To: Board of Scientific Counselors, National Center for Environmental Health/ Agency for Toxic Substances and Disease Registry

From: Work Group on Revision of the Blood Lead Reference Value, BSC Lead Poisoning Prevention Subcommittee

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Re: Consensus Recommendations on Revision of the Blood Lead Reference Value

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In 2010, the CDC Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) convened a work group to evaluate new approaches, terminology, and strategies for defining elevated blood-lead levels (BLLs) among children. On January 4, 2012, building on the work group's recommendations, ACCLPP approved a report entitled "Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention." The findings of the report included recommendations that CDC abandon the term "level of concern" with respect to childhood BLL, and instead "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 updated by CDC every four years based on the most recent population based blood lead surveys among children." (ACCLPP, 2012; page 3).

The 2012 ACCLPP report recommended that capillary or venous BLL results equal to or greater than the reference value be confirmed by repeat testing, and that values confirmed to be ≥ 5 µg/dL be followed by a series of response actions. Child-specific response actions recommended for BLLs between 5 and 45 µg/dL included: a) parental lead education; b) follow-up blood lead monitoring; c) complete history and physical examination; d) laboratory assessment of iron status; e) environmental investigation and lead hazard reduction; and f) neurodevelopmental monitoring.[1] (ACCLPP, 2012; pages 29-30).

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[1] An abdominal x-ray was also recommended if particulate ingestion was suspected.

With respect to "environmental investigation" and "lead hazard reduction," the ACCLPP report recommended that the response action should include:

> "Home visits by CLPPP staff, community health workers, Maternal and Child Health home visiting programs, and other systems to assess the home, advise occupants, report observations and lead test results, and make referrals in response to identified lead hazards [page 26]…. The scope of an 'environmental assessment' will vary based on local resources and site conditions. However, this would include at a minimum a visual assessment of paint and housing conditions, but may also include testing of paint, soil, dust, and water and other lead sources discussed previously…. This may also include looking for exposure from imported cosmetics, folk remedies, pottery, food, toys, etc. which may be more important with low level lead exposure." (ACCLPP, 2012; page 30)."

ACCLPP additionally recommended that, "Clinicians should ensure that BLL values at or above the reference value are reported to local and state health and/or housing departments if no mandatory reporting exists and collaborate with these agencies in providing the appropriate services and resources to children and their families." (ACCLPP, 2012, page 18).

In a document finalized on June 7, 2012, CDC decided to "concur in principle" with ACCLPP recommendations concerning the establishment of blood lead reference value.[2] Specifically, CDC affirmed its intent to apply the following "specific means" to address or implement the recommendations:

> "a. Use the reference value in recommendations that involve follow-up evaluation of children after BLL testing.
> b. Use the reference value as defined to identify high-risk childhood populations and geographic areas most in need of primary prevention.
> c. Provide this information, including specific high-risk areas, to a wide variety of federal, state, and local government agencies and nongovernment organizations interested in lead-poisoning prevention.
>
> In addition, CDC will update the value every 4 years using the two most recent NHANES surveys. The updated reference value will be posted at www.cdc.gov/nceh/lead and widely distributed through various Web-based LISTSERV sites, pediatric associations, and partners at the federal, state,

[2] Concur in principle was defined to mean, "We [CDC] agree, but we do not have the funding, staff, or control over the means to implement the recommendation. The response highlights strategies that have been shown to be effective, however a commitment to implement actions cannot be made due to our lack of control over available resources." (CDC, June 7, 2012; page 3).

> and local level. Updated reference values will be reported in the National Report on Human Exposures to Environmental Chemicals and other relevant journals." (CDC, June 7, 2012, page 7).

With respect to the recommendation regarding clinician reporting of BLLs greater than or equal to the reference value, CDC noted, "Although this recommendation is directed to clinicians, CDC may play a supportive role in enhancing the recommendation through CDC's continued work with testing laboratories, point-of-care instrument manufacturers, and clinical health care providers to ensure the availability of high-caliber laboratory services. In addition, most of the state CLPPPs funded by CDC have mandatory reporting laws in place, and those that do not are required to implement such laws during this year of funding."

