Measuring Blood Lead Levels <5 µg/dL: How Low Can Labs Go?

Patrick J. Parsons, PhD, C.Chem., FRSC
Chief, Laboratory of Inorganic and Nuclear Chemistry
Deputy Director, Division of Environmental Health Sciences, Wadsworth Center
New York State Department of Health Albany, New York, USA

May 9, 2013
Disclaimer

Use of trade names and references to specific manufacturers does **not** imply an endorsement by the New York State Department of Health (NYSDOH), the Association of Public Health Laboratories (APHL), or the Clinical and Laboratory Standards Institute (CLSI).
Outline

- New definition of elevated blood lead level in children: 2012
- Centers for Disease Control and Prevention's (CDC’s) lead level of concern: 1960s to present
  - Relationship to laboratory technology
- CDC’s Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP)
- Current analytical methods for blood lead
- Federal criteria for blood lead proficiency testing (PT) performance
- Blood lead limit of detection (LoD) considerations
- Summary and questions
ATLANTA — For the first time in 20 years, a federal panel is urging the government to lower the threshold for lead poisoning in children....Wednesday’s vote by the Advisory Committee on Childhood Lead Poisoning Prevention would lower the definition of lead poisoning for young children from 10 micrograms of lead per deciliter of blood to 5 micrograms. The CDC has accepted all of the panel’s recommendations in the past.

Associated Press; published: January 4, 2012
NATIONAL RECOMMENDATIONS FOR PREVENTING LEAD POISONING

CDC

Role of the Analytical Laboratory
ANALYTICAL METHODS FOR BLOOD LEAD MEASUREMENTS AND CDC’S LEVELS OF CONCERN

Historical Background
Analytical Methods for Blood Lead Testing

Abbreviation: AA, atomic absorption.
Analytical Methods for Blood Lead Testing (cont’d)

Abbreviations: AA, atomic absorption; ASV, anodic stripping voltammetry.
Analytical Methods for Blood Lead Testing (cont’d)

Abbreviations: AA, atomic absorption; ASV, anodic stripping voltammetry.
Analytical Methods for Blood Lead Testing (cont’d)

CDC blood lead level of concern (µg/dL)

- 70 µg/dL
- 60 µg/dL
- 40 µg/dL
- 30 µg/dL
- 25 µg/dL
- 10 µg/dL


Abbreviations: AA, atomic absorption; ASV, anodic stripping voltammetry.
 CDC blood lead level of concern (µg/dL)


0 10 20 30 40 50 60 70

5 µg/dL

10 µg/dL

25 µg/dL

30 µg/dL

40 µg/dL

60 µg/dL

Colorimetric
Delves Cup
ASV
Flame AA
Flame AAS
(DC-AAS)

Graphite Furnace
Atomic Absorption
Spectrometry
(GFAAS)

Inductively Coupled
Plasma Mass
Spectrometry
(ICP-MS)

Analytical Methods for Blood Lead Testing (cont'd)

Abbreviations: AA, atomic absorption; ASV, anodic stripping voltammetry; POC, point-of-care.

**Myth 1:** Capillary blood obtained by fingerstick cannot be used for a blood lead test because of lead contamination from skin and a small sample volume.

**Myth 2:** Analytical techniques are not sensitive enough to measure lead at the lower action level.

**Myth 3:** Most clinical laboratories can’t measure lead very accurately at the lower action level.
CDC Advisory Committee On Childhood Lead Poisoning Prevention (ACCLPP)

- Reviews and reports regularly on childhood lead poisoning prevention practices
- Recommends improvement in national childhood lead poisoning prevention efforts
- Develops written recommendations for the prevention and control of childhood lead poisoning
CDC ACCLPP 2012 Laboratory Workgroup Membership

Chair: *Patrick J. Parsons, PhD, C. Chem., FRSC (NYSDOH)

Members: Valerie Charlton, MD, MPH (CA DOH / CLPPB)
         Leland McClure, PhD, D-ABFT (Quest Diagnostics)
         *Megan Sandel, MD, MPH (Boston Medical Center)
         Donald Simmons, PhD (UIHL) APHL Liaison
         Noel Stanton, MS (WSLH)

CDC Staff: Walter Alarcon, MSc, PhD (CDC / NIOSH)
           Mary Jean Brown, ScD, RN (CDC / NCEH)
           Jeffery M. Jarrett, MS (CDC / NCEH)
           Robert L. Jones, PhD (CDC / NCEH)

* ACCLPP voting members
Charge to the Laboratory Workgroup

1. PT Limits

- The Laboratory Workgroup (LWG) will address whether blood lead PT acceptability limits should be more stringent than the current Clinical Laboratory Improvement Amendments (CLIA) '88 standard of ±4 µg/dL or ± 10% (whichever is greater), and, if so, what they should be.

