UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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SUBJECT: CASAC Review of Third External Review Draft Integrated Science Assessment for Lead

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The Third External Review Draft Integrated Science Assessment for Lead (draft Pb ISA) prepared by the Environmental Protection Agency's (EPA) National Center for Environmental Assessment – Research Triangle Park Division (NCEA –RTP) as part of EPA's ongoing review of the national ambient air quality standards (NAAQS) for lead (Pb) was released on November 27, 2012. This third external review draft ISA integrates the scientific evidence for review of the primary (health-based) and secondary (welfare-based) NAAQS for Pb and provides draft findings, conclusions and judgments on the strength, coherence and plausibility of the evidence. The ISA is intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health which may be expected from the presence of [a] pollutant in ambient air" (Clean Air Act, Section 108; 42 U.S.C. 7408). The draft ISA will be reviewed by the Clean Air Scientific Advisory Committee (CASAC) Pb NAAQS Review Panel (the Pb CASAC Panel) at a public meeting on February 5-6, 2013. We have distributed the draft Pb ISA to the Pb CASAC Panel. I am requesting that you forward our charge to the Pb CASAC Panel.

Following the review of the third external review draft ISA, NCEA-RTP staff will produce a final Pb ISA projected for release in the Spring of 2013 that addresses comments received from the CASAC Pb Panel and the public. The final Pb ISA, in conjunction with additional technical assessments, will provide the scientific basis for EPA's decision regarding the adequacy of the current standards for Pb to protect human health, public welfare, and the environment.

We look forward to the Pb CASAC Panel review of the third draft ISA at the upcoming meeting. Should you have any questions regarding the draft Pb ISA, please feel free to contact Dr. Mary

Ross (919-541-5170, Ross.Mary@epa.gov) or Dr. Ellen Kirrane (919-541-1340, Kirrane.Ellen@epa.gov).

Charge to the Pb CASAC Panel

This draft ISA includes revisions based on the comments and advice provided by the CASAC Pb Panel and public comments on the second external review draft ISA. Specific revisions to the third draft Pb ISA were described in EPA's recent response (September 18, 2012) to the CASAC Pb Panel's review letter (July 20, 2012) on the second draft Pb ISA. We have carefully considered all of the comments provided by the CASAC Pb Panel members and the public in creating this third draft ISA. In particular, we focused on several key overarching points raised by the CASAC Panel:

- integration of evidence across scientific disciplines;
- enhancing critical review of studies;
- improving transparency of the application of the framework for causal determination;
- reconsidering the health and ecological endpoints around which conclusions were formed and/or received emphasis.

Changes to the content and structure of the draft ISA are highlighted below together with the new charge questions for this CASAC Pb Panel review. These charge questions are not intended to limit the scope of the Panel's review, rather these charge questions are intended to assist the Panel by highlighting specific areas where the Agency has responded to prior comments of the Panel or where the Agency raises emerging issues to the attention of the Panel for comment.

Preamble; Legislative and Historical Background (formally Preface)

The Ozone CASAC Panel recommended that flow diagrams be included in the Preamble of the third draft Ozone ISA to more effectively and clearly communicate the process of ISA development and the NAAQS review process. Thus, based on the CASAC support for these diagrams, they were also incorporated into the preamble of the third draft Pb ISA and will be further updated to reflect revisions made for the final Ozone ISA. In addition, the text of the preamble was revised to read, "In discussing the causal determination, EPA characterizes the evidence on which the judgment is based, including strength of evidence for individual endpoints within the ~~major~~ outcome category **or group of related endpoints**." This change was introduced because, as recommended by the CASAC Pb Panel, conclusions were drawn for specific health endpoints, rather than major outcome categories, in the third draft of the Lead ISA.

The Ozone CASAC Panel also recommended renaming the Preface of the draft Ozone ISA to reflect its historical content. Consistent with this change, the Preface was renamed in the third draft Pb ISA and text describing pre-promulgation history of the Lead NAAQS was added.

Please review and comment on the effectiveness of these revisions to the third draft Pb ISA. Please comment on the extent to which these sections of the ISA provide a useful and effective format for presenting introductory materials for this and future ISAs. Please recommend any revisions that may further improve the clarity of discussion.

