Preliminary Comments from Members of the CASAC Lead Review Panel on EPA's Integrated Science Assessment for Lead (Third External Review Draft – November 2012)

Received as of 02-01-13

Mr. George Allen

General Comments

The revisions to Chapter Three are responsive to the panel's comments on the second ISA draft. Many minor and some major changes have been made that improve the readability of the document and address specific weak points of the second draft.

The additions to section 3.4.1.1, Sample Collection, are an improvement to the description of the "state of the science" for measurement of particles greater than 10 microns, clearly illustrating the challenges in designing a new FRM to replace the Hi-Volume sampler where sampling of larger particles is of interest. While it is understood that EPA will not have completed work on design and characterization of an improved "larger particle" FRM for this cycle of the Pb NAAQS, I encourage the Agency to continue this process.

The presentation of available data showing the range of Pb concentrations larger than 10 microns diameter near sources is useful, and shows a very wide range of results. Some of this is related to the actual air concentrations, but given the very wide range of methods used for sampling this size range and near-source sites, it is possible that much of the variation is due to the type of sampler being used or the wide range in near-source characteristics and other factors including wind speed. Overall for [non-airport] near-source sites the amount of airborne Pb greater than 10 microns is typically between 10 and 30%, with much of that less than 15 microns diameter. In the context of the NAAQS, this is not a large amount given the uncertainty of linkage between air Pb and dose. The ISA also appropriately notes that particles larger than ~15 microns deposit close to the source. This may inform the process of development of a new FRM since the effort to validate a sampler with a 15 micron size cut is substantially less than attempting to go higher – even to 17 or 18 microns. This applies both to the design and the FRM wind tunnel testing process. I urge the Agency to consider if the effort to go with a sampler for particles larger than 15 microns has value in terms of the data needs of the Pb monitoring network.

The Summary and Conclusions section (3.7) is well written, and covers the key points of the chapter. Section 3.7.3 (Ambient Monitoring) implies that a 15 micron sampler would be adequate, which I agree with. However, the end of section 3.4.4.1 considers the upper particle size range of interest as 15 to 20 microns. As noted before, effective sampling of 20 micron particles is much more difficult if not completely impractical for a FRM sampler than for 15 microns. Also, this section concludes with a sentence that isn't fully supported by this chapter (section 3.4.1.1): "The existing samplers reasonably capture the airborne fraction of ambient Pb that is available for human exposure". The discussion of sampling issues, available technology, and relevant size for sampling larger particles is clear that while there are promising candidates for evaluation (the low-vol TSP louvered inlet for example), they have not been fully characterized for wind speed effects as required for use as a FRM sampler.

The topic of elevated air Pb near general aviation airports is discussed, but there are no data from the 15 pilot sites that were scheduled to start sampling early in 2012. If any of these data are available (e.g., in AQS or even possibly preliminary data not in AQS), it would be useful to include it in the final version of the ISA.

Minor comments on Chapter 3

Pg 3-10, line 14: It may be worth noting here that the "solid particles" formed by condensation are (very) fine mode [sub-micron] Pb just to be clear.

Pg 3-15, line 6-7: this section describes wood burning other than for space heating, not just "wood burning".

Section 3.2.2.6, pages 3-23 and 3-24: tire wear particle size is first described as sub-micron (Maher 2008), and then as "coarser sizes" (Chon 2010). This discrepancy needs to be addressed or discussed.

Pg 3-54, line 10: "mor layer" needs to be defined on first use (O-horizon?)

Dr. Herbert Allen

Comments on Chapter 7 – Ecological Effects of Lead

Draft 3 of the ISA is greatly improved over earlier versions. The document is well written and, although lengthy, reasonably easy to follow. The authors have done an excellent job of summarizing and integrating a large amount of information. By reporting all concentrations in mass units (e.g. mg/kg or mg/L), rather than some in mass and others in molar units, it is much easier to make comparisons of results from different studies.

I only have a few major comments which are followed by several more minor ones.

It is now very clear that the concentrations producing effects vary by many orders of magnitude. These ranges, and the effects attributed to them, are quite important in presenting the Synthesis of New Evidence (Section 7.3.11 and 7.4.11) and in the Causal Determination sections that follow these. A graphic for terrestrial and for aquatic effects that relates the various effects on the abscissa to concentration on the ordinate could serve to summarize the information in a useful manner. The environmental concentration range should be shown. Some effects, although real, have little or unproven applicability to environmental situations. The ISA discusses concentrations that vary more than 8 orders of magnitude, far more than the range of environmental concentrations.

A primary factor controlling bioavailability in both aquatic and terrestrial systems is the solubility of the tested material. Lead is typically added as either the chloride or the nitrate salt. Both dissociate completely to release lead ions, Pb2+. The lead ions can react with ligands in the solution to form soluble complexes and insoluble precipitates. For solutions of a near neutral pH the solubility of lead is low and many of the concentrations reported in the review likely exceed the solubility of lead hydroxide, cerrusite, PbCO3, or hydrocerrusite, Pb3(OH)2(CO3). Hydrocerrusite is not even mentioned as one of the important solids (page 7-91 lines 11-14). A paragraph should be added to the chapter discussing solubility, its importance, and its calculation, for example with the EPAs MINTEQ program.

