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# Draft NTP Monograph on Health Effects of Low-level Lead:

# Neurological Effects

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# Neurological Effects of Low-level Pb

- Principle Neurological health effects of Pb
  - **Children**
    - Neurocognitive and neurobehavioral effects
    - More recent studies on attention and delinquent behavior
    - Some prospective studies of prenatal Pb exposure
  - **Adults**
    - Neurodegenerative disease – ALS and essential tremor
    - Decreased cognitive performance - (bone Pb)
- ATSDR and EPA conclude
  - Pb has negative effects on neurocognitive ability and neurobehavioral outcomes in children
- Animal data support neurotoxicity of Pb

# Major Neurological Effects Considered

- Cognitive Function
- Behavior
- Neurodegeneration
- Sensory Organs

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# Cognitive Function

# Decreased Academic Achievement

- **Academic achievement**
  - Broad-based measure of cognitive function in children
  - Measured with numerous tests
  - Also determined by class rank or end of grade testing

**NTP Conclusions**: *sufficient* evidence that childhood blood Pb levels <10µg/dL and <5µg/dL are associated with decreased academic achievement and,

*inadequate* evidence for prenatal blood Pb levels <10µg/dL

# Decreased Academic Achievement – Child Blood Pb Evidence

**NTP Conclusions**: *sufficient* evidence <10µg/dL and <5µg/dL in children based on:

- Multiple prospective and cross-sectional studies
  - Associations with blood Pb levels <10 and 5µg/dL
  - Consistency of effects on several measures of academic achievement
- **Supported by**
  - Association with teeth dentin bone Pb
  - Similar effects in children at higher blood Pb levels
  - Animal data on Pb-associated decrease in learning tests
- **Note**
  - lack of studies with prenatal exposure data

# Decreased IQ

- **IQ**
  - Broad-based measure of cognitive function
  - Pb-associated IQ data are only in children
  - Measured with numerous tests

**NTP Conclusions**: *sufficient* evidence that blood Pb levels <10µg/dL are associated with decreased IQ in children, *limited* evidence for child blood Pb <5µg/dL, and

*limited* evidence for prenatal blood Pb <10µg/dL

# Decreased IQ – Child and Prenatal Evidence

**NTP Conclusions**: *sufficient* evidence <10µg/dL and *limited* evidence <5µg/dL in children based on:

- Multiple prospective and cross-sectional studies reporting associations with blood Pb levels <10µg/dL in children
  - Consistency of effects on several measures of IQ
  - Pooled analysis (Lanphear, 2005) and Meta-analyses (e.g., Schwartz, 1994)
- Effects <5µg/dL observed in 1 cross-sectional study
- **Supported by**
  - Similar effects in children at higher blood Pb levels
  - Association with bone Pb (tibia and teeth)
  - Animal data
- **Note**
  - Mixed evidence of association with maternal or cord blood Pb <10; therefore, *limited* evidence for prenatal <10µg/dL

# Decreases in Other General or Specific Measures of Cognitive Function

- **Other general and specific measures**
  - Measured with numerous tests
  - Broad-based tests and for specific cognitive domains
  - Tests designed for children or **adults**

**NTP Conclusions**: *sufficient* evidence that blood Pb levels <10µg/dL and <5µg/dL are associated with decreased cognitive function in children,

*limited* evidence for prenatal Pb <10 and 5µg/dL,

*and limited* evidence **in older adults** at blood Pb levels <10µg/dL

# Decreases in Other General or Specific Measures of Cognitive Function – Child and Prenatal Evidence

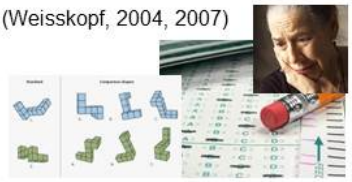
**NTP Conclusions**: *sufficient* evidence <10µg/dL and <5µg/dL in children based on:

- Multiple prospective and cross-sectional studies reporting associations with blood Pb levels <5µg/dL
  - Consistency of effects on multiple cognitive measures
- **Supported by**
  - Association with bone Pb
  - Similar effects in children at blood Pb levels >10µg/dL
  - Animal data
- **Note**
  - Mixed evidence of association with maternal blood Pb <5µg/dL; therefore, *limited* evidence for prenatal blood Pb levels <10µg/dL and<5µg/dL