Chapters 1 (Executive Summary) and 2 (Integrative Overview)

Consistent with CASAC recommendations, the language in Chapter 1 was simplified to improve the readability for a non-technical audience. Call-outs were added to Chapters 1 and 2 for ease of accessing more detailed discussions in the rest of the ISA. Both chapters were updated to reflect revisions in subsequent chapters. The public health significance section was revised to focus on cognitive effects in children and cardiovascular effects in adults.

Highlights of revisions made to address CASAC comments on enhancing the critical review of the data and the systematic application of the framework for causal determination are discussed in greater detail under the charge question for Chapter 5. Revisions made to address the CASAC recommendation regarding specific health endpoints in the Pb ISA, rather than organ system effects, are evident in the following tables and text that appear in Chapters 1 and 2 of the third draft Pb ISA:

Table 1-1, Table 2-2
Section 2.6.1 Nervous System Effects
Section 2.6.1.1 Children: Cognitive Function Decrements, Attention-Related Behavior Problems, Internalizing Behaviors, Conduct Problems in Children and Young Adults, Sensory Function Decrements, Motor Function Decrements
Section 2.6.1.2 Adults: Cognitive Function, Psychopathological Effects, Sensory Function Decrements, Neurodegenerative Disease
Section 2.6.2 Cardiovascular Effects: Hypertension, Subclinical Atherosclerosis, Coronary Heart Disease, Cerebrovascular Disease
Section 2.6.3 Renal Effects: Reduced Kidney Function
Section 2.6.4 Immune System Effects: Atopic and Inflammatory Conditions, Decreases in Host Resistance, Autoimmunity
Section 2.6.5 Hematological Effects: Decreased Red Blood Cell Survival and Function, Heme Synthesis
Section 2.6.6 Reproductive and Developmental Effects: Development, Birth Outcomes, Male Reproductive Effects, Female Reproductive Effects
Section 2.6.7 Cancer

Although causal determinations for ecological effects are consistent between Chapters 2 and 7, in Chapter 7 causal determinations for reproductive, growth, survival, neurobehavioral, hematological, and physiological stress endpoints are presented separately for terrestrial, freshwater and saltwater organisms (Sections 7.3.12, 7.4.12 and 7.4.21, respectively). In Chapter 2 (Section 2.7.3) causal determinations for the same endpoints are further integrated across terrestrial, freshwater and saltwater taxa. Links are provided in the text to the corresponding sections.

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.

Chapter 3 – Ambient Lead: Source to Concentration

The integrative synthesis (Section 3.7 - Summary and Conclusions), was revised per CASAC recommendations. CASAC recommendations regarding additional synthesis were predominately related to Section 3.5 (Ambient Air Pb Concentrations). This section was made more concise with an eye towards synthesis of the relevant data. Information was moved to the Chapter 3 Appendix where appropriate. Additionally, integration was improved through expanded cross-referencing between Chapter 3 and the exposure section of Chapter 4 (Section 4.1). To further address CASAC comments, data describing the size distribution of PM containing Pb was restored (Section 3.5.3.2 and Appendix Section 3.8.4) with elimination of data below the limit of detection. Size distribution data from a recent literature review was also incorporated. A brief discussion and

data regarding global disposition of Pb were added to Section 3.2. Information regarding alternate methods for measuring size-resolved Pb in PM was added to Section 3.4.

Please comment on the adequacy of these and other changes in responding to the Panel's comments. Please provide comment on revisions that may further improve the utility of this chapter for interpretation of health evidence in subsequent chapters.

