U.S. Environmental Protection Agency
Clean Air Scientific Advisory Committee (CASAC)
Lead Review Panel
Public Meeting

EPA Presentation of Revisions to Draft Lead Integrated Science Assessment

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February 5, 2013

Timeline for Lead ISA

1st External Review Draft	→	May 6, 2011
CASAC Meeting	→	July 20-21, 2011
2nd External Review Draft	→	February 2, 2012
CASAC Review	→	April 10-11, 2012
3rd External Review Draft	→	November 2012
CASAC Review of the draft ISA and draft Policy Assessment	→	February 5-6, 2013
Final	→	June 2013 target

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Chapters in Draft Lead ISA

Preamble

Legislative and Historical Background

1. Executive Summary
2. Integrative Summary
3. Ambient Lead: Source to Concentration
4. Exposure, Toxicokinetics, and Biomarkers
5. Integrated Health Effects of Lead Exposure
6. Potentially At-Risk Populations
7. Ecological Effects of Lead

EPA United States Environmental Protection Agency

Major Revisions

Chapters 1 and 2

- Executive and Integrative Summaries -

- Conclusions drawn for specific health endpoints
- Enhanced critical review of the studies and transparency in the application of the framework for causal determination
- Revised executive summary to be more accessible to a non-technical audience
- Added more cross-referencing

Chapter 3
- Ambient Lead: Source to Concentration-

Additional cross-referencing to link Chapters 3 & 4.

Section 3.2: Sources

- Figure 3-5: shows point source facilities and airports estimated to emit 0.5 tons or more per year.
- Figure 3-6: Five year totals (tons) for mining, production, imports and exports

Section 3.4: Monitoring

- Expanded table and discussion of PM samplers available for Pb sampling.

Chapter 3
- Ambient Air Pb Concentrations-

Section 3.5

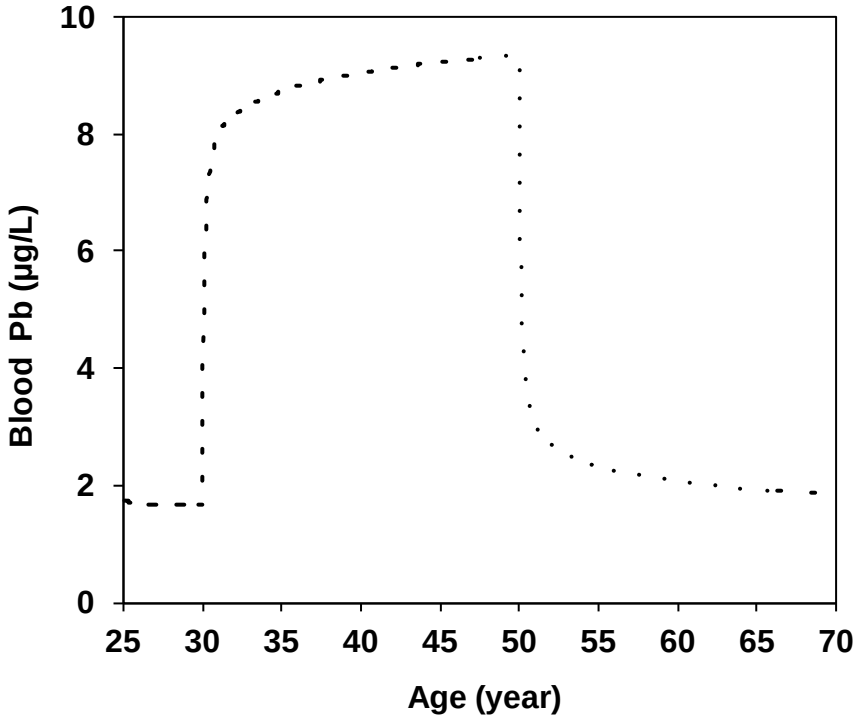
- Moved much of detailed data to the Appendix.
- Included tables comparing co-located Pb measurements for different sampling size cuts (Table 3-8 and Appendix Tables 3-26 to 3-28).
- Pearson and Spearman (appendix) correlation coefficients included in Section 3.5.4: Pb in a Multipollutant Context
- Streamlined background section to focus on natural background.