- The LWG should draft a letter from the ACCLPP to the appropriate federal agency recommending that a change in CLIA '88 regulations be implemented that would tighten the minimum acceptable PT limits for blood lead.
2. Practice Standards for POC Lead Testing

- The LWG should address the need for recommended standards of practice for those using POC blood lead testing.
Charge to the Laboratory Workgroup

3. Alternative Matrices for Assessing Exposure to Lead

➢ The LWG should investigate and report to the ACCLPP on the efficacy, reliability, and validity of measuring lead in saliva as an index of lead exposure.

❖ The LWG should investigate and report to the ACCLPP on the reliability and validity of measuring lead in other nontraditional matrices such as sweat, hair, nails, and packed red cells as indices of lead exposure.

CDC ACCLPP. October 2009.
4. Environmental Lead Analytical Issues

➢ The LWG should investigate and report back to the ACCLPP on the reliability of current technologies for assessing the lead content of paint, plastics, and other environmental samples; laboratory capacity; and capability for handling.
5. Reference Intervals for Adult Lead Exposure

The LWG should investigate and report back to the ACCLPP on how clinical laboratories should report the reference interval for adult lead exposure. Currently, many laboratories report <30, <20 as “normal” for adult blood lead levels.
On November 17, 2010, the ACCLPP proposed the formation of a workgroup to recommend new approaches, terminology, and strategies for defining elevated blood lead levels among children.

Approximately 250,000 US children aged 1–5 years have blood lead levels greater than 10 µg/dL, the level at which CDC recommends public health actions be initiated. This standard was adopted in October 1991.
• Recommended how to best replace the blood lead “level of concern.” Multiple approaches may be considered, including:
  ➢ Conduct a health risk assessment for lead using the same approaches as with any other chemical.
  ➢ Conduct a risk assessment focused exclusively on IQ deficits associated with lead exposure to children, as reported in the available literature.
  ➢ Establish a reference range for children based on the most recent national survey of blood lead levels.
  ➢ Review the lowest practical level of laboratory quantification of lead in blood as a possible limitation in establishing new guidance.
January 4, 2012

- The ACCLPP voted to approve the report, “Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention.”

- Requested CDC and US Department of Health and Human Services to accept the report recommendations.

CDC’s response:

www.cdc.gov/nceh/lead/ACCLPP CDC_Response_Lead_Exposure_Recs.pdf

- Calls for CDC to eliminate use of the term “blood lead level of concern.”
- Calls for adopting a reference level for blood lead as the 97.5th percentile, or the level at which 97.5 percent of population have lower blood lead levels.
- Based on the most recent National Health and Nutrition Examination Survey (NHANES) data: ≥ 5 μg/dL
- Based resolution on a growing body of scientific literature that adverse health effects may arise from blood lead levels lower than 10 μg/dL.
US Childhood Lead Poisoning

≈250000 children 1–5 have blood lead levels ≥10 µg/dL

Because the definition of an elevated blood lead level is now lowered to ≥5 µg/dL, then the number of elevated blood lead levels almost doubles to 450000.
CDC’s Fourth National Report on Human Exposure to Environmental Chemicals (2009)

National Center for Environmental Health
Division of Laboratory Sciences

...currently includes values for 246 environmental chemicals and nutritional indicators in people.