At a meeting of the National Center for Environmental Health Board of Scientific Counselors (BSC) on June 29, 2016 and a meeting of the Board of Scientific Counselors Lead Poisoning Prevention Subcommittee (LPPS) on September 19, 2016, CDC reported the results of the United States NHANES Survey for 2011-2014. The 97.5th percentile BLL for children aged 1- 5 years was 3.5 µg/dL. CDC asked the BSC and the LPPS for guidance regarding "the implications of establishing a new blood lead reverence value that is lower than 5 μg/dL." In the discussion that followed, it was noted that the three major clinical laboratory methods used to measure BLL – ICP-MS, GFAAS, and LeadCare point of care instruments – were characterized by different analytical precision and limits of detection. The analytical precision associated with particular BLL measurement performed by a specific methodology influences the degree of confidence that a reported result equals or exceeds a defined blood lead reference value when the reported result is within a few micrograms per deciliter of that reference value.

The LPPS convened a work group on revision of the blood lead reference value composed of some LPPS members, BSC members, and subject matter experts from the NCEH Division of Laboratory Sciences (DLS) to investigate and assess the analytical precision of low-level blood lead measurements conducted by clinical laboratories in the United States using different methodologies. Of particular interest were data that might inform on clinical laboratory precision near 5 µg/dL and 3.5 µg/dL.

To the knowledge of the LPPS work group, no national or other wide-scale comparative analysis of clinical laboratory precision in BLL measurement near 5 µg/dL or 3.5 µg/dL by ICP-MS, GFAAS, and LeadCare instruments had heretofore been undertaken or published. To address this issue, DLS obtained and analyzed data available from laboratory proficiency programs administered by the Wisconsin State Laboratory of Hygiene, the DLS Lead and Multi-element Proficiency (LAMP) program, and the New York Department of Health

Wadsworth Center Clinical Laboratory Evaluation Program. The data available from these programs facilitated an estimation of the measurement precision of each of the three analytical at a BLL of 5 µg/dL. However, because creation and circulation by the proficiency programs of BLL target specimens at or near 3.5 µg/dL was sparse, the precision associated with clinical laboratory measurements at or near that value could not be estimated.

Current DLS estimates of precision for BLLs at or near 5 µg/dL, according to the analytical methodology utilized, are presented in the table below.

Best estimates of precision of blood lead measurements at 5 µg/dL			
Analytical Method	Number of results	95 % Confidence Interval around 5 µg/dL if only one blood sample from the patient	95% Confidence Interval around 5 µg/dL if average of two successive samples from patient*
ICP-MS	769	± 0.97	± 0.69
GFAAS	908	± 1.5	± 1.1
LeadCare II	1469	± 1.8	± 1.3

*Based on the formula $\sigma_{\bar{x}} = \sigma / \sqrt{n}$, the standard deviation of the mean of two samples drawn from the same distribution equals the standard deviation of the distribution divided by √2

The information in the table provides a clinician with useful information regarding measurement precision that is usually not included in clinical laboratory report forms. The 95% confidence interval, which represents ± 1.96 standard deviations, should be symmetrically applied. For example, if analysis of a single blood lead specimen from a patient by GFAAS yielded a BLL of 5 µg/dL, the clinician could infer with 97.5 percent confidence that the true value was no lower than 3.5 µg/dL. If the average of two successive blood lead specimens from a patient analyzed by GFAAS were 5 µg/dL, it could be inferred with 97.5 percent confidence that the true value were no lower than 3.9 µg/dL. As noted previously, ACCLPP recommended that response actions to an elevated blood lead concentration should be initiated only after a confirmatory measurement (ACCLPP, 2012, page 28).

