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

Presentation of Revisions to the Draft

Integrated Science Assessment for Lead

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Timeline for Lead ISA

1st External Review Draft	→	May 6, 2011
CASAC Meeting	→	July 20-21, 2011
CASAC Letter	→	December 9, 2011
2nd External Review Draft	→	February 2, 2012
CASAC Review	→	April 10-11, 2012
Final ISA	→	August 2012 target
Proposed Rulemaking	→	January 2014 target
Final Rulemaking	→	November 2014 target

Chapters of the 2nd ERD Lead ISA

Preamble

Preface

Chapter 1: **Executive Summary**

Chapter 2: Integrative Health and Ecological Effects Overview

Chapter 3: Ambient Lead: Source to Concentration

Chapter 4: Exposure, Toxicokinetics, and Biomarkers

Chapter 5: Integrated Health Effects of Lead Exposure

Chapter 6: Potentially At-Risk Populations

Chapter 7: Ecological Effects of Lead

Charge: Chapters 1 and 2

Please review and comment on the effectiveness of these revisions. Please comment on the extent to which Chapters 1 and 2 comprise a useful and effective approach for presenting this summary information and conclusions. Please recommend any revisions that may improve the scientific accuracy or presentation of these summary sections and the conclusions therein.

Chapter 3 – Source to Concentration

- Incorporated findings from 2006 AQCD throughout
- Updated National Emissions Inventory (NEI) Data
- Pb in non-air media
- Enhanced comparison and contrast of alternative Pb-PM FRM collection methods
- Expanded discussion of interpretation of measured concentrations
- New Sections:
  - **Other (non-FRM) Analysis Methods for Total Lead**
  - **Background Lead Concentrations (Trans-oceanic Transport)**
  - **Concentrations from Non-source Oriented Monitors**

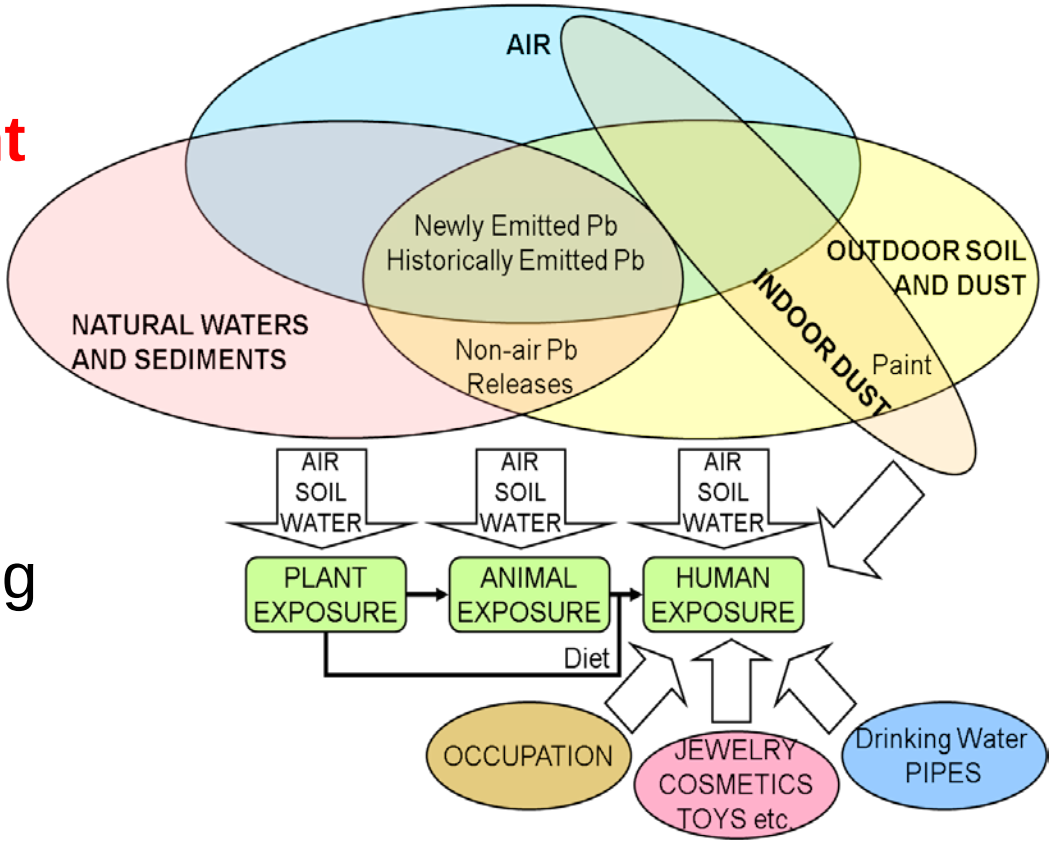
Charge: Chapter 3

Please comment on the adequacy of these and other changes to the chapter and recommend any revisions to improve the discussion of key information. Is material clearly, succinctly, and accurately provided? Where appropriate, please provide guidance that may refine the scientific interpretation and/or improve the representation of the science.

