Lab Performance at Low Blood Lead Concentrations

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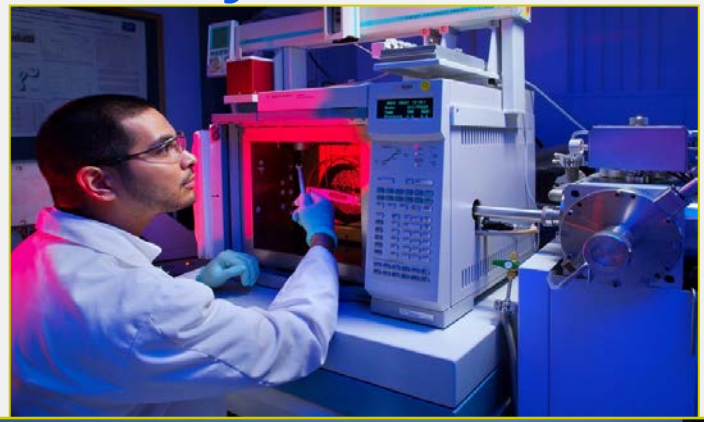
A Snapshot of our Laboratory

- State-of-the-art facilities: 2 new buildings, 150,000 sq. ft.
- Highly trained staff – 400 employees (250 FTEs), 108 PhDs and 7 MDs
- Advanced analytical instruments

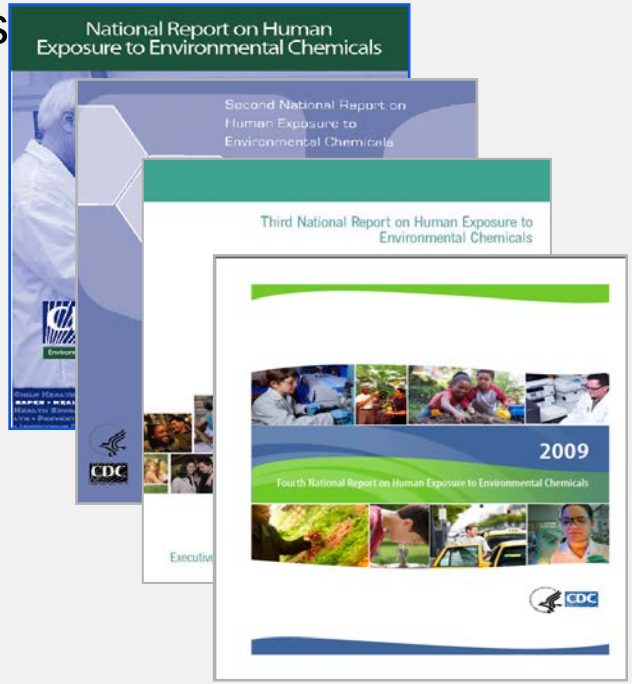


Laboratory Program Areas

- National Biomonitoring Program
- Emergency Response: Chemical and Radiation
- Tobacco and Smoking Addiction
- Newborn Screening
- Nutrition
- Selected Chronic Diseases
- Selected Infectious Diseases

Responding to Epidemics and Providing Information to make Informed Decisions Involving Chemical Exposures

- Measuring over 500 environmental chemicals and radionuclides in people
- Human exposure and health effects studies: about 60-70 per year– e.g., Bisphenol A in polycarbonate bottles and Brominated Fire Retardants in furniture and electronics
- *"National Reports on Human Exposure to Environmental Chemicals"*
  - *Fourth Report– December 2009*
  - *Updated Tables– January 2019*



