Measurement Challenges at Low Blood Lead Levels

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abstract

In 2012, the Centers for Disease Control and Prevention (CDC) adopted its Advisory Committee on Childhood Lead Poisoning Prevention recommendation to use a population-based reference value to identify children and environments associated with lead hazards. The current reference value of 5 µg/dL is calculated as the 97.5th percentile of the distribution of blood lead levels (BLLs) in children 1 to 5 years old from 2007 to 2010 NHANES data. We calculated and updated selected percentiles, including the 97.5th percentile, by using NHANES 2011 to 2014 blood lead data and examined demographic characteristics of children whose blood lead was ≥90th percentile value. The 97.5th percentile BLL of 3.48 µg/dL highlighted analytical laboratory and clinical interpretation challenges of blood lead measurements ≤5 µg/dL. Review of 5 years of results for target blood lead values <11 µg/dL for US clinical laboratories participating in the CDC's voluntary Lead and Multi-Element Proficiency quality assurance program showed 40% unable to quantify and reported a nondetectable result at a target blood lead value of 1.48 µg/dL, compared with 5.5% at a target BLL of 4.60 µg/dL. We describe actions taken at the CDC's Environmental Health Laboratory in the National Center for Environmental Health, which measures blood lead for NHANES, to improve analytical accuracy and precision and to reduce external lead contamination during blood collection and analysis.

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No safe blood lead concentration in children has been identified.[1,2] Lead can affect nearly every system in the body and is especially harmful to the developing central nervous systems of children.[3] Chronic lead exposure may occur with no obvious symptoms, but it has been associated with developmental delay, sluggishness and fatigue, weight loss, irritability, and learning difficulties.[3] In 2012, the Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) recommended using a population-based reference value, calculated as the 97.5th percentile of blood lead in children 1 to 5 years old in the United States, instead of a blood lead "level of concern" to identify children and environments associated with lead hazards.[2] Based on the 2007–2010 NHANES blood lead results, the reference value was 5 µg/dL. The ACCLPP recommended that CDC update the reference value every 4 years, based on the most recent NHANES blood lead data for children 1 to 5 years old.[2] CDC concurred or concurred in principle with the ACCLPP recommendations.[4]

Using available NHANES 2011 to 2014 data, we calculated the 97.5th

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percentile at 3.48 μg/dL (95% confidence interval, 2.65–4.29 μg/dL), ~30% lower than the current reference value. Our objective is to describe the laboratory implications of a decreasing trend in blood lead concentrations (referred to as blood lead levels [BLLs]) in US children and the clinical interpretation challenges that result from the variability of measurement of low BLLs. Because the CDC has not made a final decision about changing the current reference value of 5 μg/dL, we refer to a calculated 97.5th percentile rather than a reference value.

THE CHALLENGE FOR LABORATORIES THAT MEASURE BLOOD LEAD

As BLLs in US children have declined over time (Fig 1), acceptability criteria for laboratory performance of blood lead analysis in proficiency testing (PT) programs have become more rigorous, requiring laboratories to change processes and technologies. Before 1992, PT performance was judged satisfactory if the laboratory reported results for test samples that were within ±6 μg/dL or ±15% of the assigned (target) concentration for individual PT samples.[5] The Clinical Laboratory Improvement Amendments (CLIA) of 1988 tightened the acceptability criteria for blood lead measurements to ±4 μg/dL or ±10%, whichever is greater.[6] In 2010, the ACCLPP recommended that the criteria be reduced to ±2 μg/dL or ±10%, whichever is greater,[2] noting that the majority of laboratories measuring blood lead were already achieving measurement errors of ±2 μg/dL at these concentrations.[7] However, the acceptability criteria in the CLIA regulations have not been updated.

Measuring ever-lower BLLs required laboratories to shift to

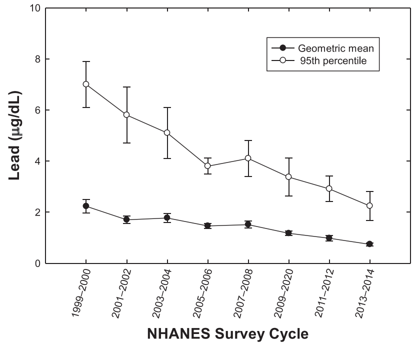

FIGURE 1
NHANES blood (μg/dL) lead geometric mean and 95th percentile by survey cycle. Note the steady decline in the BLLs in US children since 1999.