http://www.cdc.gov/exposurereport/
NHANES Blood Lead: 1999-2004

Blood lead levels (in µg/dL) for the US population

<table>
<thead>
<tr>
<th>Age group</th>
<th>Survey years</th>
<th>Geometric mean (95% conf. interval)</th>
<th>95th</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>99-00</td>
<td>1.66 (1.60-1.72)</td>
<td>5.00 (4.70-5.50)</td>
<td>7970</td>
</tr>
<tr>
<td></td>
<td>01-02</td>
<td>1.45 (1.39-1.51)</td>
<td>4.50 (4.20-4.70)</td>
<td>8945</td>
</tr>
<tr>
<td></td>
<td>03-04</td>
<td>1.43 (1.36-1.50)</td>
<td>4.20 (3.90-4.40)</td>
<td>8373</td>
</tr>
<tr>
<td></td>
<td>05-06</td>
<td>1.29 (1.23-1.36)</td>
<td>3.91 (3.64-4.18)</td>
<td>8407</td>
</tr>
<tr>
<td></td>
<td>07-08</td>
<td>1.27 (1.21-1.34)</td>
<td>3.70 (3.50-3.90)</td>
<td>8266</td>
</tr>
<tr>
<td></td>
<td>09-10</td>
<td>1.12 (1.08-1.16)</td>
<td>3.34 (3.14-3.57)</td>
<td>8793</td>
</tr>
<tr>
<td>1-5 years</td>
<td>99-00</td>
<td>2.23 (1.96-2.53)</td>
<td>7.00 (6.10-8.30)</td>
<td>723</td>
</tr>
<tr>
<td></td>
<td>01-02</td>
<td>1.70 (1.55-1.87)</td>
<td>5.80 (4.70-6.90)</td>
<td>898</td>
</tr>
<tr>
<td></td>
<td>03-04</td>
<td>1.77 (1.60-1.95)</td>
<td>5.10 (4.10-6.60)</td>
<td>911</td>
</tr>
<tr>
<td></td>
<td>05-06</td>
<td>1.46 (1.36-1.57)</td>
<td>3.80 (3.49-4.54)</td>
<td>968</td>
</tr>
<tr>
<td></td>
<td>07-08</td>
<td>1.51 (1.37-1.66)</td>
<td>4.10 (3.40-5.19)</td>
<td>817</td>
</tr>
<tr>
<td></td>
<td>09-10</td>
<td>1.17 (1.08-1.26)</td>
<td>3.37 (2.63-4.11)</td>
<td>836</td>
</tr>
</tbody>
</table>
Current Methods for Blood Lead

- More detailed information can be found in:
  - CLSI document C40-A
    *Analytical Procedures for the Determination of Lead in Blood and Urine; Approved Guideline (2001)*
  - CLSI document C40
    *Measurement Procedures for the Determination of Lead Concentrations in Blood and Urine (Coming soon)*
Analytical Procedures for the Determination of Lead in Blood and Urine; Approved Guideline

Volume 21 Number 9

Patrick J. Parsons, Ph.D., C.Chem., FRSC, Chairholder
J. Julian Chisolm, Jr., M.D.
H. Trevor Delves, Ph.D., C.Chem., FRSC
Reginald Griffin, Ph.D.
Elaine W. Gunter, M.T.(ASCP)
Walter Slavin
Noel V. Stanton, M.S.
Robert Vocke, Ph.D.
Current Methods for Blood Lead

- GFAAS, ETAAS

Abbreviations: ETAAS, electrothermal atomic absorption spectrometry; GFAAS, graphite furnace atomic absorption spectrometry.
Graphite Furnace Atomic Absorption Spectrometry

LoD: ≈1 µg/dL
LoQ: 2–3 µg/dL
Cost: $30K–$50K
High complexity
Automated

Abbreviations: LoD, limit of detection; LoQ, limit of quantitation.
Current Methods for Blood Lead

- GFAAS, ETAAS
- ASV (benchtop)
Anodic Stripping Voltammetry

LoD: $\approx 2$–$3\ \mu g/dL$
LoQ: $\approx 10\ \mu g/dL$

Cost: $\$10K$–$\$15K$

High complexity

Nonautomated

No longer available, but current users are still supported.
Current Methods for Blood Lead

- GFAAS, ETAAS
- ASV (benchtop)
- ICP-MS
Inductively Coupled Plasma Mass Spectrometry

- Detector
- Quadrupole mass analyzer (10 × 10⁻¹⁰ Torr)
- Interface (4–8 × 10⁻¹⁰ Torr)
- Sample solution
- ICP Ion Source (760 Torr)
Inductively Coupled Plasma Mass Spectrometry

LoD: 0.05–0.2 µg/dL
LoQ: 0.3–0.7 µg/dL
Cost: $180K–$250K
Very high complexity
Automated
Inductively Coupled Plasma Mass Spectrometry

LoD: 0.05–0.2 µg/dL
LoQ: 0.3–0.7 µg/dL
Cost: $180K–$250K
Very high complexity
Automated
Inductively Coupled Plasma Mass Spectrometry

LoD: 0.05–0.2 µg/dL
LoQ: 0.3–0.7 µg/dL
Cost: $180K–$250K
Very high complexity
Automated
Inductively Coupled Plasma Mass Spectrometry Sector Field ICP-MS

LoD: ≈0.016 µg/dL

LoQ: ≈0.055 µg/dL

$500K cost +

Isotope ratios

Very, very high complexity

Automated
Current Methods for Blood Lead

➤ GFAAS, ETAAS

➤ ASV (benchtop)