www.cdc.gov/exposurereport

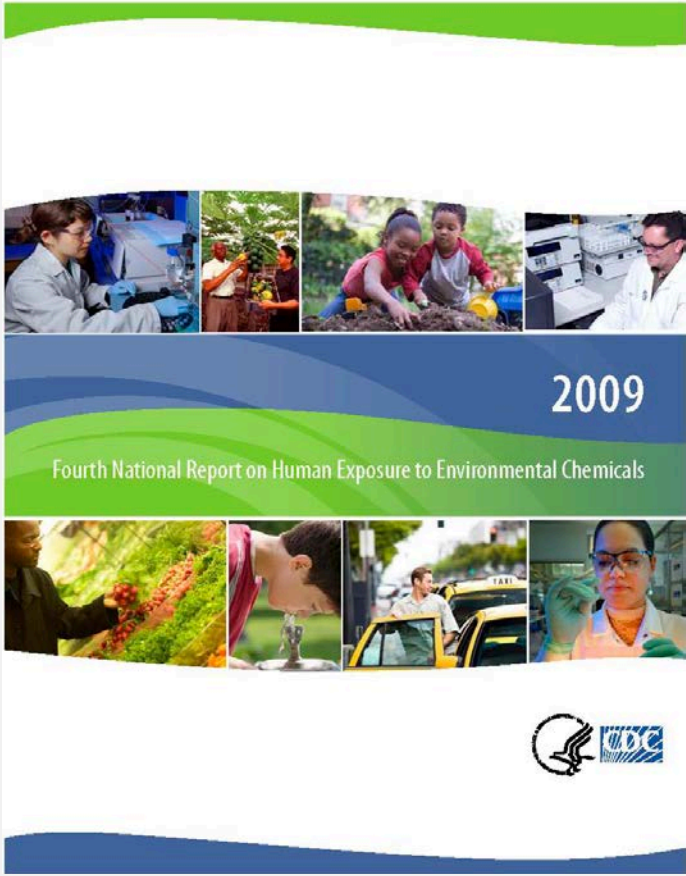
Fourth National Report on Human Exposure to Environmental Chemicals

- Approximately 9000 people each 2 year period

- Nationally representative samples for years:1999-2000, 2001-2002, 2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012, 2013-2014, 2015-2016, and 2017-2018

- Updated tables released 1/2019

www.cdc.gov/exposurereport



Three main methods to measure blood lead

- **ICP-MS** – Inductively coupled plasma mass spectrometry
- **GFAAS** – Graphite furnace atomic absorption spectroscopy
- **Leadcare II** – Point-of-care (POC) portable blood lead instrument

LeadCare FDA Safety Recall Issue

FDA Safety notice: *"FDA Warns Against Using Magellan Diagnostics LeadCare Testing Systems with Blood Obtained from a Vein: FDA Safety"*

"The FDA is warning facilities such as laboratories or health clinics that Magellan Diagnostics' LeadCare Testing Systems may underestimate BLLs and give inaccurate results when processing **venous** blood samples."

https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-using-magellan-diagnostics-leadcare-testing-systems-blood-obtained-vein-fda-safety

Request from the 2017 NCEH/ATSDR Board of Scientific Counselors, Lead Poisoning Prevention Subcommittee