# Decreases in Other General or Specific Measures of Cognitive Function – Evidence in Adults

**NTP Conclusions**: *limited* evidence <10µg/dL **in older adults** based on:

- Decreased cognitive function reported in older adults at blood Pb levels <10µg/dL
  - Normative Aging Study (Payton, 1998; Wright, 2003)
  - Study of older women in Pennsylvania and Baltimore (Muldoon, 1996)
- **Supported by**
  - Association with bone Pb and change in cognition over time
    - Bone Pb and blood Pb (Payton, 1998)
    - Bone Pb not blood: Baltimore Memory Study (Shih, 2006), Nurses Health Study (Weuve,2009)
    - Bone Pb and change in cognition: Normative Aging Study (Weisskopf, 2004, 2007)
- **Note**
  - Mixed results from blood Pb studies
    Rural China (Gao, 2008), Sweden (Nordberg, 2000)



# Behavior

# Increased Diagnosis of ADHD

- **Attention Deficit Hyperactivity Disorder (ADHD)**
  - Behavioral diagnosis
  - Can be determined by diagnostic interview
  - Also determined by use of stimulant medication

**NTP Conclusions**: *sufficient* evidence that blood Pb levels <10µg/dL and <5µg/dL are associated with ADHD in children,

*limited* evidence for prenatal Pb <10µg/dL,

*inadequate* evidence **in adults** at Pb <10µg/dL

# Increased Diagnosis of ADHD - Evidence

**NTP Conclusions**: *sufficient* evidence <10µg/dL and <5µg/dL in children based on:

- Multiple prospective and cross-sectional studies
  - Prospective studies with blood Pb <10µg/dL (Canfield, 2003)
  - Consistent associations with blood Pb levels <5µg/dL
- **Supported by**
  - Studies reporting association with bone Pb
  - Animal data on Pb-associated increased distractibility
- **Note**
  - Few studies report association with maternal or cord blood Pb; *limited* evidence for prenatal Pb <10µg/dL
  - No studies with **adult** blood Pb levels; *inadequate*

## Increased Delinquent, Criminal or Antisocial Behaviors

- **Problem Behaviors**
  - **Delinquent, criminal or antisocial behaviors**
    - Measured with numerous tests
    - Also determined by criminal records

**NTP Conclusions**: *sufficient* evidence that blood Pb levels <10µg/dL and <5µg/dL are associated with antisocial behaviors including delinquent or criminal behavior in children,

*limited* evidence for prenatal Pb <10µg/dL, and

*inadequate* evidence **in adults** at Pb levels <10µg/dL

## Increased Delinquent /Criminal/ Antisocial Behaviors - Evidence

**NTP Conclusions**: *sufficient* evidence <10µg/dL and <5µg/dL in children based on:

- Multiple prospective and cross-sectional studies reporting associations with blood Pb levels <10µg/dL in children
  - Consistency between behavioral tests and criminal arrests
  - Large cross-sectional study Pb <1µg/dL; n=3081; (NHANES 2001-4; Braun, 2008)
- **Supported in children by**
  - Consistent association with bone Pb
  - Similar effects in children at higher blood Pb levels (>10µg/dL)
  - Animal data on Pb-associated inappropriate responding
- **Note**
  - Mixed evidence of association with maternal or cord <10; *limited* evidence for prenatal Pb <10µg/dL
  - No studies with adult blood Pb levels

## Psychiatric Outcomes Including Anxiety and Depression

- **Problem Behaviors**
  - **Psychiatric outcomes**
    - Including anxiety, depression, and panic disorder

**NTP Conclusions**: *insufficient* evidence in children, and *limited* evidence that blood Pb levels <10µg/dL **in adults** are associated with psychiatric outcomes