Chapter 4
- Exposure, Toxicokinetics, Biomarkers-

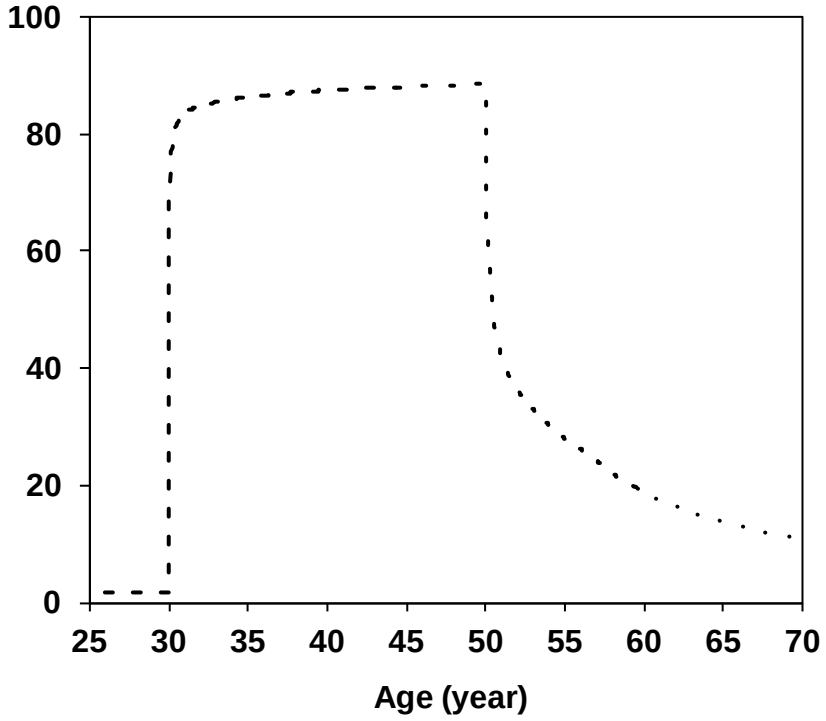
- Clarified differences between size distributions of ambient air Pb and soil/dust Pb
- Expanded discussion of the air related exposure contribution to total Pb exposure
- Integrated and linked discussion with Chapter 3
- Expanded discussion of the relationship between Pb exposure and biomarkers
- Expanded discussion of the blood Pb – air Pb relationship and uncertainty in air-to-blood slopes

