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

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Dr. Herbert A. Allen 2
Dr. Deborah Cory-Slechta 5
Dr. Chris E. Johnson 7
Dr. Susan Korrick 9
Mr. Richard Poirot 14
Dr. Michael Rabinowitz 27
Dr. Ian von Lindern 31

Dr. Herbert A. Allen

Comments on Chapter 7 - Ecological Effects of Lead

This draft of the ISA represents a substantial improvement of the document. Chapter 7 is well-written and comprehensive. The assessments are based on the studies presented and are easily followed. I have a number of relatively minor points to make. These are listed in the sequence that they appear in the document rather than by relative importance.

p. 7-6. L. 21. - Not only is the lead bound by the organic matter, but it also forms cabonato- and sulfide precipitates.

p. 7-8 L. 1 and 3.- t1/2 should be t1/2

p.7-11. L. 2 and 5. - MgCl should be MgCl2

p. 7-26. L. 11-28. - This is an excellent summary.

p. 7-32. L. 20-31. - This is an excellent introduction.

p. 7-36. L.35. - nitrate rather than Nitrate

p. 7-50. L. 14-17. - This sentence is not clear.

p. 7-70. L. 6-16. - This presents only the inorganicic species that are present. To state that these are the forms that are present is not true and is countered elsewhere. In addition to these inorganic forms, lead humate is present in the solid phase and lead fulvate is present in solution.

p. 7-71. L. 16. - Delete “both”.

p. 7-75. L. 5. and p. 7-134. L. 7. - “commercially-derived humic acid” is a poor description. If this was Aldrich Humic Acid, state that as this is a widely used material.

p. 7-75. L. 13. - µmole is a unit of mass, not of concentration. If this was 1 µmole/liter, write 1 µM. The unit µM means µmolar or µmole/liter. This error occurs in a number of other locations. I have tried to find them all and to note them.

p. 7-85. L. 8. - 2.9 and 6.6 mg Pb is not in the correct units. The mass of plant tissue considered mudt be presented. Perhaps this should be mg Pb/ g plant. Likewise, in the next line, the mass of sediment must be indicated. Perhaps this should be 0.3 mg/ g sediment.

p. 7-88. L. 16. - The volume of water is not indicated. Perhaps this should be 0.05 µM rather than 0.05 µmole.

p. 7-88. l. 34. - Perhaps “rate” should be deleted as time is not a variable.

p. 7-92. L. 8. - Report the concentration of Pb not of Pb-nitrate. An example of a good style is p. 7-93. l. 20.

p. 7-92. L. 24-26. - This is not clear. Why is the average Pb in sediment given together with the range of values for body burden? Why not provide ranges for both or use mean values for both? Is this whole body?

p. 7-101. L. 18 - µmole is a unit of mass, not of concentration.

p. 7-102. L. 8, 14 and 35. - mmol is a unit of mass, not of concentration.

p. 7-102. L. 15. - µmol is a unit of mass, not of concentration.

p. 7-103. L. 6. - mmol is a unit of mass, not of concentration (twice).

p. 7-104. L. 2. - Na+ not Na2+. Ca2+ not Ca+.

p. 7-110. L. 36 and 37. - Ca2+ not Ca+.

p. 7-110. L. 38. - Probably Ca2+ not Ca.

p. 7-111. L. 1. - Probably Zn2+, Cd2+, Na+, Cl-, Ag+, and Cu2+.

p. 7-111. L. 2 and 4. - Probably Ca2+ and Na+.

p. 7-111. L. 17 and 23. - Ca2+ not Ca+.

p. 7-113. L. 8. - Were these exposure concentrations analytically verified? These are among the lowest concentrations cited in this chapter and this are of importance in establishing the concentrations that can elicit biological response. 10 nM Pb is approximately 2 µg/L. Low concentrations of Pb are difficult to maintain and, of course, the potential for contamination always exists.

p. 7-114. L. 9 - The unit is not expressed clearly, but I take it to be 0.3-0.48 g Pb/ kg wet fish • day. This value is HUGE. Is the unit for Pb mass correct?

p. 7-114. L. 26. - The second value in the list should probably be 0.01 rather than 001.

p. 7-115. L. 6. - These concentrations are even less than those in p. 7-113. L. 8. On a weight basis they correspond to 0.02 to 0.2 µg Pb/L. That is a concentration below that found in most freshwaters. If goldfish are representative of all fish, the conclusion is that most fish are affected by environmental lead

exposure. This is a very serious finding and the results should be very carefully assessed and the discussion should be increased.

p. 7-119. L. 29. - The citation is subscript.

p. 7-127. L. 16-22. - Because the chemical reactions involved in considering critical load should be expressed with molar units rather than weight units, the difference in critical loads for different metals should also be compared on a molar basis. The atomic weight of Pb is more than 3 times that of Cu, Ni, and Zn. Comparing moles a metal loading at the critical load, the value for lead is approximately a factor of 3 greater than that for the other metals, not an order of magnitude greater.

p. 7-133. L. 20-25. - The constancy of Na+, Ca2+, and Mg2+ concentrations is true for marine systems that are little influenced by fresh water. However, very important saltwater systems are embayments and estuaries. Saltwater systems encompass a range of salinities from just above that of freshwater to full strength seawater.

p. 7-152. L. 21-25. - This is not what is shown on the next page. Bioaccumulation does primarily occur from uptake of Pb from water via the gills.

p. 7-166. L. 17. - Is there a chlorophyll that contains Ca?

Dr. Deborah Cory-Slechta

Comments on Chapter 5

My comments on Chapter 5 are primarily editorial, with one exception. I am concerned about associating lead with ADHD. All but one of these studies is based on teacher and/or parent report and not a clinical diagnosis, hence the reliability of such a diagnosis is questionable. There is significant support for an association of Pb with attention-related behaviors, and maybe this is the appropriate terminology, unless there is some reference that can show reliability of teacher/parent reports to actual clinical diagnosis.

p. 5-26; lines 16-20; are the increases vs. decreases related to Pb level and perhaps indicative of a non-linear curve?

p.5-27, lines 22-24; again, could it also be indicative of non-linear concentration-effect functions?

p. 5-47, lines 25-27: increased apoptosis of what?

p. 5-55, lines 11-12: I think significant caution needs to be exercised in ascribing Pb exposure to ADHD. Most of the studies cited in support of this are based on parent and or teacher reports and not on an actual clinical diagnosis, which makes them far less credible (albeit teacher reports are likely better than parents).

p. 5-75, Figure 5-5: It would be helpful if the actual names of the tests were used here; they are for some of the studies, but not others, e.g., for Chiodo the table lists ‘perseverative errors’, but on what test? The specific tests are not listed in Table 5-5 either for many of the studies, just references to e.g., Cantab. It would be particularly useful to somehow incorporate the specific test names (e.g., rule learning and reversal is the IntraExtra Dimensional Shift Set).

p. 5-88 line 4: change mouse to rodent, the test is used with both rats and mice

p. 5-89, line 5-6: again, the name of the specific test being referred to should be included. To cite this as ‘components of the Cantab’ is confusing as there is not “the Cantab” but a menu of specific tests one can use from Cantab.

p.5-91, line 14: should be two months not two weeks

p. 5-99, lines 4-7. Its not clear why this distinction is being made; for both humans and animals, the subjects assess the ability to complete a task when the ‘rules change’. That is the same thing as say ‘changes in reinforcement’.

p. 5-114, lines 23-24. Not sure that it is really appropriate to say that the relevance of the plasma Pb fraction is not clear; we know that this is the fraction that delivers Pb to soft tissue. For example, in

chelation studies, e.g., Korean workers after CaEDTA, it is the plasma Pb compartment that shows increases in Pb even as blood Pb levels decline and in animal studies that same procedure results in increases in tissue Pb levels, including brain.

p. 5-120, lines 9-20: it would be more appropriate to describe the test as "shift focus to another dimension of the stimulus that defines correct responding (e.g., color to shape)"

pp. 5-128-132. Here again, I repeat the concern about linking Pb to ADHD specifically which is a clinical diagnosis. All but one of the cited studies for this section relies on parent and or teacher reports, which is far less confirmatory. Options include citing this significant limitation, looking at the literature to see how predictive teacher reports of ADHD are relative to clinical diagnosis, or describing these as 'attention-related' deficits.

p. 5-138, lines 16: should change "absence of a fixed schedule of reinforcement" to something like " time interval preceding the availability of reward opportunity".

p. 5-138, line 19: change 'interresponse rates' to 'interresponse times'

p. 5-138, line 27 change 'repeat-acquisition' to either 'repeated acquisition' or 'repeated learning'

p. 5-150, line 9, change "frontal striatum' to 'frontal cortex and striatum'

p. 5-150, line 10, delete space before period after 'density'

p. 5-151, line 6, change 'processed' to 'processes'

p. 5-207, lines 21-25. A reference needs to be added for this description of outcomes.

Comments on Chapter 6

I have no major comments for Chapter 6, the revised version of the draft has addressed my prior comments. The only thing that I think would still be useful is some indication of magnitude of the differences in Pb toxicity that can occur with some of the factors that confer susceptibility or risk. In particular, while polymorphisms can induce differential risk, what is the magnitude of the differences that they are associated with? It would seem that an understanding of the risk associated with such factors would be useful for risk assessment and for the question of whether or not the current methods of ascribing safety factors of 3 or 10, for example, actually accommodate those susceptibilities.

Dr. Chris E. Johnson

In my review of the 2nd Draft ISA, I focused my attention on chapters 3 and 7. I hope to have additional comments, particularly on Chapters 1 and 2 at the CASAC Review Panel meeting on April 10-11.

Comments on Chapter 3

Chapter 3 of the 2nd Draft ISA is generally well written, as was the first draft. The deficiencies in the first draft have largely been addressed. While there are a few issues that panelists are likely to raise, this is a very impressive summary of the sources, transport and fate of Pb in the environment.

