UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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June 4, 2013

EPA-CASAC-13-004

The Honorable Bob Perciasepe
Acting Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: CASAC Review of the EPA's *Integrated Science Assessment for Lead (Third External Review Draft – November 2012)*

Dear Acting Administrator Perciasepe:

The Clean Air Scientific Advisory Committee (CASAC) Lead Review Panel met on February 5, 2013, to peer review the EPA's *Integrated Science Assessment for Lead (Third External Review Draft – November 2012)*, hereafter referred to as the Third Draft ISA. The charge questions from the agency, the CASAC's consensus responses to the agency's charge questions and the individual review comments from the CASAC Lead Review Panel are enclosed. The CASAC's key points are highlighted below.

The CASAC commends the EPA for substantial revisions to the Second Draft ISA based upon its prior advice (July 2012). The CASAC believes that the ISA will serve as a scientifically sound foundation for the Lead (Pb) National Ambient Air Quality Standards (NAAQS) review. There is no need for the CASAC to review another draft of the ISA; however, the CASAC offers additional comments and recommendations on improving the document, as well as repeats some comments and recommendations that were not previously addressed.

The description in the ISA of the state of the science for measurement of particles greater than 10 micrometers has been improved. The CASAC has previously recommended that the EPA develop a new Pb air sampler to replace the high-volume total suspended particulates sampler. Although it is understood that the EPA will not have completed work on design and characterization of an improved "larger particle" sampler for this cycle of the Pb NAAQS, the EPA is encouraged to continue this process.

The application of the causal framework is clearer and better documented in the revised ISA. In general, the new health endpoint groupings are appropriate and contribute to greater clarity of causal determinations for all major organ systems. This new approach has the greatest impact on improving the section describing health effects related to the nervous system; however, standard naming conventions (e.g. clinical terminology and classification) should be used in the description of behavioral outcomes. In addition, there are several errors of health or study outcome categorization for the nervous system review and there are a few instances where appropriate specific health endpoints are the focus of the

literature review but the causal determination is applied, inappropriately, to a more general organ system.

The ISA should provide greater transparency in differentiating between the designations "likely to be causal relationship" between Pb exposures and health outcomes and "suggestive of a causal relationship." The EPA should be explicit in discussing the uncertainties and limitations which contributed to the designation. Additionally, the ISA should be clear about whether human data or animal data contributed to the causal determination. The EPA should change the designation between low level Pb exposure and renal dysfunction from "likely to be a causal relationship" to "suggestive of a causal relationship." The reasons for this change include: inconsistency of the epidemiological findings in large high-quality studies; absence of a demonstrated pathological mode of action for Pb nephrotoxicity in humans or animals at blood Pb concentrations less than 10 micrograms per deciliter; and the plausibility of reverse causation as an explanation for the association.

In reviewing literature, the EPA raises particular study design concerns multiple times throughout the ISA (e.g., lack of adjustment for parenting quality and poor representativeness of the study population), but their relevance to interpretation of a given study is not discussed. The representativeness of study populations is emphasized as a limitation in a number of nervous system studies. However, the lack of generalizability does not impact the validity of a study (unless there is effect measure modification). Therefore, in some cases, the findings of such studies may have been disproportionately discounted.

The EPA has integrated an extraordinary amount of information about at-risk populations and employs a useful framework(s) for critically reviewing and integrating information. However, indication of the relative magnitude of the effect modification from the risk factors is still missing. It would be extremely useful to add a table, with appropriate interpretive text, that summarizes the magnitude of effect modification that these various risk factors impose.

Although the ISA provides a fair and balanced evaluation of the existing scientific information on the ecological effects of Pb, one major concern is the inability to relate ecosystem effects to the concentrations of Pb that exist in air, soil, and water. For ecosystems, an important source of the Pb in soil and water is atmospheric deposition and transport processes. A critical loads approach is needed to establish this relationship. Research should be conducted to develop, calibrate, and test models applicable to the development of critical loads for Pb and other metals in the United States.

Tables that summarize the key studies leading to the causal determinations of the ecological effects of Pb are an important addition to the ISA. In addition to these tables, it would be useful to include a graph showing the various effects as a function of the exposure concentration. The environmental concentration range also could be shown. Distinctions should be made on the graph between measured concentrations and nominal concentrations (if there are not measured concentrations).

The CASAC appreciates the opportunity to provide advice on the ISA and looks forward to the EPA's response to the advice provided here.

Sincerely,

/signed/

Dr. H. Christopher Frey, Chair
Clean Air Scientific Advisory Committee

Enclosures

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U.S. Environmental Protection Agency
Clean Air Scientific Advisory Committee
CASAC Lead Review Panel (2010-2013)

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Consensus Responses to Charge Questions on
EPA's Integrated Science Assessment for Lead
(Third External Review Draft – November 2012)

Preamble; Legislative and Historical Background

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

The newly included flow diagrams in Figures I, II, and III of the Preamble in the *Integrated Science Assessment for Lead (Third External Review Draft – November 2012),* hereafter referred to as the Third Draft ISA, are helpful in summarizing the process employed to develop the ISA documents for criteria pollutants. However, it is not clear whether the strict criteria set forth in Figure II for a "study selected for inclusion in an ISA" reflects the actual process applied in the ISA for lead (Pb). As noted in the CASAC comments on the previous two Pb ISA documents, as well as in comments on this Third Draft ISA, the Pb ISA is an enormous document, unparalleled in the scope of its review of the vast literature on inorganic lead. By this very nature, it includes many studies that fall short of the ideal design and quality criteria presented in Figure II. For example, there are limitations in how particular studies of the effects of Pb on attention in children have adjusted for confounding by familial covariates, or how certain studies of the association of Pb on renal dysfunction have accounted for covariates that influence the course of chronic kidney disease (see the consensus responses to the Chapter 5 charge questions for further details). Contrary to the implication of Figure II, it is often acceptable to include such studies in the ISA, as long as the limitations are clearly identified and their contribution to the weight of evidence for causal inference is appropriately modulated.

The revised approach to causal determination in the Third Draft ISA that now examines specific health endpoints within an organ system, rather than broad organ system effects, is a welcome improvement. As detailed in the consensus responses for the other chapters, the health effects criteria in Table II that distinguish "likely to be a causal relationship" from "suggestive of a causal relationship" are sometimes challenging to apply. In these circumstances, there should be an expanded discussion in Table II (or in the narrative) of the nature of the evidence that informed the judgment in favor of one category versus another.

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

Please comment on the adequacy of these and other changes to the chapters and recommend any revisions to improve the discussion of key information. Please recommend any revisions that may further improve the clarity of discussion.

Section 1.2 (page 1-3) briefly notes that there are multiple pathways that ultimately result in human exposure to ambient (atmospheric) Pb. However, Chapters 1 and 2 should include an expanded discussion of the relative contributions of the direct and indirect air-related pathways to overall human Pb exposure. For example, as noted in Tables 4-1 and 4-2, direct inhalation of Pb in ambient air at

currently prevalent levels makes a minor contribution to total exposure. The indirect contribution of ambient Pb to Pb in outdoor soil and indoor dust is more substantial, as might be the contribution of legacy air emissions to Pb in the current diet. Chapters 1 and 2 should have an expanded discussion of the challenges in characterizing air-related exposure, perhaps including Figure 3-2 that appears in the draft Policy Assessment (PA), and an explanation of "recent air" and "past air," as well as dietary Pb that appears in section 3.4.4 of the draft PA.

The revised approach to weight-of-the evidence causation determinations in the ISA represents a major improvement in that it separately assesses the findings for specific health endpoints rather than for major outcome categories/organ systems.

Pb is distinguished from many other toxicants by the existence of an extensive database of human studies of relatively low-level environmental exposure. Therefore, human data have been of particular value in the assessment of adverse effects at low levels of Pb exposure. In instances where the ISA has relied predominantly on animal toxicology rather than human epidemiology to arrive at a weight-of-the evidence causation assessment, such as the "likely to be causal" determination for immune system effects and for cancer, this should be explicitly noted in the narrative and summary tables.

Choosing between the causal determinations of "likely to be a causal relationship" and "suggestive of a causal relationship" for health effects of Pb can be challenging. Different evaluators may reach reasonable but divergent decisions after reviewing the same set of data. A transparent causation assessment that acknowledges uncertainty and reasonable differences in judgment is needed. The EPA should consider a different causation determination for certain endpoints, such as reduced kidney function, and could also consider a different causation determination for certain endpoints such as attention-related behavioral problems at low Pb dose. It is unclear why the EPA concludes that the designation of low levels of Pb exposure and renal dysfunction is "likely to be a causal relationship" rather than "suggestive of a causal relationship" considering: (a) inconsistency of the epidemiological findings in large high quality studies; (b) absence of a demonstrated pathological mode of action for Pb nephrotoxicity in humans or animals at blood Pb concentrations less than 10 μg/dL; and (c) the plausibility of reverse causation as an explanation for the association (See the response to the Chapter 5 charge questions for further detail). With respect to Pb and attention-related behavioral problems, Chapters 1 and 2 should acknowledge that the evidence for a causal relationship is based predominantly on findings in human and animal studies where the Pb exposure has resulted in blood Pb concentrations $\geq$ 10 μg/dL, and that additional study of the relationship at lower blood Pb concentrations is advisable.

The CASAC urges the EPA to acknowledge in the ISA that although primary production of Pb in the United States is decreasing, there are still global Pb environmental health issues due to increased U.S. Pb exports and increased global levels of Pb production.

The revision of section 2.9.1 (Public Health Significance) to focus on cognitive effects in children and cardiovascular effects in adults is appropriate, as these endpoints are characterized by well-established causal relationships and extensive downstream effects on public health and societal well-being. The discussion of the Weiss concept on page 2-63, line 9 should be edited from "in children with high and low intelligence" to "across the full range of IQ." In like manner, the sentence on line 11, although accurate, appears out of context since the Weiss concept does not involve changes in relative risk. For enhanced clarity, Figure 2-1 should be re-drawn to apply specifically to the hypothetical impact of change in mean population blood Pb on IQ (as intended by Weiss, 1988).

Section 2.9.5 (Reversibility and Persistence of Neurotoxic Effects of Lead) should note that, in addition to the cited study of Bellinger et al. (1990), other longitudinal studies have observed improved cognition in children with declining blood Pb concentrations (Ruff et al., 1993; Liu et al., 2002; Chen et al., 2005; Hornung et al., 2009). However, the extent to which such improvement represents biological reversibility of Pb-related effects, the influence of enrichment-related intervention, or the development of compensatory mechanisms remains uncertain.

Chapter 3 – Ambient Lead: Source to Concentration

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

The revisions to Chapter 3 are responsive to the CASAC's comments on the Second Draft ISA. Many minor and some major changes have been made that improve the readability of the document and address specific weak points of the Second Draft ISA.

The additions to section 3.4.1.1, Sample Collection, are an improvement to the description of the "state of the science" for measurement of particles greater than 10 micrometers, clearly illustrating the challenges in designing a new Federal Reference Method (FRM) to replace the high-volume (Hi-Vol) sampler where sampling of larger particles is of interest. Although it is understood that EPA will not have completed work on design and characterization of an improved "larger particle" FRM for this cycle of the Pb National Ambient Air Quality Standards (NAAQS) review, the EPA is strongly encouraged to continue this process.

The presentation of available data showing the range of Pb concentrations with diameters larger than 10 micrometers near sources is useful, and shows a very wide range of results. Much of the variation is due to the type of sampler being used or the wide range in near-source characteristics and other factors including wind speed. Overall for (non-airport) near-source sites, the amount of airborne Pb greater than 10 micrometers is typically between 10-30%, with much of that less than 15 micrometers diameter. In the context of the NAAQS, this is not a large proportion given the uncertainty of linkage between air Pb and dose. The ISA also appropriately notes that particles larger than approximately 15 micrometers in aerodynamic diameter deposit close to the source. This may inform the process of developing a new FRM because the effort to validate a sampler with a 15 micrometer cut size is substantially less than for larger cut sizes (even at just 17 or 18 micrometers). This applies both to the sampler design and the FRM wind tunnel testing process. The EPA should consider whether the effort to develop a sampler for particles larger than 15 micrometers has value in terms of the data needs of the Pb monitoring network.

The Summary and Conclusions section (3.7) is well written, and covers the key points of the chapter. Section 3.7.3 (Ambient Monitoring) implies that a 15 micrometer sampler would be adequate. However, the end of section 3.4.4.1 considers the upper particle size range of interest to be as high as 20 micrometers, but the need for data in the 15 to 20 micrometer particle diameter size range is not clear. Also, this section concludes with a sentence that is not fully supported by this chapter (section 3.4.1.1): "The existing samplers reasonably capture the airborne fraction of ambient Pb that is available for human exposure." The Pb doses from inhalation and ingestion are highly uncertain, as are the transfer functions for airborne Pb in various particle sizes to surfaces from which hand-to-mouth uptake and

ingestion are likely. Nasal deposition and subsequent ingestion can occur with some particles larger than 15 micrometers. However, the chapter does not provide much discussion of what the desirable particle size characteristics of an atmospheric Pb sampler should be, nor does it strongly justify the "reasonableness" of the existing Hi-Vol Total Suspended Particulates (TSP) sampler in that regard.

The discussion of sampling issues, available technology, and relevant size for sampling larger particles makes clear that although there are promising candidates for evaluation (e.g., low-volume TSP inlets), they have not been fully characterized for wind speed effects as required for use as a FRM sampler. A goal for this effort would be convergence of what is both feasible and desirable.

