



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

SEP 18 2012

THE ADMINISTRATOR

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

Dear Dr. Samet:

Thank you for your July 20, 2012, letter in which you provided the Clean Air Scientific Advisory Committee Lead Review Panel's comments on the U.S. Environmental Protection Agency's *Second External Review Draft Integrated Science Assessment for Lead*, released for public comment and peer review in February 2012. We at the EPA very much appreciate the panel's thorough review and constructive thoughts.

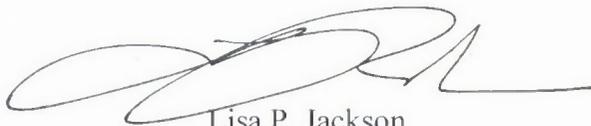
The EPA is carefully considering your advice and making revisions to address your comments and recommendations as well those offered by the public. I have enclosed an overview of the major revisions being incorporated into the third external review draft of the ISA. These include:

- Increasing the synthesis and integration of scientific evidence across disciplines and enhanced critical review of studies;
- Expanding the characterization of the strengths and limitations of the epidemiologic studies by including tables in chapter 5 that characterize the statistical methods and study design of the individual studies evaluated in the ISA;
- Focusing critically on appraising groups of studies with similar designs and methodological approaches;
- Expanding the comprehensive review of literature on studies relevant to understanding how air-related exposure can contribute to total lead exposure;
- Improving the critical assessment of the estimates of the air Pb/blood Pb slope factors discussed in the chapter by adding a discussion of the uncertainties influencing interpretation of the studies;
- Focusing on the most relevant ecological endpoints – survival growth and reproduction – while discussing sub-organismal responses in the context of supporting evidence for evaluating ecological effect studies in chapter 7; and
- Developing tables containing study details on survival, growth and reproduction in terrestrial and aquatic organisms.

A second key focus of revisions is improving the transparency with which the causal framework described in the preamble is applied to the health- and ecological-effects evidence. In implementing the causal framework, judgments will be focused on more specific health endpoints or groups of related health endpoints. To improve the transparency and clarity of our evaluation and conclusions, tables explicitly linking the health-effects evidence to the framework for causal determination will be included in chapter 5. In addition, language to further inform and describe the causal determinations will be added to the ecological effects chapter.

The EPA's efforts to protect the environment can only be as good as the science upon which they are based. Your independent critical reviews help to ensure that we use the best science to protect our nation's environment. Please accept my gratitude for all your hard work.

Sincerely,

A handwritten signature in black ink, appearing to read "Lisa P. Jackson", with a large, stylized flourish at the end.

Lisa P. Jackson

Enclosure

A handwritten note in black ink that says "Thank you!" with a period at the end.



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

SEP 18 2012

THE ADMINISTRATOR

H. Christopher Frey, Ph.D.
Chairman
Lead Review Panel
Clean Air Scientific Advisory Committee
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Dear Dr. Frey:

Thank you for your July 20, 2012, letter in which you provided the Clean Air Scientific Advisory Committee Lead Review Panel's comments on the U.S. Environmental Protection Agency's *Second External Review Draft Integrated Science Assessment for Lead*, released for public comment and peer review in February 2012. We at the EPA very much appreciate the panel's thorough review and constructive thoughts.

The EPA is carefully considering your advice and making revisions to address your comments and recommendations as well those offered by the public. I have enclosed an overview of the major revisions being incorporated into the third external review draft of the ISA. These include:

- Increasing the synthesis and integration of scientific evidence across disciplines and enhanced critical review of studies;
- Expanding the characterization of the strengths and limitations of the epidemiologic studies by including tables in chapter 5 that characterize the statistical methods and study design of the individual studies evaluated in the ISA;
- Focusing critically on appraising groups of studies with similar designs and methodological approaches;
- Expanding the comprehensive review of literature on studies relevant to understanding how air-related exposure can contribute to total lead exposure;
- Improving the critical assessment of the estimates of the air Pb/blood Pb slope factors discussed in the chapter by adding a discussion of the uncertainties influencing interpretation of the studies;
- Focusing on the most relevant ecological endpoints – survival growth and reproduction – while discussing sub-organismal responses in the context of supporting evidence for evaluating ecological effect studies in chapter 7; and
- Developing tables containing study details on survival, growth and reproduction in terrestrial and aquatic organisms.

A second key focus of revisions is improving the transparency with which the causal framework described in the preamble is applied to the health- and ecological-effects evidence. In implementing the causal framework, judgments will be focused on more specific health endpoints or groups of related health endpoints. To improve the transparency and clarity of our evaluation and conclusions, tables explicitly linking the health-effects evidence to the framework for causal determination will be included in chapter 5. In addition, language to further inform and describe the causal determinations will be added to the ecological effects chapter.

The EPA's efforts to protect the environment can only be as good as the science upon which they are based. Your independent critical reviews help to ensure that we use the best science to protect our nation's environment. Please accept my gratitude for all your hard work.

Sincerely,

A handwritten signature in black ink, appearing to read 'Lisa P. Jackson', with a stylized, flowing script.

Lisa P. Jackson

Enclosure

A handwritten note in black ink that says 'Thank you!' in a cursive, friendly script.

Overview of Major Revisions

Preamble and Preface

The Preamble is being revised based on comments from the Ozone and Lead (Pb) CASAC panels. The Preface is being revised to include additional information on the NAAQS for Lead initiation and pre-promulgation history.