Question: *Please comment on the adequacy of … [the] changes to the chapter and recommend any revisions to improve the discussion of key information?*

The discussion of the limitations of current and alternative methods for measurement of total suspended particulate Pb is a good addition and strengthens the document. I will leave it to others with more expertise in atmospheric physics and chemistry to comment on the quality of these amendments. Similarly, the editing of questionable data appears to have made for a more cohesive discussion of national trends.

The addition of section (3.5.5) on background Pb concentrations is a good idea. However, I think it needs some work. The issue of how to define "background" is never fully resolved. In the first paragraph, the policy relevant background (PRB) is defined as "those concentrations that would occur in the U.S. in the absence of anthropogenic emissions in continental North America. This definition contrasts with the more scientific definition of a "natural" background, unaffected by any anthropogenic sources. Both are difficult to assess, but the natural background is probably easier. In any event, the section never actually comes to a conclusion on what the background levels might be. The section is comprised of several paragraphs explaining why it is so hard to estimate PRB levels. Surely it is possible to bracket a range for background airborne, soil and aquatic Pb concentrations.

The additional work done on section 3.6.1, relating soil Pb to air Pb is very useful.

Question: *Is material clearly, succinctly, and accurately provided?*

The material presented in Chapter 3 was, I thought, generally accurate, complete and relevant. It is clearly presented. It is hard to call a 200-page chapter "succinct," but this is a complicated topic, and to a certain extent, the CASAC demanded the level of detail found in this second draft document.

Question: …*provide guidance that may refine the scientific interpretation and/or improve the representation of the science.*

In the areas of my expertise – soil and water chemistry – Chapter 3 does an excellent job in laying out a clear conceptual model for the behavior of Pb. I have no recommendations for refinement at this time.

Comments on Chapter 7

Chapter 7 of the 2nd Draft ISA is also nicely organized and well-written. I focused most my attention on the areas of terrestrial systems and ecosystems-level issues. The changes made to these sections of Chapter 7 add some valuable depth to what was already a generally good survey of the literature.

Question: *Please comment on … various revisions and other changes to the chapter and recommend any revisions to improve the discussion of key information?*

The two most notable additions to the terrestrial effects sections of Chapter 7 were: (1) additional discussion of ecosystem receptors and the Biotic Ligand Model; and (2) increased discussion of ecosystem services. These are welcome additions, though the application of the receptor concept in terrestrial systems is difficult to generalize across biomes.

As I commented on the previous draft, the discussion of ecosystem services in the case of terrestrial Pb is contextual. Terrestrial soils provide a service to aquatic ecosystems by sequestering Pb through sorption and coprecipitation. At the same time, this very process potentially damages services that the same systems provide, such as agricultural production. What is in the 2nd Draft ISA is valuable, but only tells half of an admittedly complicated story.

Dr. Susan Korrick

Chapter 5 – Integrated Health Effects

Overall Comments and Considerations:

In general, Chapter 5 of this 2nd draft Pb ISA addressed a number of the comments made in review of the 1st draft. Specifically, in a number of sections it improves upon key issues identified in review of the 1st draft including: (1) more explicitly identifying the state-of-knowledge as of the 2006 AQCD as a baseline upon which to build; (2) using a better weight of evidence analysis in assessing the literature on a particular health outcome by better assessment of the consistency and strength of findings across studies, confounding, implications of effect modification, etc.; (4) improving the integration of toxicologic and epidemiologic literature both in terms of the relevance of outcomes (e.g., drawing parallels among homologous or related measures in animal models and human studies) and exposure levels (e.g., identifying studies of animal exposures within range of typical contemporary non-occupationally exposed populations); (5) more explicitly discussing exposure timing and its toxicologic implications; and (6) acknowledging limitations in using 'current' blood Pb as a measure of relevant exposure especially in older populations. In addition, the revision has updated its organization to improve readability and interpretability – e.g., presenting data in some tables ordered by exposure level and cohort, using more consistent units of exposure measurement for toxicologic studies, etc.

However, while assessing the overall quality of the revised document in general terms, this reviewer found it challenging to follow-up on how this 2nd draft addresses reviewer comments from the 1st draft in more particular terms. In contrast to journal peer review, e.g., there was no documentation either in a written point-by-point response to review or in highlighted text of what has been added, deleted or edited from the previous draft. In a 500-page document, this makes tracking progress particularly difficult. Furthermore, where previous reviewer recommendations have not been followed, there is no mechanism for understanding why this was the case. Indeed, in a few cases, previous recommendations based on factual inaccuracies were not corrected (e.g., see summary of Kim et al. 2009b [p. 5-62 to 63, figure 5-3] where blood Mn units are reported in μg/dL but should be μg/L. As currently reported, these Mn levels are substantially higher than Kim et al. describes and than reasonable expectation and thus are important to the study's interpretation). Lastly, in a few sections, it appears there has been cut-and-paste editing such that some text has lost logical progression. In the extreme, sentences and even content, appear to have been re-arranged in such a way that the text does not make any sense at all (e.g., see the discussion of Pb and ALS on page 5-164, lines 20-36).

Chapter 5 Charge Questions:

1. *Please comment on the extent to which the revised discussion of the evidence and the causal determinations accurately reflect the weight of evidence for endpoints within a major outcome category and the strengths and limitations of studies (e.g., study design, control for potential confounding, statistical analysis) that comprise the evidence base.*

This revised (2nd) draft does a better job than the 1st draft in reflecting the weight of evidence in causal determinations. It does so in several ways: focusing on findings that are consistent across the literature on a topic and acknowledging limitations to inferences where findings are inconsistent, acknowledging whether confounding may impact results, and including caveats based on study design limitations. Also, some new studies have been added and weak ones (e.g., case reports) removed which are appropriate updates. The conclusion, e.g. for the nervous system section, begins with a general comment about a 'causal' relationship of Pb with nervous system effects and then indicates which specific associations (e.g., childhood cognitive function and inattention) largely motivate this conclusion based on the weight of evidence. This is a useful approach. However, implementation of these improvements varies by health outcome. E.g., in the review of child neurodevelopmental literature there is not much discussion of how study design limitations might impact the weight of evidence (e.g., there is limited, if any, discussion of the relative value of cross-sectional vs. longitudinal analyses or self-reported diagnosis in studies of ADHD) whereas the review of adult neurodegenerative disease more consistently acknowledges study design issues (e.g., potential reverse causality in case-control studies).

2. *Please comment on the adequacy with which evidence has been integrated between toxicological and epidemiological studies, in particular: the increased emphasis on toxicological findings most relevant to Pb-associated effects in humans; the discussion of results from homologous or parallel tests (e.g., response inhibition, blood pressure, renal function); and discussion of evidence describing modes of action for Pb-associated health effects. (a) Has coherence of findings among related endpoints been sufficiently described? (b) Please comment on the effectiveness of the integration of scientific evidence both within sections for specific endpoints and summary sections.*

This revision integrates toxicology and human literature much more effectively than the 1st draft by having a clearer focus on homologous/parallel outcomes between the animal and epidemiologic literature. E.g., in the discussion of nervous system effects, animal assessments are explicitly described in terms of which human assessments they parallel (there's a nice example of this on p. 5-99 in the discussion of cognitive flexibility). Similarly, mechanistic toxicity/mode of action studies are discussed in terms of relevant human effects. Also, there is more discussion and explicit description of exposure levels in the toxicology literature reviewed (e.g., inclusion of blood Pb and, in some cases, even bone Pb levels in animals) so relevance to human exposures can be more clearly delineated. However, some areas were not consistently addressed. E.g., for nervous system effects, a number of the animal studies reviewed had exposures well in excess of those typical of current human populations; if, or how, this might impact applicability to humans was not addressed. Similarly experimental animal exposure routes (e.g., intraperitoneal injection) to human exposures was not explicitly addressed in the nervous system literature review.

3. *Please comment on the extent to which conclusions regarding the blood and bone Pb levels with which various health effects are associated in epidemiologic studies accurately reflect the weight of evidence given the study designs and statistical methods employed and populations examined (e.g., school-aged children, adolescents, adults without occupational exposure, adults with occupational exposure). (a) Are inferences regarding the specific Pb exposure scenario (e.g., level, timing, frequency, and duration) that contributed to the observed associations consistent with the evidence?*

Generally, this revised draft is careful to distinguish between settings (based on study design, study population, etc.) in which a given Pb exposure level (in blood or bone) is likely associated with a particular health outcome and settings in which a given Pb exposure level may not directly account for observed health effects because of the possible contribution of previously elevated or longer term exposures. Likewise, there was clear acknowledgement that blood Pb in adults includes information about past exposure (via bone Pb mobilization, e.g.). However, apropos of charge item #2 above, there were some instances of an apparent disconnect between relevant exposures in human as compared to animal data. E.g., for neurodevelopmental toxicities, there was a recurrent theme of prenatal/early life exposures being key to Pb neurotoxicities in developing animals whereas a number of recent human studies suggest that concurrent (later childhood) Pb exposure may be the most toxic. This seeming discrepancy and the possible risk represented by concurrent childhood blood Pb (especially in the context of early life exposure) was not really addressed.

Specific Comments:

Nervous system effects

Page 5-79: How does "past exp via maternal bone Pb" impact cord blood? Is this comment assuming there were higher exposures in earlier pregnancy prior to delivery absent some exogenous exposure source? Are there data to support this? E.g., calcium demands in pregnancy, especially early in pregnancy, are relatively small (e.g., compared to lactation) so differential effects on Pb mobilization across pregnancy seem unlikely.

Page 5-53: Removed case study from this section which is good but same concerns as with 1st draft. MRI studies cited include children (ages 9-13), some cross-sectional analyses, so description of "young adults with prior childhood Pb exposures" (Cecil et al. 2005) does not seem accurate.

Figures 5-2 & 5-3: BPb levels and effect estimates look different for some studies compared with 1st draft, not clear what changed or why (e.g., used concurrent vs. lifetime exposure effect estimates for Canfield et al., 2003a?)

Page 5-63, figure 5-3: As with 1st draft, Mn units should be mcg/L not mcg/dL. This matters since, otherwise, it looks as if Mn exposures were enormous in the population and interpretation of relative Pb contribution is more complicated.