newer technologies with lower method limits of detection (LODs) and improved accuracy and precision. Methods in the 1970s were based on flame absorption spectroscopy, followed by methods based on electrothermal atomic absorption spectrometry and anodic stripping voltammetry. In the 1990s inductively coupled plasma mass spectrometry (ICP-MS) was introduced, and newer generations of ICP-MS have even higher sensitivity and lower background levels. These changes in analytical methods have made it possible for laboratories to achieve lower LODs and make accurate, precise blood lead measurements significantly <5 μg/dL. Nonetheless, achieving accurate and precise measurements at blood lead concentrations <5 μg/dL is an analytical challenge for CLIA-exempt instruments (eg, LeadCare II analyzer with an LOD of 3.3 μg/dL). In addition to highly technical measurement methods, such as ICP-MS, special precautions are needed to avoid external lead contamination of the blood collection devices and instrument reagents.

The CDC's Environmental Health Laboratory in the National Center for Environmental Health (EHL-NCEH) plays an important public health role in blood lead measurement that includes NHANES sample analyses that serve as reference values for US children and adults. Lot screening has been an important activity used by CDC's laboratory to exclude entire lots of devices or items used in blood collection (eg, butterfly needles, collection tubes, alcohol and iodine wipes) or analytical laboratory materials (eg, pipette tips, reagents) with unacceptable lead contamination that could result in falsely elevated BLLs. In addition, the CDC's ICP-MS analytical method timing, calibrator placement, calibration regression type, sample introduction system, and reagent composition were optimized for accurate and precise determination of lead in blood at low concentrations. By using all these measures, the EHL-NCEH achieved a blood lead LOD of 0.07 μg/dL for the 2013 to 2014 NHANES period.

As BLLs in United States children continue to decrease, more laboratories will need to be able to accurately measure concentrations below their current LODs. To do so, laboratories will need to consider various modifications, including selecting the optimal analytical method and testing for lead contamination of laboratory reagents and supplies used in the laboratory (eg, aliquotting devices, cryovials). Lead contamination also may occur during blood sample collection because of external skin contamination and small amounts of lead in the blood collections materials (eg, needles, vials, anticoagulants in tubes). Precautions to avoid skin contamination during blood collection are well known to clinicians and clinics that conduct lead testing. However, manufacturers of blood collection devices may need to consider testing these devices (referred to as "screening") for even lower levels of lead contamination that interfere with laboratory measurements and take actions to prevent lead contamination during production.

Although each device, reagent, or item that has contact with a child's blood may have only a small amount of lead, these sources are additive to a blood sample throughout the preanalytical and analytical process. Such contamination may have little impact to measurements of blood lead at values of ≥10 μg/dL; however, the sum of contamination sources may contribute significantly to blood lead measurements near or below the current reference value. It is a principle for blood lead or any analytical measurement that as the measurement approaches the LOD, the variability around the measurement increases significantly.[8] Therefore, as BLLs continue to decline, laboratories may need to lower their analytical LODs by using analytical process improvements, technology changes, or both. We describe several approaches used by the EHL-NCEH to improve analytical accuracy and precision and to reduce lead contamination during blood collection and specimen analysis.

METHODS

Data

The CDC's National Center for Health Statistics conducts the NHANES. The design is a complex, multistage, probability cluster sample designed to represent the US population based on age, sex, and race/ethnicity.[9] The survey has been continuous since 1999 and is intended to assess the health and nutritional status of the civilian, noninstitutionalized US population. Data are collected annually from ∼5000 participants through interviews, surveys, physical examinations, and clinical specimens. Data are publicly released in 2-year cycles. The NHANES incorporates sample population weights to account for the unequal selection probabilities caused by the cluster design, nonresponse, and planned oversampling of certain subgroups.[9] The National Center for Health Statistics Ethics Review Board approved all content, and all participants provided signed, informed consent before data and specimen collection. Data from NHANES 2011 to 2014 used for this analysis were from public release files available from the NHANES Web site. We used blood lead values (in μg/dL) and the following sociodemographic variables: sex, age, race and ethnicity, and annual household income. Age categories were 1 to 2, 3 to 4, and 5 years; race and ethnicity categories were self-reported as non-Hispanic white, non-Hispanic black, non-Hispanic Asian, and Hispanic, which includes Mexican American and other Hispanic. Annual household income was categorized as <$20 000, $20 000 to $44 999, and ≥$45 000.