## Psychiatric Outcomes / Anxiety and Depression - Evidence

**NTP Conclusions**: *insufficient* evidence in children, and *limited* evidence **in adults** <10µg/dL based on:

- Several cross-sectional studies reporting associations with blood Pb levels <10µg/dL **in adults**
  - NHANES 1999-2004 [n=1,987 adults] (Bouchard, 2009)
    - Increased odds ratio for major depression disorder and panic disorder
  - Normative Aging Study [n=526 adults] (Rhodes, 2003)
    - Associated with combined measure including anxiety and depression
- **Supported in adults by**
  - Association with bone Pb (Rajan, 2007; Rhodes, 2003 – Normative Aging Study)
  - Animal data on Pb-associated increased depression-related outcomes
- **Note**
  - Few studies in children and blood Pb levels >10µg/dL (Wasserman, 1998; Roy, 2009)

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# Neurodegeneration

# Increased Risk for ALS

- **Amyotrophic lateral sclerosis (ALS)**
  - Disease characterized by progressive degeneration of motor neurons

**NTP Conclusions**: *limited* evidence that blood Pb levels <10µg/dL are associated with ALS **in adults**

# Increased Risk for ALS - Evidence

**NTP Conclusions**: *limited* evidence that blood Pb levels <10µg/dL are associated with ALS **in adults** based on:

- Several case-control studies with blood Pb levels <10µg/dL
  - New England cohort (Kamel, 2002, 2003, 2005)
  - US veterans (Fang, 2010)
- **Supported by**
  - Effects of Pb in mouse model of severe ALS
- **Potential reverse causality**
  - Less activity may cause greater bone and Pb mobilization
  - Increased survival time in ALS patients with bone Pb (Kamel, 2008)
  - Fang, 2010 study results are against reverse causality
    - ALS association with blood Pb remains, after
    - Adjusting for biomarkers of Pb mobilization from bone

# Increased Risk for Essential Tremor - Evidence

**NTP Conclusions**: *limited* evidence that blood Pb levels <10µg/dL and <5µg/dL are associated with essential tremor **in adults** based on:

- Several case-control studies with blood Pb levels <5µg/dL
  - New York cohort (Louis, 2003; 2005, 2011)
  - Turkey cohort (Dogu, 2007)

- **Supported by**:
  - Animal data on Pb-related increase in tremor

# Alzheimer's and Parkinson's Disease - Evidence

**NTP Conclusions**: *inadequate* evidence that blood Pb levels <10µg/dL are associated with Alzheimer's or Parkinson's disease in adults based on:

- No studies with blood Pb levels <10µg/dL
- Few studies examining potential association with Pb

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# Reduced Sensory Organ Function

# Decreased Auditory Acuity

- **Auditory**
  - Higher hearing thresholds equate to hearing loss
  - Changes to auditory system
    - Increased latency of brainstem auditory evoked potential (BAEP)

**NTP Conclusions**: *sufficient* evidence that blood Pb <10µg/dL is associated with decreased auditory acuity in children,

*limited* evidence for prenatal Pb <10µg/dL,

*limited* evidence in **adults** at Pb <10µg/dL

# Decreased Auditory Acuity – Child and Prenatal Evidence

**NTP Conclusions**: *sufficient* evidence <10µg/dL in children based on:

- Several large cross-sectional studies blood Pb <10µg/dL
  - NHANES II (n=4,519) increased hearing threshold (Schwartz, 1987)
  - Hispanic Health and Nutrition Survey (n=3,545) (Schwartz, 1991)
    - Age range of 4-19 and subjects age 18 and 19 are considered adults
- Also increased latency of brainstem auditory evoked potentials (BAEP)
  - Study of Polish children (n=155) (Osman, 1999)

- **Supported by**
  - Similar effects in children/adults at blood Pb >10µg/dL (Otto and Fox, 1993; Robinson, 1985, Otto, 1985)
  - Animal data on Pb-related decrease in auditory acuity

- **Note**:
  - Few studies with maternal blood Pb <10µg/dL; therefore, *limited* evidence prenatal <10µg/dL

# Decreased Auditory Acuity – Adult Evidence

**NTP Conclusions**: *limited* evidence <10µg/dL **in adults** based on:

- Several studies in adults with blood Pb levels <10µg/dL
  - Cross-sectional (Hwang, 2009; Forst, 1997)
  - Case-control (Chuang, 2007)
- Increased hearing thresholds and BAEP

