

07-19-11 Preliminary Draft Comments from Clean Air Scientific Advisory Committee (CASAC) Lead Review Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

**Preliminary Comments from Members of the CASAC Lead Review Panel on
EPA’s Integrated Science Assessment for Lead (First External Review Draft – May 2011)
(Updated July 19, 2011)**

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Comments from Mr. George A. Allen

Comments on Chapter 3 - Ambient Lead: Source to Concentration

Charge Question 3: To what extent are the atmospheric science and air quality analyses presented in Chapter 3 clearly conveyed and appropriately characterized? Is the information provided regarding Pb source characteristics, fate and transport of Pb in the environment, Pb monitoring, and spatial and temporal patterns of Pb concentrations in air and non-air media accurate, complete, and relevant to the review of the Pb NAAQS? Does the ISA adequately characterize the available evidence on the relationship between ambient air Pb concentrations and concentrations of Pb in other environmental media?

Overall, the document is well written, comprehensive, and reflects a very detailed review by EPA staff of all aspects the state of the science. As with the O3 ISA, it may be too comprehensive in some areas, and could benefit from editing to reduce the overall length and improve the focus of the chapter.

A notable omission in section 3.4.1 is any discussion of current work being done by EPA to develop a better “uber-coarse” sampler for Pb greater than 10 um. This section discusses the substantial limitations of the present HiVol FRM sampler for Pb, but doesn’t suggest anything better other than PM10, which can underestimate Pb in some near-source scenarios (but not GA airports). ORD needs to publicly commit to the work already underway to develop a low-vol “larger” particle sampler in time for designation as a Pb FRM for this review cycle.

Another area of general concern is that there is no meaningful discussion of Pb in wildfire and residential space heating woodsmoke. There is Pb in WS, and especially for valley towns where WS concentrations can be high for much of the winter, this maybe the primary air exposure pathway for “new” Pb. Page 3-102, line 28 notes that fine Pb is fairly soluble, and thus would be expected to be present in wood, just as Hg and sulfur are, especially in the eastern US.

Specific comments follow (page, line[s]).

3-2, 14-16: The 2008 NEI does report GA aircraft as 49% of all Pb emissions, but the % that is relevant to human exposure is likely much much less, since most of those emissions are at altitude and are in the fine mode; thus they may deposit as wet Pb, or deposit outside of the US. Thus, the impact on “new” ground level air Pb is likely to be much less than the emission inventory suggests. The way it is stated here may be confusing in this context. I fully support the phase-out of Pb in AvGas on general principle, but I am not convinced that AvGas Pb is a significant exposure in the context of the current Pb NAAQS.

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3-4, 8 and 15-16: it may be worth noting that this smelter (Doe Run in MO, the largest single point source of Pb in this country) is closing by the end of 2013 -- sooner than the binding 2016 date. This event would present a rare opportunity to study the changes in soil Pb over time after the smelter closes. EPA should fund an extra-mural study (STAR?) that starsampling a year before the smelter shuts down, insuring that near-soil sampling areas are isolated from potential cleanup efforts required by the settlement.

3-5, 5: same issue as pg 3-2, above.

3-7, 3: The median Pb value should be reported here, since the data are highly log-normal. The 0.3 ug/m³ value shown here is an outlier in this study; this should be noted. There is also substantial uncertainty in the data quality for this sample; given the lack of runtime data, this sample would be voided in AQS. For the very first sample day to be much higher than subsequent samples makes the sample further suspect, including the high sample from site A that same day.

3.2.2.5 [Roadway sources]: While Pb wheel weights are currently a major source, it should be noted here that several [at least 7] states have already banned their use, and EPA is planning a NPRM in 2012 to ban them. Once banned, their use will drop rapidly. More quantitative information on Pb in tires would be helpful to better understand their contribution to NR Pb.

3-14, 6: The discussion abruptly switches from Pb-PM to PM concentrations. Is it intended to be "Pb-PM" on this line?

3-17, 10-13: Pb in WS, and 3-22, 26-29: these cites seem to contradict each other re: Pb in wildfire WS. See general comments above.

3-53, 22-26: it should be noted that the dichotomous sampler is a preferred way to measure Pb-coarse in areas where the fine to coarse Pb ratio is greater than 1. There a dichot sampler currently approved as an FEM for PM-coarse.

3-56, 10: says 9 elements from Improve, but there are up to 24 reported. Some may be of use in this analysis.

3-60, 19-22: Can the single particle mass spec method measure large Pb without substantial losses in the sample train?

3-69, 8-14: should tires as a source of near-road (NR) Pb be noted here? As Pb wheel weights are phased out, tire wear may become [one of] the largest NR Pb sources of "new" Pb.

3-69, 29-32: 8 ng/m³ Pb isn't much of an industrial source value; this needs clarification.

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3-104, 3: “lower rate of error” -- a different term [precision?] should be used here.

3-104, 28-31: it is unclear what dataset is being summarized on line 31.

Comments from Dr. Herbert E. Allen

Comments on Chapter 2 - Integrative Health and Ecological Effects Overview

The authors have prepared a very well-written overview of the health and ecological effects of Pb. There are several items that should be modified and there is some recent literature that could be incorporated. The items in this review are presented in the order they appear within the chapter.

2-7 line 8. The correlations of Pb with Zn, Br, Cu, and K should be further investigated. Page 2-2 line 28 indicates that ~49% of total atmospheric Pb emissions come from piston engine aircraft. With such a high percentage of the emissions arising from a single source, for the correlations of Zn, Br, Cu, and K indicated in page 2-5 line 8, the emissions of these elements from piston engine aircraft would necessarily need to be high relative to other sources. Certainly, this is likely for Br (in the absence of a significant sea salt input). However, is it also reasonable for the other elements? Emission factor data and very simple modeling should be used to resolve this rather than just providing a speculation. Also, in line 7 “metals” should be replaced by “elements” as Br is not a metal.

2-7 lines 23-25. Even in areas not near smelters the smelters in operation prior to modern control technologies were responsible for a large amount of the emissions of metals to the atmosphere. How important are historic mining and smelting as the origins of Pb in soil and sediment?

2-10 Section 2.5.1. Neurological Effects is very well presented. It does an excellent job of integrating the information.

2-30 lines 14-16. Aging of lead and other metals in soil is an important phenomenon that greatly affects bioavailability. The fundamental physicochemical processes involved in sorption must be understood and formulated into appropriate kinetic models of sorption that incorporate chemical speciation.

2-34 lines 17-19. The LC50 is a poor measure to compare to environmental concentrations. Most LC50 values are for acute, not chronic, exposures. Consequently, if the environmental concentration were to reach the LC50 value it is unlikely that there would be a sustainable population. A lower toxicity, such as LC5 or LC10, is more reasonable to compare to environmental concentrations.

2-34 lines 29-30. This 50-fold range in the LC50 value for larval fathead minnows for differing pH and concentrations of DOC and CaSO₄ clearly demonstrates the importance of the chemistry of the exposure medium to the effect. The importance of these factors that modify toxicity and

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are accounted for by the Biotic Ligand Model (Di Toro et al., 2001).

2-35 lines 13-14. Many of these Pb concentrations exceed its solubility. Such data have historically confounded the literature and have necessitated additional studies of toxicity.

2-38 lines 2-9. Do the adverse effects of Pb on reproduction in invertebrates and vertebrates occur at environmental concentrations of Pb?

2-40 lines 1-4. The sediments used in this study were oxidized by the sample treatment process. This would have eliminated acid volatile sulfide from the sample and modified the bioavailability of the added Pb. Thus, the sediments cannot be considered to be in their natural state and caution should be applied to the interpretation of this and to other studies in which the sediment chemistry has likewise been modified.

2-40 line 31. Sulfide should be added to pH and organic matter as an important environmental variable that affects Pb bioavailability and toxicity.

2-41 lines 4-16. The EPA Equilibrium Partitioning Sediment Benchmarks (Hansen et al., 2005) should be mentioned. These provide a means to evaluate which sediments will not exhibit toxicity.

2-43 lines 13-16. I do not understand the sentence “The level at which Pb elicits a specific effect is more difficult to establish in terrestrial and aquatic systems due to the influence of environmental variables on Pb bioavailability and toxicity and substantial species differences in Pb susceptibility.” What is implied in the phrase “more difficult to establish in terrestrial and aquatic systems”? Is this a comparison to human health? These and other environmental variables affect the bioavailability for humans.

References

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Comments on Chapter 7 - Ecological Effects of Lead

The authors have prepared a very well-written and comprehensive review of recent literature on the ecological effects of lead. There are several items that should be modified and there is some recent literature that could be incorporated.

7-9 line 28 through 7-10 line 4. Great care should be exercised in the use of selective extraction data such as the results of Ettler et al. (2005) cited in the ISA. The assignment of specific geochemical associations to the results of these extractions has been demonstrated not to be valid by a number of researchers (e.g., Tipping et al., 1985; Rapin et al., 1986; Kheboian and Baur, 1987; Martin et al., 1987; and Qing et al., 1994). Not only are metals released from the indicated geochemical phases indicated, but they are also released from other phases. Although Ettler et al. (2005) assumed the extracted fractions were related to bioavailability, no bioavailability was actually determined. The lack of any toxicity or metal uptake data in their paper does not provide the necessary level of assurance that the results of these extraction procedures can be used to infer relative bioavailability. Indeed, there is not even a citation to any published study in which such a relationship has been demonstrated.

7-11 line 28 through 7-12 line 3. What this and other studies actually show is that relating effects to total concentrations of metal in soil (mg/kg) is inappropriate. The better effects relationships that were found with respect to the soil pore water concentrations are because the pore water represents the equilibrium partitioning and thus bioavailability.

7-35 lines 20-21. New exposure-response data are presented in several papers (Chen et al., 2010; and Kopittke et al. 2011).

7-36 line 31. ISO is the International Standards Organization. It is not a European methodology.

7-65 lines 14-18. Here and in a number of other places, BCF and BAF factors have been used. However, BCF is a poor factor to use in the hazard assessment of metals. Bioaccumulation factors are used as an important aspect in the hazard assessment for hydrophobic organic compounds (e.g. PCBs and DDT). For such compounds the BCF for a biological species is approximately constant and the concentration in the organism is proportional to the concentration in the environment (Chapman et al., 1996). Thus, high BCF values indicate highly bioaccumulated materials that warrant consideration for regulation as a consequence of the biological effects that these materials may cause in the organism or to the food chain. However, this is not the case for metals (with the possible exception of mercury). The BCF for an organism is not a constant, but is highly dependent on exposure conditions, including the concentration of the metal in the environment. A very extensive study of the relationship of bioaccumulation to exposure concentration of metals, including lead, has been published by McGeer et al., 2003). They found that in almost all cases the BCF decreased with increased exposure concentration. Thus, if one considers a high BCF as a predictor of hazard, increasing

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the environmental concentration of the metal would then lead to a lower anticipated hazard. Clearly, this is not the case. The error lies in consideration of BCF values for metals as anything more than the ratio of two values, the concentration in the organism and the concentration in the environment. As this ratio is not a constant, it not only lacks any predictive or assessment value.

Problems with the BCF can be further seen in the present document. Consider the data for BCF for aquatic plants. In the 2006 report the range of BCF values was from 840 to 20,000. The new data in Table 7-3 has a range 0.01 to 1500. The maximum value for the new data is less than a factor of 2 greater than the minimum value in the older report. The total range of BCF values is now 0.01 to 20,000. This is a range of 2,000,000. Furthermore, the range of BCF values for duckweed (*Lemna* sp.) is now 0.01 to 3,560. This is a range of 356,000 which clearly is too great to be of any use in assessments. Furthermore, if the maximum and minimum values are considered, very different conclusions can be drawn regarding the potential hazard of lead. The low BCF value of 0.01 indicates that there is no hazard of Pb. The high BCF value of 3,560 is above a commonly used assessment criterion of 1,000 and suggests that Pb is a hazard. Clearly, BCF is an inappropriate measure to assess the hazard of Pb. The document needs to provide a better assessment of the utility (or lack thereof) of BCF values rather than simply reporting the data from the literature.

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Tipping, E., Hetherington, N.B., Hilton, J., Thompson, D.W., Bowles, E. and Hamilton-Taylor, J. 1985. Artifacts in the use of selective chemical extraction to determine distributions of metals between oxides of manganese and iron. *Anal. Chem.* 57: 1944-1946.

Comments from Dr. Deborah Cory-Slechta

Comments on Chapter 5 - Integrated Health Effects of Lead Exposure

General Comments

1. Several places in the text refer, especially in describing in vitro studies, of the use of 'levels as low as' or 'to as little as' and then cite concentrations that are not considered low. Certainly 1 uM is not a low concentration. And in some cases (e.g., p. 5-6), a level of 5 uM is listed as low. It would be useful to provide some context about the relationship of in vitro exposure levels to human exposures and blood Pb levels.
2. In descriptions of some human studies, the population described as controls have blood lead levels in the range that are now considered to be associated with effects, even in some adult studies. This should be pointed out and the effects of the study qualified accordingly.
3. There are many examples of studies of gene-Pb exposure interactions throughout Chapter 5 describing the health effects of Pb. None of these describe the magnitude of the effect of this interactions. Are these actually biologically relevant or of such small magnitude as to not be pertinent? Here too context is important. All such interaction outcomes where cited should include information on the extent/magnitude of the effect.
4. In cases of interaction effects, i.e., effect modification, it is not always possible to rule out the fact that the interaction was due to altered lead toxicokinetics. For example, numerous studies are cited in which anti-oxidants are stated to reverse effects of Pb. The description of these studies is generally not sufficient to fully understand the methodological details. But it was not always clear that some anti-oxidant, for example, co-administered with lead did not reverse its effects per se, but instead, altered its toxicokinetics. This would significantly alter the presumed (and often stated) interpretation of anti-oxidant mechanisms.
5. It would be far preferable and facilitate comparisons if all blood lead measures used the same units, preferably ug/dl; this may mean converting the units used in some of the cited studies.
6. The importance of effect modification is included in some places in the document, but it would be useful to address it in the summary of health effects as well, particularly as, dependent upon the context, it can result in effects of lead at even lower levels of exposure than when lead occurred in the absence of that modifier. Gender is also an important effect modifier and it is particularly astounding, given the size of the lead literature, how little we know about gender differences, but they are, when examined, far reaching.

Specific Comments

1. p. 5-44, lines 16-36. One interpretation that has to be considered with respect to studies of life stages of vulnerability is that the early effects of lead exposure on intellectual function cause early academic retardation that by itself, above and beyond subsequent lead exposure, would itself lead to later academic problems. Clearly, children who do not learn the basics early in school will have increasing problems later on because of that.
2. P. 5-51. It would be helpful and easier for the reader to have the same y axis values on all 4 plots in Figure 5-3 as it allows direct comparison of the magnitude of effects across conditions.
3. P. 5-52 and 5-53, Specific Indices of Cognitive Function. It is surprising that no mention is included here of the Canfield et al., 2004 study.
4. P. 5-61 lines 27-29. Albeit limited, the brain does generate stem cells as well, which this statement ignores.
5. P. 5-62, lines 32-35. This statement is a gross over-generalization as it is already clear that different environmental toxicants/insults differ in their impacts on males vs. females.
6. P. 5-68, lines 1-19. The point of the paragraph is not really clear.
7. P. 5-73, lines 1-16. It is important to continue to point out that questions regarding differences in sensitivity of different developmental periods of exposure in human studies will always be complicated by the problem that the measures at different stages differ in their sensitivity.
8. The section beginning on Toxicological studies is confusingly organized. For example, why are studies of morris water maze on p. 5-75 lines 1-2 and 5-76 lines 1-21 separated out; these are essentially studies of learning as are studies subsequently described on p. 5-77 lines 12-28 and subsequently.
9. The statement on p. 5-77 lines 1-2 stating that deficits in working memory are thought to underlie the associations between blood Pb levels and ADHD in humans is highly simplistic and not reflective of the literature in general on ADHD.
10. P. 5-79 Figure 5-13; it is important to point out that offspring stress was actually PS followed by OS, not OS alone.
11. P. 5-83; the word water appears to be a mistake in the title for Table 5-8
12. P. 5-84; there was a prior study by Brockel and Cory-Slechta in 1998 where postweaning Pb exposures associated with blood Pbs of 9 ug/dl were likewise not affected in a sustained attention task.
13. P. 5-85, lines 27-32. This summary seems highly overstated and over-generalized based on what is a very small literature.
14. P. 5-94, Figure 5-17. The magnitude of effect in this study was very small and this figure provides an artificial amplification that is misleading.
15. P. 5-98 and 5-99. It is not clear why Canfield et al. 2004 is not included in this section.
16. P. 5-108, lines 24-26; Toxicological Studies of Neurobehavioral Outcomes. What references support statements such as cerebellum as a target of Pb?
17. P. 5-11-, lines 15-16; again, this is an over-generalization.

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18. P. 5-112, line 18, please note psychological stress is not necessarily a negative factor. Indeed, a growing literature documents the ability of early stress to promote resiliency.
19. P. 5-113, lines 3-5; the original reference is not White et al., but Cory-Slechta, 2004.
20. P. 5-114 and p. 5-119, lines 3-13. The changes that occur in auditory brainstem evoked response, found in both human and animal studies, seem to be suggested only as related to hearing deficits. In fact, however, alterations in interpeak latencies are clearly indicative of myelination status as well as impairments in synapse formation. This is never mentioned.
21. P. 5-117. The use of the phrase gestational Pb exposure in a rodent model is likely overstated; it is impossible to turn off exposure to the offspring specifically at PND10 given the kinetics of Pb.
22. P. 5-123, line 21. The use of the adjective 'old' in referring to 12-14 week old rats is a mis-statement; that adjective is used for animals that are significantly older, e.g., 18 mos of age.
23. P. 5-125, line 28. It should be noted that no dementia has ever been established in these models, however.
24. P. 5-135, lines 2-4. The notion that strategies involving glial transmission or D-serine supplementation might be used for Pb exposure is premature and also not realistic for low level Pb exposure, particularly given that it is likely to have multiple other effects. It is not clear that this statement belongs in the document.
25. P. 5-138, lines 11-12 suffer from the same issue described in #24 above.
26. P. 5-143, comparisons of magnitude of lead effects across sociodemographic groups may well be confounded by floor effects, i.e., it would be difficult to pick up as great an effect in low SES communities, where average IQ score, for example, may already be quite low.
27. P. 5-147, lines 21-23. This seems like an overstatement of the animal literature and is very likely to depend upon the outcome measures that are used; postweaning rats are very sensitive to lead and in fact effect in that model have been reported at blood Pbs of 9 ug/dl, the lowest levels examined to date. Unless some specific references can be provided demonstrating actual comparisons across more than one endpoint, this statement should be qualified.
28. P. 5-178, lines 1-8. What is the magnitude of the change caused by the polymorphisms?
29. P. 5-189, line 11, no year for the reference
30. P. 5-228, lines 21-31. Since the actual exposures protocols are not explicitly described, it is not evident that the antioxidants worked not by reversing oxidative stress, but by toxicokinetic mechanisms, decreasing lead uptake for example, which would lead to quite a different interpretation of the results. This issue applies to other sections describing reversal of Pb effects by e.g., antioxidants, chelators, etc.
31. P. 5-229, lines 1-16. This paragraph again underscores the importance of breaking out gender in both toxicological and epidemiological studies.
32. P. 5-229, lines 24-26. It isn't clear how this interpretation relates to this study, since lead is not 'metabolized'.