➤ ICP-MS

➤ Handheld ASV, ie, LeadCare®
Handheld ASV

LeadCare® I
No longer available, but users are still supported.
LoD: \( \approx 2 \, \mu g/dL \)
Cost: $2K–$3K
Moderately complex
Nonautomated

LeadCare® II
LoD: \( \approx 3 \, \mu g/dL \)
Cost: $2K–$3K
CLIA-waived
Nonautomated
A review of the current federal criteria used to assess acceptable performance for blood lead testing in PT programs

Laboratory Workgroup Advisory Committee on Childhood Lead Poisoning Prevention (November 16, 2010)
Charge #1 to Laboratory Workgroup

- The LWG will address whether blood lead PT acceptability limits should be more stringent than the current CLIA '88 standard of ± 4 µg/dL or ± 10% (whichever is greater) and, if so, what they should be.

- The LWG should draft a letter from the ACCLPP to the appropriate federal agency recommending that a change in CLIA '88 regulations be implemented that would tighten the minimum acceptable PT limits for blood lead.

* ACCLPP, October 2009
BPb performance limits

Lab result – TV (µg/dL)

Blood Lead Target value (µg/dL)

±4/±10%
BPb performance limits

Lab result – TV (µg/dL)

Blood Lead Target value (µg/dL)

-10 -8 -6 -4 -2 0 2 4 6 8 10

Blood Lead Target value (µg/dL)

Lab result – TV (µg/dL)

-10 -8 -6 -4 -2 0 2 4 6 8 10

BPb performance limits

±4/±10%

±3/±10%
BPb performance limits

Lab result – TV (µg/dL) vs. Blood Lead Target value (µg/dL)

- Red line: ±4
- Green line: ±3
- Blue line: ±2/±10%

Arbitrary data
Laboratory Performance Within Individual Events
NYSDOH – All Laboratories

Acceptable Lab Performance, %

- 100%
- 90%
- 80%
- 70%
- 60%
- 50%
- 40%

2009-1
N = 105

2009-2
N = 104

2009-3
N = 101

2010-1
N = 100

±4 μg/dL or ±10%
±3 μg/dL or ±10%
±2 μg/dL or ±10%
±1 μg/dL or ±10%

Reproduced with kind permission, Jeff Jarrett (CDC)
Changing the Proficiency Testing Criteria

Acceptable Performance (%) as a Function of Blood Lead Concentration for NYSDOH (All Laboratories)

Acceptable Performance, %

Target Value, µg/dL

Note: Target values determined by referee group.

N = 100 – 105 (depending on sample)

Reproduced with kind permission, Jeff Jarrett (CDC)
Sample BE09-07 From NYSDOH, Event 2 (All Laboratories)

Figure 3a. Blood Lead Laboratory PT Performance
Sample BE09-07 from NY Event 2009-2
All Labs

Observed Blood Lead, ug/dL

Results in Ascending Order

- ASV LeadCare
- ASV 3010B
- GFAAS
- ICP-MS

Reproduced with kind permission, Jeff Jarrett (CDC)
1. Clinical Laboratory Improvement Advisory Committee (CLIAC) should make the recommendation that the Centers for Medicare & Medicaid Services (CMS) tighten the criteria for assessing acceptable performance for blood lead testing in PT programs from the current CLIA '88 regulatory standard of ± 4 µg/dL or ± 10% to ± 2 µg/dL or ± 10%.

2. CLIAC should request blood lead PT programs immediately to begin providing laboratory performance grades based on performance criteria of ± 2 µg/dL or ± 10% in addition to the existing ± 4 µg/dL or ± 10% CLIA criteria.
CLSI document C40-A (2001)

Recommended that the acceptable criterion for blood lead laboratory performance at 10 µg/dL be tightened to ±2 µg/dL (ie, ±20%)
- Can current analytical methods for blood lead support measurements below 5 µg/dL?

- Are the current (method) LoDs adequate?

- How low can laboratories go?