Chapter 4 – Exposure, Toxicokinetics, and Biomarkers

In response to CASAC comments, the discussion of differences in particle size distributions of airborne Pb laden particles from those in dust and soil was expanded. Clarification was provided to differentiate the size distribution of dust and soil particles from the size distribution of ambient air particulate matter. The influence of dust and the size of soil particles on Pb concentration and transport via tracking and adherence to hands was also clarified. As noted above, additional cross-referencing between Chapters 3 and 4 was included in the current draft to enhance integration between sections on particle size distribution and exposure. Tables, figures, and sections that serve as illustrative examples of the revisions relating to particle size distribution are listed below:

Section 3.5.3.2 Studies of Pb-bearing PM size distribution in the literature
Table 3-9 Summary of studies reporting Pb Size distribution in the peer-reviewed literature
Figure 3-27 Size distribution of Pb-containing dust collected near busy (HWY 1) and low traffic (HWY 17) highways.
Section 3.8.4 Size Distribution of Pb-bearing PM
Table 3-26 Correlations and average of the concentration ratios for co-located monitors, TSP versus PM_{10}, TSP versus $PM_{2.5}$, and PM_{10} versus $PM_{2.5}$
Table 3-27 Metadata for studies of Pb-PM size distribution
Table 3-28 Size distribution for various studies described in Table 3-27
Section 4.1.1.1 Particle Size Distributions for Airborne-Pb, Dust-Pb, and Soil-Pb

Factors affecting exposure were synthesized in Section 4.1.3. These factors include air-related pathways (e.g., Pb deposited to urban gardens or agricultural crops and ingested, exposure to outdoor soil or dust containing Pb) and non-air-related pathways (e.g., Pb in drinking water from pipe corrosion, occupational exposures, and exposures through consumer products). Some of these factors were also introduced in Section 4.1.1 during introduction of the conceptual model for air-related pathways of Pb exposure.

Discussion of the relationship between biomarkers and exposure was expanded in Sections 4.3.5 (Relationship between Pb in Blood and Pb in Bone) and 4.5 (Empirical Models of Pb Exposure-Blood Pb Relationships). Table 4-2 was added to exemplify IEUBK predictions of pathway contributions to concurrent blood Pb levels. Discussion of the contribution of Pb from ambient air and other pathways to blood Pb was augmented. Information on potential biases and factors that may affect observed air-to-blood relationships was added. The discussion of the relationship between Pb in bone and blood was expanded, in part, to clarify effects of long-term Pb clearance from bone.

Please comment on the adequacy of these and other changes in responding to the Panel's comments. Please provide comment on revisions that may further improve the utility of this chapter for interpretation of health evidence in subsequent chapters.

Chapter 5 – Integrated Health Effects of Lead Exposure

In the revised draft, causal determinations for health effects were drawn for more specific groups of related outcomes instead of major organ systems. Please comment on the appropriateness of these new endpoint groupings. Further, please comment on the extent to which the text and new summary tables support the application of the causal framework in deriving causal determinations. How consistently and appropriately was the causal framework applied across the endpoint groups? A listing of the summary tables is below:

Table 5-17	Summary of evidence supporting nervous system causal determinations
Table 5-24	Summary of evidence supporting cardiovascular causal determinations
Table 5-31	Summary of evidence supporting renal causal determinations
Table 5-34	Summary of evidence supporting immune causal determinations
Table 5-35	Summary of evidence supporting RBC survival and heme synthesis causal determinations
Table 5-48	Summary of evidence supporting reproductive and developmental causal determinations
Table 5-50	Summary of evidence supporting cancer and genotoxicity causal determinations

Clarity in the description and the conceptualization of behavioral outcomes was enhanced by soliciting advice from experts in the fields of neuropsychology and neurotoxicology on how to categorize individual nervous system outcomes into broader categories. For example, experts considered IQ, learning, memory, executive function, and academic performance as indicators of cognitive function (Section 5.3.2) and inattention, impulsivity, hyperactivity, and attention deficit hyperactivity disorder as indicators of attention-related behavioral problems (Section 5.3.3). Rather than discussing all of the epidemiologic evidence and then all of the toxicological evidence, we reorganized by outcome group and discussed the epidemiology and toxicology together (e.g. Section 5.3.2.3 Learning and Memory in Children [p. 5-94 of the redline version] and Section 5.3.2.4 Executive Function in Children [p. 5-114 of the redline version] integrates evidence from both disciplines).

To clarify the rationale for the conclusions drawn regarding the strength of evidence for particular health endpoint groupings, the discussions of the health effects of Pb were expanded with 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 potential for reverse causation in epidemiologic studies and Pb exposure route and concentration in toxicological studies.

