

04-11-12 Draft key points for discussion at the April 11, 2012, Public Meeting of the CASAC Lead Review Panel. They do not represent CASAC consensus advice nor EPA policy. Do not cite or quote.

**Draft Key Points for Discussion at the April 11, 2012 Public Meeting of the CASAC Lead Review Panel
4/11/12 draft, 6:30am**

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Preface, Preamble, Chapters 1 (Executive Summary) and 2 (Integrative Summary)

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.

In addition, please comment 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.

1. As per prior CASAC recommendations, the causal determination analysis would benefit from a substantial revision that a) focuses on specific health endpoints as opposed to organ system effects, and b) assesses the weight of the evidence for causation after systematically and critically evaluating the data for:
 - a. Strength of study designs (in accordance with the standard epidemiological hierarchy: prospective cohort study, nested case control, case control, cross-sectional, etc)
 - b. Consistency in terms nature and strength of association
 - c. The extent to which associations arising from chance, bias, or confounding may be ruled out with reasonable confidence
 - d. Demonstration of a dose-response, focusing particularly on the presence of effects at current or former environmental lead doses (i.e. BLL < 25)
 - e. Biological plausibility at low dose demonstrated by findings from toxicological investigations
2. Particular concerns exist for the causation analysis regarding behavioral outcomes in children, and renal outcomes. Behavioral outcomes in children should be distinguished from effects on cognitive function
3. The 2nd draft ISA appropriately recognizes that adverse effects of lead in adults cannot confidently be imputed to contemporary blood lead concentrations (i.e. BLL < 10 µg/dL) because the populations in which they have been observed sustained higher blood lead concentrations in the past (i.e. BLLs of 10 to 25 µg/dL in the decades prior to 1980).
4. Longterm (i.e. decades) of BLLs across the range of 10 to 25 µg/dL probably bear a causal relationship to an increased risk of adverse cardiovascular endpoints (increased BP, hypertension, CV mortality) in adults

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5. The section on public health significance of low level lead exposure could prudently focus on the endpoints of cognitive decrements in children and adverse cardiovascular effects in adults - endpoints with a probable causal determination
6. An increased risk of elevated lead exposure associated with fluoridation of public water supply systems has not been established, and reference to such a relationship should be omitted in the absence of sufficient relevant evidence

ADDITIONAL ITEMS PER CHAPTER SUMMARIES

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Chapter 3 – Source to Concentration

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.

Of the changes listed, the second ERD adequately address the CASAC's comments with the exception of the following four topics.

3.2.2.5, *Description of air Pb emissions from wood burning* discusses the contribution of this source to air Pb, primarily from wildfires, as a “potentially uncontrollable source”. There is still no meaningful discussion of avoidable Pb exposures from residential space heating woodsmoke; this may be the primary air exposure pathway for “new” Pb in rural or small valley towns where woodsmoke PM concentrations can be high for much of the winter. [Chapter four cites one limited study (Molnar, n=18) on these exposures with minimal discussion because p=0.06.].

3.4.1.2, *Expanded description of TSP FRM and related sampling methods*, has substantial new helpful content in response to comments on the first draft ISA, especially on the current FRM HiVol sampling method. A limited discussion on the possibilities of and need for a better alternative FRM has been added, but still ends with “...there is a continued need to assess the feasibility of a revised TSP sampler design...” without discussing how to move forward towards a revised FRM TSP sampler. Consider addressing what would be acceptable for sampler performance -- cut size, shape, and wind speed dependence. While it may not be within the traditional scope of an ISA, an expanded discussion on the state of the (aerosol) science supporting possible alternatives to the HiVol FRM would be useful to address the many and long-standing CASAC comments on this topic.

3.5.3, *Removal of EPA AQS data table for ambient air Pb particle size information*. All data on Pb size is useful since there isn't much available. The summary of AQS data in Table 3a-13 in the appendix of the first draft should be fixed per first draft comments, not removed. Better use could be made of material in the Cho paper. Refer to the Cavender/Schmidt EPA memo on Pb in air size data, and consider further broadening the scope beyond “studies in the peer reviewed literature”.