- Are all blood lead methods equal in analytical performance?
Interlaboratory Relative Standard Deviation by Method

Data taken from NYSDOH PT program for blood lead 2009-2011

- ASV 3010
- GFAAS
- ICPMS
- LC
Interlaboratory Relative Standard Deviation by Method

Data taken from NYSDOH PT program for blood lead 2009-2011

- ASV
- GFAAS
- ICPMS
- LC

©2013 Clinical and Laboratory Standards Institute. All Rights Reserved.
Interlaboratory Relative Standard Deviation by Method

Data taken from NYSDOH PT program for blood lead 2009-2011

Interlaboratory % RSD (PT)

- ASV 3010
- GFAAS
- ICPMS
- LC

©2013 Clinical and Laboratory Standards Institute. All Rights Reserved.
Interlaboratory Relative Standard Deviation by Method

Data taken from NYSDOH PT program for blood lead 2009-2011

- ASV 3010
- GFAAS
- ICPMS
- LC

±2 µg/dL

Blood Lead µg/dL
Data taken from NYSDOH PT program for blood lead 2009-2011

- ASV 3010
- GFAAS
- ICPMS
- LC

Interlaboratory % RSD (PT)

Blood Lead μg/dL

5 µg/dL

±2 µg/dL
NIST SRM 955c

National Institute of Standards & Technology

Certificate of Analysis

Standard Reference Material® 955c

Toxic Metals in Caprine Blood
Adult goats dosed with lead acetate
Blood units blended in class 100 conditions to produce four Pb levels: a baseline and three progressively elevated levels
  - Levels 2, 3, and 4 were further supplemented with inorganic arsenic, cadmium, and mercury (as inorganic mercury, methylmercury, and ethylmercury)
Homogeneity testing and Cd and Hg information values: Wadsworth using ICP-MS and GFAAS
Certified Pb Values: NIST using isotope dilution ICP-MS (ID-ICP-MS).
Comparison of clinical methods with isotope dilution inductively coupled plasma mass spectrometry for the new standard reference material 955c lead in caprine blood

Karen E. Murphy, * William F. Guthrie, Thomas W. Vetter, Gregory C. Turk, Christopher D. Palmer, Miles E. Lewis, Jr., Ciaran M. Geraghty and Patrick J. Parsons

In this article we describe the production and certification of the new NIST SRM 955c and compare the performance of the more rapid, clinical-based methods with ID-ICP-MS.

Table 1. Certified Lead Concentrations and Uncertainties for SRM 955c

<table>
<thead>
<tr>
<th>Concentration Levels</th>
<th>Lead (µg/dL)</th>
<th>Lead (µmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>0.424 ± 0.011</td>
<td>0.02047 ± 0.00053</td>
</tr>
<tr>
<td>Level 2</td>
<td>13.950 ± 0.080</td>
<td>0.6733 ± 0.0038</td>
</tr>
<tr>
<td>Level 3</td>
<td>27.76 ± 0.16</td>
<td>1.3400 ± 0.0076</td>
</tr>
<tr>
<td>Level 4</td>
<td>45.53 ± 0.27</td>
<td>2.198 ± 0.013</td>
</tr>
</tbody>
</table>

http://www.nist.gov/srm/
SRM 955c Level 2

Method Means: L 2

Difference of Means: L 2

GFAAS BPb Performance for SRM 955b at 4 µg/dL

An 8% to 9% bias for GFAAS at 4.04 µg/dL = +0.3–0.4 µg/dL, which is very good!

Summary

- 5 µg/dL is now the new 10 µg/dL.
- GFAAS and ICP-MS are excellent high complexity reference methods.
- LeadCare® II is well established for blood lead POC screening.
- Update of the CDC laboratory chapter is expected some time in 2013–2014.
- Revised version of CLSI document C40 is coming soon.
- LeadCare II POC® practice standards expected soon from CDC.
- NIST SRM 955c Toxic Metals in Caprine Blood is available and certified for accuracy/validation assessments for blood lead.
- CMS update of the CLIA PT regulations from ±4 to ±2 expected soon.
## Acknowledgments

**CDC ACCLPP LWG:**
- Valerie Charlton
- Leland McClure
- Megan Sandel
- Donald Simmons
- Noel Stanton

**CDC Staff:**
- Walter Alarcon
- Mary Jean Brown
- Jeffery M. Jarrett
- Robert L. Jones

**CLSI C40-A2 Authors:**
- Uttam Garg
- Montserrat González Estecha
- Robert L. Jones
- Jennifer Lowry
- Nelly Manay
- Robb Morse
- Heather Mowers
- Patrick J. Parsons
- Erlo Roth
- Noel V. Stanton
- Douglas F. Stickle

**CLSI Staff:**
- Patrice E. Polgar
- Megan L. Tertel

**APHL Staff:**
- Denise Korzeniowski

**NIST:**
- Karen Murphy
- Will Guthrie
- Tom Vetter
- Greg Turk
Thank You

Questions?