

Guidelines for Measuring Lead in Blood Using Point of Care Instruments

Advisory Committee on Childhood Lead Poisoning Prevention
Of the Centers for Disease Control and Prevention

October 24, 2013

Disclaimer

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Abbreviations

ACCLPP – Advisory Committee on Childhood Lead Poisoning Prevention

ASV – Anodic stripping voltammetry

BLL – Blood lead level

CDC – Centers for Disease Control and Prevention

CLIA – Clinical Laboratory Improvement Amendments of 1988

EDTA – Ethylenediaminetetraacetic acid

FDA – Food and Drug Administration

GFAAS – Graphite furnace atomic absorption spectrometry

POC – Point of care instrument

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Executive Summary

Clinical laboratories primarily assess lead exposure using whole blood lead measurements. Although a number of human tissues and body fluids also reflect lead exposure, the concentration of lead in whole blood has gained wide acceptance as the most useful tool for screening and diagnostic testing, primarily because of contact between the blood and the entire body, and the equilibrium between lead in blood and lead in organs and tissues. In very young children, lead in whole blood is an indicator mainly of recent exposure although there can be input to total blood lead from past accumulation in the body. In adults and particularly lead workers, the past accumulation can be a more prominent contributor to total blood lead.

Guidance has been previously published for the clinical laboratory testing community involved in the collection of blood for the measurement of lead by high complexity laboratory methods. The present document provides guidelines for point of care blood lead testing using methods waived from the provisions of the Clinical Laboratory Improvement Amendments of 1988 by the Food and Drug Administration based on its low complexity. The document also briefly describes specific guidance for the use of the LeadCare® II instrument as this is the only POC device for blood lead testing currently commercially available for use in the U.S. These guidelines are consistent with “Low Level Lead Harms Children: A Renewed Call for Primary Prevention” approved by the Advisory Committee on Childhood Lead Poisoning Prevention in January 2012. In May 2012, the Centers for Disease Control and Prevention concurred with the recommendations in the January 2012 document.

1. Introduction

Lead is a toxic metal whose widespread use has caused extensive environmental contamination and health problems in many parts of the world. Lead is a cumulative toxicant that affects multiple body systems, including the neurologic, hematologic, gastrointestinal, cardiovascular, and renal systems. Chronic exposure often causes hematological effects, such as anemia, or neurological disturbances, including headache, irritability, lethargy, convulsions, muscle weakness, ataxia, tremors and paralysis. Acute exposures may cause gastrointestinal disturbances (e.g., anorexia, nausea, vomiting, and abdominal pain), hepatic and renal damage, hypertension and neurological effects (e.g., malaise, drowsiness, and encephalopathy) that may lead to convulsions and death. Children are particularly vulnerable to the neurotoxic effects of lead, and even low levels of exposure can cause adverse neurocognitive effects including poor academic performance and behavioral problems that in some cases may be irreversible. No safe blood lead threshold for the adverse effects of lead on infant or child neurodevelopment has been identified (1). Recent evidence suggests that the dose-effect relationship might be supralinear, with a steeper dose response and potential risk for an adverse health effect such as IQ loss at BLLs < 10 µg/dL compared with BLLs ≥ 10 µg/dL (2-4).

The CDC Advisory Committee on Childhood Lead Poisoning Prevention in 2012 recommended that a reference value based on the 97.5th percentile of the National Health and Nutrition Examination Survey- generated BLL distribution in children 1-5 years old (currently 5 µg/dL) be used to identify children with an elevated blood lead level. As of 2012, there were approximately 450,000 U.S. children with blood lead levels above this cut-off value that should trigger lead education, environmental investigations, and additional medical monitoring.

The clinical diagnosis of lead poisoning can be difficult when there is no clear history of exposure because poisoned individuals can be asymptomatic, and signs and symptoms, when they are present, are relatively non-specific. Laboratory investigations are the most definitive way to diagnose lead-exposed individuals and, therefore, play an essential role in the identification and management of lead poisoning and in the assessment of occupational and environmental lead exposure.

Advisory Committee on Childhood Lead Poisoning Prevention

The Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) was established by the CDC to advise and guide the CDC regarding new scientific knowledge and technical advances and their practical implications for childhood lead poisoning prevention efforts. The overall goal of the ACCLPP is to provide advice that will assist the nation in reducing the incidence and prevalence of childhood lead poisoning. ACCLPP is charged with evaluating information about the health effects of 1) lead exposure in children, 2) the epidemiology of childhood lead poisoning, 3) implementation issues, and other factors. Furthermore, according to its charter, ACCLPP:

- reviews and reports regularly on childhood lead poisoning prevention practices;
- recommends improvement in national childhood lead poisoning prevention efforts; and

- develops written recommendations for the prevention and control of childhood lead poisoning.