Chapter 4
- temporal profile of blood Pb -

Relatively Low Exposure

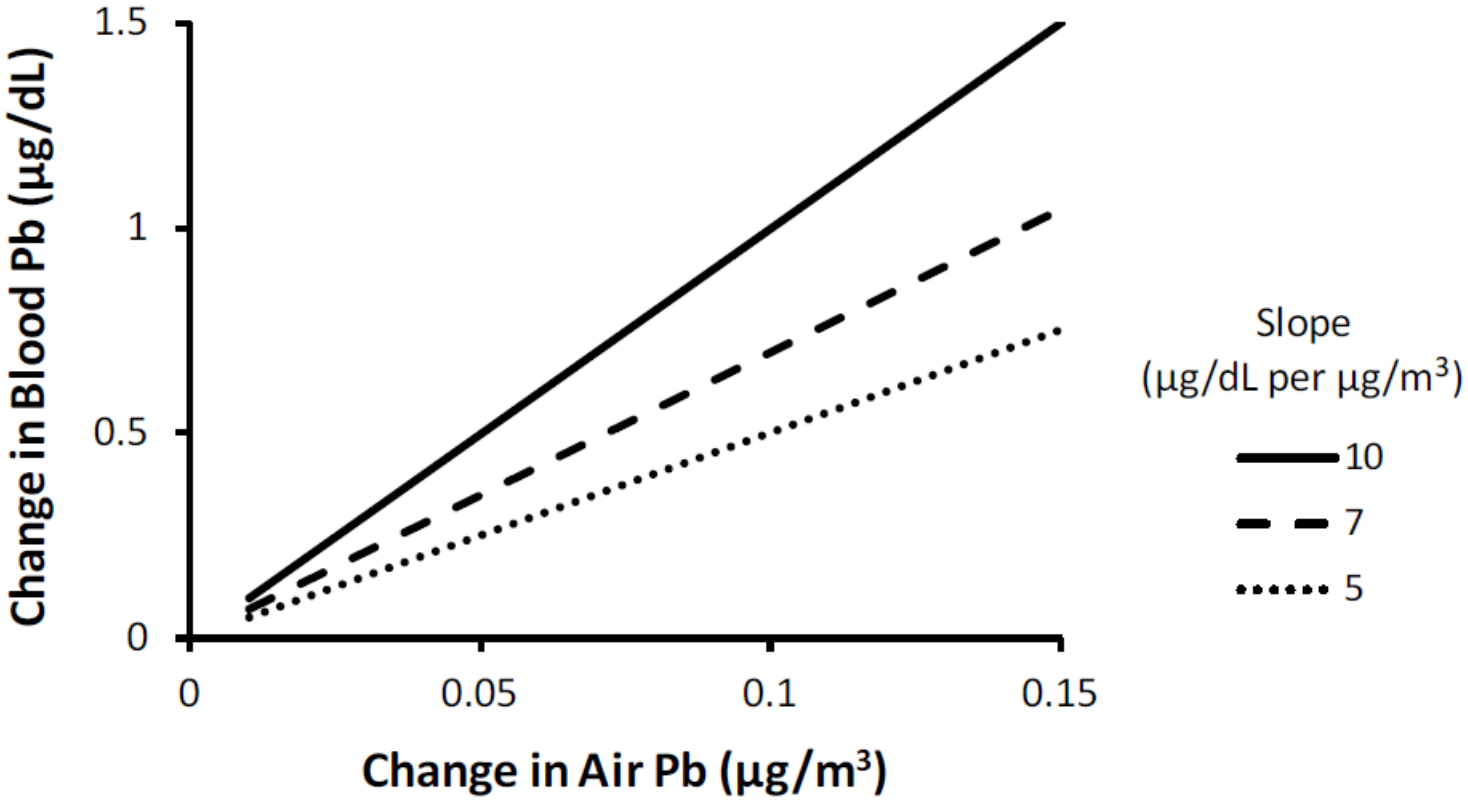


Relatively High Exposure



Blood Pb concentration from Fig. 4-11 and New Fig. 4-12

Chapter 4
– air-to-blood slopes –



NEW Figure 4-25

Chapter 5 – Critical Assessment

Epidemiology: study design and methods, potential confounding, reverse causation

- Details added to tables and text
- Strengthened critique of study design and outcome ascertainment for ADHD
- Added discussion of potential confounding by nutritional status for hematological and developmental effects
- Enhanced discussion of potential reverse causation for renal and immune effects

Toxicology: oral exposure route and concentrations within one order of magnitude of human blood Pb levels

These factors evaluated more explicitly in causal determinations

Chapter 5
- Integration and Synthesis-

Incorporated advice from experts in neuropsychology and neurotoxicology

- Categorizing nervous system outcomes
- Drawing parallels in behavioral constructs in humans and animals, e.g., response inhibition

Epidemiologic and toxicological evidence integrated more closely by outcome group

- Executive Function (Section 5.3.2.4, pg 5-101)
- Inattention and Impulsivity (Section 5.3.3.1, pg 5-140)

Causal Determinations
- specific health endpoint groupings -

2nd External Release Draft		3rd External Release Draft	
Organ System	**Causal Determination**	**Endpoint Group**	**Causal Determination**
Nervous	Causal		
		Cognitive Function Decrements / Children	Causal
"Based most heavily on **cognitive function** decrements and **inattention** in **children …**"		Cognitive Function Decrements / Adults	Likely Causal
		Attention-Related Behavioral Problems / Children	Causal
		Misconduct / Children and Young Adults	Likely Causal
		Internalizing Behaviors / Children	Likely Causal
		Psychopathological Effects / Adults	Likely Causal
		Sensory Function Decrements / Children	Likely Causal
		Sensory Function Decrements / Adults	Suggestive
		Neurodegenerative Diseases	Inadequate
		Motor Function Decrements / Children	Likely Causal
Cardiovascular	Causal		
"..long-term Pb exposure is associated with cardiovascular effects in adults with the largest body of evidence demonstrating associations of Pb with increased **blood pressure and hypertension**"		Hypertension	Causal
		Subclinical Atherosclerosis	Suggestive
		Coronary Heart Disease	**Causal**
		Cerebrovascular Disease	Inadequate