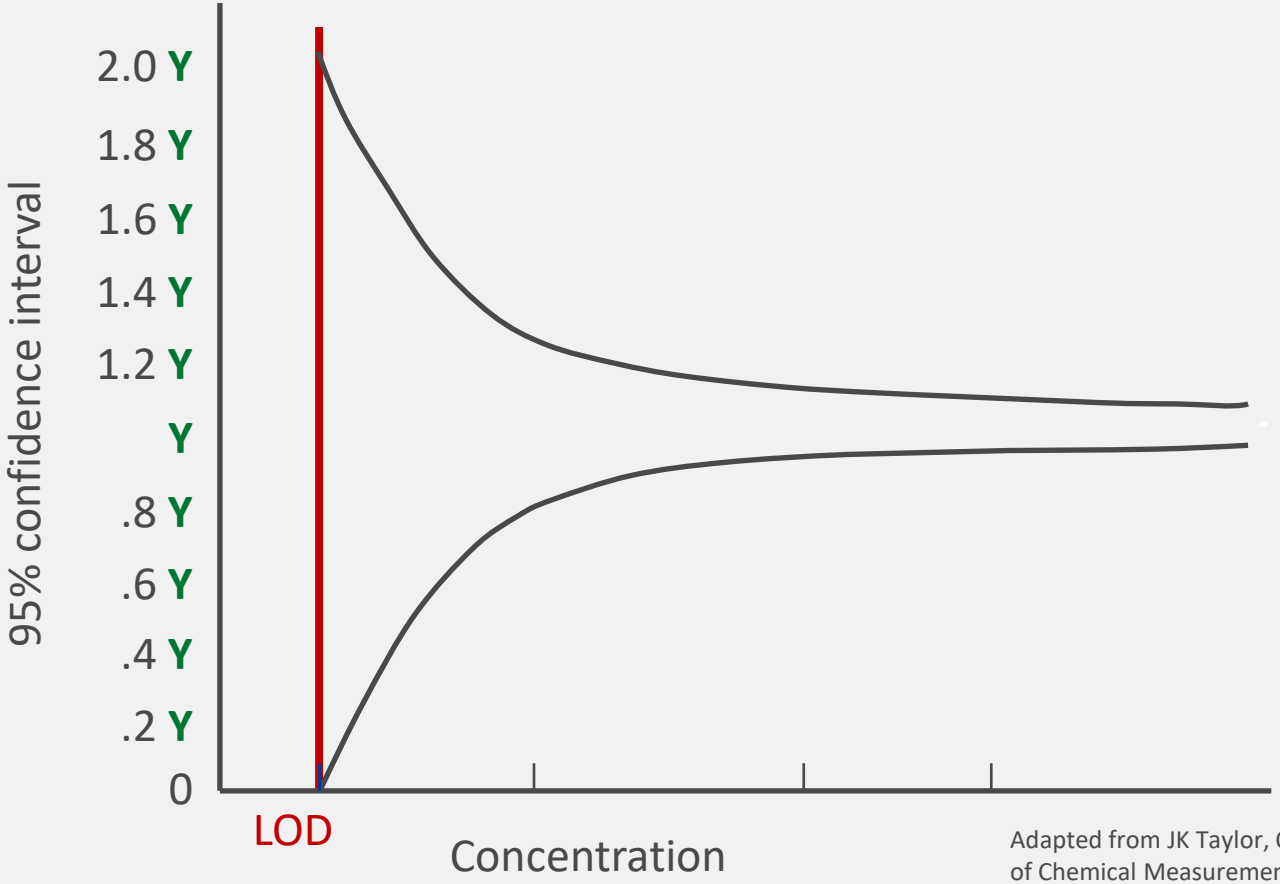
"Examine the implications of the level of quantitation and precision of the three primary laboratory methods (ICP-MS, GFAAS, and POC – LeadCare II) for the positive and negative predictive value of blood lead tests obtained in the setting of a possible revised reference value (RV) of 3.5 µg/dL."

Questions surrounding of measurement issues

- **Sensitivity**
  - For each of the three methods, is 3.5 µg/dL above the limit of detection (LOD)?

- **Precision**
  - For each of the three methods, is the precision of measurement at 3.5 µg/dL adequate for clinical use?

Imprecision increases non-linearly near the limit of detection



Adapted from JK Taylor, Quality Assurance of Chemical Measurements, 1987.