There is a need for improved characterization of Pb emitted from use of aviation gasoline on ambient Pb concentration in areas near general aviation airports. If airborne Pb data from 15 pilot sites near general aviation airports are available in EPA's Air Quality System (AQS), or even possibly preliminary data not in AQS, it would be useful to include them in the final version of the ISA with caveats, as needed. Recent and ongoing studies of the Pb air quality and effects associated with Pb emitted from general aviation operations should be considered for inclusion in the ISA both here and in other relevant chapters. For example, a recent study (Perugini et al., 2011) indicates that there are elevated levels of Pb in honeybees near general aviation airports.

Chapter 4 – Exposure, Toxicokinetics and Biomarkers

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

The CASAC commends EPA for clearly summarizing the information on exposures, toxicokinetics and biomarkers in Chapter 4. The lucid description of topic strengths, weaknesses, and limitations found in the introductory and concluding sections are well done. Chapter 4 credibly explains and applies mechanistic and empirical models, and provides illustrative figures of several Pb exposure scenarios and the impact on blood and bone Pb biomarkers. The EPA appropriately summarizes exposure data through a balanced use of tables and figures to convey complex information. However, in addition to the current summary of the phase-down of lead as a gasoline fuel additive, the chapter should also note the significant emission and air Pb reductions achieved in the vicinity of point sources. The major reductions in point source emissions were achieved through a combination of pollution control and relocation of industry. The summary of Pb in consumer products is helpful, but the discussion might include any conclusions on how exposure to Pb in consumer products might impact blood Pb levels (quantitatively if possible – for example, see VanArsdale et al., 2004).

The presentation and discussion of air-to-blood relationships is thorough, and the inclusion of potential biases and factors that possibly affect observed air-to-blood relationships improves the discussion. Conclusions or summary statements regarding the utility of estimated or measured relationships for current Pb exposures (and even lower) would be helpful. Specifically, the EPA is encouraged to consider the comments on Chapter 4 provided by the individual panel members for examples relative to (1) potential limitations of current mechanistic models to predict blood Pb levels at low level exposure; (2) the uncertainty associated with extrapolation of lower bounds of blood Pb from figures that present

empirical data on air-to-blood Pb relationships; and (3) adding discussion of estimates of percent contribution of air Pb to blood Pb associated with alternative slope factor estimates.

Chapter 5 - Integrated Health Effects of Lead Exposure

In the revised draft, causal determinations for health effects were drawn for more specific groups of related outcomes instead of major organ systems. Please comment on the appropriateness of these new endpoint groupings.

In general, the new health endpoint groupings are appropriate and contribute to greater clarity of causal determinations for all major organ systems. This new approach has the greatest impact on the section describing health effects related to the nervous system but there are revisions recommended for the approach used in this section. In the description of behavioral outcomes, use of a standard naming convention (e.g. clinical terminology and classification) is recommended. Specifically, behaviors currently listed as "attention-related" (inattention, impulsivity, hyperactivity, etc.)" and those related to conduct problems/disorders would be appropriately grouped under the label of "externalizing behavior." Other domains (depressive symptoms, anxiety) should be maintained in a separate section on "internalizing behavior." Schizophrenia is a psychotic disorder, and is neither internalizing nor externalizing. The literature on such behaviors can still be summarized for each behavior individually. For example, the ISA could summarize studies of attention, impulse control, hyperactivity, and oppositional behavior, one at a time. Then the causal assessment could be reorganized to look at the externalizing behaviors as a group and to acknowledge differences in Pb causality among the various categories of externalizing behaviors.

In addition, there are several errors of health categorization or study outcome categorization for the nervous system review (see specific individual panel member comments by Drs. Canfield, Korrick, and Wasserman). For example, schizophrenia is not a mood disorder, phobic anxiety is a subcategory of anxiety, and "opposition defiance" is not a meaningful term.

Lastly, there are a few instances where appropriate specific health endpoints are the focus of the literature review but the causal determination is applied, inappropriately, to a more general organ system. For example, the relationship between Pb and sensory function is most consistent for audition, not vision. But the causal framework was applied to all sensory function rather than focusing on the appropriate specific endpoint of auditory function.

Further, please comment on the extent to which the text and new summary tables support the application of the causal framework in deriving causal determinations.

This draft provides clearer and better documented support for the application of the causal framework than did the previous draft. The new summary tables, in combination with the text summaries, clearly demonstrate the causal framework that was applied. However, it is difficult to determine what degree and type of uncertainty informed the judgment to distinguish between "likely causal" versus "suggestive" determinations. As there is unlikely to be consensus even among experts in assigning this middle ground of causality, it is important that Chapter 5 explicitly identify the uncertainties that contribute to a less than causal association. For example, the chapter concludes that studies assessing the relationship of low level Pb exposure with renal function support a "likely causal" relationship whereas

the previous draft deemed this relationship as "causal." As noted in the consensus response to the Chapter 2 charge questions, the CASAC questions the designation of the association between low level Pb exposure and renal dysfunction as "likely to be a causal relationship" instead of "suggestive of a causal relationship." As discussed further below, the CASAC considers the latter category to be more appropriate.

How consistently and appropriately was the causal framework applied across the endpoint groups?

In general, the causal framework is consistently and appropriately applied across health endpoints. (See the response to the previous charge question). Several associations in the Second Draft ISA were assigned as "causal," yet the CASAC had concerns about those designations due to uncertainties in the literature. Except as noted below (e.g. renal dysfunction), these associations have now been appropriately revised in the Third Draft ISA to reflect these uncertainties.

Please comment on the adequacy of the discussion of the strengths and limitations of the evidence in the text and tables within Chapter 5 and in the evaluation of the evidence in the derivation of causal determinations.

In general, this draft applies a balanced approach to reviewing the literature, including: giving prospective studies priority over those with cross-sectional designs; explicitly acknowledging potential for residual confounding where applicable; and commenting on the likelihood (or not) of participation bias affecting results. In addition, the generalizability of specific study populations to the U.S. general population is considered. In keeping with this approach, new summary tables provide detail regarding strengths and limitations of the evidence. However, there are some basic issues regarding the literature review that are vague. For example, summary tables reportedly list nervous system studies in order of strength of study design. Aside from prospective studies being listed before cross-sectional ones, the additional ordering criteria are never explicitly given. In some cases, studies that confirmed an adverse effect of Pb appear to be given more weight than studies that revealed inconsistencies in the evidence, but the rationale for that order is not provided.

Certain study design concerns are repeated multiple times throughout the chapter – lack of adjustment for parenting quality, poor representativeness of the study population – but their relevance to interpretation of a given study is not discussed. The narrative in section 5.3.3 repeatedly notes that a limitation of the studies of behavior in Pb-exposed children is the failure to control for "parental caregiving quality." This feature should be more clearly explained (e.g., the extent to which it may be measured by the Home Observation for Measurement of the Environment [HOME] score). In addition, literature which establishes "parental caregiving quality" as a predictor of attention performance in children should be cited. Several relevant papers can aid in an independent search for the most appropriate papers (Matas et al., 1978; Jacobvich and Sroufe, 1987; Dunham and Dunham, 1995; Moore and Dunham, 1995; Bornstein et al., 1997; Evans et al., 1999). The representativeness of study populations is emphasized as a limitation in a number of nervous system studies; e.g., results of studies with a high prevalence of maternal pregnancy alcohol consumption or drug use appeared to be downplayed on this basis. However, the lack of generalizability does not impact the validity of a study (unless there is effect measure modification). Thus, in some cases, these findings may have been disproportionately discounted.

For behavioral outcomes, there is repeated mention of uncertainties regarding the correlation of parental psychopathology with parenting quality. This commentary does not address the most relevant point concerning parental psychopathology as a potential confounder of some behavioral outcomes. Residual confounding by parental psychopathology is discussed as a substantial study design limitation in the CASAC's prior review of the Second Draft ISA, given that many behavioral disorders (e.g., attention deficit hyperactivity disorder [ADHD]) have strong familial components (which may operate via parenting behavior, and/or genetic contributions to disorder type). Certain forms of parental psychopathology might be associated with increased Pb exposure risk through multiple direct and indirect mechanisms, including parental neglect, increased exposure to unremediated Pb hazards, and other pathways. The narrative in section 5.3.3 continues to characterize the studies by Cho et al. (2010) and Nicolescu et al. (2010) as having controlled for "parental psychopathology." However, the ISA should note that a critical examination of these studies calls into question the adequacy with which this was done in these investigations (please see Dr. Kosnett's individual comments for further detail).

The CASAC continues to recommend that the analysis of renal dysfunction in Chapter 5 (section 5.5) present a more balanced approach that adequately discusses the strengths and limitations of all of the relevant literature. In particular, aspects of this analysis that were of concern in the First and Second Draft ISA documents continue to be of concern in the current draft. Thus, in an effort to provide explicit guidance, the following text is a detailed exposition of the key issues.

In the CASAC's review of the Second Draft ISA (July 20, 2012, top of page 3) the consensus comments state, "With respect to renal effects, the narrative should offer a more balanced assessment in which the strength of the evidence for causal inference is tempered by inconsistency in the literature (underscored by the existence of studies that observed no significant relationship or a relationship in which increasing blood Pb levels were associated with improved renal function)." A similar concern over inconsistency in the literature is expressed in the CASAC review of the First Draft ISA (December 9, 2011, top of page A-10). It is therefore noteworthy that sections of the Third Draft ISA that address this topic continue to use virtually identical language to that which appeared in the Second Draft ISA. Page 2-24, line 6 *et seq.*, section 2.6.3 of the Third Draft ISA reads:

> The epidemiologic evidence from prospective and cross-sectional studies *consistently* [emphasis added] demonstrates a relationship between higher blood Pb level and reduced kidney function (e.g., lower creatinine clearance, higher serum creatinine, and lower GFR) in nonoccupationally-exposed adults with mean concurrent or baseline blood Pb levels of 2-10 μg/dL. Associations were observed after adjustment for multiple potential confounding factors such as age, sex, comorbid cardiovascular conditions, BMI, smoking, and alcohol use.

In like manner, page 5-376, Line 17 *et seq.*, reads:

> As illustrated in Figure 5-31 and Table 5-25, studies *consistently* [emphasis added] demonstrate associations between higher blood Pb level and lower renal function in adults. These general population studies provided critical evidence that the effects of Pb on the kidney occur at much lower doses than previously appreciated based on occupational exposure data.

The foregoing discussion and tables in the Third Draft ISA do not acknowledge the lack of a statistically significant relationship between Pb and serum creatinine in the large population-based study by de Burbure et al. (2003). Although this study was mentioned in prior individual panel member comments, it

is omitted from Table 5-25 (and elsewhere in the Third Draft ISA). Section 5.5 should further note in its repeated reference to the study by Tsaih et al. (2004) that a statistically significant relationship between blood Pb and change in serum creatinine was confined to post-hoc analyses of the relatively small subset of subjects who had diabetes or hypertension. Although Section 5.5 repeatedly refers to the two Normative Aging Study (NAS) investigations by Kim et al. (1996) and Tsaih et al. (2004) as offering "consistent" evidence (e.g., see page 5-422, line 18), the ISA should note that these NAS studies in fact did not replicate each other. The former study observed a statistically significant association between blood Pb and prospective decline in serum creatinine in the large NAS cohort, but the latter study did not.

Elsewhere in Section 5.5, particularly in the summary subsections, the analysis would be improved by a more balanced discussion of other inconsistent observations in the literature. As recently reviewed by Evans and Elinder (2011) (a paper still not cited in the Third Draft ISA despite the CASAC's prior consensus recommendation to do so), studies in cohorts with both environmental and occupational Pb exposure have yielded markedly different results. Several investigations of satisfactory quality have not observed any association between low or moderate Pb exposure and renal dysfunction, and in some studies, such as Weaver et al. (2003), Roels et al. (1994) and deBurbure et al. (2006), blood Pb concentration was associated with biomarkers of *improved* renal function. In the discussion of the study by Weaver et al. (2009) on page 5-392, a balanced analysis could clearly indicate that the study reported a *positive* correlation between baseline (blood and bone) Pb measurements and creatinine clearance, and that in male workers, prospective increases in blood Pb were associated with a *decline* in serum creatinine. It is conceivable that the aforementioned observations may represent Pb-induced hyperfiltration, but this would be an uncertain and untested hypothesis. Overall, as emphasized in prior CASAC consensus comments and individual panel member comments, the epidemiology associating low to moderate level Pb exposure with renal dysfunction is not consistent.

The opportunity for better balance in presentation of the renal literature's strengths and weaknesses emerges in several other places in Section 5.5. The large population-based case-control study combined with a prospective component by Evans et al. (2010) is discussed on page 5-387. This study found that occupational Pb exposure had no association with the incidence or progression of chronic kidney disease (Evans et al., 2010). After enumerating nearly all the cases in Sweden, the odds ratio for incident severe chronic kidney disease (CKD) was 0.97 (95% C.I. 0.68 – 1.38) in Pb-exposed participants compared with non-exposed participants. In the study's prospective component, Pb exposure was found to have no impact on the rate of decline of severe CKD. Yet when this entirely negative study is discussed on page 5-387 of the Third Draft ISA, the analysis somewhat paradoxically remarks, "The results overall do not provide strong evidence that Pb exposure was associated with renal effects." Limitations of the study are then presented. This approach to exposition and critique can be contrasted to that applied to the positive prospective studies of chronic kidney disease and Pb exposure reported by Lin and coworkers as well as Yu and coworkers (works cited on pages 5-386 to 5-387). The nearly full-page discussion of these studies (further summarized in Table 5-26) omitted any mention of the studies' limitations. However, as noted in past individual CASAC panel member comments on the Second Draft ISA, these studies are subject to major drawbacks that limit their causal inference, particularly inadequate blinding during the follow-up period, an important consideration in a condition such as chronic renal insufficiency in which medical treatment and medical and dietary compliance strongly influence change in renal function. Moreover the statistical models in these prospective studies did not account for how prospective changes in covariates that affect renal function, such as diet or blood pressure, may have influenced the outcome. In the chelation studies by Lin cited in the ISA, there was no indication that change in blood Pb or urine

Pb excretion after calcium ethylenediaminetetraacetic acid (CaEDTA) chelation had any impact on any measure of renal function. Given the prominence with which these studies have been profiled in Section 5.5, a more balanced discussion that details their limitations is recommended.

