early fall. In addition to seasonal patterns in behavior (e.g., outdoor activities), seasonal patterns in weather (humidity and wind velocity) that promote re-entrainment and transport of dust Pb may contribute to the observed seasonal patterns in PbB (Laidlaw et al. 2005, 2012).

In addition to the ingestion of hand soil/dust through normal hand-to-mouth activity, some children engage in pica behavior (consumption of nonfood items), which can put them at increased risk through ingestion of large amounts of soil contaminated with Pb. It has been estimated that an average child may ingest between 20 and 50 mg of soil/day and that a pica child may ingest ≥5,000 mg of soil/day (LaGoy 1987; Mielke et al. 1989). If the soil contains 100 μg/g of Pb, an average child may be exposed to 5 μg Pb/day from this source alone (Mielke et al. 1989), and a pica child may be exposed to >100 times that amount.

Improper removal of Pb from housing known to contain Pb-based paint can significantly increase Pb levels in dust, thus causing Pb toxicity in children living in the home during the Pb-removal process. Four such cases have been documented (Amitai et al. 1987). In January 1995, the New York State Department of Health identified 320 children in 258 households in New York State (excluding New York City) with PbBs ≥20 μg/dL that were considered to be attributable to residential renovation and remodeling (CDC 1997a).

Workers occupationally exposed to Pb can carry Pb home on clothing, bodies, or tools (take home exposure). PbBs of children in households of occupationally exposed workers were almost twice those of children in neighboring homes whose parents were not occupationally exposed to Pb (median ranges were 10–14 and 5–8 μg/dL, respectively) (Grandjean and Bach 1986). Young children (<6 years old) of workers exposed to high levels of Pb in workplace air at an electronic components plant (61–1,700 μg Pb/m^3 ambient concentrations) had significantly elevated PbBs (13.4 μg/dL) compared with children from the same locale whose parents did not work in the electronics plant (7.1 μg/dL) (Kaye et al. 1987). Based upon data collected from 1987 to 1994, children aged 1–5 years (n=139) of workers whose occupation resulted in Pb exposure had a geometric mean PbB of 9.3 μg/dL as compared to a U.S. population

geometric mean of 3.6 μg/dL (Roscoe et al. 1999). Of this group, 52% of the children had PbBs ≥10 μg/dL compared to 8.9% of the U.S. population and 21% had PbBs ≥20 μg/dL compared to 1.1% of the U.S. population (Roscoe et al. 1999). Exposures of Pb workers' families have been identified in nearly 30 different industries and occupations. Industries in which exposure of family members has been reported most often include Pb smelting, battery manufacturing and recycling, radiator repair, electrical components manufacturing, pottery and ceramics, and stained glass making (NIOSH 1995). Children of Pb-exposed construction workers may also be at increased risk (Whelan et al. 1997).

Children may be exposed to Pb because of activities associated with certain hobbies and artistic activities practiced by adults in the home. Some of the more obvious hobbies and activities involving use of Pb-containing materials include casting, stained glass, pottery, painting, glassblowing, and screenprinting. Activities involving use of Pb-containing materials should always be done in an area well-ventilated with outdoor air and should never be done with children in the same room or in close proximity. Maas et al. (2005) indicated that high levels of Pb are prevalent in inexpensive cosmetic jewelry that is sold to the general public at retail stores.

Accidental or intentional ingestion of folk remedies (e.g., Chinese herbal medicines and Ayurvedic medicines containing Pb) or use of the Pb containing eye cosmetic tiro in children (discussed in Section 5.5.5) represents another source for potential Pb-poisoning in children. Sindoor, a cosmetic and cultural/religious powder used Hindu cultures, has been found to contain very high amounts of Pb (Lin et al. 2010). Hair dyes formulated with Pb acetate represent a potential source for Pb-poisoning both by accidental ingestion and by hand-to-mouth activity following contact with Pb-contaminated surfaces, including dyed hair of adults (Mielke et al. 1997).

Children may be exposed to Pb through the inhalation of second-hand smoke. Mannino et al. (2003) employed data from the NHANES III and analyzed PbBs of children aged 4–16 years who were exposed to high, low, and intermediate levels of second-hand smoke. Serum levels of the nicotine biomarker cotinine were used to classify the children into one of the three second-hand smoke exposure categories. The geometric mean PbBs were 1.5, 1.9, and 2.6 μg/dL for children with low (≤0.050–0.104 ng/mL), intermediate (0.105–0.562 ng/mL), and high (0.563–14.9 ng/mL) serum cotinine levels, respectively (Mannino et al. 2003).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to workers exposed to Pb in the workplace and family members of workers exposed via take home exposure, other population groups are at risk for potential exposure to high levels of Pb. These include populations residing in older housing or buildings that contain deteriorating leaded paint or that have galvanized pipes, Pb service lines, or scales that contain Pb within a distribution public water system; in high-traffic areas with legacies from leaded gasoline; near sites where Pb was produced or disposed; or near one of the NPL hazardous waste sites where Pb has been detected in some environmental media (ATSDR 2015; EPA 2014c, 2016g). Since Pb is often detected in tobacco and tobacco smoke, persons who use chewing tobacco or smoke or are exposed to second-hand smoke, may have higher PbB levels than persons that do not use these products (Apostolou et al. 2012; Bonanno et al. 2001; Richter et al. 2013). Recent studies have also found e-cigarettes to be a potential source of Pb exposure (Olmedo et al. 2018). Other Pb sources that can contribute to elevated exposures to individual children include mouthing or ingestion of toys containing Pb and consumption of candy and folk remedies that contain Pb (CDC 2002b, 2018c).

General population exposure is most likely to occur through the ingestion of food and water contaminated with Pb. Based on a multimedia Pb exposure modeling analysis for children 1–5 years old at upper percentiles of PbB in the U.S. population, soil and dust ingestion are dominant exposure pathways, but for lower percentiles, other age groups (e.g., younger children), or specific local U.S. locations, the main exposure source/pathway could be different (Zartarian et al. 2017). However, some individuals and families may be exposed to additional sources of Pb in their homes. This is particularly true of older homes that may contain Pb-based paint. In an attempt to reduce the amount of exposure due to deteriorating leaded paint, the paint is commonly removed from homes by burning (gas torch or hot air gun), scraping, or sanding. These activities have been found to result, at least temporarily, in higher levels of exposure for families residing in these homes. In addition, those individuals involved in the paint removal process (i.e., do-it-yourself renovators and professionals who remove Pb) can be exposed to such excessive levels that Pb poisoning may occur (Chisolm 1986; Fischbein et al. 1981; Rabinowitz et al. 1985). Special populations at risk of high exposure to tetraethyl Pb include workers at hazardous waste sites and those involved in the manufacture and dispensing of tetraethyl Pb (Bress and Bidanset 1991).

CHAPTER 6. ADEQUACY OF THE DATABASE

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

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

6.1 Information on Health Effects

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

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

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

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

6.2 Identification of Data Needs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.3 Ongoing Studies

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

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

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

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

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

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

Source: NIH Reporter 2017

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding Pb in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for information on procedures for deriving MRLs, as well as the deliberations and conclusions regarding derivation of MRLs for Pb.

Table 7-1. Regulations and Guidelines Applicable to Lead (Pb)

Agency	Description	Information	Reference
	Air		
EPA	RfC	No data	IRIS 2002, 2004
EPA	NAAQS	0.15 µg/m^3 [a]	EPA 2016e
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	No data	EPA 2018c
	National primary drinking water regulations for inorganic lead		EPA 2009
	TT	TT5	
	Action level	0.015 mg/L[b]	
	Public health goal	zero	
	RfD		
	Tetraethyl lead	1 x10^{-7} mg/kg/day[c]	IRIS 2002
WHO	Drinking water quality guidelines		WHO 2017
	Provisional guideline value, lead	0.01 mg/L (10 µg/L)[d]	
FDA	EAFUS[e]	No data	FDA 2013
	Cancer		
ACGIH	Carcinogenicity classification		
	Lead (inorganic compounds as Pb)	A3[f,g]	ACGIH 2001a, 2018
	Lead chromate (as Pb or chromium)	A2[h,i]	ACGIH 2001b, 2018
	Tetraethyl lead	A4[j,k]	ACGIH 2001c, 2018
HHS	Carcinogenicity classification		NTP 2016
	Lead and lead compounds	Reasonably anticipated to be human carcinogens[l]	

Table 7-1. Regulations and Guidelines Applicable to Lead (Pb)

Agency	Description	Information	Reference
EPA	Carcinogenicity classification		IRIS 2004
	Lead and compounds (inorganic)	B2[m,n]	
IARC	Carcinogenicity classification		
	Lead	Group 2B[o,p]	IARC 1987, 2017
	Lead compounds, inorganic	Group 2A[q,r]	IARC 2006, 2017
	Lead compounds, organic	Group 3[s,t]	IARC 2006, 2017
	Occupational		
ACGIH	TLV		ACGIH 2018
	Lead	0.05 mg/m^3	
	Lead chromate (as Pb)	0.05 mg/m^3	
	Lead chromate (as chromium)	0.012 mg/m^3	
	Tetraethyl lead	0.1 mg/m^3	
	BEI		
	Lead in blood	20 µg/100 mL[u]	
OSHA	PEL (8-hour TWA) for general industry		
	Lead (elemental, inorganic and organic soaps)	0.5 mg/m^3	OSHA 2016a
	Tetraethyl lead and tetramethyl lead	0.075 mg/m^3 [v]	OSHA 2016b
	PEL (8-hour TWA) for construction and shipyards		
	Lead (elemental, inorganic and organic soaps)	50 µg/m^3	OSHA 2016c, 2016d
	Tetraethyl lead	0.1 mg/m^3 [v]	OSHA 2016e, 2016f
	Tetramethyl lead	0.15 mg/m^3 [v]	OSHA 2016e, 2016f
	Action level (8-hour TWA) for general industry, construction		
	Lead (elemental, inorganic and organic soaps)	30 µg/m^3	OSHA 2016a, 2016c
	Medical removal protection for general industry		OSHA 2016a
	Temporary removal blood lead level	≥60 µg/dL	
	Return to work blood lead level	<40 µg/dL	
	Medical removal protection for construction and shipyards		OSHA 2016c
	Temporary removal blood lead level	≥50 µg/dL	
	Return to work blood lead level	<40 µg/dL	
NIOSH	REL (8-hour TWA)		
	Lead and compounds (as Pb)	0.05 mg/m^3	NIOSH 2016b
	Tetraethyl lead (as Pb)	0.075 mg/m^3 [v]	NIOSH 2016c
	IDLH		
	Lead and compounds (as Pb)	100 mg/m^3	NIOSH 2016b
	Tetraethyl lead (as Pb)	40 mg/m^3	NIOSH 2016c

Table 7-1. Regulations and Guidelines Applicable to Lead (Pb)

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016d
DOE	PACs-air		DOE 2016
	Lead		
	PAC-1	0.15 mg/m^3	
	PAC-2	120 mg/m^3	
	PAC-3	700 mg/m^3	
	Tetraethyl lead		
	PAC-1	0.5 mg/m^3	
	PAC-2	5.5 mg/m^3	
	PAC-3	33 mg/m^3	
	Lead acetate		
	PAC-1	5 mg/m^3	
	PAC-2	55 mg/m^3	
	PAC-3	330 mg/m^3	
	Lead carbonate		
	PAC-1	0.19 mg/m^3	
	PAC-2	24 mg/m^3	
	PAC-3	900 mg/m^3	
	Lead dioxide and lead sulfide		
	PAC-1	0.17 mg/m^3	
	PAC-2	140 mg/m^3	
	PAC-3	810 mg/m^3	
	Lead tetroxide		
	PAC-1	0.17 mg/m^3	
	PAC-2	130 mg/m^3	
	PAC-3	770 mg/m^3	
	Lead oxide		
	PAC-1	0.16 mg/m^3	
	PAC-2	130 mg/m^3	
	PAC-3	750 mg/m^3	
	Lead sulfate		
	PAC-1	0.22 mg/m^3	
	PAC-2	170 mg/m^3	
	PAC-3	1,000 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Lead (Pb)

Agency	Description	Information	Reference
	Lead phosphate		
	PAC-1	0.2 mg/m^3	
	PAC-2	150 mg/m^3	
	PAC-3	910 mg/m^3	
	Lead chloride		
	PAC-1	0.2 mg/m^3	
	PAC-2	160 mg/m^3	
	PAC-3	940 mg/m^3	
	Lead chromate		
	PAC-1	0.036 mg/m^3	
	PAC-2	16 mg/m^3	
	PAC-3	97 mg/m^3	
	Lead bromide		
	PAC-1	0.27 mg/m^3	
	PAC-2	200 mg/m^3	
	PAC-3	1,200 mg/m^3	
	Lead nitrate		
	PAC-1	0.24 mg/m^3	
	PAC-2	180 mg/m^3	
	PAC-3	1,100 mg/m^3	
	Lead iodide		
	PAC-1	0.33 mg/m^3	
	PAC-2	270 mg/m^3	
	PAC-3	1,600 mg/m^3	
	Lead fluoroborate		
	PAC-1	0.28 mg/m^3	
	PAC-2	220 mg/m^3	
	PAC-3	1,300 mg/m^3	
Miscellaneous Federal Guidance			
CDC	PbB reference value	5 µg/dL[w]	CDC 2012d, 2012f
EPA	Soil screening level	400 ppm[x]	EPA 1994e, 1998; 2016f

Table 7-1. Regulations and Guidelines Applicable to Lead (Pb)

Agency	Description	Information	Reference
HUD	Dust lead hazard action levels[y]		HUD 2017
	Floors	≥10 µg/ft^2	
	Window sills	≥100 µg/ft^2	
	Dust lead clearance action levels[y]		
	Interior floors	<10 µg/ft^2	
	Porch floors	<40 µg/ft^2	
	Window sills	<100 µg/ft^2	
	Window troughs	<100 µg/ft^2	

[a]Not-to-exceed air Pb concentration of 0.15 µg/m^3 in total suspended solids for a 3-month rolling average, evaluated over a 3-year period (i.e., the 3-month rolling average cannot exceed 0.15 µg/m^3 over a 3-year period). Based on a variety of lines of evidence including human epidemiological evidence for a variety of adverse health effects in children and other at-risk populations, most notably effects on the developing nervous system.
[b]Potential health effects from long-term exposure above the MCL include delays in physical or mental development in infants and children (children could show slight deficits in attention span and learning abilities) and kidney problems and high blood pressure in adults.
[c]Based on histopathology of liver and thymus; POD = LOAEL: 1.2x10^{-3} mg/kg/day; composite uncertainty factor=10,000; confidence=medium.
[d]The guideline value is designated as provisional on the basis of treatment performance and analytical achievability because it is extremely difficult to achieve a lower concentration by central conditioning, such as phosphate dosing.
[e]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[f]A3: confirmed animal carcinogen with unknown relevance to humans.
[g]Based on demonstrated carcinogenicity of soluble lead compounds in animals.
[h]A2: Suspected human carcinogen.
[i]Based on experimental animal and epidemiological studies that demonstrated a low degree of carcinogenicity.
[j]A4: not classifiable as a human carcinogen.
[k]Based on inconclusive evidence of carcinogenicity in rodent bioassays.
[l]Based on sufficient evidence of carcinogenicity in experimental animals.
[m]Group B2: probable human carcinogen.
[n]Based on sufficient evidence of carcinogenicity in animals.
[o]Group 2B: possibly carcinogenic to humans.
[p]Based on inadequate evidence for carcinogenicity to humans and sufficient evidence for carcinogenicity of inorganic lead compounds in animals.
[q]Group 2A: probably carcinogenic to humans.
[r]Based on limited evidence of carcinogenicity of inorganic lead in humans and sufficient evidence of carcinogenicity in experimental animals. Also based on sufficient evidence of carcinogenicity of inorganic compounds in experimental animals, sufficient evidence of carcinogenicity of Pb acetate, Pb subacetate, Pb chromate, and Pb phosphate in experimental animals, and based on inadequate evidence of carcinogenicity of Pb oxide, Pb arsenate, tetraethyl Pb, and Pb powder in experimental animals.
[s]Group 3: not classifiable as to carcinogenicity to humans.
[t]Based on inadequate evidence of carcinogenicity in humans and inadequate evidence of carcinogenicity in experimental animals.
[u]2016 Notice of Intended Change for BEI: 200 µg/L.
[v]Skin designation.
[w]Based on 97.5th percentile of NHANES PbB distribution in children 1–5 years of age.
[x]Based on evidence for adverse effects on the developing nervous system in association with PbB in the 2–8 µg/dL range.
[y]Based on evidence for adverse effects on the developing nervous system in association with PbB <5 µg/dL.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; BEI = biological exposure index; CDC = Centers for Disease Control and Prevention; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; HUD = Housing and Urban Development; IARC = International Agency for Research on Cancer;

Table 7-1. Regulations and Guidelines Applicable to Lead (Pb)

Agency	Description	Information	Reference

IDLH = immediately dangerous to life or health concentration; IRIS = Integrated Risk Information System; LOAEL = lowest-observed-adverse-effect level; MCL = maximum contaminant level; NAAQS = National Ambient Air Quality Standard; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; POD = point of departure; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TT = treatment technique; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children. Effects are diverse and exposure to Pb is associated with toxicity to every organ system. For the most studied endpoints (neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental), effects occur at the lowest PbBs studied (≤5 µg/dL). Exposure thresholds for effects on specific organ systems have not been identified (i.e., no safe level has been identified). Cognitive deficits in children occurring at the lowest PbB concentrations (≤5 µg/dL) are the best substantiated effects. However, because the lowest PbBs are associated with serious adverse effects (e.g., declining cognitive function in children), MRLs for Pb have not been derived.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR LEAD

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with exposure to Pb.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for Pb. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. The inclusion criteria used to identify relevant studies examining the health effects of Pb are presented in Table B-1.