Lot Screening

The EHL-NCEH screens a representative sample (usually 50 items) from each manufacturing lot of devices that come into contact with patient blood during collection, analysis, or storage or are used in the laboratory's analytical process for lead measurement. This screening is an essential preliminary step to accurately quantify blood lead and other metals. Without screening lots of blood collection and analytical materials and rejecting materials that are contaminated, there is a risk that ≥1 of the items could contain an amount of lead that is higher than LOD for the blood lead method. This contamination can result in falsely elevated BLLs. Examples of devices screened include needles, blood tubes (evacuated blood tubes, capillary tubes, cryovial storage tubes), syringes, and lancets. Each device is set up in a manner that mimics the way it is used in the field.

Deionized water is used as the screening solution for blood collection and storage devices that are either composed of stainless steel (needles) or come into contact with the stainless steel–containing devices (blood collection tubes). In general, the procedure involves rinsing a predetermined volume of water through the device, such as a butterfly or a needle. The lead concentration is measured in each collected rinse solution. The procedure is similar for screening laboratory devices used in the analytical process, such as pipette tips and autosampler vials.

A sample of analytical reagents from the same lot are also screened by measuring the lead concentration in a predetermined aliquot. Screen failure is defined by an equation that is based on the sample volume used, the LOD (eg, 0.25 μg/dL for blood lead in 2011–2012), and the expected mean concentration in the population (<1 μg/dL for 1- to 5-year-old children).[10] For each of its projects involving blood lead measurement, the laboratory either provides materials that have been screened or informs its collaborators of the manufacturer lot number that passed screening so that "clean" materials can be purchased.

Blood Lead Measurements

Whole blood specimens were collected by venipuncture performed with needles, disposable skin wipes, and blood collection tubes with anticoagulant. All collection supplies were lot screened and determined to be free of significant lead contamination. Samples were aliquoted with screened pipettes and

TABLE 1 Results of Manufacturer Lot Screening (2009–2016) for Multiple Devices Used in Blood Collection and BLLs (µg/dL) at the 97.5th Percentile in Children 1–5 y Old (NHANES 2009–2014)

NHANES, y	LOD, µg/dL	No. Lots Tested for Blood Metals	No. Lots Failed	Percentage of Failures, %	Geometric Mean, µg/dL	BLL at 97.5th Percentile, µg/dL
2009–2010	0.3	112	1	0.89	1.17	4.48
2011–2012	0.25	49	2	4.08	0.97	3.83
2013–2014	0.07	129	29	22.5	0.76	2.80
2015–2016[a]	0.07	85	30	35.3	N/A	N/A

N/A, blood lead results not available for NHANES 2015–2016. As the LOD decreases, the percentage of blood collection device lots (failures) increases, because of unacceptable metal contamination that could falsely elevate measurement results.
[a] From January 2015 to May 2016; not a completed NHANES cycle.

stored at ≤−20°C until they were shipped on dry ice to the CDC's EHL-NCEH, where they were stored frozen (≤−20°C) and analyzed within 3 weeks of collection.

Measurements were made[11] with the ELAN DRC II ICP-MS (PerkinElmer, Waltham, MA) and analysis tubes that had been previously lot screened. The method LOD was 0.25 µg/dL for NHANES 2011 to 2012 and 0.07 µg/dL for NHANES 2013 to 2014. The CDC ICP-MS analytical method timing, calibrator placement, calibration regression type, sample introduction system, and reagent composition were optimized for accurate and precise determination of lead at low concentrations in blood.

Lead and Multi-Element Proficiency

The Lead and Multi-Element Proficiency (LAMP) program is a voluntary performance and quality assurance program designed to promote high-quality whole blood lead, cadmium, mercury, selenium, and manganese measurements.[12] Participating laboratories analyze a set of blood samples that the CDC prepares by using standard reference materials, with analytical target values linked to the National Institute of Standards and Technologies Standard Reference Materials. The LAMP program ships 3 to 4 samples per challenge, 4 challenges a year, to the participating laboratories. After analyzing the samples in duplicate on 2 separate runs, each laboratory reports its results to the CDC. The CDC compiles the results by analytical method and reports both the laboratory group summary statistics and individual laboratory summary results, compared with the CDC target value and the laboratory group or consensus means. The blood lead target values ranged from 0.18 to 66 µg/dL for the study period of 2011 to 2015. To evaluate the accuracy and precision of the participating laboratories for this report, we reviewed results with a target value <11 µg/dL and included only laboratories that were continuously participating since 2011. Approximately 180 laboratories are enrolled in LAMP, and 66 US laboratories (15% academic, 6% federal government, 30% state government, 49% private) have been continuously participating since 2011, missing ≤3 rounds during this period. We used an imputed value ($LOD/\sqrt{2}$) when results were submitted as less than LOD. In this report, we evaluated performance in measuring blood lead at concentrations ≤11 µg/dL for the continuously participating laboratories.