Limits of Detection and Quantitation

Limit of Detection (LOD)

- the lowest level at which the magnitude of the measurement is greater than the uncertainty of the measurement
- at the limit of detection, measurement uncertainty is ~±100 %

Limit of Quantitation (LOQ)

- is the lowest level the lab decided is quantitatively meaningful or is their lower reporting level based on “policy” decisions

Limits of laboratory-developed tests vary by lab and over time

- ICP-MS, GFAAS

Limits of manufacturer-developed tests are fixed (FDA cleared)

- LeadCare 1, LeadCare II, LeadCare Ultra, LeadCare Plus

Limits of Detection (LOD) and Lower Reporting Limits, µg/dL

Reported by Labs	ICP-MS	GFAAS	LeadCare II	LeadCare Ultra LeadCare Plus
Published LOD	0.05 – 1.06	0.08 – 1.5	Fixed at 3.3**	Fixed at 1.9
Lower reporting limits*	0.02 – **5**	0.1 – **5**		

* Examples reported to WSLH and CDC LAMP programs during testing events

** LeadCare II LOD determined by using non-laboratory trained personnel (CLIA Waived criteria)

Summary of measurement issues

- **Sensitivity**
  - For each of the three methods, is 3.5 µg/dL above the limit of detection (LOD)?