On page 7-124 and 7-125 the foliar proline concentrations in a macrophyte were reported to increase in a concentration-dependent manner as the Pb concentration increased from 20,720 to 1,036,000 µg Pb/L. The upper concentration of 1,036,000 µg Pb/L is over 1 g/L. Unless the pH was exceeding low, virtually all the Pb was in the form of a precipitate, not in a soluble form. It is interesting that biochemical and cytological effects such as this are found at high concentrations relative to traditional endpoints such as death and reproduction for which lower concentrations produce effects.

The information on page 7-33 line 22 duplicates that on page 730 line 28.

Anecic earthworms reach depths of 6 feet, not 6 inches (page 7-36 line 8).

The observation on page 37 line 7 that honeybees collected near an airport have the highest concentration of Pb is very interesting and likely very important. Aviation fuel contains Pb.
On page 7-39 lines 21-22 the phrase "…with high absorption of cerussite and Mn-Pb oxides and poor absorption of galena and anglesite." Should be changed to "…with high absorption of Pb from cerussite and Mn-Pb oxides and poor absorption of Pb from galena and anglesite."

On page 7-44 lines 10-11 there is aan error in the concentration conversion. 10 mM Pb is 2072 mg/L not 10,360 mg/L.

On page 7-44 line 34 "theses" should be "these"

On page 7-47 lines 24 and 25 mM, which means mmol/L, should be changed to mmol.

On page 7-47 line 26 "nitrite" should be "nitrate".

The discussion of ionoregulation (page 7-134 lines 8-24) is particularly well written and helpful.
On page 7-136 lines 19-20. The value 0.08 nM/100 embryos is probably incorrect. This means 0.08 nmoles/L/100embryos. Likely it should be 0.08 nmoles/100 embryos.

The summary on page 7-157 beginning at line 19 and the corresponding section for effects terrestrial systems are very good. This is where the figure that relates the various effects to exposure concentrations would be helpful.

On page 158 line 13 please do not advocate the use of LOEC. Many papers have discussed the reasons for this. The use of LC10 is fine.

On page 166 line 18-20 the LC50 value is derived because it is a stable value and is less dependent on the method used than are other computed values (e.g. LC10). It is not used to suggest that this value be used as a regulatory limit or as a value that is desirable for an ecosystem.

Dr. Deborah Cory-Slechta

Comments on 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.

The chapter is improved over the prior version. Improvements include the more specific delineation of at risk sources in terms of biological vs. environmental for example. In addition, the Chapter better summarizes the strength of the evidence with respect to each of the factors that are considered.

What is missing is any sense of the relative magnitude/importance of the risk factors. It is stated that the magnitudes are discussed in Chapter 5, but its not clear that they are discussed there, and it makes it more difficult for the reader to have to go back and try to track them down. It would be extremely useful to have a summary table that summarizes the magnitude of effects these various factors impose. It may be the case that there are very consistent effects of any given factor, but if the magnitude of the risk modification is 2%, for example, how important are they?

Dr. Cliff Davidson

Comments on Chapter 3

The third version of Chap. 3 of the ISA has been revised according to CASAC comments. Pages 3-2 to 3-22 appear to be a reasonable summary of the National Emission Inventory for Pb, and includes information on lead wheel weights from the Aucott and Caldarelli (2002) study, as requested by CASAC.

Section 3.3 starting on page 23 discusses deposition of lead. While the information in this section seems reasonable, there could be a mention that lead deposition allows for a link between airborne lead and an ingestion pathway, e.g., food from urban gardens (I didn't see this written explicitly, although it might be in the document).

In section 3.4.1, limitations of the FRM and alternative methods of sampling have been discussed on pages 3-60 to 3-68. The discussion of low volume samplers, saturation samplers, and passive samplers is good. It is unclear why the Andersen impactor reported concentrations 97% higher than the Texas A&M sampler for PM_4 but only 14% higher for PM_{10} (page 3-66). One would expect better agreement as particle size decreases. (Why did EPA choose to highlight this specific difference?)

Revisions made to the airborne lead size distribution discussion in section 3.5.3 starting on page 3-96 are reasonable. The new discussion on background lead levels in section 3.5.5, page 3-109, is reasonable. The section concludes with an estimate of background airborne lead concentrations as requested by CASAC; the given estimate is 0.02 to 1 ng/m^3, which is consistent with the literature values in remote areas. The given range varies by a factor of 50; it is probably difficult to decrease this spread. We know PM concentrations can vary by more than this depending on whether sampling is done in a remote area with vegetation and soil, or on an ice sheet far from exposed soil and seaspray. If PM total mass can vary greatly in geographically different remote areas, one could expect airborne lead to vary greatly as well.