Possibly in response to the CASAC's review of the First Draft ISA, a new subsection in chapter 5 of the Second Draft ISA entitled "Reverse Causality" was included to address the hypothesis that associations between blood Pb and renal function may be due, at least in part, to decreased Pb excretion as a consequence of renal dysfunction. The consensus comments of the CASAC's review of the Second Draft ISA nevertheless suggested that a more balanced approach to consideration of the reverse causality hypothesis was warranted. This concern continues with respect to section 5.5.2.4 "Reverse Causality" in the Third Draft ISA. Rather than offering a balanced, neutral approach to this unresolved issue, section 5.2.2.5 concludes on page 5-400, line 3 *et seq.*:

> In summary, several lines of evidence support that reverse causality does not contribute substantially to associations between higher blood Pb levels and worse kidney function. These lines of evidence include prospective data observing that baseline Pb measures are associated with subsequent declines in renal function, that associations in prospective studies persist among adults with normal renal function, that renal failure does not increase Pb biomarker levels and that reduction of Pb levels by chelation improves kidney function. However, this bidirectional relationship is still possible and additional research is needed to *fully exclude* [emphasis added] the hypothesis. In particular prospective data are required as is research to determine if normal kidney function influences blood Pb levels.

The CASAC considers reverse causation a completely plausible hypothesis, and it questions the validity and persuasiveness of each of the "lines of evidence" cited in the foregoing paragraph. Prospective studies may have observed an association between blood Pb concentration and a biomarker of renal dysfunction (such as serum creatinine) because the prospective development of renal dysfunction can prospectively result in diminished Pb excretion and higher blood Pb concentrations. The existence of the association in "adults with normal renal function" does not exclude reverse causation because even in individuals with "normal renal function," pharmacokinetic clearance of a xenobiotic substance (whether Pb or a drug) that undergoes predominantly renal excretion, is inversely related to glomerular filtration rate. For example, this has been demonstrated for the renally-cleared organometal drug, carboplatin, where plasma levels correlate with glomerular filtration rate even in patients with normal renal function (Calvert et al., 1989). Contrary to the supposition in section 5.2.2.5, some studies have observed elevated blood Pb concentrations (Behringer et al., 1986; Colleoni et al., 1993; Davenport et al., 2009) and bone Pb concentration (Winterberg et al., 1990) in renal failure patients without any apparent history of elevated Pb exposure. Finally, as noted previously, the studies by Lin et al. purporting to associate chelation with improved renal function were subject to major design limitations, and in any case, failed to report a statistical association between any Pb exposure variable and any renal function measure.

The capacity of prolonged high dose Pb exposure to cause histopathologically demonstrable nephropathy is indisputable. However, in view of (a) the inconsistency of the epidemiological findings in large high quality studies of low to moderate Pb exposure; (b) the absence of a demonstrated pathological mode of action for Pb nephrotoxicity in humans or animals at low blood Pb concentrations; and (c) the plausibility of reverse causation as an explanation for the association, the EPA should designate the association between low level environmental Pb exposure (e.g., blood Pb concentrations

less than 10 µg/dL) and renal dysfunction as "suggestive of a causal relationship" rather than "likely to be a causal relationship."

Please also comment on the extent to which the nervous system outcomes have been grouped into appropriate constructs and the extent to which appropriate parallels were drawn between nervous system endpoints examined in humans and animals.

In general, the nervous system outcomes have been grouped into appropriate outcomes and constructs with reasonable parallels drawn between human and animal endpoints. Also, pairing the toxicology summaries with the specific relevant epidemiology, rather than summarizing the two literature streams separately, is helpful for assessing coherence of findings across disciplines. Distinguishing between symptoms or formal psychometric test results versus clinical diagnoses is clearer in this draft and is important to maintain. (See the response to the first charge question of this chapter for more specific comments on areas that could be improved related to this question.)

Chapter 6 - Potentially At-Risk Populations

Please comment on the adequacy of these revisions to clarify the consideration of potential at-risk populations and recommend any revisions to improve the characterization of key findings and scientific conclusions.

The chapter is improved over the prior version. Improvements include the more specific delineation of at-risk sources in terms of biological versus environmental, for example. In addition, the chapter better summarizes the strength of the evidence with respect to each of the factors that are considered. The EPA has managed to integrate an extraordinary amount of information and to employ useful framework(s) for critically reviewing and integrating information.

However, any sense of the relative magnitude of the effect modification from the risk factors is still missing. It is stated that the magnitudes are discussed in Chapter 5, but it is not clear that they are actually discussed there. It would be extremely useful to have a summary table that summarizes the magnitude of the effects modification these various risk factors impose. There may be very consistent effects of any given factor, but if the magnitude of the effect modification from the risk factor is 2%, for example, how important are they? It may not be feasible to find a common metric for the variety of comparisons that would need to be made, but some form of comparison in terms of magnitude of effect modification or other relevant metrics is critical to policy as it relates to how to utilize existing resources.

Sections on risk include multiple endpoints and different associations between risk factors and increased risk of Pb health effects (for example, sometimes for males and sometimes for females), which is confusing. Each section's last paragraph draws this out concretely. However, it would be more helpful to the reader to provide a roadmap at the beginning of each section in the first paragraph with respect to the end points and associations between risk factors and increased risk of Pb health effects that are addressed within the section.

The EPA should acknowledge that there are many childhood conditions that collectively account for a substantial percentage of children for whom there might be hypothetical reasons to predict increased (or

decreased) risk of Pb health effects, such as: low and very low birth weight; prenatal exposure to alcohol, cocaine, heroin, or tobacco; birth asphyxia; serious head trauma; and numerous genetic conditions associated with developmental delays. Also, children with sickle cell anemia are at increased risk for peripheral neuropathies.

Chapter 7 - Ecological Effects of Lead

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

The revised Chapter 7 is greatly improved, and with minor modifications will be an adequate discussion of the literature and is suitable to provide the information necessary to support the PA.

Adequacy

The new information contained in the ISA is insufficient to reach significantly modified assessments compared to those made in the 2008 PA. There are studies on additional organisms that principally strengthen, but do not modify, the previous assessments. There has been important new information on the influence of modifying chemical factors and "aging" of Pb on bioavailability. Few deleterious ecological effects have been noted at Pb concentrations found in environments that have not been impacted by major point sources of Pb (i.e., within one to two orders of magnitude of background levels).

Scientific Soundness

The chapter provides a fair and balanced evaluation of the existing scientific information. However, one major concern is the inability to relate ecosystem effects to the concentrations of Pb that exist in air, soil, and water. For ecosystems, an important source of the Pb in soil and water is atmospheric deposition and transport processes. A critical loads approach would be most appropriate to establish this relationship. Research should be conducted to develop, calibrate, and test models applicable to the development of critical loads for Pb and other metals in the United States.

Usefulness

The chapter presents a review of existing knowledge and new studies in terrestrial, freshwater, and marine systems, which is followed by a section presenting the causal determinations. Tables 7.4 to 7.6, which summarize the key studies leading to the causal determinations, are an important addition to the ISA. In addition to these tables, it would be useful to include a graph for each of the three system types, in which the various effects are shown as a function of the exposure concentration. The environmental concentration range also could be shown. Distinctions should be made on the graph between measured concentrations and nominal concentrations (if there are not measured concentrations).

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Appendix A

Agency Charge

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
National Center for Environmental Assessment

OFFICE OF
RESEARCH AND DEVELOPMENT

January 7, 2013

SUBJECT: CASAC Review of Third External Review Draft Integrated Science Assessment for Lead

FROM: John Vandenberg, Ph.D. /s/
Director
National Center for Environmental Assessment
Research Triangle Park Division (B243-01)

TO: Aaron Yeow, M.P.H.
Designated Federal Officer
Clean Air Scientific Advisory Committee
EPA Science Advisory Board Staff Office (1400R)

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

Following the review of the third external review draft ISA, NCEA-RTP staff will produce a final Pb ISA projected for release in the Spring of 2013 that addresses comments received from the CASAC Pb Panel and the public. The final Pb ISA, in conjunction with additional technical assessments, will

provide the scientific basis for EPA's decision regarding the adequacy of the current standards for Pb to protect human health, public welfare, and the environment.

We look forward to the Pb CASAC Panel review of the third draft ISA at the upcoming meeting. Should you have any questions regarding the draft Pb ISA, please feel free to contact Dr. Mary Ross (919-541-5170, Ross.Mary@epa.gov) or Dr. Ellen Kirrane (919-541-1340, Kirrane.Ellen@epa.gov).

Charge to the Pb CASAC Panel

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

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

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

Preamble; Legislative and Historical Background (formally Preface)

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

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

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

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

Consistent with CASAC recommendations, the language in Chapter 1 was simplified to improve the readability for a non-technical audience. Call-outs were added to Chapters 1 and 2 for ease of accessing

more detailed discussions in the rest of the ISA. Both chapters were updated to reflect revisions in subsequent chapters. The public health significance section was revised to focus on cognitive effects in children and cardiovascular effects in adults.

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

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

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

Please comment on the adequacy of these and other changes to the chapters and recommend any revisions to improve the discussion of key information. Please recommend any revisions that may further improve the clarity of discussion.

Chapter 3 – Ambient Lead: Source to Concentration

The integrative synthesis (Section 3.7 - Summary and Conclusions), was revised per CASAC recommendations. CASAC recommendations regarding additional synthesis were predominately related to Section 3.5 (Ambient Air Pb Concentrations). This section was made more concise with an eye towards synthesis of the relevant data. Information was moved to the Chapter 3 Appendix where appropriate. Additionally, integration was improved through expanded cross-referencing between Chapter 3 and the exposure section of Chapter 4 (Section 4.1). To further address CASAC comments,

data describing the size distribution of PM containing Pb was restored (Section 3.5.3.2 and Appendix Section 3.8.4) with elimination of data below the limit of detection. Size distribution data from a recent literature review was also incorporated. A brief discussion and data regarding global disposition of Pb were added to Section 3.2. Information regarding alternate methods for measuring size-resolved Pb in PM was added to Section 3.4.

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

Chapter 4 – Exposure, Toxicokinetics, and Biomarkers

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

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

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

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

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

Chapter 5 – Integrated Health Effects of Lead Exposure

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

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

Clarity in the description and the conceptualization of behavioral outcomes was enhanced by soliciting advice from experts in the fields of neuropsychology and neurotoxicology on how to categorize individual nervous system outcomes into broader categories. For example, experts considered IQ, learning, memory, executive function, and academic performance as indicators of cognitive function (Section 5.3.2) and inattention, impulsivity, hyperactivity, and attention deficit hyperactivity disorder as indicators of attention-related behavioral problems (Section 5.3.3). Rather than discussing all of the epidemiologic evidence and then all of the toxicological evidence, we reorganized by outcome group and discussed the epidemiology and toxicology together (e.g. Section 5.3.2.3 Learning and Memory in Children [p. 5-94 of the redline version] and Section 5.3.2.4 Executive Function in Children [p. 5-114 of the redline version] integrates evidence from both disciplines).
To clarify the rationale for the conclusions drawn regarding the strength of evidence for particular health endpoint groupings, the discussions of the health effects of Pb were expanded with additional details on strengths and limitations of the evidence, with respect to issues such as study design, consideration of potential confounding factors, analytical methods, and potential for reverse causation in epidemiologic studies and Pb exposure route and concentration in toxicological studies.

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

Section 5.3.2 Cognitive Function: Revisions to clarify the approach to the assessment were made (pp. 5-63 and 5-64 of the redline version).
Section 5.3.2.1 Full Scale IQ in Children: Evidence from prospective studies discussed first (p. 5-64 of redline version) while cross-sectional studies are discussed later as supporting evidence (p. 5-81 of redline version).

Section 5.8.1 Effects on Development: Section reorganized to start with the strongest epidemiologic studies (i.e. NHANES analyses). Studies in Table 5-36 were reordered to follow the text discussion.

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

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

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

Chapter 6 – Potentially At-Risk Populations

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

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

Please comment on the adequacy of these revisions to clarify the consideration of potential at-risk populations and recommend any revisions to improve the characterization of key findings and scientific conclusions.

Chapter 7 – Ecological Effects of Lead

The CASAC panel provided a number of comments that prompted focused revisions of Chapter 7. A new section on Pb fate and transport in ecosystems (Section 7.2) and summary tables for studies of reproduction, growth, and survival endpoints including key modifying factors were added (Section 7.6). Causal statements and their organization were revised to place greater emphasis on endpoints that are

most clearly linked to effects at the population-level and higher (reproduction, growth, and survival) while additional organism- and sub-organism level responses (neurobehavior, hematological effects, and physiological stress) are now considered in the context of secondary responses (Sections 2.1, 2.7.3, 7.3.12, 7.4.12, 7.4.21, and Tables 2-3 and 7-3). In addition, causal statements were further separated into freshwater and saltwater biota. Clarifying language was added to Sections 2.1 and 7.5 to indicate that causal determinations were based on various routes of exposures to Pb, often under controlled experimental conditions, and are not specific to air deposition. Throughout the chapter, more synthesis of effects on ecosystem receptors has been added and units have been standardized to express exposure dose consistently. Specifically, aqueous concentrations of Pb are reported as µg Pb/L, sediment and soil concentrations as mg Pb/kg, and concentration in solutions applied to soil or extracted from soil in mg Pb/L solution.