Statistical Analysis

Percentiles

Percentiles for blood lead in children ages 1 to 5 years were calculated in SUDAAN version 11.0.0 (Research Triangle Institute, Research Triangle Park, NC). SUDAAN uses sample weights and calculates variance estimates that account for the complex survey design. Confidence intervals for percentiles were adapted from the methods of Korn and Graubard[13] and Woodruff.[14]

Children With BLLs at the 90th Percentile or Higher

Multiple logistic regression analysis was used to examine characteristics of children with BLLs at or above the 90th percentile, chosen to provide a larger sample size relative to the higher percentiles. Analyses were adjusted for sex, age group, race and ethnicity, and annual household income. An α level of .05 was used to determine statistical significance.

RESULTS

Lot Screening Failures

Because the CDC's analytical LOD for lead in whole blood has decreased over time, and BLLs in the United States population have decreased over time, lot screening has resulted in more "failures" due to unacceptable lead contamination. Between January 2009 and February 2016, the laboratory screened 359 manufacturing lots of needles, blood collection tubes, cryovials, and other items for lead. The decline in LOD and BLLs

TABLE 2 Sample-Weighted Percentiles of BLLs (μg/dL) for US Children (NHANES 2011–2014)

NHANES, y	Sample Size, *n*	Selected Percentiles (95% Confidence Intervals)				
		50th	75th	90th	95th	97.5th
2011–2012						
1–5 y	713	0.95 (0.87–1.04)	1.34 (1.2–1.66)	2.26 (1.88–2.65)	2.91 (2.41–3.83)	3.83 (2.53–6.43)[a]
2013–2014						
1–5 y	818	0.74 (0.68–0.80)	1.08 (0.94–1.24)	1.58 (1.33–1.90)	2.24 (1.68–2.64)	2.80 (2.31–3.93)[a]
2011–2014						
1–5 y	1531	0.82 (0.75–0.89)	1.21 (1.09–1.32)	1.90 (1.64–2.24)	2.57 (2.26–3.05)	3.48 (2.65–4.29)[a]

[a] *n* = 19, 32, and 46, respectively, for sample sizes for the 97.5th percentile in NHANES 2011–2012, 2013–2014, and 2011–2014.

TABLE 3 Demographic Distributions of the Weighted Adjusted Proportion (%) of US Children With BLLs (μg/dL) at the 97.5th Percentile or Higher, Versus Below the 97.5th Percentile (NHANES 2011–2014)

	<97.5th Percentile (95% Confidence Interval)	≥97.5th Percentile (95% Confidence Interval)	*P*[a]
Age, y			
1–2	38.0 (36.1–39.9)	52.6 (27.8–76.2)	.04
3–4	43.0 (40.0–46.0)	37.0 (19.3–59.1)	
5	19.0 (16.9–21.3)	10.3 (5.3–19.3)	
Sex			
Male	50.9 (48.3–53.5)	61.7 (37.8–81.1)	.43
Female	49.1 (46.5–51.7)	38.3 (18.9–62.3)	
Race and ethnicity			
All Hispanic	27.4 (21.3–34.5)	13.7 (4.8–33.4)	.06
Non-Hispanic blacks	14.8 (11.2–19.2)	30.9 (10.4–63.3)	
Non-Hispanic whites	52.8 (44.2–61.2)	52.8 (19.7–83.6)	
Non-Hispanic Asians	5.1 (3.9–6.6)	2.6 (0.4–16.6)	
Annual household income			
<$20 000	20.6 (17.3–24.4)	40.8 (30.1–52.4)	.006
≥$20 000	79.4 (75.6–82.7)	59.2 (47.6–69.9)	

[a] χ^2 test.