Dr. Sean Hays

Comments on Chapter 4

General Comments

- 4.3.5 Relationship between Pb in blood and Pb in bone: This section was well written and some insightful conclusions were drawn.
- I appreciate and liked the summary of data/studies that have investigated the relationship between lead in air and blood leads. In particular, the historical perspectives around the declines in the use of lead in gasoline and related decreases in blood leads in the US and other countries is helpful for establishing the context around setting a lead NAAQS.
- The description of the empirical models, and their strengths and weaknesses, is good. Again, many of the empirical models were developed using data from smelter/mining communities, which are very different than the scenarios involving setting a NAAQS. These empirical models would be helpful for setting a SAAQS (Smelter Ambient Air QS), but not so much for setting a NAAQS.
- I still wish the agency would provide a summary of the sources of lead exposures for the general population and the general proportions as a function of age and blood lead levels. For instance, for children with blood lead levels above 5, 10, etc. ug/dL , what proportion of their lead exposure is coming from air, water, soil, dust, consumer products, paint, etc. Do these proportions change as a function of age and blood lead levels? This is what is needed to provide more informed decisions on how the NAAQS should/could be improved. I would love to see some pie charts for the following ages/PbB (even if they are educated guesses):
    - Children < 2 yrs, 2-6 yrs of age, 6-18 yrs of age, 18-40, >60 yrs of age
        - PbB <2 ug/dL
        - PbB 2-5 ug/dL
        - PbB 5-10 ug/dL
        - PbB > 10 ug/dL

Specific Comments

- Page 4-68, Line 28: Reference to Figure 4-9 should instead be to Figure 4-10.
- Figures 4-9, 11 & 12: Figures that mix Time-integrated Blood Pb and instantaneous concentrations are confusing. There is no need to reproduce the instantaneous bone or body burden when they are provided in the paired figure above.
- Page 4-84, lines 20-33: The ISA presents an analysis of How was this analysis done? Was it modeled? Not enough detail is provided for the reader to follow.
- Page 4-139: The paragraph from lines 21-31 is overly biased. The second to last sentence in particular. This sentence should be revised to read “Still, uncertainty may be expected to remain about parameters in complex exposure-biokinetic models.”

Dr. Chris Johnson

Comments on Chapter 7: Ecological Effects of Lead

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.

Several revisions were made to the Ecological Effects chapter of the Second Draft ISA to improve its organization and effectiveness. A new section (7.2) has been on Pb fate and transport in ecosystems. While I have no objection to adding this section, much of this content is repeated from Chapter 3, and little of it is used in the following sections of Chapter 7. For example, section 7.2.2 covers half-lives and time to achieve 95% of steady state, yet there appears to be no use of these concepts in the rest of the document.

An important criticism of this chapter of the Second Draft ISA was that information from individual studies was not well integrated into meaningful syntheses with sound technical interpretation. The terrestrial sections of this Third Draft (7.3.1 to 7.3.9) are much improved in this regard, with good summaries at the end of each section synthesizing the interpretations.

Perhaps the most important revision to this chapter of the ISA is the addition of Tables 7.4, 7.5 and 7.6. These helpful tables summarize the most relevant data leading to the conclusions regarding the causal determinations.

Finally, the discussion of bioavailability is much improved and integrated with the discussion of biomagnification.

A persistent problem in the analysis of ecological effects, especially ecosystem effects, is the inability to develop meaningful relationships between Pb concentrations in air and Pb concentrations in soils and water. This disconnect ultimately limits our ability to set an ecosystem-based secondary standard for Pb despite clear indications of causal relationships between Pb exposure and most biotic responses. This is not a new problem. However, one may hope that in the near future there will be sufficient data to close this gap and develop a ecologically based secondary standard, perhaps using a critical loads approach.

With regard to terrestrial effects, Chapter 7 of this Third Draft ISA is a well-written and comprehensive summary of current scientific understanding.

Mr. Richard Poirot

Comments on Chapter 3

Chapter 3 is much improved, with revisions responsive to previous comments. The new discussion of alternative sampling methods (and desired and/or feasible Pb sampling characteristics), the additional presentation of Pb size distribution data, and a better synthesis between Chapter 3 and 4 - are all notable improvements. The red-line track-changes version was extremely helpful to the review process, as was the HERO database, although I encountered frequent "traffic delays" with the latter, which were irritating but not debilitating. All my comments are minor, and I don't think it would be necessary to see another revised draft of this chapter.

P 3-1, lines 9-11: This sentence could be deleted since it doesn't add any useful information, since you later provide a nice summary of chemical forms (Table 3-1) from the 2006 CD, and since you summarize many post-2006 studies that do provide added information on chemical forms (and/or chemical associations) from various emissions sources on pp 3-10 through 3-17, and elsewhere in the ISA.

P 3-2, line 33 and 3-3, line 1: Is resuspended soil Pb included in the "Miscellaneous" category (and if so could it be mentioned here)?

P 3-6, lines 3, 4: Could these 182 sources and their emissions be listed in an appendix?