The literature on health effects of Pb in humans is enormous, with countless epidemiological studies in workers and the general population, including children. Due to the extent of the Pb database in humans, it is impossible to cite all, or even most, of the studies on health effects of Pb. Thus, no attempt was made to conduct a comprehensive review of the epidemiological literature. Epidemiological studies were selected to identify the major lines of evidence regarding health effects in humans. The literature database on adverse effects of Pb in laboratory animals also is extensive. Although the literature on adverse effects of Pb in laboratory animals also is extensive, due to the large number of available epidemiological studies, results of animal studies were not considered for the identification of health effects associated with Pb. This potentially leaves out discussion of effects that may have been observed in animal models that have not been studied in humans and that may be future targets of human epidemiology and clinical toxicology studies. Animal studies were included in discussion of mechanisms of toxicity of Pb and toxicokinetics.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Internal Exposure Metric
Blood Pb Concentration (PbB)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Immunological effects
- Neurological effects
- Reproductive effects
- Developmental effects
- Other noncancer effects
- Cancer

Toxicokinetics
- Absorption
- Distribution
- Metabolism
- Excretion
- PBPK models

Biomarkers
- Biomarkers of exposure
- Biomarkers of effect

Interactions with other chemicals

Potential for human exposure
- Releases to the environment
  - Air
  - Water
  - Soil
- Environmental fate
  - Transport and partitioning
  - Transformation and degradation
- Environmental monitoring
  - Air
  - Water
  - Sediment and soil
  - Other media
- Biomonitoring
  - General populations
  - Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the existing toxicological profile for Pb (ATSDR 2007). To avoid interagency redundancy, ATSDR reviewed the EPA (2014c) *Integrated Science Assessment (ISA) for Lead* to identify studies relevant to the toxicological profile. Thus, the literature search was restricted to studies published between 2013 and February 2016. The following main databases were searched in February 2016:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, and Medical Subject Headings (MeSH) terms for Pb. The query strings used for the literature search are presented in Table B-2.

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
PubMed	
2/2016	(("Lead/toxicity"[mh] OR "Lead/adverse effects"[mh] OR "Lead/poisoning"[mh] OR "Lead/pharmacokinetics"[mh] OR "Lead/blood"[mh] OR "Lead/cerebrospinal fluid"[mh] OR "Lead/urine"[mh] OR "Lead/antagonists and inhibitors"[mh] OR ("Lead/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh]))) OR ("Lead"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "toxicokinetics"[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Lead"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Lead"[majr] AND cancer[sb]) OR ("Lead/pharmacology"[majr]) OR ("Lead"[mh] AND ((population health[tw] AND ("public health"[MeSH Major Topic] OR "public health administration"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health practice"[MeSH Terms] OR "public policy"[MeSH Terms])) OR (population[tw] AND "health care quality, access, and evaluation"[MeSH Major Topic] AND "demography"[MeSH Major Topic] AND "health services"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "population characteristics"[MeSH Major Topic] AND "social environment"[MeSH Major Topic]) OR ("health services accessibility"[MeSH Terms] AND "demography"[MeSH Terms] AND disparities[tw]) OR (population health[ti] AND ("health care quality, access, and evaluation"[MeSH Terms] OR "preventive health services"[MeSH Terms] OR "health planning"[MeSH Terms] OR "health policy"[MeSH Terms] OR "demography"[MeSH Terms] OR "health expenditures"[MeSH Terms] OR "income"[MeSH Terms] OR "population dynamics"[MeSH Terms] OR "social determinants of health"[MeSH Terms] OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	"socioeconomic factors"[MeSH Terms] OR "population characteristics"[MeSH Terms] OR "health promotion"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health/methods"[Mesh Terms])) OR (population health[tw] AND ("community health services"[MeSH Major Topic] OR "health services"[MeSH Major Topic] OR "health services research"[MeSH Major Topic] OR "delivery of health care"[MeSH Major Topic] OR "health planning"[MeSH Major Topic] OR "health policy"[MeSH Major Topic] OR "preventive health services"[MeSH Major Topic] OR "health care evaluation mechanisms"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "public health/education"[MAJR] OR "public policy"[MeSH Major Topic] OR "quality of life"[MeSH Major Topic] OR "health surveys"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "demography"[MeSH Major Topic] OR "socioeconomic factors"[MeSH Major Topic] OR "health behavior"[MeSH Major Topic] OR "attitude to health"[MeSH Major Topic] OR "social environment"[MeSH Major Topic] OR "social welfare"[MeSH Major Topic] OR "population characteristics"[MeSH Major Topic] OR "vulnerable populations"[MeSH Major Topic] OR "residence characteristics"[MeSH Terms] OR "poverty"[MeSH Major Topic] OR "healthcare disparities"[MeSH Major Topic])) OR ("health status indicators"[MeSH Terms] AND "mass screening/methods"[MAJR] AND "morbidity"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "public health practice"[MeSH Major Topic] AND "outcome assessment (health care)"[MeSH Terms]) OR (built environment[tw] AND ("public health"[MeSH Major Topic] OR (("population"[MeSH Terms] OR "population"[All Fields] OR "population groups"[MeSH Terms] OR ("population"[All Fields] AND "groups"[All Fields]) OR "population groups"[All Fields]) AND ("health"[MeSH Terms] OR "health"[All Fields])))) OR ((socioeconomic[tw] OR inequality[tw] OR inequalities[tw] OR disparity[tw] OR disparities[tw] OR equity[tw] OR inequity[tw] OR inequities[tw] OR policy[tw] OR policies[tw] OR determinants[tw]) AND population health[tw] NOT medline[sb]) AND english[la] NOT letter[pt])) OR ("Tetraethyl Lead/toxicity"[mh] OR "Tetraethyl Lead/adverse effects"[mh] OR "Tetraethyl Lead/poisoning"[mh] OR "Tetraethyl Lead/pharmacokinetics"[mh] OR "Tetraethyl Lead/blood"[mh] OR "Tetraethyl Lead/cerebrospinal fluid"[mh] OR "Tetraethyl Lead/urine"[mh] OR "Tetraethyl Lead/antagonists and inhibitors"[mh] OR ("Tetraethyl Lead/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh]))) OR ("Tetraethyl Lead"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "toxicokinetics"[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Tetraethyl Lead"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Tetraethyl Lead"[majr] AND cancer[sb]) OR ("Tetraethyl Lead/pharmacology"[majr]) OR ("Tetraethyl Lead"[mh] AND ((population health[tw] AND ("public health"[MeSH Major Topic] OR "public health administration"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health practice"[MeSH Terms] OR "public policy"[MeSH Terms])) OR (population[tw] AND "health care quality, access, and

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	evaluation"[MeSH Major Topic] AND "demography"[MeSH Major Topic] AND "health services"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "population characteristics"[MeSH Major Topic] AND "social environment"[MeSH Major Topic]) OR ("health services accessibility"[MeSH Terms] AND "demography"[MeSH Terms] AND disparities[tw]) OR (population health[ti] AND ("health care quality, access, and evaluation"[MeSH Terms] OR "preventive health services"[MeSH Terms] OR "health planning"[MeSH Terms] OR "health policy"[MeSH Terms] OR "demography"[MeSH Terms] OR "health expenditures"[MeSH Terms] OR "income"[MeSH Terms] OR "population dynamics"[MeSH Terms] OR "social determinants of health"[MeSH Terms] OR "socioeconomic factors"[MeSH Terms] OR "population characteristics"[MeSH Terms] OR "health promotion"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health/methods"[Mesh Terms])) OR (population health[tw] AND ("community health services"[MeSH Major Topic] OR "health services"[MeSH Major Topic] OR "health services research"[MeSH Major Topic] OR "delivery of health care"[MeSH Major Topic] OR "health planning"[MeSH Major Topic] OR "health policy"[MeSH Major Topic] OR "preventive health services"[MeSH Major Topic] OR "health care evaluation mechanisms"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "public health/education"[MAJR] OR "public policy"[MeSH Major Topic] OR "quality of life"[MeSH Major Topic] OR "health surveys"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "demography"[MeSH Major Topic] OR "socioeconomic factors"[MeSH Major Topic] OR "health behavior"[MeSH Major Topic] OR "attitude to health"[MeSH Major Topic] OR "social environment"[MeSH Major Topic] OR "social welfare"[MeSH Major Topic] OR "population characteristics"[MeSH Major Topic] OR "vulnerable populations"[MeSH Major Topic] OR "residence characteristics"[MeSH Terms] OR "poverty"[MeSH Major Topic] OR "healthcare disparities"[MeSH Major Topic])) OR ("health status indicators"[MeSH Terms] AND "mass screening/methods"[MAJR] AND "morbidity"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "public health practice"[MeSH Major Topic] AND "outcome assessment (health care)"[MeSH Terms]) OR (built environment[tw] AND ("public health"[MeSH Major Topic] OR (("population"[MeSH Terms] OR "population"[All Fields] OR "population groups"[MeSH Terms] OR ("population"[All Fields] AND "groups"[All Fields]) OR "population groups"[All Fields]) AND ("health"[MeSH Terms] OR "health"[All Fields])))) OR ((socioeconomic[tw] OR inequality[tw] OR inequalities[tw] OR disparity[tw] OR disparities[tw] OR equity[tw] OR inequity[tw] OR inequities[tw] OR policy[tw] OR policies[tw] OR determinants[tw]) AND population health[tw] NOT medline[sb]) AND english[la] NOT letter[pt])) OR ("lead poisoning"[mh])) AND (2013/01/01 : 3000[mhda] OR 2013/01/01 : 3000[crdt] OR 2013/01/01 : 3000[edat] OR 2013/01/01 : 3000[dp])
	(("lead acetate"[nm] AND (("Organometallic Compounds/toxicity"[mh] OR "Organometallic Compounds/adverse effects"[mh] OR "Organometallic Compounds/poisoning"[mh] OR "Organometallic Compounds/pharmacokinetics"[mh] OR "Organometallic Compounds/blood"[mh] OR "Organometallic Compounds/cerebrospinal fluid"[mh] OR "Organometallic Compounds/urine"[mh] OR "Organometallic Compounds/antagonists and inhibitors"[mh] OR ("Organometallic Compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh]))) OR ("Organometallic Compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "toxicokinetics"[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Organometallic Compounds"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Organometallic Compounds"[majr] AND cancer[sb]) OR ("Organometallic Compounds/pharmacology"[majr]) OR ("Organometallic Compounds"[mh] AND ((population health[tw] AND ("public health"[MeSH Major Topic] OR "public health administration"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health practice"[MeSH Terms] OR "public policy"[MeSH Terms])) OR (population[tw] AND "health care quality, access, and evaluation"[MeSH Major Topic] AND "demography"[MeSH Major Topic] AND "health services"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "population characteristics"[MeSH Major Topic] AND "social environment"[MeSH Major Topic]) OR ("health services accessibility"[MeSH Terms] AND "demography"[MeSH Terms] AND disparities[tw]) OR (population health[ti] AND ("health care quality, access, and evaluation"[MeSH Terms] OR "preventive health services"[MeSH Terms] OR "health planning"[MeSH Terms] OR "health policy"[MeSH Terms] OR "demography"[MeSH Terms] OR "health expenditures"[MeSH Terms] OR "income"[MeSH Terms] OR "population dynamics"[MeSH Terms] OR "social determinants of health"[MeSH Terms] OR "socioeconomic factors"[MeSH Terms] OR "population characteristics"[MeSH Terms] OR "health promotion"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health/methods"[Mesh Terms])) OR (population health[tw] AND ("community health services"[MeSH Major Topic] OR "health services"[MeSH Major Topic] OR "health services research"[MeSH Major Topic] OR "delivery of health care"[MeSH Major Topic] OR "health planning"[MeSH Major Topic] OR "health policy"[MeSH Major Topic] OR "preventive health services"[MeSH Major Topic] OR "health care evaluation mechanisms"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "public health/education"[MAJR] OR "public policy"[MeSH Major Topic] OR "quality of life"[MeSH Major Topic] OR "health surveys"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "demography"[MeSH Major Topic] OR "socioeconomic factors"[MeSH Major Topic] OR "health behavior"[MeSH Major Topic] OR "attitude to health"[MeSH Major Topic] OR "social environment"[MeSH Major Topic] OR "social welfare"[MeSH Major Topic] OR "population characteristics"[MeSH Major Topic] OR "vulnerable populations"[MeSH Major Topic] OR "residence characteristics"[MeSH Terms] OR "poverty"[MeSH Major Topic] OR "healthcare disparities"[MeSH Major Topic])) OR ("health status indicators"[MeSH Terms] AND "mass screening/methods"[MAJR] AND "morbidity"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "public health practice"[MeSH Major Topic] AND "outcome assessment (health care)"[MeSH Terms]) OR (built environment[tw] AND ("public health"[MeSH Major Topic] OR (("population"[MeSH Terms] OR "population"[All Fields] OR "population groups"[MeSH Terms] OR ("population"[All Fields] AND "groups"[All Fields]) OR "population groups"[All Fields]) AND ("health"[MeSH Terms] OR "health"[All Fields])))) OR ((socioeconomic[tw] OR inequality[tw] OR inequalities[tw] OR disparity[tw] OR disparities[tw] OR equity[tw] OR inequity[tw] OR inequities[tw] OR policy[tw] OR policies[tw] OR determinants[tw]) AND population health[tw] NOT medline[sb]) AND english[la] NOT letter[pt])))) OR ("lead azide"[nm] AND (("Azides/toxicity"[mh] OR "Azides/adverse effects"[mh] OR "Azides/poisoning"[mh] OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	"Azides/pharmacokinetics"[mh] OR "Azides/blood"[mh] OR "Azides/cerebrospinal fluid"[mh] OR "Azides/urine"[mh] OR "Azides/antagonists and inhibitors"[mh] OR ("Azides/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh]))) OR ("Azides"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "toxicokinetics"[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Azides"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Azides"[majr] AND cancer[sb]) OR ("Azides/pharmacology"[majr]) OR ("Azides"[mh] AND ((population health[tw] AND ("public health"[MeSH Major Topic] OR "public health administration"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health practice"[MeSH Terms] OR "public policy"[MeSH Terms])) OR (population[tw] AND "health care quality, access, and evaluation"[MeSH Major Topic] AND "demography"[MeSH Major Topic] AND "health services"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "population characteristics"[MeSH Major Topic] AND "social environment"[MeSH Major Topic]) OR ("health services accessibility"[MeSH Terms] AND "demography"[MeSH Terms] AND disparities[tw]) OR (population health[ti] AND ("health care quality, access, and evaluation"[MeSH Terms] OR "preventive health services"[MeSH Terms] OR "health planning"[MeSH Terms] OR "health policy"[MeSH Terms] OR "demography"[MeSH Terms] OR "health expenditures"[MeSH Terms] OR "income"[MeSH Terms] OR "population dynamics"[MeSH Terms] OR "social determinants of health"[MeSH Terms] OR "socioeconomic factors"[MeSH Terms] OR "population characteristics"[MeSH Terms] OR "health promotion"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health/methods"[Mesh Terms])) OR (population health[tw] AND ("community health services"[MeSH Major Topic] OR "health services"[MeSH Major Topic] OR "health services research"[MeSH Major Topic] OR "delivery of health care"[MeSH Major Topic] OR "health planning"[MeSH Major Topic] OR "health policy"[MeSH Major Topic] OR "preventive health services"[MeSH Major Topic] OR "health care evaluation mechanisms"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "public health/education"[MAJR] OR "public policy"[MeSH Major Topic] OR "quality of life"[MeSH Major Topic] OR "health surveys"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "demography"[MeSH Major Topic] OR "socioeconomic factors"[MeSH Major Topic] OR "health behavior"[MeSH Major Topic] OR "attitude to health"[MeSH Major Topic] OR "social environment"[MeSH Major Topic] OR "social welfare"[MeSH Major Topic] OR "population characteristics"[MeSH Major Topic] OR "vulnerable populations"[MeSH Major Topic] OR "residence characteristics"[MeSH Terms] OR "poverty"[MeSH Major Topic] OR "healthcare disparities"[MeSH Major Topic])) OR ("health status indicators"[MeSH Terms] AND "mass screening/methods"[MAJR] AND "morbidity"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "public health practice"[MeSH Major Topic] AND "outcome assessment (health care)"[MeSH Terms]) OR (built environment[tw] AND ("public health"[MeSH Major Topic]

