UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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THE ADMINISTRATOR

Jonathan M. Samet, M.D.
Chairman
Clean Air Scientific Advisory Committee
Science Advisory Board
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Dear Dr. Samet:

Thank you for your December 9, 2011, letter providing the Clean Air Scientific Advisory Committee Lead Review Panel's comments on the U.S. Environmental Protection Agency's *First External Review Draft Integrated Science Assessment for Lead,* May 2011. We at the EPA greatly appreciate the panel's thorough review and constructive comments.

My staff carefully considered your comments and recommendations as well as the comments we received from the public. The EPA's revisions address both consensus and individual CASAC comments and also incorporate findings of additional studies published through September 2011. Attached is an overview of the major revisions in the *Second External Review Draft of the Integrated Science Assessment for Lead.* Some of the key changes made in response to the CASAC's comments are highlighted below.

The lead panel offered a number of recommendations to enhance the organization and presentation of the evidence in the ISA. Your committee provided similar recommendations regarding the *First External Review Draft of the Integrated Science Assessment for Ozone.* In response to these comments, we added a preamble, a preface and an executive summary. The restructuring was intended to bring the integrative overview discussion forward in the document and make it more accessible to the reader. The preamble is applicable to all ISAs and includes the more general sections on ISA development and the causality framework from chapter 2. The preface includes sections on legislative background, the history of previous reviews and the status of the current review. Chapter 2, the integrative summary, is now the first substantive chapter of the ISA.

The CASAC generally supported the EPA's conclusions on the health effects in the first draft of the lead ISA, and the major conclusions have not changed. However, the EPA modified the presentation of the evidence to reflect our rigorous "weight of the evidence" assessment approach and allow more transparency in the application of the framework for causal determination. Specifically, in chapters 2 and 5, we characterize the weight of evidence for each endpoint within a broad outcome category and specify the particular endpoints that contribute most heavily to the causal determination. We also more directly acknowledge uncertainties relating to the frequency, timing, duration and level of lead exposure

contributing to the associations of blood lead with health effects observed in older children and adults who are likely to have had higher past than recent lead exposure. New sections that discuss the public-health significance of findings were also added to the document in chapters 2 and 5. In chapters 2 and 5 we also strengthened our integration of epidemiologic and toxicological studies based on homologous endpoints, and we sharpened and focused our evaluation of the toxicological evidence to emphasize findings that were most relevant to human health, e.g., effects at low lead concentrations and dietary routes of exposure.

Chapter 3 integrates current findings with the science presented in the 2006 Air Quality Criteria Document to describe the state of the science on lead. Discussions were added or enhanced on monitoring technology, natural background lead concentrations, particle size distribution and on non-air sources of lead exposure. In chapter 4 we revised and expanded sections relating to biokinetic and exposure models, and we enhanced the discussion of the critical evaluation of studies of the relationship between air lead and blood lead.

In chapter 6 the CASAC panel's advice on the use of a broad definition of "susceptibility" has been carefully considered. As in the second draft ISA for ozone, we have used the term "at-risk" rather than susceptibility where an overarching term is appropriate and made several refinements to the discussion at the beginning of the chapter on Potentially At-Risk Populations.

In chapter 7 we revised the conclusions for ecological effects to consider effects in terrestrial and aquatic systems separately. Causal determinations are now accompanied by additional data on lead levels at which effects are observed. The determination of causality for bioaccumulation as it affects ecosystem services has been removed from the second draft.

We recognize that our efforts to protect the environment can be only as good as the science on which they are based. Independent critical reviews such as yours help to ensure that we use the best science to protect public health and our nation's environment. Please accept my appreciation for your hard work and thoughtful review.

Sincerely,

Lisa P. Jackson

Attachment

ATTACHMENT

Overview of Revisions in the Second Draft Lead ISA in Response to CASAC Peer Review Comments dated December 9, 2011

General

Throughout the document, the editorial suggestions provided by individual CASAC members were reviewed and considered in developing the second external review draft. In addition, we expanded summaries of findings from previous Air Quality Criteria Documents (AQCDs) to provide information on the context and contribution of more recent data on Pb toxicity to the body of evidence as a whole. Section callouts were refined to improve consistency across chapters and facilitate cross-referencing within the document.