P 3-9, line 4: It might be informative to know the destinations and end uses of the increasing Pb exports.

P 3-14, line 9: Change "vary" to "varies" or "can vary".

P 3-15, lines 5-13: These large differences in Pb emissions (10% at 500 ^{o}C to 85% at 850 ^{o}C) have important implications for the partitioning of Pb in smoke vs. ash from residential wood stoves – for which maximum combustion temperatures typically only reach the middle of this range. Subsequent Pb exposure routes could also be quite different, as wood stove ash is often deposited in gardens or on icy driveways. Conversely, wild fires may reach much higher temperatures, burn the uppermost humic soil layers, etc.

P 3-16, line 33: If 2.7 to 5% of the mass of all wheel weights were deposited to the road daily (and assuming tires are periodically rebalanced), then 100% of wheel weights would be lost in a month or less. I don't believe it.

P 3-17, line 5: Does "disbursed" mean emitted to the ambient air?

P 3-17, lines 18, 19: Fauser's 90% of tire wear particles < 1 micron is not logical.

P 3-17 and 3-18 in general: This is a very interesting discussion, but doesn't provide much confidence that the most important source(s) of roadway-related Pb emissions (and particle sizes) are very well known (wheel weights, brake wear, tire wear, unleaded gas, diesel, road line paint, historically deposited roadside Pb, etc.).

P 3-20, line 13 – and elsewhere: The terms "loading" and "loading rate" can be somewhat confusing and might benefit from some explanation here or somewhere. I assume that in this case we're talking about "loading" units something like µg Pb/m^2 in dust which is extracted from these various surfaces, while "loading rate" (used elsewhere) has units like µg Pb/m^2/yr. How surface dust concentrations, loading loading rate, and flux are measured – and in particular what particle sizes are captured in such sampling – would be of interest.

P 3-24-3-28: The sections on transport and deposition are clearly written and informative. You make a compelling argument for the decreasing solubility of Pb (and importance of larger particles) as fine fraction Pb-containing particles interact with and are incorporated onto coarser (primarily crustal) particles. A potentially important but missing part of the story relates to the fate of soluble Pb in wet deposition as it percolates through soil. If Pb remains in solution, it would tend to pass through surface soil layers and thus be unavailable for re-suspension, but if it is quickly bound to surface organic matter or alkaline crustal compounds, it would be more readily available for re-suspension or direct uptake and ingestion. Potentially also historically deposited Pb on/near the soil surface may be removed after years of relatively Pb-free but still acidic precipitation. There is more detailed discussion of this later in section 3.3.3.3, but it isn't focused at all on potential re-suspension from urban roadside or other near-source soils. Some discussion of the fate of (previously) soluble Pb in soils would be informative in or prior to Section 3.3.1.3. See for example: Maclean and Bledsoe (1992), Yobouet et al. (2010).

McLean, J. E. and B. E. Bledsoe (1992) Behavior of Metals in Soils, U. S. EPA Ground Water Issue, EPA/540/S-92/018. http://www.epa.gov/superfund/remedytech/tsp/download/issue14.pdf

Yobouet Y. A., K. Adouby, A. Trokourey and B. Yao (2010) Speciation in contaminated soils, *International Journal of Engineering Science and Technology*, Vol. 2(5), 802-812.

In addition, details on spatial gradients in soil or dust or biota Pb (rates at which concentrations decline with distance) near current or historical sources could be informative for exposure assessments or to guide future air monitoring approaches.

P 3-27, line 1: Add "on" after "focused".

P 3-27, lines 15 and 16: You could delete "For example", since it doesn't follow the preceding sentence.

P 3-27, line 29: The sentence meaning and context are unclear.

P 3-27, lines 30-35: You could change "at" to "near" in line 3, as the upper bound Pb V_d reported in the 2006 CD was 1.3 cm/s. Also, the 12-17 mg/m^2-year dry Pb deposition reported here for Tokyo Bay was not more than 10 times the upper bound of the range reported in the 2006 CD - which included 8.4-14

mg/m^2-year dry Pb deposition reported by Yi *et al.*, (2001) near Lake Michigan for 1993-1995 (see p. 2-57 of the 2006 CD).
P 3-28, lines 12 and 13: You could delete "transition", as Pb is not a "transition metal".

P 3-28, lines 15, 16: Emissions, concentration and deposition of coarse particles could be driven by diurnal changes in wind speed – regardless of whether the source was anthropogenic or natural. Conversely, there are many anthropogenic sources that operate at night.

P 3-29, lines 7, 12 and 13: An increase of 0.84% in air Pb for each 1% increase in airborne soil is not necessarily "minor", as it suggests that if airborne soil concentrations were doubled, airborne Pb concentrations would nearly double as well (increase 84%), and that soil is the predominant source of airborne Pb (I must be missing something here).

P 3-31, lines 30, 31: This has important implications for the spatial representativeness of "air" samples containing particles larger than 20 µm, as well as for the design of an alternative (to hi-vol TSP) Pb sampler.