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	OR (("population"[MeSH Terms] OR "population"[All Fields] OR "population groups"[MeSH Terms] OR ("population"[All Fields] AND "groups"[All Fields]) OR "population groups"[All Fields]) AND ("health"[MeSH Terms] OR "health"[All Fields]))))) OR ((socioeconomic[tw] OR inequality[tw] OR inequalities[tw] OR disparity[tw] OR disparities[tw] OR equity[tw] OR inequity[tw] OR inequities[tw] OR policy[tw] OR policies[tw] OR determinants[tw]) AND population health[tw] NOT medline[sb]) AND english[la] NOT letter[pt])))) OR ("lead chromate"[nm] AND (("Chromates/toxicity"[mh] OR "Chromates/adverse effects"[mh] OR "Chromates/poisoning"[mh] OR "Chromates/pharmacokinetics"[mh] OR "Chromates/blood"[mh] OR "Chromates/cerebrospinal fluid"[mh] OR "Chromates/urine"[mh] OR "Chromates/antagonists and inhibitors"[mh] OR ("Chromates/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh]))) OR ("Chromates"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "toxicokinetics"[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Chromates"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Chromates"[majr] AND cancer[sb]) OR ("Chromates/pharmacology"[majr]) OR ("Chromates"[mh] AND ((population health[tw] AND ("public health"[MeSH Major Topic] OR "public health administration"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health practice"[MeSH Terms] OR "public policy"[MeSH Terms])) OR (population[tw] AND "health care quality, access, and evaluation"[MeSH Major Topic] AND "demography"[MeSH Major Topic] AND "health services"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "population characteristics"[MeSH Major Topic] AND "social environment"[MeSH Major Topic]) OR ("health services accessibility"[MeSH Terms] AND "demography"[MeSH Terms] AND disparities[tw]) OR (population health[ti] AND ("health care quality, access, and evaluation"[MeSH Terms] OR "preventive health services"[MeSH Terms] OR "health planning"[MeSH Terms] OR "health policy"[MeSH Terms] OR "demography"[MeSH Terms] OR "health expenditures"[MeSH Terms] OR "income"[MeSH Terms] OR "population dynamics"[MeSH Terms] OR "social determinants of health"[MeSH Terms] OR "socioeconomic factors"[MeSH Terms] OR "population characteristics"[MeSH Terms] OR "health promotion"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health/methods"[Mesh Terms])) OR (population health[tw] AND ("community health services"[MeSH Major Topic] OR "health services"[MeSH Major Topic] OR "health services research"[MeSH Major Topic] OR "delivery of health care"[MeSH Major Topic] OR "health planning"[MeSH Major Topic] OR "health policy"[MeSH Major Topic] OR "preventive health services"[MeSH Major Topic] OR "health care evaluation mechanisms"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "public health/education"[MAJR] OR "public policy"[MeSH Major Topic] OR "quality of life"[MeSH Major Topic] OR "health surveys"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "demography"[MeSH Major Topic] OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	"socioeconomic factors"[MeSH Major Topic] OR "health behavior"[MeSH Major Topic] OR "attitude to health"[MeSH Major Topic] OR "social environment"[MeSH Major Topic] OR "social welfare"[MeSH Major Topic] OR "population characteristics"[MeSH Major Topic] OR "vulnerable populations"[MeSH Major Topic] OR "residence characteristics"[MeSH Terms] OR "poverty"[MeSH Major Topic] OR "healthcare disparities"[MeSH Major Topic])) OR ("health status indicators"[MeSH Terms] AND "mass screening/methods"[MAJR] AND "morbidity"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "public health practice"[MeSH Major Topic] AND "outcome assessment (health care)"[MeSH Terms]) OR (built environment[tw] AND ("public health"[MeSH Major Topic] OR (("population"[MeSH Terms] OR "population"[All Fields] OR "population groups"[MeSH Terms] OR ("population"[All Fields] AND "groups"[All Fields]) OR "population groups"[All Fields]) AND ("health"[MeSH Terms] OR "health"[All Fields])))) OR ((socioeconomic[tw] OR inequality[tw] OR inequalities[tw] OR disparity[tw] OR disparities[tw] OR equity[tw] OR inequity[tw] OR inequities[tw] OR policy[tw] OR policies[tw] OR determinants[tw]) AND population health[tw] NOT medline[sb]) AND english[la] NOT letter[pt]))) OR ("lead nitrate"[nm] AND (("Nitrates/toxicity"[mh] OR "Nitrates/adverse effects"[mh] OR "Nitrates/poisoning"[mh] OR "Nitrates/pharmacokinetics"[mh] OR "Nitrates/blood"[mh] OR "Nitrates/cerebrospinal fluid"[mh] OR "Nitrates/urine"[mh] OR "Nitrates/antagonists and inhibitors"[mh] OR ("Nitrates/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh]))) OR ("Nitrates"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "toxicokinetics"[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Nitrates"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Nitrates"[majr] AND cancer[sb]) OR ("Nitrates/pharmacology"[majr]) OR ("Nitrates"[mh] AND ((population health[tw] AND ("public health"[MeSH Major Topic] OR "public health administration"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health practice"[MeSH Terms] OR "public policy"[MeSH Terms])) OR (population[tw] AND "health care quality, access, and evaluation"[MeSH Major Topic] AND "demography"[MeSH Major Topic] AND "health services"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "population characteristics"[MeSH Major Topic] AND "social environment"[MeSH Major Topic]) OR ("health services accessibility"[MeSH Terms] AND "demography"[MeSH Terms] AND disparities[tw]) OR (population health[ti] AND ("health care quality, access, and evaluation"[MeSH Terms] OR "preventive health services"[MeSH Terms] OR "health planning"[MeSH Terms] OR "health policy"[MeSH Terms] OR "demography"[MeSH Terms] OR "health expenditures"[MeSH Terms] OR "income"[MeSH Terms] OR "population dynamics"[MeSH Terms] OR "social determinants of health"[MeSH Terms] OR "socioeconomic factors"[MeSH Terms] OR "population characteristics"[MeSH Terms] OR "health promotion"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health/methods"[Mesh Terms])) OR (population health[tw] AND ("community

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	health services"[MeSH Major Topic] OR "health services"[MeSH Major Topic] OR "health services research"[MeSH Major Topic] OR "delivery of health care"[MeSH Major Topic] OR "health planning"[MeSH Major Topic] OR "health policy"[MeSH Major Topic] OR "preventive health services"[MeSH Major Topic] OR "health care evaluation mechanisms"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "public health/education"[MAJR] OR "public policy"[MeSH Major Topic] OR "quality of life"[MeSH Major Topic] OR "health surveys"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "demography"[MeSH Major Topic] OR "socioeconomic factors"[MeSH Major Topic] OR "health behavior"[MeSH Major Topic] OR "attitude to health"[MeSH Major Topic] OR "social environment"[MeSH Major Topic] OR "social welfare"[MeSH Major Topic] OR "population characteristics"[MeSH Major Topic] OR "vulnerable populations"[MeSH Major Topic] OR "residence characteristics"[MeSH Terms] OR "poverty"[MeSH Major Topic] OR "healthcare disparities"[MeSH Major Topic])) OR ("health status indicators"[MeSH Terms] AND "mass screening/methods"[MAJR] AND "morbidity"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "public health practice"[MeSH Major Topic] AND "outcome assessment (health care)"[MeSH Terms]) OR (built environment[tw] AND ("public health"[MeSH Major Topic] OR (("population"[MeSH Terms] OR "population"[All Fields] OR "population groups"[MeSH Terms] OR ("population"[All Fields] AND "groups"[All Fields]) OR "population groups"[All Fields]) AND ("health"[MeSH Terms] OR "health"[All Fields])))) OR ((socioeconomic[tw] OR inequality[tw] OR inequalities[tw] OR disparity[tw] OR disparities[tw] OR equity[tw] OR inequity[tw] OR inequities[tw] OR policy[tw] OR policies[tw] OR determinants[tw]) AND population health[tw] NOT medline[sb]) AND english[la] NOT letter[pt]))) OR ("lead oxide"[nm] AND (("Oxides/toxicity"[mh] OR "Oxides/adverse effects"[mh] OR "Oxides/poisoning"[mh] OR "Oxides/pharmacokinetics"[mh] OR "Oxides/blood"[mh] OR "Oxides/cerebrospinal fluid"[mh] OR "Oxides/urine"[mh] OR "Oxides/antagonists and inhibitors"[mh] OR ("Oxides/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh]))) OR ("Oxides"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "toxicokinetics"[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Oxides"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Oxides"[majr] AND cancer[sb]) OR ("Oxides/pharmacology"[majr]) OR ("Oxides"[mh] AND ((population health[tw] AND ("public health"[MeSH Major Topic] OR "public health administration"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health practice"[MeSH Terms] OR "public policy"[MeSH Terms])) OR (population[tw] AND "health care quality, access, and evaluation"[MeSH Major Topic] AND "demography"[MeSH Major Topic] AND "health services"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "population characteristics"[MeSH Major Topic] AND "social environment"[MeSH Major Topic]) OR ("health services accessibility"[MeSH Terms] AND "demography"[MeSH Terms] AND disparities[tw]) OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	(population health[ti] AND ("health care quality, access, and evaluation"[MeSH Terms] OR "preventive health services"[MeSH Terms] OR "health planning"[MeSH Terms] OR "health policy"[MeSH Terms] OR "demography"[MeSH Terms] OR "health expenditures"[MeSH Terms] OR "income"[MeSH Terms] OR "population dynamics"[MeSH Terms] OR "social determinants of health"[MeSH Terms] OR "socioeconomic factors"[MeSH Terms] OR "population characteristics"[MeSH Terms] OR "health promotion"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health/methods"[Mesh Terms])) OR (population health[tw] AND ("community health services"[MeSH Major Topic] OR "health services"[MeSH Major Topic] OR "health services research"[MeSH Major Topic] OR "delivery of health care"[MeSH Major Topic] OR "health planning"[MeSH Major Topic] OR "health policy"[MeSH Major Topic] OR "preventive health services"[MeSH Major Topic] OR "health care evaluation mechanisms"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "public health/education"[MAJR] OR "public policy"[MeSH Major Topic] OR "quality of life"[MeSH Major Topic] OR "health surveys"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "demography"[MeSH Major Topic] OR "socioeconomic factors"[MeSH Major Topic] OR "health behavior"[MeSH Major Topic] OR "attitude to health"[MeSH Major Topic] OR "social environment"[MeSH Major Topic] OR "social welfare"[MeSH Major Topic] OR "population characteristics"[MeSH Major Topic] OR "vulnerable populations"[MeSH Major Topic] OR "residence characteristics"[MeSH Terms] OR "poverty"[MeSH Major Topic] OR "healthcare disparities"[MeSH Major Topic])) OR ("health status indicators"[MeSH Terms] AND "mass screening/methods"[MAJR] AND "morbidity"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "public health practice"[MeSH Major Topic] AND "outcome assessment (health care)"[MeSH Terms]) OR (built environment[tw] AND ("public health"[MeSH Major Topic] OR (("population"[MeSH Terms] OR "population"[All Fields] OR "population groups"[MeSH Terms] OR ("population"[All Fields] AND "groups"[All Fields]) OR "population groups"[All Fields]) AND ("health"[MeSH Terms] OR "health"[All Fields])))) OR ((socioeconomic[tw] OR inequality[tw] OR inequalities[tw] OR disparity[tw] OR disparities[tw] OR equity[tw] OR inequity[tw] OR inequities[tw] OR policy[tw] OR policies[tw] OR determinants[tw]) AND population health[tw] NOT medline[sb]) AND english[la] NOT letter[pt])))) OR ("lead sulfide"[nm] AND (("Sulfides/toxicity"[mh] OR "Sulfides/adverse effects"[mh] OR "Sulfides/poisoning"[mh] OR "Sulfides/pharmacokinetics"[mh] OR "Sulfides/blood"[mh] OR "Sulfides/cerebrospinal fluid"[mh] OR "Sulfides/urine"[mh] OR "Sulfides/antagonists and inhibitors"[mh] OR ("Sulfides/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh]))) OR ("Sulfides"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "toxicokinetics"[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Sulfides"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Sulfides"[majr] AND cancer[sb]) OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	("Sulfides/pharmacology"[majr]) OR ("Sulfides"[mh] AND ((population health[tw] AND ("public health"[MeSH Major Topic] OR "public health administration"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health practice"[MeSH Terms] OR "public policy"[MeSH Terms])) OR (population[tw] AND "health care quality, access, and evaluation"[MeSH Major Topic] AND "demography"[MeSH Major Topic] AND "health services"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "population characteristics"[MeSH Major Topic] AND "social environment"[MeSH Major Topic]) OR ("health services accessibility"[MeSH Terms] AND "demography"[MeSH Terms] AND disparities[tw]) OR (population health[ti] AND ("health care quality, access, and evaluation"[MeSH Terms] OR "preventive health services"[MeSH Terms] OR "health planning"[MeSH Terms] OR "health policy"[MeSH Terms] OR "demography"[MeSH Terms] OR "health expenditures"[MeSH Terms] OR "income"[MeSH Terms] OR "population dynamics"[MeSH Terms] OR "social determinants of health"[MeSH Terms] OR "socioeconomic factors"[MeSH Terms] OR "population characteristics"[MeSH Terms] OR "health promotion"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health/methods"[Mesh Terms])) OR (population health[tw] AND ("community health services"[MeSH Major Topic] OR "health services"[MeSH Major Topic] OR "health services research"[MeSH Major Topic] OR "delivery of health care"[MeSH Major Topic] OR "health planning"[MeSH Major Topic] OR "health policy"[MeSH Major Topic] OR "preventive health services"[MeSH Major Topic] OR "health care evaluation mechanisms"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "public health/education"[MAJR] OR "public policy"[MeSH Major Topic] OR "quality of life"[MeSH Major Topic] OR "health surveys"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "demography"[MeSH Major Topic] OR "socioeconomic factors"[MeSH Major Topic] OR "health behavior"[MeSH Major Topic] OR "attitude to health"[MeSH Major Topic] OR "social environment"[MeSH Major Topic] OR "social welfare"[MeSH Major Topic] OR "population characteristics"[MeSH Major Topic] OR "vulnerable populations"[MeSH Major Topic] OR "residence characteristics"[MeSH Terms] OR "poverty"[MeSH Major Topic] OR "healthcare disparities"[MeSH Major Topic])) OR ("health status indicators"[MeSH Terms] AND "mass screening/methods"[MAJR] AND "morbidity"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "public health practice"[MeSH Major Topic] AND "outcome assessment (health care)"[MeSH Terms]) OR (built environment[tw] AND ("public health"[MeSH Major Topic] OR (("population"[MeSH Terms] OR "population"[All Fields] OR "population groups"[MeSH Terms] OR ("population"[All Fields] AND "groups"[All Fields]) OR "population groups"[All Fields]) AND ("health"[MeSH Terms] OR "health"[All Fields])))) OR ((socioeconomic[tw] OR inequality[tw] OR inequalities[tw] OR disparity[tw] OR disparities[tw] OR equity[tw] OR inequity[tw] OR inequities[tw] OR policy[tw] OR policies[tw] OR determinants[tw]) AND population health[tw] NOT medline[sb]) AND english[la] NOT letter[pt])))) OR ("lead carbonate"[nm] AND (("Carbonates/toxicity"[mh] OR "Carbonates/adverse effects"[mh] OR "Carbonates/poisoning"[mh] OR "Carbonates/pharmacokinetics"[mh] OR "Carbonates/blood"[mh] OR "Carbonates/cerebrospinal fluid"[mh] OR "Carbonates/urine"[mh] OR "Carbonates/antagonists and inhibitors"[mh] OR ("Carbonates/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh]))) OR ("Carbonates"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "toxicokinetics"[mh:noexp] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Carbonates"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Carbonates"[majr] AND cancer[sb]) OR ("Carbonates/pharmacology"[majr]) OR ("Carbonates"[mh] AND ((population health[tw] AND ("public health"[MeSH Major Topic] OR "public health administration"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health practice"[MeSH Terms] OR "public policy"[MeSH Terms])) OR (population[tw] AND "health care quality, access, and evaluation"[MeSH Major Topic] AND "demography"[MeSH Major Topic] AND "health services"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "population characteristics"[MeSH Major Topic] AND "social environment"[MeSH Major Topic]) OR ("health services accessibility"[MeSH Terms] AND "demography"[MeSH Terms] AND disparities[tw]) OR (population health[ti] AND ("health care quality, access, and evaluation"[MeSH Terms] OR "preventive health services"[MeSH Terms] OR "health planning"[MeSH Terms] OR "health policy"[MeSH Terms] OR "demography"[MeSH Terms] OR "health expenditures"[MeSH Terms] OR "income"[MeSH Terms] OR "population dynamics"[MeSH Terms] OR "social determinants of health"[MeSH Terms] OR "socioeconomic factors"[MeSH Terms] OR "population characteristics"[MeSH Terms] OR "health promotion"[MeSH Terms] OR "public health/education"[Mesh Terms] OR "public health/methods"[Mesh Terms])) OR (population health[tw] AND ("community health services"[MeSH Major Topic] OR "health services"[MeSH Major Topic] OR "health services research"[MeSH Major Topic] OR "delivery of health care"[MeSH Major Topic] OR "health planning"[MeSH Major Topic] OR "health policy"[MeSH Major Topic] OR "preventive health services"[MeSH Major Topic] OR "health care evaluation mechanisms"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "public health/education"[MAJR] OR "public policy"[MeSH Major Topic] OR "quality of life"[MeSH Major Topic] OR "health surveys"[MeSH Major Topic] OR "public health administration"[MeSH Major Topic] OR "demography"[MeSH Major Topic] OR "socioeconomic factors"[MeSH Major Topic] OR "health behavior"[MeSH Major Topic] OR "attitude to health"[MeSH Major Topic] OR "social environment"[MeSH Major Topic] OR "social welfare"[MeSH Major Topic] OR "population characteristics"[MeSH Major Topic] OR "vulnerable populations"[MeSH Major Topic] OR "residence characteristics"[MeSH Terms] OR "poverty"[MeSH Major Topic] OR "healthcare disparities"[MeSH Major Topic])) OR ("health status indicators"[MeSH Terms] AND "mass screening/methods"[MAJR] AND "morbidity"[MeSH Major Topic]) OR ("health status indicators"[MeSH Major Topic] AND "public health practice"[MeSH Major Topic] AND "outcome assessment (health care)"[MeSH Terms]) OR (built environment[tw] AND ("public health"[MeSH Major Topic] OR (("population"[MeSH Terms] OR "population"[All Fields] OR "population groups"[MeSH Terms] OR ("population"[All Fields] AND "groups"[All Fields]) OR "population groups"[All Fields]) AND ("health"[MeSH Terms] OR "health"[All Fields])))) OR ((socioeconomic[tw] OR inequality[tw] OR inequalities[tw] OR disparity[tw] OR disparities[tw] OR equity[tw] OR inequity[tw] OR inequities[tw] OR policy[tw] OR policies[tw] OR determinants[tw]) AND population health[tw] NOT medline[sb]) AND english[la] NOT letter[pt])))) OR (("Lead fluoroborate"[tw] OR "Borate(1-), tetrafluoro-, lead (2+)"[tw] OR "Lead borofluoride"[tw] OR "Lead boron fluoride"[tw] OR "Lead