    Yes
- **Precision**
  - For each of the three methods, is the precision of measurement at 3.5 µg/dL adequate for clinical use?

    Yes

Blood lead proficiency testing program data sources

- Wisconsin State Laboratory of Hygiene (WSLH)
  - Blood Lead Regulatory PT Program
  - Laboratory Response Network – Chemical (LRN-C)
- New York State Department of Health (NYSDOH) Wadsworth's Trace Elements in Blood PT Program
- CDC's Lead and Multielement Program (LAMP)
- Centre de toxicologie du Québec (CTQ)
  - PCI: Interlaboratory Comparison Program
  - QMEQAS: Quebec Multielement External Quality Assessment Scheme

Blood lead proficiency testing CLIA requirements

- 5 unknown samples sent 3 times per year
- Required for
  - ICP-MS, GFAAS, LeadCare I, LeadCare Ultra, LeadCare Plus
- Not required for LeadCare II

Number of participating labs by method by provider

	WSLH	NYS DOH	CDC LAMP	CTQ
ICP-MS	20 – 45	15 – 30	~40	10 – 40
GFAAS	~40	1 – 45	~30	0 – 50
LeadCare II	~350	0 – 10	~10	0

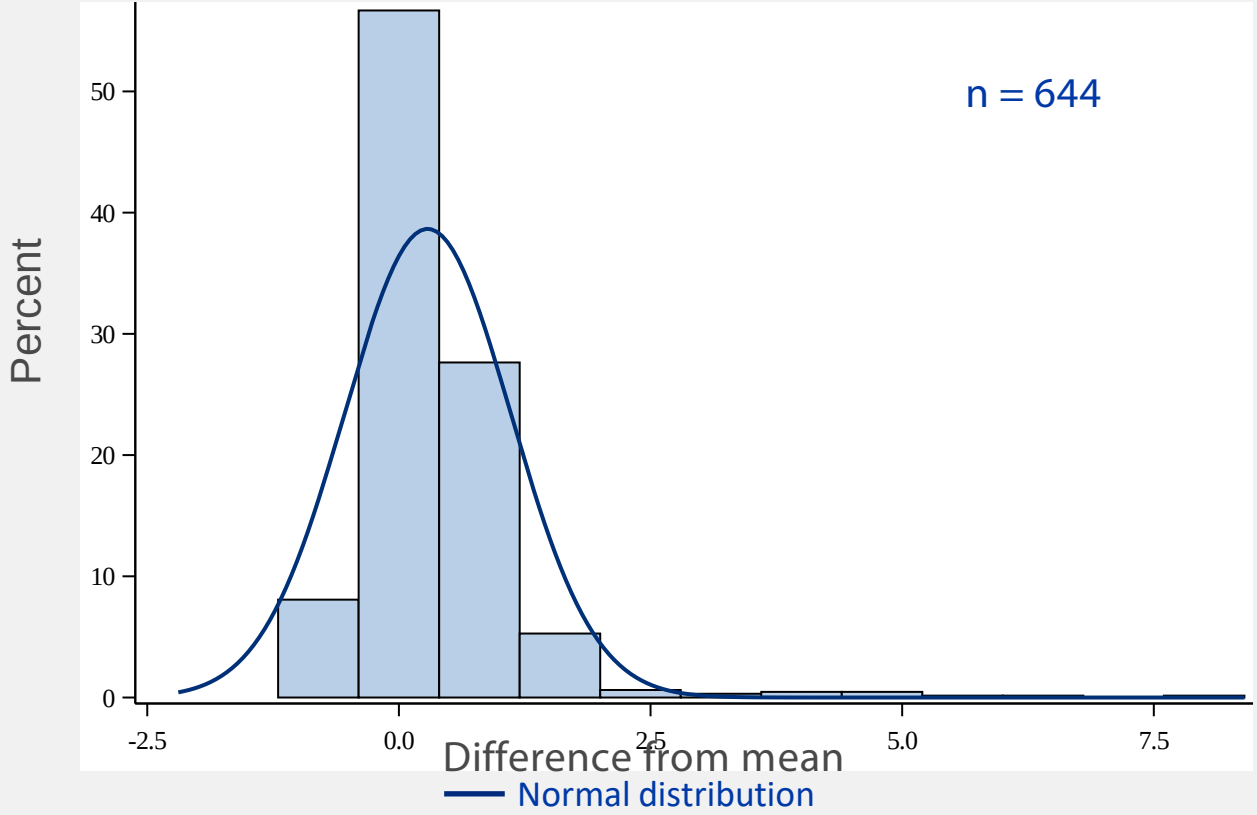
Data selection from proficiency testing (PT) programs

