NTP
National Toxicology Program

NTP Monograph on Health Effects of Low-Level Lead

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Meeting of the NTP Board of Scientific Counselors
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Introduction

Lead (Pb) exposure remains a significant health concern for children and adults despite policies and practices that have resulted in continued progress toward reducing exposure and lowering blood lead levels in the U.S. population.

Scope of the NTP Monograph

- NIOSH nominated low-level lead for evaluation
- The NTP Board of Scientific Counselors expressed unanimous support for the evaluation
  - Focus on health effects at blood lead <10μg/dL (May 2010)
- The evaluation is focused on epidemiological data for health effects at blood lead levels <10μg/dL
  - Health effects are well established at higher levels
  - CDC's definition* of elevated blood lead was ≥10μg/dL for all ages
- The monograph represents and overview of the science to date on potential health effects from low-level lead exposure

Key Questions

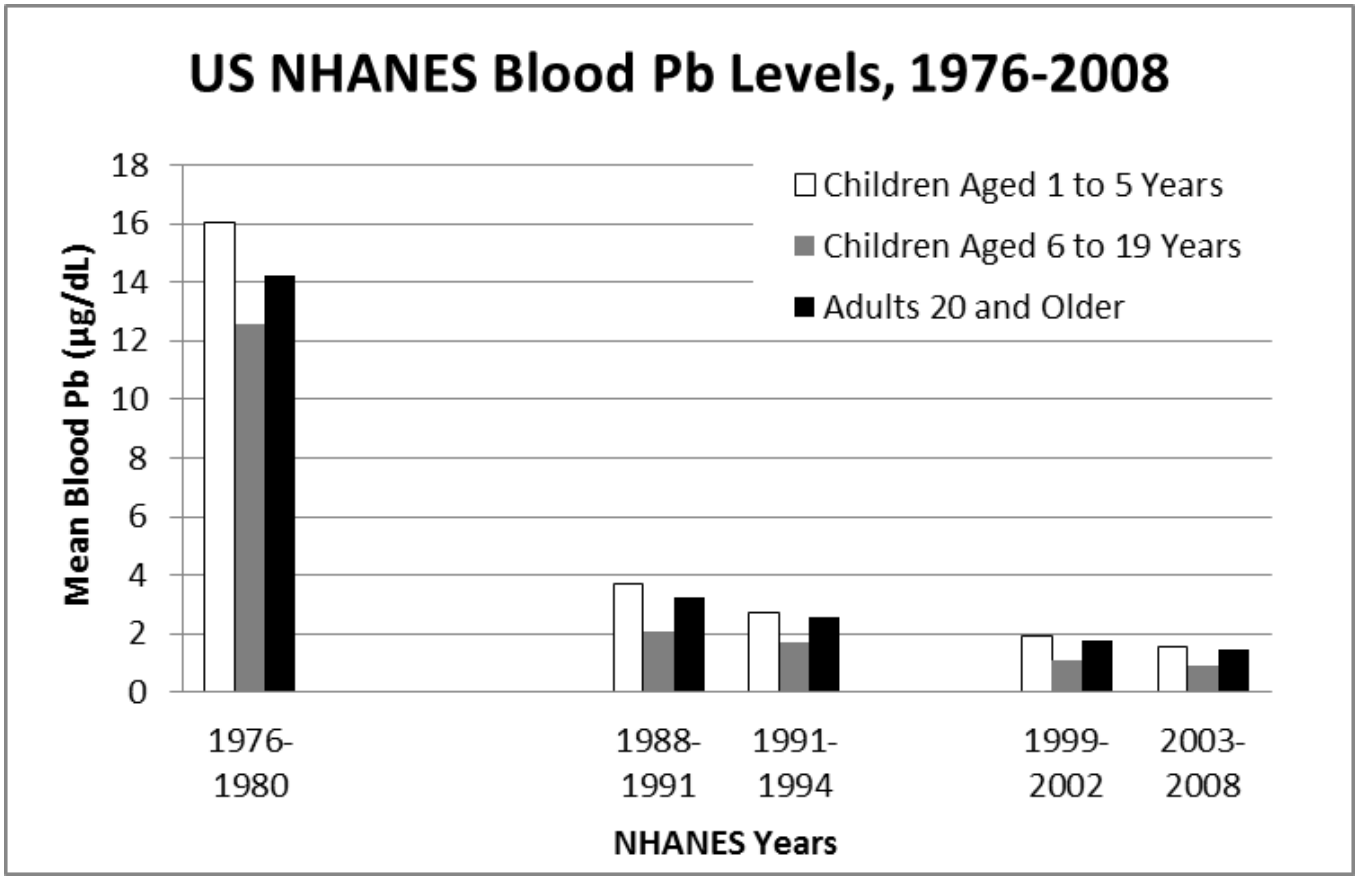
What is the evidence that adverse health effects are associated with blood lead levels <10μg/dL?