3.5.5, *Background air Pb levels*. Some constraints on estimates of “PRB” Pb would be helpful.

Other comments:

In general, material is clearly presented. There are some sections that would benefit from revisions to improve clarity. Parsing and additional synthesis of literature results would improve readability of some sections; sometimes it is necessary to refer to references to better understand the summary results in the text.

3.5.4. Use of Spearman rank r alone to describe associations with other pollutants may not be appropriate or informative; consider also presenting or evaluating Pearson or other parametric r.

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Filtering results to those that are meaningful for source ID use instead of reporting everything would make the material more accessible.

It would be helpful to link the chapter 4 discussion of exposures with chapter 3 air measurements. One example would be the wood smoke topic (3.2.2.5 and 4.1.3.1).

Cover Letter bullets for Chapter 3:

1. All data on Pb size is useful since there isn't much available. The summary of AQS size data in Table 3a-13 in the appendix of the first draft should be fixed per first draft comments, not removed. Better use of material in Cho paper. Refer back to Cavender/Schmidt memo.
2. Need better linkage between chapter 4 personal exposures and chapter 3 ambient concentrations.
3. Pb low-volume FRM sampler: the Panel commends agency progress towards a new "TSP" FRM. Additional detail on the path forward is needed. What would be acceptable for larger particle performance, wind speed dependence?

Chapter 4 – Exposure, Toxicokinetics and Biomarkers

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.

1. Additional synthesis and summary of information is needed on the following:
 - a. Section 4.1 – example, Section 4.1.3.3 (Dietary Lead Exposure) – Information is factual, but the reader will benefit from more interpretation, context, and summary. Include additional discussion to explain the importance and impact of the reviewed data to the ISA.
 - b. Section 4.1.1, p. 4-6 – The additional paragraph is helpful at presenting quantitative estimates of % contribution of air Pb to blood Pb. Include a table that summarizes this information, distinguishing between estimates based on modeling (e.g., IEUBK) and empirical studies. Then add text to synthesize/summarize this information with specific focus on the importance of changes in these % contribution estimates over time, or as a function of the low end vs high end blood leads.
 - c. Add a section that relates estimates of blood Pb / air Pb slopes to the original goals of the ISA as presented in the Integrated Review Plan, which called for an uncertainty analysis that provides a foundation to review the NAAQS. For example, the ISA can demonstrate how a particular slope factor translates into a corresponding change in PbB at the GM and 95th percentile of the distribution assuming a lognormal distribution with GSD =1.6 (a model adopted in IEUBK).
2. Additional discussion and perspectives on the relevance of information as presented is needed:
 - a. Figure 4-22 – very helpful addition to demonstrate the various slopes, particular to emphasize the differences in the model selection (e.g., log-log, log-linear, etc). However, given the focus of the NAAQS is at the low end of the air Pb range presented, EPA should 1) comment on the challenge of estimating the low-end of the curves (i.e., < 0.2 $\mu\text{g}/\text{m}^3$) from data collected, and 2) comment specifically on the magnitude of difference in estimates and representativeness of the statistical models applied to empirical data. Then, tie this back to estimates of expected change in blood Pb associated with change in NAAQS (see 1(c) above).
 - b. Comment on the importance of measurement errors associated with historical Pb TSP measurements. How does this uncertainty likely contribute to 1) estimates of air Pb / blood Pb slopes; 2) estimates of predicted blood Pb from epidemiological data; and 3) corresponding uncertainty in predicted change in blood Pb associated with reduction in air Pb (see 1(c) above).