Laboratory Work Group Charge

In keeping with this assignment, ACCLPP established the Laboratory Work Group in November 2011 to investigate and report on five issues:

- proficiency testing (PT) limits;
- guidelines for point of care lead testing;
- alternative matrices for assessing exposure to lead;
- environmental lead analytical issues; and,
- reference intervals for adult lead exposure.

This document provides guidelines for point of care (POC) blood lead testing. The workgroup will take up the other issues in the future.

Today, clinical laboratories primarily assess lead exposure with whole blood lead measurements. Although a number of human tissues and body fluids also reflect lead exposure, the concentration of lead in whole blood has gained wide acceptance as the most useful tool for screening and diagnostic testing, primarily because of contact between the blood and the entire body, and the equilibrium between lead in blood and lead in organs and tissues [5-7]. In very young children, lead in whole blood is an indicator mainly of recent exposure although there can be input to total blood lead from past accumulation in the body. In adults and particularly lead workers, the past accumulation can be a more prominent contributor to total blood lead.

Guidance has been previously published [8], for the clinical laboratory testing community involved in the collection of blood for the measurement of lead by high complexity laboratory methods. The present document provides guidelines for POC blood lead testing and briefly describes specific guidance for the use of the LeadCare® II instrument as this is the only POC device for blood lead testing currently commercially available for use in the U.S.

Available Point of Care Instruments

A portable instrument for the determination of lead in blood at the point of care was developed in collaboration with the CDC, and is based on anodic stripping voltammetry (ASV) with disposable screen-printed electrodes. The initial instrument, named “LeadCare®,” was commercialized in 1997 and became known as “LeadCare® I” when the second generation “LeadCare® II Blood Lead Test System” was commercialized in 2006. LeadCare® I was classified by the Food and Drug Administration (FDA) as moderately complex; LeadCare® II is classified by FDA as Clinical Laboratory Improvement Amendments of 1988 (CLIA)-waived, indicating a lower level of complexity with fewer regulatory requirements. The FDA is responsible for the categorization of commercially marketed *in vitro* diagnostic tests into one of three CLIA regulatory categories based on their potential for risk to public health:

- tests of high complexity;
- tests of moderate complexity; and
- waived tests.

Thus, the LeadCare® II device does not require skilled laboratory personnel to be operated and has been approved by the FDA for use at nontraditional laboratory settings such as federally funded Women, Infants, and Children clinics, other health clinics, physician office labs, schools and mobile health units. It is also a useful tool for point of care blood lead testing in epidemiology studies at locations where transport of blood samples to certified laboratories is difficult. It allows the determination of the patient's blood lead level (BLL) in approximately 3 minutes from a 50- μ L sample of capillary (finger-stick) or venous blood. The reportable range of BLLs is between 3.3 - 65 μ g/dL, and use at the point of care allows for immediate venous blood draw for confirmation of elevated lead levels by a certified laboratory. The single-use sensor, sample container, reagents and calibration equipment are provided as disposable units that are pre-calibrated by the manufacturer. Comparison of this device by the FDA with a reference method based on graphite furnace atomic absorption spectrometry (GFAAS) indicated that it was fit for purpose in the hands of people unaccustomed to performing laboratory tests. This device is now routinely used for screening purposes. The manufacturer has previously recommended that any sample greater than 10 μ g/dL be confirmed by a reference method and that if the user is concerned about accuracy of results near 10 μ g/dL that the confirmation threshold be set at 8 μ g/dL.

Guidelines for POC blood lead testing

1. Universal Precautions:

Wear personal protective equipment (PPE) such as gloves, lab coat and safety glasses when handling human blood. Disposable materials that are in contact with human blood should be disposed of in a labeled biohazard material hazard bag or sharps container and autoclaved. The work area should be decontaminated with a 10% (by volume), 9 parts cool water and 1 part sodium hypochlorite solution (typically aqueous solutions of 5.25%–6.15% sodium hypochlorite usually called household bleach) or similar disinfectant when work is finished.

2. Contamination Control in the Work Environment:

Designate a clean work area by minimizing contamination from ambient airborne and surface lead during specimen collection and analysis.

Discussion: Clean area refers to space that is dedicated to testing for blood lead and is typically cleaned on a daily basis or when contamination occurs by wet wiping work surfaces.

3. Contamination Control in Materials and Specimen Collection:

Implement procedures to ensure that materials and techniques used in blood collection and processing steps are free from significant lead contamination.

Discussion:

- a. Significant lead contamination refers to an amount of lead that would change the observed blood lead level by more than 1 µg/dL.
- b. Cumulative contamination from multiple materials which come into contact with the blood specimen during collection and processing needs to be considered.
- c. Use supplies that are recommended or provided by the manufacturer for blood lead testing.
- d. Should an unexpected number of elevated blood lead test results occur, contamination from materials and/or containers might merit an investigation.
- e. ***Work with clinical health care providers to ensure proper collection techniques, including the importance of preparing the skin collection site prior to collection of capillary specimens[6, 8].***

4. Contamination Control in Specimen Processing:

If blood specimens are collected for multiple analyses including lead testing, a volume sufficient for the initial lead test and any repeat testing should be transferred to a lead-free tube under clean conditions before any other processing or testing occurs to the specimen.