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	fluoborate"[tw] OR "Lead tetrafluoroborate"[tw] OR "Lead(II) tetrafluoroborate"[tw] OR "Lead bis(tetrafluoroborate)"[tw] OR "Blei(II)-iodid"[tw] OR "Plumbous iodide"[tw] OR "Plumbum jodatum"[tw] OR "C.I. 77613"[tw] OR "Lead iodide"[tw] OR "Lead diiodide"[tw] OR "Lead(II) iodide"[tw] OR "Chromic acid lead salt with lead molybdate"[tw] OR "Chromic acid, lead and molybdenum salt"[tw] OR "Lead chromate molybdate"[tw] OR "Lead molybdate chromate"[tw] OR "Lead molybdenum chromate"[tw] OR "Molybdenum-lead chromate"[tw] OR "Chromium lead molybdenum oxide"[tw] OR "Lead-molybdenum chromate"[tw] OR "Tricinat"[tw] OR "3,3-didehydro-6,8,9-trinitro-2,4-Dioxa-3-plumbabicyclo[3.3.1]nona-1(9),5,7-triene"[tw] OR "Lead styphnate"[tw] OR "Lead trinitroresorcinate"[tw] OR "Lead tricinate"[tw] OR "Lead(II) styphnate"[tw] OR "1,3-Benzenediol, 2,4,6-trinitro-, lead(2+) salt"[tw] OR "2,4,6-trinitro-1,3-Benzenediol lead(2+) salt"[tw] OR "Lead 2,4,6-trinitro-m-phenylene dioxide"[tw] OR "Lead trinitroresorcinate"[tw] OR "[styphnato(2-)]Lead"[tw] OR "2,4,6-trinitroResorcinol, lead(2+) salt"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[sh:noexp] OR lead/ai))) AND (2013/01/01 : 3000[mhda] OR 2013/01/01 : 3000[crdt] OR 2013/01/01 : 3000[edat] OR 2013/01/01 : 3000[dp])
	(("pb"[ti] NOT medline[sb]) AND (2013/01/01 : 3000[crdt] OR 2013/01/01 : 3000[edat] OR 2013/01/01 : 3000[dp])) NOT ((("Lead"[ti] OR "C.I. 77575"[ti] OR "C.I. Pigment Metal 4"[ti] OR "CI 77575"[ti] OR "CI pigment metal 4"[ti] OR "Omaha & grant"[ti] OR "Pb-S 100"[ti] OR "Plumbum"[ti] OR "SSO 1"[ti] OR "Plumbous acetate"[ti] OR "Salt of saturn"[ti] OR "Unichem PBA"[ti] OR "RD 1333"[ti] OR "Plumbous bromide"[ti] OR "Plumbous chloride"[ti] OR "Phoenicochroite"[ti] OR "Plumbous chromate"[ti] OR "Chrome orange"[ti] OR "Blei(II)-iodid"[ti] OR "Plumbous iodide"[ti] OR "Plumbum jodatum"[ti] OR "C.I. 77613"[ti] OR "Plumbous nitrate"[ti] OR "Bleimonoxid"[ti] OR "Bleioxyd"[ti] OR "C.I. 77577"[ti] OR "C.I. Pigment Yellow 46"[ti] OR "CI 77577"[ti] OR "CI Pigment Yellow 46"[ti] OR "Litharge"[ti] OR "Massicot"[ti] OR "Massicotite"[ti] OR "Plumbi monoxidum"[ti] OR "Plumbous oxide"[ti] OR "Plumbum oxydatum"[ti] OR "C.I. 77622"[ti] OR "CI 77622"[ti] OR "Perlex paste 500"[ti] OR "Perlex paste 600A"[ti] OR "Plumbous phosphate"[ti] OR "Trilead bis(orthophosphate)"[ti] OR "Trilead phosphate"[ti] OR "Tricinat"[ti] OR "3,3-didehydro-6,8,9-trinitro-2,4-Dioxa-3-plumbabicyclo[3.3.1]nona-1(9),5,7-triene"[ti] OR "Anglislite"[ti] OR "C.I. 77630"[ti] OR "C.I. Pigment White 3"[ti] OR "CI 77630"[ti] OR "CI pigment white 3"[ti] OR "HB 2000"[ti] OR "Mulhouse White"[ti] OR "Natural anglesite"[ti] OR "Pigment White 3"[ti] OR "TS 100 sulfate"[ti] OR "C.I. 77640"[ti] OR "CI 77640"[ti] OR "Galena"[ti] OR "P 37 filter"[ti] OR "Plumbous sulfide"[ti] OR "Plumbane, tetraethyl-"[ti] OR "Tetra(methylethyl)lead"[ti] OR "Tetraethyllead"[ti] OR "Tetraethylplumbane"[ti] OR "Cerussete"[ti] OR "Cerussite"[ti] OR "Plumbous carbonate"[ti]) NOT medline[sb]) AND

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	(2013/01/01 : 3000[crdt] OR 2013/01/01 : 3000[edat] OR 2013/01/01 : 3000[dp]))
	****From the search results of this string, items that included "lead to" in titles were later removed using Endnote:** ((("Lead"[ti] OR "C.I. 77575"[ti] OR "C.I. Pigment Metal 4"[ti] OR "CI 77575"[ti] OR "CI pigment metal 4"[ti] OR "Omaha & grant"[ti] OR "Pb-S 100"[ti] OR "Plumbum"[ti] OR "SSO 1"[ti] OR "Plumbous acetate"[ti] OR "Salt of saturn"[ti] OR "Unichem PBA"[ti] OR "RD 1333"[ti] OR "Plumbous bromide"[ti] OR "Plumbous chloride"[ti] OR "Phoenicochroite"[ti] OR "Plumbous chromate"[ti] OR "Chrome orange"[ti] OR "Blei(II)-iodid"[ti] OR "Plumbous iodide"[ti] OR "Plumbum jodatum"[ti] OR "C.I. 77613"[ti] OR "Plumbous nitrate"[ti] OR "Bleimonoxid"[ti] OR "Bleioxyd"[ti] OR "C.I. 77577"[ti] OR "C.I. Pigment Yellow 46"[ti] OR "CI 77577"[ti] OR "CI Pigment Yellow 46"[ti] OR "Litharge"[ti] OR "Massicot"[ti] OR "Massicotite"[ti] OR "Plumbi monoxidum"[ti] OR "Plumbous oxide"[ti] OR "Plumbum oxydatum"[ti] OR "C.I. 77622"[ti] OR "CI 77622"[ti] OR "Perlex paste 500"[ti] OR "Perlex paste 600A"[ti] OR "Plumbous phosphate"[ti] OR "Trilead bis(orthophosphate)"[ti] OR "Trilead phosphate"[ti] OR "Tricinat"[ti] OR "3,3-didehydro-6,8,9-trinitro-2,4-Dioxa-3-plumbabicyclo[3.3.1]nona-1(9),5,7-triene"[ti] OR "Anglislite"[ti] OR "C.I. 77630"[ti] OR "C.I. Pigment White 3"[ti] OR "CI 77630"[ti] OR "CI pigment white 3"[ti] OR "HB 2000"[ti] OR "Mulhouse White"[ti] OR "Natural anglesite"[ti] OR "Pigment White 3"[ti] OR "TS 100 sulfate"[ti] OR "C.I. 77640"[ti] OR "CI 77640"[ti] OR "Galena"[ti] OR "P 37 filter"[ti] OR "Plumbous sulfide"[ti] OR "Plumbane, tetraethyl-"[ti] OR "Tetra(methylethyl)lead"[ti] OR "Tetraethyllead"[ti] OR "Tetraethylplumbane"[ti] OR "Cerussete"[ti] OR "Cerussite"[ti] OR "Plumbous carbonate"[ti]) NOT medline[sb]) AND (2013/01/01 : 3000[crdt] OR 2013/01/01 : 3000[edat] OR 2013/01/01 : 3000[dp]))
4/2016	((((("Lead dioxide"[tw] OR "C.I. 77580"[tw] OR "CI 77580"[tw] OR "Lead Brown"[tw] OR "Lead oxide"[tw] OR "Lead peroxide"[tw] OR "Lead superoxide"[tw] OR "Lead(IV) oxide"[tw])) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[sh:noexp] OR lead/ai)) OR (("C.I. 77580"[ti] OR "CI 77580"[ti]) NOT medline[sb]) OR (("C.I. 77578"[ti] OR "C.I. Pigment Red 105"[ti] OR "CI 77578"[ti] OR "CI Pigment Red 105"[ti] OR "Gold satinobre"[ti] OR "Heuconin 5"[ti] OR "Mennige"[ti] OR "Mineral Orange"[ti] OR "Mineral Red"[ti] OR "Minium"[ti] OR "Paris Red"[ti] OR "Pigment Red 105"[ti] OR "Plumboplumbic oxide"[ti] OR "Sandix"[ti] OR "Saturn Red"[ti] OR "Trilead tetraoxide"[ti] OR "Trilead tetroxide"[ti] OR "azarcon"[ti]) NOT medline[sb])) AND (2013/01/01 : 3000[mhda] OR 2013/01/01 : 3000[crdt] OR 2013/01/01 : 3000[edat] OR 2013/01/01 : 3000[dp])
Toxline	
2/2016	7439-92-1 [rn] AND 2013:2016 [yr] [not] PubMed [org] [not] pubdart [org]

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	(301-04-2 [rn] OR 13424-46-9 [rn] OR 10031-22-8 [rn] OR 7758-95-4 [rn]) AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]
	(7758-97-6 [rn] OR 13814-96-5 [rn] OR 10101-63-0 [rn] OR 12709-98-7 [rn] OR 10099-74-8 [rn]) AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]
	(1317-36-8 [rn] OR 7446-27-7 [rn] OR 15245-44-0 [rn] OR 7446-14-2 [rn] OR 1314-87-0 [rn]) AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]
	(78-00-2 [rn] OR 598-63-0 [rn]) AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]
	(39377-56-5 [rn] OR 16040-38-3 [rn] OR 11119-70-3 [rn]) AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]
	("lead" NOT "nih reporter" [org]) AND 2013:2016 [yr] [not] PubMed [org] [not] pubdart [org]
	("c i 77575" OR "c i pigment metal 4" OR "ci 77575" OR "ci pigment metal 4" OR "omaha & grant" OR "pb s 100" OR "plumbum" OR "sso 1" OR "plumbous acetate" OR "salt of saturn" OR "unichem pba" OR "rd 1333" OR "plumbous bromide" OR "plumbous chloride" OR "phoenicochroite" OR "plumbous chromate" OR "chrome orange" OR "blei (ii) iodid" OR "plumbous iodide") AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]
	("plumbum jodatum" OR "c i 77613" OR "plumbous nitrate" OR "bleimonoxid" OR "bleioxyd" OR "c i 77577" OR "c i pigment yellow 46" OR "ci 77577" OR "ci pigment yellow 46" OR "litharge" OR "massicot" OR "massicotite" OR "plumbi monoxidum" OR "plumbous oxide" OR "plumbum oxydatum" OR "c i 77622" OR "ci 77622" OR "perlex paste 500" OR "perlex paste 600a" OR "plumbous phosphate") AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]
	("trilead bis (orthophosphate) " OR "trilead phosphate" OR "tricinat" OR "3 3-didehydro-6 8 9-trinitro-2 4-dioxa-3-plumbabicyclo 3 1] nona-1 (9) 5 7-triene" OR "anglislite" OR "c i 77630" OR "c i pigment white 3" OR "ci 77630" OR "ci pigment white 3" OR "hb 2000" OR "mulhouse white" OR "natural anglesite" OR "pigment white 3" OR "ts 100 sulfate" OR "c i 77640" OR "ci 77640" OR "galena") AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]
	("p 37 filter" OR "plumbous sulfide" OR "plumbane tetraethyl " OR "tetra (methylethyl) lead" OR "tetraethyllead" OR "tetraethylplumbane" OR "cerussete" OR "cerussite" OR "plumbous carbonate") AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]
4/2016	("lead tetroxide" OR "lead orthoplumbate" OR "lead oxide" OR "lead tetraoxide" OR "lead tetroxide" OR "orange lead" OR "red lead") AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]
	("c i 77578" OR "c i pigment red 105" OR "ci 77578" OR "ci pigment red 105" OR "gold satinobre" OR "heuconin 5" OR "mennige" OR "mineral orange" OR "mineral red" OR "minium" OR "paris red" OR "pigment red 105" OR "plumboplumbic oxide" OR "sandix" OR "saturn red" OR "trilead tetraoxide" OR "trilead tetroxide" OR "azarcon") AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]
	("lead dioxide" OR "c i 77580" OR "ci 77580" OR "lead brown" OR "lead oxide" OR "lead peroxide" OR "lead superoxide" OR "lead (iv) oxide") AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]
	(1309-60-0 [rn] OR 1314-41-6 [rn]) AND 2013:2016 [yr] AND NOT PubMed [org] AND NOT pubdart [org]