Page 5-64: Try to consistently provide Pb exposure levels, not done for some studies (Kordas et al, 2011; Roy et al., 2011)

Pages 5-66: Apparent and repeated emphasis on HOME as a key confounder throughout this section seems misdirected (e.g., see page 5-102). Clearly HOME is important but a broader and more balanced discussion of confounding overall would be more useful. HOME is just one component of a large number of key potential confounders for child nervous system effects.

Page 5-68: Moffitt et al., 2001 should be Jedrychowski et al. 2009a; line 7 insert larger *decrease* in MDI

Page 5-69: It is unclear what text is saying about interaction between Pb and folate in determination of MDI effects. Does folate lower blood Pb levels or decreased target tissue sensitivity to Pb's toxicity at the same level of exposure? Importance of distinction between exposure modification and effect modification seems blurred.

Page 5-78: Five Korean studies (should be *cities*?) with null findings but didn't give reference or BPb levels….need reference Cho et al., 2010.

Page 5-100: No chelation discussion for humans? Is succimer trial too old (main result NEJM 2001)?

Page 5-101: Weight of evidence "based on frequency of examination", what does this mean? In this section and elsewhere, some discussion integrating what's known about critical exposure periods in epidemiologic literature and what current thinking is re. the meaning of concurrent blood Pb and its association with cognitive function in children would be helpful. E.g., is there some 'acute' blood Pb effect postnatally? Is high concurrent blood Pb a proxy for identifying children with consistent high Pb exposures over time? Or something else?

Page 5-117: PbxGene interaction commentary for adult cognitive function: "Results were ***NOT*** uniform across…cognitive tests…"

Page 5-119/120: Recent studies looked at concurrent BPb – distinction btw cross-sectional vs. prospective designs not always clear. Cannot always infer that concurrent BPb is most potent if lack information about earlier life BPb levels and their relationship with behavior outcomes. Text is unclear on this point although this does not mitigate importance of concurrent exposure, always must consider the possibility of reverse causation.

Page 5-120, lines 11 & 15: Should be increases in ***inattention***, not attention…or ***"increased inattention"***

Table 5-10: Several NHANES analyses for ADHD dx – ADHD dx in NHANES from parental report (+/- Rx use). Limitations of this outcome measure should be mentioned. E.g., outcome reporting bias, outcome measurement error, and possible confounding by regional differences in diagnosis (there are differences in medical practice by regions in the U.S.) and regional differences in Pb exposure risk.

Page 5-132: Do not understand logic of statements re. confounding for ADHD analyses. Specifically, for parental ADHD to be a confounder of Pb-ADHD behavior, parental Pb does not have to be highly associated with parental ADHD (which is in current text). Given the strong familial component of ADHD risk, parental ADHD would only have to be correlated with child Pb to be a confounder.

Page 5-142: Opler et al. (2004, 2008) assessing schizophrenia using δ–ALA level as a proxy for BPb (>15) is an important outcome but limitations of exposure assessment and how to integrate these studies into the context of this document need to be clear.

Page 5-155: This page is one example of an issue that comes up elsewhere: units for bone Pb measures in animals are incorrect. This impacts the interpretability of the exposure information. Units are reported incorrectly as μg/dL whereas they should be μg/gm bone mineral.

Page 5-160: Pb effects on retina "are modified by dose of Pb" seems an odd way to describe the literature. Was this meant to indicate that a number of the Pb-associated changes in vision in the toxicology literature do not follow a monotonic (or even threshold) dose-response? If so, say so, and then discuss what these atypical dose-response relationships might mean, if they are biologically plausible, and, if not, if that undermines the robustness of any observed associations.

Page 5-165: The motor section, last paragraph looks as if it's been cut and pasted so it no longer makes sense (plus punctuation problems). "The collective body of evidence demonstrates that within the same population of children…" doesn't make sense. Where are the "observations that Pb exposure affects development and function of …[motor]…systems"?

Page 5-162: The description of findings re. seizures in animal models doesn't explain the basic experimental study design/premise before jumping into results so the text is hard to follow– this happens several times throughout descriptions of the animal literature for nervous system effects.

Page 5-164: For ALS, discussion of potential for differential survival time to bias Pb association is very, very confusing. It is impossible to follow the argument, I suspect something was edited in a way that muddled content.

Page 5-167: line 12 – replace PD with ET.

Page 5-168: The discussion of the toxicology literature's evidence of a possible role of of microglial cells in neuro-inflammatory processes is confusing, talks about two cell types without specifying which two cell types are intended. Was text cut and pasted into the wrong place?

Page 5-169: Toxicologic evidence of Pb-induced cell apoptosis is largely observed at very high exposures; this issue is not acknowledged and its potential relevance, or lack of, to current population exposures is not mentioned but should be.

Page 5-170: Incongruities btw epidemiology and animal studies of Pb and AD may not just be because of wrong exposure time (i.e., developmental exposure matters most and epidemiology largely relies on adult exposure measures). Even recent animal studies are largely conducted at doses well in excess of expectation for current non-occupationally exposed aging adults. The potential role of exposure level on incongruities is not discussed but should be. Are authors assuming a non-threshold effect? If so this should be discussed and explained. This is an example where integration between toxicology and epidemiology literature could be improved.

Page 5-219: Clarify what's cross sectional and what's prospective for ADHD studies.

Page 5-221: For line 18 "temporality" should be "directionality"?

Page 5-224, lines 23-27: Cannot say weight of evidence supports concurrent exposure as most deleterious and then in the next sentence indicate that considerable uncertainty exists on critical exposure period. Latter seems the better conclusion.

Mr. Richard Poirot

Overall, **Chapter 3** is much improved, with changes responsive to previous review comments. The discussion of historical changes to emissions inventories is much more clearly presented. The expanded discussions on natural and intercontinental background Pb and on air Pb/ soil/Pb relationships are helpful. The HERO system works flawlessly and represents a major improvement to the review process.

I was disappointed that the comparison of collocated Pb measurements in different size fractions was removed (rather than repaired – to include only concurrent, above-MDL, paired samples), as I think there could be useful information content there. At a minimum, you might just append the Cavender & Schmidt (2007) memo comparing Pb in different PM sizes prepared for the previous NAAQS review, although hopefully this might be updated to include a few more years of data. You could also reproduce the similar (table 3) information in the excellent Cho *et al.* (2011) literature review paper. Possibly you could also summarize the size distribution results derived from the many studies you cite (and several others listed below) using MOUDI samplers in a single table or graphic. Of particular interest would be information about how Pb particle size distributions might change over time, by season, by proximity to different source types, or as a function of concentration or chemical composition. It would also be helpful if information on particle size, concentration and/or composition presented in Chapter 3 could be more directly linked to the exposure and toxicokinetics information in Chapter 4.

The discussion of limitations of the current TSP FRM sampler has been much improved, and various other Pb sampling (& analytical) methods are reviewed. However, there isn't really much discussion of practical alternatives, such as the louvered lo-vol inlet - or scaled-up version of it (Kenny et al., 2005), other than to indicate they "could be tested". There is also no discussion, in chapter 3 or 4, relating to what particle cut size(s) would be most desirable in a Pb FRM. The "Integrative Summary" states (p 2-6) that "the Pb-TSP indicator was retained in 2008 in recognition of the role of all PM sizes in ambient air Pb exposures", but relatively little information is presented (in Chapter 4 or elsewhere) on what the role(s) of different Pb particle sizes actually are in terms of human exposure and uptake. Arguably inhalation (fine particle only) is more efficient than ingestion (Hodgkins *et al.*, 1991); ingested fine particles are absorbed more efficiently than coarse ones (Barltrop and Meek, 1979); and are composed of more inherently soluble Pb compounds than coarse particles. Fine particles penetrate more efficiently into indoor environments – by various transfer mechanisms, and once deposited to surfaces, are more readily picked up and ingested (Juhasz *et al*., 2011). So arguably, a sampler (like the TSP hi-vol) that excludes progressively larger fractions of progressively larger particles (and does so most effectively when high wind speeds suspend the highest concentrations of ultra-coarse particles) – may not be so bad after all…

Chapter 3 concludes that our understanding of TSP sampling errors, particle size distributions, and possible alternative samplers has not changed much since the last review cycle. This is true enough, but unless we plan to hear similar laments in each subsequent Pb NAAQS review cycle, we need to start thinking more proactively about alternative sampling approaches. What are the desired particle cut size characteristics for sampling Pb in the ambient air? If a sampler could be developed that would consistently capture particles larger (or smaller) than those captured by the hi-vol under different wind

conditions, would that be an improvement? Are there practical upper particle cut size limits to what can be consistently achieved for different wind conditions by filter sampling techniques, and might these size limits also be justified by the spatial (population) representativeness of the resulting measurements, and/or by the decreasing bio-relevance of larger particle sizes? Is there a need to start routinely collecting additional information on particle size distributions at sites with high Pb concentrations?

Specific Comments

P 3-1, lines 25-26: Maybe insert "a majority of" before "ambient airborne lead", as you indicate on p 3-8 that organic Pb – which may comprise up to 20% of Pb emitted from piston aircraft - would remain largely in vapor phase.

P 3-5, lines 4-5: It's not clear what "this category" refers to. Should there be some preceding statement indicating what (relatively large) % of Pb was emitted from what (relatively small) % of the largest emitting counties? Along similar lines, it might be helpful to include something like a list of the largest point sources, at least summarized by category, if not by name. Given that there are 20,000 airports contributing to the largest total emission category (with roughly half the Pb emitted at/near the airport), it's hard to get a sense of how individual airports compare with other large Pb sources.