P 3-34, lines 21-23: Although you refer to a "nominal dissolved phase", you might put "dissolved phase" in quotes to emphasize that there may well be particles passing through a 0.45 µm filter – for example as you report from observations of McKenzie et al. (2008) on p 3-41, line 3.

P 3-40, lines 3-10: Its not clear what you mean by "uniform" size distribution. In line 3, do you mean "Pb in PM" or just "PM" in general, and do you mean that the Pb concentrations were similar (uniform) in particles of different sizes? If so, this implies that the Pb is present throughout the larger (and smaller) particles, rather than on the surface of the particles or more concentrated in/on the smaller particles.

P 3-40, line 22: This road paint contribution of 46% of Pb in heavy traffic dust sounds important, and should be mentioned in Section 3.2.2.6.

P 3-41, line 16: How is "dissolved" defined here?

P 3-60, line 1 and elsewhere: The term "TSP" is used inconsistently in this section - with several different meanings - and would benefit from clearer definition(s) or alternative nomenclature. In line 1 the verbal definition (and origin of the acronym) is given as "total suspended particles", a hypothetical and un-measurable concept. "TSP", in the context of the Pb-TSP FRM basically means "whatever the Hi-Vol TSP sampler captures". "TSP" is also used (incorrectly) to describe the "mass median aerodynamic diameter" in Table 3-3 and in subsequent discussion of several of the current alternative sampling methods to describe what the Texas A&M Lo-Vol TSP sampler, the UIUC Isokenetic TSP sampler, and the Airmetric MiniVol collect – although these samplers all have particle cut size characteristics which are different from each other and from Hi-Vol TSP sampler. A fourth different meaning of "TSP" is implied by the term "revised TSP sampler" – meaning a yet to be developed alternative to the Hi Vol , which if it were preferable, would clearly not collect the same TSP as the Hi Vol, or other currently available so-called TSP samplers.

What if you had a few lines or text box up front, (and made minor changes in the text and tables) something like:

> TSP is an acronym for Total Suspended Particles, an hypothetical and un-measurable concept. In this chapter, we use the term TSP to mean "particles with the size characteristics of those collected by the high volume (Hi Vol) TSP sampler" and Pb-TSP to mean "Pb in particles collected by the Hi Vol TSP sampler". When referring to alternative existing or future samplers with an upper 50% particle cut size larger than 10 microns, but not identical to the Hi Vol TSP sampler, we use the term "TSP" in quotes.

PP 3-63 and 3-64, Table 3-3: You could change the 4th column heading to something like "Particle Size Characteristics" and when TSP is indicated for samplers other than the hi-vol, put "TSP" in quotes.

P 3-68, lines 2-8: This (surrounding paragraph) is an excellent summary, and the points raised here - that the relevant size distribution for ambient sampling is smaller than that of the settled dust, and that particles > 20 µm are too large to be transported more than a few seconds – indicate that there may be some convergence of "what's desired" for Pb-PM sampling, and "what's feasible" for filter-based sampling with size selective inlets.

P 3-91, lines 10-18: Could you add a bit more detail on how far upwind and downwind these sites are?

P 3-97, lines 15-18 (and Table 3-8): This is a good addition from last draft. The description on p 3-97 (used data from sites with at least 30 paired, collocated samples where both were above MDL) is different from the note at bottom of Table 3-8, which says "… comparisons were limited to monitors where all samples were above the MDL…" The same note is also used in Table 3-26 in the appendix on page 3-205. I assume the Table notes aren't quite what you mean, and what you do mean is something like "…comparisons were limited to samples from sites which had at least 30 pairs of collocated samples, with both samples above the MDL and where both monitors reported data at STP…"

P 3-107, lines 1-4 and Figure 3-25: I notice that Figure 3-25 has changed from the previous draft (in which K had the second highest correlation with Pb, after Zn, and am just curious why the figure changed? Also, in listing the elements with low to moderate correlations (p 3-107, lines 2-3), it seems somewhat arbitrary to exclude K which is barely lower than Br and is followed by a much larger step reduction in correlation with K^+. These relatively high correlations of Pb with K and K^+ - as well as with EC & OC – suggest a possible influence from wood smoke.

Dr. Ian von Lindern

Comments on the Preamble; Legislative and Historical Background (formally Preface)

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.

Preamble: Inclusion of the flow diagrams from the Ozone document and discussion of the regulatory history in the in the Preamble is an improvement to the document and does enhance the effectiveness and clarity in communicating the ISA process in the NAAQS review. The diagrams are largely self-informative and don't necessarily rely on the text to interpret, and are congruent with the descriptions as well. Figure III is an exception, where the Term "Evergreen" Literature Search and Study Selection is not defined or discussed and seems to imply some proprietary or specialized criteria. The parenthetical in Figure III refers to Figure II, but no specific reference to this method is found there or in the text. Some of the text in the Preamble suggests that the discussion and figures may have been lifted from the Ozone document, and although appropriate could be edited to be more "lead friendly". The discussions relative to controlled human exposure or animal toxicological studies are, perhaps, more pertinent to ozone than the lead review. The section on Concepts in Evaluating Adversity of Health Effects, for example, emphasizes lung function as opposed to a more common lead related adverse health effect.