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

Appendix B

Compendium of Individual Comments by CASAC Lead Review Panel Members on
EPA's Integrated Science Assessment for Lead
(Third External Review Draft – November 2012)

Mr. George A. Allen

General Comments

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

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

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

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

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

Minor comments on Chapter 3

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

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

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

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

Dr. Herbert Allen

Comments on Chapter 7 – Ecological Effects of Lead

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

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

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

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

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

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

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

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

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

On page 7-44 line 34 “theses” should be “these”

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

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

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

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

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

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

Dr. Richard Canfield

Comments on Chapter 5 – Integrated Health Effects of Lead Exposure

1. Appropriateness of new endpoint groupings
    a. The new organization by endpoint groupings is a nice improvement. I would like to discuss the underlying conceptual scheme and also the wording during the meetings. My key question is why the term "externalizing behaviors" was not adopted whereas "internalizing behaviors" was adopted (e.g., table 2.2 and page 5-169 (line 7)). The term "attention-related behavior problems" is nonstandard and seems to imply a link between some broad definition of attention and child conduct. It also suggests a possible narrower interpretation in which it would be just another term for ADHD. The table below (from Behavioral, Social, and Emotional Assessment of Children and Adolescents , Whitcomb and Merrell, 2012) provides a categorization scheme and behavior descriptions that might be helpful for arriving at descriptors that accurately represent the behavior categories as they are pertinent to lead exposure studies. As I see it, one could use "externalizing behaviors" as the general term and then break it down into "attention/hyperactivity problems" and "conduct problems." Of course, as the child leaves the protection of the school-based disciplinary structures then conduct problems become delinquency and criminality.

    b.

Major Characteristics of Three Domains of Externalizing Behavior Disorders Derived From Quay's (1986) Literature Review

Undersocialized Aggressive Conduct Disorder
Assaultive behavior (fights, hits)
Disobedient and defiant behavior
Temper tantrums
Destructive behavior
Impertinent or "sassy"; uncooperative
Attention seeking
Domineering/threatening behavior
Demanding/disruptive behavior; loud and boisterous
Irritable and explosive
Negativity and refusal
Restlessness, hyperactivity
Dishonest and undependable
Socialized Aggressive Conduct Disorder
"Bad" companions
Truancy from home and school
Gang membership
Steals with others; steals at home
Lies and cheats
Stays out late at night
Loyalty to delinquent friends
Attention Deficit Hyperactivity Disorder
Poor concentration, short attention span, distractibility
Daydreaming
Poor coordination and clumsiness
Stares into space; preoccupied
Passivity and lack of initiative
Fidgeting and restless behavior
Fails to complete tasks
Lazy or sluggish behavior, drowsiness
Impulsivity
Lack of interest, general boredom
Hyperactive motor behaviors

2. Extent to which the text and new summary tables support the application of the causal framework
    a. The text and tables are now much more clearly and explicitly linked to the causal framework. What seems a bit inconsistent is the weight given to studies that confirm an

adverse effect of lead as compared to studies that reveal inconsistencies in the evidence. The paragraph-length descriptions of the levels of causal determination presented in PreambleTable II provide a nice balance of considering both confirmatory and non-confirmatory or inconsistent evidence but in the summary tables (e.g., 5-17) there is a column for "Key Supporting Evidence" but not for "Key Opposing Evidence."

3. Consistency and accuracy of applying causal framework across endpoint groupings. [Still working on consistency and accuracy…will comment after going through all the tables.]
    a. Table 5-17 (p. 5-281): This is a tremendously helpful table and the authors merit congratulations on a job well done. Suggestions:
        i. On p. 5-282 under "Key Supporting Evidence" for the epidemiological findings from toxicology studies the descriptions of the effects on learning do not accurately reflect the findings in Stangle, et al., 2007. Those authors characterize their findings as a deficit in associative ability (on their page 206): "*Pb-induced learning deficits and efficacy of succimer treatment.* Both the High-Pb and Mod-Pb groups learned the basic rules of the visual discrimination task and attention task 1 more slowly than the controls, indicating lasting impairment in the associative ability as a result of a short period of early Pb exposure, as previously reported (e.g. Garavan et al. 2000)."
        ii. Also, I wonder if the Garavan paper is relevant to cite here (I don't recall the exposure levels.)
        iii. A minor formatting issue: for example, on page 5-282 consider adding a heading across the top to indicate that the contents of the table are a continuation of the previous page pertaining to cognitive function deficits in children. When going back and forth between the various tables it is easy to lose track of the endpoint grouping.
        iv. The evidence for Pb effects on internalizing behaviors is very much weaker than for externalizing behaviors ("conduct problems") but both reach the "likely causal" threshold. I would like CASAC and EPA to discuss this contrast as a tool for evaluating the model for causal determination and the accuracy and consistency of its application.
        v. Evidence for sensory function deficits (page 5-286) seems to teeter on the Likely Causal/Suggestive of Causal edge. Is one (1) strong epidemiological study accompanied by one (1) cross sectional study sufficient evidence for Likely Causal? Also, the primate study had exposures from 33-170 ug/dL. Is that a relevant exposure range and were the effects a consequence of the higher exposure animals?
        vi. For neurodegenerative diseases it is noted that, "occupational studies did not consider Mn co-exposures" but control or lack of control for Mn is not consistently mentioned with respect to occupational studies for other endpoint groupings (e.g., psychopathological effects in adults). In cognitive function decrements in adults it is noted that occupational studies did not consider other

occupational exposures but Mn is not singled out in the way it is for neurodegenerative diseases.

b. Table 5-24
    i. As for other tables, consider "continuation" headings when evidence relevant to a given outcome spills onto the back of a page (e.g., 5-370).
c. Table 5-31
    i. This table summarizes a very complex area of research and it is very helpful to have entries in "Key Supporting Evidence" that explicitly identifies issues that add uncertainty to the causal determination.
d. Table 5-34
    i. Maybe I missed the explanation for this but why is it that the outcome categories in this table do not match the outcome categories presented in figure 5-34 (page 5-429)?
e. Table 5-35
    i. I did not find an MOA section for heme synthesis.
f. Table 5-48
    i. It could be misleading to have the bold heading "Effects on Development – Causal" that corresponds only to delayed puberty and not to postnatal growth or impaired organ systems. Consider breaking those out as separate endpoints so there will be a more clear indication of the level of evidence for Pb effects on postnatal growth and impaired organ systems.
    ii. Page 5-635 replace "spermatiogenesis" with "spermatogenesis".
    iii. Should there be headings for effects on hormone levels and fertility? Currently it jumps from mode of action on sperm to inconsistent evidence regarding hormone levels.
g. Table 5-50
    i. Is it possible to include information about Pb exposure levels in the epidemiological studies?

4. Expanded discussion of strengths and limitations of evidence for health effects for individual endpoints
    a. Renal (5.5)
        i. This is very helpful, particularly the section summarizing Lin's chelation studies.
        ii. I suggest changing the word "prudent" to "parsimonious" or "plausible" on page 5-392.
        iii. On page 5-399 line 14 it would be helpful to link back to the excellent discussion of independent effects of EDTA on kidney function on pages 5-391 and 5-392.
    b. Immune (5.6.5)
        i. Nicely done.
    c. Asthma and allergy (5.6.5.2)
        i. Again, a very helpful section for interpreting the following studies.
        ii. Page 5-457 line 29 delete the word "in"

iii. Page 5-458 line 2 change to ”direct causal” relationship with Pb exposure.

5. Prioritizing studies with strongest designs
    a. 5.3.2 Cognitive function
        i. For the reader who is not very familiar with IQ testing, I fear they will come away with the notion that all IQ tests are divided into verbal and performance subscales and produce an overall FSIQ. That particular terminology derives from the Wechsler products and not all studies of Pb and IQ used those tests.
        ii. I think it is important to make clear what the most important studies are and I also think great care must be taken to make sure the reader knows what are the attributes that go into the ranking. In particular, I caution against using any shortcuts when referring to the basis for ranking studies. For example, in this charge question only the strength of the design is noted whereas the representativeness of the study population is an extremely important criterion (hence the relatively low rankings of the Wasserman et al. and Tong et al. studies). Also, the sense of quality must be put into an appropriate context; i.e., some studies are “better” (more useful) than others for addressing the particular issues of concern for this ISA and at this time in history.
    b. 5.3.2.1 FSIQ
    c. Another issue with the ranking -- some might see the pooled analysis as a version of the Rochester analysis but with a less consistent measure of FSIQ and a cobbling together of SES and other covariate measures, all of which introduces error variance. We tried to make the pooled analysis as “uniform” as possible but compromises are necessary when bringing together disparate data sets. One perspective is that the pooled analysis revealed the “true” concentration-response relationship for low level exposures. Another perspective is that the Rochester and Boston cohorts contributed nearly all the data to the analyses dealing with effects < 10 ug/dL and given that each of those studies achieved greater consistency in measurement of the outcome and the covariates than was possible in the pooled analysis, those studies should be considered more influential. I’m not sure this sort of issue rises to the level of a need for revision of the ISA but if others on CASAC or in EPA pick up on it then we should discuss it.
    d. 5.8.1 Effect on development
        i. It’s not clear to me why the Wu et al. study is listed first when the Selevan et al. study does a more nuanced analysis (stratified by ethnicity) and considered a broader array of covariates. Selevan also considered a broader age range (8-18 rather than 8-16).
        ii. I found it very difficult to extract the key information from Table 5-36. The data are inherently complicated but the outcomes (e.g., Breast development) are not easy to distinguish from other text in the column. Maybe they could be bolded. Also, it would be much easier to read if the information in the adjusted effects estimate column did not word wrap.

Other wording issues, questions, queries

5-55 line 19: The word "substantiated" includes the connotation that the primary studies were somehow not as real or accurate as the pooled analysis, whereas compromises on covariate selection in the combined analysis makes it arguably weaker evidence. Possibly the term "is further supported by" would convey the idea that the pooled study adds to what we already knew rather than being the study that makes the original research "substantial."

5-56 lines 32-37: The characterization of the empirical foundation of the supralinear concentration-response relationship is imprecise and the quality of the evidence varies widely among the studies cited. Kordas was a cross-sectional study that found weak evidence for a supralinear effect and was based on concurrent Pb in childhood whereas Canfield et al. used lifetime average blood lead and IQ tests at two different ages. I suggest dividing up the references into a stronger and weaker group with the Kordas paper (on which I am a co-author) in the weaker pile.

5-67 line 25: It could be noted that home cleanliness and pica are likely to be proxies for exposure. If so, including them in the regression model would control for the exposure itself.

5-72 line 23: Please check to see if a lack of variation in parental education and income is also a plausible explanation for the absence of an association with FSIQ.

5-73 line 3: "a **large** majority"

Lines 20-23: The logic of the sentence beginning, "The few weak or null associations…" is unclear to me. Wouldn't the use of similar confounding factors strengthen the importance of these null findings? Is something different being said here as compared to what is said at the bottom of page 5-70 (and some other places) regarding how one evaluates the importance of the Cleveland study?

Paragraph beginning on line 28: This seems misplaced in the cross-sectional study section. Also, it seems mostly equivalent to the last paragraph on page 5-70.

5-74 line20: A primary reference for characterizing the Bayley test (which is done quite well in this ISA) and its status as a test of mental function is: McCall, R.B., P.S. Hogarty, and N. Hurlburt, *Transitions in infant sensorimotor development and the prediction of childhood IQ*, in *American Psychologist*, C.S. Gersoni and K.B. Little, Editors. 1972, American Psychological Association: Washington, D.C. p. 728-748.

5-532 line 6: For consistency, comment on covariate control for the Wu study (or list them). When the Selevan study is noted for including many potential confounders but no confounder information is given for Wu then the reader easily concludes that Wu had no covariate control.

5-533 Figure 5-37: Suggest changing "Puberty" to "Puberty onset".

5-695 Check units for bone lead measures, g/g or ug/g?

Dr. Deborah Cory-Slechta

Comments on Chapter 6 – Potentially At Risk Populations

Please comment on the adequacy of these revisions to clarify the consideration of potential at-risk populations and recommend any revisions to improve the characterization of key findings and scientific conclusions.

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

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

Dr. Cliff Davidson

Comments on Chapter 3

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

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

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

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

Dr. Philip E. Goodrum

Comments on Chapter 4

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

In general, EPA was largely responsive to comments from the CASAC committee on Chapter 4, and suggestions to better integrate Chapters 3 and 4. Specific comments are given in the table below for each of the comments and recommendations that CASAC provided on ISA Version 2.