- Blood pools used in 2010 - 2019 PT challenge events
- Blood lead concentration means are 3.0 – 4.1 µg/dL
- LeadCare II data from 3 samples (92% of submitted results)
- Calculated difference of each result from pool mean
- Excluded outliers based on 4 sigma criteria

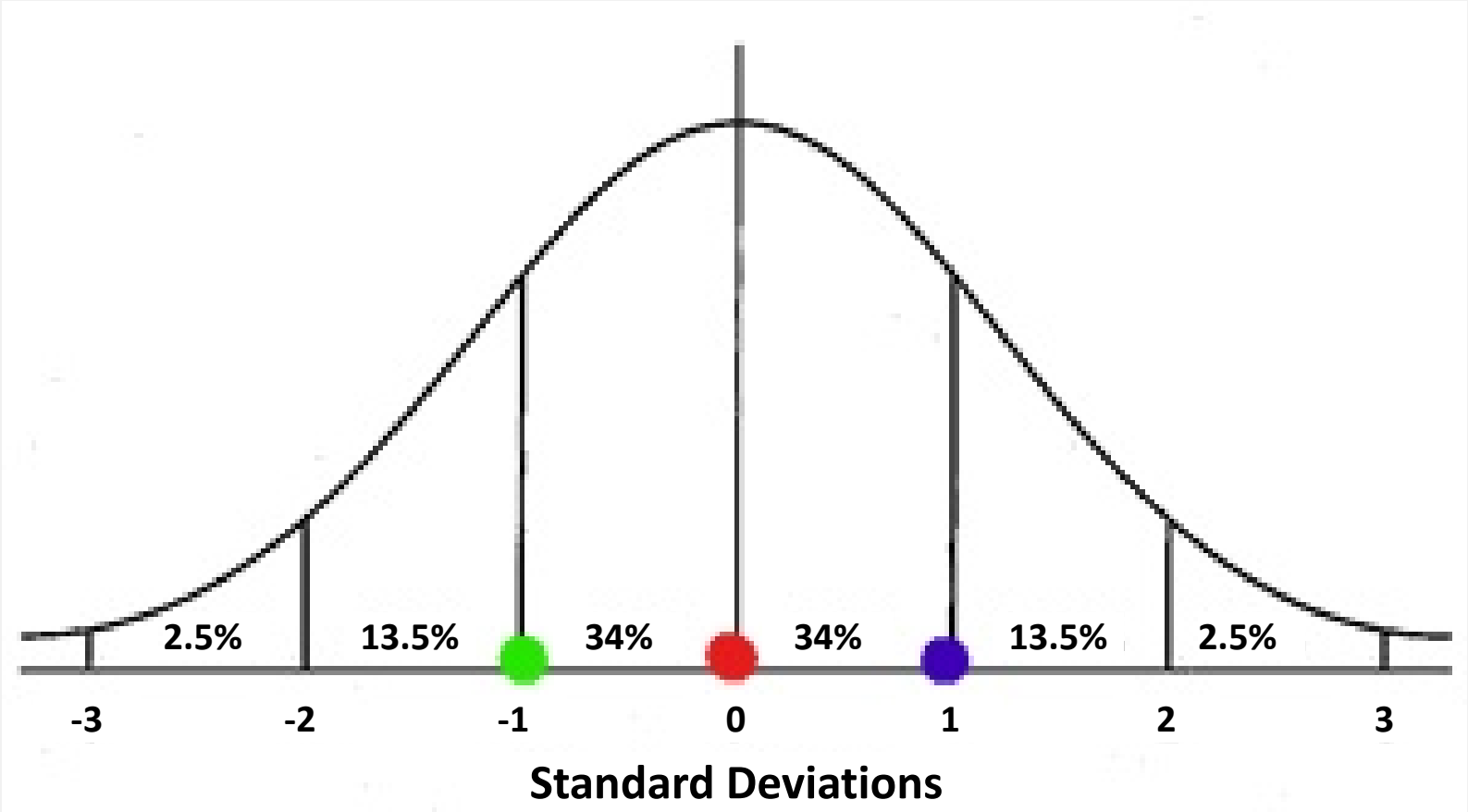
Data by test type

	# submitted results	<LOD (%)	N >LOD
LeadCare II	1028	37%	644
GFAAS	690	2.5%	673
ICP-MS	942	2.9%	915

LeadCare II – difference in measurements from pool mean for PT samples (3.5 – 4.1 µg/dL)