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
Toxcenter	
2/2016	FILE 'TOXCENTER' ENTERED AT 13:10:46 ON 19 FEB 2016 L1 198675 SEA FILE=TOXCENTER 7439-92-1 L2 11485 SEA FILE=TOXCENTER 301-04-2 OR 13424-46-9 OR 10031-22-8 OR 7758-95-4 OR 7758-97-6 OR 13814-96-5 OR 10101-63-0 OR 12709-98-7 OR 10099-74-8 OR 1317-36-8 OR 7446-27-7 OR 15245-44-0 OR 7446-14-2 OR 1314-87-0 OR 78-00-2 OR 598-63-0 L3 382 SEA FILE=TOXCENTER 39377-56-5 OR 16040-38-3 OR 11119-70-3 L4 205804 SEA FILE=TOXCENTER L1 OR L2 L5 111 SEA FILE=TOXCENTER L3 NOT L4 L6 205915 SEA FILE=TOXCENTER L1 OR L2 OR L3 L7 193807 SEA FILE=TOXCENTER L6 NOT PATENT/DT L8 26193 SEA FILE=TOXCENTER L7 AND ED>=20130101 L9 23356 SEA FILE=TOXCENTER L7 AND PY>2012 L10 26193 SEA FILE=TOXCENTER L8 NOT TSCATS/FS DIS SAVED ACT TOXQUERY/Q --------- L11 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L12 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,IT) L13 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L14 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L15 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L16 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L17 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L18 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L19 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L20 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L21 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L22 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L23 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L24 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L25 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	L26 QUE (ENDOCRIN? AND DISRUPT?) L27 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L28 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L29 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L30 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L31 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L32 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L33 QUE (NEPHROTOX? OR HEPATOTOX?) L34 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L35 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L36 QUE L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33 OR L34 OR L35 L37 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L38 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L39 QUE L36 OR L37 OR L38 L40 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L41 QUE L39 OR L40 --------- L42 26504 SEA FILE=TOXCENTER L8 OR L9 L43 5804 SEA FILE=TOXCENTER L42 AND L40 L44 12460 SEA FILE=TOXCENTER L42 AND L41 L45 10471 SEA FILE=TOXCENTER L42 AND L36 L46 1752 SEA FILE=TOXCENTER L43 NOT L45 L47 12223 SEA FILE=TOXCENTER L45 OR L43 L48 1808 SEA FILE=TOXCENTER L47 AND MEDLINE/FS L49 3320 SEA FILE=TOXCENTER L47 AND BIOSIS/FS L50 7088 SEA FILE=TOXCENTER L47 AND CAPLUS/FS L51 7 SEA FILE=TOXCENTER L47 NOT (L48 OR L49 OR L50) L52 9699 DUP REM L48 L49 L50 L51 (2524 DUPLICATES REMOVED) ANSWERS '1-9699' FROM FILE TOXCENTER L*** DEL 1808 S L47 AND MEDLINE/FS L*** DEL 1808 S L47 AND MEDLINE/FS L53 1808 SEA FILE=TOXCENTER L52 L*** DEL 3320 S L47 AND BIOSIS/FS L*** DEL 3320 S L47 AND BIOSIS/FS L54 2567 SEA FILE=TOXCENTER L52

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	L*** DEL 7088 S L47 AND CAPLUS/FS L*** DEL 7088 S L47 AND CAPLUS/FS L55 5318 SEA FILE=TOXCENTER L52 L*** DEL 7 S L47 NOT (L48 OR L49 OR L50) L*** DEL 7 S L47 NOT (L48 OR L49 OR L50) L56 6 SEA FILE=TOXCENTER L52 L57 7891 SEA FILE=TOXCENTER (L53 OR L54 OR L55 OR L56) NOT MEDLINE/FS L58 2661 SEA FILE=TOXCENTER L57 AND PY=2013 L59 2407 SEA FILE=TOXCENTER L57 AND PY=2014 L60 1634 SEA FILE=TOXCENTER L57 AND PY=2015 L61 225 SEA FILE=TOXCENTER L57 AND PY=2016 L62 964 SEA FILE=TOXCENTER L57 NOT (L58 OR L59 OR L60 OR L61) D SCAN L58 D SCAN L59 D SCAN L60 D SCAN L61 D SCAN L62 FILE 'TOXCENTER' ENTERED AT 10:11:57 ON 24 FEB 2016 L1 198871 SEA FILE=TOXCENTER 7439-92-1 L2 11498 SEA FILE=TOXCENTER 301-04-2 OR 13424-46-9 OR 10031-22-8 OR 7758-95-4 OR 7758-97-6 OR 13814-96-5 OR 10101-63-0 OR 12709-98-7 OR 10099-74-8 OR 1317-36-8 OR 7446-27-7 OR 15245-44-0 OR 7446-14-2 OR 1314-87-0 OR 78-00-2 OR 598-63-0 L3 384 SEA FILE=TOXCENTER 39377-56-5 OR 16040-38-3 OR 11119-70-3 L4 206120 SEA FILE=TOXCENTER L1 OR L2 OR L3 L5 193989 SEA FILE=TOXCENTER L4 NOT PATENT/DT L6 26375 SEA FILE=TOXCENTER L5 AND ED>=20130101 ACT TOXQUERY/Q --------- L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	OVUM?) L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L22 QUE (ENDOCRIN? AND DISRUPT?) L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L29 QUE (NEPHROTOX? OR HEPATOTOX?) L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L35 QUE L32 OR L33 OR L34 L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 1602 SEA FILE=TOXCENTER L6 AND (L33 OR L34) ACT LEAD1/A --------- L39 (198675)SEA FILE=TOXCENTER 7439-92-1 L40 (11485)SEA FILE=TOXCENTER 301-04-2 OR 13424-46-9 OR 10031-22-8 OR 7758-95-4 OR 7758-97-6 OR 13814-96-5 OR 10101-63-0 OR 12709-98-

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	7 OR 10099-74-8 OR 1317-36-8 OR 7446-27-7 OR 15245-44-0 OR 7446-14-2 OR 1314-87-0 OR 78-00-2 OR 598-63-0
	L41 (382)SEA FILE=TOXCENTER 39377-56-5 OR 16040-38-3 OR 11119-70-3
	L42 (205915)SEA FILE=TOXCENTER L39 OR L40 OR L41
	L43 (193807)SEA FILE=TOXCENTER L42 NOT PATENT/DT
	L44 (26193)SEA FILE=TOXCENTER L43 AND ED>=20130101
	L45 (23356)SEA FILE=TOXCENTER L43 AND PY>2012
	L46 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L47 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L48 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L49 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L50 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L51 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L52 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L53 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L54 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L55 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L56 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L57 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L58 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L59 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L60 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L61 QUE (ENDOCRIN? AND DISRUPT?)
	L62 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L63 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L64 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L65 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L66 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L67 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	GENETIC(W)TOXIC?) L68 QUE (NEPHROTOX? OR HEPATOTOX?) L69 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L70 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L71 QUE L46 OR L47 OR L48 OR L49 OR L50 OR L51 OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58 OR L59 OR L60 OR L61 OR L62 OR L63 OR L64 OR L65 OR L66 OR L67 OR L68 OR L69 OR L70 L72 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L73 (26504)SEA FILE=TOXCENTER L44 OR L45 L74 (5804)SEA FILE=TOXCENTER L73 AND L72 L75 (10471)SEA FILE=TOXCENTER L73 AND L71 L76 12223 SEA FILE=TOXCENTER L75 OR L74 --------- L77 252 SEA FILE=TOXCENTER L38 NOT L76 L78 8 SEA FILE=TOXCENTER L77 AND MEDLINE/FS L79 26 SEA FILE=TOXCENTER L77 AND BIOSIS/FS L80 218 SEA FILE=TOXCENTER L77 AND CAPLUS/FS L81 0 SEA FILE=TOXCENTER L77 NOT (L78 OR L79 OR L80) L82 237 DUP REM L78 L79 L80 (15 DUPLICATES REMOVED) ANSWERS '1-237' FROM FILE TOXCENTER D SCAN L82
4/2016	FILE 'TOXCENTER' ENTERED AT 12:37:35 ON 06 APR 2016 L1 1212 SEA FILE=TOXCENTER 1309-60-0 L2 621 SEA FILE=TOXCENTER 1314-41-6 L3 997 SEA FILE=TOXCENTER (L1 OR L2) NOT PATENT/DT L4 174 SEA FILE=TOXCENTER L3 AND ED>=20130101 L5 156 SEA FILE=TOXCENTER L3 AND PY>2012 L6 178 SEA FILE=TOXCENTER L4 OR L5 ACT TOXQUERY/Q --------- L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L22 QUE (ENDOCRIN? AND DISRUPT?)
	L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L29 QUE (NEPHROTOX? OR HEPATOTOX?)
	L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31
	L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L35 QUE L32 OR L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 24 SEA FILE=TOXCENTER L6 AND L37
	L39 0 SEA FILE=TOXCENTER L38 AND MEDLINE/FS
	L40 24 DUP REM L38 (0 DUPLICATES REMOVED) ANSWERS '1-24' FROM FILE TOXCENTER

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	D SCAN L40

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance priority list (SPL) resource page, and other items as needed. Regulations applicable to Pb were identified by searching international and U.S. agency websites and documents.

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
2/2016	Compounds searched: 7439-92-1, 301-04-2, 13424-46-9, 10031-22-8, 7758-95-4, 7758-97-6, 11119-70-3, 13814-96-5, 10101-63-0, 12709-98-7, 10099-74-8, 1317-36-8, 7446-27-7, 16040-38-3, 15245-44-0, 7446-14-2, 39377-56-5, 1314-87-0, 78-00-2, 598-63-0, 1309-60-0, 1314-41-6
NTP	
2/2016	"Lead" OR "7439 92 1" OR "301 04 2" OR "13424 46 9" OR "10031 22 8" OR "7758 95 4" OR "7758 97 6" OR "13814 96 5" OR "10101 63 0" OR "12709 98 7" OR "10099 74 8" OR "1317 36 8" OR "7446 27 7" OR "15245 44 0" OR "7446 14 2" OR "1314 87 0" OR "78 00 2" OR "598 63 0" OR "39377 56 5" OR "16040 38 3" OR "11119 70 3" OR "C I 77575" OR "C I Pigment Metal 4" OR "CI 77575"
	"CI pigment metal 4" OR "Omaha & grant" OR "Pb-S 100" OR "Plumbum" OR "SSO 1" OR "Plumbous acetate" OR "Salt of saturn" OR "Unichem PBA" OR "RD 1333" OR "Plumbous bromide" OR "Plumbous chloride" OR "Phoenicochroite" OR "Plumbous chromate" OR "Chrome orange" OR "Blei(II)-iodid" OR "Plumbous iodide" OR "Plumbum jodatum" OR "C I 77613" OR "Plumbous nitrate" OR "Bleimonoxid" OR "Bleioxyd" OR "C I 77577" OR "C I Pigment Yellow 46" OR "CI 77577" OR "CI Pigment Yellow 46" OR "Litharge" OR "Massicot" OR "Massicotite" OR "Plumbi monoxidum" OR "Plumbous oxide" OR "Plumbum oxydatum" OR "C I 77622" OR "CI 77622" OR "Perlex paste 500" OR "Perlex paste 600A" OR "Plumbous phosphate" OR "Trilead bis(orthophosphate)" OR "Trilead phosphate" OR "Tricinat" OR "3 3-didehydro-6 8 9-trinitro-2 4-Dioxa-3-plumbabicyclo[3 3 1]nona-1(9) 5 7-triene" OR "Anglislite" OR "C I 77630" OR "C I Pigment White 3" OR "CI 77630" OR "CI pigment white 3" OR "HB 2000" OR "Mulhouse White" OR "Natural anglesite" OR "Pigment White 3" OR "TS 100 sulfate" OR "C I 77640" OR "CI 77640" OR "Galena" OR "P 37 filter" OR "Plumbous sulfide" OR "Plumbane tetraethyl-" OR "Tetra(methylethyl)lead" OR "Tetraethyllead" OR "Tetraethylplumbane" OR "Cerussete" OR "Cerussite" OR "Plumbous carbonate"
3/2016	"1309 60 0" OR "1314 41 6" OR "C I 77580" OR "CI 77580" OR "C I 77578" OR "C I Pigment Red 105" OR "CI 77578" OR "CI Pigment Red 105" OR "Gold satinobre" OR "Heuconin 5" OR "Mennige" OR "Mineral Orange" OR "Mineral Red" OR "Minium" OR "Paris Red" OR "Pigment Red 105" OR "Plumboplumbic oxide" OR "Sandix" OR "Saturn Red" OR "Trilead tetraoxide" OR "Trilead tetroxide" OR "azarcon" OR "Lead dioxide" OR "Lead Brown" OR "Lead peroxide" OR "Lead superoxide" OR "Lead(IV) oxide" OR "Lead tetroxide" OR "Lead orthoplumbate" OR "Lead tetraoxide" OR "Orange Lead" OR "Red Lead"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
NIH RePORTER	
6/2017	Text Search: "1,3-Benzenediol, 2,4,6-trinitro-, lead(2) salt" OR "2,4,6-trinitro-1,3-Benzenediol lead(2) salt" OR "2,4,6-trinitroResorcinol, lead(2) salt" OR "3,3-didehydro-6,8,9-trinitro-2,4-Dioxa-3-plumbabicyclo[3.3.1]nona-1(9),5,7-triene" "[styphnato(2-)]Lead" OR "Acetic acid lead(2) salt" OR "Acetic acid, lead salt" OR "Acetic acid, lead(2) salt" OR "Anglislite" OR "azarcon" OR "Blei(II)-iodid" OR "Bleimonoxid" OR "Bleioxyd" OR "Borate(1-), tetrafluoro-, lead (2)" OR "C.I. 77575" OR "C.I. 77577" OR "C.I. 77578" OR "C.I. 77580" OR "C.I. 77613" OR "C.I. 77622" OR "C.I. 77630" OR "C.I. 77640" OR "C.I. Pigment Metal 4" OR "C.I. Pigment Red 105" OR "C.I. Pigment White 3" OR "C.I. Pigment Yellow 46" OR "Carbonic acid, lead(2) salt)" OR "Cerussete" OR "Cerussite" OR "Chrome orange" OR "Chromic acid (H2CrO4), lead(2) salt" OR "Chromic acid lead salt with lead molybdate" OR "Chromic acid, lead and molybdenum salt" OR "Chromic acid, lead salt" OR "Chromic acid, lead(2) salt" OR "Chromium lead molybdenum oxide" OR "Chromium lead oxide" OR "CI 77575" OR "CI 77577" OR "CI 77578" OR "CI 77580" OR "CI 77622" OR "CI 77630" OR "CI 77640" OR "CI pigment metal 4" OR "CI Pigment Red 105" OR "CI pigment white 3" OR "CI Pigment Yellow 46" OR "Freemans White Lead" OR "Galena" OR "Gold satinobre" OR "HB 2000" OR "Heuconin 5" OR "Lead (II) chloride" OR "Lead 2,4,6-trinitro-m-phenylene dioxide" OR "Lead acetate" OR "Lead azide" OR "Lead bis(tetrafluoroborate)" OR "Lead borofluoride" OR "Lead boron fluoride" OR "Lead Bottoms" OR "Lead bromide" OR "Lead Brown" OR "Lead carbonate" OR "Lead chloride" OR "Lead chromate" OR "Lead chromate molybdate" OR "Lead di(acetate)" OR "Lead diacetate" OR "Lead diazide" OR "Lead dibasic acetate" OR "Lead dibromide" OR "Lead dichloride" OR "Lead diiodide" OR "Lead dinitrate" OR "Lead dioxide" OR "Lead element" OR "Lead flake" OR "Lead fluoborate" OR "Lead fluoroborate" OR "Lead iodide" OR "Lead metal" OR "Lead molybdate chromate" OR "Lead molybdenum chromate" OR "Lead monooxide" OR "Lead monosulfate" OR "Lead monosulfide" OR "Lead monoxide" OR "Lead nitrate" OR "Lead orthophosphate" OR "Lead orthoplumbate" OR "Lead oxide" OR "Lead peroxide" OR "Lead phosphate" OR "Lead protoxide" OR "Lead S 2" OR "Lead S2" OR "Lead styphnate" OR "Lead sulfate" OR "Lead sulfide" OR "Lead sulfide (PbS)" OR "Lead sulphate" OR "Lead sulphide" OR "Lead superoxide" OR "Lead tetraethide" OR "Lead tetraethyl" OR "Lead tetrafluoroborate" OR "Lead tetraoxide (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects Text Search: "Lead tetroxide" OR "Lead tricinate" OR "Lead trinitroresorcinate" OR "Lead(2) sulfate" OR "Lead(2) acetate" OR "Lead(2) azide" OR "Lead(2) bromide" OR "Lead(2) carbonate" OR "Lead(2) chloride" OR "Lead(2) nitrate" OR "Lead(2) oxide" OR "Lead(2) phosphate" OR "Lead(2) sulfide" OR "Lead(II) acetate" OR "Lead(II) azide" OR "Lead(II) bromide" OR "Lead(II) carbonate" OR "Lead(II) chloride" OR "Lead(II) chromate" OR "Lead(II) iodide" OR "Lead(II) nitrate" OR "Lead(II) oxide" OR "Lead(II) phosphate" OR "Lead(II) styphnate" OR "Lead(II) sulfate" OR "Lead(II) sulfide" OR "Lead(II) tetrafluoroborate" OR "Lead(IV) oxide" OR "Lead, tetraethyl-" OR "Lead-molybdenum chromate" OR "Litharge" OR "Massicot" OR "Massicotite" OR "Mennige" OR "Mineral Orange" OR "Mineral Red" OR "Minium" OR "Molybdenum-lead chromate" OR "Mulhouse White" OR "Natural anglesite" OR "Nitric acid, lead(2) salt" OR "Normal lead orthophosphate" OR "Omaha & grant" OR "Orange Lead" OR "P 37 filter" OR "Paris Red" OR "Pb-S 100" OR "Perlex paste 500" OR "Perlex paste 600A" OR "Phoenicochroite" OR "Phosphoric acid, lead salt" OR "Phosphoric acid, lead(2) salt" OR "Pigment Red 105" OR "Pigment White 3" OR "Plumbane, tetraethyl-" OR "Plumbi monoxidum" OR "Plumboplumbic oxide" OR "Plumbous acetate" OR "plumbous bromide" OR "Plumbous carbonate" OR "Plumbous chloride" OR "Plumbous chromate" OR "Plumbous iodide" OR "Plumbous nitrate" OR "Plumbous oxide" OR "Plumbous phosphate" OR "Plumbous sulfide" OR "Plumbum" OR "Plumbum jodatum" OR "Plumbum metallicum" OR "Plumbum oxydatum" OR "RD 1333" OR "Red Lead" OR "Rough lead bullion" OR "Salt of saturn" OR "Sandix" OR "Saturn Red" OR "SSO 1" OR "Sugar of lead" OR "Sulfuric acid,