- What neurological, immune, cardiovascular, renal, reproductive, and developmental effect(s) are associated with blood lead levels <10μg/dL?
- What is the blood lead level associated with a given health effect (i.e., <10μg/dL or <5μg/dL)?
- At which life stage (childhood or adulthood) is the effect identified?
- Are there data to evaluate the association between bone lead and the health effect and how does the association to this biomarker of lead exposure compare to the association with blood lead ?

What Does it Mean to Refer to Blood Lead <10μg/dL?

- Blood lead reflects an equilibrium between current environmental lead exposure and the body burden of lead
- **Blood lead**
  - Reflects current exposure
  - Widely available exposure metric
- **Bone lead**
  - Reflects cumulative exposure
  - Bone stores 70 – 95% of total body burden
  - Data are not widely available

US Blood Lead Levels



- Children age 1-5 have higher blood lead levels
- Adults today may have had higher childhood levels

Blood Lead Level <10μg/dL

- Multiple studies report significant associations between concurrent blood lead levels <10μg/dL and health effects in adults
- The association with blood lead is supported by:
  - Consistency of effects across epidemiological studies
  - Coherence with animal data
- It is well recognized that the role of early-life lead exposure cannot be discriminated from the role of concurrent blood lead in adults without additional long term studies

Organization of the Monograph

- Executive Summary
- Methods
- Exposure
- Health Effects Sections
  - Neurological Effects
  - Immune Effects
  - Cardiovascular Effects
  - Renal Effects
  - Reproductive and Developmental Effects


National Toxicology Program
U.S. Department of Health and Human Services

DRAFT NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

OCTOBER 14, 2011

Office of Health Assessment and Translation
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Peer Review Date: November 17-18, 2011

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Basis for Conclusions on Health Effects of Lead

- **Primary literature** - epidemiological studies with mean blood lead levels <10μg/dL
  - Careful consideration of study design and confounders

- **Supported by**
  - Bone lead data
  - Laboratory animal data
  - Authoritative sources
    - US EPA 2006 Air Quality Criteria Document for Lead
    - ATSDR 2007 Toxicological Profile for Lead
    - Technical advisors
    - Expert peer review

Peer Review of the draft NTP Monograph

- An independent expert panel reviewed the draft Monograph on the Health Effects of Low-level Lead during a public meeting held November 17-18, 2011 in RTP

-- Joel Pounds, PhD (chair)	Pacific Northwest National Laboratory, Richland, WA
-- Deborah Cory-Slechta, PhD	University of Rochester School of Medicine and Dentistry, Rochester, NY
-- Pam Factor-Litvak, PhD	Columbia University, New York, NY
-- Eliseo Guallar, MD, DrPH	Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD
-- Bruce Lanphear, MD, MPH, TM	University of British Columbia, Vancouver, British Columbia, Canada
-- Michael Pollard, PhD	The Scripps Research Institute, San Diego, CA
-- Stephen Rothenberg, PhD	National Institute of Public Health, Ministry of Mexico, Cuernavaca, Morelos, Mexico
-- Vostratola Vaziri, MD, MACP	University of California, Irvine Medical Center, Orange, CA
-- Richard Wedeen, MD	UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ

Peer Review of the draft NTP Monograph

- The panel agreed with the draft NTP overall conclusions on health effects associated with blood lead <10 µg/dL for
  - Cardiovascular
  - Renal
  - Immune
- The panel recommended changing the draft summary conclusion from *sufficient* evidence of an association at blood lead <10 ug/dL to blood lead <5 ug/dL for
  - Neurological effects in children
  - Reproductive effects in adult women
- The NTP concurred with the panel on all recommendations on the conclusions regarding health effects of lead

Approach to Develop Health Effects Conclusions

- NTP Considered four possible conclusions for specific health effects in each area:
  - **Sufficient Evidence of an Association**
  - **Limited Evidence of an Association**
  - **Inadequate Evidence of an Association**
  - **Evidence of No Association**

Presentation of NTP Conclusions

- Health effects sections begin with a statement of the NTP's conclusion on whether or not the effect is associated with blood lead <10μg/dL or <5μg/dL
  - Age at which it is identified
  - Timing of exposure associated with the effect
- Key data and principal studies discussed in detail
- Summary includes:
  - Support from experimental animal data
  - Consistency with previous EPA and ATSDR reports

Example - Increased Hypersensitivity in Children

NTP Conclusion: *limited* evidence <10µg/dL based on:

- A prospective study reporting
  - An association between maternal and cord blood lead <10µg/dL and sensitization to common allergens (Jedrychowsky, 2011)
  - Diagnosed <u>in children</u> by skin prick testing at age 5

- **Supported <u>in children</u> by:**
  - Lead-related increases in serum IgE in children
  - Increased odds ratio for sensitization by skin prick test associated with lead-dustfall in children (Heinrich, 1999; ecological study)

skin prick test

Example - Increased Hypersensitivity in Children

- Summary of the basis for conclusion of *limited* evidence for an association with blood lead <10µg/dL
  - Single prospective study with sensitization at blood lead <10µg/dL
  - Strengthened by evidence supporting lead-related increase in IgE
    - 5 cross-sectional studies with blood lead <10µg/dL and elevated IgE
    - IgE associated with hair lead in newborns (Annesi-Maesano, 2003)
    - IgE associated with lead-dustfall in children (Heinrich, 1999; ecological)
    - Limited animal data report lead-related increases in IgE
  - Database and sample size limited
  - Lacks consistent evidence for related endpoints