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33. P. 5-231, Figure 5-46. It would be very helpful if additional ticks could be added to the x axis.
34. P. 5-232, Section 5.5.4 Effects of Exposure to Lead Mixtures. An important study by Mejia et al. 1997 is relevant and should be cited here as it appears to show that lead content in brain tissue can be increased by co-exposure to arsenic.
35. P. 5-233, line 33, the year is missing for the reference.
36. P. 5-267, line 9, reference is missing the year.
37. P. 5-272, line 19, seems to be inconsistent with p. 5-271.
38. P. 5-287, lines 21-23, what is the magnitude of the effect of the polymorphism?
39. P. 5-317, line 12, missing the reference.
40. P. 5-360, line 9 and line 29, missing reference.

Comments from Dr. Cliff Davidson

Comments on Chapter 1 – Introduction

The selection criteria for inclusion of studies seem reasonable. The decision to focus on exposures within one order of magnitude of current exposures also seems reasonable. There are some specific comments regarding Chapter 1, as follows.

1. Figure 1-1 states that studies not addressing exposure and/or effects of air pollutants under review are excluded. But the text states (on page 1-9, lines 18-23) the following:

“All relevant epidemiologic, animal toxicological, and ecological and welfare effects studies published since the last review were considered, including those related to exposure-response relationships, mode(s) of action (MOA), and susceptible populations. Additionally, air quality and emissions data, studies on atmospheric chemistry, environmental fate and transport, as well as issues related to Pb toxicokinetics and exposure were considered for inclusion in the document.”

Thus it appears that studies addressing emissions, atmospheric chemistry, and fate and transport, in addition to exposure and effects, were included in the document.

2. Typo on page 1-13, lines 3-5 (“informs” should be “inform”):

3. Also on page 1-13, the text states:

“These MOAs, as they pertain to Pb exposures of short or longer duration, informs our understanding of indirect effects that Pb may exert more broadly on ecosystem structure, function and services.”

What are “MOAs”? This abbreviation is not in the list at the front of Chapter 1.

4. Page 1-16, lines 22-28 deal with causality for direct human exposure in controlled chambers. This is irrelevant for Pb, since there are no human chamber studies for this pollutant, so this paragraph may be considered unnecessary. The paragraph is as follows:

“Causality determinations are based on the evaluation and synthesis of evidence from across scientific disciplines; the type of evidence that is most important for such determinations will vary by assessment. The most direct evidence of a causal relationship between pollutant exposures and human health effects comes from controlled human exposure studies. This type of study experimentally evaluates the health effects of

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administered exposures in human volunteers under highly-controlled laboratory conditions. Controlled human exposure studies are not done for Pb, and thus, are unavailable for consideration.”

5. Section 1.6.2 begins by defining “causality” and “association” on page 1-17. It might be better to move these definitions earlier – for example, section 1.6 starts on page 1-15 and starts using the terms well before they are defined.

6. The following sentence on page 20, lines 22-24, is grammatically incorrect:

“Confidence that unmeasured confounders are not producing the findings is increased when multiple studies are conducted in various settings using different subjects or exposures; each of which might eliminate another source of confounding from consideration.”

Comments on Chapter 2 - Integrative Health and Ecological Effects Overview

This chapter appears to be a useful summary of the rest of the document. The key challenge in communicating the ISA results to varied audiences is that there is a lot of information included in the ISA, and it will take some effort for readers to track down what they are looking for. Is it possible to develop an alphabetical index by topic areas? The framework for causal determination seems reasonable, and it appears to have been applied in a reasonable way. The integration of findings in the literature across health and ecological studies also appears to be reasonable. There are some specific comments with regard to Chapter 2, as follows.

1. On page 2-3, lines 8-9, the text states:

“Global atmospheric Pb deposition peaked in the 1970s, followed by a more recent decline.”

What is the purpose of “more recent” in this sentence? Shouldn’t this be simply “followed by a decline”?

2. On page 2-4, lines 1-2, the text states:

“The FRM is based on flame AAS. ICPMS is under consideration as a new FRM for Pb-TSP.”

Perhaps the reasons for the delay in obtaining acceptance of ICP-MS could be mentioned.

3. On page 2-4, line 11. Typo: “network” appears twice.

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4. On page 2-4, lines 16-17: The following sentence seems obvious – not sure why it is needed:

“Non-source oriented monitors were those monitors not considered to be source oriented.”

5. On page 2-10, lines 11-14, the text states:

“Both epidemiologic studies (in children) and toxicological studies, demonstrated neurocognitive deficits in association with blood Pb levels at and below 10 µg/dL, and evidence from both disciplines supported a nonlinear exposure-response relationship, with greater effects estimated for lower blood Pb levels.”

Why are there greater effects estimated for lower blood levels? This is confusing.

6. Some sections of Chapter 2 summarizing important results do not refer to the sections of later chapters where the details are found. But some sections of Chapter 2 do refer to the later chapters, such as this part of Section 2.8.4.1 on page 2-50:

“2.8.4.1. Children

Children may be more highly exposed to Pb compared to adults without occupational exposure to Pb, through their behaviors (e.g., hand-to-mouth contact). Blood Pb levels are highest among the youngest children and decrease with increasing age of the child (Table 6-1). Biokinetic factors that vary by age, including bone turnover and absorption, also affect blood Pb levels. Childhood, as a susceptibility factor related to Pb exposure and dose, is discussed in more detail in section 6.1.1.1. The kinetics of Pb, and how absorption, distribution, and elimination may vary depending on lifestage, is discussed in Section 4.2. 7

It is recognized that Pb can cross the placenta to affect the developing nervous system of the fetus (Sections 4.2.2.4, 5.3.2.1) and there is evidence of increased susceptibility to the neurocognitive effects of Pb exposure during several lifestages throughout childhood and into adolescence (for more detail, see Section 5.3.2.1). Further, Pb exposure is associated with effects on the renal (Section 5.5.2.3), immune (Section 5.6) and heme synthesis and RBC function (Section 5.7) of children. A limited number of studies of immune parameters, transferring saturation, and iron-deficiency anemia that stratified children by age report stronger associations among the youngest children. Childhood, as a susceptibility factor related to Pb-induced health effects, is discussed in more detail in Section 6.2.1.1.”

Note that there is a typo on the seventh line above (“sectin”).

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These referrals to later chapters are helpful, but listing so many sections such as in the paragraph above for all of Chapter 2 may be too time-consuming, and makes it difficult to read. In any case, there is currently an inconsistency in that some sections of Chapter 2 do not include any referrals to later chapters, while others do. Perhaps referring to major sections in later chapters would be a good compromise to apply throughout Chapter 2 (e.g., refer to sections 3.1 and 3.1.2, etc., but not 3.1.2.3).

7. On page 2-46, bottom of the page, the text states:

“The Schnaas (2004) had a particularly strong experimental design in that is the only longitudinal study in which blood Pb concentration was monitored repeatedly in individual children from age 6 months to 10 years.”

It appears that a word or words are missing. Perhaps the intended sentence begins “The Schnaas (2004) study had a particularly strong experimental design....”

8. On page 2-49, the text states:

“This body of with the addition of more recent studies is presented Figure 2-2.”

Again, a word or words are missing.

9. On page 2-50, the text states:

“Menke et al. (2006), reporting a non-linear relationships”

Note that “relationships” should be “relationship”.

Comments on Chapter 3 - Ambient Lead: Source to Concentration

The information on atmospheric sciences and air quality in this chapter appear to be a good summary. They are, in general, clearly conveyed. The information on sources, fate and transport, monitoring, and spatial and temporal patterns seem relevant and thoroughly researched. The discussion of relationships between air Pb and concentrations in other environmental media also appear to be reasonable. There are some specific comments on Chapter 3, as follows.

1. On page 3-7, the text states:

“Gidney et al. (2010) point out that, where tetraethyl Pb is used as an additive in piston engine aircraft fuel, the fuel also contains ethylene dibromide to act as a Pb “scavenging agent.” When ethylene dibromide reacts with Pb, it forms Pb bromide and Pb oxybromides, which are more volatile.”

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It is not clear why the scavenging agent is used. If ethylene dibromide reacts to form more volatile species, then there will be more Pb emitted (in gaseous form). How is that helpful?

2. On page 3-9, the text states:

“Tan et al. (2006) compared several emissions sources in Shanghai, China. They estimated emission values for on-road exhaust from use of Pb-free gasoline (238 ± 5 mg/kg), vehicle exhaust from leaded on-road gasoline ($7,804 \pm 160$ mg/kg), coal combustion ($1,788 \pm 37$ mg/kg), metallurgic dust ($6,140 \pm 130$ mg/kg), soil (11.7 ± 0.3 mg/kg), and cement (103 ± 2 mg/kg). Pb-free automobile gasoline has been in use in Shanghai since 1997. The isotope ratios for each of these emission sources were determined. Based on the 4.4×10^7 tons of coal combusted annually in Shanghai, an average coal Pb concentration of 13.6 ± 6.6 mg/kg, and an emission factor of 0.5, approximately 300 tons Pb was being emitted annually in association with fine PM. They concluded that a major priority should be to reduce Pb emissions from coal combustion now that the contribution from vehicle exhaust emissions has decreased.”

Why did the authors conclude that Pb reduction from coal should be a major emphasis, considering that Pb from leaded gasoline is four times greater? Should the last sentence state “now that the contribution from vehicle exhaust is expected to decrease in the future”?

3. On page 3-11, the text states:

“The 2006 Pb AQCD (U.S. EPA, 2006) cited an estimate by Harris and Davidson (2005) that more than 90% of airborne Pb emissions in the South Coast Basin of California were from soil resuspension. Since publication of the 2006 Pb AQCD (U.S. EPA, 2006), further analysis of the Harris and Davidson (2005) paper has revealed that the contributions of Pb from piston engine aircraft were underestimated compared with the 2002 NEI. Assumptions of spatial uniformity incurred by the “continuously stirred reactor” mass balance model and for mixing layer height used by Harris and Davidson (2005) were also not valid because Pb concentrations are spatially heterogeneous at the urban scale; see Section 3.5. Therefore, the estimate of 90% of airborne Pb from resuspension is not employed in the current assessment.”

The paper by Harris and Davidson is being discredited here, but why? The reasons do not appear to be based on sound science. If the NEI estimates of 2002 are used, the mass balance changes very little. Furthermore, many mass balances in the literature use the “continuously stirred reactor” model, and it is acknowledged in the paper as merely an estimate. There was very good agreement between the estimates cited from measurements and estimates cited from emissions data. So why exclude this value of 90% by discrediting the paper? It is the only estimate

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available, and this is a high ranking peer reviewed journal. I suggest the following revised paragraph which says the same thing without discrediting the paper:

“The 2006 Pb AQCD (U.S. EPA, 2006) cited an estimate by Harris and Davidson (2005) that more than 90% of airborne Pb emissions in the South Coast Basin of California were from soil resuspension. This value was obtained by constructing mass balances rather than direct measurements of lead alongside roads, and hence is merely an estimate. Currently, measured data are not available with sufficient spatial resolution to discern the specific contribution of soil Pb resuspension to air Pb concentration, but resuspended soil Pb cannot be eliminated as a potential major source of airborne Pb.”

4. On page 3-42, the text states:

“Additional research highlighted the importance of taking forest cycling and litter throughput account in estimating input by deposition.”

The word “into” is missing after “throughput”.

5. On page 3-52, the text discusses the rationale for choosing the TSP sampler over the PM10 sampler, and states:

“The rationale for this decision included recognition of exposure due to Pb-TSP that would not be captured by PM₁₀ sampling, the paucity of information documenting the relationship between Pb-PM₁₀ and Pb-TSP at the broad range of Pb sources in the U.S., and uncertainty regarding the effectiveness of a Pb-PM₁₀-based NAAQS in controlling ultracoarse Pb-PM near sources where Pb concentrations are highest (73 FR 66991).”

It is not clear why a measurement method with such a high variability is preferred – we won’t know how much of the Pb is associated with particle diameters greater than 5 micrometers, or even what the true concentration of particles with diameters above 5 micrometers is. I feel this is a weak justification that could be strengthened.

6. On page 3-64, the text reads:

“Non-source oriented monitors were those monitors in the system not designated to be source oriented”

I don’t see why this sentence is needed – the definition appears obvious.

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7. On page 3-76, the text reads:

“For both Pb-PM₁₀ (Figure 3-21) and Pb-PM_{2.5}, (Figure 3-22) monthly average concentrations are considerably higher in the fall than in other seasons, with lowest the three highest monthly average concentrations observed in September, October, and November, and the average September concentration more than double the average December concentration.”

It appears that the word “lowest” in the third line should be deleted.

8. On page 3-84, the text states:

“The strongest association was with Zn (median R = 0.51).”

As part of the ISA, was there any attempt to look at the literature for other chemical species, e.g., Zn, in an effort to understand the Pb data?

9. On page 3-103, the text states:

“In contrast, Pb associated with coarse PM is usually insoluble, and removed by dry deposition.”

It should be noted in the text that dry deposition may not be an “ultimate sink” because particles which dry deposit are often subsequently resuspended and redeposited many times before reaching a site where further transport is unlikely. The same is, of course, true for any deposition mechanism, but it is especially true for dry deposition onto dry ambient surfaces.

Comments from Dr. Chris E. Johnson

Comments on Chapter 3 - Ambient Lead: Source to Concentration

Chapter 3 of the ISA document is generally well written. The treatment of Pb sources, characterization of emitted Pb, and fate and transport were informative, relevant, and sufficient. The other sections were more uneven, often relying heavily on very few studies, or presenting data that were confusing or off-target. Further details may be found in my responses to the specific charge questions, and some other review comments that follow.

Specific Charge Questions:

Question: To what extent are the atmospheric science and air quality analyses presented in Chapter 3 clearly conveyed and appropriately characterized?

Others on the CASAC are better prepared to answer this question than I am. For my part, as a non-expert in the atmospheric sciences area, I found the information to be generally clearly conveyed and understandable. I do have some concerns about some of the data analyses presented in section 3.5, however. The major concerns are presented here, and a minor concern in the “Additional Review Comments” below.

The data for Pb concentration in air is cobbled together from four networks, which were set up for different purposes. None of them appear to be particularly well suited to the assessment of the level of attainment of the current NAAQS for Pb. Nor does there appear to be an obvious way to use the data from these networks to model, with high confidence, attainment of the NAAQS. This is a serious concern, and needs to be addressed, if not now, by the time of the next NAAQS review.

Section 3.5.3.1 includes a statistical analysis of the AQS data to understand the particle-size distribution of lead-bearing particulate matter. The data appear to be fraught with problems. For example, in several cases, the content of PM_{2.5} is greater than the total suspended particle content, which is clearly impossible. Similarly, some of the data indicate that the PM_{2.5} content is greater than the PM₁₀ content, which is also impossible. The document tries to draw some conclusions from these data, but I wonder if this analysis is really productive. Given the concerns that exist in the scientific community about the performance of the high-volume samplers (that are the basis of the Pb-TSP measurement), and the impossible particle-size ratios that come from the data, it might be best to scrap this analysis entirely and use the literature observations (section 3.5.3.2).

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Question: Is the information provided regarding Pb source characteristics, fate and transport of Pb in the environment, Pb monitoring, and spatial and temporal patterns of Pb concentrations in air and non-air media accurate, complete, and relevant to the review of the Pb NAAQS?

Chapter 3 of the ISA generally does a good job in the areas of source characterization and the fate and transport of Pb. The material in these sections was, I thought, generally accurate, complete and relevant.

The discussion of Pb monitoring suffered some weaknesses related to the *ad hoc* nature of the monitoring network from which nation-wide data were gathered. This issue was discussed in the previous charge question.

The presentation of Pb monitoring and the spatial and temporal patterns of Pb in air and non-air media was somewhat lacking in the areas of soil, rain, and natural waters.

Soil. The section on soil (3.6.1) focused entirely on urban/suburban soils, smelter-impacted soils, and soils affected by Pb shot. There are good, long-term studies of spatial and temporal variation in trace metals in forest soils as well which could and should be discussed here. One is the Kaste (2006) work, already cited in the chapter. Another is the work of Evans et al. (Evans, G.C., S.A. Norton, I.J. Fernandez, J.S. Kahl, and D. Hanson. 2005. Changes in concentrations of major elements and trace metals in northeastern US-Canadian sub-alpine forest floors. *Water Air Soil Pollut.* 163:245–267).

Rain. The only recent information cited in section 3.6.3 are from studies in Canada and Europe. Are there truly no recent data on the spatial and/or temporal changes in precipitation Pb concentrations from monitoring in the United States?

Natural Waters. The section on natural waters is exclusively about one study in Ontario, Canada. Is no one in the United States monitoring Pb concentrations in streams and rivers? Is no one looking at lakes?

Question: Does the ISA adequately characterize the available evidence on the relationship between ambient air Pb concentrations and concentrations of Pb in other environmental media?

The ISA does not adequately address the relationship between ambient air Pb and concentrations in other media. Having said that, one must admit that with the possible exception of precipitation, such relationships are nearly impossible to develop. This issue, perhaps more than any other, confounds efforts to develop a secondary, welfare-based standard for Pb. One exception to this criticism is the discussion in section 3.6.1 on the relationship between Pb-TSP and soil Pb in a study near El Paso, TX.

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Additional Review Comments:

3-25, lines 12-31: One factor that should be discussed in this paragraph about wet deposition is the pH of the rain. Large reductions in sulfur emissions have resulted in steadily increasing precipitation pH, especially in the Midwest and Northeast, which experienced chronic acid rain for decades. Presumably, increasing pH in water vapor will reduce Pb solubility and therefore affect wet deposition.