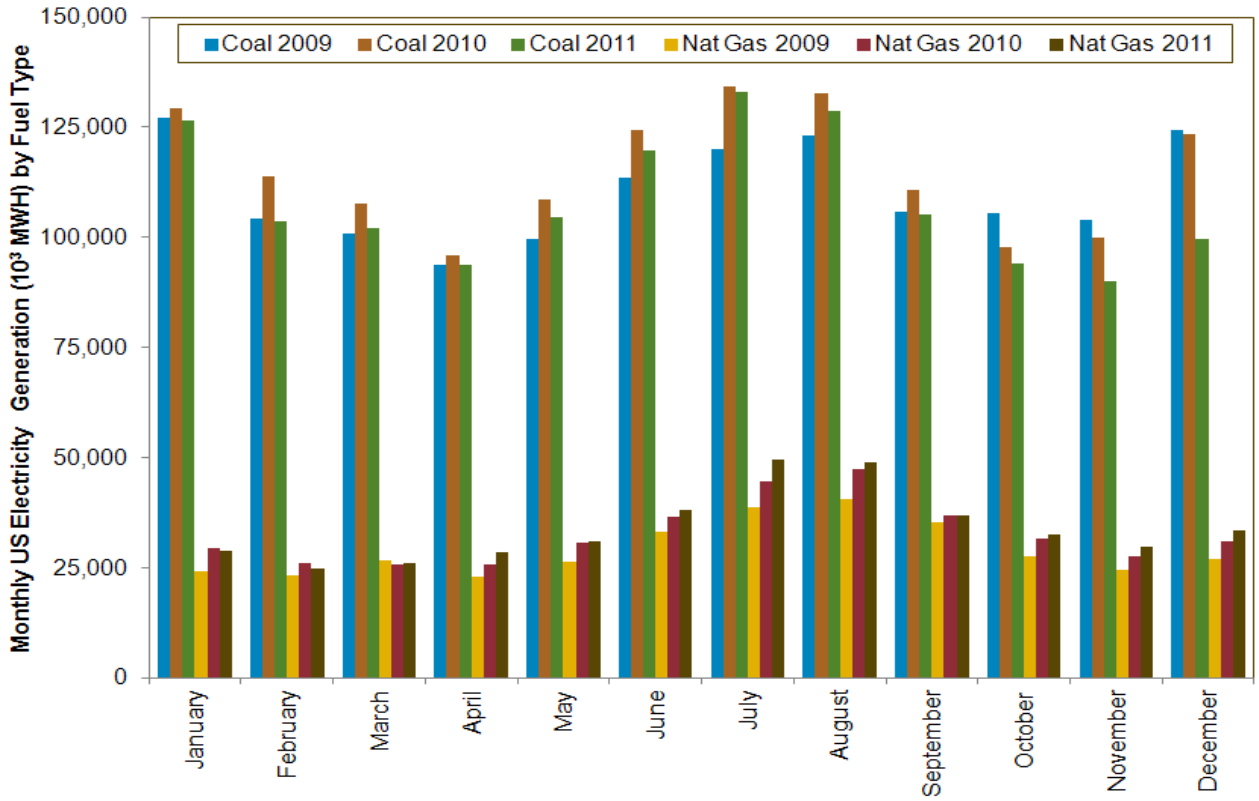
P 3-9, line 2: Can you indicate how far downwind of the smelter the concentrations were 35 x higher? It's also not clear what "(0.625-0.880 $\mu g/m^3$)" refers to. I assume it might be the range of measured downwind concentrations. If so, you might move it to follow "downwind" – rather than "upwind".

P 3-9, lines 20-21: I assume this estimate of "nationwide median fugitive emissions" is specific to secondary Pb processing facilities? Also, in this section you use the terms "secondary", "smelting", "processing" and "recovery". Do these have different meanings? If so, some explanation would help.

P 3-10, line 11: Is there any indication of what fraction of Pb from coal combustion is in the form of relatively insoluble $PbSO_4$? See for example Tan *et al.* (2006), Xie *et al*. (2009).

P 3-10, lines 15-19: I wasn't aware that such large amounts of crude oil (Pb emissions similar to residual oil) were being burned. Also, adding these estimates for coal (200 tons/yr), crude (100-500 tons/yr), and residual oil (25-700 tons/yr), yields a range of 325 to 1400 tons/yr. This is a large range and a factor of 2 to 10 greater than the 149 tons from fuel combustion presented in Figure 3-3. Are emissions estimates really this uncertain, and if so (or if not) some additional discussion seems warranted.

P 3-11, lines 16-18: Just citing West Virginia patterns for US seems simplistic. I think there's generally a summer peak in US power demand due to air conditioning, but the summer peak in utility coal burning is not much higher than a secondary winter peak, as much of the increased summer power demand is supplied by seasonally cheap natural gas.



From: http://www.eia.gov/electricity/monthly/epm_table_grapher.cfm?t=epmt_1_2

P 3-11, lines 21-22: Maybe mention that this 63% Pb from incinerators was based on just 6 sample days.

P 3-12, lines 17-20: Again, it seems worth mentioning that this 20% Pb from Canadian wildfires was out of 6 days, 1 or 2 of which included the highest wildfire smoke concentrations ever seen in that region.

P 3-14, line 12: This higher concentration of Pb in the 0.18 to 0.32 µm size mode does not seem consistent with ground-up wheel weights (i.e. it's not the fine tail of the coarse mode). Can you offer other explanations, or at least observe that there may be other roadway (or regional) sources of fine mode Pb? See for example Thorpe and Harrison (2008), Maher et al. (2008).

P 3-16, line 14: Maybe change "comparison" to "difference".

P 3-16, lines 30-31: It's not clear what these percentages refer to. A month after demolition, was Pb 18% higher, 18% higher and 29% higher in dust on alleys, sidewalks and roadways than it was in those locations prior to demolition?

P 3-21, line 4: You might add something like "and systematic reductions in emissions from other lead sources" after "motor vehicles". Over the past 20 years, most of the Pb emissions reductions and air improvements have come from non-MV sources.

P 3-21, lines 8-12: [Seems like this paragraph belongs in section 3.3.1.2 (Deposition)]. I also think you overstate the solubility argument. Particle size dynamics are a more important contributing factor to the different removal mechanisms than solubility. Large particles will dry deposit relatively quickly whether they are soluble or not, nor would they tend to be removed predominantly by wet deposition processes if they were more soluble. For example, the current GEOS-CHEM treatment of (soluble) sea salt aerosol deposits ¾ of small particles (<4µ) by wet deposition, and ¾ of large particles (>4µ) by dry deposition. (http://wiki.seas.harvard.edu/geos-chem/index.php/Sea_salt_aerosols).

Fine particles do not dry deposit efficiently in any case, and insoluble components of fine particles are often coated/mixed with soluble species in internally mixed aerosols, and readily removed by wet deposition processes. Freshly emitted (fine particle) black carbon, for example, is considered primarily hydrophobic, but ages over time, becomes mixed with soluble species, becomes hydrophilic, and is removed primarily by wet deposition (Reimer *et al.*, 2010). An average of 47% of Pb in 2005 and 2006 wet deposition samples in the eastern Mediterranean was insoluble (Theodosi *et al.*, 2010). This paper also includes interesting observations of seasonal patterns in wet & dry Pb deposition, and changes in solubility with precipitation pH.

P 3-24, lines 3-6: You could change "at" to "near" in line 3, as the upper bound Pb V_d reported in the 2006 CD was 1.3 cm/s. Also, the 12-17 mg/m^2-year dry Pb deposition reported here for Tokyo Bay <u>was not</u> more than 10 times the upper bound of the range reported in the 2006 CD - which included 8.4-14 mg/m^2-year dry Pb deposition reported by Yi *et al.*, (2001) near Lake Michigan for 1993-1995 (see p. 2-57 of the 2006 CD).

P 3-24, line 32: You could change "in locations near" to "at" or "from".

P 3-25, lines 6-11: I don't understand why a "smoothed" gradient indicates resuspension. With no resuspension, I would still expect a relatively smooth gradient in deposition of pollutants away from long-term emission sources – maybe declining with the log of distance from source. More detail is needed to explain this. Also, any spatial pattern of lead in soil would likely reflect historical air concentrations and sources (including resuspension), rather than influence from current sources.

P 3-28, lines 29-31: These measurements indicating relatively greater resuspension of fine Pb than coarse are an interesting contrast with the model estimates of relatively greater suspension of coarse than fine particles on preceding page (p 3-27, lines 11-19).

P 3-39, lines 11-12: Is this (1 µg/l) the concentration of Pb (rather than DOC or Fe)?

P 3-46, line 17: What is "high quality deciduous litter"?

P 3-47, lines 32-37: You first refer to what Perdrial *et al*. "postulated", but then refer to it as "important new evidence".

P 3-53, lines 23-24: This sentence needs work.

P 3-56, line 14: In discussing the TSP FRM sampling biases with wind speed, it might also be worth noting that the lower collection efficiencies for larger particles at higher wind speeds coincide with (windy) conditions most conducive to suspending large Pb containing particles and sustaining their atmospheric presence over longer times and distances. Conversely, on days when samplers are not running, the TSP FRMs are also susceptible to passive sampling artifacts, increasing with increasing wind speed and particle size (McFarland *et al.*, 1979).

P 3-57, lines 6-7: "…have been thoroughly reviewed" (20 years ago). It would be helpful somewhere to include some discussion of what particle size(s) it would be desirable to collect (are most relevant to human exposure). Here or in Chapter 4, some discussion of how particle size characteristics relate to Pb uptake would be helpful, along with a more proactive demonstration that coarse particle Pb – within some size limits - is, in fact, of equal importance as fine Pb. How would we expect a given Blood Pb: Air Pb ratio to shift, if the size distribution of Air Pb particles shifted to larger (or smaller) particles?

P 3-57, line 29: Don't you mean "low-volume" PM_{10}?

p. 3-85, lines 4-5: While Pb compounds in PM may have relatively high densities, particle size is typically a more important factor, and it's only the larger particles (regardless of their densities – within limits) that tend to settle out quickly. Pb incorporated in small particles tends to be combined with other (lower-density) compounds and/or is not efficiently deposited near its emission sources – hence the wide spatial distribution of historical automotive Pb in remote locations.