CASAC's Comments on ISA Version 2		**Comments on ISA Version 3**
1	Additional synthesis and summary of information is needed on the following	
1a	Section 4.1 – example, Section 4.1.3.3 (Dietary Lead Exposure) – Information is factual, but the reader will benefit from more interpretation, context, and summary. Include additional discussion to explain the importance and impact of the reviewed data to the ISA. This recommendation can be generalized to all chapters of the ISA document – EPA should review each section and determine if, in addition to summarizing the information/data available, the implications of this information is also conveyed.	Text was added to effectively convey the implications of the exposure pathway-specific summaries. For example, Dietary Pb exposure is discussed in 4.1.3.3. A paragraph was added (p.4-28, lines 19-32) to tie together multi-source contributions to Pb in food items.
1b	Section 4.1.1, p. 4-6 – The additional paragraph is helpful at presenting quantitative estimates of % contribution of air Pb to blood Pb. Include a table that summarizes this information, distinguishing between estimates based on modeling (e.g., IEUBK) and empirical studies. Then add text to synthesize/summarize this information with specific focus on the importance of changes in these % contribution estimates over time, or as a function of the low end vs high end blood leads.	Addition of Table 4-2 summarizes % contribution to median and 95^{th} percentile blood Pb, assuming GSD = 2.1. The text should further discuss the implications of the modeling results presented in this table – specifically, increasing the air Pb from 0.14 to 0.87 $\mu g/m^3$ (a factor of 0.7) yields an increase in blood Pb of 0.2 µg/L for the median (slope =0.27 µg/L per $\mu g/m^3$) and 0.7 µg/L (0.96 µg/L per $\mu g/m^3$).
1c	Add a section that relates estimates of blood Pb / air Pb slopes to the original goals of the ISA as presented in the Integrated Review Plan, which called for an uncertainty analysis that provides a foundation to review the NAAQS. For example, the ISA can demonstrate how a particular slope factor translates into a corresponding change in blood Pb at the GM and 95^{th} percentile of the distribution assuming a lognormal distribution with GSD =1.6 (a model adopted in IEUBK).	See comments on 1b.
2	Additional discussion and perspectives on the relevance of information as presented is needed:	

2a	Chapter 4 leaves the impression that from a multipathway exposure perspective, direct inhalation of air Pb is generally a relatively minor contributor to total dose compared to soil/dust ingestion, diet, water ingestion and other routes of exposure (although some exceptions are noted, such as populations living in the vicinity of an airport). This may raise questions regarding the interpretation of the blood Pb / air Pb slopes, or the potential for a reduction in NAAQS to have a meaningful effect on blood Pb. Chapter 3 provides a more explicit discussion of the correspondence between air Pb and multiple exposure media (beyond air itself). Need better linkage between Chapter 3 and Chapter 4.	Pages 415-416, addition of new paragraphs explain some of the uncertainties associated with developing slope estimates from empirical data, appropriately concluding on a neutral tone "..[uncertainties] may lead to both positive and negative biases in the [slope factor] estimates from individual studies. New sections on particle size help to make the point that particle size governs exposure routes and that inhalation is not the only exposure route for Pb in air.
2b	Section 4.2.1, p. 4-30, lines 24-28 – expand this discussion to include the concept that time-integrated blood Pb reflects an aggregation of the biological processes that includes both recent Pb bioavailability/absorption as well as inputs from soft tissue and bone.	This points were added.
2c	Figures 4-8; 4-9; and 4-11 – the simulations are very informative and help to illustrate the temporal profile of Pb in blood, bone, and overall body burden. The text (p. 4-63) indicates that the simulations represent an exposure scenario in which a child experiences "..a constant Pb intake (from age 2-5) via ingestion… followed by an abrupt decline in intake." Additional details regarding the exposure/dose would be useful - specifically what constant Pb intake was administered, and when intake was abruptly reduced – was this set at zero or some non-zero baseline? Further clarification on the relevance/interpretation of the time averaging would be useful since it is unclear how the reduction in variance attributable to the averaging can be related to the experimental data. Consider removing the time-weighted average blood Pb panel.	These additional notes were added.
2d	Figure 4-22 – very helpful addition to demonstrate the various slopes, particularly to emphasize the differences in the model selection (e.g., log-log, log-linear, etc). The shapes of the response curves are very divergent at low air concentrations. Given the focus of the NAAQS is at the low end of the air Pb range presented, EPA should 1) comment on the challenge of estimating the low-end of the curves (i.e., < 0.2 $\mu g/m^3$) from data collected, and 2) comment specifically on the magnitude of difference	The figures are still included, but I did not see this additional discussion included in Version 3.

	in estimates and representativeness of the statistical models applied to empirical data. EPA should conduct an independent analysis of the underlying studies and determine if a common model can be used to describe all the datasets. Then, tie this back to estimates of expected change in blood Pb associated with change in NAAQS (see 1(c) above).	
2e	The ISA presents a range of blood Pb / air Pb slope factors without pinpointing a subset of estimates that may be more relevant to the objectives of the REA. To the extent that EPA has already identified a "best estimate" of a slope factor, or a range of best estimates, this information should be included in the ISA, accompanied by a discussion for the rationale that supports the selection.	Paragraph added to p. 4-130
2f	Comment on the importance of errors associated with estimates of particle size distributions from historical Pb TSP measurements. How does this uncertainty likely contribute to 1) estimates of air Pb / blood Pb slopes; 2) estimates of predicted blood Pb from epidemiological data; and 3) corresponding uncertainty in predicted change in blood Pb associated with reduction in air Pb (see 1(c) above).	Additional discussion on TSP was added.
2g	Section 4.1.1 presents the conceptual model for a multi-pathway assessment. Page 4-6 (lines 8 to 34) discusses the relevance of particle size distributions for inhalation and soil/dust ingestion exposure pathways. The first sentence (line 8) states: *Particle size of Pb-PM is relevant to transport through various media leading to exposure*. Restate this or expand the introduction to emphasize that all particle sizes are relevant to lead exposure assessment in general, and to understanding the air Pb / blood lead relationship specifically.	Chapter 3 and 4 include this overall message.
2h	Historical perspective on change in Pb sources over time associated with change in blood Pb – Chapters 3 and 4 remained somewhat biased towards gasoline Pb phase down (e.g., Section 3.7.1; Section 4.4.1, p. 4-78, introductory paragraph); also emphasize the role of reductions in emissions in the vicinity of point sources as presented subsequently (e.g., pp. 4-84 to 4-86).	Concepts are included on page 3-28.
3	The following contradictions need to be addressed:	
3a	Clearance rates for blood Pb – the text (e.g., 4-62) suggests that the rate of change may be slow following cessation, such that blood Pb will remain elevated years after exposure ends. Yet, the narrative	Additional discussion was added on clearance rates.

	discussion at the top of page 4-67, and the model simulations in Figure 4-11 (ICRP modeling) suggests exactly the opposite – a rapid decline in blood Pb following cessation. EPA should provide more description regarding model assumptions (e.g., how was baseline exposure factored in?), and comment on whether this relationship may differ for higher blood Pb that corresponds with adult occupational exposure. Literature that provides empiric observation for change in blood lead following cessation of exposure that resulted in moderate elevations (e.g., blood Pb in the 10 to 25 ug/dL range) for various time durations should be discussed (if available).	
	% Pb in blood - Page 4-39 (line 23) and 4-120 (line 22) report that 1% of body burden is in blood, whereas 4-49 (line 12) reports 5%.	In Section 4.3 (Biomarkers, page 4-52, line 23), 5% was changed to 1% for consistency

Dr. Sean Hays

General Comments on Chapter 4

- 4.1.13.5 Exposure to lead from consumer products: Providing this data is extremely valuable. Table 4-7 is especially helpful. However, the discussion of the importance of exposure to lead from consumer products is extremely sparse and seems inadequate. Surely there are studies available that provide some context on the impact of PbB due to lead exposures to consumer products. Consider discussing the study by VanArsdale (VanArsdale JL, Leiker RD, Kohn M, Merritt TA, Horowitz BZ. Lead poisoning from a toy necklace. Pediatrics. 2004 Oct;114(4):1096-9.). While this is likely the worse case example, it may still be informative nonetheless. Other examples would be very helpful.
- 4.3.5 Relationship between Pb in blood and Pb in bone: This section was well written and some insightful conclusions were drawn.
- I appreciate and liked the summary of data/studies that have investigated the relationship between lead in air and blood leads. In particular, the historical perspectives around the declines in the use of lead in gasoline and related decreases in blood leads in the US and other countries is helpful for establishing the context around setting a lead NAAQS.
- The description of the empirical models, and their strengths and weaknesses, is good. Again, many of the empirical models were developed using data from smelter/mining communities, which are very different than the scenarios involving setting a NAAQS. These empirical models would be helpful for setting a SAAQS (Smelter Ambient Air QS), but not so much for setting a NAAQS.
- Table 4-12 is very telling about how our understanding of blood-air relationship is shaped by high airborne lead exposures and/or high blood lead levels. Most studies had blood lead levels that exceeded 10. No studies have captured current exposures and the relationship (if any) between blood lead and air lead for the general population who are not exposed to point sources of air emissions.
- Figure 4-22 & 4-24: These figures seem to imply that blood lead levels decline to zero at zero air Pb levels. I'm not sure the underlying data support this extrapolation. Consider truncating the figure at a higher blood lead levels (For Figure 4-24, truncate at the air [0.05] & blood level [10 ug/dL]).
- I still wish the agency would provide a summary of the sources of lead exposures for the general population and the general proportions as a function of age and blood lead levels. For instance, for children with blood lead levels above 5, 10, etc. ug/dL , what proportion of their lead exposure is coming from air, water, soil, dust, consumer products, paint, etc. Do these proportions change as a function of age and blood lead levels? This is what is needed to provide more informed decisions on how the NAAQS should/could be improved. I would love to see some pie charts for the following ages/PbB (even if they are educated guesses):
    - Children < 2 yrs, 2-6 yrs of age, 6-18 yrs of age, 18-40, >60 yrs of age
        - PbB <2 ug/dL
        - PbB 2-5 ug/dL
        - PbB 5-10 ug/dL
        - PbB > 10 ug/dL

Specific Comments on Chapter 4

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

Dr. Philip Hopke

In general, EPA has done a good job of responding to comments on the prior versions and this draft of the ISA is in good shape.

Comments on Chapter 3

This version is quite well written and is pretty much ready to go. There are some useful new results that EPA may wish to take note of

Sources

Wood Combustion - Lead concentrations in 132 samples of wood pellets and 23 samples of wood chips from the northeastern US were presented by Chandrasekaran et al. (2012). It appears that some of the commercially available pellets used waste wood that included lead-painted material. The actual compositions of the emissions measured in the effluent of two high efficiency, low emissions commercial scale wood pellet boilers burning virgin wood pellets were provide by Chandrasekaran et al. (2011).

Analytical methods

There is now a semi-continuous field monitoring system for elements, the Cooper Environmental Services Ambient Metals Monitor (Xact 620) for Near-Real Time PM10 Metals Monitoring that is now commercially available. It has been used in several field studies and deserves a mention as an approach that would permit near real-time monitoring of lead in ambient PM.

References cited

Chandrasekaran, S.R., J. Laing, T.M. Holsen, S. Raja, P.K. Hopke, (2011) Emission Characterization and Efficiency Measurements of High Efficiency Wood Boilers, *Energy and Fuels* 25, 5015–5021.

Chandrasekaran, S.R., P.K. Hopke, L. Rector, G. Allen, L. Lin, 2012. Chemical Composition of Wood Chips and Wood Pellets, *Energy and Fuel* 26: 4932−4937.

Dr. Chris E. Johnson

Comments on Chapter 7: Ecological Effects of Lead

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

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

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

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

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

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

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

Dr. Susan Korrick

Comments on Chapter 5: Integrated Health Effects of Lead Exposure

1. *"....Causal determinations for health effects were drawn for more specific groups of related outcomes instead of major organ systems. Please comment on the appropriateness of new endpoint groupings..."*

The Nervous System Effects section, in particular, has been re-organized into more specific outcomes. E.g., Cognitive function in children has been divided into sections focused on specific tests and/or cognitive domains such as "full scale IQ", Bayley Scales of Infant Development, Learning and Memory , Executive Function and Academic Performance and Achievement. Similarly, the previous draft's "Behavioral Effects" section has been divided according to behavioral phenotypes -- Attention-related behavioral problems, Conduct problems, Internalizing problems, etc. In general, this a much better approach than in the previous draft and facilitates a more focused and critical discussion of the literature. This, in turn, makes the causal determinations clearer and better justified.

The only limitation of this approach is that some specific groups of related outcomes may not be optimal or appropriate. In addition, the choice of studies to include in each specific group was sometimes confusing. E.g., on p. 110 and Table 5-9, the summary of studies of academic achievement includes a study of the WRAML Verbal Learning test. This is an odd choice as it is a pure memory task (the child is asked to recite a simple word list from memory after hearing it read); this task is unrelated to vocabulary or other acquired verbal skill. These are not critical limitations but it is useful to keep in mind that there is still some misclassification among the health groupings.

2. *"...Further, please comment on the extent to which the text and new summary tables support the application of the causal framework in deriving causal determinations?"*

This draft provides clearer and better documented support for the application of the causal framework than was the case in the previous draft. Especially helpful in this regard are the new summary tables that parallel the text summaries of causal determination for each health measure.

3. "*...How consistently and appropriately was the causal framework applied across endpoint groups?"*

In general, this draft applied a more balanced approach to reviewing the literature than previous drafts. The approach included giving prospective studies priority over those with cross-sectional designs, explicitly acknowledging potential for residual confounding where applicable, and commenting on the likelihood (or not) of participation bias affecting results. In addition, the generalizablity of specific study populations to the U.S. general population was considered. In keeping with this approach, tables summarizing study findings provided more detail (study size, design, participation rates, confounders considered, modeling approach, etc.) than previously which is a valuable update. But there were a number of basic issues that were vague. E.g., summary tables indicated that nervous system studies were listed in order of strength of study design. Aside from prospective studies being listed before cross-sectional ones, the additional 'ordering' criteria were unclear and never explicitly explained. E.g., large cross sectional studies were often listed as lower priority than very small ones. On p. 5-123 the BMS (Baltimore Memory Study) did not adjust for potential confounding by smoking and alcohol, a potentially important weakness in studies of adult cognitive function and Pb, yet BMS is 1st in Table 5-

10. Was adjustment for smoking and alcohol considered over-adjustment since these can be important correlates of exposure? Some discussion of this would have been useful.