3-28, lines 7-9: This sentence contains an incomplete thought – “...concentrations in surface waters are highest near sources of pollution before substantial Pb by flushing, evaporation and sedimentation.”

3-39, line 33 to 3-40, line 1: “This was likely due to the presence of organic-bound colloids smaller than 0,45 um rather than true Pb dissolution.” Is this a hypothesis, or is there evidence for these “dissolved” colloids?

3-34, line 24: Some words are missing from this sentence.

3-37, lines 29-30: “The generally high dissolved Pb stores and high stream water DOC concentrations.” is an incomplete sentence.

3-38, lines 27-28: “...anthropogenic acidification of upland waters is likely to continue due to nitrogen leaching from the surrounding catchment...” This is **highly** debatable, especially in areas of the United States which are demonstrating recovery of surface water pH and alkalinity after decades of elevated acid rain.

3-73, lines 24-27: Do the data really support the generalizations made here about seasonal patterns? Looking at Figure 3-19, it looks to me like the seasonal pattern is Spring > Fall > Summer > Winter
Have appropriate statistical tests been carried out to “prove” this pattern?

3-88, Table 3-9: Is this table complete? Some lines have no Min, Med, or Max (see for example Chicago 2008 and 1987).

3-90, Figure 3-27: The figure legend should indicate what the numbers in the map itself represent. I would guess that they are the number of samples collected in each neighborhood zone?

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Comments on Chapter 7 - Ecological Effects of Lead

In reviewing Chapter 7 of the Draft Integrated Science Assessment for Lead, and reflecting on the charge questions, I focused most my attention on the areas of terrestrial systems and ecosystems-level issues. Chapter 7 of the ISA document is extremely well written, especially the sections on terrestrial systems. Summaries of relevant studies are deftly written and informative, without being overly long.

This chapter of the ISA pretty religiously restricted itself to literature published since the 2006 Air Quality Criteria Document (AQCD), and there is a lot to cover. There is almost no mention of data published before 2005, aside from comments that the recent literature confirms and expands on conclusions made in the 2006 AQCD. Presumably, this means that the authors found no reasons to re-interpret the older literature. For the most part I would agree, with exceptions noted later in these remarks.

It was sobering to see how much of the literature discussed in Chapter 7 was not done in the United States. Even European studies seem to be getting rarer. The review was heavily dependent on work done in south Asia (i.e. India) and southeastern Asia (i.e. China). This probably reflects growing concerns in those areas about metal pollution, and (generally) declining concerns in North America.

Specific Charge Questions:

Question: Effects on terrestrial and aquatic ecosystems are first considered separately. They are then integrated by classes of endpoints (bioaccumulation, growth, mortality, hematological effects, development and reproduction, neurobehavior, community and ecosystem effects). Does the panel consider this approach appropriate?

There is no perfect way to organize an integrated assessment of effects in complex systems. This seems to me to be a reasonable way to construct the assessment.

Question: Is it appropriate to derive a causal determination for bioaccumulation as it affects ecosystem services?

This is a tricky issue because bioaccumulation is at once an “effect” and a regulating ecosystem service. The mussels that accumulate Pb, for example, provide a valuable service to coastal and estuarine ecosystems, perhaps to their own detriment and the detriment of their predators. Counter-intuitively, the value of this service actually increases with increased Pb loading. This goes against the spirit of the risk assessment being attempted here, and I would suggest that it is not appropriate.

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Question: *Has the ISA adequately characterized the available information on the relationship between Pb exposure and effects on individual organisms and ecosystems, as well the range of exposure concentrations for the specific endpoints?*

This is an impossible question to answer. The literature on terrestrial effects is not deep, and I was very pleasantly surprised at the ability of the authors to uncover relevant studies in the global scientific literature. It is certainly possible that they missed some valuable studies, but I am not aware of them.

Question: *Are there subject areas that should be added, expanded upon, shortened or removed?*

The ISA treats terrestrial and aquatic ecosystems separately. This editorial decision is expedient for a number of reasons, and I would not suggest changing it. However, one casualty of this approach is that the linkage between the two is lost. Loadings to aquatic ecosystems, especially freshwater systems, are primarily derived from the runoff of terrestrial systems. There is no discussion in Chapter 7 of the ISA of watershed processes as they influence aquatic systems. This is, in my view, a key omission.

Question: *If the ISA was expanded to consider dose-response in terrestrial systems, should we limit data to field soils?*

Given the clear effect of “aging” on the biological cycling of Pb in terrestrial ecosystems, it would probably be best to limit such an analysis to field soils. However, if the literature is not deep enough to come to any conclusions based on field soils alone, it may be necessary to use results from artificial soils (i.e., growth media).

Question: *If the ISA were expanded to consider dose-response in aquatic systems, how might we most efficiently present toxicity data that varies greatly by organism, and environmental parameters that influence bioavailability (pH, dissolved organic carbon etc.)?*

The effects sub-sections of the aquatic ecosystems section of Chapter 7 are already organized by major organism type (plants, invertebrates, vertebrates). The vertebrates sections are further divided into fish, mammals, etc. If the decision is made to include dose-response studies, emphasis should be placed on studies showing effects at the lowest levels, with some statistical tools (e.g., histograms, box plots) used to characterize overall variability.

Additional Review Comments:

7-9, lines 22-23: “...Pb adsorption to sandy loam clay was a function of both (1) Fe and Mn oxide interactions...” This is ambiguous. Interactions between what and what?

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7-10, lines 3-4: This final sentence stands in stark contrast to pre-2005 literature on Pb in forest soils, which demonstrated that in virtually all studies the exchangeable Pb was a very small fraction of total soil Pb.

7-10, lines 23-25: What is the “humified bottom layer”? Also, the contrast set up by “whereas” isn’t really a logical contrast, from a soils perspective. This should be clarified.

7-11, lines 7-8: “...with aging defined primarily as leaching following initial influx, but also as binding and complexation.” This is not a sufficient or satisfactory definition of “aging.” Leaching is a physical process, binding and complexation are chemical processes. Pb in soils subjected to these processes is not “aged” but rather is undergoing physico-chemical transformation to new fractionation.

7-14, lines 11-12: It would be useful to know how Klaminder et al. (2005) measured “direct adsorption” from the atmosphere.

7-14, lines 16-21: “...correlated with Pb in the litter layer, where Pb comes from atmospheric deposition...” Pb in litter may be derived from geological sources, and returned to the soil through recycling. Also, in most forests, the litter layer and the fermented layer below are active rooting zones, possible sources of Pb uptake.

7-15, lines 16-22: If spruce is not a reliable species for metal dendrochronology (discussed on pp. 7-14 and 7-15), then can these results be trusted?

7-16, lines 20-22: The final sentence of this section is important and should be emphasized earlier, and in summary sections of the chapter. Cycling of Pb in forest vegetation is very minimal in a wide range of ecosystem types.

7-21, lines 27-29: Based on the Coeurdassier et al. (2007) study, it would appear that snails increase Pb bioavailability.

7-25, Table 7-2: Is it possible to assess, semi-quantitatively at least, the confidence level for a hypothesis that the bioaccumulation factor for terrestrial species is less than 1?

7-29, lines 7-10: The lack of a response in soils spiked with smelter ash indicates that the added Pb must be in a soluble form to affect growth.

7-34, lines 7-8: “...mean nestling mortality was 2.5 and 1.7 higher...” This doesn’t make sense. First, should this be “2.5 and 1.7 times higher...”? Second, why are there two numbers for only one contrast (after vs. before)? Please clarify.

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7-36, lines 8-14: No effect with spiked soils, but an effect with soil leachate. Once again, the importance of soluble Pb.

7-39, lines 4-8: Soil microbial activity declined for two weeks, then recovered. Is this adaptive behavior, or a change in community structure?

7-40, lines 16-18: "...exposure...can alter the structure of soil decomposer communities, which could in turn decrease decomposition rates." I do not see the evidence for making the connection between structure and function here.

7-41 to 7-42, section 7.2.7.: The section on critical loads is disappointing. After the second paragraph, it does not deal with critical loads. The message seems to be that we lack too much critical information to compute critical loads adequately. This section needs to review the major components of critical loads estimation and discuss where we have good information, and where we lack good information.

7-43, lines 2-4: Given the many studies highlighted in this ISA, should the Pb Eco-SSLs be updated?

7-45, lines 1-3: Afforestation of agricultural land normally leads to organic matter accumulation over time. Thus, "old fields" would appear to be low vulnerability ecosystems.

7-48, lines 10-12: The evidence in this ISA would seem to be quite clear that Pb is attenuated in terrestrial food webs. I think that the document could be much more forceful than "...no consistent evidence of trophic magnification was found."

7-61, lines 11-13: Units must be wrong here. 145 ug Pb/mg would be 14.5% Pb!

7-61, line 29: "...exposed to water concentrations of up to 100 umol Pb..." Presumably this is umol per liter.

7-65, lines 14-18, Table 7-3: The BCFs in the previous AQCD were much, much higher than (most) of the BCFs in Table 7-3. What explains the sudden drop in reported bioaccumulation? A re-assessment of the pre-2005 studies would seem to be in order.

7-98, line 26: There is no context for "study sites 2 and 3."

7-101, lines 31-33, Section 7.3.7.: As with the terrestrial section, the half-hearted attempt to look at critical loads is highly disappointing. Even if no studies have been published, it would be useful for EPA to know the state of the science. What information do we have and what do we lack for the construction of critical loads models for aquatic systems?

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7-110, lines 1-7: The aquatic effects section of Chapter 7 has waffled on the issue of Pb transfer up the food chain. The data presented in this ISA for aquatic fauna seem to indicate that Pb is transferred up the food chain pretty well.

Section 7.4: On the whole I would agree with the causality determinations presented in this section of the ISA. The one exception is section 7.4.1. (“...there is a causal relationship between Pb exposures and bioaccumulation of Pb that affects ecosystem services associated with terrestrial and aquatic biota.”) First, I don’t think that the case has been made for a causal relationship between Pb exposures and bioaccumulation in terrestrial systems. Second, I would not agree that there is evidence that any such bioaccumulation has had a substantial impact on ecosystem services.

Comments from Dr. Michael Kosnett

The following are my preliminary comments on the draft Integrated Science Assessment for Lead (May 2011). They are subject to revision as I continue my review and analysis of the document.

The discussion in Chapter 1 of the criteria used to consider studies for review and analysis in the ISA is reasonable. Studies of subjects who have blood lead concentrations within one order of magnitude of the general US population equates to cohorts with blood lead concentrations approximately less than 40 µg/dL. This is appropriate for a document intended to focus on risks associated with environmental rather than occupational lead exposure. It appears that these criteria has been consistently and appropriately applied. The HERO system functioned well as a means to retrieve studies that were cited in the document.

In chapter 2, a summary statement on lead biomarkers appearing on page 2-8, line 22 read, “Blood lead in adults is typically more an index of recent exposures than body burden.” In my opinion, as a general finding, this statement is incorrect and should be revised. For example, in many of the important cohort studies of middle-aged to elderly adults used to assess the impact of lead exposure on cardiovascular and cognitive function (e.g. the Normative Aging Study [NAS], or the Baltimore Memory Study [BMS]) the mean and median blood lead concentration was approximately 5 µg/dL. This was 3 to 4 fold higher than the median or mean blood lead concentration of the overall US population, and more than 4 fold higher than the median or mean blood lead concentration of teenagers. Teenagers have the highest indicate per body weight of food and beverages, the predominant source of contemporaneous lead exposure to the general population. It is clear that the blood lead concentration of the adults participating in the NAS and BMS, as well as most adults greater than 60 years of age, largely reflects higher skeletal lead stores accumulated earlier in life, as opposed to their current external lead intake.

The application of the causal determination criteria in Chapter 2 and Chapter 5 often lacks transparency, and would benefit by a more specific and structured approach. It is problematic that the narrative takes the approach of opining on the weight of evidence for causation for broad categories such as “neurological effects” or “cardiovascular effects” or “reproductive effects and birth outcomes”, rather than evaluating more specific health outcomes within each category. For example, although the causation assessments in Section 2.5.1 and Section 5.3.8 conclude that “there is a causal relationship between Pb exposures and neurological effects”, the analysis in these subsections does little to differentiate the weight of the evidence as it applies to such widely divergent neurological effects as cognitive function in children, essential tremor in adults, cognitive function in adults, and ADHD in children. The summary Tables 2-2 and 2-3, which imply that there is evidence for a causal impact for lead on cognitive function in both children *and adults* at a blood lead of 5 µg/dL, belie the fact that while there is ample evidence to

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establish cognitive impacts in children, the evidence for a similar impact on adults is nowhere near as compelling. It is puzzling how Table 2-3 singles out the NHANES III study by Krieg et al (1990) to support the conclusion that a blood lead of 5 µg/dL has a “causal” impact on diminished cognitive function in adults, when in fact this study reported no significant impact of blood lead on cognitive tests in adults age 20 to 59 or ≥ 60 years of age. Moreover, Section 5.3.2.4 “Epidemiological studies of cognitive function in adults” concluded, “In summary, among adults without occupational exposures to Pb, there is *weak evidence* for an association between blood lead levels and cognitive function” (emphasis added). Indeed, the relatively few studies that have found an association between low blood lead concentrations and aspects of cognitive function in adults, such as Muldoon et al, 2006, Payton et al, 1998, and Wright et al, 2003, (surprisingly not discussed in Section 5.3.2.4) were conducted in elderly populations who sustained prolonged periods of much higher blood lead concentrations (e.g. 10 to 25 µg/dL) earlier in life.

With respect to other “neurological effects”, such as essential tremor in adults and ADHD, the ISA would also benefit from a more rigorous presentation of a weight of the evidence analysis that Tables 2-2 and 2-3 imply yields a “causal relationship” at a blood lead concentration of ≤ 5 µg/dL. While intriguing, the epidemiological evidence that supports the relationship between lead exposure and essential tremor this is limited to two cross-sectional studies conducted in middle aged to elderly adults, who by virtue of their age sustained decades of much higher blood lead concentrations. Moreover, the pathogenesis of essential tremor is poorly understood, and there is no experimental animal or in vitro data that provide a model of lead induced essential tremor at low dose or establish a particular mode of action. With respect to the implicit finding of a “causal” relationship between blood lead concentration less than 5 µg/dL and ADHD, the narrative would benefit from a critical evaluation of limitation in the epidemiological studies that might temper the certainty of this conclusion, including a) the lack of control for parental ADHD in all the studies; b) the cross-sectional nature of the studies; c) the sole reliance on blood lead in late childhood and the lack of information on blood lead level as toddlers; and d) incomplete ascertainment in some studies of covariates such as prenatal tobacco exposure. The analysis might also address the implications for lead causation of ADHD of the observation that a marked rise in ADHD incidence has occurred during a period of dramatic decline in population lead exposure.

Section 5.4 of the ISA reviews recent epidemiological studies that demonstrate an association between lead exposure and blood pressure and/or hypertension, as well as cardiovascular mortality. This topic is exceedingly important, because hypertension and related cardiovascular diseases are pre-eminent causes of morbidity and mortality in the United States. While the evidence presented in the prior 2006 lead air criteria document (AQD) and the current draft ISA convincingly establish that environmental lead exposure is a cause of hypertension and cardiovascular morbidity and mortality, there is considerable uncertainty regarding the dose of lead at which these endpoints emerge. Knowledge of this dose, including evidence of any potential threshold, would be of paramount importance in the establishment of a NAAQS based

on these endpoints. The statement in Section 5.4.1 “Both human and animal studies provide consistent evidence for an association of increased BP and arterial hypertension with chronic exposure to Pb resulting in adult blood Pb levels below 5 µg/dL” is not supported by the available data. All of the epidemiological studies cited in the past AQD and the current IAS that demonstrate an association between blood lead and blood pressure, hypertension, or cardiovascular morbidity or mortality have been conducted in populations that likely experienced blood lead concentrations > 5 µg/dL for a significant proportion of their lifetimes. The epidemiological studies have been mainly conducted in middle aged to elderly adults who, notwithstanding their current low blood levels, lived a substantial proportion of their lives prior to 1980, when background blood lead concentration was typically in the range of 10 to 25 µg/dL. As noted in the narrative, in several of these cohorts (such as those examined in the Normative Aging Study), the association of lead to blood pressure or hypertension is more strongly predicted by bone lead than by blood lead, consistent with the influence of cumulative lead exposure accrued in part during these earlier decades. In addition to receiving a substantial contribution to cumulative lead exposure in early life, these cohorts were subject to what may have been unique developmental impacts of blood lead concentrations > 10 µg/dL on their cardiovascular system. At the present time, there appear to be no human or animal¹ studies that demonstrate the effect of lead on blood pressure, hypertension, or cardiovascular disease in subjects whose blood lead concentration never exceeded 5 µg/dL. The ISA would benefit from a revision that reflects this unresolved and important issue.

A somewhat similar problem has occurred with respect to the ISA’s assessment of renal effects in Section 5.4 and Section 2.5.3. The draft ISA’s assessment is that blood lead concentrations as low as 2 µg/dL are associated, on a causal basis, with renal insufficiency demonstrated by a low calculated GFR (glomerular filtration rate). In my opinion, a conclusion of causal assessment at that blood lead concentration is not supported by the scientific literature for several reasons. First, many of the studies that associated blood lead concentrations of this magnitude with diminished GFR were conducted in cohorts in which most of the members lived a substantial proportion of their lives with much higher blood lead concentrations (in the range of 10 to 25 µg/dL). Second, the epidemiological evidence that associates blood lead and GFR is subject to reverse causation. Since lead undergoes substantial renal excretion, elevations in blood lead concentration can be a consequence of decreased GFR, rather than a cause of reduced GFR. The explanation against reverse causation offered in the ISA that “...the association between blood Pb and serum creatinine occurred over the entire serum creatinine range, including the normal range where reverse causality would not be expected” has no apparent experimental support and is unpersuasive. On the contrary, steady state serum creatinine is inversely proportional to GFR,

¹ Regarding animal studies, the statement on page 5-165, “An array of studies have provided evidence that extended exposure to low levels of Pb (<5 µg/dL) can result in delayed onset of hypertension in experimental animals that persists long after the cessation of Pb exposure” is not supported by data presented in the ISA. Section 5.4.2.2, and Figure 5-167 refer to two animal studies, Chang et al, 2005 and Tsao et al 2000, that the document implies show an effect of lead on increased blood pressure at blood lead concentrations < 5 µg/dL. However, neither of these studies reaches such conclusions nor do they present data that establishes such a finding.

and in any person, decrements in GFR are associated with increases in serum creatinine even when the serum creatinine remains in the normal range. Third, the epidemiological data has not yielded consistent findings, and in some cohorts with low level environmental lead exposure, blood lead concentration was associated with biomarkers consistent with improved renal function (e.g. lower serum creatinine, de Burure et al, 2006). It is conceivable, but unknown, whether this represents lead induced hyperfiltration. Fourth, the toxicological literature reviewed in the ISA offers no evidence, in either human or animal studies, of a demonstrable nephrotoxic lesion or mechanism induced by a blood lead concentration of 2 µg/dL. On the contrary, early biomarkers of tubular damage have not consistently emerged in occupational cohorts or animal studies until blood lead concentrations are generally higher by an order of magnitude.