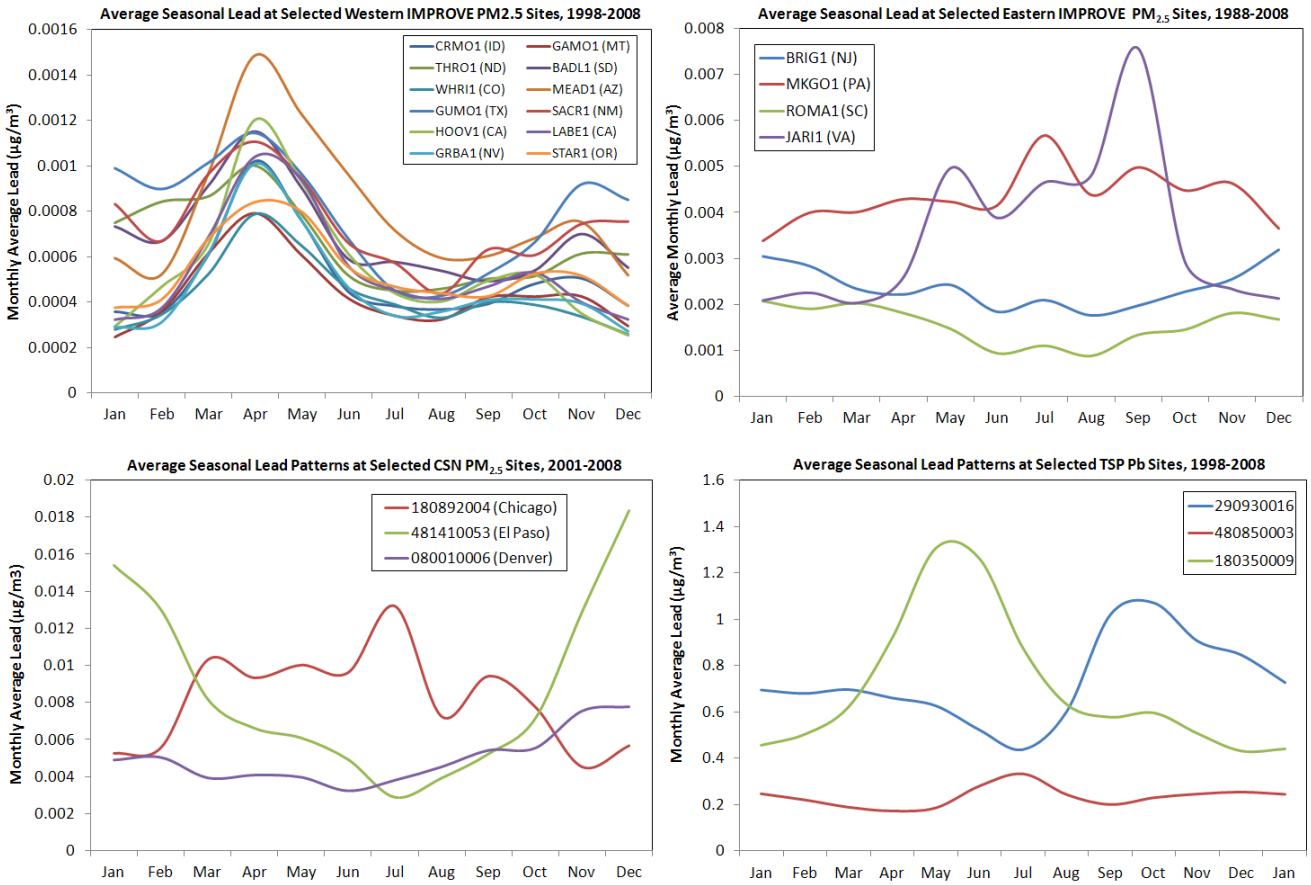
P 3-86, line 6: Could you give an example of what you mean by high spatial variability? It might be helpful to put this in context by comparing to the spatial variability of other pollutants.

P 3-85, line 36: Add "m" after "2".

P 3-88, Figure 3-20: This is a good example. It might be useful to have some other graphical depictions of long-term Pb trends to help support the emission inventory trends - for example: http://www.epa.gov/airtrends/lead.html .

P 3-93-96: There appears to be very little seasonal variability in the ambient Pb data as summarized here (hard to see any), and only very slight summer peaks in some of the Appendix 3.8.1 tables. This seems inconsistent with various recent analyses of Mielke, Laidlaw and others suggesting summer (or dry season) peaks in both fine soil and Pb. There do seem to be relatively strong seasonal peaks in children's blood lead in many studies. While several of these are mentioned in Chapter 4, there's not much associated discussion of potential causal or contributing factors. Other older and newer studies that might be considered include: Baghurst *et al*., 1992; US EPA, 1996; Yiin *et al*., 2000; Kemp *et al*., 2007; Havlena *et al*., 2009; Mielke *et al*., 2011; Laidlaw *et al*., 2011a, b). It might be useful to include some discussion of similarities & differences in seasonal patterns of air Pb and blood Pb, along with explanations of mechanisms that may contribute to the seasonal blood Pb increases.

I also think the aggregated summary nature of Figures 3-24 through 3-26 may be masking some of the unique seasonal patterns at individual sites – that may be revealing of source influences, or may affect exposure patterns. Note for example, the (low concentration but) distinct April peak in $PM_{2.5}$ Pb at remote Western IMPROVE sites, which would be consistent with Asian transport (van Donkelaar et al., 2008; Ewing et al. 2010, DePaolo, 2011). Note also the different seasonal patterns in other rural & urban $PM_{2.5}$ sites and at selected source-oriented TSP sites.



P 3-96, lines 10-16: You could add a category where Pb is mainly <2.5 µm – as would be expected from piston engine aircraft and other fuel combustion sources.

p. 3-97, line 2: You could add "TSP" before "sampling".

P 3-97, line 24 – and on following few pages: I note that you cite partial results from 7 or so different studies that all employed MOUDI samplers. What about summarizing all the MOUDI results in a single table or graphic to give an indication of similarities & differences in the particle size distributions observed in these different studies from different locations – possibly adding a few others like Albuquerque *et al*. (2012), Csavina *et al*. (2011), Fang and Huang (2011), Gao (2009), Lin *et al*. (2005), Wang *et al.* (2005), etc.

P 3-99, lines 33-37: You indicate that Pb and As were highly correlated in PM_{10} samples. It would be helpful to know if Pb:As correlations were lower in the fine and ultrafine samples from Hays *et al*. (2011), as this could help support (or not) the wheel weight hypothesis.

P 3-100, line 5: Do you mean "ng/m^3"?

P 3-100, line12: How "low"?

P 3-100, lines 22-24: How do the east & west directions relate to sampler orientation to the roadway, and is there any indication of roadway influence – in the larger or smaller size fractions? Possibly the review of this study could be deleted here as it's repeated in more detail in the following section – and is more relevant to the "non-road influences at near-road sites" theme of that section.

P 3-100: Another possibly useful reference on roadway Pb influences on air & soil Pb, vertical soil profiles and bioavailability is Preciado and Li (2006). Maher *et al*. (2008) present recent evidence of vehicle exhaust fine particle Pb deposition on leaves of roadside trees. Several more recent publications by Mark Laidlaw (2011a, b) make a persuasive case for the importance of resuspended roadside soils. See also his extensive bibliography at http://www.urbanleadpoisoning.com .

P 3-104, lines 10-11: Could you give an explanation for the large decrease in collocated sites – from 129 in 2007-08 to only 16 in 2009. Intuitively one would expect an increase in sites with the tighter new 2008 Pb NAAQS.

P 3-104, Figures 3-28 & 3-29: I'm suspicious about the several perfect 1.0 correlations between Pb and SO_2, $PM_{2.5}$ and CO in figure 3-28. Do all the "source" and "non-source" categories in these figures refer to the associated pollutants or to the Pb (or both)? I would imagine it might be possible to have a source-oriented PM_{10} site where collocated Pb measurements were not considered source-specific. What would be a "source" site for ozone?

P 3-105, line 32: So what's the implication of the Pb-humate observation?

P 3-107, Table 3-10: Considering $PM_{2.5}$ is included in PM_{10}, and PM_{10} in TSP, some of the numbers and huge differences in correlations for the different size fractions look very suspicious. For example the correlation between Pb and Fe is 0.43 for TSP, 0.99 for PM_{10} and -0.51 for $PM_{2.5}$. For Pb vs. Ni the correlations are 0.08 for TSP, 0.99 for PM_{10} and -0.67 for $PM_{2.5}$. I don't believe it, and suggest double-checking these numbers and either find a way to explain, comment critically, or delete the reference.

P 3-108, Figure 3-30: I like this figure! It might be instructive to show something similar for IMPROVE data. Also, some discussion of the relatively high correlation between Pb and K seems warranted. K is often a good tracer for wood smoke, although fireworks are also a large but only occasional source, and K is also contributed by soil and sea spray. None of the above – with the possible exception of woodsmoke (from forest fires) has been suggested as an important Pb source.

P 3-109, lines 23-25: Needs work.

P 3-110, line 1: Add “Pb” before “concentrations”.

P 3-110, lines 7-14: The seasonal patterns of Pb at many remote western US IMPROVE sites show a distinct (but very low concentration) Spring peak, which would be consistent with Asian transport. See figure below p 3-106 comment.

P 3-112, line 1: I think you mean “contemporary”, not “contemporaneous”.

P 3-112, line 23: Is “debrided” the right word here? Maybe peeling, degrading, flaking…

P 3-113 and generally: It’s helpful to include sample depths when you report soil concentrations, which you do in some cases but not in others.

P 3-113, lines 27-30: This indication of declining Pb concentrations in soils (is the only one discussed here but) could be an important point suggesting that current Pb loading rates are insufficient to sustain Pb concentrations at locations where resuspension of historically deposited Pb may be important. See also the roadside soil Pb profiles in Preciado and Li (2006), which show highest Pb concentrations at depths of 0.25 to 0.3 meters, decreasing substantially toward the surface.

P 3-114, lines 29-30: As indicated previously, some explanation would help understand why smooth gradients imply resuspension.

P 3-117, line 28: Add “g” after “µ”.

P 3-118: At some point in this section (or elsewhere), it would be helpful to discuss mechanisms like resuspension and air movement vs. tracking on shoes, etc. by which soil Pb gets incorporated into indoor dust (Layton and Beamer, 2009). Any information on the influence of particle size on these transport mechanisms would be helpful.