Lack of adjustment for parental caregiving quality seemed to play a disproportionately large role in prioritizing child nervous system outcomes although the role of this covariate in confounding for some nervous system outcomes was unclear. For behavioral outcomes, there was repeated emphasis on whether or not parental behavioral disorders were accounted for and whether parental psychopathology correlated with parenting quality. This was an issue of concern in the previous draft given that many behavioral disorders (e.g., ADHD) have strong familial components. Also, "representativeness" of study populations was emphasized as a limitation in a number of nervous system studies (e.g., studies with a high prevalence of maternal pregnancy alcohol consumption or drug use appeared to be downgraded because of this issue). Although generalizability is important in interpreting study findings, unless there is effect measure modification by the unique features of the study population, it should not impact the internal validity of a study's findings. Examples of studies down weighted because of this issue include IQ studies in cohorts in Detroit, MI (e.g., Chiodo et al., 2204; 2007) and null findings in the prospective Cleveland, OH cohort (e.g., Greene et al. 1992). In fact, the Cleveland cohort's null associations were described as having "weaker implications" because of its "lack of representativeness" (see p. 69-70,75, etc.) The reasoning here is presumably not based on the validity of the findings? It's a bit unclear.

4. *"Please comment on the adequacy of the discussion of the strengths and limitations of the evidence in the text and tables within Chapter 5 and in the evaluation of the evidence in the derivation of causal determinations..."*

As in charge #3 above. There were a few cases, where causal determination needed refinement. E.g., (p. 272), in nervous system effects, Pb's relationship with sensory findings are most consistent for hearing, not vision, but conclusions seem to encompass all sensory functions. Conclusions should be more clearly focused on hearing alone. The causal analysis for renal effects was updated to be more nuanced than in the previous draft, acknowledging uncertainties re. reverse causality and methodologic concerns in prospective epidemiologic studies in which change in serum creatinine was assessed after adjustment for baseline Cr as this analytic approach can be biased. Thus, the conclusion of "likely causal" (rather than "causal") is an improvement compared with the previous draft. Still, it is a challenge to determine how the distinction between causal determinations of “likely causal” or “suggestive” were made.

5. "Please also comment on the extent to which the nervous system outcomes have been grouped into appropriate constructs and the extent to which appropriate parallels were drawn between nervous system endpoints examined in humans and animals..."

In general, the nervous system outcomes have been grouped into appropriate outcomes and constructs with reasonable parallels drawn between human and animal endpoints. Also, pairing the toxicology summaries with the specific relevant epidemiology rather than summarizing the two literature streams separately, was helpful for assessing coherence of findings across disciplines. A few specifics could be clearer. E.g., on p. 92, Pb-associated impaired animal FI (Fixed Interval) operant conditioning is used to support effects of Pb on attention-related problems. Is FI attention, or impulse control? Also, as per charge question #1, there are some nervous system groupings for the human literature that could be improved. E.g., I agree with Dr. Canfield's suggestion that Externalizing Behavior would be a better umbrella to describe a number of the behaviors currently subsumed under attention-related outcomes.

Specific Comments:

Mechanisms:

p 30: not sure why heterogeneity of species, exposure duration, and metrics precluded assessing role of non-linearities in dose-response as a source of inconsistent findings....is the issue whether or not the D-R is a threshold?

p 37: How do gonadal cells have decreased plasma IGF1?

p 39: It is good that Pb-chromate studies are reportedly not included for genotoxic effects although in the section on Cancer-related outcomes, these studies are still summarized and considered.

Nervous system:

p 55: Description "attention-related behavioral problems" is good

p 57: This is a good overview of exposure across childhood (later periods as well as cumulative) likely being detrimental (FSIQ) in epidemiologic literature (not just focused on prenatal/perinatal periods per some animal literature). Also, acknowledged issue of correlation of exposures over time and persistence of effects is useful.

p 68: Emphasis on attenuated adjusted effect estimates not "losing precision" (ie still statistically significant) doesn't preclude residual confounding given evidence of reasonably strong confounding among known/measured covariates considered in models. Text seems to imply otherwise.

p. 75: Table 5-4: It would be good to indicate that Hu et al. is also the same Mexican study population (different subset?) as Telez-Rojo and Claus Henn.

p. 77 & 80: There is a comment re. the uncertainty of exposure scenarios' contribution to associations between cord blood Pb and MDI since there is increased mobilization of Pb from bone to blood in pregnancy. What does this mean? How would a given cord blood Pb level mean something different because of bone Pb mobilization?

p. 84: Use of the WCST as a memory/learning task seems odd. It is an indicator of executive function and cognitive flexibility (e.g., set shifting).

p. 90: This seems an odd definition of working memory ("info that changes frequently and is not stored permanently")

p.101: line 23: "Stoop" should be "Stroop"

p. 103, Table 5-8: Bellinger et al. 1994a (need to adjust signs for 95% CI; scores reversed so negative is worse but 95% CI are all positive values)

p. 104, Table 5-8: For 3 studies on this page, can't tell if test scores were 'adjusted' (as in 1st half of table on previous page) so negative effect estimate means worse performance. Otherwise, looks as if Pb is associated with better performance as, e.g., fewer WCST errors, shorter Stroop time?

p. 105: Can't tell why some studies mentioned briefly in text but results not summarized in any table or specifics (Nelson and Espy 2009, e.g.)

p. 110: Table 5-9: WRAML Verbal Learning is not a test of academic performance or achievement. Other odd choices in this table which includes KABC at age 4 yrs (or PPVT at age 7 yrs), etc. Presumably these are more measures of innate intelligence rather than explicit school achievement especially in a 4-year-old?

p. 110: Table 5-9: Fergusson – what does it mean to leave school with no qualifications?

p. 111: Table 5-9: Leviton for Reading/BTQ, what does RR estimate reflect?

p. 116: Leviton *did* or *did not* adjust for SES/parenting quality?

p. 118-119: In summary language, text sometimes reverts back to using "cognitive function" effects while also discussing specifics such as FSIQ, memory/learning, executive function where available studies and strength of associations may be more variable….Unfortunately, this does not make full use of the outcome specificity that was addressed with new review organization. It is important to maintain specific and consistent terminology.

p. 120: Bone Pb does not contribute to childhood blood Pb to the same degree as in adults because bone is such a rapidly growing compartment in children. Still, it is true that concurrent blood Pb may reflect past exposures in children but it's perhaps a more subtle issue than in adults. Also, concurrent blood Pb may reflect past exposure in as much as exposures in childhood are correlated over time.

p. 5-128: Table 5-10: looks as if Gao et al. (2008) saw beneficial Pb effects?

p. 5-131: Tendency to be overly broad -- enhanced Pb effect on MMSE in NAS with HFE variant "firm conclusions are not warranted" means what? Conclusions about the mechanism behind effect modification by HFE cannot be made? Conclusions need to be cautious because of increased type 1 error with subgroup analyses? These are very different interpretations so wording needs to be clearer on this issue.

p. 5-124, Table 5-10: Effect estimates expressed as SD scores are not always specified...it would be helpful to label these consistently.

p. 5-140: Consider how to better categorize response inhibition/impulse and attention (see discussion from summary for this chapter re. recommendations for better organization of behavioral measures).

p. 5-148: 'Not clear how adjustment for parental psychopathology self-report (in studies of attention-related behaviors) relates to caregiving quality…' This was a recommended adjustment because of the familial component of some behaviors and the theoretical possibility that parental psychopathology could affect caregiving and thus not only be a predictor of outcome but a confounder of the Pb-behavior

association. This same comment repeats throughout the sections on behavior-type outcomes (e.g., p-157). It's not clear what it means.

p. 4-149: Per last review request, it's good that Wasserman and Canfield null attention studies are now included (lower BPb, smaller n, younger age kids; prospective cohorts but looked at concurrent exposure)

p. 5-150: Problem with using case-control design (ADHD cases) to study continuous measures of behavior is not related to the potential for biased participation by Pb exposure but to the non-representativeness of the distribution of outcome measures. Specifically, it is biased to do analyses assessing continuous outcomes related to the outcome upon which case-control selection was based. One way to account for this problem and eliminate bias is to do analyses weighted by sampling probability. This study is listed relatively high among the cross-sectional ones despite this important limitation.

p. 5-158: There is the potential for reporting bias in parental report of ADHD diagnosis in NHANES. But text says, "however…examination of multiple risk factors and outcomes in NHANES reduces…likelihood of biased…reporting of ADHD by parents of children with higher Pb exposure". This type of statement repeats throughout the chapter. Issue of parent-reported ADHD diagnosis in NHANES has potential biases that are completely unrelated to the breadth of the study's outcomes and risk factors. E.g., regional/SES/cultural differences in dx may correspond to regional/SES/cultural differences in exposure risk. Indeed the text goes on to say, "states with higher Pb poisoning have lower ADHD rates…and these data reduce potential for confounding of associations in NHANES…by regional differences in BPb levels and ADHD prevalences…" The lower ADHD rates in more exposed states could be related to diagnostic bias, not true differences in rates. In this case, there could be negative confounding by region so that failure to adjust for region could lead to an underestimation of Pb-ADHD associations.

p. 179: Frequent comment that cross-sectional studies make "temporal sequence between Pb exposure and development of a health outcome uncertain" [approximate quote]. It's even a more basic issue than that since the direction of the association is potentially unclear or unknown in a cross sectional study. An indeterminant temporal sequence can be a problem in a longitudinal study too depending on frequency, timing, and type (blood vs bone, e.g.) of exposure assessment relative to outcome assessment.

p. 183: "Epidemiologic evidence of Pb-associated schizophrenia is inconclusive…" I would say it's almost non-existent. One cited study used δ-ALA levels, not Pb measures, making interpretation difficult.

p.235: Schnaas et al. 2006 is not reported in Table 5-15 despite text referring to it there

p. 238: It's good that distinction betweem inverted U-shaped dose-response and supralinear D-R is made clear as, with the latter, one still sees adverse effects with increasing exposure

pp. 254-55: Public health significance does a good job explaining the hypothetical nature of this analysis and defining the assumptions made in estimating changes in proportions of individuals in tails of the IQ distribution with Pb-associated shifts in mean IQ.

p. 256: In this public health analysis, one may even underestimate the adverse population effect given, e.g., at least some evidence of potentially greater Pb-related decrements in children with poorer performance (see Miranda et al. 2009 with greater Pb-related decrements in EOG achievement test results for kids with lower EOG scores).

p. 264: Use of parental history of psychopathology not intended to measure just caregiving quality (as text seems to imply) but is an important potential confounder based on the strong familial component of some behavioral disorders. Its role as a confounder would depend on its relation with Pb exposure risk which may not be completely clear….

p. 264+: Challenge with evidence for attention-related behaviors is that there may be stronger effects at higher Pb levels than relevant currently, more likely seen in older kids (e.g., null Canfield and Wasserman studies in younger children (4-5 yrs)). Evidence for ADHD itself is weaker (case-control studies)

p. 273: Motor seems smaller body of literature so inconsistencies are more noticeable; +/- agree with "likely causal association"

p. 278: Limited studies on adult psychopathology, +/- agree with "likely causal association"

p. 279: Evidence is suggestive for Pb and adult sensory function (limited past evidence now enhanced by just one NAS study and weak case-control study) – perhaps would consider it "inadequate to determine…."

Cardiovascular effects:

No new specific comments

Renal effects:

p. 421+: It is noted that "treatment" (with antioxidants & chelators) sections have been removed from Renal Effects section which is appropriate. (see detailed comments in summary statement)

Immune system effects:

p. 428: Acknowledgement of small epidemiologic evidence base is important to have included. However, the statement that recent findings in humans have contributed to increased understanding of Pb's immunotoxicity seems an overstatement. Of the few human studies cited for this health outcome, a number were null, or there were substantial inconsistencies among study findings, or exposures were not representative of current population levels (in occupational cohorts), or available studies had substantial design limitations (e.g., no consideration of key potential confounders, including other occupational exposures in Pb exposed workers) or numbers of children in higher Pb-exposed categories was very small, or confidence limits on effect estimates were wide (e.g., pp. 462, 481). Thus, the contribution of the epidemiologic literature to understanding from the toxicological literature is, at best, limited. In fact for some outcomes (e.g., p. 439) even animal studies have limited applicability to human exposure either by virtue of exposure route (injection) or level (high). Throughout this section, limitations of the

epidemiologic literature is mentioned. Again, the basis for this summary statement at the beginning of the section is unclear.

p. 432: In critically reviewing this literature, the text does not clearly prioritize study strengths and weaknesses. E.g., perhaps one of the most notable issues with Karmaus et al., is lack of a monotonic or biologically plausible dose-response relationship. This observation is made but is enumerated as part of a list of other features (adjustment for confounders except SES, likelihood of participation bias, etc.) so its relative importance is not discussed.

p. 433: Language here is unclear – what is meant by the statement that associations of Pb with T cell abundance among 6-35-month olds was influence by those with bood Pb > 15 µg/dL? Does it mean these more exposed children represented a few influential outliers or high leverage points thereby undermining the validity of the findings? Or is influence meant to imply the relationship was only seen at these higher exposure levels? These interpretations are very different and the reader is given no clear sense of which is meant. More specific analyses and interpretation of such literature is needed here. Otherwise, in reviewing the epidemiologic literature, this section provides a list of issues without integrating, prioritizing or interpreting the meaning of what's listed.

p. 440: It's good that limitations of cross-sectional epidemiologic studies acknowledged.

p. 452: As per p. 428, to summarize evidence re. Pb and IgE as having "coherence [of evidence] between epidemiologic and toxicologic findngs" seems an overstatement especially given limitations of epidemiologic literature discussed (e.g., uncontrolled for potential key confounders, lack of mono-tonic dose-response, cross sectional design, etc.).

p. 460: A theme that recurs throughout this chapter (in fact, for all health outcomes, not just those related to immune function) is that "the potential for selection bias is reduced because multiple exposures and outcomes were examined…" Selection bias can arise in a number of ways many of which are independent of knowledge of the particular exposure or outcome of interest to a study. Thus, this type of argument cannot be used as the sole basis for eliminating possible selection bias.

p. 480: As per above comments for the introduction to this section (p. 428) the role of collective epidemiologic evidence in supporting the causality determination for most immune function outcomes ("likely causal") seems over-stated. There is some explanation on pp. 486-487 but the logic is unclear. E.g., is the determination "likely" because of uncertainty in the human epidemiologic data but certainty in the animal/experimental literature? E.g., for "atopic and inflammatory conditions", both epidemiologic and toxicologic literature are described as consistently supportive of associations and the association is deemed "likely causal". But the same level of causation was also applied to "decrease in host resistance" where epidemiologic data was considered "not sufficiently informative". It is unclear why these two scenarios are assigned the same degree of causation.