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	lead(2) salt" OR "Tetra(methylethyl)lead" OR "Tetraethyl lead" OR "Tetraethyllead" OR "Tetraethylplumbane" OR "Tricinat" OR "Trilead bis(orthophosphate)" OR "Trilead phosphate" OR "Trilead tetraoxide" OR "Trilead tetroxide" OR "TS 100 sulfate" OR "Unichem PBA" OR "Yellow Lead Ocher" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
	Text Search: "lead" not ("lead academic" or "lead optimization") (Advanced), Search in: Projects Limit to: Project Title, AdminIC: All, Fiscal Year: Active Projects
	Text Search: "blood lead" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

Review articles were identified and used for the purpose of providing background information and identifying additional references. In addition, tree-searching of published literature was conducted to identify other publications. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

The 2016 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 12,829
- Number of records identified from EPA (2014c) ISA document and other strategies: 1,192
- Total number of records to undergo literature screening: 14,021

B.1.2 Literature Screening

A three-step process was used to screen the literature search to identify relevant studies on Pb:

- Secondary refinement in Endnote
- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, an secondary refinement process was used to remove studies with the phrase "lead to" in the title. Following this secondary refinement, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

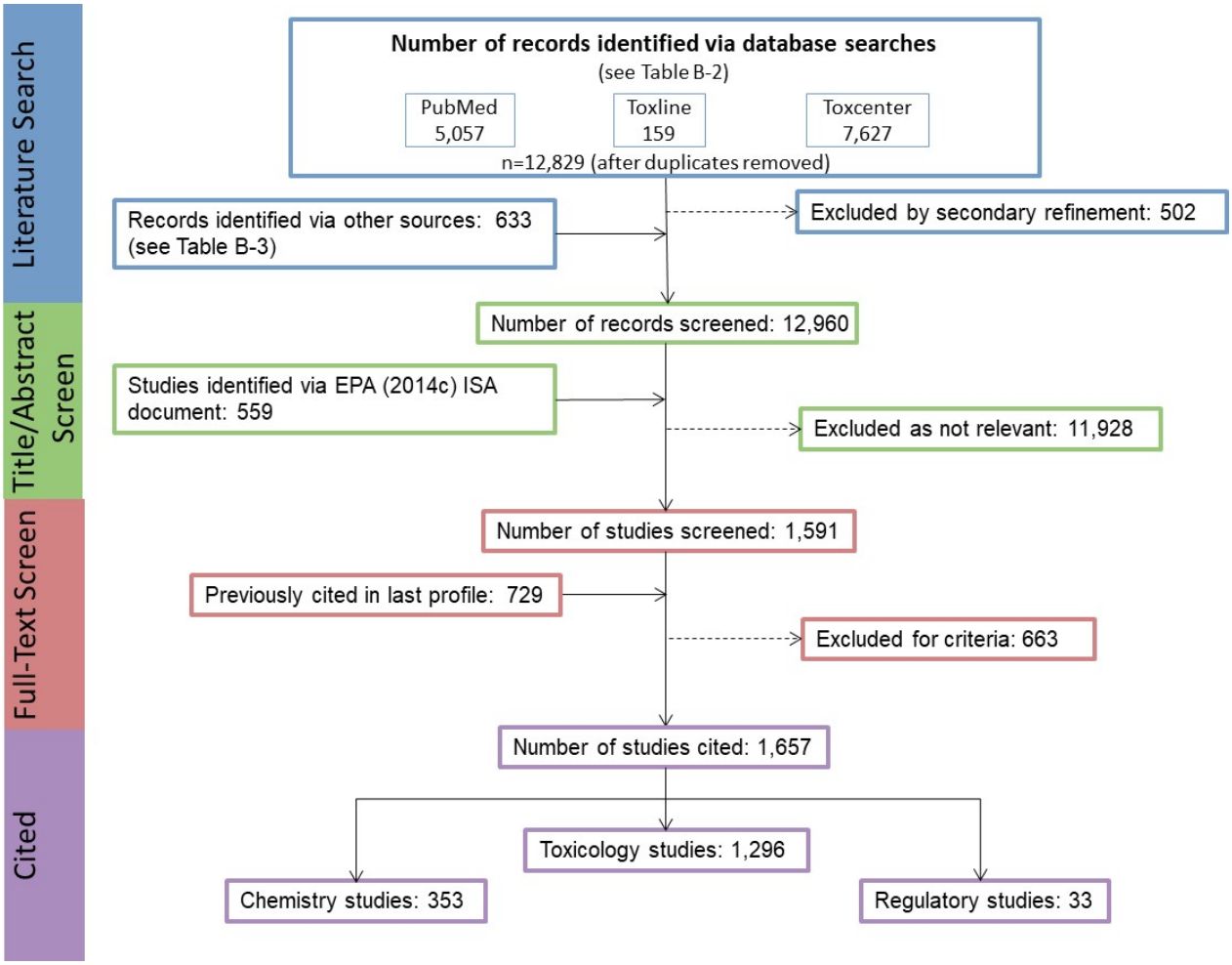
- Number of records excluded by secondary refinement: 502
- Number of studies identified via other strategies: 633
- Number of titles and abstracts screened: 12,960
- Number of studies identified via EPA (2014c) ISA document: 559
- Number of studies considered relevant and moved to the next step: 1,591

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 1,591
- Number of studies cited from the pre-public draft of the toxicological profile: 729
- Total number of studies cited in the profile: 1,657

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. September 2016 Literature Search Results and Screen for Pb



APPENDIX C. INGESTION OF LEAD DEBRIS

The main focus of this ATSDR Toxicological Profile for Lead is on health effects of chronic low-level environmental exposures. The profile also provides information on the clinical presentation of acute Pb toxicity, which occurs when large amounts of Pb are ingested. In children, this often occurs through ingestion of paint chips containing Pb, Pb-contaminated soils, or other non-solid forms of Pb. Ingestion of solid forms of Pb (Pb debris) is a unique exposure scenario in which there is accidental or purposeful ingestion of visible debris containing Pb. This exposure may be acute (debris is expelled or removed from the body soon after ingestion) or chronic (Pb debris is retained within the body, leading to continued elevation in PbB). There are several sources of Pb debris, including Pb shot or other debris found at firing or artillery ranges, or Pb shot found in wild game meats. The information presented below reviews toxicokinetics and adverse health effects of ingested Pb debris. Information regarding the chemistry, fate, and transport of Pb debris is reviewed in Chapter 5.

Overview. No controlled studies in humans have evaluated bioavailability or toxicity of ingested Pb debris (e.g., Pb shot and other Pb-containing debris from artillery or shooting ranges). Available information is anecdotal, obtained from case reports. Thus, data are not sufficient to determine the bioavailability of ingested Pb debris or to develop dose-response relationships for toxicity. Case reports of individuals ingesting Pb debris are summarized in Table C-1; these reports demonstrate the following:

- PbB rises rapidly (within hours to a few days) following ingestion of Pb debris.
- The clinical presentation of toxicity following ingestion of Pb debris is the same as that observed for acute Pb poisoning from ingestion of other forms of Pb (see Section 2.2).
- Severity of toxicity of ingested Pb debris will depend upon how much Pb is absorbed (e.g., toxicity is related to PbB; see Section 2.2).
- The onset of toxicity can be rapid (within hours to a few days).
- Following removal of Pb debris from the body, PbBs decrease; however, applying clinical protocols for chelation therapy results in a more rapid decrease in PbB.
- Ingested Pb debris can be retained in the appendix of some individuals and continue to contribute to elevated PbB.

Table C-1. Selected Case Studies of Ingestion of Solid Lead (Pb) Debris or Pb Retained in Gunshot Wounds

Reference and exposure	Blood lead concentration (PbB) (µg/dL)	Effects	Treatment
Banner et al. 2012 A 15-year-old boy ingested a "handful" of Pb shot. He was admitted to the hospital for treatment 14 days after exposure.	• Post-ingestion o 8 days: 54 o 14 days: 41 • Post-treatment (2 weeks): <5	• Most Pb was located in the appendix (14 days post-ingestion) • Abdominal pain • Elevated free erythrocyte protoporphyrin	• Whole bowel irrigation • Appendectomy • Chelation
CDC 2006 A 4-year-old boy with previously diagnosed microcephaly and mental delays ingested a metallic charm containing Pb. Time from exposure to first medical visit was not reported.	At death: 180	• Charm was retained in the stomach (was not removed) • Intractable vomiting • Cerebral edema • Seizures • Death	Supportive therapy
Clifton et al. 2002 A 21-month-old girl ingested Pb BB pellets. She was taken to the hospital approximately 6 hours post-ingestion.	• Pre-ingestion (routine): 12 • Post-ingestion (6 hours): 47 • Post-removal of pellets: 25 • Post-treatment (10 days): 16	• Hyperactivity • No signs of neurological or gastrointestinal toxicity	• Bowel irrigation • Colonoscopy for removal of pellets • Chelation
Cox and Pesola 2005 A 73-year-old woman ingested Pb shot in game over decades.	Not reported	• Pb shot accumulated in the appendix • No information on adverse health effects was reported	Not reported
Durlach et al. 1986 A 30-year-old man ingested Pb shot in game regularly over an unspecified period of time.	• At initial examination: 67.4 • Post-treatment o 10 days: 52.2 o 13 days: 24.5 o 1 month: 36.8 o 1.5 months: 31.6	• Pb shot accumulated in the appendix • Acute abdominal pain	• Bowel irritation • Chelation • Appendectomy

Table C-1. Selected Case Studies of Ingestion of Solid Lead (Pb) Debris or Pb Retained in Gunshot Wounds

Reference and exposure	Blood lead concentration (PbB) (µg/dL)	Effects	Treatment
Fergusson et al. 1997 A 4-year-old girl ingested a Pb fishing sinker. She was evaluated in the emergency room within 1 hour of ingestion.	• Day of ingestion: 4 • Day after ingestion: 16	No signs of toxicity observed	Endoscopy
Gerhardsson et al. 2002 A man in his "late 40s" had retained Pb shot following a gunshot wound to the shoulder. Reconstructive surgery occurred 54 days post-accident. Some, but not all, of the Pb shot was removed during surgery.	Approximate (data presented graphically), time after accident: • 25 days: 28 • 50 days: 41 • 54 days (day of surgery): 55 • ~60 days: 31 • 75 days: 48 • 200 days: 36 • 375 days: 30	• No signs of toxicity observed • Not all of the Pb shot could be removed during surgery	Surgical removal of Pb pellets
Guilaard et al. 2006 A 2-year-old boy ingested toy money made from pure metallic Pb.	Time post-ingestion • 1 day: 31.3 • 8 days: 61.1 • 1 month: 30.0 • 4 months: 24.9 • 10 months: 9.9	• Development of microcytic anemia and increased blood zinc protoporphyrin • No signs of toxicity observed	• Removal of object • Chelation (8 days post-ingestion)
Gustavsson and Gerhardsson 2005 A 45-year-old woman with elevated PbB was found to have Pb shot in her intestine from ingestion of game. The Pb shot was spontaneously eliminated. Time from ingestion was estimated to be sometime between 1993 and 2001.	Time of assessment: • January 2002: 55.0 • April 2003 (2 months post-elimination): 34.5 • November 2003: 7.2	• Malaise and fatigue • "Diffuse gastrointestinal symptoms"	No treatment (object was spontaneously eliminated)

Table C-1. Selected Case Studies of Ingestion of Solid Lead (Pb) Debris or Pb Retained in Gunshot Wounds