Discussion: Specimen contamination from other testing areas may be minimized by implementing this protocol. As an alternative, the test for blood lead can be completed prior to other testing.

5. Use of Fingerstick (Capillary) Blood:

If a capillary tube is used to collect a blood specimen ensure there are no air-gaps present in the capillary during collection.

Discussion: This specimen is appropriate for screening purposes only and is typically

used with a POC device. Consult the manufacturer's packaging / package insert(s) for additional details including the mixing of blood with anticoagulant reagents.

6. **Use of Venous Blood:** When using a venous blood specimen for the analysis, the laboratory should ensure the quality of the blood specimen.

Discussion:

- a. Venous blood is the preferred specimen for blood lead testing purposes.
 - b. Use blood tubes containing either ethylenediaminetetraacetic acid (EDTA) or heparin as anticoagulants during blood collection. Venous specimens submitted for lead analysis that are collected in EDTA tubes and are less than half full shall be rejected as unsatisfactory for analysis by ASV.
 - c. Use tan topped tubes (certified lead free), royal blue topped tubes containing EDTA (certified for a limited number of trace elements including lead) or other tubes, containing an anti-coagulant, which have been tested and found to be suitable for blood lead measurements.
 - d. Refer to manufacturer's insert for instructions on sample mixing. Make sure to thoroughly mix the blood before withdrawing an aliquot for processing.
 - e. Blood specimens with visible clots shall be rejected as unsatisfactory for analysis
7. **Storage Requirements for Specimens and Test Kit Components:** Laboratories should store blood specimens, test kit components, and blood specimen preparations under conditions in agreement with manufacturer recommendations.

Discussion: *using the LeadCare® II analyzer as an example*

- a. Patient Blood: 50-90 °F (10-32°C). Do not refrigerate. Test within 24 hours of collection.
 - b. Mixture of Blood and Treatment Reagent: If stored at room temperature, test within 48 hours. If refrigerated, test within 7 days.
 - c. Test Kit and Blood Controls: 60-80 °F (15-27 °C). Do not freeze or refrigerate. Keep away from direct sunlight.
 - d. Consult the manufacturer's packaging / package insert(s) for additional details.
8. **Operation Environment for Instrument:** Laboratories should only operate the point of care analyzer within the manufacturer designated environmental conditions.
- Discussion: Consult manufacture's package insert for information about temperature, humidity, air-flow and altitude considerations. Contact manufacturer directly for information about the use of LeadCare® II in harsh climates and with populations living at altitudes exceeding 8,000' due to unique blood chemistry (glutathione peroxidase levels)[7] .

9. **Instrument Power Source:** In locations where the electrical power is unreliable, it is preferable to use battery power to run tests.

Discussion: POC technology based on electrochemical principles can be sensitive to fluctuations in electrical power. If a stable AC electrical power supply cannot be ensured, use battery power for the POC analyzer instead of the AC adapter. For

planning purposes, consult the instrument user guide regarding the number of tests which can normally be performed using a set of commercially available batteries.

10. **Use of Test Kit Components:** Laboratories should only use test kit components within the manufacturer designated expiration dates and only in the combinations designated by the manufacturer.

Discussion:

- a. Items such as treatment reagents, blood lead controls, and test sensors may have separate expiration dates.
- b. QC materials should only be used with the manufacturer designated sensor lot(s).

11. **Instrument Calibration:** The laboratory should perform instrument calibration in accordance with the manufacturer's requirements.

12. **Quality Control:** Laboratories should develop routine quality control practices. Two quality control samples at clinically significant blood lead levels should be analyzed each time the instrument is set up for an analytical run. At a minimum, two levels of quality control shall be run:

- a. on each new test kit lot;
- b. on each new shipment of a test kit(s);
- c. by each new operator (someone who has not performed the test for two weeks);
- d. When problems (storage, operator, instrument, or other) are suspected or identified.

Discussion: The frequency of quality control (QC) should reflect the volume of testing, which will be lab specific. In high throughput laboratories where more than one POC device is in daily use, routine QC may include inter-POC comparisons on common daily QC samples, examination of trends in the QC data, and monitoring operator competency. In the event that problems are detected with internal QC samples, root cause analysis should be undertaken and corrective action(s) may be warranted. Laboratories can keep records documenting quality control procedures. Such records should be kept for 2 years unless otherwise dictated by other agencies.