Normal analytical laboratory distribution of results

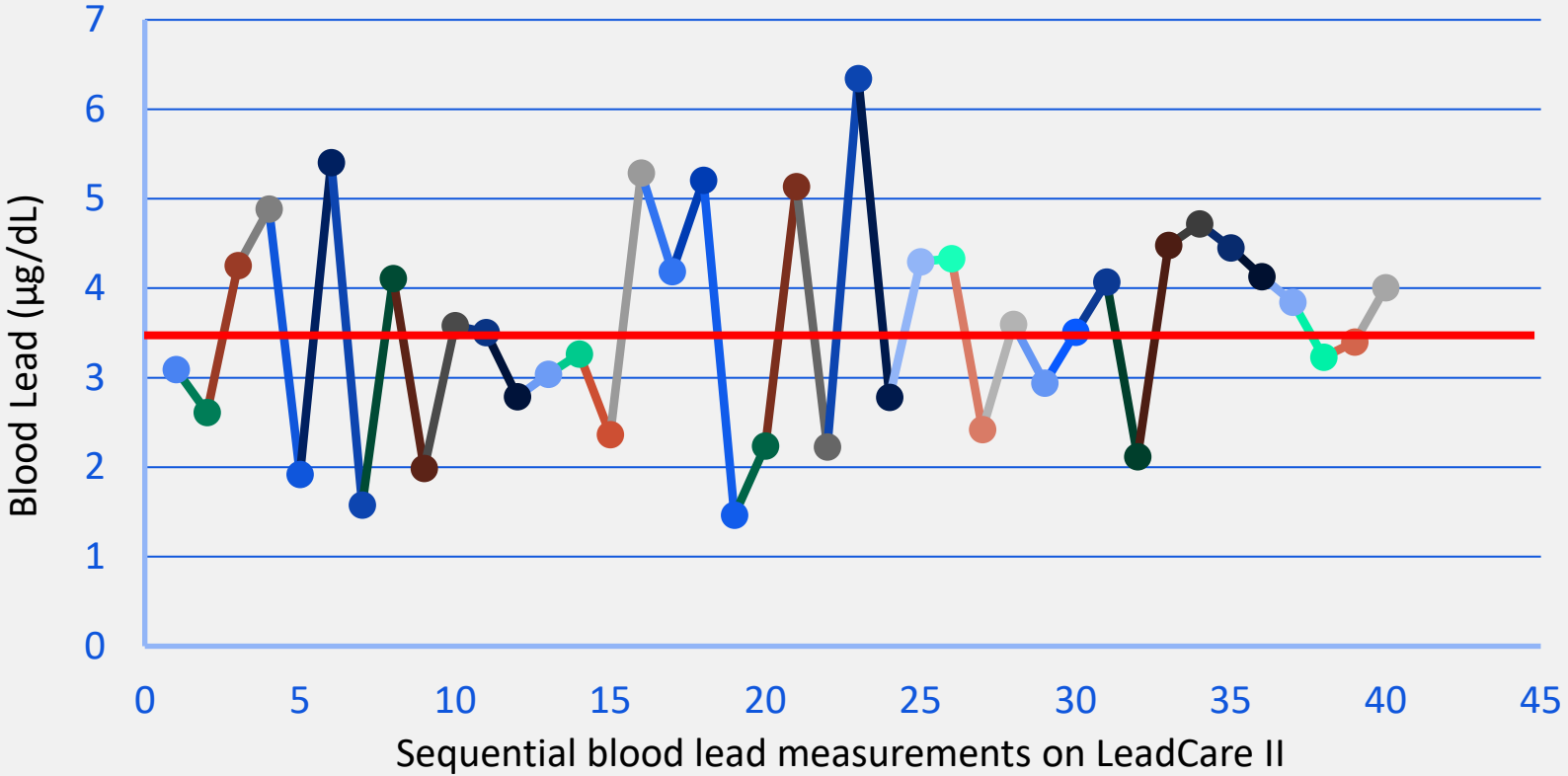


Best estimates of precision of blood lead measurements between 3.0 to 4.1 µg/dL

	95% confidence interval (µg/dL)	N
LeadCare II*	± 1.8	1028
GFAAS**	± 1.6	673
ICP-MS**	± 0.83	915

*<LOD treated as zero. SD estimated from proc-univariate as (97.5th - 50th percentile)/2.
** <LOD excluded

Simulation of sequential blood lead measurements for a person with constant, true blood lead of 3.5 µg/dL using the LeadCare II



NHANES Blood Lead Percentiles for Children age 1-5 years

NHANES	Sample Size	Geometric Mean	50th	75th	90th	95th	97.5th
2011-2014	1531	0.86 (0.80-0.93)	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)
2 cycles each							
2015-2018	1419	0.71 (0.66-0.77)	0.65 (0.60-0.71)	1.04 (0.94-1.16)	1.66 (1.49-1.86)	2.41 (1.9-3.01)	3.44 (2.68-4.22)

Summary

- Precision estimates are based on pools from Proficiency Testing providers with blood lead mean concentrations between 3.0 and 4.1 µg/dL
- Precision for measurements made at between 3.0 and 4.1 µg/dL are similar to estimates reported previously for 4.0 to 6.0 µg/dL
- Blood tube manufacturers should consider offering blood tubes < 0.2 µg/dL blood lead equivalent (CDC criteria is 0.1 µg/dL)
- Improving precision of methods continues to be important

Acknowledgements

Dr. Jerry Thomas

For more information, contact NCEH/ATSDR
1-800-CDC-INFO (232-4636)
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