Reference and exposure	Blood lead concentration (PbB) (µg/dL)	Effects	Treatment
Hatten et al. 2013 • Case 1: A 15-year-old boy ingested rifle cartridges approximately 1 month prior to evaluation.	Case 1 • Initial assessment: 146 • 19 days post-treatment: 53 • 3 months post-treatment: 38	Case 1 • Decreased activity level • Vomiting, diarrhea, anorexia • Hyperactive patellar and brachioradialis reflexes	Case 1 • Cartridges removed by endoscopy • Chelation
• Case 2: A 65-year-old woman ingested several handfuls of bullets.	Case 2: Days after ingestion • Day 1: 9.7 • Day 2: 25.7 • Day 3: 40.5 • Day 60: 17.2	Case 2 • No signs of toxicity were observed	Case 2 • Endoscopy
Larsen and Blanton 2000 A 9-year-old boy ingested Pb shot in game; the Pb shot was retained in the appendix.	Not reported	• Abdominal pain and anorexia	Appendectomy
Lyons and Filston 1994 A 4-year-old boy ingested Pb shot, which was lodged in his appendix.	• Peak (time of assessment not reported): 23 • Prior to surgery (1.5 months after ingestion): 12	• Abdominal discomfort, nausea, vomiting, diarrhea • Headache	Appendectomy
Madsen et al. 1988 Seven patients with Pb shot retained in the appendix.	Range: 4.6–18.2	Not reported	Not reported
McKinney and McKinney 2000 A 5.5-year-old girl ingested several Pb pellets.	Time after ingestion • 13 hours: 57 • 36 hours: 79 After treatment: • 14 days: 14.3 • 6 months: 25	• Vomiting and abdominal pain • Decreased blood hemoglobin and hematocrit • “Mild” speech and language delays noted post-treatment	• Whole bowel irrigation • Chelation

Table C-1. Selected Case Studies of Ingestion of Solid Lead (Pb) Debris or Pb Retained in Gunshot Wounds

Reference and exposure	Blood lead concentration (PbB) (µg/dL)	Effects	Treatment
McNutt et al. 2001 A 45-year-old male ingested 206 Pb bullets. Medical evaluation occurred 5 days after ingestion. Bullets were spontaneously eliminated over 4–47 days after first medical evaluation.	Time after ingestion: • 5 days: 391 • 10 days: 171 • 25 days: 41 • 6 weeks: 24	• Abdominal pain and gastrointestinal bleeding • Anemia	Chelation started at initial medical visit
McQuirter et al. 2004 Subjects (n=451) 1-year following gunshot wound with retained bullets.	• PbB at time after injury: 1.9 • % with PbB ≥10 (days after injury) o 0 days: 2.1 o 3 days: 7.6 o 18 days: 25.1 o 3 months: 38.1 o 6 months: 28.5 o 12 months: 15.8	Not reported	Not reported
MMWR 2004 A 4-year-old boy ingested a Pb medallion.	• 2–3 weeks after ingestion: 123 • After treatment: 57	• Abdominal pain, vomiting, diarrhea • Normocytic anemia, elevated protoporphyrin	• Endoscopy • Chelation
Mowad et al. 1998 An 8-year-old boy ingested several Pb fishing sinkers. Medical assessment was within 1 days of ingestion.	Time after ingestion: • 1 day: 53 • 6 days: 45 (start of chelation) • 1 month: 3	No signs of toxicity observed	• Bowel irrigation • Colonoscopy • Chelation
Treble and Thompson 2002 A 2.5-year-old girl ingested Pb pellets.	Time after ingestion • 1.5 hours: 56 • 29 hours: 35 • 94 hours: 35	No signs of toxicity observed	Laxatives

Table C-1. Selected Case Studies of Ingestion of Solid Lead (Pb) Debris or Pb Retained in Gunshot Wounds

Reference and exposure	Blood lead concentration (PbB) (µg/dL)	Effects	Treatment
Zardawi and Siriweera 2013 An 8-year-old boy ingested Pb pellets in game over a 2-year period.	Elevated PbB (17.4–27.4) over 2 years Pellets observed in appendix	Hyperactivity	• Bowel irrigation • Appendectomy

Confounding Factors. There are several uncertainties from case reports on ingestion of Pb debris. Therefore, it is not possible to determine dose, bioavailability, or accurate plasma-time concentration curves. Uncertainties include:

- Baseline PbB data are rarely available. Thus, it is difficult to determine the contribution of ingested Pb debris to measured PbB following ingestion.
- Time from ingestion of Pb debris to first clinical evaluation and PbB assessment is often unknown.
- No quantitative data on the dose of Pb ingested in debris are reported.
- No quantitative data on fecal excretion of ingested Pb are reported.
- Information on the chemical composition of Pb debris often is not reported.
- No information on potential differences in the bioavailability of different types of Pb debris is available

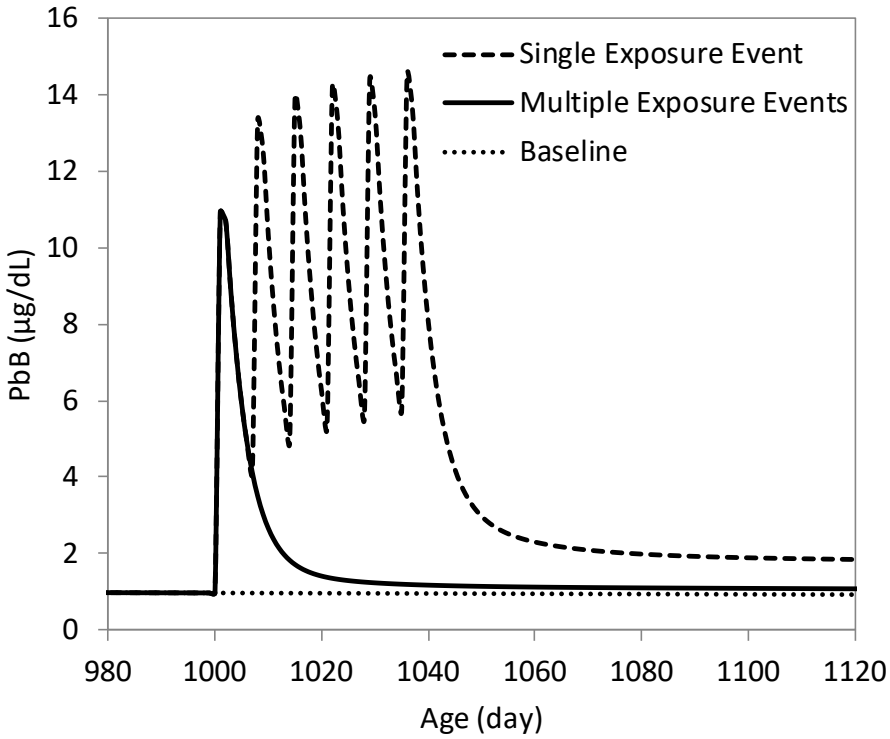
Bioavailability of Pb Debris. No quantitative estimates on the bioavailability of Pb debris in humans are available. Several case reports show increased PbB following ingestion of Pb debris, demonstrating that ingested Pb is absorbed (CDC 2006; Clifton et al. 2002; Durlach et al. 1986; Fergusson et al. 1997; Greensher et al. 1974; Guillard et al. 2006; Hatten et al. 2013; McKinney and McKinney 2000; McNutt et al. 2001; MMWR 2004; Mowad et al. 1998; Treble and Thompson 2002); see Table C-1 for details. However, due to lack of information on ingested dose, quantitative estimates of absorption cannot be determined. No information on bioavailability of Pb debris in animals was identified. Lead debris retained within the body will continue to contribute to elevated PbB until it is removed from the body, either spontaneously or by medical intervention (Banner et al. 2012; Clifton et al. 2002; Durlach et al. 1986; Gerhardsson et al. 2002; Guilaard et al. 2006; McQuirter et al. 2004).

Lead debris must become bioaccessible (i.e., soluble) in the gastrointestinal tract in order for it to be absorbed. It is likely that processes thought to contribute to rendering ingested soil Pb bioaccessible also are important in rendering ingested Pb debris bioaccessible (see Section 3.1.1). IVBA assays that measure extractable Pb have not been evaluated for predicting bioavailability or RBA of ingested Pb debris, although one study found that IVBA measured at gastric pH predicted the relatively high *in vivo* RBA (100%) of firing range soils (Bannon et al. 2009; see Section 3.1.1).

Although dose-PbB relationships and bioavailability cannot be reliably established from the published case history of Pb debris ingestion, it is possible to use exposure-biokinetics models to reconstruct the time course of PbB expected for a given acute dose of soluble Pb and, from this, estimate the relative

bioavailability of Pb from ingested Pb shot that would result in a given peak PbB. This scenario assumes that Pb debris is not retained in the body. The AALM-LG (EPA 2014a) can simulate the internal biokinetics of Pb associated with daily doses of Pb. This model predicts that a child 30 months of age who has a baseline PbB of 1 µg/dL would experience a 10 µg/dL increase in PbB in response to ingestion of approximately 1 mg of soluble Pb (Figure C-1). The peak PbB would occur during the day of ingestion and PbB would return to approximately 120% of baseline in approximately 35 days following the dose. If this prediction is extrapolated to the ingestion of Pb shot or other debris, the 1 mg dose of soluble Pb could occur in association with a dose of 100 mg of debris having an RBA of 1%, or 1 g of debris having an RBA of 0.1% (see Section 3.1.5.4 *EPA All Ages Lead Model [AALM]* for more information). Figure C-1 also shows the predicted PbB pattern for six repeated, weekly events in which the child ingested 1 mg of soluble PbB. This would result in periodic increases in PbB, with the maximum following each exposure event increasing until a pseudo-steady-state PbB was reached at approximately 14.5 µg/dL (13.5 µg/dL above baseline). The PbB would return to approximately 120% of baseline in approximately 570 days after the last exposure event. This longer time to baseline following multiple exposures reflects the accrual of Pb in bone with multiple dosing and the relatively slow transfer of Pb from bone to blood after exposure ceases (see Section 3.1).

Figure C-1. PbB Predicted from AALM-LG for a 0.9 mg Dose of Soluble Pb Ingested by a Child 30 Months of Age



Ingestion of soil from firing ranges may also contribute to PbB. A study in juvenile swine of eight soils (sieved to <250 µm) from small arms firing ranges showed a relative bioavailability range of 77–140%, with a mean of 108 % (SD or SE [not specified]: 18%). Soil from this site largely consisted of highly bioavailable Pb carbonate. However, this study does not provide information on bioavailability of Pb debris.

Retention of Pb Debris in the Appendix. Case reports show that Pb debris can be retained within the appendix (Banner et al. 2012; Cox and Pesola 2005; Durlach et al. 1986; Larsen and Blanton 2000; Lyons and Filston 1994; Madsen et al. 1988; Reddy 1985; Zardawi and Siriweera 2013); see Table C-1 for details. For this to occur, the appendix must be oriented with respect to the cecum in such a way to allow objects to pass through the appendiceal-cecal orifice; approximately 45% of the population have appendices with this orientation. However, approximately 65% of the population have appendices that might hinder foreign body access into the appendiceal lumen due to atypical anatomic position, adhesions, or kinks (Klinger et al. 1998). In addition to orientation of the appendix, the physical size and shape of the debris likely contribute to retention. Although it is not possible to determine the incidence of Pb debris lodged in the gastrointestinal tract or the appendix because not all

cases of ingestion of Pb debris are reported in the published literature, approximately 45% of the population is predisposed to retention of Pb debris on orientation of the appendix.

Toxicity of Ingested Pb Debris. Regardless of the source of Pb (e.g., ingested Pb debris, Pb paint, Pb-contaminated soil, occupational exposure), once Pb is absorbed into the body, toxicity will be related to PbB; thus, bioavailability and duration of elevated PbB, rather than the form of Pb ingested, will determine adverse health outcomes. If ingested Pb debris is not retained by the body, toxicity of PbB would be consistent with that described for acute Pb toxicity. A summary of peak PbBs and associated toxicity following exposure of ingested Pb debris is shown in Table C-2. Severity of toxicity increases with PbB. At PbB ≤47 µg/dL, the only adverse health effect observed was a single report of headache at a PbB of 12 µg/dL. With increased PbB, effects were observed in several organ systems and severity of effects increased. At a PbB range of 54–146 µg/dL, abdominal colic, vomiting, hematological effects, and neurological effects were observed, and at a PbB of 180 µg/dL, severe effects (seizure and cerebral edema) leading to death were observed. In most cases, the onset of toxicity occurs within hours or days of ingestion. If PbB remains elevated, either due to inadequate medical intervention or Pb that is retained within the body (i.e., appendix, gastrointestinal tract, etc.) adverse health effects associated with chronically elevated PbB would be expected to occur (see Chapter 2, Health Effects). As reviewed in Chapter 2, PbBs ≤10 µg/dL are associated with adverse health effects to numerous organ systems, including developmental and neurological effects, with severity exhibiting dose-dependence. Given the many factors that can affect development of Pb-induced toxicity, case reports of individuals cannot provide generalizations of exposure-response relationships. Therefore, epidemiological studies of exposed populations should be consulted to provide general exposure-response data for toxicity associated with prolonged exposure to retained Pb debris.

Table C-2. Peak Blood Lead Concentration (PbB) and Acute Toxicity Associated with Ingestion of Lead (Pb) Debris

Peak PbB (µg/dL)[a]	Effects associated with Pb exposure	References
12–16	No effects observed	Fergusson et al. 1997
	Headache	Lyons and Filston 1994
40.5–47	No effects observed	Clifton et al. 2002; Hatten et al. 2013
54–61	No effects observed	Mowad et al. 1998; Treble and Thompson 2002
	Abdominal colic	Banner et al. 2012
	Hematological effects[b]	

Table C-2. Peak Blood Lead Concentration (PbB) and Acute Toxicity Associated with Ingestion of Lead (Pb) Debris

Peak PbB (µg/dL)[a]	Effects associated with Pb exposure	References
79	Abdominal colic and vomiting	McKinney and McKinney 2000
	Hematological effects[c]	
	Neurological effects[d]	
123	Abdominal colic, vomiting, diarrhea Hematological effects[e]	MMWR 2004
146	Vomiting	Hatten et al. 2013
	Neurological signs[f]	
180	Vomiting	CDC 2006
	Seizures	
	Cerebral edema	
	Death	
391	Abdominal colic, gastrointestinal bleeding	McNutt et al. 2001
	Anemia	

[a]Peak blood Pb reported.
[b]Elevated free erythrocyte protoporphyrin or microcytic anemia and increased blood zinc protoporphyrin.
[c]Decreased blood hemoglobin and hematocrit.
[d]"Mild" speech and language delays.
[e]Normocytic anemia, elevated protoporphyrin
[f]Decreased activity level and hyperactive patellar and brachioradialis reflexes.

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APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absolute Bioavailability (ABA)—The amount of Pb absorbed expressed as a fraction or percent of ingested.

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Action Level (OSHA) – Employee exposure, without regard to the use of respirators, to an airborne concentration averaged over an 8-hour period.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioaccessibility (BA)—Fraction or percent of Pb in a medium (e.g., soil) that is released from the medium in the gastrointestinal tract so that it can be available to absorptive transport mechanisms (e.g., transcellular carriers or channels, paracellular diffusion).

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In vitro* bioaccessibility (IVBA)—**Bioaccessibility predicted from an *in vitro* extraction assay.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Relative bioavailability (RBA)—Absolute bioavailability (ABA) of Pb in a test material (e.g., soil) expressed as a fraction or percent of the ABA of a reference material (e.g., lead acetate).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—TRI tracks the management of certain toxic chemicals that may pose a threat to human health and the environment. U.S. facilities in different industry sectors must report annually how much of each chemical is released to the environment and/or managed through recycling, energy recovery, and treatment. (A "release" of a chemical means that it is emitted to the air or water, or placed in some type of land disposal.)