Main Findings of the NTP Monograph

Prepublication copy available at: http://ntp.niehs.nih.gov/go/36443

- Both children and adults are vulnerable to the effects of lead
- There is evidence for many adverse health effects in both children and adults at blood lead levels below 10μg/dL and for some below 5μg/dL
- The NTP findings are consistent with and extend what other agencies have found in recent reviews
  - 2007 ATSDR Toxicological Profile for Lead
  - 2006 EPA Air Quality Criteria Document for Lead *and draft 2012 update*

The NTP's Conclusions for Major Health Effects

Sufficient evidence that blood Pb levels <10µg/dL are associated with adverse effects …

Adults

Cardiovascular Function

Renal Function

Lower Birth weight

Children

Decreased Cognitive Function

Decreased Hearing

Reduced Growth

Increased Attention-related and Problem Behaviors

Delayed Puberty

NTP Conclusions on Health Effects of Low-level Lead in Children: Blood Lead Levels <5μg/dL

Conclusion	Principal Health Effects
Sufficient	• Decreased IQ, academic achievement, and specific cognitive measures • Increased incidence of attention-related and problem behaviors
Limited	• Delayed puberty • **Decreased kidney function in children age 12 and older**

NTP Conclusions on Health Effects of Low-level Lead in Children: Blood Lead Levels <10μg/dL

Conclusion	Principal Health Effects
Sufficient	• Delayed puberty • **Reduced postnatal growth** • Decreased hearing
Limited	• Increased hypersensitivity/allergy by skin prick test to common allergens
Inadequate	• Asthma, eczema, non-allergy immune function, cardiovascular effects, renal function in children under age 12

Table 1.2. NTP conclusions on health effects of low level Pb by major health effect areas

Health Area	Population or Exposure window		NTP Conclusion	Principal Health Effects	Blood Pb Evidence
Neurological	Prenatal		*Limited*	Decrease in measures of cognitive function	Yes, <5µg/dL
			Limited	Decreased IQ, increased incidence of attention-related and problem behaviors, decreased hearing	Yes, <10µg/dL
	Children		*Sufficient*	Decreased academic achievement, IQ, specific cognitive measures; increased incidence of attention-related and problem behaviors	Yes, <5µg/dL
			Sufficient	Decreased hearing	Yes, <10µg/dL
	Adults		*Sufficient*	Increased incidence of essential tremor	Yes, <10µg/dL
			Limited	Psychological effects, decreased hearing, decreased cognitive function, increased incidence of ALS	Yes, <10µg/dL
			Limited	Increased incidence of essential tremor	Yes, <5µg/dL
Immune	Children		*Limited*	Increased hypersensitivity/allergy by skin prick test to common allergens	Yes, <10µg/dL
			Inadequate	Asthma, eczema	Unclear
	Adults		*Inadequate*		Unclear
Cardiovascular	Children		*Inadequate*		Unclear
	Adults		*Sufficient*	Increased blood pressure and increased risk of hypertension	Yes, <10µg/dL
			Limited	Increased cardiovascular-related mortality and ECG abnormalities	Yes, <10µg/dL
Renal	Children < age 12		*Inadequate*		Unclear
	Children 12 or older		*Limited*	Decreased glomerular filtration rate	Yes, <5µg/dL
	Adults		*Sufficient*	Decreased glomerular filtration rate	Yes, <5µg/dL
Reproductive and Developmental	Prenatal		*Limited*	Reduced postnatal growth	Yes, <10µg/dL
	Children		*Sufficient*	Delayed puberty and reduced postnatal growth	Yes, <10µg/dL
			Limited	Delayed puberty	Yes, <5µg/dL
	Adults	Women	*Sufficient*	Reduced fetal growth	Yes, <5µg/dL
			Limited	Increase in spontaneous abortion and preterm birth	Yes, <10µg/dL
		Men	*Sufficient*	Adverse changes in sperm parameters and increased time to pregnancy	Yes, ≥15-20µg/dL
			Limited	Decreased fertility	Yes, ≥10µg/dL
			Limited	Increased spontaneous abortion	Yes, >31µg/dL
		Adults	*Inadequate*	Stillbirth, endocrine effects, birth defects	Unclear

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Technical Advisors

Peer-Review Panel Members

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					Yes, <10µg/dL
					Yes, <5µg/dL
Immune					Yes, <10µg/dL
					Unclear
					Unclear
Cardiovascular					Unclear
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Renal					Unclear
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Reproductive and Developmental	Prenatal		*Limited*	Reduced postnatal growth	Yes, <10µg/dL
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Thank You.

Any Questions?