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- c. Historical perspective on change in Pb sources over time associated with change in blood Pb – Chapters 3 and 4 remained somewhat biased towards gasoline Pb phase down; also note the role of reductions in emissions in the vicinity of point sources.
3. The following contradictions need to be addressed:
- a. Clearance rates for blood Pb – the text (e.g., 4-62) suggests that the rate of change may be slow following cessation, such that blood Pb will remain elevated years after exposure ends. Yet, the narrative discussion at the top of page 4-67, and the model simulations in Figure 4-11 (ICRP modeling) suggests exactly the opposite – a rapid decline in blood Pb following cessation. EPA should provide more description regarding model assumptions (e.g., how was baseline exposure factored in?), and comment on whether this relationship may differ for higher blood Pb that corresponds with adult occupational exposure. Literature that provides empiric observation for change in blood lead following cessation of exposure that resulted in moderate elevations (e.g., blood Pb in the 10 to 25 ug/dL range) for various time durations should be discussed (if available). Discuss the impact of model selection on simulated change in BLL (e.g. Leggett versus O’Flaherty) .
 - b. % Pb in blood - Page 4-39 (line 23) and 4-120 (line 22) report that 1% of body burden is in blood, whereas 4-49 (line 12) reports 5%.

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Chapter 5 – Integrated Health Effects of Lead

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.

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.

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?

The revised draft for Chapter 5 incorporates a number of important improvements. These include better integration of the epidemiology and toxicology literature with a clearer focus on comparing homologous tests and exposures in animal and human studies. A new section on the public health significance of nervous system effects is informative and well done. There is consistent acknowledgement that contemporary blood Pb levels in adults (and older children) may not directly account for observed health effects because of the likely contribution of previously higher or longer term exposures.

For childhood IQ, adult nervous system effects, blood pressure, and other cardiovascular outcomes, analyses of consistency (or not) across the literature, confounding, and study design issues were improved. However, for most remaining health measures, a number of concerns identified in the 1st draft review remain. Key among these are:

(1) Incomplete critical assessment of each study reviewed to determine the strength of the observed associations. E.g., could observed associations be attributable to confounding, bias, chance, or other study design limitations, including limitations related to cross sectional design?

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(2) Lack of transparency regarding causal determination. E.g., a *balanced* analysis of the strengths and weaknesses of the literature (see item #1 above) and causal determination criteria outlined in the document's preface were not explicitly applied.

(3) Lack of clarity in description and conceptualization of behavioral outcomes. E.g., behavioral check lists or formal psychometric tests of attention should not be equated with clinical ADHD. The homologies of animal behavior tests to human tests are correct in some cases but incorrect in others. Comparable behavioral assessments are necessary for meaningful comparison of findings across human studies.

(4) Examples of the above limitations: (a) the strength of literature relating Pb with childhood cognition versus behavior is not the same but text implies it is; (b) for renal outcomes, this document is more measured than the 1st draft but still does not address major concerns: (1) reverse causation, (2) inconsistencies and uncertainties in the literature, and (3) lack of a mechanism for renal effects at BPb < 15 µg/dL.

(5) Lack of clarity regarding exposure level(s) at which observed effects are likely to occur.

(6) The appearance of a potential confirmation bias in the document – e.g., studies of null associations are sometimes not mentioned (e.g., Pb and child behavioral publications: Wasserman et al. and Canfield et al. [add specific refs?]).

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Chapter 6 – Potentially At-Risk Populations

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.

1. In general the group felt that the expanded discussion better captures the intricacies associated with ‘at risk’ populations. The re-organization of the chapter into related factors also makes it more cohesive and better integrated.
2. The revised Chapter 6 adequately defines some factors as having limited evidence based on strength of available evidence.
3. Some issues still remaining include the extent to which these risk factors actually modify the magnitude of the impacts of lead exposure. As currently constructed, there is no way to discern which of these risk factors is most critical and certainly a better understanding of magnitude of the impact would be of assistance for risk assessment and management.
4. Given the differences between maternal self-esteem (how was it actually measured) vs. stress imposed in rat models, such a homology should certainly be limited or at least qualified.
5. Concerns were expressed about the interpretation of the Wang and Fowler study with a recommendation that it be re-checked for accuracy (p. 6-3, lines 33-35).
6. If fluoride co-exposure with lead does increase blood lead, as suggested in the material below, then this should be added to Ch. 6, and tied to the citation in Chapter 2.
Coplan, M. J., S. C. Patch, et al. (2007). "Confirmation of and explanations for elevated blood lead and other disorders in children exposed to water disinfection and fluoridation chemicals." *Neurotoxicology* 28(5): 1032-1042.