Chapter 4 – Exposure

Environmental Exposure Assessment Methodologies:

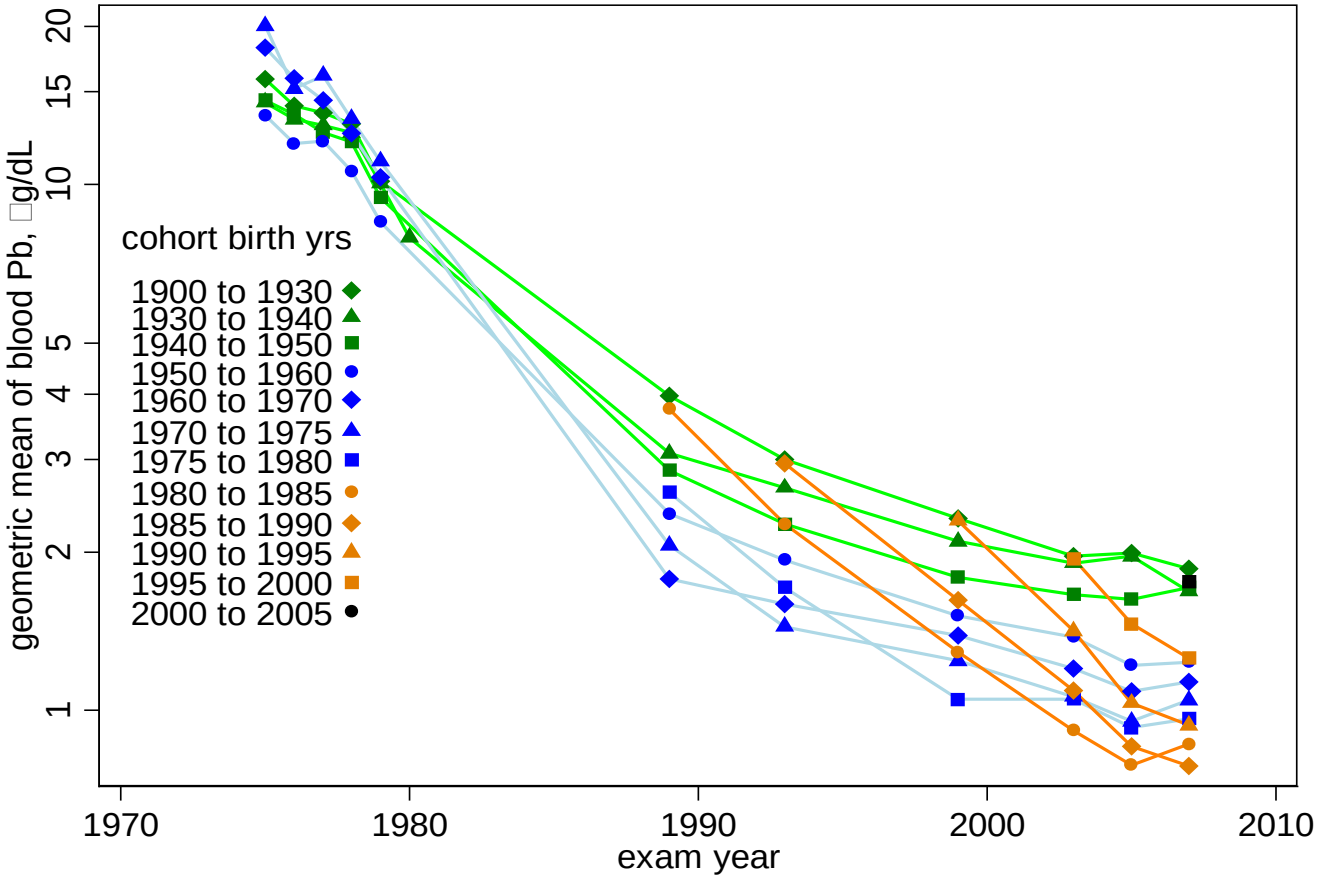
- TSP-Pb
- Dust sampling
- IEUBK
- Dispersion modeling
- Exposure models