Red = Change from the 2nd to the 3rd draft

Causal Determinations

2nd External Release Draft		3rd External Release Draft	
Organ System	**Causal Determination**	**Endpoint**	**Causal Determination**
Renal "evidence consistently demonstrates a relationship between higher blood Pb level **and kidney dysfunction** …"	Causal	Decreased Kidney Function	**Likely Causal**
Immune "continuum of related immune parameters that demonstrate a **stimulation of Th2 responses** in **toxicological studies** combined with the **supporting epidemiologic evidence in children**"	Causal	**Atopic and Inflammatory Conditions** **Decreases in Host Resistance** **Autoimmunity**	**Likely Causal** Likely Causal Inadequate
Heme Synthesis and RBC Function "The consistency in findings in epidemiologic studies of **occupationally-exposed adults** and **children** …"	Causal	Decreased RBC Survival Altered Heme Synthesis	Causal Causal
Reproductive and Developmental "with a focus on the strong relationship observed with detrimental effects on **sperm** and **delayed puberty onset** …"	Causal	Development Birth Outcomes Male Reproductive Function Female Reproductive Function	Causal Suggestive Causal Suggestive
Cancer "The **animal toxicological literature** continues to provide the strongest evidence …"	Likely Causal	Cancer	Likely Causal

Chapter 5 – Transparency

(Table 5-17)

Attribute in Causal Framework	Key Supporting Evidence	References	Pb Biomarker Levels Associated with Effects
Attention-related Behavioral Problems in Children (e.g., inattention, impulsivity, hyperactivity, ADHD) – **Causal**			
Consistent associations from multiple high quality epidemiologic studies with relevant blood Pb levels	Evidence from prospective studies for inattention, impulsivity, and hyperactivity in association with prenatal (maternal or cord), earlier childhood, and lifetime avg blood Pb and tooth Pb levels in children ages 7-17 yr and young adults 19-24 yr in U.S., U.K., Australia, New Zealand.	Ris et al. (2004), Fergusson et al. (1993), Bellinger et al. (1994a), Chandramouli et al. (2009), Leviton et al. (1993)	Blood Pb: means 6.8 µg/dL (prenatal cord), 14 µg/dL (lifetime avg to age 11-13 yr), Group with age 30 mo >10 µg/dL Tooth Pb (age 5-8 yr) means: 3.3, 6.2, 14 µg/g
	Most studies adjusted for SES, maternal education, and parental caregiving quality. Some also considered parental IQ, smoking, birth outcomes. A few considered substance abuse, nutritional factors.	Burns et al. (1999) with the most extensive consideration for potential confounding Sections 5.3.3.1, 5.3.3.2, 5.3.3.3	
	Studies had population-based recruitment with moderate to high follow-up participation not conditional on blood or tooth Pb level.		
	Associations found with neuropsychological tests (CPT) and teacher and parent ratings using widely-used, structured questionnaires.		
	Associations with inattention ratings inconsistent in prospective studies examining children with lower blood Pb levels, but children were younger, <5 yr	Wasserman et al. (2001), Canfield et al. (2003b) Section 5.3.3.1	Concurrent blood Pb means 6.5 µg/dL
	Supporting evidence from cross-sectional studies for associations of concurrent blood Pb level with inattention, impulsivity, and hyperactivity, and total ADHD rating in children ages 8-15 yr.	Cho et al. (2010), Nicolescu et al. (2010), Froehlich et al. (2009), Silva et al. (1988) Sections 5.3.3.1, 5.3.3.2, 5.3.3.3	Concurrent Blood Pb means 1.9-11.1 µg/dL
	Cross-sectional studies had less extensive consideration for potential confounding, particularly parental caregiving quality.		
Epidemiologic evidence supported by toxicological results with relevant exposures	Impulsivity indicated by premature responses, increased perseveration, decreased pause time between events on tests of response inhibition in rodents and monkeys with relevant dietary postnatal Pb exposures.	Stangle et al. (2007), Brockel and Cory-Slechta (1998), Rice (1985), Brockel et al. (1999b) Section 5.3.3.1	Blood Pb: 15, 25 µg/dL in monkeys after infancy only exposure, 11, 29 µg/dL in rats after 40-day postweaning exposure, 10, 26 µg/dL after 3, 7 mo postweaning exposure
Evidence clearly describes mode of action	See above for cognitive function in children		