Specific revisions include prioritizing studies to emphasize those with the strongest design (e.g., prospective studies with serial measurements of lead biomarkers and health outcomes, analysis of several potential confounding factors) in both the text and conclusions. Some illustrative

examples of such revisions are below:

Section 5.3.2 Cognitive Function: Revisions to clarify the approach to the assessment were made (pp. 5-63 and 5-64 of the redline version).
Section 5.3.2.1 Full Scale IQ in Children: Evidence from prospective studies discussed first (p. 5-64 of redline version) while cross-sectional studies are discussed later as supporting evidence (p. 5-81 of redline version).
Section 5.8.1 Effects on Development: Section reorganized to start with the strongest epidemiologic studies (i.e. NHANES analyses). Studies in Table 5-36 were reordered to follow the text discussion.

The potential for confounding and other biases, as they affected the body of literature contributing to the causal determinations, were highlighted in the summary tables referenced above. Additionally, revisions to the text and other tables in the document were made. Illustrative examples of such revisions are below:

Section 5.5 Renal Effects: Critical assessment of the influence of reverse causality expanded (i.e. Section 5.5.2.4 or 5.5.2.5, pp. 5-539 to 5-541 in redline version)
Section 5.6.5 Immune-based Diseases (e.g. discussion of limitations to studies of viral or bacterial infection on p. 5-613 redline version)
Section 5.6.5.2 Asthma and Allergy: Discussion of confounding, selection bias and reverse causality expanded (e.g. pp. 5-614 to 5-624 of the redline version)

Please comment on the adequacy of the discussion of the strengths and limitations of the evidence in the text and tables within Chapter 5 and in the evaluation of the evidence in the derivation of causal determinations. Please also comment on the extent to which the nervous system outcomes have been grouped into appropriate constructs and the extent to which appropriate parallels were drawn between nervous system endpoints examined in humans and animals.

Chapter 6 – Potentially At-Risk Populations

The O_3 CASAC panel encouraged the development of standard terminology and concepts for assessing populations at risk that could be applied broadly across the criteria pollutants. To help synthesize the evidence, a new classification system was created for considering risk factors and that system has been incorporated into the third draft Pb ISA. Similar to the approach used to determine causal relationships, each factor in the Pb ISA was evaluated and classified based on the weight of evidence within and across disciplines.

In addition, staff evaluated whether there were adequate numbers of studies for a given health endpoint or group of related health endpoints within an at-risk factor to allow the magnitude of the modification by that potential at-risk factor to be evaluated across studies. Evidence from studies of genetic risk, race/ethnicity that may modify the effect of lead exposure on the cardiovascular system indicating increased risk of certain groups within the population was highlighted (Section 2.9.1).

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.

Chapter 7 – Ecological Effects of Lead

The CASAC panel provided a number of comments that prompted focused revisions of Chapter 7. A new section on Pb fate and transport in ecosystems (Section 7.2) and summary tables for studies of reproduction, growth, and survival endpoints including key modifying factors were added (Section 7.6). Causal statements and their organization were revised to place greater emphasis on endpoints that are most clearly linked to effects at the population-level and higher (reproduction, growth, and survival) while additional organism- and sub-organism level responses (neurobehavior, hematological effects, and physiological stress) are now considered in the context of secondary responses (Sections 2.1, 2.7.3, 7.3.12, 7.4.12, 7.4.21, and Tables 2-3 and 7-3). In addition, causal statements were further separated into freshwater and saltwater biota. Clarifying language was added to Sections 2.1 and 7.5 to indicate that causal determinations were based on various routes of exposures to Pb, often under controlled experimental conditions, and are not specific to air deposition. Throughout the chapter, more synthesis of effects on ecosystem receptors has been added and units have been standardized to express exposure dose consistently. Specifically, aqueous concentrations of Pb are reported as µg Pb/L, sediment and soil concentrations as mg Pb/kg, and concentration in solutions applied to soil or extracted from soil in mg Pb/L solution.

Please comment on the adequacy, scientific soundness and usefulness of the material presented and recommend specific revisions to improve the discussion of key information in Chapter 7.