TABLE 4 Results of Multiple Logistic Regressions to Examine Associations Between Demographics and BLLs at or Above the 90th Percentile in Children Ages 1–5 y, NHANES 2011–2014

Category	≥90th Percentile (95% Confidence Interval)
Age, y	
1–2	3.90 (1.69–8.99)
3–4	2.44 (1.44–4.13)
5	1 (reference)
Sex	
Male	1.25 (0.82–1.90)
Female	1 (reference)
Race and ethnicity	
All Hispanic	0.64 (0.32–1.28)
Non-Hispanic blacks	1.34 (0.64–2.81)
Non-Hispanic whites	1 (reference)
Non-Hispanic Asians	1.19 (0.47–3.01)
Annual household income	
<$20 000	8.99 (5.05–16.01)
$20 000–$44 999	4.93 (2.71–8.98)
≥$45 000	1 (reference)

in children 1 to 5 years old was accompanied by an increase in the percentage of lot screen failures. In NHANES 2009 to 2010, with a mean BLL of 1.17 μg/dL and LOD of 0.3 μg/dL, <1% of 112 screened lots failed. In 2015, with a blood lead LOD of 0.07 μg/dL, the failure rate was 35% of 85 lots screened (Table 1).

Selected percentiles and 95% confidence intervals of blood lead concentrations in children 1 to 5 years old from the NHANES period 2011 to 2014 are presented in Table 2, as are the 50th, 75th, 90th, and 97.5th percentiles based on NHANES 2011 to 2014.

Children With BLLs at the 90th Percentile or Higher

Annual household income <$20 000 and age <3 years were significant predictors for a BLL ≥3.48 μg/dL (P = .006 and P = .04, respectively) (Table 3). We also observed a greater proportion of non-Hispanic blacks and boys with BLLs above the 97.5th percentile than below this percentile.

Multiple logistic regression results are presented in Table 4. Both age (P = .005) and income ($P \leq$ .0001) were statistically significant. Relative to 5-year-olds, children 1 to 2 years and 3 to 4 years old had a 3.9 and 2.4 times higher risk, respectively, of having a BLL at the 90th percentile or higher. Children in households with annual incomes

TABLE 5 LAMP Results for BLLs <10 μg/dL Reported by 66 Continuously Participating US Laboratories (2011–2015)

Sample ID	Target Value[a] (±3 SDs)	No. Laboratories Reported Results	Accurate Within a *z* Score of ±2, or Reported as Less Than LOD	No. Laboratories Reported Less Than LOD	% of Laboratories Reported Results Within a *z* Score of ±2 or Reported as Less Than LOD	Consensus Mean (SD)	RSD, %
1503	0.18 (0.03–0.33)	46	46	25	100	0.96 (0.81)	84
1402	0.20 (0.00–0.44)	48	48	25	100	0.94 (0.77)	82
1205	0.31 (0.22–0.40)	53	48	20	91	0.86 (0.78)	91
1304	0.34 (0.25–0.43)	52	50	20	96	0.92 (0.78)	85
1210	0.38 (0.35–0.41)	51	51	21	100	0.94 (0.64)	68
1101	0.42 (0.06–0.78)	54	53	18	98	0.85 (0.86)	101
1409	0.45 (0.36–0.54)	45	45	19	100	1.08 (0.76)	70
1212	1.20 (1.14–1.26)	51	50	25	98	1.33 (0.5)	38
1201	1.28 (1.16–1.40)	54	50	25	93	1.33 (0.7)	53
1207	1.48 (1.42–1.54)	55	53	22	96	1.45 (0.53)	37
1302	4.60 (3.94–5.26)	55	53	3	96	4.15 (0.77)	19
1407	4.69 (4.33–5.05)	45	45	2	100	4.52 (0.45)	10
1505	5.02 (4.15–5.89)	45	44	1	98	4.73 (0.87)	18
1404	5.30 (4.73–5.87)	47	47	2	100	4.86 (0.77)	16
1203	5.43 (5.03–5.82)	55	51	1	93	5.15 (0.997)	19
1312	6.11 (5.60–6.62)	46	42	1	91	5.4 (1.14)	21
1204	6.40 (5.74–7.06)	53	53	0	100	6.15 (0.68)	11
1506	6.67 (5.59–7.75)	45	43	0	96	6.23 (0.73)	12
1305	8.75 (8.48–9.02)	52	51	0	98	8.44 (1.18)	14
1310	8.97 (8.67–9.27)	46	43	0	93	8.27 (1.23)	15
1502	9.16 (7.66–10.66)	47	47	0	100	8.25 (0.68)	8
1508	10.13 (8.84–11.42)	45	45	1	100	9.7 (0.96)	10
1411	10.32 (8.73–11.91)	47	44	0	94	9.66 (1.37)	14
1405	10.35 (7.32–13.38)	47	46	1	98	9.42 (1.36)	14
1209	10.37 (9.44–11.30)	55	54	0	98	10.26 (1.02)	10
1403	10.90 (10.0–11.8)	48	46	0	96	10.42 (1.34)	13