13. **Repeat Analysis of Original Specimen:** Reanalyze specimens with blood lead values at or above the upper reference range 97.5 percentile value for children ($\geq 5 \mu\text{g}/\text{dL}$ for 2012-2016) [8] if the volume of the original specimen permits, to determine, e.g., if the initial analysis was a contamination error. Use the average of the two consecutive test results to determine whether the discrepancy is large enough to require a third analysis. When large discrepancies (see below for definitions) are obtained between two consecutive test results, either:

- a. Perform a third analysis; or
- b. Report test results as inconclusive, add a comment that there was insufficient specimen to repeat the analysis, and refer patient for confirmatory testing (See Guideline 14).

Discussion:

- a. A new aliquot from the original specimen should be used for the reanalysis. Specimen volume for capillary specimens may be insufficient for retesting purposes. In this case, report initial result and refer patient for confirmatory testing (See Guideline 14).
- b. Large discrepancies between two consecutive tests are defined as differences exceeding 3 µg/dL for blood lead levels 5 to 20 µg/dL; 4 µg/dL for values 21 to 40; or 10% for values exceeding 40 µg/dL. In these cases, the specimen should be analyzed a third time, the outlier result should be discarded and either report the average or the first obtained of the remaining results. For any result exceeding 5 µg/dL, or if there is any uncertainty in the validity of the test, the patient should be referred for confirmatory testing (See Guideline 14).

14. Confirmatory Testing: When blood lead concentrations greater than or equal to 5 µg/dL [8] are obtained, the laboratory must either:

- a. Refer the specimen to a CLIA certified lab for confirmatory testing by a method categorized by CLIA as a high complexity test (e.g. Inductively Coupled Plasma Mass Spectrometry, or GFAAS if sufficient venous blood remains,) or
- b. If there is insufficient sample for another analysis, see Guideline 15.

Discussion:

- a. An unopened venous specimen is preferable for confirmatory testing. When this is not possible or feasible (e.g. with young children), and the confirmed result is also elevated, the confirming laboratory can acknowledge the issue on the test report. Test result comment example: "The test specimen may have been compromised during previous testing. Result should be confirmed with another venous blood specimen."
- b. Preliminary results may be released with a comment that results of confirmatory testing are pending.

15. Reporting POC Results to Clinical Health Care Providers: Blood lead levels at or above the reference value (≥ 5 µg/dl for 2012-2016) established by the CDC[8] require further investigation.

Discussion: The following comment can be used on laboratory test reports to clinical health care providers: "For children 5 years old and younger, blood lead levels ≥ 5 µg/dl indicate that they may have been exposed to lead at levels higher than most children. The blood lead level should be confirmed using a venous blood sample and a CLIA certified high complexity analytic method according the recommendations of the Advisory Committee on Childhood Lead Poisoning Prevention.[8] Since no safe BLL in children has been identified, no detectable level should be considered 'normal'."

16. Requirements for Reporting Results to State or Local Health Authorities:

Report all blood lead test results to the appropriate state or local agency as required by law.

Discussion: Regulations vary by state as to timeframes, mechanisms for reporting (e.g.,

paper records or electronic reporting) and data elements. POC testing providers should follow their local requirements. Contact information for state lead programs can be found at www.cdc.gov/nceh/lead.

17. **Reporting Potential Contamination:** If a specimen is received in a blood collection container that is not certified for blood lead testing, and the result is above the reference value ($\geq 5\mu\text{g/dL}$ for 2012-2016)[8], indicate on the report that the use of unverified containers can produce a falsely elevated result.

Discussion: Trace element “free” tubes or containers that have been lot-tested in-house are acceptable alternatives to manufacturer certified blood lead tubes, and need not be footnoted in the test report.

18. **Internal Quality Assurance (method comparison):** When specimens have been referred for confirmatory testing, laboratories are encouraged to compare and maintain a log of blood lead results obtained from their POC device(s) with results reported using the confirmatory reference method.

Discussion:

- a. Differences in results greater than $3\mu\text{g/dL}$ for blood lead levels 5 to $20\mu\text{g/dL}$; $4\mu\text{g/dL}$ for values 21 to $40\mu\text{g/dL}$; or 10% for values exceeding $40\mu\text{g/dL}$ require further investigation.
- b. A review of competency reviews of testing personnel as well as data from quality control and proficiency testing can provide insights on testing performance.

19. **External Quality Assurance:** Participation in external quality assurance program for blood lead (e.g. proficiency testing programs) provides a valuable assessment of facilities’ analytic performance using POC device.

Discussion: While there is no Federal requirement for laboratories using a test categorized as waived under CLIA’88 regulations to participate in proficiency testing (some states require regular participation in proficiency testing to receive Medicaid or Child Health Insurance Program reimbursement for test costs), laboratories are strongly encouraged to participate in external quality assessment programs such as proficiency testing to evaluate their performance regularly.

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