The Preamble also seems to suggest that the principal objective of the document and outcome of the ISA process is to establish causation. Several terms are interchangeably used "causal determination, causal nature, causal relationship, inferring causation, causal claim, web of causation, determination of causality, evidence for causation" are all used within a few paragraphs. Is there a universal meaning or different definition for these terms? In either case, it was an improvement to more specifically relate these conclusions to individual endpoints, rather than major outcome categories. The addition of text describing pre-promulgation history of the Lead NAAQS is also an important addition to the document. However, the historic discussion does not emphasize that the review process for criteria pollutants was modified between the 2006 and 2011 five-year reviews for lead. The changes implemented markedly decreased the scope of the review, analyses, and conclusions available to those making policy determinations. This issue is discussed in more detail in my Policy Assessment (PA) comments.

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

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.

The revisions to Chapter 1 have improved the readability for a non-technical audience. The call-outs added to Chapters 1 and 2 are a distinct improvement and convenience in reviewing the document. The

updates are reflective of the critical revisions in the individual chapters. The introduction, however, could perhaps reflect a bit more of the Preamble, and the criteria for determining "Policy Relevant Considerations" if the Executive Summary is intended to be a stand-alone section.

Chapter 2 "summarizes and synthesizes the recently available scientific evidence … to best inform the review of the current NAAQS…". The discussions and associated Tables provide an effective summary and pertinent discussion of the health effects endpoints that should be considered in the policy review. The analysis of health end points reflects the considerable knowledge base that has evolved regarding lead health effects over the past three decades. Nearly 74 pages in this chapter are dedicated to health effects in this summary. Conversely, 5 pages summarize sources, ambient concentrations, exposure, toxicokinetics and biomarkers. No pages discuss production, use, and disposition of lead in US commerce.

The summary does indicate that lead is multimedia pollutant and that consideration of the behavior of lead in other media is important to understanding the sources, transport, exposure and integrative effects of lead toxicity. However, EPA has forgotten that lead, as opposed to other criteria pollutants, is a commodity ubiquitous in society. Lead continues to be mined, refined, produced, fabricated, utilized, disposed of, recycled and recovered, remanufactured and redistributed; and offers the opportunity for human exposure throughout this cycle. The EPA's policy decisions with respect to regulating certain segments of the lead cycle will always have health significant effects somewhere else. The CDs and Staff Papers of the 1970s, 80s and 90s, and to a limited extent in 2006, addressed lead's role in society and exposures and policies in regulating lead throughout this cycle. The decreases in US population's blood lead levels and associated health effects were not achieved solely from the NAAQS. This public health success story was the result of integrated efforts across a number of regulatory programs and voluntary actions informed by multi-media multi-disciplinary, and multi-programmatic efforts.

There is little doubt the NAAQS was a key component in achieving these reductions, and had positive indirect effects on public health by inducing the substitution of non-lead alternatives for many of society's uses. However, there were also negative impacts, often associated with the relocation of processes, emissions, exposures and disease beyond the jurisdiction of the NAAQS. The decisions to discontinue monitoring and assessment of lead's behavior in US and global commerce deprives policy-makers and critics the opportunity to assess and address these effects. In that regard, the synthesis fails to "best inform the review of the current NAAQS".

Comments on Chapter 4 – Exposure, Toxicokinetics, and Biomarkers

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 comprehensively provides an accurate interpretation of the science as related to exposure, toxicokinetics, and biomarkers that is reflective of the current understanding and practice in risk assessment activities. The overall discussion of the health significance and interrelationship of the toxicokinetics and biomarkers is informative and well presented. This chapter also provides a concise

summary of exposure / blood lead relationship representative of the current scientific consensus for this important segment of risk assessment process.

Both Chapters 3 and 4, however, remain biased toward the gasoline phase down in this regard and should note the significant emission and air lead reductions achieved in the vicinity of point sources. The major reductions in point source emissions were achieved through a combination of pollution control and relocation of the industry. The export of the mineral processing operations had profound effects with respect to risk co-factors in the US and exposures abroad. Also important in the US were effects associated with decreases in other metal-related pollutant concentrations decreases in other media and levels of ecological risk, both locally and regionally. These effects were both attendant to and independent of the phase down and curtailments in industrial emissions.

The addition of Table 4-2 to showing IEUBK predictions of pathway contributions to concurrent blood Pb levels is illustrative of the multimedia aspects of lead exposure. Presenting the potential biases and factors possibly affecting observed air-to-blood relationships improves the discussion.

Dr. Gail Wasserman

Overall this reads very well, and is a sound document. Staff have managed to integrate an extraordinary amount of information and to employ useful framework(s) for critically reviewing and integrating information. Well done!

Preamble

This section reads well and is clearly presented.