In general, the numerous tables in Chapter 5 that offer details (“characteristics and quantitative data”) of selected epidemiological studies pertaining to broad health endpoints should include a column that comments on the strengths and limitations of each study in terms of causal assessment. The summarized information should also note negative findings (e.g. the notable absence of a predictive effect of blood lead in studies that reveal a predictive effect of bone lead). For ease of reference, abbreviations should be explained in the caption to each table.

Section 5.2 of the document offers an extensive discussion of various modes of action of lead observed in toxicological studies (mainly conducted in cellular preparations or whole animal experiments) across a wide range of exposure concentrations. Table 5.2 seeks to relate the “dose” of lead (in vitro or ex vivo) associated with various modes of action to human health effects. The table suggests that of all the modes of action listed, only altered ion status might be expected to be relevant to human health effects observed at blood lead concentrations in the range of current environmental interest (i.e. 1 to 10 µg/dL). A whole blood lead concentration of 1 to 10 µg/dL corresponds to a plasma blood lead concentration of approximately 0.01 to 0.1 µg/dL, or 0.1 to 1 µg/L², which is approximately 0.5 to 5 nM (nanomolar). Since it is lead in plasma that is available for uptake into cells of key target organs such as the brain, kidney, gonads, and vascular endothelium, the narrative might consider emphasizing only those modes of action for which there is evidence of action at cellular concentrations of 5 nM or less. Lead’s interaction with protein kinase C and calmodulin mediated processes are particularly relevant in this regard.

The narrative should highlight and emphasize toxicological findings from animal studies in which the animal’s exposure and/or blood lead concentration approximates that which occurs to humans with low level environmental lead exposure. For example, the median lead concentration of the human diet is approximately 3 ppb and the median blood lead concentration is approximately 1.6 µg/dL (see Table 4-1). However, the document extensively discusses experiments in which laboratory animals were fed diets containing on the order of 100 to 2000 ppm lead, or had blood lead concentrations on the order of 15 to 150 µg/dL (or higher), without

² As noted in Section 4.2.2.1, ≤ 1% of lead in blood is present in the plasma in individuals with low level environmental exposure; the value of 6% implied in line 7 of 5.2.3.3 should be corrected.

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considering the relevance of these relatively high values to the potential health impact of much lower lead exposure to humans.

From a temporal standpoint, it appears that some of the key health impacts associated with environmental lead exposure in humans, such as hypertension and cardiovascular disease, renal insufficiency, and adverse neurological outcomes (such as cognitive dysfunction or possible neurodegeneration *in adults*) are the consequence of longterm cumulative exposure. For example, days to weeks of exposure to lead resulting in blood lead concentrations in the range of 10 to 25 µg/dL do not appear to induce elevated blood pressure or hypertension in humans that is observable in that time frame. Instead, evidence suggests that the risk emerges after years of such exposure. Lead exposure in childhood has not been associated with elevated blood pressure or hypertension in childhood (cf Chen et al, 2006; Gump et al 2005; Factor-Litvak et al, 1996), although it has been associated with the latent development of increased blood pressure in early adulthood (Gerr et al, 2002). Accordingly, the likely modes of action underlying the development of lead-induced hypertension are not those associated with acute or subacute pharmacological action, but rather those compatible with slow, insidious onset and/or long latency. Therefore, in seeking coherence between many of the chronic human health outcomes discerned in epidemiological studies and plausible mode(s) of action supported by toxicological studies, the narrative should focus on slow or latent processes, such as, but not limited to, epigenetic impacts on gene expression, or remodeling of tissue structure or responsiveness (e.g. in brain, kidney or vascular endothelium).

In view of the foregoing, the document could be shortened by omitting discussion of toxicological studies that have examined lead doses and/or modes of action that are not relevant to the actions of lead plausibly associated with insidious or latent low dose human health effects. Those toxicological studies that by virtue of dose and temporal pattern are relevant to these human endpoints should be summarized in tables that identify key aspects of dose and study design, and that comment on strengths and limitations. Figures such as Figure 5-29 which omit the study citation and other key data are relatively unhelpful.

Additional preliminary comments on the ISA’s discussion of specific health endpoints:

Neurocognitive function. The ISA’s discussion of recent studies that demonstrate an effect of in utero and childhood low level lead exposure on cognitive function are of particular interest, because this endpoint formed the basis of the last revision of the NAAQS for lead. The comprehensive review of recent studies provided in the narrative and the tables supports and extends the observations and conclusions reached in the 2006 assessment. A few relatively minor points warrant comment:

a) In section 5.3.2.1, the discussion of the study by Kim et al (2009) highlights its importance as a study that demonstrated an impact of lead on full scale IQ in a population with blood lead < 5 µg/dL, (thus representing a cohort with the lowest blood lead for which FSIQ was the primary

endpoint). However, the discussion, including the caption to Figure 5-3, should provide a clearer indication that the value of this study is tempered by the finding that a *statistically significant* impact of lead on FSIQ was confined to subjects with relatively high blood manganese (>14 µg/dL). In like manner it appears misleading for the findings of this study to be referred to, without citation and qualification, in Section 5.3.8 Summary and Causal Determination, which states (page 5-147, line 13), “In the cumulative body of evidence, negative associations between blood Pb level and IQ are best substantiated at mean blood Pb levels in the range of 5-10 µg/dL; *however, an association was observed in a recent study with a mean blood Pb level of 1.73 µg/dL.* [emphasis added]

b) Section 5.3.2.1 addresses the important and challenging issue of age-based susceptibility to lead-associated neurodevelopmental deficits by noting that while adverse impacts of lead on the entire range of development (in utero, early childhood, and late childhood) have been observed in epidemiological studies, “...concurrent blood Pb level appears to be the best predictor of neurodevelopmental effects in children.... Thus, the course of cognitive development may be modified in children, depending on concurrent blood Pb levels or positive caregiving environment” (page 5-73, lines 12-16). It is unclear how this important conclusion is mirrored in Chapter 2, which states, “Collectively, the epidemiological evidence has not identified one unique time window of exposure that poses the greatest risk to cognitive function in children (Figure 2-3)” (Section 2.8.3, line 28). Figure 2-3, which is the same as Figure 5-10³, provides data abstracted from Table 2 of Bellinger et al (1990) in support of the primary importance of concurrent blood lead, and the improvement in IQ that may ensue with declining blood lead in childhood. However, it would appear that data from Table 3 of Bellinger et al (1990), rather than Table 2, is more suited to this point.

Renal effects. Table 5-43 depicts “the change in kidney metric [e.g. biomarkers of renal function such as serum creatinine or estimated GFR] per µg/dL blood Pb, at 1 µg/dL.” This is misleading, because in virtually all of these studies, most of the subjects had blood lead concentrations considerably higher than 1 µg/dL, and the validity of extrapolation of the study findings to a blood lead concentration of 1 µg/dL is not established.

On page 5-129, the prospective study of renal function in patients with chronic renal insufficiency reported by Yu et al (2004) is described as a “hallmark” study illustrating the impact of low blood lead concentration (< 5 µg/dL) on renal function. Given the multiple limitations of this study, such an endorsement seems unwarranted. The study’s limitations include, in part: a) sparse information regarding subject recruitment; b) the unacknowledged likelihood, based on the range of blood lead concentration and EDTA provoked urine lead excretion, that many study subjects had substantially higher blood lead concentrations prior to enrollment; c) lack of blinding during the follow-up period, an important consideration in a condition such as renal insufficiency in which medical treatment and medical and dietary

³ The beginning of the caption to Figure 5-10 omits the superscript “a” that is found in the caption of Figure 2-3.

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compliance strongly influence change in renal function; d) statistical analysis using a Cox proportional hazards model that adjusted the hazard ratio for renal function deterioration only on baseline covariates, rather than an alternative survival analysis that would adjust for changes in key covariates, such as blood pressure or protein intake, during the extensive period of follow-up; e) failure to report possible interactions between lead biomarkers and other covariates in the proportional hazards analysis. Similar unacknowledged major limitations exist for the chelation studies conducted by these same investigators that are discussed on pages 5-223 to 5-224, including the important observation that change in renal function in the chelated subjects was not related to any lead biomarker. The statement in the draft ISA suggesting that if these observations are replicated, “chelation could yield important public health benefits” appears to be premature. In any case, it would be highly inadvisable to retain even this qualified endorsement of an unproven therapy in the ISA document, whose principal purpose is to review the association between lead exposure and health effects.

Comments from Dr. Roman Lanno

Comments on Chapter 2 - Integrative Health and Ecological Effects Overview

Chapter 2 presents the integrative summary and conclusions from the Pb ISA with a discussion of evidence presented in detail in subsequent chapters.

Is this a useful and effective summary presentation?

The structure and presentation of Chapter 2 is logical and provides a good summary of the approach and the rationale behind causal determinations for human health and welfare. Leaving out many specific references is fine here since this summary is intended for a broader audience and a completely scientific format may prove distracting for many readers. Figure 2-1 provides particularly good synopsis of spectrum of scientific evidence for human health effects of Pb. The tables within sections summarizing data for causal determinations are good, as is the final summary table, 2-8.

Is the framework for causal determination appropriately applied?

Please comment on approaches that may improve the communication of key ISA findings to varied audiences. The health and ecological effects of Pb are mediated through multiple interconnected modes of action and there is substantial overlap between the ecological and health endpoints considered in the causal determinations. Since the mechanism of Pb toxicity is likely conserved from invertebrates to vertebrates to humans in some organ systems, the scientific evidence was integrated across the disciplines of health and ecology. Please comment on this approach e.g., is this a useful and effective integration of the scientific evidence?

The discussion of commonalities in modes of toxic action across varied taxa is important and intuitive for ecotoxicologists, but I'm not sure how it will be viewed by human health toxicologists. Overall, the argument for various general modes of toxic action is strengthened by presenting similar findings from many taxonomic groups and this is captured very well in section 2.7.1, Modes of Action Relevant to Downstream Health and Ecological Effects.

One way of increasing the readability of this section (and the entire ISA document) would be the standardization of units used in expressing concentrations for measured parameters and especially for Pb dose. Blood Pb levels are consistently expressed as ug/dL and there is some useful discussion about expressing blood Pb levels using ug/L if we were to consider even lower blood Pb levels in assessments. However, Pb doses are expressed in a number of ways which make interpretation for the reader very difficult, especially if they are not scientists. For example, consider Table 2-6 which deals strictly with human data. Blood Pb levels are clearly expressed in

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ug/dL, but Pb dose is presented in pM, nM, uM, and ppm. Although it may be difficult to standardize M expressions due to the many orders of magnitude difference, ppm is not a very meaningful expression of dose. This should at least be converted to SI units, mg/L, but more usefully, expressed as a molar value, so as to facilitate comparison with other Pb dose measurements in the table.

Following up on Table 2-6, I checked Krieg (2007) and it was not very clearly stated what the Pb dose was, so where did the 20 ppm come from? In Wiebe and Barr (1988), the dose was 20 ppm in drinking water, not air, so this should at least be expressed in mg/L. In Huel et al. (2008), Pb and As were measured in hair samples of women as exposure dose and correlated with Ca pump activity in RBCs from umbilical cord blood. In Kern et al. (2000), *in vitro* tests were conducted examining the conformation of calmodulin in the presence of Ca and Pb and dose was expressed as pM of free metal ion, Pb^{2+} or Ca^{2+} . In order to make the interpretation of dose easier, it would be good to include additional information regarding the medium in which Pb dose was measured (e.g., hair, *in vitro* test solution, drinking water). This would reduce confusion in the interpretation of Pb dose. Additionally, it would be important to include the form of Pb that was measured as dose (e.g., total Pb, modeled Pb^{2+}), so as to incorporate the concept of bioavailability into the measurement of dose. This may be less applicable in human health exposures, but is very important when examining ecological data.

With respect to the ecological effects section of Chapter 2, a summary of the various endpoints used to assess Pb toxicity are presented, but unlike the human health section, very few measures of dose are presented. As discussed above, the comparison of modes of toxic action among taxa is a good idea, but at least some measures of dose should be provided for ecological exposures. Even though ecological exposure measures may not translate directly into human exposure values, for those readers that would like to make a comparison, the values would be presented. Summary tables of responses and doses (as in Table 2-6) would provide a good summary and make interpretation of the ecological data somewhat clearer.

Additional comments related to specific sections of Chapter 2 are provided below.

Comments on Chapter 7 - Ecological Effects of Lead

Chapter 7 is a discussion of the ecological effects of Pb. Effects on terrestrial and aquatic ecosystems are first considered separately. They are then integrated by classes of endpoints (bioaccumulation, growth, mortality, hematological effects, development and reproduction, neurobehavior, community and ecosystem effects).

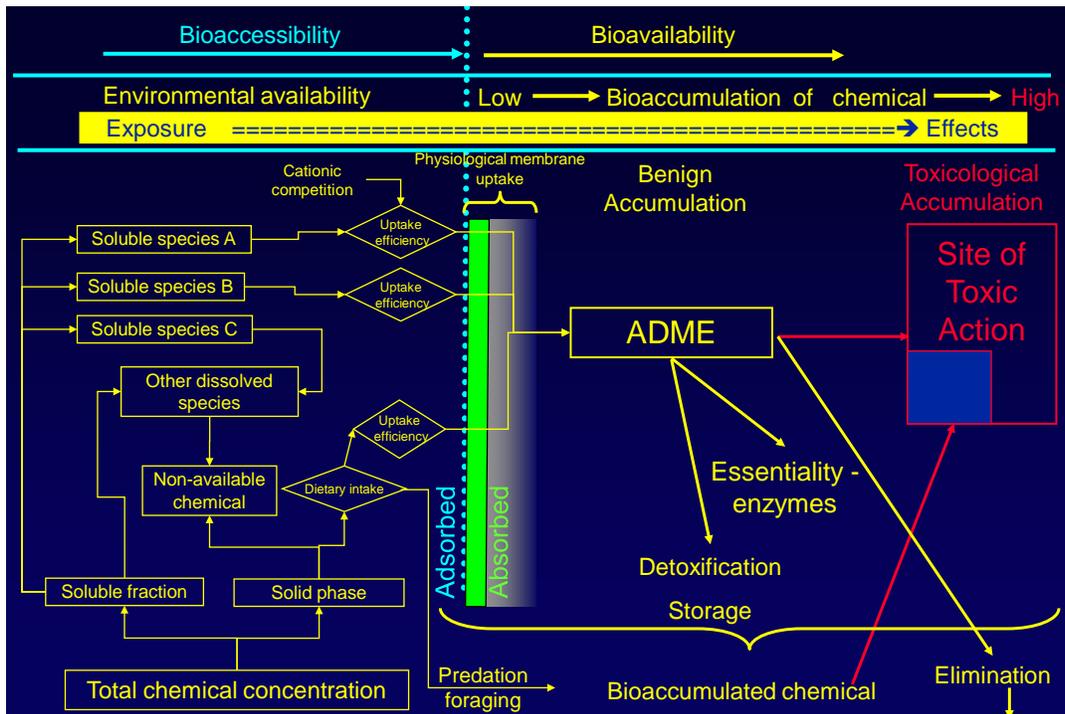
Does the panel consider this approach appropriate?

This approach is complete but involves some redundancy as some data sets can be used in more than one topic area. Overall, the reiteration is useful and this structure is easy to follow.

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Is it appropriate to derive a causal determination for bioaccumulation as it affects ecosystem services?

This is a grey area question. Of itself, the bioaccumulation of Pb is not a toxic effect, but the normal adaptation of an organism to maintain homeostasis when challenged by a stressor. The magnitude of the stressor determines whether there is an effect (see schematic of bioavailability below). At low levels of Pb exposure, the rate of uptake of Pb is such that organisms that can bioaccumulate Pb will do so in a manner that partitions or detoxifies Pb within the normal range of physiological functions. This can be termed benign bioaccumulation. Once the rate of uptake of Pb exceeds the capacity of the organism to detoxify Pb, toxic effects become evident within the exposed organism, so at this point, bioaccumulation is no longer benign, but toxic. In terms of ecosystem services, there will be a level of bioaccumulation at a lower trophic level (benign or toxic) that will be ingested by a higher trophic level. If this level of Pb bioaccumulation in the lower trophic level results in a toxic effect in the higher trophic level, then a causal determination is warranted for bioaccumulation. If there is enough substantive evidence that trophic transfer results in toxicity, then a causal assessment is appropriate. Most of the available data suggests that biodilution is the predominant fate of Pb during trophic transfer, but some studies suggest some effects, so a causal determination is probably warranted.



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Has the ISA adequately characterized the available information on the relationship between Pb exposure and effects on individual organisms and ecosystems, as well the range of exposure concentrations for the specific endpoints?

I guess this depends upon one's perspective. Since this document focuses on new data since 2006, the range of exposure concentrations presented in text and tables covers that time period. In the context of all available information, the newer data may not be adequately characterized. The newer data should be adequately characterized by providing some information on the relevance of this data to existing data. This could be accomplished by providing all-inclusive tables or figures (e.g., species sensitivity distribution) with all the other relevant data from previous ISAs that could be used to make a decision regarding a secondary NAAQS for Pb. For example, data on chronic toxicity from the current ISA could be plotted on an existing SSD for Pb from previous ISA documents using different color symbols so it is immediately evident where the new data lie, similar to the presentation for human data in Figures 2-2 and 2-3.

Are there subject areas that should be added, expanded upon, shortened or removed?

Page 7-8: A summary of background Pb levels in soils, similar to what is presented on page 7-50 for the Aquatic Ecosystem Effects section, would be useful in the interpretation of the relative Pb levels used in soil toxicity tests. A reasonable presentation of background Pb levels in US soils is available in the US EPA EcoSSL guidance document for Pb (US EPA 2005).