<u>Hematologic effects:</u>

p. 508: One key characteristic of the epidemiologic literature associating Pb with RBC survival and function is that almost all, if not all, human studies involve relatively high exposure levels. E.g., there are few, if any, that observed effects with blood Pb < 10 µg/dL and many observe effects at substantially

higher levels. Whether this is a limitation of existing literature or reflects a likely threshold for certain of Pb's hematologic toxicities is not discussed but should be.

p. 511: It is useful to point out the likely differential sensitivity of various hematologic parameters to Pb with, e.g., ALAD levels perhaps being more sensitive than other indices.

p. 514: The majority of childhood studies reviewed had mean blood Pb<15 µg/dL (range 8-22); these all represent relatively high exposures by today's U.S. standards.

p. 516: A causal relationship of Pb with decreased RBC survival and function seems appropriate; the challenge the ISA does not clearly address is whether that relationship is causal at typical current population blood Pb levels.

Table 5-35: Blood Pb levels in many of the described epidemiologic studies are relatively high (children<15, occupational cohorts < 20 µg/dL); there are few studies in the current blood Pb range. Use of the term "relevant" levels could be misleading in this context.

Reproductive and developmental effects:

General:
(1) It is good that table summaries of epidemiologic literature now include sample size and confounder information (some of which was missing from previous drafts). This applies to other sections as well.

(2) Analogous to hematologic effects, male reproductive effects in the epidemiologic literature are strongest at relatively high blood Pb levels. A clearer synthesis of findings specific to the few studies with low level blood Pb would be helpful.

Other organ systems:

p. 656: The summary of Machida et al. (2009) is a bit confusing. As a cross-sectional analysis, this studied modeled predictors of blood Pb including biomarkers of bone turnover and bone density. Surprisingly, bone mineral density was *positively* associated with blood Pb, the opposite of the association observed in studies described earlier in this section. However, it is important to keep in mind that the modeled analysis was not looking at how well Pb predicted the bone measures but the reverse direction of association. This point is not clear in the paragraph and should be.

p. 659: The "likely causal" determination for effects on bone and teeth may be a bit optimistic. For bone, there is only one reasonably strong epidemiologic study (Kahlil et al. 2008). The remaining referenced epidemiologic studies for adult bone measures are all cross sectional. The likelihood of reverse causality in a cross sectional analysis (with blood Pb as the exposure marker) is substantial for this health endpoint. Specifically, higher bone turnover and associated declines in bone density would cause increased Pb mobilization from bone and therefore higher blood Pb. Thus, inferences about causality for bone density/turnover-related health outcomes are based on only one study (there was not epidemiologic assessment of these associations for the 2006 Pb AQCD). Indeed, because of the unique nature of these bone outcome measures, even longitudinal studies are susceptible to reverse causality as bone metabolism changes gradually over time and thereby could affect blood Pb levels prior to outcome

assessment. A more conservative approach to causal determination, at least for this outcome within the "other organ system" section, is recommended.

Cancer:

p. 700: As in the 2nd draft ISA, the designation of "likely causal" is based on strong toxicologic evidence without consistent epidemiologic evidence. This determination is further complicated by two factors that are discussed in this section but not explicitly mentioned in the concluding statement. First, most of the supportive toxicologic evidence is likely (blood Pb equivalents are not given) at relatively high doses compared to current U.S. population exposures. Second, many of the mechanistic studies supportive of the toxicologic findings use Pb chromate so it is not possible to determine whether observed effects are secondary to Pb vs. chromate, a known human carcinogen. Thus the role of Pb as a probable human carcinogen (per IARC, e.g.) at exposure levels relevant to current population exposures is unclear. Some discussion/acknowledgement of these uncertainties in the concluding paragraph would be useful.

Dr. Michael Kosnett

The following are comments on the 3rd external draft Integrated Science Assessment for Lead (February 2012) prepared subsequent to CASAC Lead Review Panel meeting of February 5-6, 2013. These comments focus on the Preamble, Executive Summary (Chapter 1), and Integrative Summary (Chapter 2), but also include comments on Health Effects (Chapter 5).

The revision to causation determination in the 3rd draft ISA that now separately weighs the evidence for specific health endpoints rather than for major outcome categories/organ systems as had been the case in the 2nd draft ISA is a major improvement.

Two key summary tables in Chapter 2 are Table 2-2 (Summary of causal determinations between exposure to Pb and health outcomes) and Table 2-8 (Summary of evidence from epidemiologic, animal toxicological and ecological studies on the effects associated with exposure to Pb). Blood lead level (BLL) associated with the causal determination is not mentioned at all in Table 2-2, and only sporadically in Table 2-8, a less than optimal approach given that NAAQS are particularly concerned with the low levels of environmental exposure prevalent today. It would be desirable for Table 2-8 to consistently note the blood lead concentration associated with the health endpoint under consideration. In like manner, the blood lead range highlighted in the table should be consistent with those mentioned in the summary sections of Chapter 2. An important example of inconsistency in this regard involves the discussion of "Attention-Related Behavior Problems" on page 2-17, and the corresponding second row of Table 2-8 (page 2-78). The narrative on page 2-17 (Section 2.6.1.1) predominantly mentions BLLs >10 µg/dL (the lowest mentioned was 6.8 µg/dL). However, the second column of the second row of Table 2-8 focuses on lower blood lead levels, stating:

> Recent studies in children continue to support associations of blood Pb levels with inattention and hyperactivity in children ages 8-17 years. In several recent studies, associations were found with concurrent blood Pb in populations with mean blood Pb levels 1–5 µg/dL; however, the influence of higher past Pb exposures in these older children cannot be excluded. A few case-control studies found higher concurrent blood Pb levels in children with ADHD.

With respect to attention-related behavior problems in children, I think it would be prudent to revise or at least qualify the causal determination in Table 2-2 and page 2-17, to include additional relevant limitations in Table 2-8. Table 2-8 (in contrast to table 5-11) fails to note the inconsistency of the findings in studies conducted in children with BLL < 10 ug/dL. In particular, the important weight of the negative (i.e. nonsignificant) findings in prospective studies by Burns et al (1999, in boys), Wasserman et al (2001), Canfield et al (2003), and Chandramouli et al (2009) is not given adequate emphasis.[1] In addition, the summary narrative in Table 2-8 and the narrative in Section 2.6.1.1 (page 2-17) could note that an important caveat in derivation of a causal determination remains the inability of any study to date to effectively control for parental behavioral psychopathology. This is a major limitation, given that many aspects of behavior (such as attention disorders) are highly heritable traits.[2] This is acknowledged

[1] Wasserman et al (2001) is incorrectly classified as a cross-sectional study in Table 5-11. Canfield et al (2003) is classified as a cross-sectional study, although it is more likely a prospective study given its prospective design, and the observation that serial blood lead measurements conducted on the subjects averaged less than 10 ug/dL at multiple time points

[2] The narrative in section 5.3.3 repeatedly notes that a limitation of the studies of behavior outcome in lead exposed children is the failure to control for what is termed "parental caregiving quality." This feature should be more clearly explained (e.g.

briefly in the narrative at the top of page 5-159, which represents an improvement over prior discussion of this aspect of confounding in the 2nd draft ISA. In like manner, the more detailed and balanced discussion in 5.3.16.2 (Evidence for Attention-related Behavioral Problems in Children, p 5-263) represents a considerable improvement over the shorter discussion of causation in section 5.3.13.2 of the 2nd draft ISA. For example, the paragraph beginning on page 5-265, line 25 specifically acknowledges the limitations of the studies that have associated lead exposure with ADHD, stating, "Because of the cross-sectional or case-control design of studies and lack of consideration for potential confounding by parental caregiving quality or attention-related problems, the ADHD evidence is not a major consideration in drawing conclusions about the relationship between Pb exposure and attention-related behavioral problems." It is problematical, however, that mention of such limitations and inconsistencies does not appear in the integrated summary in Chapter 2.

As currently written, the integrated summary in Chapter 2 concludes that there is a causal relationship regarding "attention related behavioral problems", just as it concludes there is a causal relationship regarding cognitive function deficits. However, Chapter 2 lacks a succinct acknowledgement that the strength of the evidence for the latter is considerably stronger than it is for the former, and that with respect to BLLs < 10 of contemporary concern, the epidemiological data is consistent and adequately adjusted for confounding for cognition, but not for attention -related behavioral problems[3]. I recommend that the causal determination for this endpoint conclude that the weight of the evidence supports a causal relationship at BLL > 10, but is "suggestive of a causal relationship" at BLL < 10.

An entirely new section that appears on page 2-76 entitled "2.9.7 Ecological Effects and Corresponding Pb Concentrations" merits reappraisal and revision. The opening statement reads:

> "There is limited evidence to relate ambient air concentrations of Pb to levels of deposition onto terrestrial and aquatic ecosystems and to subsequent movement of atmospherically-deposited Pb through environmental compartments (e.g., soil, sediment, water, biota)."

This would appear to be somewhat at odds with the paragraph on page 2-75 that reads:

> "There is adequate evidence that proximity to areas with Pb sources, including areas with large industrial sources, is associated with increased Pb exposure. Relatively high concentrations of ambient air Pb have been measured near sources, compared with large urban areas without sources and high Pb exposures have been documented near Superfund sites."

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the extent to which it may be measured by the HOME score). In addition, literature which establishes "parental caregiving quality" as a predictor of attention performance in children should be cited. The narrative in section 5.3.3 continues to characterize the studies by Cho et al, 2010, and Nicolescu et al, 2010 as having controlled for "parental psychopathology." However, as noted in my comments on the 2nd draft ISA, a critical review of these studies lends considerable doubt that these studies did so in an adequate manner. In the Korean study by Cho et al (2010), which in fact *failed* to report a consistent positive association between lead and indices of ADHD or attention in most of the measures that were examined, the adjustment for parental psychology consisted of having the parents of 590 children note in a questionnaire whether they ever had ADHD or any other neuropsychiatric disorder. Implausibly, less than 5 percent responded affirmatively. Moreover, the variable was not included the multivariable models. In the Romanian study by Nicolescu, parents were asked by telephone interview whether either had been diagnosed with "psychological/psychiatric problems." However, the extent of positive response was not reported, and even though "family psychopathology" was the factor with the *strongest* bivariate correlation with child ADHD rating by the parents, it was *not* included in the multivariable models of child attention or ADHD (see caption to Figure 2 in Nicolescu et al, 2010).

[3] The data linking BLL > 10 to an array of attention-related behavioral problems are more consistent.

Further discussion at the CASAC lead review panel meeting indicated that compared to the effect of lead on humans, the impact of lead on nonhuman biota and ecosystems is indeed limited. It might be worthwhile for the ISA to explicitly note that humans constitute the ecological receptors for which lead toxicity has been most extensively characterized.

Although the 3rd draft ISA has appropriately downgraded the determination in the 2nd draft ISA that reduced renal function is "causally associated" with low-level environmental lead exposure, the current classification of the relationship as a "likely causal relationship" may still represent an overstatement. The summary discussion of effects in section 2.6.3 (page 2-24) continues to include the statement:

> The epidemiologic evidence from prospective and cross-sectional studies *consistently demonstrates* a relationship between higher blood Pb level and reduced kidney function (e.g., lower creatinine clearance, higher serum creatinine, and lower GFR) in nonoccupationally-exposed adults with mean concurrent or baseline blood Pb levels of 2-10 μg/dL [emphasis added].

As was pointed out in the review of the 1st and 2nd draft of the ISA, this is incorrect and should be revised. The large general population study by de Burbure et al (2003) found no significant association between blood lead and serum creatinine or other biomarkers of renal function in multivariable regression models. In the Normative Aging Study (Tsai et al, 2004) there was no significant association between either blood lead or bone lead and serum creatinine in subjects without hypertension or diabetes. In addition, it is important to consider that many epidemiological studies of subjects with a range of occupational lead exposure have not observed an inverse relationship between blood lead and reduced renal function, including studies that have actually found a positive association between blood lead and renal function (Roels et al, 1994; Weaver et al, 2003a).