- **Supported by**
  - NHANES study of subjects age 4 to 19 (Schwartz, 1987, 1991)
    - Individuals age 18-19 considered adults for this assessment
  - Similar effects in adults at higher blood Pb levels
  - Association with bone Pb (Park, 2010-Normative Aging Study)
  - Animal data on Pb-related decrease in auditory acuity

# Visual Effects – Evidence

**NTP Conclusions**: *inadequate* evidence that blood Pb levels <10µg/dL are associated with effects on vision in children or **in adults** based on:

- Few Studies at Pb levels <10µg/dL
  - 2 studies in children (Boucher, 2009; Altmann, 1998)
  - No studies in adults at Pb levels <10µg/dL

## The NTP's Conclusions for Neurological Effects

There is *sufficient* evidence that blood Pb levels <10µg/dL are associated with adverse neurological effects in children and *limited* evidence in adults.

# Specific Neurological Charge Questions

i. Please comment on whether the scientific evidence presented supports the NTP's conclusions.

ii. Please comment on whether you agree/disagree with the NTP's conclusions. Explain why. Identify any references that should be cited.

a. **Cognitive function**: academic achievement, IQ, and other general and specific measures
b. **Behavior**: attention deficit hyperactivity disorder (ADHD), problem behaviors, and psychological effects
c. **Neurodegeneration**: amyotrophic lateral sclerosis (ALS), Alzheimer's disease, essential tremor, and Parkinson's disease
d. **Sensory organs**: auditory and visual

**Table 4.3: NTP conclusions on neurological effects of low-level Pb – part 1**

| Health Effect | Population or Exposure Window | Conclusion | Blood Pb Evidence | Bone Pb Evidence |
|---|---|---|---|---|
| **Cognitive Function:** Academic Achievement | Prenatal | *Inadequate* | No studies located | Not studied |
| | Children | *Sufficient* | Yes, <5µg/dL | Yes, tooth dentin Pb |
| **Cognitive Function:** IQ | Prenatal | *Limited* | Yes, <10µg/dL | Not studied |
| | Children | *Sufficient* | Yes, <10µg/dL | Yes, tibia and tooth dentin Pb |
| | | *Limited* | Yes, <5µg/dL (one study) | |
| **Cognitive Function:** Other general and specific measures | Prenatal | *Limited* | Yes, <5µg/dL | Not studied |
| | Children | *Sufficient* | Yes, <5µg/dL | Yes, tibia and tooth dentin Pb |
| | Older adults | *Limited* | Yes, <10µg/dL | Yes, tibia and patella Pb |
| **Behavior** -ADHD | Prenatal | *Limited* | Yes, <10µg/dL | Not studied |
| | Children | *Sufficient* | Yes, <5µg/dL | Yes, tibia and tooth dentin Pb |
| | Adults | *Inadequate* | No studies located | Not studied |
| **Behavior**-Problems | Prenatal | *Limited* | Yes, <10µg/dL | Not studied |
| | Children | *Sufficient* | Yes, <5µg/dL | Yes tooth dentin Pb, bone, hair |
| | Adults | *Inadequate* | No studies located | Not studied |

| Table 4.3: NTP conclusions on neurological effects of low-level Pb - part 2 | | | | |
|---|---|---|---|---|
| **Health Effect** | **Population or Exposure Window** | **Conclusion** | **Blood Pb Evidence** | **Bone Pb Evidence** |
| **Psychological effects:** Depression, Anxiety, other | Prenatal | *Inadequate* | No studies located | Not studied |
| | Children | *Inadequate* | Unclear, some data >10µg/dL | Not studied |
| | Adults | *Limited* | Yes, <10µg/dL | Tibia and patella Pb |
| **NeuroDegeneration**: ALS | Adults | *Limited* | Yes, <10µg/dL | Yes, tibia and patella |
| **ND**: Alzheimer's disease | Adults | *Inadequate* | No studies <10µg/dL located | Not studied |
| **ND**: Essential Tremor | Adults | *Limited* | Yes, <10µg/dL | Not studied |
| **ND**: Parkinson's disease | Adults | *Inadequate* | No studies <10µg/dL located | Yes, tibia, PBPK -cumulative |
| **Sensory Function**: Auditory | Prenatal | *Limited* | Yes, <10µg/dL | Not studied |
| | Children | *Sufficient* | Yes, <10µg/dL | Not studied |
| | Adults | *Limited* | Yes, <10µg/dL | Yes, tibia and patella |
| **Sensory Function:** Visual | Prenatal | *Inadequate* | No studies located | Not studied |
| | Children | *Inadequate* | Yes, <10µg/dL | Not studied |
| | Adults | *Inadequate* | No studies <10µg/dL located | Not studied |