Another useful addition would be background schematics on the concept of bioavailability to ecological receptors and one for specifics of the biotic ligand model (BLM). The bioavailability schematic can be found in the US EPA Framework for Metals Risk Assessment (2007). The BLM schematic can be found in any number of papers that describe the model. Both these diagrams can form a focus when discussing the bioaccessibility, bioavailability, bioaccumulation, and toxicity of metals in aquatic, sediment, and soil media. They would also provide a graphic illustration of the concepts central to any discussion of metal toxicity to ecological receptors.

One point of clarification that would be useful is distinguishing between bioconcentration and bioaccumulation and ensuring that these terms are used in the proper context throughout the document in the discussion of Pb bioavailability to ecological receptors. Bioconcentration and bioconcentration factor (BCF) refer to uptake of a compound strictly from water and are usually constructs of laboratory exposures. Bioaccumulation and bioaccumulation factor (BAF) refer to the summative uptake of a compound from all possible media (e.g., water and/or air + diet), so if organisms are being fed in the lab during tests or for almost all field exposures, bioaccumulation is the proper term to use.

The concept of bioavailability should be incorporated into the discussion of Pb exposure by clearly defining the chemical measure of exposure. Measurements of exposure can be total Pb (a

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vigorous acid digest of the medium), dissolved (total Pb in solution passed through a 0.45 μ m filter), solvent extracted (total Pb in a weak acid or weak salt extract of a sediment or soil), solid-phase extract (total Pb in diffusion gradient thin films (DGTs) or cation-exchange resin that diffuse through a membrane and hydrogel layer), free ion can be measured directly (maybe not for Pb), or based upon models such as WHAM, the Pb^{2+} concentration can be estimated from total dissolved Pb and other water chemistry parameters such as pH, DOC, carbonates, etc. Various combinations of these techniques can be used to estimate free Pb ion in water, sediment pore water, and soil solution.

In order to have any idea of how all the modifying factors of Pb bioavailability alter bioaccumulation and toxicity in various environmental media, Pb concentrations must be measured in some way. Data from any studies only expressing exposure as nominal concentrations is excluded from EcoSSL or Water Quality Criterion development data sets. There appear to be a number of references in the ISA where this is the case, so care must be taken in describing the relevance of these studies if they are to be included in the ISA.

If the ISA was expanded to consider dose-response in terrestrial systems, should we limit data to field soils?

Absolutely, artificial soil (AS) is not a soil, but a standardized test substrate, and data generated using AS has no relevance to any application in real soils. Artificial soil is used as a reference condition (not necessarily a good one) in standardized laboratory bioassays with soils and as a standardized test matrix for conducting “proof of concept”-type bioassays with soil invertebrates. In the development of EcoSSLs, the US EPA did not consider data generated using AS as acceptable for the development of EcoSSLs.

If the ISA were expanded to consider dose-response in aquatic systems, how might we most efficiently present toxicity data that varies greatly by organism, and environmental parameters that influence bioavailability (pH, dissolved organic carbon etc.)?

Probably the best way to present dose-response data for aquatic systems would be to standardize dose to the free Pb ion using an aquatic metal speciation model such as WHAM. The next step would be to standardize further with a biotic ligand and effect to create a Pb BLM, but I’m not familiar with how far this has been developed.

Another approach may be to “bin” values in a more qualitative way and construct species sensitivity distributions (SSDs) for a certain range of conditions. By selecting the most important water quality parameters that modify Pb bioavailability (e.g., hardness, DOC) within the range of these parameters normally found in US waters, toxicity data could be examined under conditions of high (e.g., low pH, hardness, DOC), moderate (e.g., intermediate pH, hardness, DOC), and low (e.g., high pH, hardness, DOC) bioavailability. This would be similar to using a water hardness regression to determine site-specific guidelines for Pb and also to the approach used for

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the development of Ecological Soil Screening Levels for soil.

Additional comments on Chapter 7

Page 7-10, line 8-9 – “Pb had been removed by resident plant species” – does removed imply that the plants took up Pb and the plants were harvested, to completely remove the Pb? Otherwise, Pb will simply be recycled into the system via plant residues.

Page 7-14, lines 11-12 – “direct adsorption from the atmosphere” – does this mean that the Pb was then absorbed by the tree or was it measured as surficial, adsorbed Pb?

Line 16 – “incidental processing” should be defined here

Page 7-17, line 23 – these are low levels of Pb in soil and represent background concentrations in many soils. Data from experiments with low levels of Pb in soils must be interpreted carefully and raises the question of how to consider data from organisms exposed to low levels of Pb.

Page 7-19, lines 24-27 – If no evidence for a regulatory mechanism for Pb was observed, (i.e., no saturation of uptake mechanisms?) why would snails have to grow additional soft tissue to retain additional Pb? Please clarify.

Page 7-20, line 5 – What were the correlation coefficients?

Page 7-21, lines 24-26 – Worms increasing soil pH via mucous secretions seems highly unlikely and soil pH is very stable? If soil pH were increasing then why would Pb bioavailability increase? The needs rewording or removal.

Page 7-24, line 12 – What are Rumex K-1 plants?

Page 7-25, lines 10-12 – These statements require references

Page 7-27, lines 4-6 – Exactly what is stated here? Is it being implied that photosystem II effects of Pb would be expected in all plants? That would only be if Pb is translocated to or absorbed by leaves and shoots. If Pb doesn't get to the chlorophyll (e.g., by physiological exclusion mechanisms) then toxicity would not be observed. I think this sentence needs to be reworded.

Page 7-29, line 28 – What is the relevance of hydroponically grown plants to the toxicity of metals in soils. This is a huge extrapolation and no hydroponics data was used in the development of EcoSSLs.

Page 7-30, lines 10-28 – Are these tests conducted in agar? If so, they have little relevance to soil toxicology. Are these developmental and behavioural effects specific to Pb?

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Page 7-31, lines 9-14 – Is an increase in cellulase activity actually a negative effect on the worms? Seems to me that would enhance digestion of plant material.

Page 7-31, lines 22-26 – Topical application to snails – this is not a standard methodology applied to soil organisms. Was the 500-2,000 ug Pb applied to the snails the mass of Pb applied or the concentration of the topical solution and how was dose ensured? Was the LD50 and internalized dose or was it still surficial?

Page 7-35, lines 6-8 – I don't see the relevance of in vitro oocyte exposure to NAAQS development.

Page 7-36, 1st paragraph – What type of soil was used?

Page 7-36, 3rd paragraph – Were these LC50s incipient lethal levels or just 28-day exposures? Since there were no differences in Pb content between species, it's possible that an ILL had been reached.

Page 7-36, 4th paragraph, line 34 – *P. kimi* populations would be extirpated in Artificial Soil? The relevance here is not clear.

Page 7-37, 1st paragraph – Nominal concentrations in an undefined soil type is not information that can be used.

Page 7-40, 2nd paragraph – This interpretation is unclear. If species composition of microbial communities changed, the authors cannot state that decomposition rates may decrease unless they measured decomposition. This is due to functional redundancy of microbial communities in soil.

Page 7-47, line 22 – change “layer” to “horizon”

Page 7-52, line 2 – change “qualities” to “quantities”

Page 7-63, line 3 – I think *Lemna* are free-floating and not rooted macrophytes

Page 7-66, line 36 – What does “significant amounts of metal” mean? Statistically significant relative to controls or reference organisms?

Page 7-67, line 21 – Should this be “exoskeleton > mid-gut gland > muscle > hemolymph”?

Page 7-68, lines 9-11 – Are these values actually different? They don't seem to be unless the precision of the measurements is really high?

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Page 7-68, last paragraph and Table 7-4 – BCF and BAF appear to be used interchangeably and their use should be consistent.

Throughout the text, the statements “accumulated significant amounts of metal”, “significantly increased”, or “detected at elevated levels” are used, but the relevance of these statements is often missing. Were Pb levels higher than in controls or reference organisms, higher than in organisms exposed to different concentrations, etc.? These need to be clarified.

Page 7-73, line 27 – remove “internally”

Page 7-87, line 24 – change “aspirate” to “aspartate”

In terms of quality assurance/quality control (QA/QC) of the experimental design and data measurements, what determines whether data from recent studies is used in the assessment or development of a NAAQS for Pb? As I’ve noted in many cases for soil toxicity tests, many of these studies would be excluded from EcoSSL development since they do not meet QA/QC criteria for soil toxicity data and have no relevance to assessing the toxicity of Pb in soil. How are data used where Pb exposures are very high by an exposure pathway that has low relevance to environmental exposures (e.g., in vitro exposures)?

Page 7-92, line 26 – Should this be “epidermal absorption” to gain an internal dose?

Page 7-92, line 32 – *Xenopus laevis* is the African Clawed Frog (not a toad)

Page 7-94, line 23 – This is a low EC20 but it is also unbounded? What is the preferred method for expressing this type of data?

Page 7-95, lines 9-13 – This is a comparison of toxicity in between freshwater and marine bivalves

Page 7-95, lines 34-35 – How many molts actually occur in 10 days and is this a realistic parameter?

Page 7-104, section on Species Sensitivity

Bioaccumulation may not be a toxic effect if it’s in the realm of normal homeostasis of an organism, so differences in Pb bioaccumulation by different species does not necessarily have anything to do with sensitivity to Pb.

Page 7-105, lines 10-11 – Aren’t exoskeleton and hardened exterior tissue the same thing?

Page 7-110, line 5 – replace “bioconcentrated” with “bioaccumulated”

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Page 7-110, line 7 and page 7-61, line 16 – The term “biodilution” is used to describe two different processes. Page 7-61 is “growth dilution” in relation to bioaccumulation studies

Page 7-114, line 8 – It’s unclear to me which routes of entry actually occur in plants. Stomata are on the undersides of leaves and aerial Pb can enter the leaf through the stomatal openings. What about Pb that is deposited on the upper surface of the leaf? Does this enter the leaf as well or does it only remain adsorbed to the surface?

Page 7-116, lines 17-18 – Limited information is available on growth effects on invertebrates since growth is not a measured endpoint in most standardized invertebrate tests since it’s too variable and often organisms lose weight during tests due to substrate effects.

Page 7-117, line 27 – Heat shock proteins are a non-specific stress response and it’s not clear to me how they are relevant to Pb exposure.

Comments from Mr. Richard Poirot

Comments on Chapter 3 - Ambient Lead: Source to Concentration

Charge Question: Chapter 3 provides a wide range of information to inform the exposure and health sections of the ISA. To what extent are the atmospheric science and air quality analyses presented in Chapter 3 clearly conveyed and appropriately characterized? Is the information provided regarding Pb source characteristics, fate and transport of Pb in the environment, Pb monitoring, and spatial and temporal patterns of Pb concentrations in air and non-air media accurate, complete, and relevant to the review of the Pb NAAQS? Does the ISA adequately characterize the available evidence on the relationship between ambient air Pb concentrations and concentrations of Pb in other environmental media?

Chapter 3 generally provides an adequate review of the most recently available information on atmospheric emission sources, transport, ambient air concentrations, size distributions, spatial and temporal patterns, deposition and fate of lead in the environment. Many of the studies cited focus on Pb in a single environmental media, and there is relatively little information indicating how concentrations of Pb in soils (or wet or dry deposition, surface waters, sediments, indoor surfaces, etc.) would be expected to change in relation to future changes in air emissions and ambient air concentrations. I think this is primarily a limitation in the available literature, rather than a shortcoming of the ISA.

The authors stick closely to the assignment of focusing on “the latest scientific information” (1/06-3/11) available since the 2008 Pb NAAQS review, and this makes at times for uneven “recent literature review” discussions that seem to provide a paragraph summarizing the details of each new paper, without demonstrating how or why the new information advances or re-directs the state of scientific understanding in ways that would support or challenge the current NAAQS. I’m not a fan of the “only what’s new” approach and think that at a minimum, there should be a clearly-stated summary of the existing conceptual (model) understanding at the start of each new section. If this summarizes the last ISA (or in this case CD), it won’t work very well if the previous ISA or CD was itself just a summary of what was new 5 years earlier. One possible approach would be to have introductory sections summarizing the “existing conceptual understanding”, with a following section (or appendix) documenting the “new literature” that simply summarizes the relevant new publications, and a concluding section that indicates specifically how the existing conceptual understanding has been modified (if at all). Another approach might be to have a standing “state of the scientific understanding” document (more like the original CDs) that is periodically modified where and if the new information warrants changes. A “track changes” view would be a good way for reviewers to see what’s both new and important.

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The Chapter 3 appendix provides interesting and useful information reflecting on spatial patterns and particle size distributions from the (limited) available ambient measurement data. As indicated in specific comments below, Table 3A-13 reveals uncomfortably high incidences of illogical particle size results where there was apparently more Pb measured in PM₁₀ than TSP (1/5 of sites), in PM_{2.5} than in TSP (1/5 of sites) and in PM_{2.5} than in PM₁₀ (2/5 of sites). Collectively, these illogical results suggest relatively widespread prevalence of poor quality Pb measurements. Additional information and discussion is needed on the different sampling methods, filter media and blank characteristics, analytical and sample extraction methods, and accuracy and precision characteristics of the measurements employed in these Pb size comparison (and spatial distribution) studies. This is especially important given the wide range of acceptable FEM analytical methods for Pb and continuing concerns over the highly variable cut size characteristics of the current hi-vol TSP FRM.

Specific Comments

p. 3-2, lines 15-16 (and p. 3-1, line 22): Some additional explanation seems warranted to account for how Pb emissions from piston aircraft engines increased from < 10% of total in 2006 AQCD (based on 2002 NEI) to 49% of total in 2008. Did everything else decrease a lot (I doubt it), or was there a difference in inventory methodologies? In Figure 3-2, it looks like 2002 piston aircraft emissions were about 33% of total (not < 10%).

p. 3-3, Figure 3-2: Is there an explanation for the increase in miscellaneous Pb emissions from 2005 to 2008?

p. 3-4, line 2 and elsewhere: Piston aircraft emissions are referred to here as “direct point source emissions”. Are individual planes (or airports) considered to be “point sources”? What fraction of the 590 tons of aircraft Pb is emitted at/near airports, vs. along the flight paths?

p. 3-4, lines 14, 15: The “upper 0.1% of stationary emissions came from 33 counties” doesn’t sound right. I think there are about 3,100 counties (or equivalent jurisdictions) in the US, so 33 counties would be about 1% of counties (emitting only the upper 0.1% of stationary source Pb emissions?).

p. 3-10, Subheading under “Roadway-Related Sources”: I think you probably mean “Contemporary” (not “Contemporaneous”).

p. 3-11, lines 15-27: This is not especially helpful – re-suspended soil lead contributes somewhere between 90% of total and “can’t be ruled out”.

p. 3-14, line 2: So what happens to the 25% of Pb in fuel which is not emitted in auto exhaust?

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p. 3-15 to 3-18: The discussion on Pb source apportionment is rambling and not especially helpful, switching focus from the chemical composition of Pb-containing compounds from sources to receptor model attribution of total Pb to sources, to composition of Pb-containing particles in the atmosphere. Many of the summarized studies – from Beijing, Shanghai, Mexico City, etc. may not be very relevant to current US sources. Conversely, no information is presented showing any source attribution to, or expected or measured chemical composition of Pb emitted from piston engine aviation fuel use.

p. 3-18, line 7: You might refer to “Pb-Zn-Cl-containing” particles to make it clear that 73% of $PM_{2.5}$ particles were not composed entirely of these 3 elements.

p. 3-22, line 16: It’s not clear why Pb in re-suspended road dust should exhibit a bimodal distribution. Can some explanation be provided to indicate the different sources expected to be contributing to this bimodal size distribution?

p. 3-26, lines 1, 2: The Pb dry deposition flux in new measurements was considerably greater in industrialized urban areas than it was in the 2006 Pb CD? What does this mean? Is this based on just 1 study in Tokyo Bay, and are you sure the units are right (see below)?

p. 3-26, line 11: Is it possible you mean 12-17 $mg/m^2/yr$ (rather than $\mu g/m^2/yr$)? Otherwise it seems inconsistent with the (30x higher) 0.49 $mg/m^2/yr$ bulk wet deposition at an a rural forested central Ontario site, and with the dry deposition flux ranges of 0.04 to 4 $mg/m^2/yr$ and 2 to 3 $mg/m^2/yr$ attributed on p. 3-22 (lines 4 and 11) to the 2006 Pb CD. A range 12-15 $\mu g/m^2/yr$ wouldn’t be “more than 10 times the upper bound” (of 4 $mg/m^2/yr$ or 4000 $\mu g/m^2/yr$) from the 2006 CD.

p. 3-27, line 6: Not clear what is 0.002 to 0.3% of what?

p. 3-28, line 1: “under” what?

p. 3-28, line 2: You could change “substantial” to something like “important” or “relatively large”, since the size of the resuspension contribution would be at least as large (and likely larger) in the vicinity of current major sources.

p. 3-28, line 28: Delete either “is” or “originates”.

p. 3-31, line 1: Is this “TSP” in water? If so, please define. If it’s in the air, more explanation is needed.

pp. 3-33 to 3-40: This lengthy review of Pb in runoff and associated transport and deposition mechanisms is detailed and occasionally interesting, but it’s not clear how this “new” information (mostly pertaining to transport of historically deposited Pb, is relevant to the review

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of an ambient air Pb NAAQS. Possibly here or elsewhere you could include some discussion of the relatively extensive sampling and analysis of flood-deposited Pb-containing sediments in post-Katrina New Orleans. This (flood water transport) mechanism could be a potentially important transport pathway for re-distribution and re-emission of historically deposited Pb to the ambient air. See for example: Plumlee et al. (2006) USGS environmental characterization of flood sediments left in the New Orleans area after Hurricanes Katrina and Rita, 2005—Progress Report: U.S. Geological Survey Open-File Report 2006-1023, 74 p. <http://pubs.usgs.gov/of/2006/1023/pdf/OFR-2006-1023.pdf> .

p. 3-37, lines 29-30: Part of this sentence (“The generally high...DOC concentrations”) must be missing.

p. 3-42, line 33: Add “into” before “account”.

p. 3-56, line 1: The objective of IMPROVE isn’t “to protect visibility” per se, but rather “to monitor visibility and the pollutants which impair it”.