Chapter 4 -Toxicokinetics and Biomarkers

- Greater distinction and more consistency in the usage of the terms absorption, bioavailability, and bioaccessibility
- Air-Pb to blood-Pb slopes were reevaluated across the range of air Pb concentrations available in a given study with an emphasis on the central tendency of air Pb concentrations in each study.
- Section on bone Pb measurement was expanded.
- Expanded discussion on the effects of both past and current Pb exposure on blood Pb levels.

Decline in blood Pb in different NHANES birth cohorts



Source: Adapted from data from the NHANES (NCHS, 2010)

Charge: Chapter 4

With consideration of these revisions, please comment on the accuracy of the interpretation of the science. Are uncertainties and limitations of relevant data, methodologies and approaches adequately discussed? Where appropriate, please provide specific recommendations to refine the scientific interpretation and/or improve the representation of the science.

Chapter 5 - Causal Determinations for the Health Effects of Lead

Outcome	Causality Determination
Nervous System Effects (Section 5.3.13)	Causal Relationship
Cardiovascular Effects (Section 5.4.7)	Causal Relationship
Renal Effects	Causal Relationship
Immune System Effects (Section 5.6.8)	Causal Relationship
Effects on Heme Synthesis and Red Blood Cell Function (Section 5.7.7)	Causal Relationship
Reproductive and Developmental Effects (5.8.10)	Causal Relationship
Cancer (5.10.5)	Likely Causal Relationship

Based upon the framework described in the Preamble , a determination of causality was made for a broad outcome category (i.e., nervous system effects) by evaluating the coherence of evidence across disciplines and across a spectrum of related endpoints. However, the evidence on which the causal judgment is based, including the strength of evidence for the individual endpoints within the major outcome category, is characterized within the discussion. Causal determinations were made within approximately 1-2 orders of magnitude of current levels.

Chapter 5 – Health Effects

- Causal Determination Summaries
  - Presentation of the evidence was modified to better reflect the weight of the evidence assessment approach and enhance the transparency of application of the framework for causal determination.