Chapter 6
- At Risk Populations -

	Health Effects
Adequate evidence	There is substantial, consistent evidence within a discipline to conclude that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable this includes coherence across disciplines. Evidence includes multiple high-quality studies.
Suggestive evidence	The collective evidence suggests that a factor results in a population or lifestage being at increased risk of an air pollutant-related health effect relative to some reference population or lifestage, but the evidence is limited due to some inconsistency within a discipline or, where applicable, a lack of coherence across disciplines.
Inadequate evidence	The collective evidence is inadequate to determine if a factor results in a population or lifestage being at increased risk of an air pollutant-related health effect relative to some reference population or lifestage. The available studies are of insufficient quantity, quality, consistency and/or statistical power to permit a conclusion to be drawn.
Evidence of no effect	There is substantial, consistent evidence within a discipline to conclude that a factor does not result in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable this includes coherence across disciplines. Evidence includes multiple high-quality studies.

Chapter 6 - Conclusions

Factor Evaluated	Classification
Childhood (Section 6.2.1, 6.3.1)	Adequate
Older Adulthood (Section 6.2.1, 6.3.1)	Suggestive
Sex (Section 6.2.2, 6.3.2)	Suggestive
Genetics (Section 6.3.3)	Suggestive
Pre-existing Disease[a] (Section 6.3.4)	Suggestive
Smoking Status (Section 6.3.5)	Inadequate
Socioeconomic Status (SES) (Section 6.2.4, 6.3.6)	Suggestive
Race/Ethnicity (Section 6.2.3, 6.3.7)	Adequate
Proximity to Pb Sources (Section 6.2.5)	Adequate
Residential Factors (Section 6.2.6)	Adequate
Body Mass Index (BMI) (Section 6.3.8)	Inadequate
Alcohol Consumption (Section 6.3.9)	Inadequate
Nutrition (Section 6.3.10)	Adequate
Stress (Section 6.3.11)	Suggestive
Maternal Self-Esteem (Section 6.3.12)	Inadequate
Cognitive Reserve[a] (Section 6.3.13)	Inadequate
Other Metals (Section 6.3.14)	Suggestive

[a]Possible mediator

Chapter 7
- Ecological Effects -

- Focus on survival, growth and reproduction, sub-organismal responses are secondary
- Added table summaries (including media-based exposure concentrations and key abiotic modifying factors)
- Increased synthesis and technical evaluation of evidence for ecological effects of Pb
- Additional clarifying language in regards to causal determinations
- Units standardized throughout (µg/L, mg/kg)

Chapter 7 - Causal Determinations

Level		Effect	Terrestrial	Freshwater	Saltwater
Community and Ecosystem Level Effects			Likely Causal	Likely Causal	Inadequate
Population–Level Endpoints	**Organism–Level Responses**	Reproductive and Developmental Effects-Plants	Inadequate	Inadequate	Inadequate
		Reproductive and Developmental Effects-Invertebrates	Causal	Causal	Suggestive
		Reproductive and Developmental Effects-Vertebrates	Causal	Causal	Inadequate
		Growth-Plants	Causal	**Likely Causal**	Inadequate
		Growth-Invertebrates	**Likely Causal**	Causal	Inadequate
		Growth-Vertebrates	Inadequate	Inadequate	Inadequate
		Survival-Plants	Inadequate	Inadequate	Inadequate
		Survival- Invertebrates	Causal	Causal	Inadequate
		Survival- Vertebrates	**Likely Causal**	Causal	Inadequate
		Neurobehavioral Effects-Invertebrates	Likely Causal	Likely Causal	Inadequate
		Neurobehavioral Effects- Vertebrates	Likely Causal	Likely Causal	Inadequate
	Sub-organismal Responses	Hematological Effects-Invertebrates	Inadequate	**Likely Causal**	Suggestive
		Hematological Effects-Vertebrates	Causal	Causal	Inadequate
		Physiological Stress-Plants	Causal	**Likely Causal**	Inadequate
		Physiological Stress-Invertebrates	**Likely Causal**	**Likely Causal**	Suggestive
		Physiological Stress-Vertebrates	**Likely Causal**	**Likely Causal**	Inadequate

General Charge to CASAC

Please comment on the adequacy of these and other changes to the chapters and recommend any revisions to improve the discussion of key information. Please recommend any revisions that may further improve the clarity of discussion.