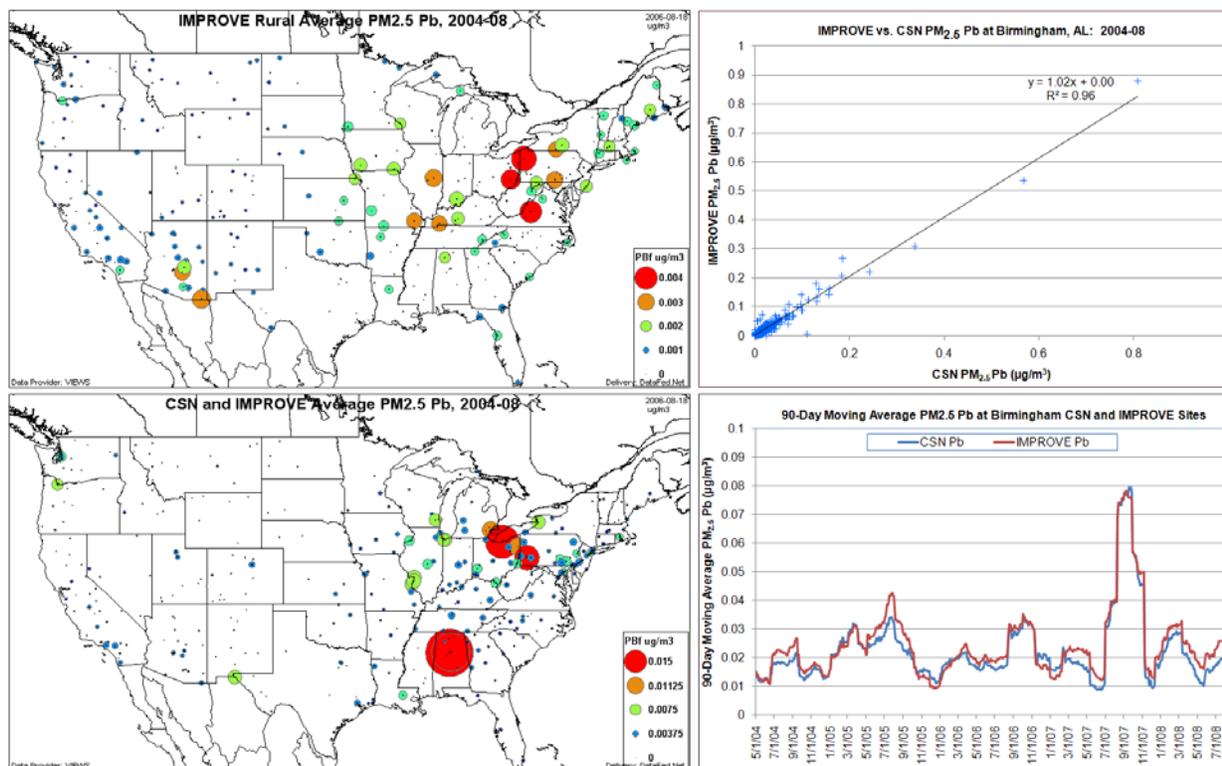
p. 3-56, line 10: There are more than 9 XRF elements; more like 24 for IMPROVE.

p. 3-66 or elsewhere: Other than the Figure 3-13, there doesn’t seem to be a clear presentation of the names, locations, monthly and 3-month maxima and variability of sites exceeding 2007-09 Pb design values. Could a table providing that information be provided here or in the appendix?

p. 3-68 or elsewhere in this section: It might be informative to present some summary spatial and temporal patterns of PM_{2.5} Pb from IMPROVE sites, to convey general background patterns and to show how low these rural, fine particle concentrations are – relative to standards. Also these could be more directly compared to the occasionally much higher urban CSN PM_{2.5} Pb data – hopefully using something other than the dreaded “county plots”, which I just don’t find very informative. The figure below shows an example of recent 5-year averages from the two PM_{2.5} networks, for which the Pb data from collocated sites appear to be quite comparable. You could also show temporal trends for nearly 10 years from CSN and 20 years from some IMPROVE sites.

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Figure 1. Five-Year Average PM2.5 Pb from Rural IMPROVE and Urban CSN sites: 2004-08



p. 3-68 & 3-69: I don't like the approach here of describing information in the chapter which is only displayed in the appendices. At least provide an example or illustration of what you're describing here in the chapter.

p. 3-76, line 2: Delete "lowest". Also, you might indicate if the observed seasonal differences are statistically significant or if similar seasonal patterns were apparent in other time periods.

p. 3-77, line 18 and elsewhere: It isn't clear (to me) why you are using a ρ (rho) correlation metric, rather than the more familiar r or r^2 . Sometimes ρ is used to denote the population correlation, rather than the sample correlation, but ρ is also often used to connote the Spearman's rank-order (non-parametric) correlation. If you are intentionally using a non-parametric method, you might indicate this, explain why, and include an illustration that Pb data (in all size ranges) are not normally distributed.

p. 3-78: It might be helpful to include some mention of the analytical (and extraction) methods generally employed for quantifying Pb in the different size fractions which are compared here, as those differences may help explain some of the (occasionally illogical) differences in concentrations. See below.

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p. 3-78, lines 12, 13: An average $PM_{2.5}$ Pb/ PM_{10} Pb ratio > 1 warrants additional discussion. Looking at Table 3A-13 on p. 3-166 & 167 of the Chapter 3 Appendix, it is disconcerting to note that:

PM_{10} Pb $>$ TSP Pb at nearly 20% (5/27) of collocated TSP and PM_{10} Pb sites,
 $PM_{2.5}$ Pb $>$ TSP Pb at nearly 20% (8/45) of collocated TSP and $PM_{2.5}$ Pb sites, and
 $PM_{2.5}$ Pb $>$ PM_{10} Pb at nearly 40% (19/49) of collocated PM_{10} and $PM_{2.5}$ Pb sites.

These high incidences of illogical results raise concerns about the quality of all Pb measurements, and call for further analysis and explanation. In addition, I note that many of the collocated Pb data sets utilized in Table 3.8.2 in the Appendix appear to be identical to those employed in a similar analysis conducted for the previous Pb NAAQS review, reported in a 4/22/08 memo from Mark Schmidt and Kevin Cavender (http://www.epa.gov/ttn/naaqs/standards/pb/data/20080428_scalingfactors.pdf). The correlation metric in that previous analysis was different (r^2 vs. the current ρ) although I would expect the r^2 to generally be more stringent (a lower number), but at a number of sites the former r^2 was higher than the current ρ . There was also an “average ratio” (of PM_{10} Pb to TSP Pb) reported for each site in the Schmidt & Cavender memo, which is different for than the “average ratio” reported in the current Table 3.8.2 for many of those sites and data periods of record which were presumably the same in both analyses. Some explanation for these differences seems warranted. There is a fairly substantial database of Pb (and other XRF elements) from a Canadian dichotomous sampler network, where analytical methods were consistent for fine and coarse fractions, and where relevance to current/recent US concentrations and size distributions would be high.

p. 3-80, lines 24, 25: Was Pb highly correlated with As in both the coarse and ultrafine fractions in the Hays et al. study?

p. 3-80, line 32: Do you mean Pb in $PM_{0.1}$ was 15 times higher in the tunnel than by the roadside?

pp. 3-80 – 3-81: The Figure 3-23 results summarized from Sabin et al. (2006) raise questions about (a) What were the particle cut size characteristics of the samplers used in that study? and (b) How well would the current TSP sampler capture the different particle sizes observed in that study?

pp. 3-80 – 3-82: This is an interesting discussion. Possibly some of the results you cite from other countries might not be directly relevant to US if Pb sources and historical trends are different.

pp. 3-83 – 3-84: Is there an explanation for the large reduction in the number of sites with collocated Pb and other pollutants in 2009, compared to 2007-2008?

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P 3-86, Figure 3-26: It might convey information more clearly if the co-pollutants were sorted by highest to lowest median or average correlations with Pb, rather than alphabetically.

p. 3-87, lines 6-7: Is the more rapid Pb accumulation in soils from Pb salts than from sewage sludge or fly ash due to higher Pb concentrations in the salts, or from better retention in soils or from both concentration and retention?

p. 3-88, line 14: Explain the meaning of “TSP” in soil samples.

p. 3-88 – 3-95: In discussing Pb concentrations in soils or sediments, it would be helpful to indicate or at least generally summarize the depth of the soil and sediment samples for which you report concentrations.

p. 3-92, lines 16, 17: I don’t agree that “these results suggest that soil Pb concentration tends to be spatially heterogeneous in the absence of a source”. In the absence of any Pb sources, there would be no Pb. In the absence of strong anthropogenic Pb emission sources contributing to Pb deposition, the soil Pb concentrations would be determined by natural soil Pb content, which would not tend to exhibit especially high spatial variability.

p. 3-92, line 29: Although Pb air monitoring was not formally conducted as part of the WACAP study, fine particle Pb was measured at IMPROVE sites at about $\frac{3}{4}$ of the national parks included in the WACAP study.

p. 3-93, line 18: You could insert “average” after “highest”, as it appears from Table 3-10 that the highest peak Pb concentration was observed in Baltimore.

p. 3-95, Figure 3-29: There is no “background” displayed in this figure, as indicated in the caption.

p. 3-98, lines 4, 20 and elsewhere: Could you use consistent units to describe Pb concentrations in rain, snow, surface waters, etc. – rather than switching from $\mu\text{g/l}$ to pg/g to ng/l ?

p. 3-98, line 22: the reference ([collated in 2008](#)) works electronically, but not in hard copy. You could change this to ([Lee et al., 2008](#)).

p. 3-99, lines 28-30: Some additional explanation of $^{206}\text{Pb}/^{207}\text{Pb}$ ratios would be helpful. Otherwise its hard to see that a ratio of 1.16 is “far from” 1.19. In general, this entire paragraph, extending onto p. 3-100, is not very informative and could be clarified.

p. 3-102, lines 17-21: This summary of Pb speciation, including the statement that Pb speciation was “fairly well characterized” in the 2006 CD, is not especially informative. What are the predominant Pb compounds that we expect to find in the current ambient air in the vicinity of

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various Pb sources? Does 20% of Pb emitted from piston aviation engines persist as gaseous organic compounds (unmeasured by PM samplers) or is this just 20% of Pb bromide and dibromide compounds (and are they in gas or particle phase)?

p. 3-102, line24: This may be true, but I don't recall mention in the chapter that "global" Pb deposition peaked in the 1970s, and think that might be a difficult thing to document with confidence.

p. 3-103, line 24: Delete "that".

p. 3-134, line3: The text indicates that "the comparison tables include the Pearson correlation coefficient (r)" but the table legends indicate ρ (rho), which is presumably the Spearman rank-ordered correlation. So which is it, and if it's Pearson r , why is this different than the metric used to correlate Pb in different size fractions?

p. 3-134, lines 11-18: Can you indicate how means were calculated where (sometimes high) fractions of the samples were below MDL?

p. 3-140, Table 3A-7 and elsewhere in Appendix: It's difficult to understand the 3 separate values (rows) showing "correlations" between each pair of sites without flipping back several pages in the text. Perhaps you could provide a clearer legend, an explanatory note at bottom of each table, or add a column repeating ρ , P90 and COD for each row. Possibly also rename these "Comparisons..." rather than "Correlations..." in the table captions, since it's not just correlations that are presented.

p. 3-165: The table above indicates that monitors A, B and C are all "source-oriented", while the figure caption refers to source and non-source-oriented monitors.

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Comments from Dr. Michael Rabinowitz

What follows are comments prompted by the text of the documents, arranged by page, and responses to EPA's General and Specific Charges. Which topics to add or subtract, emphasize, shorten, or re-enforce as key concepts, are addressed.

Specific Charge Question 2.

Is this a useful and effective summary?

Yes. It frames the right questions and presents adequate answers.

Is the framework for causal determination appropriately applied?

Yes, but I'd like to see nested models to help show the extent to which Pb is an independent risk factor in the epidemiological modeling, where so much variance is shared. For more, see p 1-19.

Approaches that may improve the communications of key findings?

I can think of no other overall approaches that might be useful. Among my comments arranged by page are several minor editorial changes to help clarify some points, such as Table 3-1, or Figure 4, for example.

Also, see comments at the end about host factors being important, but environmental Pb is a far biggest predictor of PbB. Looking at these host factors helps us identify sub-populations at risk, whose protection drives our calculations, and may offer ideas about mitigation. Still, the more that can be done to lower environmental Pb levels, the less important these other concerns become.

Is combining the health and the ecological effects of lead a useful and effective integration of the scientific evidence?

Generally, yes. Why not look at the evidence that each provides together? We are obligated to protect both realms. MOAs can be clarified, for example. My only real concern is direct conversion of doses and concentrations among species. Because humans and animals occupy different environments and have different eating habits, our sensitivities to environmental lead may be more or less than some other animals. We have seen marine animals take up more lead if they live in the sediments versus animals that live in the water column. Furthermore, the fraction of the whole body burden that is in blood most likely varies among species. Fish, birds,, bovine, and human hemoglobins likely bind Pb with somewhat different strengths, which would

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profoundly affect their biokinetic distributions. That could be very useful. We have cases of Pb poisoned, nectar feeding birds and, and in another setting, meadow grazed horses, each being a sentinel species, their particular sensitivities bringing journalists before human health was further imperiled. So, yes, I am a fan of this approach.

Comments Arranged by Page:

Page xi, Members and affiliations - after 30 years, my affiliation with Harvard has ended, so, although retired, please replace with Marine Biological Laboratory, where I have been since 1986.

Page xxii, Acronyms and Abbreviations - These 17 pages demonstrate the wide range of disciplines tapped by the authors of this document: Biology, psychology, medicine, chemistry, physics, geology and mathematics, but add MOA, mode of action, from page 1-9, line 20.

Page 1-1, line 2 - remove second comma. This is a long but not compound sentence. consider.....evidence, and it communicates....

Page 1-14 - clear exposition of organization

Page 1-19, line 20 - "detect and control". Also, I wish efforts could be made to show the extent or strength of the confounding, in the context of the effect size for lead and for the whole model's predictive power (r^2). The presentation, and the researchers they cite and the journal reviewers they must satisfy seem content to show that Pb has a non-zero coefficient in multiple regression models, for example, of children's mental performance. But, because of the extent of the confounding, this is different than showing that Pb is an independent risk factor. Pb and these other risk factors share considerable variances, particularly in some of the higher risk populations, where Pb exposure and other risk factors often coexist. The relative size of this non-zero coefficient, the size of the Pb effect, should be shown in terms of the model r^2 , or goodness of fit. How good is that model's fit with and without a Pb term in a series of nested models? Does the r^2 increase significantly when a Pb term is offered? How much do the confounders' strength shift towards the Pb term, with which it shares variance, when Pb term is introduced? This would help a reader see how much is caused by Pb compared to other risk factors, preventable and otherwise.

My concern is that at increasing low lead levels, where the lead effects is small, blood lead can still be measured relative accurately (often to 2 significant figures) but other, stronger variables, such as maternal education or richness of the child's home environment can be more difficult to measure, subject to reporting errors, and are often entered as broadly categorical variables, while lead is a continuous variable. For these reasons I remain a bit skeptical that at these low levels, effects that have been attributed to lead are fully caused by lead.

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Page 1-20, line 1 - Might you want to say anything here about how sample sizes often limit how much stratification can be done.

Page 2-6, line 22 - perhaps.....related to the re-suspension of the Pb

Page 2-6, line 28 - I would like to see the reference of the change in ratios and sources. Does this mean the sources changed their isotopic composition or the relative importance of various sources has changed? Fuel additive Pb isotopes varied among markets and over time. Was a change in food Pb IC seen? The document does not really need reference to isotopes at this point, unless further clarification proves useful.

Page 2-6, line 36 - how about "after ingestion occurs"

Page 2-7, line 2 - in vivo is a function of the co-presence or absence of food, host factors such as anemia, iron and calcium status, in vitro particle size and reagents

Page 2-8, line 2 - lactation, fever (more likely), fractures, menopause

Page 2-8, line 16 - indicating higher recent exposures...

Page 2-9, line 17 -...burden, but not practical. Actually urinary output after chelation challenge has been a useful measure of labile body pools of Pb.

Also, on the topic of urinary Pb, the IC of urine tracks plasma Pb on a hourly basis (if you want to say more). Urine reflects the filterable fraction of PbB, which equilibrates with the larger pool of RBC-bound Pb over an hourly time scale.

Page 2-11, line 27 - I'm a bit skeptical because some proto- porphyrins themselves are behavioral neurotoxins (recall King George III's porphyria) and the amount of Pb needed to induce ALAD elevations are typically above 15 ug/dL in humans, anemic or not.

Page 2-15, line 15 - but what about the fact that PbB has fallen >10 fold, from > 20 to < 2 ug/dL, but BP has not. It seems like an insensitive relationship. I appreciate the historical significance that this BP-PbB relationship was a selling point for the removal of Pb fuel additives in the 1970's because the target population was middle aged to older males (congressmen worried about their blood pressure).

Page 2-16, line 17 - I liked this

Page 2-18, line 32 - for humans, the values are much higher, so these rats seem much more sensitive to Pb

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Page 2-20, lines 15-16 - The trends here are a bit confusing to me. PbB levels have dropped, and age of puberty have dropped, If inverse, the PbB goes up, then delays goes down.

Page 2-20, line 25 - Got me curious about any protective effects. Were these in occupational settings?

Page 2-24, line 30 - true, and maybe 1000 times lower than in circa 1980.

Page 2-25, line 2 – No, this type of axis scaling axis will not change the shape of curve. Also, ppm is not ug/L (that's ppb). This type of error is troubling.

Page 2-46, line 29 and whole section - Just a summary reminder that the slope will be steeper for children.

The contribution of air Pb to soil and hence to humans is real, but much less efficient than direct inhalation.

Page 2-51, line 8 - In other words, decline attributed to Pb could be accounted for by the extent to which the confounders are harder to separate from a Pb effect at lower Pb levels.

Page 2-51, line 15 - Is this difference statistically significant? The ranges certainly overlap.

Page 3-4 - A question: all of the sources except aircraft emit Pb close to ground level where we live, while aircraft emissions are largely high in the troposphere, aside from take-offs. Does this matter or is this factored in somehow? So, is Figure 3-5 based on sales of fuels or where it was emitted?

Page 3-7, line 11 - 2 gr / gal for an automobile fuel would have been mid-range, high-lead high-test back in the day.

Page 3-7, line 19 -which are make the Pb combustion products (Pb halides) more volatile. (but they are not more volatile than TEL)

Page 3-8 - If we compare line 32, China's 122 kt/yr with US values of about 1 kt/yr from pages 3-3 and 3-4, and knowing that China is upwind of the US, and knowing China's increasing reliance on coal, rapidly building new coal burning power plants at the rate of about one per month. Therefore, I wonder how much of our air Pb values are under our national control. We could have zero domestic emissions, but measurable airborne Pb.

Page 3-9, Section 3.2.2.4 - I'm not sure the first example is that useful. The European example is better.