P 3-122 & 3-123, Figures 3-33 and 3-34: I don’t understand these figures and think additional explanation is needed. Why is the 1992-94 pattern - showing a large increase at Atlanta with declining concentrations downstream - so different from the closely overlapping 1990-1995 sediment pattern which shows no increase at Atlanta for that period or for any other time period back to 1975? Is this just because in the samples used to construct Figure 3-34, there were no samples near Atlanta (about 650 miles upstream) until you get to about 500 miles downstream? If this is the case, the lines between the 2 right-hand points are likely misleading as they suggest gradual increase from 750 to 500 miles, when in fact we expect a large step up at 650 miles, followed by gradual decline downstream. Adding further confusion, it looks like the largest concentrations in 3-34 at 500 miles occur where the Pb background (shown only in 3-33 but included in the 3-34 caption) jumps up.

P 3-123, lines 10 & 13: Could you report the MDL?

P 3-124, lines 11-18: This paragraph seems unnecessary – or could be shortened to “There are no routine measurements of Pb in precipitation in the US.”

p 3-125, line 15: I don't think "the greatest reductions occurred in late 1990s" is really correct for either Europe or the US. In the US, I would think the greatest reductions in Pb emissions, air & deposition likely occurred in the late 1970s and early 1980s (see Figures 3-1 & 3-20). Maybe you could say something like "prior to 1990, with relatively smaller reductions in recent years". As indicated above, some graphic illustrations showing long-term decreases in air Pb would be helpful.

P 3-129, line 75 (& Fig 3-37): A possible explanation for this extreme value at Noatack could be fugitive emissions from (or similar bedrock ore deposits to) the relatively nearby Red Dog mine (one of the largest Zn & Pb mines in the world). See: http://www.reddogseis.com , Hasselbach *et al*. 2005, and http://dec.alaska.gov/air/reddog.htm.

P 3-139, lines 8-18: As indicated in comment on p 3-29, I think you overstate the importance of solubility. Also, if coarse Pb is predominantly insoluble, then presumably it's less readily adsorbed when ingested, and may be relatively less injurious than its (soluble, respirable) fine particle counterparts.

P 3-139, line 21: You might add "most" before "surface waters". Surely there are some where current or past mining or smelting operations or other sources are locally more important than atmospheric deposition (for example Kurkjian *et al*. 2004; EPA Region 9 (2012); Coeur Alaska, inc. v. Southeast Alaska Conservation Council). While it seems logical that atmospheric deposition has been the most important source of Pb input to most surface waters historically, I wonder how current Pb deposition rates compare to resuspension from sediments (p 3-140, lines 1-3), or urban runoff contaminated by Pb wheel weights, historically deposited Pb, etc.? For example Davis *et al*. (2001) estimated that wet and dry Pb deposition contributed less than 20% of total Pb loading in urban runoff.

P 3-140, lines 26: This may be true, although it seems like you haven't tried very hard. You could have included some discussion of the excellent Cho *et al*. (2011) review paper, included a more carefully conducted update of the comparison of Pb in different size fractions included in the last draft Pb ISA (but dropped here), summarized the results from the various (at least 7) MOUDI studies you list here, and added a few others such as Albuquerque *et al*. (2012), Csavina *et al*. (2011), Fang and Huang (2011), Gao (2009), Lin *et al*. (2005) Wang *et al.* (2005), etc.

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Dr. Michael Rabinowitz

General Remarks in Response to Charge Question for Preamble, Preafce, Chapters 1 and 2:

This draft is much improved, particularly with the inclusion of these summary chapters, and by the placing of the causation discussion in the Preamble. This allows a reader to get a clear picture with sufficient, but not excessive, detail. I must assume some readers will only read Chapter 1, and a few more might read Chapter 2. In that role it appears to be an effective and useful resource.

Looking at Chapter Five and how its content was captured by Chapter, it appears adequate.

Specific Comments on Table of Comments

Table of Contents - why not add add the Preamble and Preface pagination?

Specific Comments on Preamble

p. xlviii, Evaluating Evidence - good, well written

p. li, line 34 - Two examples of effect modifiers are given: pre-existing disease (ok) and socio-comic status. I suggests not using socio-economic status because it's a notorious confounder. May I suggest nutritional status in its place as an effect modifier.

Specific Comments on Preface

p. lxvii, line 8, History - maybe add: It was recognized early that unlike other priority pollutants, such as ozone, lead exposure is multi-media, and that regulating air exposure did reduce total exposure, but other sources and pathways were at work.

Specific Comments on Chapter 1

p. 1-3 - add somewhere line 6 or 11 most of us get most of our daily lead intake from dietary sources. line 11 suggest add: Soil naturally contains some lead and can also act as a reservoir...

p. 1-5, line 11 - ....decreased, after an initial rapid decrease in blood lead, a subsequent slower decline mainly reflects the gradual .....

p. 1-8, line 17 - maybe also add uncertainty about the permanence or reversibility of lead effects. Some effects are reversible, such as interruption of the heme pathway, while others such as nerve conduction appear permanent. (?) maybe add at 1-10 line 21

p. 1-14, line 21 - fact that lead occurs naturally in soil and biota have evolved to accommodate this fact.

For example, many plants (grasses) sequester large amounts....

p. 1-15, line 21 - suggest add .....disease, assuming the shapes of the distribution stay the same.

p. 1-16, line 12 - suggest particle size and composition.

p. 1-17, line 30 - add maybe also sensitivity to lead decreasing with age.

p. 1-18, line 4 - suggest making a stronger statement. Certainly some genetic factors, nutritional status and.... place individuals are higher risk of lead susceptibility.

Specific Comments on Chapter 2

Needs to explicitly address: How do important uncertainties (line 13) translate into uncertainties in PbB standards?

p. 2-3 - I liked this part

p. 2-9, section 2.2.3, line 1 - Please, must, change word "measurable". Not helpful, only a tribute to analytical chemists. Suggest elevated Pb concentrations.

p. 2-23, line 11 - suggest At lower levels Pb was also observed.....

p. 2-23, line 16 - I maybe be wrong but isn't there a threshold for the ALAD response, near 15 ug/dL.

p. 2-23, line 28 - suggest removal of rat sentence. I thought we said animal data would not be used for dose comparison, only for mechanisms.

p. 2-28, line 7 - by the species and even the strain and its history of lead exposure

p. 2-29, line 5 - the waxy cuticle layer of the leaf tissue effectively binds particulate lead and little enters the leaf stoma.

p. 2-33, line 3 - maybe add ingestion of suspended (filterable) lead bearing particles

p. 2-33, line 28 - but not biomagnified nor bio-accumulated (to use a more accepted term). This is in contrast with mercury, where fish achieve higher concentrations than algae, and carnivorous fish have more than algae eaters.

p. 2-33, line 33 - can you give a value? how toxic?

p. 2-56, line 24 - ...there is no evidence. seems like a clumsy sentence that could be easily misinterpreted. suggest re-write.

p. 2-59, lines 7 to 13 - good, well written

p. 2-61, Table 2-7 - Looking at the slopes which summarize the air lead-blood lead relationship, it was tempting for me to see how me earlier experimental assessments of this slope compare, both from clinical work in Los Angeles and epidemiological work in Boston. Following the template of the table these two estimates follow:

Adult Populations
Ref hero id 815254 Magnitude of lead intake from respiration
Location: West Los Angeles
Years: 1973-1975
Subjects: Adult Male Veterans (n=5)
Analysis: Long term metabolic balance ward with constant duplicate diets, stable isotope dietary tracer with and without HEPA filtered air.

Model: linear changes in blood lead from changes in air, incomplete labeling of blood from dietary lead, and urinary output exceeding dietary uptake
Blood Pb: mean 19, range 17 to 25 ug/dL
Air Lead: 0.07 to 1.9 ug/m^3
Slope: 4.4

Children Populations
Ref hero id 093549 Lead in umbilical blood, indoor air, tap water and gasoline in Boston

Location: Boston
Years: 1980-1981
Subjects: Umbilical cord consecutive births n~7000
Analysis: Regression of 14 monthly mean cord blood (n~ 500) against mean indoor air lead (n~12)
Model: Linear
Blood Pb: 4.3-7.0 ug/dL (monthly mean)
Air Lead .02 to .2 ug/m^3 (monthly mean)

Slope: 9.1 (est 7 to 10) r=0.71 p<.01

Although there was a statistical relationship between monthly average air lead and monthly average cord blood, many other factors were much more predictive of blood lead levels, including parity, smoking, and indoor dust lead levels. Regarding subsequent childhood blood lead levels in this population, they did not correlate with their indoor air lead levels. Soil lead, dust lead, lead paint and refinishing activity were strong predictors.

We all recognize this blood lead slope is not a constant of nature, like the charge on an electron, where successively better measurements will yield better estimates of a specific underlying value. Rather the slope has a spread in values, reflecting variations seen among populations.

Taken together there is real consistency, within a factor of two, but also variations among populations and are evident. One would expect the slope would be steeper for children compared to adults because of their higher metabolic rate.

p. 2-62, Table 2-7 - Rodregues et al. I suspect the value is remarkably low because respirators were worn and the measured air was clipped on outside the respirator. Look into that and maybe drop.

p. 2-74, line 2 - adolescence and the onset of menstruation at which time.

p. 2-76, line 8 - add increased incidence of carriers of the gene for hemochromatosis, which results in increased gut uptake of lead

p. 2-79, Table 2-9 - line about nutrition, why not add calcium and zinc deficiencies?

Dr. Ian von Lindern

Preface, Preamble, Chapters 1 and 2

Please review and comment on the effectiveness of these revisions. Please comment on the extent to which Chapters 1 and 2 comprise a useful and effective approach for presenting this summary information and conclusions. Please recommend any revisions that may improve the scientific accuracy or presentation of these summary sections and the conclusions therein.

Addition of the Preamble and Executive Summary has markedly improved the readability and comprehensiveness of the document. The previous draft was well-edited, as are the added sections. The explanation and summaries progress from the most brief to a relatively full (but nevertheless) concise presentation of the salient issues brought out in the ISA. The historic perspective incorporating the findings of the previous AQCD findings are a particularly strong addition to the document.