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
IVBA	*in vitro* bioaccessibility
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram

NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
RBA	relative bioavailability
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RR	relative risk or risk ratio
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor

U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

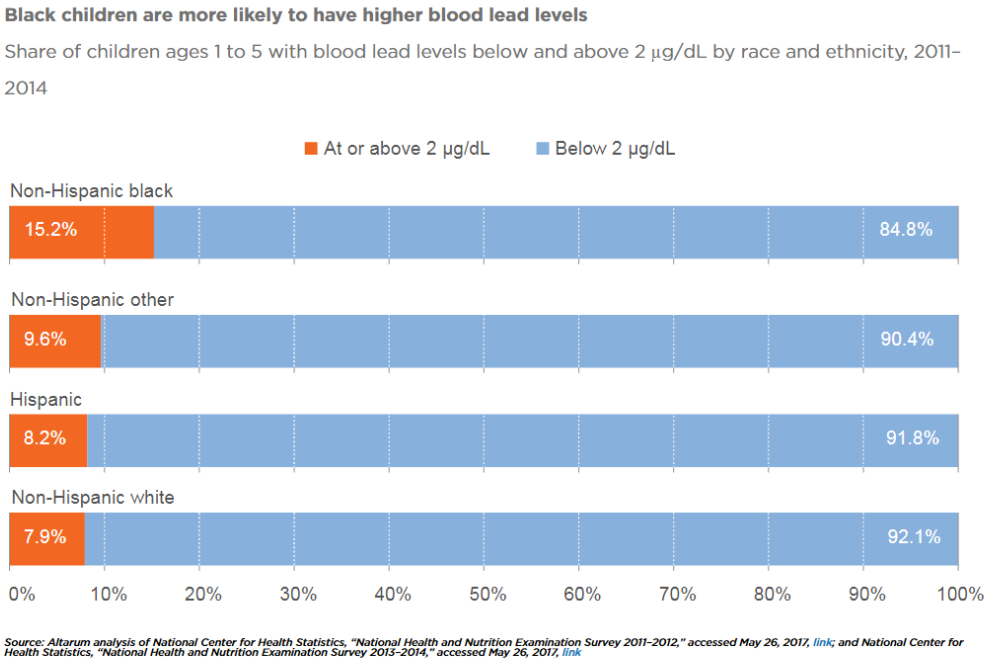
HB 1542_ACY_Gardiner
Uploaded by: Rock, Melissa
Position: FAV

EQUITY FOR ALL KIDS

ADVOCATES FOR CHILDREN AND YOUTH

To: Chairs Barve and Clippinger and members of the Environment and Transportation and Judiciary Committees
From: Shamoyia Gardiner, Education Policy Director
Re: House Bill 1542: Baltimore City - Lead Poisoning Testing Program and Lead Poisoning Prevention Fund
Date: March 6, 2020
Position: Support

There is no safe amount of lead in children's blood. The Centers for Disease Control (CDC) advises that even one microgram per deciliter of lead is enough to lower an individual's IQ by several points. Sustained exposure to this neurotoxin allows lead to accumulate in the bloodstream, causing a host of negative impacts not limited to: irritability, mood disorders, appetite loss, and developmental delays.[1] Lead poisoning has also been linked to violent crime, as evidenced by longitudinal studies in Flint, Michigan.[2] As an illustrative point, the presence of **a sugar packet's worth of lead dust in a two-bedroom home is enough to poison a child**.[3]



[1] Centers for Disease Control.
[2] Zahran et. al. *Four Phases of the Flint Water Crisis: Evidence from Blood Lead Levels in Children.* August, 2017.
[3] Meier, Helen. Department of Epidemiology, University of Wisconsin-Milwaukee.

An in-depth study revealed that in Detroit, MI environmental lead exposure has resulted in increased risk for: reading difficulties; course failure; attention deficit hyperactivity disorder, antisocial behavior, and delinquency. The same investigation found that 38%, 30.1%, and 31.8% of students receiving special educational services had blood lead levels of 5 micrograms/deciliter or less, between 5 and 10 micrograms/deciliter, and more than 10 micrograms/deciliter, respectively.[4] Indeed, reports of student misbehavior in parts of the state with higher rates of childhood lead exposure is unsurprising.

Children who are lead poisoned are 7 times more likely to drop out of school and 6 times more likely to become involved in the juvenile justice system. Given the racial disparities in who experiences lead poisoning, **this is yet another driver of the racial disparities in educational outcomes and criminal justice system involvement.**

Strong correlational data exists to indicate that high blood lead levels in children negatively impact academic outcomes and/or strain schools' operating budgets to provide additional services to students who may not have needed them, had they had not been poisoned. Data also demonstrates higher rates of lead poisoning in children who live in predominantly Black parts of the country like Flint, Detroit, and Baltimore City, as these areas have been created through explicitly racist redlining housing policies. It is not enough to lament the circumstances of hundreds of thousands of children—**it is incumbent upon this body to take action to address the crisis.**

Last year, the General Assembly passed the Lead Reduction and Remediation Act, though this did not guarantee sufficient funding for all affected schools to repair and/or replace lead-contaminated pipes or water outlets. While most schools in Baltimore City have banned drinking from all sinks and water fountains**, 519 schools across the state have been found to have elevated levels of lead in the drinking water supply**.[5]

HB 1542 offers an opportunity to take action: this bill establishes the Lead Poisoning Prevention Fund, which utilizes a $0.25/gallon fee paid by paint manufactures and wholesalers to help providers purchase lead poisoning testing equipment. This bill (as amended by the sponsor) addresses a clear and prevalent barrier to universal lead testing in Baltimore City: by providing testing on-site, health care providers can create an environment which ensures that transportation, working schedules, and other factors don't stop families from getting their children tested for lead poisoning. As early identification is key to early intervention, **ACY strongly urges a favorable report on this bill.**

[4] Tarr, et. al. *The Effects of Lead Exposure on School Outcomes Among Children Living and Attending Public Schools in Detroit, MI.*

[5] http://www.greenandhealthyhomes.org/home-health-hazards/lead

MedChi, MDAAP_Pam Kasemeyer_UNF_HB1542
Uploaded by: Kasemeyer, Pam
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MedChi

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TO: The Honorable Kumar P. Barve, Chair
Members, House Environment and Transportation Committee
The Honorable Nick Mosby

FROM: Pamela Metz Kasemeyer
J. Steven Wise
Danna L. Kauffman
Richard A. Tabuteau

DATE: March 6, 2020

RE: **OPPOSE** – House Bill 1542 – *Public Health – Lead Poisoning Testing Program and Lead Poisoning Prevention Fund*

On behalf of the Maryland State Medical Society (MedChi) and the Maryland Chapter of the American Academy of Pediatrics (MDAAP), we submit this letter of **opposition** for House Bill 1542.

House Bill 1542 establishes a Lead Poisoning Prevention Fund, a special fund administered by the Secretary of Health, funded by a 25-cent per gallon fee paid by paint manufacturers and wholesalers based on the number of gallons of paint sold in the State and third-party reimbursements from health care providers who are reimbursed by insurers for providing lead testing. The fund is intended to provide financial support to health care providers to test for lead and to purchase lead poisoning testing equipment. The bill also makes several changes to the State's Lead Poisoning Screening Program including the imposition of penalties on providers and labs who fail to test or report test results. While well intentioned, the above-named organizations do not think it advances the substantial work now being done to enhance lead testing, prevention, and intervention and could actually create unintended consequences that impedes the current program.

For instance, the bill's reference to testing versus screening fails to recognize that the fingerstick lead test is technically a screening test that is done as a blood test, fulfilling the state requirement for a blood lead sample. Also as noted above, using physician reimbursement for the lead testing to supply the proposed fund would be unfair to the practices that use the reimbursement for their costs in performing in-office screening. Furthermore, labs and offices performing blood lead tests were already obligated to report the results and there is no substantial evidence that failure to report results is a problem, thereby making the penalty provisions unnecessary and would not provide a substantial revenue source to the proposed fund.

In October 2015, the State released the Maryland Targeting Plan for Areas at Risk for Childhood Lead Poisoning (the 2015 targeting plan). The 2015 targeting plan and accompanying proposed regulations called for blood lead testing at 12 months and 24 months of age throughout the State. Previously, only children living in certain at-risk zip codes or who were enrolled in Medicaid were targeted for testing. As a result, since March 28, 2016, any geographic area within the State is considered an "at-risk" area for lead exposure. Under current regulations, all children born on or after January 1, 2015, must be tested for lead poisoning. Children born prior

to January 1, 2015, must be tested for lead poisoning if they reside in an at-risk area, as designated by the 2004 Targeting Plan for Areas at Risk for Childhood Lead Poisoning. There is also currently a Lead Poisoning Prevention Fund within the Maryland Department of the Environment (MDE) that consists of all fees collected and penalties imposed under the Subtitle 8 (Reduction of Lead Risk in Housing) of the Environment Article. MDE must use the fund to cover the costs of fulfilling program implementation costs for MDE and the Lead Poisoning Prevention Commission and for program development for these activities.

House Bill 1542 will not result in additional lead testing for Maryland's children and may actually result in fewer providers being willing to do onsite testing and submit for reimbursement, thereby reducing the number of children tested. There is appreciation for the sponsor's desire to address lead poisoning prevention, but House Bill 1542 is not a mechanism that achieves those objectives. An unfavorable report is requested.

For more information call:
Pamela Metz Kasemeyer
J. Steven Wise
Danna L. Kauffman
Richard A. Tabuteau
410-244-7000

ACA_Richard Tabuteau_UNF_HB1542
Uploaded by: Tabuteau, Richard
Position: UNF

TO: The Honorable Kumar P. Barve, Chair
Members, House Environment and Transportation Committee
The Honorable Nick Mosby

FROM: Richard A. Tabuteau
Pamela Metz Kasemeyer
J. Steven Wise

DATE: March 6, 2020

RE: **OPPOSE** – House Bill 1542 – *Public Health – Lead Poisoning Testing Program and Lead Poisoning Prevention Fund*

The American Coatings Association (ACA) is a voluntary, non-profit trade association working to advance the needs of the paint and coatings industry and the professionals who work in it. The organization represents paint and coatings manufacturers, raw materials suppliers, distributors, and technical professionals. ACA advises members and advances positions on legislative, regulatory and judicial issues, based on a thorough evaluation of issues through experience and understanding of the paint and coatings industry. On behalf of ACA, we submit this letter of **opposition** for House Bill 1542.

House Bill 1542 dramatically reforms Maryland's current lead screening, prevention and intervention programs. As proposed, the new framework will not enhance the current commitment of the State to increase screening and will likely divert attention and resources away from fundamental prevention-focused activities. Effective childhood lead exposure prevention programs must be focused on a multi-source, multi-pathway problem. Maryland has been a leader in passing sound and balanced legislation which sets duties of care for landlords and others and gives incentives for meeting those duties in a complementary way. Similarly, Maryland has prioritized a robust prevention program aimed at increasing screening for lead in order to ensure early intervention. The proposed approach to increased screening reflected in House Bill 1542 would assess a fee on all paint manufactures, regardless of whether they ever manufactured paint that contained lead. The bill also requires providers who are reimbursed for screening for lead by insurance carriers to contribute their reimbursement to the fund which in essence penalizes the providers for doing the screening they have been asked to do and could lead to a decrease in screening, not an increase.

Over the last half century, ACA has actively worked with many governments and nonprofit organizations to provide education and training on the dangers of childhood lead poisoning and the safe removal of lead-based paint from residential housing. ACA urges this committee to stay focused on the goal of eliminating childhood lead poisoning and to reject this bill.

For more information call:
Richard A. Tabuteau
Pamela Metz Kasemeyer
J. Steven Wise
410-244-7000

MDH_INFO_HB 1542
Uploaded by: Shek, Heather
Position: INFO

Maryland
DEPARTMENT OF HEALTH
Larry Hogan, Governor · Boyd K. Rutherford, Lt. Governor · Robert R. Neall, Secretary

March 6, 2020

The Honorable Kumar P. Barve
Chair, House Environment and Transportation Committee
Room 251, House Office Building
Annapolis, MD 21401-1991

RE: HB 1542 – "Public Health - Lead Poisoning Testing Program and Lead Poisoning Prevention Fund" – Letter of Information

Dear Chair Barve and Committee Mebers:

The Maryland Department of Health (the Department) is submitting this letter of information for HB 1542 – Public Health - Lead Poisoning Testing Program and Lead Poisoning Prevention Fund. This bill would require the Department to establish a universal lead testing program for each child in the State. Each child would be required to be tested at 12 and 24 months, except where the testing conflicts with a parent's or guardian's religious beliefs. HB 1542 further establishes financial penalties for health care providers that fail to test a child's blood lead level, and for medical laboratories that fail to report a lead level to the Maryland Department of the Environment. This bill also establishes a 25-cent fee for each gallon of paint sold in the State to be paid into a Lead Poisoning Prevention Fund (Fund) to offset costs related to testing blood lead levels.

Maryland statute currently allows the Department to determine whether blood lead testing or "screening" by the health care provider (using a series of questions regarding the child's environmental risks) is more appropriate, according to the Department's analysis of data related to the geographic distribution of lead hazards. As of 2016, Maryland requires all children to be tested for lead at 12 and 24 months (Code of Maryland Regulations 10.11.04), based on the 2015 report identifying all jurisdictions as areas where children are "at risk" of lead poisoning.[1] This bill would remove the Department's discretion to modify blood lead testing requirements based on the analysis of testing data to identify local trends and tailored strategies. Instead, HB 1542 would compel all health care providers to test all children at ages 12 and 24 months, regardless of any current or future analysis of risk by the Department.

As of 2018, 23.9% of children under 6 years of age were tested for blood lead.[2] Blood lead testing for children enrolled in Medicaid or the Children's Health Insurance Program (CHIP) is

[1] Maryland Targeting Plan for Areas at Risk of Childhood Lead Poisoning (October, 2015). Available at: https://phpa.health.maryland.gov/IDEHASharedDocuments/MD%202015%20Lead%20Targeting%20Plan.pdf
[2] Maryland Department of the Environment (October, 2019). Annual Report of Childhood Blood Lead Surveillance in Maryland (Calendar Year 2018 Data). Available at:

covered, and private health insurance plans will generally cover the 12- and 24-month tests, though not necessarily tests for children under the age of 6 years who have not yet been tested. Maryland children who are uninsured could benefit from the coverage provided by the Fund. According to the U.S. Census Bureau, approximately 12,000 children under the age of 6 in Maryland are uninsured.[3] Nationally, it is estimated that close to 90% of uninsured children are eligible for (but not enrolled in) Medicaid or CHIP.[4]

Blood lead levels can be tested in two ways. The first uses capillary blood (finger stick) and does not require skilled laboratory personnel. The capillary test is useful for point of care testing (testing in provider offices), but positive results must be confirmed by the second testing method which uses venous blood and must be performed by a Clinical Laboratory Improvement Amendments-certified laboratory. The Fund would provide health care providers with access to capillary blood testing equipment, but additional follow-up testing of positive results (including false positives) would still be required.

The Department and the Department of the Environment understand that despite the current requirement for testing at 12 and 24 months, parents and children still encounter barriers to blood lead testing. The Department acknowledges the importance of point of care testing and has adopted recommendations in the 2014 report of the Task Force on Point of Care Testing to reduce barriers to point of care testing.[5] This report found that it is not clear that financial incentives are the greatest barrier to adoption of point of care testing, nor is it clear that the lack of point of care testing is the most important barrier to testing. The Department and the Department of the Environment continue to focus outreach efforts on local jurisdictions where testing rates and the total number of children not tested are lowest, and where the likelihood of finding the maximum number of lead-exposed children is greatest.

The Department notes that there is an existing Lead Poisoning Prevention Fund established in Environment Article § 6-844 with the purpose of covering the costs of lead poisoning prevention efforts at the Department of the Environment.

This bill would have a fiscal impact on the Department as additional staff would be needed to administer the Lead Poisoning Testing Program and Lead Poisoning Prevention Fund. I hope this information is useful. If you would like to discuss this further, please contact Director of Governmental Affairs Webster Ye at (410) 260-3190 or webster.ye@maryland.gov.

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https://mde.maryland.gov/programs/LAND/Documents/LeadReports/LeadReportsAnnualChildhoodLeadRegistry/LeadReportCLR2018.pdf

[3] U.S. Census Bureau; American Community Survey, 2018 American Community Survey 1-Year Estimates, Table S2702; generated using American FactFinder, 27 February 2020 at: <http://factfinder.census.gov>.

[4] American Academy of Pediatrics Analysis of United States Census Bureau, "Health Insurance Status and Coverage by State – Children Under 18," 2008-2015 American Community Survey.

[5] Report to the General Assembly by the Task Force on Point of Care Testing for Lead Poisoning (Chapter 365). Available at: https://phpa.health.maryland.gov/Documents/Final%20Report_Lead%20Poisoning%20Point%20of%20Care%20Testing.pdf

Sincerely,

Robert R. Neall
Secretary