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Page 3-11, line 14 - Can you make a stronger statement? Not major, maybe minor, or maybe currently on-road usage of gasoline contributes at most X %

Page 3-12, line 31 - maybe say: The potential for widespread dust lead pollution following demolition or sand-blasting depends on the actual site practices, such as hazardous material collection and disposal.

Page 3-13, Figure 3-6 and text - It may be noteworthy to compare current emissions' from aircraft 600 or Mainland China's 120,000 tons/yr with this old data.

Page 3-16 - In Table 3-1, maybe add the Pb ore cerrusite. Pb carbonate $PbCO_3$, which is the most toxic, occasionally becoming newsworthy, as in the Esperance episode. It is a rare ore, absent from most major deposits, but predominant in a few mining areas.

Page 3-16 - Is lawn mower exhaust a concern?

Page 3-86 - Figure 3-26, why is this important?

Page 4-12, line 26 - Dietary Pb from contaminated soil - tea strikes me as an untypical example, since we do not eat tea. The Pb must be trans-located to the lead from the soil and then infused to the beverage. To grow tea, the soils must be fairly acidic pH 4.5 to 6, which aids metal solubility, and Al rich. There is a vast literature on plant uptake of lead from soil, even prior to 1980, for a wide variety of edible crops and indicators of air pollution. For example, the response of rice crops to Pb amended paddy soils has been well documented. See: Hseu ZY, Su, SW, Lai HY, Guo HY, Chen TC, Chen ZS; Remediation techniques and heavy metal uptake by different rice varieties in metal-contaminated soils of Taiwan. Soil Science and Plant Nutrition 56; p31-52 Feb 2010.

Page 4-13, line 15 - What is sub-proportionally?

Page 4-15, line 16 - Can this be expressed up to 25% as much as drinking water... or % of the total, or ug/day. % of water as a source is not that easily understood by me.

Page 4-16, line 11 - Maybe should be Pb-Zn mining (Tar Creek?)

Page 4-17, line 11 - Do we need this example of Nigerian sawdust? Are the values that high? Do we have similar situation anywhere in US?

Page 4-18, Table 4-6 - Why did Mainland Chinese toys and jewelry and venetian blinds not make the list?

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Page 4-21 - Organic Pb - In 2nd para the combustion products of Pb+4 (TEL) are Pb+2 so Arthur's work on this topic does not go into this section about organic (Pb+4). Also, the change in PbB for each ug/cu M would yield 1000. it is closer to 3 (see 4-80). You may want to give the volume of distribution for TEL. For Pb+2, it is about 10L for adult human.

Page 4-24, Figure 4-2 - May I suggest showing only Pb compounds, drop groups 2, 5 and 8. Also, I am surprised phosphate (pyromorphite) is so high since the solubility constant is many orders of magnitude lower than anything else shown, even galena.

Page 4-26, line 13 - felt need for summary such as- no chemical form of Pb is safe, i.e. un-absorbable.

Page 4-26, line 18 - in this context, say only ...Pb in whole blood exchanges with both these compartments via the blood plasma.

Page 4-41, line 9 - maybe say ...Each tooth in the mouth has a somewhat different anatomy and period of growth. Further complicating the matter, teeth are composed of enamel, dentine and pulp. Teeth are not like blood, which is a uniform liquid, making dental sampling and interpretation more complex. The ease of collection and the concentration difference (ppm in teeth vs. ppb in blood) at times overrides these concerns.

Page 4-41, line 26 - Some prenatal Pb is still found in the dentine found under the crown rather than down the root

Page 4-42, line 10 - I do concur in that hair is really not well suited as a biomarker for Pb, but hair plays a small role in the body's loss of Pb. Some human kinetic work has been done see7- my article with George Wetherill and Joel Kopple (1976) Delayed appearance of tracer lead in facial hair. Arch Environ Hth 31: 220 - 3.

4 end - A lot has been written about individual factors that modify uptake and susceptibility to environmental Pb (genetics, gender, nutrition, age...). However, the major predictor of PbB is how much Pb is, I need to emphasize, how much Pb is in the environment, not any of the many host factors.

Comments from Dr. William Stubblefield

Comments on Chapter 7 - Ecological Effects of Lead

Chapter 7 is a discussion of the ecological effects of Pb. Effects on terrestrial and aquatic ecosystems are first considered separately. They are then integrated by classes of endpoints (bioaccumulation, growth, mortality, hematological effects, development and reproduction, neurobehavior, community and ecosystem effects).

Does the panel consider this approach appropriate?

Chapter 7 provides an excellent synthesis of the available toxicity data for lead. The chapter is well-written and well-organized and does an adequate job of addressing “new” published data (post-2006). The separation of terrestrial and aquatic ecosystem data is appropriate and the subsequent organization by endpoints and levels of biological complexity is good. Some questions may be raised regarding the inclusion of some data and endpoints; however, this will be discussed in greater detail below.

Is it appropriate to derive a causal determination for bioaccumulation as it affects ecosystem services?

This question is a bit difficult to address as posed. The process of bioaccumulation, i.e., the uptake and accumulation of environmental pollutants, may or may not have any effects on ecosystem services. Therefore, bioaccumulation should not necessarily be thought of as an adverse or toxic effect. Bioaccumulation as a result of environmental exposure can result in adverse effects to the exposed organism or to consumers of the organism but only if concentrations of the contaminant are sufficient to elicit a toxic response at a given “site of action.” In many cases bioaccumulation of metals, such as lead, in select tissues is a normal metabolic process by which an organism is able to sequester and ultimately eliminate metals, e.g. metal granule formation in mollusks. It may very well be possible to derive a “causal” relationship between exposure and the presence of metals in tissues. However, due to the non—linear relationship between exposure concentration and tissue concentration with metals, developing a quantitative relationship would be doubtful. Similar concerns exist when evaluating possible food chain related effects. Available data suggest that little tissue bound lead is bio-accessible when consumed by predators, thus leading to “biodilution” of lead concentrations as one moves up the food chain.

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Has the ISA adequately characterized the available information on the relationship between Pb exposure and effects on individual organisms and ecosystems, as well the range of exposure concentrations for the specific endpoints?

The ISA has done an excellent job of synthesizing and discussing the relationship between lead exposure and effects on individual organisms and ecosystems since 2006. Since the document relies on data that existed prior to 2006 and does not provide a summary of the extant data it is somewhat difficult to assess how adequately the document characterizes all of the available information. Summarization of all of the available data would be helpful; however, presentation of all of the available data would make the document unwieldy. Presentation of the available data in the form of a species sensitivity distribution (SSD) that identifies new versus old data would be helpful to the reader. Also, the ISA relies solely on published toxicity data available in the open literature. Additional unpublished toxicity information may be available from the lead industry given all of their efforts over the past 5+ years in developing data for compliance with the European REACH regulations. This information is likely to be available either directly from the lead industry or from the European Chemicals Agency. It should also be pointed out that the US EPA Ambient Water Quality Criteria for lead is based on 1985 or older science. In 1999 the US EPA Office of Water announced its intent to revise the existing lead criteria to reflect newer science; to date this has not been done. Clearly, based on the data summarized in the ISA, there is substantial “new” information available upon which to revise the criteria document. In moving forward with the lead air quality criteria it will be necessary for the Office of Air to consider the available new science in deriving their assessment of possible effects to organisms in the aquatic environment.

Are there subject areas that should be added, expanded upon, shortened or removed?

The ISA does a good job of covering the vast majority of post-2006 published data relating to let effects on aquatic and terrestrial organisms. It is interesting, however, that a number of endpoints such as physiological stress, hematological effects, and neurobehavioral effects are considered in this document. Traditionally the US EPA has limited their interpretation of environmental effects to those effects that can be directly related to population and community level concerns. This approach has limited endpoints considered for criteria and standards to those associated with organism survival, growth, and reproduction. Alternative biochemical or physiological level endpoints are considered only when a direct link can be made to population or community level concerns. Therefore, since no direct linkages can be made between an observation of a biochemical, behavioral, or physiologic endpoint and a population or community level concern it may be appropriate to eliminate discussion of these types of endpoints from the ISA.

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If the ISA was expanded to consider dose-response in terrestrial systems, should we limit data to field soils?

I would recommend the data should be limited to “natural” soil data. Testing can be conducted under either laboratory or field conditions but the test matrix should be a “true soil.”

If the ISA were expanded to consider dose-response in aquatic systems, how might we most efficiently present toxicity data that varies greatly by organism, and environmental parameters that influence bioavailability (pH, dissolved organic carbon etc.)?

The best approach for presenting wide differences in sensitivity among organisms is through a species sensitivity distribution (SSD) approach.

Environmental parameters that influence bioavailability are best discussed in terms of a description of the biotic ligand model. Application of the BLM to natural waters is best described by presenting the results of calculations using a series of natural waters or waters that exhibit a range of composition and chemical/physical parameters found across the United States. By presenting the data in this fashion the reader can easily ascertain the relative importance of each of the parameters on assessing lead toxicity. This applies to both the aquatic environment as well as to the terrestrial environment.

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Comments from Dr. Ian von Lindern

Overview: The draft Integrated Science Assessment (ISA) is organized, comprehensive, and presented in a logical, transparent manner. It is an impressive well-edited document that is convenient to read and digest, despite its size. The document is structured as a follow up to the EPA 2006 criteria review document and presents many of the conclusions as affirmations or supplements to the 2006 edition. The questions outlined in Section 1 are all keyed to the implications of new evidence that has evolved since the last review and how those studies inform the Agency in meeting its responsibilities.

This is an appropriate approach in light of the EPA ISA strategy, which seems to be to examine whether any new information developed since 2006 provides justification for modifying the earlier analyses.

This works well for those familiar with the previous review. However, this format i) may be challenging for uninitiated readers and reviewers, ii) does not inform the reviewer as to the historic conditions and accomplishments (in some areas), and iii) does not address weaknesses (in some areas) in the information base identified or analyses conducted in the last review.

Historic Perspective: There were challenges encountered in the previous review that indicated significant gaps in the knowledge base. These information gaps introduced uncertainties into the process that should be revisited. The last NAAQS review showed that EPA had, in maintaining the irrelevant standard from 1978-2007, “lost track” of key parameters necessary to effectively assess the health and ecological risks of airborne lead in the U.S. Relatively little data were available in several key areas for performing a responsible risk assessment.

It seems EPA intends to conclude in the Risk Assessment Planning document that, although substantive information has accumulated, little of this information changes the analyses or conclusions developed and presented in 2006. Based on the information presented, this conclusion does appear to be justified. However, there seems to be a disconnect in that i) significant data deficiencies were identified in 2006, ii) EPA is the Agency responsible to collect the data to fill these data gaps, iii) now EPA concludes the data continue to be unavailable to appropriately assess lead exposure in the country, and iv) the old risk analyses will be continued to be relied upon for another five years.

The current exposure and risk assessment strategy evaluates pilot examples representing real situations prevalent in the country. These analyses are modeling exercises based on outdated empirical relationships and little concurrent ambient data. These situations show substantial probability of exceeding the new NAAQS and attendant levels of excess risk to surrounding populations. The major problem with respect to current exposure and risk analyses is that EPA is

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unable to estimate how much of the country is subject to these excessive levels.

The ISA should point this deficiency out and ascertain whether there are technological or scientific barriers to developing the requisite information from existing sources, or through new program activities. The subsequent policy analyses should examine whether relevant databases are being developed, both internal and external to the EPA. Should EPA be developing, supporting, or implementing programmatic activities to make it possible to move from the near total reliance on risk modeling to observational and empirical analysis of contemporaneous data?

Several questions should be answered with respect to monitoring and surveillance. What data base is accumulating with respect to compliance with the new standard? Is a network established, is it adequate and effective, and are there detectable blood lead levels associated with any gradient in exposure? Have there been excursions? Certain U.S. sub-populations (e.g. immigrants and inner city children) are at substantially greater risk of exposure due to co-factors associated with different cultures, climates, dietary and nutritional regimes, as are being encountered in the global lead poisoning epidemic. Are these venues being monitored?

ISA Exposure Assessment Review: Evaluation of the Exposure Assessment portion of the document begins with Chapter 1 and extends through Chapter 4.

Chapters 1 and 2 Introduction and Integrative Health and Ecological Overview, respectively, are well organized, edited to provide a clear and transparent presentation of the intent and structure, and effectively summarize the document. Section 1.6 on causality and EPA's Framework for Causal Determination is particularly strong and organized to clearly present EPA's conclusions and justifications with respect to health issues. Section 2.7 and 2.8 are also especially pertinent additions and improvements to the Criteria Document process. Overall, the causation and health effects sections are impressive, comprehensive, and well-supported.

In contrast, there is little discussion and few conclusions presented regarding sources, uses, ambient concentrations, exposure or populations at risk. Only 4 of 72 pages in the summary Chapter 2 discuss Ambient Lead and Exposure, followed by 2 pages of Toxicokinetics and Biomarkers, compared to 16 pages of Human Health Effects and 15 pages of Ecological Effects summary. This is followed by an 18 page summary dedicated to Integration of Human Health and Ecological Effects.

The latter is a particularly good presentation and the Agency should be commended for beginning to make these connections formally in policy support documents. It is a step forward in environmental regulatory approach that will well serve both the environment and U.S. health and ecological policy. Table 2.8 in the Chapter 2 summary is particularly strong in making this point.

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Unfortunately, the relative amount of attention paid to exposure in the summary is appropriate to the makeup of the document as a whole, with more than 70% of the ISA dedicated to health effects and causality. This is also likely reflective of where research and monitoring attention and publication resources have been focused in recent years. With regard to the AQCD it also points out the greatest deficiencies in the last NAAQS process have not been addressed and are perhaps being compounded and extended in this revision.

Developing effective exposure estimates was the weakest point in the analyses that supported the current NAAQS. This was due to the lack of monitoring data available to assess contemporary exposures in the U.S., or to support the modeling analyses relied on in subsequent development of the NAAQS. Unfortunately, in the last review, the EPA was challenged in effectively estimating the extent of potential damage in the general population; the relationship between air lead levels, emissions and absorption; a safe air lead concentration; or the number of citizens exposed to potentially dangerous levels.

This weakness was identified in the 2006 AQCD and the OAQPS made the best of a poorly characterized situation. There were insufficient data to characterize active emissions and emission rates, ambient concentrations and the degree, extent and severity of ongoing redistribution of residual lead in the nation's environment. As a result, EPA relied on modeling and decades-old empirical relationships to quantify exposures. This resulted in considerable uncertainty inherent in the overall process.

Chapter 3 Ambient Lead: Source to Concentration: Chapter 3 addresses the areas identified as data gaps in the last review, and presents the information that will eventually be relied upon in developing exposure risk assessments for the U.S. population. There has been some additional ambient monitoring conducted since 2007 that better informs the Agency with respect to population exposure.

Formal and Informal Uses of Lead in the U.S.: Prior to discussing the adequacy of available ambient lead data, it is critical to note that there is no information relative to trends of commercial use and disposition of lead in U.S. commerce in the entire document. That 2006 AQCD indicated that use and consumption of lead in the U.S. were approaching levels near the peak utilization seen before the gasoline additive phase down. Yet, it seems the EPA has little or no information on the current life-cycle of lead in either the formal or informal industrial sector in the U.S. Does the Agency know how much or where this lead is being produced, used, consumed, recycled, recovered, reused, disposed of, or if it is being exported as waste? Is this information obtainable? Are any data bases available? Is the information reliable? It seems these data would inform the Agency as to where appropriate monitoring and testing should be undertaken.

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Sources of Atmospheric Lead: Sections 3.1 and 3.2 discuss sources of lead and summarize the National Emissions Inventory and discuss other anthropogenic sources of airborne lead. This discussion provides a good overview of the larger airborne sources in the U.S. and provides a county-by-county database to characterize the magnitude and extent of these sources across the country. These sections indicate that there are some quantitative data regarding larger point sources in the country and a basic understanding of source behavior with respect to numerous smaller lead sites in which the airborne pathway plays a significant role in human and ecologic exposure. However, there does not seem to be an inventory of the latter sites. How many are there? Where are these located? Is the list complete? Are there populations nearby? Are health risks in these areas addressed in other regulatory programs?

Fate and Transport: Section 3.3 provides good discussion of lead fate and transport in the environment and recognizes that the majority of environmental lead is potentially air lead in waiting, or once was air lead, and can easily be transferred to other environmental compartments of exposure significance.

Air Quality Monitoring / Surveillance: Section 3.4 is an informative discussion of lead monitoring techniques and appropriately covers the available technology to effectively monitor air lead in the U.S.

Section 3.5 does provide some new information to address the data gaps identified in 2006. There have been additional monitoring data collected in the interim that provide some concurrent information regarding airborne exposures in the U.S. Although a fair quantitative discussion and an extensive Appendix are provided, no conclusions are drawn with regard to the quality, representativeness and degree of compliance with the NAAQS as currently implemented.

With regard to compliance or implied risk, this information is confusing. It seems that “Source Oriented TSP monitors” indicate the NAAQS is being exceeded in 14 of 22 counties being monitored across the U.S. Conversely, non-source oriented monitors show levels generally well below the new NAAQS standard. Additional discussion is provided with regard to PM10 and PM2.5 monitors analyzed for lead. These networks generally seem to show overall compliance with the new NAAQS, even when TSP monitoring shows the same areas at-risk.

However, there seems to be no “take away” message with regard to these data and analyses. This is in stark contrast to the health issues presented and discussed in the document that are clearly conclusion oriented. Questions that come to mind include:

What is the appropriate monitoring technique? One method shows 2/3rds of all source oriented sites are out of compliance across the U.S.; the other method shows 3 of 323 sites exceed the criteria, but does not specify source type. Does the latter method appropriately reflect the risk associated with these sources?

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If 2/3rds of source oriented sites are out of compliance, how many of these sites are there in the country? Are there only 22 that are being effectively monitored, or hundreds or thousands not being monitored? What populations are exposed by these sites? How do these sites relate to the National Emissions Inventory presented earlier in the Chapter, or are these the other anthropogenic sites, for which there is no inventory? It seems there should either be answers provided to these questions to support a national risk assessment, or an indication that the problem is not appropriately characterized by current source inventory and monitoring efforts.

Particle Size: Section 3.5.3 addresses particle size distribution of lead-bearing particulate and seems to be oriented toward eventual monitoring and health risk assessment of lead particulate. Doubtless particle size is a critical parameter with respect to collection efficiency and transport, solubility, chemical-transformation and toxicological properties. However, it must be remembered that lead in any particle size seen within these discussions is, or soon can be, hazardous to children and other receptors.