[a] Reference materials were developed to target values between 5 and 10 μg/dL, based on the 2012 reference value of 5 μg/dL. If the reference value is lowered, future reference materials will target lower blood lead values.

of <$20 000 and $20 000 to $44 999 had a 9.0 and 4.9 times greater risk, respectively, for having a BLL at the 90th percentile or higher, relative to children from higher-income households (≥$45 000 per year).

LAMP

The LAMP challenge results for BLLs <11 μg/dL are summarized in Table 5. We found that overall, the participating laboratories had acceptable performance at all concentration challenges. More laboratories were accurate at determining BLLs >5 μg/dL than at lower concentrations. On average 40% of the values reported by laboratories for samples with low BLLs (≤1.48 μg/dL) were reported as below the LOD. At ≤1.48 μg/dL, ≤60% of laboratories reported actual values, and the average mean values (consensus mean) reported by the laboratories overestimated the BLLs when the target value was <1 μg/dL. This overestimation is due to imputation of results reported as less than LOD, which uses a value of LOD/$\sqrt{2}$. With sample ID 1503 (Table 5) as an example, if a result was reported as less than LOD, and the LOD was 3, the adjusted result was 2.1 μg/dL, whereas the target value was 0.18 μg/dL. The relative standard deviations (RSDs), an indicator of measurement precision, are also shown for each challenge sample in Table 5. The precision of a measurement is directly related to concentration, so a measurement is more precise at a higher lead concentration than at a lower concentration. Consequently, RSDs for the challenge samples increased as the target values decreased. At the lowest BLL challenge sample (0.18 μg/dL), more than half of the laboratories reported results as less than LOD. Of the 66 laboratories included in this study, 21 (31%) used ICP-MS. At ≤1.48 μg/dL (a value close to the NHANES 2011–2012 75th percentile), ~50% of the laboratories reported actual values. Conversely, ~50% of the laboratories reported results as less than LOD. The bias between the CDC's target value and the consensus mean was caused by the high percentage of laboratories

TABLE 6 Blood Lead LODs for 66 Laboratories Continuously Participating in LAMP, 2011–2015

LOD Range, μg/dL	No. Laboratories (%)
<1	15 (22.7)
1–<2	29 (43.9)
2–<3	7 (10.6)
3–5	15 (22.7)

reporting less than LOD at the low target concentrations.

The distribution of reported LODs for the laboratories that have continuously participated in LAMP from 2011 to 2015 is shown in Table 6.

DISCUSSION

BLLs in US children 1 to 5 years old have declined (Fig 1) to a point that challenges the detection limit of many laboratories. Children with BLLs at or above the 90th or 97.5th percentile for NHANES 2011 to 2014 have characteristics similar to what has been reported in past studies as risk factors: <3 years old and living in low-income households. Although not statistically significant in this small sample, the proportion of boys and non-Hispanic blacks with BLLs above the 97.5th percentile was greater than the proportion below the 97.5th percentile. This finding suggests that lead-based paint hazards continue to be a source of childhood lead exposure, but we did not have geographic details to determine residence location or housing age.[15] We could not evaluate sources of exposure and contributions from other sources, including contaminated soil, dust, drinking water, and occasional sources such as cosmetics, remedies, hobbies, and occupational take-home. Although the NHANES 2011 to 2014 sample of 1- to 5-year-old children was large, the 97.5th percentile and higher consisted of only 46 children. This limitation contributes to the wide variability around 3.48 μg/dL, with a 95% confidence interval of 2.65 to 4.29 μg/dL. Despite this limitation, NHANES is the best and possibly only data source for US population-based estimates.