In my opinion this is an excellent document that is both comprehensive and well presented as were the AQCDs produced in 1977, 1986 and 2006. However, I believe there are three fundamental weaknesses that detract from the tradition of EPA providing the seminal, scientifically sound review of the existing knowledge of lead poisoning that was fundamental to developing and implementing effective lead health policy and response throughout the world.

1. The scope of the review has been amended to an insular and less comprehensive document that will have adverse effects on the ability of both the EPA and other parties, who have historically relied on these reviews, to effect comprehensive and holistic policy.
2. The failure to collect and or assess information relative to the use and disposition of lead in US commerce, and the decision to exclude globally representative exposures, precludes the Agency from considering the effects of policy decisions in media other than air and beyond the boundaries of the US.
3. These factors, combined with diminished monitoring over the past two decades and reliance on outdated emissions inventories, reduce the Agency's ability to assess risk across the nation. As a result, EPA must rely on theoretical models, as opposed to observed exposures, to conduct appropriate risk assessments. Because so little additional information has been collected in the areas of use, consumption, emission factors, and ambient monitoring, these models will be a repeat of those supporting the 2006 documents, and will be decades out of date.

General Comments

The fundamental premise underlying the relative weakness of the ISA, in contrast to earlier AQCDs, can be found on page xlvi of the Preamble that states "… *the intent of the ISA is to provide a concise review, synthesis, and evaluation of the most policy-relevant science to serve as a scientific foundation for the review of the NAAQS, not extensive summaries of all health, ecological and welfare effects studies for a pollutant."*

EPA, subsequently, limits the ISA and the definition of *"policy relevant science"* to the *"peer reviewed literature"* and to "*exposures within one to two orders of magnitude of those currently observed in the US"*.

These limits, nevertheless, have resulted in a massive document that does a masterful job of recounting the findings of the 2006 AQCD and the state of knowledge with respect to the peer-reviewed literature from 2006-2010 regarding the health and ecological effects of low-level lead exposure in the US, Europe and Australia. An entire volume of 550 pages is dedicated to Chapter 5 the *Integrated Health Effects of Lead Exposure.* The length and detail presented in Chapter 5 is justifiable, in a health-centric sense, as a considerable amount of new information has accumulated in that relatively short amount of time.

In contrast, however, only 18 pages are reserved for *Sources of Lead* of which relatively little of the information is new. Moreover, virtually nothing is found in over 1100 pages of lead-related information regarding the uses or rates of consumption of lead, the role of lead in US and international commerce, lead production, the level of imports/exports of products and wastes, or the ultimate disposition, recovery, recycling or disposal of lead-containing materials.

The same deficiency was noted in the last NAAQS review and the 2006 AQCD was admittedly bereft of this information in comparison to the predecessor documents. It was clear at that time, as in previous iterations of the AQCD, such information was not to be found in the peer-reviewed literature. In the 1977 and 1986 AQCDs, source, production, and fate information was provided by an active lead industry in the US, and by EPA staff development and synthesis of trade, professional and commerce data sources, or so-called *grey literature*. Among CASAC's responsibilities in those years was to review the scientific credibility of those analyses and trade data, and its use in the criteria document, and ultimate formulation of lead policy.

The EPA has, through its change in approach, conveniently both made its job less challenging and short-changed the policy-makers (also making their job easier) by adopting a rule, exemplified in the ISA and, pre-destined to similarly limit policy in a myopic and insular way that concludes: *If it's not in US air, we don't care.*

The analyses then point out that air lead decreased by more than 90% from the 1970s to 2008. Similarly, dramatic decreases in blood lead levels in the US population and other biota and environmental media have also been observed. This is good news for the children, general population, and flora and fauna of the US; and should be considered a remarkable success in environmental health regulation.

However, a couple of points remain that, perhaps, question the validity of an approach that ignores the numerous areas of this planet that live two orders of magnitude above current US exposures.

i) In the last analyses of US commercial use of lead in the 2006 AQCD, domestic lead consumption had increased to levels near the peak tetra-ethyl lead years, presumably for batteries and the consumer electronics industry. However, domestic lead production had diminished as drastically as ambient air levels. At the primary smelting level, production will soon be zero as the last US smelter closes, and responsible recycling capacity in the US is limited.

   The absence of data or analyses in the ISA suggests that EPA, apparently, has little knowledge of where all this lead comes from, how it is used, how much is recovered or recycled, or its ultimate disposition. This is even though demand may likely increase as electric cars hit the markets. Rather than find out, the agency has, through the ISA, devised a way to avoid either finding out or admitting this deficiency.

ii) Beyond the US borders, in what can only be considered tragic, on a global basis today - more children are lead-poisoned, at higher absorption levels, unprecedented mortality rates, or with severe brain trauma doomed to lifetimes of stupidity and dependency - than has ever been recorded in the peer-review literature.

For EPA to apply the -*"If it's not in US air, we don't care"* position to these children, the Agency is seemingly convinced that US lead consumption and poisoned children in other countries are unrelated. However, it seems naïve to believe that a standard, with the policy implications of the NAAQS, has not influenced the magnitude and associated costs of production, recycling, recovery and disposal of lead and lead waste, and metals prices. There are numerous examples of poisoned children living in the vicinity of smelters producing lead for the US market; of discarded US car batteries poisoning children in Mexico, Latin America and the Caribbean; and of families poisoned from recovering metals from US e-waste in Africa and Asia. Previous iterations of the AQCDs provided a sound scientific basis for policy considerations in the US and were relied upon by other national and international entities to assess, bring attention to, and effect health responses to these situations. EPA, in the past, has and should continue to, take great pride in this laudable role. The ISA is silent on these issues.

Moreover, the substantial increases in both commodity and precious metals prices over the last five years have lead to unprecedented increases in both formal and informal mining, smelting and waste recovery across the globe. Yet the only mention of *global lead* in the ISA is in reference to "… only fine particulate lead is of consequence on a global basis, as most large particles fall out near the sources." This definition implies that only those particle emissions capable of dispersing into this country from overseas are significant. It is quite possible that the US sends far more lead waste across the oceans in container ships than the upper atmosphere delivers in small particles to the US.

It seems appropriate for the EPA through the ISA process to inform the Agency decision-makers, the CASAC, and eventual policy-makers and reviewers regarding the disposition of lead in US commerce, the health and environmental effects playing out on the global stage, and any connections or interactions that may be at play. It also seems incumbent on the Agency to develop the available information and subject it to the same scrutiny and evaluation that has been so well done regarding low-level health

effects within the current insular viewpoint.

Two examples of current events in the outside world that could be of interest and value to a less myopic ISA, and in providing a vetted information base for responsible policy development are discussed briefly below, There are many more.

1. The USEPA has recently concluded Trustee Settlements with Responsible Parties to guarantee cleanup of lead contaminated sites throughout the United States under CERCLA. These settlements run to billions of dollars with multi-national corporations. These funds depend on profits made by these companies producing metals largely in underdeveloped countries that do not subscribe to US pollution control standards. In these cases, the US standards and policies have contributed to the export of the US national production capacity to foreign countries subject to health and environmental exploitation. The concurrent need for these corporations to route profits to fund US cleanups could be coming at the expense of pollution control, thus exacerbating the damage done to children in these communities. Moreover, as the ISA demonstrates, human health risks in the US have been substantially diminished. As a result, the vast majority of the cleanup activities being undertaken in this country, with these trust monies, addresses ecological and water quality remedies. However, these laudable improvements in US "ecological and welfare effects" may well be coming at the cost of childhood lead poisoning in populations most vulnerable to those SES and concurrent disease risk co-factors so well identified in the ISA.

2.) There are today sites in Africa where children are dying of lead encephalopathy, in at least one case, at staggering rates. Some villages in northern Nigeria lost more than 25% of children under five years of age. An estimated 400-500 children died of lead poisoning in less than one-year in an overall population of 10,000. More than 2000 children, with blood lead levels averaging greater than 130 ug/dl, at presentation to clinics, have received multiple rounds of chelation treatment.

Another 20,000 people are likely lead poisoned and receiving no treatment. Among those are 1500 children under age 5 living in mud-hut homes with soil lead concentrations more than 1 % lead, with blood lead levels greater than 70 ug/dl, who cannot be provided treatment. A cohort of more than 5000 women, expected to have 5-10 children in their reproductive life, have persisting blood lead levels greater than 70 ug/dl. These populations live on less than $2 USD/day. More than 90% of the children presented for chelation have malaria. Mumps, measles, polio and meningitis are endemic in these communities. Last year more than 250 children under age 5, in hospital, were being simultaneously treated for lead poisoning, malaria, malnutrition and cholera,

It seems inappropriate that these situations are not considered "policy relevant" and are excluded from consideration in an "Integrated Science Assessment for Lead". It seems that, at least, a scientific review of these situations be conducted to assess whether consideration of these unprecedented case histories can contribute to the knowledge base regarding childhood lead poisoning, Moreover, it would seem appropriate to provide a properly vetted information basis for US policy-makers to assess whether regulation of lead in the US facilitates, contributes to, or possibly could help alleviate these tragedies.

Specific Comments:

Preamble Page lxvii, line 3: The History section for the NAAQS should also include (with similar reference to the key decisions) the pre-promulgation history, particularly noting that the EPA initially proposed regulating airborne lead through Best Available Technology (BAT) controls on point-source emission sources in 1974-75. The EPA was subsequently sued by public interest groups and eventually forced by the Courts to develop the NAAQS. Similarly, the promulgation was opposed and delayed by suits brought by lead industry advocates. These lawsuits were not resolved until 1980 when the NAAQS became effective. This history is important to underscore the point (well documented in the ISA discussion that follows in the document) that outside intervention by litigation has routinely been required to assist and provide guidance to the EPA in undertaking responsible review, assessment, and promulgation of lead regulation.

Preamble Page lxviii, line 29: A brief description of the actual computational basis specifically justifying the .15 ug/m^3 standard, and the rationale for averaging times would be helpful.