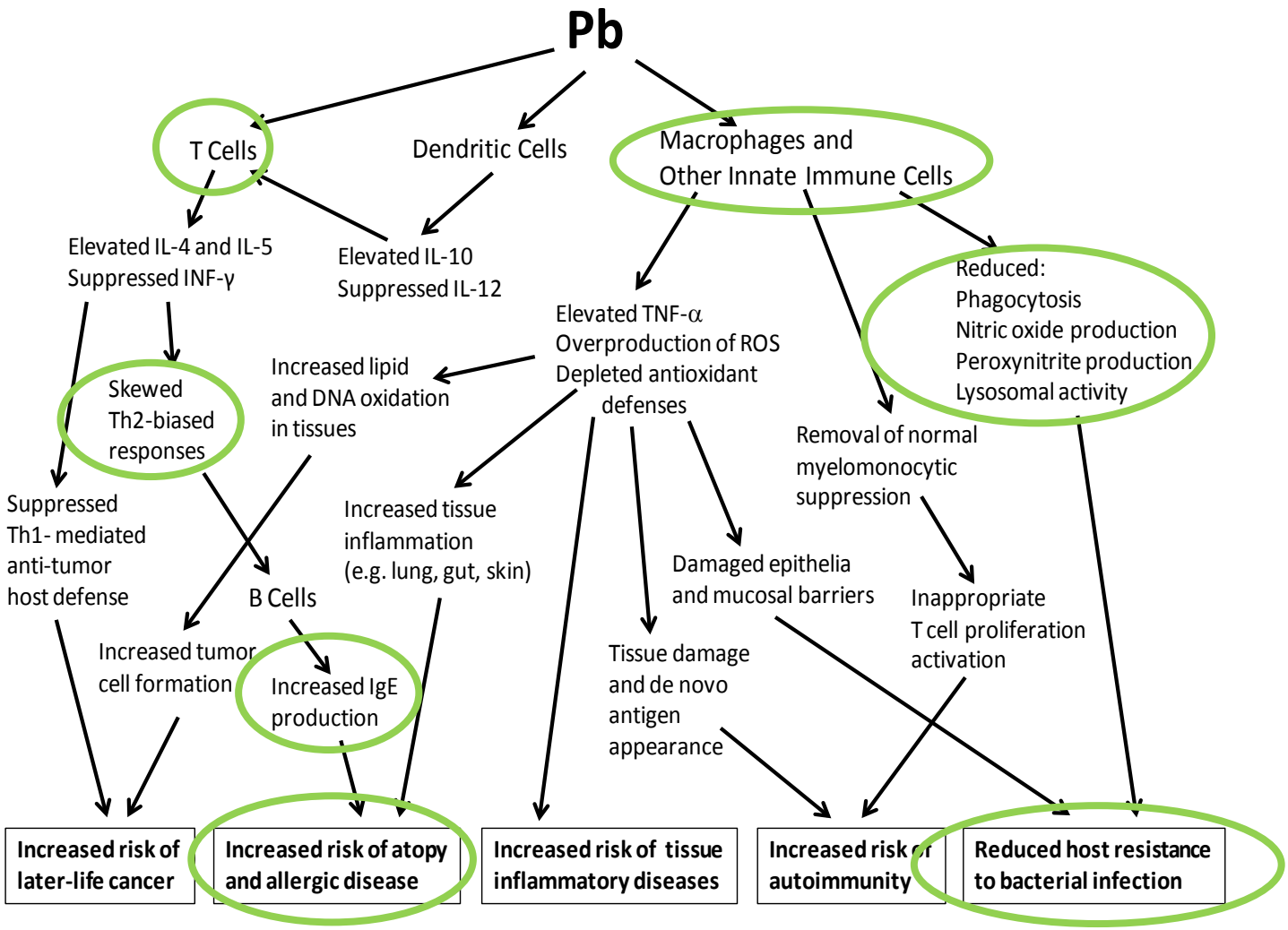
Nervous System Effects

"Based most heavily on **cognitive function decrements** and **inattention** in **children**, the collective body of evidence integrated across epidemiologic and toxicological studies is sufficient to conclude that there is a causal relationship between Pb exposures and nervous system effects."

Immune Effects

"The consistency and coherence of findings across the continuum of related immune parameters that demonstrate a **stimulation of Th2 responses** in toxicological studies combined with the supporting epidemiologic evidence in **children** are sufficient to conclude that there is a causal relationship between Pb exposures and immune system effects."

Immune Effects



Immunological pathways by which Pb exposure may increase risk of immune-related diseases.

Cardiovascular Effects

"Recent epidemiologic and toxicological studies substantiated the evidence that **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**…However, there is **uncertainty regarding the level, timing, frequency and duration** of exposure contributing to the observed associations since the populations studied were **likely to have higher past than recent exposure**...Collectively, the evidence integrated across epidemiologic and toxicological endpoints examined is sufficient to conclude that there is a causal relationship between Pb exposures and cardiovascular effects."

Charge: Chapters 1, 2 and 5

… please comment on the extent to which the discussion of the health effects evidence in Chapters 1 and 2 reflects the revisions to Chapter 5, which were designed to characterize the weight of the evidence for specific endpoints as well as the strengths and limitations of the studies.

Chapter 5 – Integration of the Health Evidence

- New Sections:
  - **Public Health Significance**
  - **Pb Exposure and Effects in Children** (Chpt 2 – draws from Chapter 5 section on lifestage)
  - **Confounding in Epidemiologic Studies of Nervous System Effects**
- Enhanced discussion of strengths and limitations of epidemiologic studies
- More explicitly acknowledge uncertainties about the level, timing, frequency, and duration of Pb exposure in studies of adults and older children.
  - Higher past exposures may contribute to the associations observed with blood Pb or bone Pb in these populations.

Chapter 5 – Integration of the Health Evidence

- Focused evaluation of the toxicological evidence on findings most relevant to effects in humans, e.g., lower Pb exposures, dietary routes of exposure, exposure durations relevant to the time course of effects in humans.
  - Studies conducted at higher levels included if they inform MOA (indicated in the text)
- Enhanced discussion of coherence between toxicological and epidemiologic studies focusing on homologous endpoints

Charge: Chapter 5

Please comment on the extent to which the revised discussion of the evidence and the causal determinations accurately reflect the weight of evidence for endpoints within a major outcome category and the strengths and limitations of studies (e.g., study design, control for potential confounding, statistical analysis) that comprise the evidence base.