Chapter 1 – Executive Summary

We prepared an executive summary, which now appears as chapter 1. Chapter 1 materials have been revised and moved, specifically:

- the more general sections on the development of the ISA and the causality framework are placed in a preamble that can support all ISAs;
- the introductory sections specific to this ISA are placed at the beginning of chapter 2; and
- sections on legislative background and history of previous reviews is in a preface in the front matter of the ISA.

Chapter 2 - Integrative Health and Ecological Effects Overview

We made revisions to eliminate redundancy and to make the text more concise, and we improved cross-referencing within the document. We revised the narrative discussion with the intent of clearly communicating the most important information from the ISA to nonsubject matter experts.

Modifications to the presentation of the evidence made in chapters 5 and 7, which were intended to reflect our rigorous weight of the evidence assessment approach and transparent application of the framework for causal determination, are reflected in chapter 2.

Tables summarizing low-level effects of Pb were removed (Table 2-2 and 2-3) and new sections that discuss the evidence supporting the public-health significance of findings were added to the document. We enhanced our discussion of adult contemporaneous blood Pb as a biomarker of Pb exposure to explicitly acknowledge uncertainties relating to the exposure frequency, duration, level and timing contributing to observed associations with blood Pb levels in chapters 4 and 5, and these enhanced discussions are reflected in chapter 2.

Chapter 3 – Ambient Lead: Source to Concentration

Throughout the chapter, we increased description of the state of the science as of the 2006 AQCD and its integration with current findings. Quantitative concentration data was added to the discussion of studies of sources and Pb-PM size distributions. Specific revisions include the following:

- Added description of changes to the National Emissions Inventory (NEI) to explain discrepancies between NEI results in the 2006 AQCD and the current ISA. (3.2.1)
- Added breakdown of piston-engine aircraft emissions by take-off/landing and in-flight cycles. (3.2.1)
- Added description of air Pb emissions from wood burning. (3.2.2.5)
- Expanded discussion of resuspension processes. (3.3.1.3)
- Expanded description of Federal Reference Methods for measuring air Pb and factors that affect collection efficiency and measurement error. (3.4.1)
- Added description of non-FRM air Pb sampling methods. (3.4.1)
- Revised discussion of air Pb monitoring networks and included information about recent changes to the networks. (3.4.2)
- Added data for non-source oriented Pb concentrations. (3.5.1.1, 3.5.2.1, 3.5.2.2)
- Removed EPA data comparing Pb concentrations measured by TSP, PM_{10}, and $PM_{2.5}$ monitors; focused discussion of size distributions around studies in the peer-reviewed literature; and added subsection headers to differentiate relevant sources and/or sampling environments (e.g. rural vs. urban). (3.5.3)
- Added a section on background air Pb levels. (3.5.5)
- Added data on rural and brownfield soil Pb concentrations. (3.6.1)
- Added data from the WACAP study on Pb concentrations in soil, sediment, water, snowpack, and biota. (throughout 3.6)

Chapter 4 – Exposure, Toxicokinetics, and Biomarkers

A new section on environmental exposure assessment methodologies and additional information on bone Pb measurements were added. We expanded discussion to allow greater distinction and more consistency in the usage of the terms absorption, bioavailability, and bioaccessibility throughout the chapter. Clarifying text was added at the beginning of the Pb biomarkers section to provide greater explanation on blood Pb measurements as an exposure biomarker and the utility of using the ICRP Pb model for assessing exposure-body burden relationships.

Chapter 5 – Integrated Health Effects of Lead Exposure

The discussion of the epidemiologic evidence was expanded to describe more explicitly the strengths and limitations of studies with respect to factors such as study design, population, and methods, statistical analysis, consideration of potential confounding, and blood Pb levels examined. The causal determinations describe more explicitly the weight of evidence for individual endpoints and specify the endpoints that contribute most heavily to conclusions regarding a major outcome category.

Discussions of associations between Pb biomarker levels and health effects in nonoccupationally exposed adults were expanded to acknowledge the likely higher past Pb exposures of adults, which influence more recent measurements of bone Pb levels and blood Pb levels. Thus, conclusions within the text and in the causal determinations regarding blood Pb levels with which associations were observed in adults acknowledge the uncertainty regarding the level, timing, frequency and duration of Pb

exposures that contributed to the associations observed with single and usually concurrent measurements of Pb in blood and bone.