Smaller edits:

P lvi L 32 perhaps should read: "methods is completely satisfactory"

P lxiv L 18 extra word? "the ISA evaluates results from across epidemiologic studies that characterize"

Chapter 2

(1) Highlighting the public health significance of cognitive and cardiac endpoints is an improvement.

P 63 The Weiss Hypothetical model. I very much appreciate this revision's clarifying that this is not based on actual data. These issues are addressed more fully in chapter 5 (p). In this instance, however, it would be better to be consistently precise, so as to not lead to misinterpretation by a reader who does not take the time to get to Chapter 5. In particular, it would be better if:

L 9 use "across the full range of IQ" instead of "with high and low intelligence"
L 13 insert "in this model, a" : For example [in this model, a], small shift in the population mean IQ may result in a substantial increase in…

(2) Other conclusions

P 70 L 19 Discussion of the timing of exposure: could insert "and in children". The document should cite our comparisons in the Yugoslavia cohort of children whose exposure was stable and those for whom it increased, examining contribution of different developmental periods to intelligence: Wasserman, G.A., Liu, X., Popovac, D., Factor-Litvak, P., Kline, J., Waternaux, C., LoIacono, N. & Graziano, J.H. (2000) The Yugoslavia Prospective Lead Study: Contributions of prenatal and postnatal lead exposure to early intelligence, Neurotoxicology and Teratology, 22, 811-818. This paper was not mentioned in the section in Chapter 5 on the review of the timing of exposure.

Smaller edits:

P 16 L 10 word missing "on tests [of]"
L 12 typo: omit "but"
L 27 SES refers to socio-economic status, not "Social Economic Status"

P 17 and P18 The sections on the various behavioral outcomes in children (attention problems, internalizing problems, conduct problems) correctly include mention of whether or not studies adjusted for parenting behavior. On the other hand, there is no mention of the contributions of parental psychopathology, which in most instances is contributory. See my discussion below of Chapter 5, charge point 4.

P 75 L 16 typo: increased[d]

Chapter 5

This chapter, which is so very extensive, works much better with the new framework.

(1) New system for organizing and inter-relating the cognitive and behavior outcomes into broader categories works very much better. The places that still need some work to be consistent with standard practice include:

P 170 L 24-25 I think the text means to refer to the various ways "conduct problems" is measured, not to different kinds of problems. Oppositional behavior is the more general terms that encompasses Oppositional Defiant Disorder. "opposition defiance" is not a meaningful term. In that case, the text should read " that examined different [measures of] conduct problems (i.e., opposition[al behavior], delinquency, externalizing problems

P 183 L1 I don't know what distinction the text means to convey by parsing into "psychopathological effects" vs such things as "aggression and criminal behavior" (which would also denote psychopathology). Perhaps what is meant is disorder vs behavior, in which case this sentence should read "Studies of Pb exposure and behavior in adults have focused on [disorder? Mental health conditions?] rather than aggression and criminal behavior.

L 7-8 The measures are symptom checklists, so the sentence should read: "…Pb levels with [symptoms of] depression and anxiety "

P 221 L 27 schizophrenia is NOT a mood disorder

P 257 L 13 I think the text is referring here to "depressive [symptoms]"

P 277 L 15. I am not sure what the three constructs are supposed to be here, as "phobic anxiety" is a sub category of "anxiety" .

(2) Concerns about discussion of appropriate parallels across species for nervous system endpoints largely met.

(3) Merging discussion of epidemiologic and toxicologic evidence by outcome is a useful integration.

(4) Expanded discussions that provide additional details on strengths and limitations of the evidence is very helpful. Two concerns about presentation of confounding remain:

In several places (P-154 L 34, and P 161 L17, and there are more) adjustment for parental psychopathology in models predicting child psychopathology is couched in text about the degree to which parental disorder does or does not relate to caregiving behavior, almost as a disclaimer. On the other hand, parental disorder is likely considered in these studies, not just a proxy for parenting behavior, but as a direct contributor. Most types of child behavior problems, including inattention, hyperactivity, conduct problems, and anxiety are highly heritable. There is a good discussion of these points on p 5-159, but perhaps this should come earlier and then that disclaimer would not have to reappear again and again.

Subcategories within cognitive and behavioral functioning are usually substantially intercorrelated, making examination of specificity complicated, and this should be noted somewhere. For example P 174 the text should point out that externalizing and internalizing (and indeed, most forms of mental health problems) are positively correlated. This is the case for cognitive outcomes as well, where intelligence is related to working memory, executive function, etc.
P 227 L 9 This is not a limitation of the prospective studies, but of studies, in general, that examine development

(5) Revisions that prioritize studies to emphasize those with the strongest design: this is very helpful!!!

Other edits

5-57 L 11. It is worth noting that in Wasserman et al 2000, we compared the impact (on intelligence at 3,4,5 and 7y) of changes in BPb among those whose exposure was stable, vs not: and the results showed a stronger impact of prenatal exposure, although even adjusting for prenatal exposure, postnatal exposure still had significant negative associations.