## e. Other neurological effects

i. Please comment on whether there are additional neurological effects in humans that may be adversely affected by low-level Pb exposure that you would recommend adding to the document.

Please comment on whether and how the additional neurological effects would affect the overall conclusions for health effects associated with blood Pb levels <10µg/dL.

# A. General Questions

1) Is the text in the draft monograph articulated clearly and correctly? Are the summary sections useful? Are the tabular information and format easily understandable? If not, please identify the specific sections that need improvement and provide specific suggestions for improvement.

2) Is the information in the draft monograph's text and tables presented objectively?
If not, please identify the specific sections that need improvement and provide specific suggestions for improvement.

| Table 4.3: NTP conclusions on neurological effects of low-level Pb | | | | |
|---|---|---|---|---|
| **Health Effect** | **Population or Exposure Window** | **Conclusion** | **Blood Pb Evidence** | **Bone Pb Evidence** |
| **Cognitive Function:** | Prenatal | *Inadequate* | No studies located | Not studied |
| Academic Achievement | Children | *Sufficient* | Yes, <5µg/dL | Yes, tooth dentin Pb |
| **Cognitive Function:** | Prenatal | *Limited* | Yes, <10µg/dL | Not studied |
| IQ | Children | *Sufficient* | Yes, <10µg/dL | Yes, tibia and tooth Pb |
| | | *Limited* | Yes, <5µg/dL (one study) | |
| **Cognitive Function:** | Prenatal | *Limited* | Yes, <5µg/dL | Not studied |
| Other general and specific | Children | *Sufficient* | Yes, <5µg/dL | Yes, tibia and tooth Pb |
| measures | Older adults | *Limited* | Yes, <10µg/dL | Yes, tibia and patella Pb |
| **Behavior** -ADHD | Prenatal | *Limited* | Yes, <10µg/dL | Not studied |
| | Children | *Sufficient* | Yes, <5µg/dL | Yes, tibia and tooth Pb |
| | Adults | *Inadequate* | No studied located | Not studied |
| **Behavior**-Problems | Prenatal | *Limited* | Yes, <10µg/dL | Not studied |
| | Children | *Sufficient* | Yes, <5µg/dL | Yes tooth Pb, bone, hair |
| | Adults | *Inadequate* | No studies located | Not studied |
| **Psychological effects:** | Prenatal | *Inadequate* | No studies located | Not studied |
| Depression, Anxiety, other | Children | *Inadequate* | Unclear, some data >10µg/dL | Not studied |
| | Adults | *Limited* | Yes, <10µg/dL | Tibia and patella Pb |
| **NeuroDegeneration**: ALS | Adults | *Limited* | Yes, <10µg/dL | Yes, tibia and patella |
| **ND**: Alzheimer's disease | Adults | *Inadequate* | No studies <10µg/dL located | Not studied |
| **ND**: Essential Tremor | Adults | *Limited* | Yes, <10µg/dL | Not studied |
| **ND**: Parkinson's disease | Adults | *Inadequate* | No studies <10µg/dL located | Yes, tibia, PBPK -cumulative |
| **Sensory Function**: | Prenatal | *Limited* | Yes, <10µg/dL | Not studied |
| Auditory | Children | *Sufficient* | Yes, <10µg/dL | Not studied |
| | Adults | *Limited* | Yes, <10µg/dL | Yes, tibia and patella |
| **Sensory Function:** | Prenatal | *Inadequate* | No studies located | Not studied |
| Visual | Children | *Inadequate* | Yes, <10µg/dL | Not studied |
| | Adults | *Inadequate* | No studies <10µg/dL located | Not studied |