It should be emphasized that the precision estimates in the table apply only to blood lead results of 5 µg/dL. It may be anticipated that the precision associated with blood lead results slightly higher than 5 µg/dL, e.g. 6, 7, or 8 µg/dL would be close to that estimated for 5 µg/dL. In like manner, the width of 95 percent confidence interval associated with a result less than 5 µg/dL, e.g. 3.5 or 4.0

µg/dL, would likely be wider than presented in the table, particularly if the analysis were performed by LeadCare instruments or GFAAS. However, the extent of the increase in the width of the 95 percent confidence intervals that would apply to results less than 5 µg/dL, a key factor in judging whether a child's BLL concentration confidently exceeds a blood lead reference value of 3.5 µg/dL, is currently unknown. To address this data gap, the DLS LAMP program intends to include blood lead targets at or near 3.5 µg/dL in its proficiency samples in 2017. DLS anticipates that proficiency programs operated by Wisconsin and New York will do so as well. The results of such proficiency testing in 2017 should allow an estimation of measurement precision associated with the three analytical methods at or near 3.5 µg/dL to be available in 2018.

Potential options for revision of the blood lead reference value at this point in time. In view of the foregoing, a reasonable course of action for 2017 is proposed. The rationale set forth in the 2012 ACCLPP report to establish a blood lead reference value equal to the 97.5 percentile of BLL for children age 1-5 based on two successive NHANES cycles (i.e. every four years) remains valid. Accordingly, the blood lead reference value should be revised to 3.5 µg/dL at this time. However, whether the BLL measurements of a child should trigger *the child-specific response actions* recommended in the 2012 ACCLPP document for a BLL equal to or greater than the reference value should depend on the nature and magnitude of the BLL measurement. As shown in Table 1, if the average of the initial and confirmatory venous BLL measurements by any methodology is ≥ 5 µg/dL, there will be 97.5% confidence that the child's true BLL exceeds the blood lead reference value of 3.5 µg/dL. In that situation the child-specific response actions recommended in the 2012 ACCLPP report should be initiated. As noted above, these include: a) parental lead education; b) follow-up blood lead monitoring; c) complete history and physical examination; d) laboratory assessment of iron status; e) environmental investigation and lead hazard reduction; and f) neurodevelopmental monitoring.

Pending the availability in 2018 of additional information regarding estimated clinical laboratory precision at BLL values of 3.5 µg/dL, if the average of the initial and confirmatory BLL measurement is ≥ 3.5 µg/dL but < 5 µg/dL, child-specific response actions should be deferred. For public health surveillance, all BLLs equal to or greater than 3.5 µg/dL should be reported to the appropriate local, state, and federal agencies and programs together with identification of the type of analytical method used to perform each measurement.

Implementation of a change in the blood lead reference value and provision of interim guidance on deferral of child-specific response actions for BLL measurements ≥ 3.5 µg/dL but < 5 µg/dL pending additional study of laboratory proficiency should be accompanied by educational messaging from CDC. This

education, optimally in the form of separate statements in lay and technical language, should aim to succinctly articulate the implications of measurement precision, limits of detection, and other aspects of clinical laboratory performance on the interpretation of low BLLs. The extent to which the magnitude of the BLL and the laboratory method may impact the confidence of parents, pediatricians, and public health officials that a BLL equals or exceeds the reference value should be discussed.

References

ACCLPP. CDC Advisory Committee on Childhood Lead Poisoning Prevention. "Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention." January 4, 2012. Available at: https://www.cdc.gov/nceh/lead/acclpp/final_document_030712.pdf

CDC. CDC Response to Advisory Committee on Childhood Lead Poisoning Prevention Recommendations in "Low Level Lead Exposure Harms Children: A Renewed Call of Primary Prevention." June 7, 2012. Available at: https://www.cdc.gov/nceh/lead/acclpp/cdc_response_lead_exposure_recs.pdf