BLLs of 5 μg/dL also present a clinical interpretation challenge. Although reported accuracy for most laboratories is ±2 μg/dL (Parsons et al[7]), the current CLIA acceptability criteria for accuracy in blood lead measurements is ±4 μg/dL (at values <40 μg/dL) which means that the true value of a blood lead reported as 4 μg/dL can be between 0 and 8 μg/dL. Therefore, when the child is retested, any result between 0 and 8 μg/dL includes the possibility that the true BLL is unchanged. It would be helpful for the clinician to explain to a parent or guardian the concept of variability in the measurement if, for example, a child's BLL goes from 4 to 8 μg/dL in the absence of a new or increased exposure.

Because almost 23% of LAMP-participating laboratories reported LODs between 3 and 5 μg/dL, it is likely that many laboratories will be unable to quantify blood lead at or near the 97.5th percentile value (Table 6). One implication for childhood lead poisoning surveillance programs is that most BLLs could be at or below the LODs of many laboratories, unable to be quantified, and therefore reported as less than LOD. Laboratories that intend to quantitate BLLs <5 μg/dL will need to lower the LOD. Also, with a higher LOD, a laboratory may risk not passing PT at values <5 μg/dL. To ensure that LAMP participants can improve precision and accuracy of blood lead measurements <5 μg/dL and to assist laboratories in testing new technology, the CDC will include more challenge samples with target blood lead values between 1 and 5 μg/dL in future performance challenges.

Manufacturers of items such as blood collection materials and containers, cryovials, and reagents need to increase awareness and to consider actions that avoid potential lead contamination during production of these items. Screening of blood collection devices is not feasible for most laboratories that provide blood lead measurements because they do not typically provide the blood collection materials. The EHL-NCEH is finding it increasingly difficult to purchase manufactured lots that pass screening, and we anticipate that the percentage of device and reagent failures is likely to increase unless changes are made in manufacturing processes.

A tightening of the blood lead acceptability criteria in PT to ±2 μg/dL (≤20 μg/dL) or ±10% from ±4 μg/dL (≤40 μg/dL) or ±10% will encourage laboratories to be aware of and proactively deal with contamination and measurement problems that often plague the analysis of blood lead at low levels. If laboratories are able to reduce contamination associated with their measurements, the LODs should improve. Currently, 33% of US LAMP-participating laboratories report a blood lead LOD ≥2 μg/dL (the 2013–2014 90th percentile for blood lead is 1.8 μg/dL). The CDC will assist in reinforcing the need for blood lead laboratories to improve contamination and measurement problems through the LAMP program. In 2017, LAMP reports will include telling participating laboratories how they would perform if a ±2 μg/dL or ±10% acceptance criteria were used.

CONCLUSIONS

The 97.5th percentile BLL based on NHANES 2011 to 2014 results in children 1 to 5 years is 3.48 μg/dL, 30% lower than the current reference value of 5 μg/dL. Although the number of children in the sample that made up the 97.5th percentile was small, they demonstrated 2 previously identified risk factors for elevated BLLs: <3 years old and living in low-income households. In addition, a higher proportion of non-Hispanic blacks and boys had BLLs above the 97.5th percentile compared with below the 97.5th percentile. The continued decrease of BLLs in children presents challenges for clinicians, laboratories, and manufacturers of blood collection devices and analytical instruments. In preparation for the 2015 to 2016 blood lead measurements for NHANES, the CDC found that 35% of devices used in blood collection for BLLs had unacceptable lead contamination. To achieve precise and accurate blood lead measurements with lower LODs, laboratories need to evaluate potential sources of external lead contamination, optimize their analytical methods for low-concentration measurements, and participate in external PT programs, considering how they would perform if tighter acceptability criteria were used. Manufacturers of devices used in blood lead sample collection could identify potential sources of lead contamination and take actions to reduce these sources. Clinicians should understand the factors affecting accurate measurements at low blood lead concentrations to better interpret BLLs and assess whether small changes are real or indicate measurement variability.

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ABBREVIATIONS

ACCLPP: Advisory Committee on Childhood Lead Poisoning Prevention
BLL: blood lead level
CDC: Centers for Disease Control and Prevention
CLIA: Clinical Laboratory Improvement Amendments
EHL-NCEH: Environmental Health Laboratory in the National Center for Environmental Health
ICP-MS: inductively coupled plasma mass spectrometry
LAMP: Lead and Multi-element Proficiency
LOD: limit of detection
PT: proficiency testing
RSD: relative standard deviation

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