Chapter 1 – Executive Summary

The language is being further simplified for a non-technical audience. Additional call-outs to subsequent chapters will be included to make it easier to locate more detailed discussions. Information on the reversibility of the effects of lead will be included here and in subsequent chapters of the document.

Chapter 2 – Integrative Summary

This chapter is being revised to include additional synthesis and integration. In general, revisions to the integrative summary will reflect changes made in Chapters 5 and 7 as well as other sections of the document. Notably, revisions to enhance the transparency of the causal determinations will be reflected in this integrative summary. Other major revisions will include the addition of a summary on lead utilization (e.g. imports, exports and production) and an enhanced critical assessment of studies on the air lead-to-blood lead relationships.

Several revisions are being made to Section 2.9.1 (Public Health Significance). Additional discussion of Figure 2-1 as a conceptual model will be included. The evidence is also being reconsidered to give appropriate emphasis to health endpoints for which uncertainties related to public health significance are relatively low.

Chapter 3 – Ambient Lead: Source to Concentration

Throughout Chapter 3, cross-referencing to relevant sections of Chapter 4 will be added. A map will be added to illustrate the magnitude of individual sources throughout the U.S., and this map will be used to discuss the comparison between individual source contributions for the various source categories. More discussion of wheel weights, with attention to new references suggested by CASAC, will also be incorporated into this section.

Discussion of sampling needs and uncertainties in capturing the ambient air Pb particle size distribution will be expanded. Options for particulate matter (PM) sampling that could be utilized for Pb monitoring will be included. The section on Ambient Air Pb Concentrations is being further synthesized with extraneous material removed or transferred to the Chapter 3 Appendix. The size distribution section is being expanded. An edited version of the collocated Pb size distribution table previously removed for the Second External Review Draft will be restored with quality assurance criteria applied. Pearson correlations will be added to the assessment, and extraneous information from the background section will be removed.

Chapter 4 – Exposure, Toxicokinetics, and Biomarkers

The chapter is being edited to distinguish size distributions of airborne PM containing Pb from the size distribution of dust and soil containing Pb. Furthermore, cross-referencing between Chapters 3 and 4 is being expanded to emphasize where sampling and measurements of Pb concentrations and size distributions, and uncertainties therein, will affect estimation of human exposure to ambient Pb via air-related pathways. Further synthesis of the Pb exposure literature is also being incorporated. In addition, revisions include expanded description of studies that evaluate air-to-blood Pb slope factors and discussion of the air Pb-to-blood Pb relationships described in the last NAAQS review.

Chapter 5 – Integrated Health Effects of Lead Exposure

In the revised draft, causal determinations for health effects are being drawn for specific groups of related outcomes instead of major organ systems with a thorough consideration of the weight of evidence as outlined in the Preamble. With consultation from an outside expert on epidemiologic methods, the discussions of the causal determinations for all health endpoints are being revised to more transparently and consistently apply the causal framework by using language from the causal framework and linking it with the key supporting evidence. Further, the causal determinations will include tables that describe what lines of evidence support specific attributes for causal relationships that are described in Table II (Weight of evidence for causal determination) of the Preamble.

The discussion of the health effects of Pb are being revised to include additional details on strengths and limitations of the evidence, with respect to issues such as study design, consideration of potential confounding factors, analytical methods, and reverse causality in epidemiologic studies and Pb exposure route and concentration in toxicological studies. These issues related to study design and methodology also will be noted in the tables within the text and are more explicitly incorporated into the evaluation of the evidence for determinations of causality.

For the neurodevelopmental outcomes, experts in neuropsychology, behavioral neuroscience, and neurotoxicology are reviewing the discussion of the evidence and will advise EPA on reorganizing the discussion of the cognition-related and behavior-related outcomes into the appropriate constructs and drawing the appropriate parallels between tests conducted in humans and animals.

Chapter 6 – Potentially At-Risk Populations

In order to broadly and consistently apply standard terminology and concepts across criteria pollutants for populations at-risk, a new classification system created for the third draft ozone ISA is anticipated to be added to Section 6.3 of Chapter 6 “Potentially At-Risk Populations”. EPA is looking forward to the CASAC comments on the 3rd draft Ozone ISA to inform the inclusion of this new approach for the Lead ISA. In addition, maternal self-esteem will be removed from discussion of stress and moved to its own section in order to better clarify the difference between the two. Also, statements are being checked for accuracy and addressed/removed.

Chapter 7 – Ecological Effects of Lead

Chapter revisions in response to CASAC comments will include additional synthesis and technical evaluation of the available evidence on Pb effects on terrestrial, freshwater and saltwater ecosystems, and an increased emphasis on growth, reproduction, and survival as ecologically relevant endpoints. In the terrestrial and aquatic sections, summary tables are being added for growth, reproductive, and survival endpoints. An additional table in each of these sections will summarize data from microcosm and field-studies that are referenced in the ISA. Causal determinations for aquatic plants, invertebrates and vertebrates are being divided into separate statements for freshwater and saltwater species. A new section on the fate and transport of Pb in ecosystems is being added that includes a table of current concentrations of Pb measured in different environmental media. Throughout the chapter, units will be standardized for consistent expression of exposure dose, and nominal studies, when included, will be identified. In the context of these chapter revisions, several causal determinations are being revised.