Executive Summary Page 1-2: The Section 1.2 discussion refers to Figure to Figure 1.1. The Figure is excellent and well described later in Chapter 4, but the discussion here seems overly brief and does not convey to the uninitiated reader the complexity of the Figure, nor the pathways the Figure represents. There seems to be a need for some transition language for the text immediately preceding and that following Figure 1.1, which moves from environmental pathway discussion abruptly to blood lead.

Chapter 2 Page 2.5 line 19: Several times in the discussion the term 0 is used to refer to the Preamble. This seems distractive and could be confusing to uninitiated readers.

Section 2.2.1 Page 2-6 line 9 and Page 2-10 line 6: These discussions refer to "… on a global scale lead is primarily associated with fine PM." In this context, and in similar discussions throughout the document, it seems that EPA by implication considers only those lead emissions that reach the US are significant on a global basis. In turn, this seems to imply that EPA defines the global atmosphere as a "source" rather than a transport mechanism, or exposure medium; that foreign populations are emitters rather than co-receptors; and that "local" emissions beyond US borders are unrelated to US policy.

Table 2-1: Including earlier concentrations observed in the US over the past few decades and those observed globally today would serve to put these relatively low exposures in an historic and international context.

Page 2-11 line 31: Description of the term "personal cloud effect" would be helpful.

Table 2-7: This Table does not include the slope estimates, nor the supporting studies, used in promulgation of the NAAQS in 1977-78. As this was the basis for EPA's NAAQS for over 25 years, it seems it should be listed for contrast with those studies reviewed to support the more recent standard and accumulating evidence.

Chapter 3 - Source to Concentration

Please comment on the adequacy of these and other changes to the chapter and recommend any revisions to improve the discussion of key information. Is material clearly, succinctly, and accurately provided? Where appropriate, please provide guidance that may refine the scientific interpretation and/or improve the representation of the science.

Sections 3.2 and 3.3: The EPA seemingly knows little about the use, consumption and ultimate disposition of lead in the US (see earlier general comments). These sections generally report the same deficient information developed for the 2006 AQCD. The synthesis of this lack of information should note the scarcity and the implications of being uninformed in this capacity.

Sections 3.4 and 3.5: This Section does a good job of describing the methods and network systems and the results of the various monitoring efforts. However, it is difficult to get any real answers to important questions in these sections. This in contrast to the health effects and ecological sections where the document provides synthesis analyses and draws significant conclusions with regard to causality, mode of action, potential effects, etc. It is difficult in the air monitoring sections to determine:

Which sites are monitored for compliance or exposure characterization?
How representative are these sites of the remainder of the country?
How many observations exceed health significant exposures or criteria?
What are the sources of those high levels?
Are measures being undertaken to control those sources?

The most informative presentations are in Tables 3-7 through 3-9 and Figures 3-23 through 3-26. These tables and figures seem to suggest that non-source- oriented lead TSP, lead-PM10, lead-PM2.5 show no lead problem with whatever is being monitored. Does this mean no lead problem for these sites, for similar sites in the US, or that these techniques are inappropriate?

Source oriented TSP, however, seems to a cause for consternation, at least at those sites being monitored. The mean concentration for all sites seems to be consistently well above the health significant level, at least for these sites. What does this imply for the overall US? What confidence does the EPA have that all significant sources are being monitored? This is particularly troublesome when it seems the Agency has little idea where, how, or in what quantities lead is used, consumed, or disposed.

In summary, there continues to be no “take away” message with regard to these data and analyses. 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?

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.

Page 3-13 line 2: spelling of “simualated”

Page 3-53 line 23: spelling of “were” where?

Section 3.6.8 and other locations: References to tissue lead concentrations should always indicate whether these values are wet weight or dry weight basis.

Chapter 4 - Exposure, Toxicokinetics and Biomarkers

The exposure section of Chapter 4 includes additional discussion of the relationship between airborne Ph-particle size distribution and exposure by inhalation and ingestion (e.g., hand-to mouth). Cross-referencing to Chapter 3 further emphasizes measurement errors and uncertainties that may affect exposure assessment for air Pb. A new section on exposure assessment methodologies was added that includes discussion of exposure representation within the IEUBK model and exposure modeling techniques.

The revised toxicokinetics section of Chapter 4 expands discussion on the effects of both past and current Pb exposure on blood Pb levels. Studies that followed blood Pb levels in individuals following cessation of high Pb exposure occupations and in children over the first several years of life were added. The section on bone Pb measurement was expanded. Air to blood slopes were reevaluated across the range of air Pb concentrations available in a given study with an emphasis on the central tendency of air Pb concentrations in each study.

With consideration of these revisions, please comment on the accuracy of the interpretation of the science. Are uncertainties and limitations of relevant data, methodologies and approaches adequately discussed? Where appropriate, please provide specific recommendations to refine the scientific interpretation and/or improve the representation of the science.

Chapter 4 is well organized, comprehensive and provides an understandable, accurate and balanced interpretation of the science as related to exposure, toxicokinetics, and biomarkers. The material added to this draft not only improves the readability of the material, but puts the information in the context of how it might be used to assess exposure and alternative techniques. The cross reference to Chapter 3 is an important addition, as uncertainties and insufficiencies in the database are key to reflect in any attempt to assess exposures.

The addition of the historical perspective provides important insight as to 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. Both Chapters 3 and 4, however, remain somewhat biased toward the gasoline phase down in this regard and would be better served by noting that significant emission and air lead reductions achieved in the vicinity of point sources. The major reductions in point source emissions were achieved through a combination of pollution control and elimination / curtailment of the industry. Two important aspects of this

realignment go unmentioned. These sources were also significant with respect to other metals and pollutant exposures that were similarly reduced. The export of the mineral processing operations also had profound effects with respect to risk co-factors in the US and exposures and systemic effects both here and abroad. Particularly important in the US were effects associated with numerous other metal-related pollutant concentration decreases in other media and levels of ecological risk, both locally and regionally. These effects were both attendant to and independent of the phase down and curtailments in industrial emissions.

The addition of the IEUBK oriented discussion illustrates the interdependence of various exposure routes. This is followed by an excellent discussion of other media that effectively summarizes the current state of knowledge with respect to relative significance of these media in acting as sources, in pathways, and as receptors. It is 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 US, Europe and Australia, where nearly all the science has been developed. It might be noted, as a prelude to Section 6, that many foreign and immigrant populations in the US engage in ethnic and cultural behaviors leaving them more susceptible to lead intake and uptake.

Chapter 4 provides a concise and well-developed discussion of the toxicokinetics that is reflective of the current understanding and practice in risk assessment activities. The overall discussion of the health significance and interrelationship of the toxicokinetics and biomarkers is informative and well presented. This chapter also provides a concise summary of exposure / blood lead relationship representative of the current scientific consensus for this important segment of risk assessment process.

Chapter 5 - Integrated Health Effects of Lead Exposure

In Chapter 5, the integration/synthesis of evidence between epidemiologic and toxicological studies and across related outcomes has been expanded throughout the text and in summaries of individual endpoints. In the summary and causal determination sections, we have described more explicitly the weight of evidence for each endpoint within a broad outcome category and specified the particular endpoints that contribute most heavily to the determination of causality. We have noted, where applicable, uncertainties regarding the specific Pb exposure periods, levels, frequency and duration that contributed to epidemiologic observations and included additional details and discussion of study limitations.

Please comment on the extent to which the revised discussion of the evidence and the causal determinations accurately reflect the weight of evidence for endpoints within a major outcome category and the strengths and limitations of studies (e.g., study design, control for potential confounding, statistical analysis) that comprise the evidence base.

Please comment on the adequacy with which evidence has been integrated between toxicological and epidemiologic studies, in particular: the increased emphasis on toxicological findings most relevant to Ph-associated effects in humans; the discussion of results from homologous or parallel tests (e.g., response inhibition, blood pressure, renal function); and discussion of evidence describing modes of action for Ph-associated health effects. Has the coherence of findings among related endpoints been

sufficiently described? Please comment on the effectiveness of the integration of scientific evidence both within sections for specific endpoints and summary sections.

Please comment on the extent to which conclusions regarding the blood and bone Pb levels with which various health effects are associated in epidemiologic studies accurately reflect the weight of evidence given the study designs and statistical methods employed and populations examined (e.g., school-aged children, adolescents, adults without occupational exposure, adults with occupational exposure). Are inferences regarding the specific Pb exposure scenarios (e.g., level, timing, frequency, and duration) that contributed to the observed associations consistent with the evidence?

Chapter 5 is monumental and is an excellent and impressive summary and synthesis of a subject area in which incredible advancements have been accomplished both in the last three decades and last five years.

Chapter 6 - Potentially At-Risk Populations

The introduction to Chapter 6 has been revised with expanded discussion to better capture the intricacies associated with characterizing populations potentially at greater risk for Ph-related health effects. Please comment on the adequacy of these revisions to clarify the consideration of potential at-risk populations, and recommend any revisions to improve the characterization of key findings and scientific conclusions.

In addition, please comment on whether the designation of some factors as having limited evidence adequately reflects the knowledge base considered and strength of evidence available.

Chapter 6 does an outstanding job of synthesizing the information from the previous chapters and identifying those populations potentially at risk due to lead exposure. However, it might be noted that these are hypothetical populations, as an effective national risk assessment is not possible due to the lack of appropriate exposure data.

Chapter 7 - Ecological Effects of Lead

The causal statements for ecological effects discussed in Chapter 7 have been reevaluated as advised by CASAC. There are now separate causal determinations for terrestrial and aquatic biota for each endpoint under consideration. In addition, the chapter now incorporates additional findings from the 2006 Pb AQCD on the effects of Pb on ecosystem receptors, an enhanced discussion of bioavailability and bioaccessibility, and separate discussions of marine and freshwater toxicity in the aquatic ecosystem section.

Please comment on the adequacy of these various revisions and other changes to the chapter and recommend any revisions to improve the discussion of key information.

Chapter 7 in and of itself is a major contribution to literature and understanding of this long-neglected aspect of both the mechanisms and the adverse effects of lead on US ecosystems and public welfare.