5-60, as well as subsequent Table 5-3. This is a discussion of the findings from the Lanphear pooling of the prospective studies. The text refers to the findings that pertain to the full pooled sample of 1333 children. The first row of Table 5-3, which provides supportive information for the Lanphear analyses refers only to the subset of 103 children with BPbs < 7.5. For clarity, perhaps information on both full and subset samples should be presented. Further, there should be some note that the Bellinger, Wasserman, and Dietrich data (and others) ALSO appear in the Lanphear report?

P 225 The section on the timing of exposure should include reference to Wasserman, G.A., Liu, X., Popovac, D., Factor-Litvak, P., Kline, J., Waternaux, C., LoIacono, N. & Graziano, J.H. (2000) The Yugoslavia Prospective Lead Study: Contributions of prenatal and postnatal lead exposure to early intelligence, Neurotoxicology and Teratology, 22, 811-818. In this paper, considering changes in blood lead levels measured during pregnancy and annually thereafter, we found that both prenatal levels as well as postnatal changes relative to prenatal levels adversely impacted child IQ. Associations with prenatal BPs were, however, stronger.

P 253 The section on public health significance: Chapter is much improved by the inclusion of this section
Smaller edits

5-74 L 26. Should read "not necessarily STRONGLY correlated" Bayley and later IQ are generally positively (and significantly) correlated, but the strength is less than for relationships across later ages.

5-101 L 23 should be STROOP test

5-139, last para: the decision about which studies of inattention were most weighted seems sound

5-140. L 22: should read "evidence in both"
L. 26 The proper spelling is Somerville

5-141 L 3: "responses"

P 160 L26 typo

P 170 L 34 provide citation for "the authors…."

P 181 L 15 what are the three self-reported disorders?

P 197 L 10 did

P 264 L 10 The proper spelling is Somerville

Chapter 6

(1) How successful is the new classification system for considering risk factors that has been incorporated into the third draft Pb ISA, whereby each factor was evaluated and classified based on the weight of evidence within and across disciplines?

This is clearly presented, and is a useful means of organizing the information presented.

(2) How useful is new approach that evaluates the adequacy of numbers of studies for health endpoints for examining the magnitude of the modification by that potential at-risk factor across studies?

Sections on risk include multiple endpoints and different associations between risk and vulnerability (sometimes, for example, for males, sometimes for females), which is confusing. Each section's last paragraph draws this out concretely, but perhaps this should be stated in the first paragraph for each section, so that the reader is not searching for common factors that are not there.

<u>Smaller edits</u>

P 1 L 27-28 not a sentence

P 5 L 13 confounders?

L 24-25 since this section considers both human and non-human studies, it would be clearer if for each point, the text could clarify which species is studied

P 8 provide units for Table

P 18 Section 6.2.6. It would be better if here the text mentioned the direction of associations

P 26 L 18 interaction(s)

P 26 L 13-14 species

The last paragraph on this page should reword its conclusions to be clearer.

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Comments on Chapter 6 - Potentially At-Risk Populations

Overall this chapter is comprehensive and I have just a few suggestions:

6-1, line 31: I suggest that after "SES may affect…" please add "housing, proximity to increased sources outside the home and malnutrition, and altered levels of household stress and mental health problems among family members."

6-1, line 32 add "and diminished access may deprive families of lead prevention screening and counseling."

6-4, line 12: Please consider adding "Infants also absorb lead more efficiently from their gastrointestinal tracks than older children and adults." There are multiple citations supporting this.

6-6, line 15: Please consider adding "respiratory rates" after "increased."

6-21, line 25: after 12% please add "(a measure both of iron deficiency without accompanying anemia and of iron deficiency anemia)".

6-22, just before **Older Adulthood**: I suggest that we discuss the fact that there is insufficient data to identify critical windows of exposure, or whether peak blood lead levels, or cumulative exposure over the preschool period or shorter periods of time before school age appear most predictive of IQ loss and neurocognitive problems.

6-30 **Pre-Exisiting Conditions:** I believe we should acknowledge that there are many childhood conditions, that collectively account for a substantial percentage of children, for whom there might be hypothetical reasons to predict increased (or decreased) vulnerability to lead exposure, such as low and very low birth weight; prenatal exposure to alcohol, cocaine, heroin and tobacco; birth asphyxia; serious head trauma; and numerous genetic conditions associated with developmental delays. Also, children with sickle cell anemia are at increased risk for peripheral neuropathies I believe.

6-33 **Smoking Status**: while we mention the one paper on prenatal tobacco smoke exposure and lead exposure being associated with higher odds of ADHD, I do not believe that there has been investigation of the relationship of SHS, either by parent report or biomarker measurement such as cotinine level, and IQ or neurocognitive problems.

6-34 **Socioeconomic Status And Race/Ethnicity**: We need 2010 census data…the demography of the US population has changed profoundly in the past 10 years with more children living in poverty and significantly increased absolute #s and percentages of children who themselves or whose parents have emigrated from Asia and the Middle East and we have no data about the lead exposure of these children or their parents.