The toxicological evidence was analyzed more critically to emphasize the findings that are more relevant to Pb-associated effects in humans, e.g., studies that used lower Pb concentrations (where available), dietary routes of Pb exposure, exposure durations relevant to the time course of effects in humans. Also, we discussed the limitations of toxicological data from studies that examined Pb chromate exposures. Studies with higher exposures were included insofar as they informed modes of action rather than environmentally relevant exposures. These exposures were noted as being higher than those likely relevant for human environmental exposures.

Across outcome categories and endpoints, the integration of evidence was increased. We include more discussion of the consistency between animal and human data with respect to homologous and parallel tests and also more discussion of the evidence for related endpoints and evidence for the modes of action that support the associations observed with health effects. The integration can be found throughout the text and in summaries within sections for individual endpoints (e.g., cognitive function, blood pressure and hypertension).

Revisions to specific sections include the following:

Section 5.2 Modes of Action

- For studies describing the effect modification by antioxidant treatment, additional details were added to describe more explicitly whether the evidence indicated an effect of antioxidants on Pb toxicokinetics or the response of the target organ.
- Table 5-2 was expanded to include details on the studies from which blood Pb levels and Pb exposure concentrations for MOAs were extracted.

Section 5.3: now Nervous System Effects

- The chapter was renamed nervous system effects to incorporate neurodevelopmental effects in children and other nervous system effects such as neurodegenerative diseases examined in adults.
- The weight of evidence for the various neurodevelopmental effects in children (e.g., IQ, specific cognitive functions, academic performance, inattention, attention deficit hyperactivity disorder, delinquent/criminal behavior) is described more explicitly with an expanded critical evaluation of the evidence with respect to study strengths and limitations.
- The integration between epidemiologic evidence was expanded to describe the consistency of findings between homologous tests in animal and human studies and consistency of findings between related and dependent outcomes.
- A new section was added to describe the evidence for Pb-associated changes in internalizing behavior (e.g., withdrawn behavior, depression) in children. The evidence base for behavioral outcomes was compared between adults with respect to the differences in outcomes examined and results found.
- A new section was added discussing the public-health significance of associations observed between blood Pb levels and neurodevelopmental outcomes in children.

Section 5.5: Renal Effects

- A new section was added to describe the evidence regarding the potential for reverse causation to influence the associations.

Section 5.6: Immune Effects

- Conclusions regarding blood Pb levels with which associations with immune effects are substantiated were revised to reflect the weight of evidence and study strengths and limitations.

Chapter 6 – Potentially At-Risk Populations

Following the advice of the ozone CASAC panel, the use of a broad definition of "susceptibility" has been carefully considered. As in the ozone ISA, we have used the term "at-risk" rather than susceptibility where an overarching term is appropriate and made several refinements to the discussion at the beginning of the chapter. In addition, we expanded the discussion to indicate when only limited evidence is available. We also added a section on residential housing and discussion on physiological factors was placed in a stand-alone section.

Chapter 7 –Ecological Effects of Pb

The aquatic ecosystem effects section was reorganized to separate freshwater and saltwater toxicity data. Causal relationships were reevaluated resulting in changes to several causal determinations. There are now separate causal determinations for terrestrial and aquatic systems for each of the following endpoints: physiological stress, hematological effects, neurobehavioral effects, development and reproduction, growth, survival and community and ecosystem level effects. For example, we concluded that the relationships between Pb exposure and community and ecological effects were "causal" in the first draft, and we have revised those determinations to "likely causal". Causal determinations are now accompanied by data on Pb levels at which effects are observed. The determination of causality for bioaccumulation as it affects ecosystem services has been removed from the second draft.

Figures and additional text were added on bioavailability and the Biotic Ligand Model. The definitions of "bioconcentration factor" (BCF) and "bioaccumulation factor" (BAF) have been refined and tables of BCF and BAF values were removed from the second draft to reflect the current EPA Framework for Metals Risk Assessment, which states that the latest scientific data on bioaccumulation do not currently support the use of BCFs and BAFs when applied as generic threshold criteria of the hazard potential of metals.

Sections on critical loads were expanded. Content within the terrestrial and aquatic sections has been restructured to reflect ecological organization, from effects at the level of the organism to effects at the level of the community and ecosystem.

Summaries of information on background levels of Pb in soils have been added along with references to the relevant sections of chapter 3.