Silicofluorides (SiFs), fluosilicic acid (FSA) and sodium fluosilicate (NaFSA), are used to fluoridate over 90% of US fluoridated municipal water supplies. Living in communities with silicofluoride treated water (SiFW) is associated with two neurotoxic effects: (1) Prevalence of children with elevated blood lead (PbB>10microg/dL) is about

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double that in non-fluoridated communities (Risk Ratio 2, $\chi^2 p < 0.01$). SiFW is associated with serious corrosion of lead-bearing brass plumbing, producing elevated water lead (PbW) at the faucet. New data refute the long-prevailing belief that PbW contributes little to children's blood lead (PbB), it is likely to contribute 50% or more. (2) SiFW has been shown to interfere with cholinergic function. Unlike the fully ionized state of fluoride (F⁻) in water treated with sodium fluoride (NaFW), the SiF anion, [SiF₆]²⁻ in SiFW releases F⁻ in a complicated dissociation process. Small amounts of incompletely dissociated [SiF₆]²⁻ or low molecular weight (LMW) silicic acid (SA) oligomers may remain in SiFW. A German PhD study found that SiFW is a more powerful inhibitor of acetylcholinesterase (AChE) than NaFW. It is proposed here that SiFW induces protein mis-folding via a mechanism that would affect polypeptides in general, and explain dental fluorosis, a tooth enamel defect that is not merely "cosmetic" but a "canary in the mine" foretelling other adverse, albeit subtle, health and behavioral effects. Efforts to refute evidence of such effects are analyzed and rebutted. In 1999 and 2000, senior EPA personnel admitted they knew of no health effects studies of SiFs. In 2002 SiFs were nominated for NTP animal testing. In 2006 an NRC Fluoride Study Committee recommended such studies. It is not known at this writing whether any had begun.

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Chapter 7 – Ecological Effects of Lead

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.

This chapter has been greatly improved by reorganizing the chapter and the addition of material. Sections have been clarified with the addition of concise introductions, by reference to previous AQCD documents, and the inclusion of brief summaries of sections appropriate. More recent information on Pb exposure, toxicity, and effects to ecological receptors has been included in separate sections for terrestrial, freshwater, and marine ecosystems. Although the revised ISA contains new information presented in an organized manner, the information is not summarized and integrated into a meaningful synthesis and little technical evaluation of extant data is provided. Summary tables listing media-based exposure concentrations (soil, freshwater, marine; nominal or measured) with their respective responses and key abiotic modifying factors (e.g., pH, organic carbon, cation-exchange capacity (soils), water hardness, etc.) would help in further organizing the data to facilitate a synthesis. A detailed table should be provided in an Appendix (e.g., 2006 Pb AQCD) with a summary of the most relevant data presented in the ISA to guide discussion. An initial discussion might include the relevance of responses observed at very high Pb levels that may not be expected in most environmental scenarios. In a similar manner, Pb exposures and effects related to very low levels should also be addressed, especially where Pb levels appear to be below analytical detection limits. Discussion could then conclude with a discussion of how the ranges of Pb found in various media (see Table 2-1) overlap with experimental concentrations. Although some discussion of bioavailability is provided, integration of this concept into the discussion of observed effects of Pb exposure in different media should be attempted.

Throughout the chapter, the consistent expression of exposure dose would help facilitate comparisons of exposures within and among studies. Exposure doses should be expressed on a mass basis (e.g., mg/kg, mg/L) for all exposures, except for comparisons between or among metals, where exposure should be expressed on a molar basis (e.g., uM). Nominal concentrations and exposures in non-standard media (e.g., hydroponic, agar) should be identified.

The US EPA Office of Water utilizes the endpoints of survival, growth, and reproduction for the development of water quality criteria. Lead that is subject to atmospheric deposition and results in ecological effects would ultimately be present in water, sediments, or soils. Survival, growth, and reproduction should be considered the most relevant endpoints, and sub-organismal responses should be discussed in the context of secondary responses.

The nature of causal determinations as related to ecological responses needs to be clarified. Are causal determinations related to aerial deposition of Pb or are they only considered in relation to laboratory exposures even though relevance to ecosystems is unclear.