Continued …

Please comment on the adequacy with which evidence has been integrated between toxicological and epidemiologic studies, in particular: the increased emphasis on toxicological findings most relevant to Pb-associated effects in humans; the discussion of results from homologous or parallel tests (e.g., response inhibition, blood pressure, renal function); and discussion of evidence describing modes of action for Pb-associated health effects. Has the coherence of findings among related endpoints been sufficiently described? Please comment on the effectiveness of the integration of scientific evidence both within sections for specific endpoints and summary sections.

Continued …

Please comment on the extent to which conclusions regarding the blood and bone Pb levels with which various health effects are associated in epidemiologic studies accurately reflect the weight of evidence given the study designs and statistical methods employed and populations examined (e.g., school-aged children, adolescents, adults without occupational exposure, adults with occupational exposure). Are inferences regarding the specific Pb exposure scenarios (e.g., level, timing, frequency, and duration) that contributed to the observed associations consistent with the evidence?

Chapter 6 - New Term: At-risk

Physiological Factors that Influence the Internal Distribution of Lead	Population Characteristics Potentially Related to Differential Lead Exposure	Factors Potentially Related to Increased Risk of Lead Induced Health Effects
Age	Age	Age
	Sex	Sex
Genetics		Genetics
		Pre-existing Disease
	Race and Ethnicity	Race and Ethnicity
	Socioeconomic Status	Socioeconomic Status
	Proximity to Pb Sources	
	Residential Factors	
		Lifestyle Factors
		Smoking
		Body Mass Index
		Alcohol Consumption
Nutrition		Nutrition
		Stress
		Cognitive Reserve
Co-exposures		Co-exposures

Childhood is a well-established at-risk lifestage

Evidence was limited for all other factors potentially related to increased risk of lead induced health effects

Charge: Chapter 6

Please comment on the adequacy of these revisions to clarify the consideration of potential at-risk populations, and recommend any revisions to improve the characterization of key findings and scientific conclusions.

In addition, please comment on whether the designation of some factors as having limited evidence adequately reflects the knowledge base considered and strength of evidence available.

Chapter 7 - Ecological Effects Sections

- New figures and text to support concepts of bioavailability; bioaccumulation factor(BAF) and bioconcentration factor (BCF) tables have been removed
- Aquatic section reorganized to separate Pb effects into freshwater and saltwater systems
- Additional information on concentrations at which effects occur in terrestrial and aquatic biota is provided
- There are now separate causal determinations for terrestrial and aquatic systems for each of the following endpoints:
  - physiological stress, hematological effects, neurobehavioral effects, developmental and reproductive effects, growth, survival and community and ecosystem level effects

Causal Determinations for Ecological Effects

Effect	Terrestrial	Aquatic[a]
Physiological Stress-All organisms	Causal	Causal
Hematological Effects-Invertebrates	**Inadequate**	Causal
Hematological Effects-Vertebrates	Causal	Causal
Neurobehavioral Effects-Invertebrates and Vertebrates	**Likely Causal**	**Likely Causal**
Developmental and Reproductive Effects-Plants	Inadequate	Inadequate
Developmental and Reproductive Effects-Invertebrates and Vertebrates	Causal	Causal
Growth-Plants	Causal	Causal
Growth-Invertebrates	**Inadequate**	Causal
Growth-Vertebrates	**Inadequate**	**Inadequate**
Survival-Plants	Inadequate	Inadequate
Survival- Invertebrates and Vertebrates	Causal	Causal
Community and Ecosystem Level Effects	**Likely Causal**	**Likely Causal**

[a] Causal determinations for aquatic biota are based primarily on evidence from freshwater organisms.

Charge: Chapter 7

Please comment on the adequacy of these various revisions and other changes to the chapter and recommend any revisions to improve the discussion of key information.

Agenda
CASAC Lead Review Panel
Public Meeting

10:30 am	Public Comments
11:00 am	Discussion of EPA Charge Questions
11:15 am	Chapter 3 – Source to Concentration
11:45 am	Lunch
1:30 pm	Chapter 4 – Exposure, Toxicokinetics and Biomarkers
2:00 pm	Chapter 5 – Integrated Health Effects of Lead
3:00 pm	Chapter 6 – Potentially At-Risk Populations
3:30 pm	Break
3:45 pm	Chapter 7 – Ecological Effects of Lead
4:45 pm	Preface, Preamble, Executive Summary (Chapter 1) and Integrative Summary (Chapter 2)
5:50 pm	Recess for the day