Concentrations in Other Media: The remainder of Chapter 3 is dedicated to summarizing lead concentrations observed in various environmental media. These are good and informative discussions. The air lead discussion does a good job of describing the large decreases noted with the gasoline phase down. It would also be important to note the decreases associated with point sources in the same time frame, particularly with respect to smelting, mineral processing and secondary recycling. The ambient air lead decreases in the vicinity of these sources were significantly greater than those achieved in urban areas through the phase down. Moreover, many of these industries were shutdown and were replaced in the global sense outside the U.S.

The document would also benefit from a larger historic perspective to the other media similar to that developed for air. Other media and biota have seen significant concentration decreases since the phase down and industry shutdown and cleanups. However, the pattern, length of time, relative magnitude and toxicological significance of these declines vary by media. It would be beneficial to note these patterns, particularly in light of the increasing interest in ecological response and potential secondary standard considerations.

Chapter 3 should develop a conclusion oriented format similar to that employed for the causality associations made in Chapter 2 and the other subject areas of the document.

Chapter 4 Exposure, Toxicokinetics and Biomarkers:

Pathways and Exposure Parameters: Chapter 4 addresses Exposure Assessment in Section 4.1 and begins with an appropriate discussion of pathways. There appears to be a typo on line 4 regarding the gasoline phase down date, but the text notes the associated historic reductions in air lead exposures. It is always good to note that significant air lead reductions also were noted in the vicinity of point sources, and other media concentration decreases were observed, both attendant to and independent of the phase down and curtailments in industrial emissions.

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This is followed by a discussion of indoor versus outdoor versus personal exposure that does not quite reach a conclusion. It seems that personal exposures are generally higher than the ambient exposures, which is important to note, and indoor versus outdoor tends to vary with site specifics and season and cannot be generalized. Soils and dusts are discussed next. The complexity and interrelationship of these variables and the role of air media in the continual exchange between these media is emphasized, but it might be noted that a clear empirical relationship between soil and dust has yet to be demonstrated, as it also likely tends to vary with specific site conditions, seasonality, etc.

The remainder of this section discusses other media and effectively summarizes the current state of knowledge with respect to relative significance of these media in acting as sources in pathways common to North America, Europe and Australia, where almost all of these studies have derived. A limited amount of discussion is provided for China. However, it should be noted that exposure sources and pathways are moderated by behavior, housing, lifestyle and cultural patterns. These patterns vary immensely for developing and middle-income countries and cultures, as compared to the U.S. Also many immigrant populations in the U.S. may engage in ethnic and cultural behaviors leaving them more susceptible to lead intake and uptake.

All of these sections would benefit from a brief description of how the concentrations and relative intakes have decreased in association with the phase down, industrial source curtailment, and decrease in lead content of consumer goods over the past three decades. Table 4.5 could benefit from some additional description of dry weight versus wet weight considerations for dietary crops and how that relates to ingestion of lead from soils versus foodstuff. Description of how concentrations and intakes from these same media can vary dramatically in cultural, ethnic and socio-economic situations differing from Europe and North America would be a benefit to the document.

In Table 4.6, one study shows lead content in ug as opposed to a concentration. A footnote would be appropriate to allow comparison to other entries in the Table.

Toxicokinetics: The toxicokinetics discussion is concise and well-developed and reflective of the current understanding and practice in risk assessment activities. The discussion could be amplified with respect to the uncertainties associated with uptake and excretion in populations outside of North America and European populations.

Biomarkers: The discussion in Section 4.3.2 Blood Lead measurements has a confusing transition from analytical techniques to ALAD from page 4-35 to 4-36. Perhaps the analytical discussion could be expanded and some transition language be inserted, or the discussion of the significance of ALAD be moved or combined with Section 4.3.4.4.

Relationship of Lead in Blood and Lead in Bone: The overall discussion of the health significance and interrelationship of these biomarkers is informative and well presented. It might

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be useful to discuss the relevance of these biomarkers in terms of internal exposure to organs and tissue and the relevance to immediate toxic health effects.

Exposure-Blood Lead Relationships: Section 4.5 through the Summary in Section 4.7 provides a concise summary of this topic area that has been well vetted in several previous SAB reviews and represents the current scientific consensus for this important segment of risk assessment process.

Chapter 4 should develop a conclusion oriented format similar to that employed for the causality associations made in Chapter 2 and the other subject areas of the document.

Policy Implications: The ISA is reflective of a long history of lead health and risk assessment and attendant regulatory programs. These actions have reduced lead exposures and health effects in the U.S. and other developed countries by orders of magnitude over the past four decades. As the populations in these countries attain ever lower blood lead levels and body burdens, investigators are observing previously undetected adverse outcomes. In the last decade, lead-related research has continued to concentrate on investigating and defining adverse effects at ever-lower exposure levels. Similarly the ISA is heavily weighted toward assessing and characterizing new information regarding health effects.

However, during this time, the EPA and other environmental regulators have diminished the monitoring and programmatic attention paid to lead, as the overt health risks have subsided. This has occurred because the ambient exposures have decreased dramatically to levels unimaginable in previous decades, and other health risks have taken priority.

Nevertheless, the demand for and consumption of lead in the U.S. have increased markedly in this century, accompanied by substantial price increases in the domestic and world market. As noted above, other general exposure considerations related to market and use factors; (i.e. emission sources, commercial uses, waste, recovery, recycling and disposition and fate of lead) in the U.S. today are poorly understood, nor have exposure parameters been quantified. There is no treatment of these factors in the ISA. It is unclear if there are any data, or whether EPA sought such information. Several other issues, generally considered in policy decisions, not included in the ISA are advancements in pollution control capacity, best available technologies, and best practices for source control.

Data Sources: Unfortunately, the best information for production data, emission information, industry transition and economic indicators is more likely to be found in the trade literature and government agency records. Much of the practical knowledge that has been developed in applying scientific findings and methods to remedial and regulatory activities is generated and housed in programmatic activities within EPA and the States. In 2006, the CASAC urged the Agency to mine these data sources in the last review. The sources cited in the ISA review seem to have been limited to the peer reviewed literature and the national

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air quality monitoring network. Perhaps in developing the attendant policy recommendations, the Agency will explore the life cycle and economic impacts of lead regulation in both this country and overseas.

Global Considerations: Although U.S. lead demand has increased, domestic production and recycling and recovery of many discarded lead products have been diverted to developing countries. Much of this is diversion results from EPA policies. On the international scene, the increased price and demand observed in the last five years has had devastating effects, substantially more severe than those observed in the 1970s. Environmental exposures and lead poisoning are increasing with several incidences of severe morbidity and substantial mortality associated with the increased demand and high price of metals. Hundreds of children have died at some sites and thousands suffer irreversible health effects that their families and communities must cope with for decades.

More children in the world die and suffer irreversible, dysfunctional brain damage due to lead poisoning today than in the last fifty years. Although air lead levels in the U.S. are at an all time low, the implications for regulation of lead releases and the impact of U.S. policies in the global environment and human health are substantial. If not in the ISA, it seems the EPA has an obligation to inform the policy makers of the global consequences of lead regulation, or lack thereof. Similarly the U.S. has an obligation to export the scientific knowledge base, consequences of irresponsible practices, and information regarding mitigation of adverse effects. The subsequent regulatory policies when implemented have ramifications, not only beyond ambient air lead levels, but throughout the world.

Comments from Dr. Gail Wasserman

Comments on Chapter 2 - Integrative Health and Ecological Effects Overview

1. I disagree with the use of the conceptual heading “neurological” to encompass what are functional (ie neuropsychological or neurocognitive deficits; neurobehavioral problems) as well as structural and mechanistic components. The super-ordinate heading would be better cast as “central and peripheral nervous system” effects (at the level of cardio-vascular, or immune-system effects). Neurological is too narrow a term for the array of functional, mechanistic, and structural problems considered under this heading. In point of fact, those of us studying neurocognitive or neurobehavioral problems are rarely neurologists, and our work is not published in neurology journals.
2. I found the framework for designating the strength of the causal evidence to be very helpful. The characterization of the minimal BLL at which effects are noted is clear.
3. Many practitioners may read the integrated summary (Chapter 2) rather than the longer, more detailed presentation of the evidence (Chapter 5). There is no mention of effect sizes or clinical significance for the neuropsychological and neurobehavioral outcomes summarized in Chapter 2. This would be essential for a cost-benefit discussion.
4. The integration of associations across human and animal species was clear and useful.

Comments on Chapter 5 - Integrated Health Effects of Lead Exposure

General points:

1. See point 1 raised for Chapter 2.
2. In some places, more cross-talk inter-relating commonalities (or their lack) between content areas reviewed would help. As examples, see specific points made below for pages 5-53, 5-57, 5-58, 5-105.
3. There is little provided in this chapter, or elsewhere, about the clinical significance of the effect sizes noted, which is important for policy-making and cost-benefit analysts. I think this holds for the effect sizes for other outcomes as well.

Also, the point I made for the REA holds here as well: there needs to be a discussion of the metrics of IQ scoring and the clinical significance of small deficits. As a practicing psychologist, I find the parsing of IQ scores into “points lost” that translates into fractions of a single point

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very uncomfortable, especially given that the standard error of measurement for most IQ tests is 5 points. There needs to be some risk/benefit awareness of the policy implications of interventions at very low blood lead levels.

4. Regarding the expansion of endpoints, I think there is already a wide array. Integration of associations within and across endpoints could be increased, though, especially concerning mechanisms. In other words, are there evaluated (or not yet evaluated) models that interrelate mechanistic impacts across several systems?

Specific points:

P 5-45. There is inconsistency across age in behavioral effects (depression in adults, ADHD in kids). Some attempt should be made to explain this.

Table 5-2 and 5-3 The Factor-Litvak paper is a secondary summary; it would be better to reference the original source, which is not cited in this chapter. That citation is:

Wasserman, G.A., Liu, X., Lolacono, N.,J., Factor-Litvak, P., Kline, J. K., Popovac, D., Morina, N., Musabegovic, A., Vrenezi, N., Capuni-Paracka, S., Lekic, V., Pretini-Redjepi, E., Hadzialjevic, S., Slavkovich, V., & Graziano, J.H. (1997). Lead exposure and intelligence in 7 year old children. *Environmental Health Perspectives*, 105, 956-962.

In another report, we noted differential impact on Visual Motor, rather than language, skill, significantly so:

Wasserman, G.A., Graziano, J.H., Factor-Litvak, P., Popovac, D., Morina, N., Musabegovic, A., Vrenzi, N., Capuni-Paracka, S., Lekic, V., Pretini-Redjepi, E., Hadzialevic, S., Slavkovich V., Kline, J., Shrout, P. & Stein, Z. (1994). Consequences of lead exposure and iron supplementation on childhood development at age four years. *Neurotoxicology & Teratology*, 16, 233-240.

P 5-52, L 29. In fact, MOST tests of neurocognitive function are interrelated, not “several”.

P 5-53 and 54 and Table 5-4. Specific Indices of Cognitive Function. It should be pointed out that these other functions contribute to intelligence, so these effects are more by way of explaining the IQ associations than additional functions impacted. It would helpful to point out if some functions are consistently more impacted than others (for example, the prospective studies often reported stronger associations with visual motor than with verbal skills). The inclusion of the Bayley MDI results in this section represents somewhat of an organizational anomaly, as this assessment is an infant developmental test, and not one that measures the differentiated areas presented in the table. Tests of “intelligence” do not generally measure skills in the early age range tapped on the Bayley, so it is often seen as an analogue to overall intelligence, appropriate

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to its age-range. On the other hand, developmental research consistently documents reduced stability and predictive validity for tests of abilities measured for infants (as opposed to preschoolers) so that the generally stronger effects shown for MDI relative to the other items in Table 5-4 should be seen in this context. Finally, the discussion of specific indices should include Canfield RL, Gendle MH, Cory-Slechta DA. Impaired neuropsychological functioning in lead-exposed children. *Dev.Neuropsychol.* 2004;26:513-40, which used the CANTAB battery.

P 5-57. In the discussion of the Surkan study, the point should be made that maternal self-esteem (like depression) is likely related to many components of childrearing that are commonly measured by an instrument such as the HOME Scale (for which most studies of children's neurocognitive or neurobehavioral function often adjust).

P 5-58. It should not be a surprise that academic performance reveals adverse associations with lead exposure, since these probably result from more primary impacts on both neurocognitive (IQ, processing) and behavioral (attention problems) functions.

P 5-62. In a section on timing of exposure and cognition, the report cites our 1998 paper, which is a study of behavior problems. We looked at timing of exposure in the paper above, in preschoolers. The accompanying table (5-7) has the correct reference. This section, on the timing of exposure, beginning on p 5-61, appears in a section on cognition, but then Table 5.5 also considers behavior problems. There is a separate later section on behavior problems, and shouldn't that section precede a discussion of the duration of exposure? Or consider the timing of behavioral effects separately when those effects are discussed, later.

P 5-69. The Wasserman et al 2000 paper compared different trajectories of lead exposure across ages 4-7y, finding independent prenatal and postnatal associations, as well as a sharply increased slope of BL/IQ association in the 0-10 ug/dl range.

Wasserman, G.A., Liu, X., Popovac, D., Factor-Litvak, P., Kline, J., Wateraux, 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.

P 5-99. The text notes that non-cognitive effects are more complex to study than are IQ tests. I do not disagree, but the report should indicate why.

P5-101, L2, also Figs 5-20 and 5-21. Text should point out that while an adverse association with BPb is generally reflected in negative associations (lower IQ with increasing BPb), for behavior problems, this association is positive (more problems with increasing BPb). Otherwise the use of the word "positive" may be confusing to some readers.

P5-105 (and others in this section). The review should consistently note what features (if any) were adjusted for in these analyses. Also, as noted, the section on adults reports associations for

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mood problems, while in children, externalizing (conduct, attention) problems are most commonly noted. Is there any way to make sense of these developmental differences in content areas?

P5-121. In discussing PD and tremor, some mention should be made of the importance of adjusting for co-exposures, particularly Mn, with commonly reported associations.

P5-127, L 29. I believe this should read “associated”, and not “association”.

There is a new paper following up the New England sample into adulthood: Mazumdar et al. Environmental Health 2011, 10:24

Comments from Dr. Michael Weitzman

Comments on Chapter 2 – Integrative Health and Ecological Effects Overview

The Lead Project team has done a remarkable job in synthesizing a vast literature and presenting it scientifically and comprehensibly.

I have one concern and one additional suggestion:

1. The only mention of lead-based paint as a source of children's exposure was on page 2-6, in the third paragraph: "Studies have suggested that blood Pb is associated with exposure to Pb paints in older homes...." It has been my understanding for quite a long time that household lead in dust, primarily from deteriorated lead based paint, is the major source of children's exposure. I believe that this is central to most pediatric and federal and local efforts to prevent childhood lead exposure. Is this deserving of more discussion?
2. While Chapter 2, 5 and 6 mention lead and delinquent behavior, there is a literature, albeit small, that shows an association between blood lead levels and violent behaviors (e.g. several studies by R. Nevin. Should these be discussed for the purposes of thoroughness?

Comments on Chapter 6 - Susceptible Populations and Lifestages

The Lead Project team is to be truly congratulated for a remarkably comprehensive and cogent review of the literature on Susceptibility Factors and Lifestages Related to (a) Lead Exposure and Dose and (b) Lead Induced Health Effects. I do think that the characteristics included are appropriate and consistent and I do believe it appropriate to include material on susceptibility factors related to Pb exposure and dose.

The following comments and suggestions are offered with the intention of improving an already excellent document:

1. There are a fair number of places in the Section concerning Lead Induced Health Effects that better belong in the Section concerning Lead Exposure and Dose, as this is often confusing as written. A few examples include (possibly) sentence 1, last paragraph, pg 6-11; sentence 2, paragraph 1, pg 6-12; paragraph one under Hormones, pg 6-16 and 6-17 and paragraph 2 under Vitamin D Receptor, pg 6-18 and 6-19.

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2. Similarly, throughout this chapter there is mention that specific topics are discussed in more detail elsewhere in the overall document and it would be extremely useful to point the reader to those sections in which specific topics are discussed in more detail.
3. For areas of discussion that rely on a small number of studies I urge caution comparable to that so well utilized elsewhere to explicitly identify the level within the five level hierarchy classifying the weight of evidence for causation.
4. In discussing Susceptibility to Lead Exposure and Dose I suggest adding discussion of:
 - a. housing—one could use various cut points, such as pre-1950 housing or pre-1970 housing—data are available on how housing stock age relates to blood lead levels. There also are data about numbers of housing units in the USA that have had windows replaced or lead related abatements or renovations (repairs) and how these relate to lead exposure and these data have, I believe, been well summarized by the National Center for Healthy Housing and HUD. Similarly, household dust lead levels clearly represent a (the) major risk factor for lead exposure, at least of children, and I suggest considering a related section on what is known about soil lead levels and coverings with grass and foundation shrubbery and blood lead levels
 - b. nutritional status-while briefly mentioned in the section on Lead Induced Health Effects, there is no parallel section on diet and lead exposure: iron deficiency is well documented to increase lead absorption from the GI tract, with a less robust literature on dietary calcium and fat intake. Given the obesity epidemic, with its associated epidemic of low Serum Vitamin D levels (as a fat soluble vitamin it is not yet clear that low serum Vitamin D levels in overweight individuals manifest comparable effects to low Vitamin D levels in the general population)
 - c. immigrant groups from countries with high lead exposure
 - d. users of folk remedies from multiple countries such as India, Mexico and those in Southeast Asia.
5. Susceptibility Factors and Lifestages and Lead Induced Health Effects - This section, again, I believe to be excellent, but would benefit from extensive cross referencing to other chapters. Several things that I think deserve some discussion include:
 - a. are children and adults with ongoing exposure at more risk than those whose exposure is more limited, and does intermittent repeated increased exposures cause additional, cumulative or multiplicative damage?
 - b. the use of low birthweight in many studies of lead effects on children is very non-specific, very low birthweight, extremely low birthweight, intraventricular hemorrhages all may (or may not) characterize vulnerable populations, as may

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- c. children who have repeated head trauma (i.e repeat concussions)
- d. those from bilingual homes
- e. those whose mothers OR fathers are depressed or suffer from other mental illnesses
- f. pg 6-21: are the associations with lead different for Type 1 and Type 2 Diabetes?
- g. are there no studies of lead exposure and obesity, or of lead leading to increased rates of co-morbidities of those who are obese (elevated cholesterol/triglycerides, hypertension, central obesity, hepatitis, hypertension) or of asthma and lead exposure?