Section 2.6.3 also includes the statement:

> "Studies in animals with long-term exposure to Pb report mixed evidence for Pb-induced kidney dysfunction and histopathological changes, including tubular atrophy and sclerosis *at relevant Pb blood and exposure levels*. [Emphasis added].

However, as indicated in the studies cited in Chapter 5, that the animal evidence for toxicological effects of lead at doses comparable to human environmental exposure are limited. In no animal studies or human studies have lead-related pathological impacts or biomarkers of renal damage been observed when lifetime BLL has remained less than 10 ug/dL. The section on "Reverse Causality" (section 5.5.2.4), would benefit from a more balanced presentation that gives more prominence to the plausibility of this hypothesis as an explanation for the association between low level lead exposure and markers of renal dysfunction. Given the inconsistent observations in environmental and occupational studies, the lack of a demonstrable pathological mode of action for lead on renal function at low dose, and the plausibility of reverse causation, I recommend that the association between low level environmental lead exposure and renal dysfunction be designated as "suggestive of a causal relationship" rather than "likely to be a causal relationship."

Revision of section 2.9.1 (Public Health Significance) to focus on cognitive effects in children and cardiovascular effects in adults is appropriate and prudent, because these are two major public health endpoints for which the causal effect of low-level environmental lead exposure is well established.

Regarding the sentence in section 2.9.1, page 2-63, line 11 that reads: "Even a small relative risk for a health effect that is highly prevalent in the population can translate into a large increase in the number of clinical cases"-- this sentence is correct, but it appears to be out of context, because the discussion by Weiss et al in that paragraph does not involve relative risk.

Re Section 2.9.2Air-Pb-to-Blood-Pb Relationships: The prior CASAC lead panel review had urged the draft ISA to critically identify which of the relationships identified in Table 2-6 were most optimal for quantitative risk assessment. It would be helpful if this assessment were specifically summarized in this section. Some of the critical analysis of these relationships in the draft Policy Assessment might be helpfully recapitulated in Chapter 2 of the ISA>

The discussion on reversibility and persistence of neurotoxic effects of Pb in section 2.9.5(page 2-71) might note that some prospective studies of lead exposed children have reported that concurrent blood lead is a better predictor of IQ than early childhood blood lead, and that declines in blood lead during childhood are associated with improved cognition (cf Bellinger et al, 1990; Ruff et al 1995; Liu et al 2002; Chen et al 2005; Hornung et al, 2009). However, there is uncertainty regarding the extent to which such improvement represents biological reversibility of lead-related effects, the influence of enrichment-related intervention, or the development of compensatory mechanisms.

It is appropriate that the 3rd draft of the ISA has deleted reference (in Section 2) to fluoridation as a factor that potentially increases the risk of Pb-related health effects.

Section 5.4.2.2 (Toxicology) reviews studies in animals that have examined the relationship between blood lead and blood pressure. Only two studies purport to provide data on the blood lead / blood pressure relationship in animals whose peak blood lead concentration was less than 10 μg/dL – Tsao et al, (2000) and Nakhoul et al (1992). It is recommended that the narrative in this section express a note of caution in interpreting the mean blood lead concentrations reported for the low exposure groups in these studies, i.e. 2.15 μg/dL in Tsao et al (2000) and 5.3 μg/dL in these two studies, both of which were reportedly associated with exposing the rats to 100 ppm lead in drinking water for 8 weeks. These blood lead concentrations appear low in comparison to the dose of lead reported. In the case of Tsao et al, the value of 2.15 μg/dL implies a doubtful level of precision, given that the limit of quantitation of the authors' analytical technique (electro-thermal atomic absorption spectroscopy) is generally 2 to 3 μg/dL. It may be noted that the laboratory of Cory-Slechta and colleagues at the University of Rochester, which has published numerous studies in lead exposed rats, has found that feeding rats 50 ppm in drinking water yields blood lead concentrations of 10 to 15 μg/dL (Virgolini et al, 2008a).

Additional comments:

Page 1-2, line 20: A national "average" Pb concentration in soil of 18.9 mg/kg is cited. Given that the distribution is likely to be lognormal, can a geometric mean value be cited instead of (or in addition to) an arithmetic mean?

Page 1-4, line 12: The statement, "Overall, blood Pb levels have been decreasing among U.S. children and adults for the past twenty years" could actually be revised to state that levels have been decreasing for the past 35 years.

Page 1-4, line 15: Among children age 1-5, 95th percentile BLL in NHANES 2009-10 is 3.4 ug/dL, not 4.0 ug/dL. [See NCEH (CDC) Fourth National Exposure Report, Updated Tables, September 2012, p141]

Page 2-16, line 26: The following sentence needs editorial revision for better clarity:

> The associations consistently found in prospective studies of children with adjustment for Social Economic Status (SES), parental education and caregiving quality for associations with various indicators of cognitive function and the biological plausibility provided by evidence in animals for impairments in learning, memory, and executive function with relevant Pb exposures and evidence describing modes of action is sufficient to conclude that there is a causal relationship between Pb exposure and decrements in cognitive function in children.

Page 2-21, line 16, and page 2-22 line 16: grammatically revise sentence for clarity.

Page 2-64, line 20: The following sentence could be revised to enhance clarity. It now reads:

> The high correlation between blood pressure and clinical cardiovascular outcomes combined with the high prevalence of cardiovascular disease in the U.S. adult population translate into a large increase in the prevalence of conditions in the population.

Page 2-69 The following sentence starting on line 18 should be corrected to indicate that HR is the abbreviation for "hazard ratio", not "heart rate":

> In the NAS cohort, C-R relationships between bone Pb and mortality were approximately linear for patella Pb on the log (heart rate [HR]) scale for all cardiovascular disease (CVD), but appear nonlinear for IHD (Weisskopf et al. 2009).

Page 2-70: Sentences near bottom of page and continuing to top of next page require editing for clarity.

Page 5-376, line 9: Replacement of the word "concurrent" with the word "current", as was the case in the 2nd draft ISA, is recommended, as the word "current" expresses the meaning more clearly and accurately.

Dr. Roman Lanno

Comments on Chapter 7 – Ecological Effects of Lead

The 3rd draft of the Ecological Effects of Lead in the ISA is well written and an excellent improvement of the previous draft. In particular, the tables at the end of the chapter (Tables 7-3 to 7-6) organize a tremendous amount of data in a very accessible manner. This allows ready reference to the key data in each of the new manuscripts reviewed for this chapter. The standardization of units (e.g., mg/L, mg/kg) facilitates easier comparison of exposure doses in the studies. More importantly, it's easy to see where exposure dose is only nominal and when it is actually measured. This makes it fairly simple to see which studies are of sufficient quality to actually use as primary data for causal analysis.

The chapter is logically organized into terrestrial, freshwater, and saltwater sections, with consistent organization within sections. Breaking out freshwater and marine environments and justification re: bioavailability was very good. Although this leads to some repetition within sections, it is still easy to read and follow.

Distinction between data used in causal determination and environmental relevance for determining the secondary standard. Nominal, hydroponic, culture medium, etc.

Addition of a figure summarizing the data available on exposure levels and responses, similar to that for the Pb EcoSSL. One problem would be standardizing the data without strict data quality criteria. Distinguish between nominal and measured.

How should hydroponic data be handled? I suppose it can be used in causal analysis but not in extrapolation to soils.

Page 7-9, line 4 – What is meant by "Pb evaporation"? Do you mean Pb volatilization? To my mind this is not an important fate process for Pb.

Page 7-14, Table 7-2 – In the Pb concentration column, under vegetation, what is meant by "Grasses: 31% (percent of soil Pb in grass)"? Is this (Pb concentration in grass/Pb concentration in soil) x 100?

Page 7-18, line 15 – change "later" to "latter"
Line 31 – What is meant by "relative bioavailability"? Was bioavailability actually measured in this study or just sequential soil extracts? Relative bioavailability has a very specific meaning as defined in the bioavailability schematic, Fig 7-2. Please clarify.

Page 7-21, lines 7-8 – What are the simulated soils or soil components?

Page 7-22, line 19 – Change "). Modifying" to ") modifying"

Page 7-25, line 5 – What is meant by "organic content"? Is this organic matter content or organic carbon content? This needs to be specific since they are different measurements and needs to be addressed throughout the terrestrial section.

Line 29 – “near stationary sources” sounds like the sources are almost stationary. Perhaps “nearby stationary sources” would be better

Page 7-31, line 20 – Are these really metal-contaminated soils? These concentrations are around background levels for many soils.

Line 30 – Specific BCFs – Were these actually ratios of metal levels in plant tissues to soil pore water?
Page 7-33, line 12 – change “determined” to “observed”

Page 7-36, line 8 – Anecic worms usually burrow up to 2 m not 6 inches. Use SI units.

Page 7-40, line 22 – Change “vegetative” to “vegetation”
Line 35 – If godwits are insectivorous, then why are they eating worms? Perhaps vermivorous is more appropriate.

Page 7-46, lines 31-32 – How is it possible to compare hydroponic Pb concentrations to Pb concentrations in soil?

Page 7-50, lines 28-29 – This seems somewhat odd – Pb doesn’t usually induce metallothionein production.

Page 7-52, line 37 – Drosophila should be italicized (*Drosophila*). Genus names are always italicized. This needs to be checked throughout the chapter as there are many other places where genus names are not italicized.

Page 7-56, line 3 – change “2,2” to “2.2”

Page 7-60, lines 11-12 – What is meant by this sentence – “Because toxicity is influenced by bioavailability of soil biogeological and chemical characteristics”?

Page 7-63, line 17 – Change “type” to “types”
Line 18 – This is not clear as to what this soil Pb concentration is
Line 26 – Should the units be mg Pb/kg?

Page 7-67, line – “physiochemical” means physiological/chemical – should be physicochemical

Page 7-74, line 6 – change “rather a larger” to “rather than a larger”; “whole” to “entire”
Lines 15-16 – What is meant by “the presence of effects at elevated exposures implies effects at lower exposures”?
Page 7-77, line 15 – change 2,08 to 2.08

Page 7-79, lines 25-26 – What is a “10 day nominal exposure”? Do you mean exposed to nominal Pb concentrations?

Page 7-83, line 19 – change “were” to “was”
Line 22 – again, the “nominal” issue

Page 7-88, line 3 – change “estimate” to “estimates”
Line 7 – add parentheses – (Pb 0.001 and 0.01 mg Pb/L)

Page 7-95, line 26 – change “Kessleri” to “kessleri”

Page 7-96, line 26 – change “with” to “to”
Lines 28-34 – this section should be in the terrestrial section

Page 7-103, line 36 – delete “can”

Page 7-105, line 4 – What is meant by “saturation”?

Page 7-110, line 26 – change to “on the tissue distribution of Pb in freshwater organisms”

Page 7-114, line 18 – By “media” do you mean water?

Page 7-125, lines 18-19 – What is meant by “selective pressure on plants”? Is this in an evolutionary sense?

Page 7-151, line 18 – change “owing the” to “owing to the”

Page 7-153, line 1 – What are “high molecular weight cationic Pb species”? Is this Pb bound to proteins?

Page 7-219 – What medium were nematodes exposed in? Guo et al. 2009

Page 7-221 – change “quails” to “quail”

Mr. Richard L. Poirot

Comments on Chapter 3

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

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

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

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

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

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

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

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

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

P 3-17, lines 18, 19: Fauser's 90% of tire wear particles < 1 micron is not logical, although certain kinds of non-spherical particles may have aerodynamic properties that might be unexpected from their physical "diameters".

P 3-17 and 3-18 in general: This is a very interesting discussion, but doesn't provide much confidence that the most important source(s) of roadway-related Pb emissions (and particle sizes) are very well

known (wheel weights, brake wear, tire wear, unleaded gas, diesel, road line paint, historically deposited roadside Pb, etc.).

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

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

> McLean, J. E. and B. E. Bledsoe (1992) Behavior of Metals in Soils, U. S. EPA Ground Water Issue, EPA/540/S-92/018. http://www.epa.gov/superfund/remedytech/tsp/download/issue14.pdf
>
> Yobouet Y. A., K. Adouby, A. Trokourey and B. Yao (2010) Speciation in contaminated soils, *International Journal of Engineering Science and Technology*, Vol. 2(5), 802-812.

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

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

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

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

P 3-27, lines 30-35: You could change "at" to "near" in line 3, as the upper bound Pb V_d reported in the 2006 CD was 1.3 cm/s. Also, the 12-17 mg/m^2-year dry Pb deposition reported here for Tokyo Bay was not more than 10 times the upper bound of the range reported in the 2006 CD - which included 8.4-14 mg/m^2-year dry Pb deposition reported by Yi *et al.*, (2001) near Lake Michigan for 1993-1995 (see p. 2-57 of the 2006 CD).

P 3-28, lines 12 and 13: You could delete "transition", as Pb is not a "transition metal".

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

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

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

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

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

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

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

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

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

> TSP is an acronym for Total Suspended Particles, an hypothetical and un-measurable concept. In this chapter, we use the term TSP to mean "particles with the size characteristics of those collected by the high volume (Hi Vol) TSP sampler" and Pb-TSP to mean "Pb in particles collected by the Hi Vol TSP sampler". When referring to alternative existing or future samplers

with an upper 50% particle cut size larger than 10 microns, but not identical to the Hi Vol TSP sampler, we use the term "TSP" in quotes.

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

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

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

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

P 3-107, lines 1-4 and Figure 3-25: I notice that Figure 3-25 has changed from the previous draft (in which K had the second highest correlation with Pb, after Zn, and am just curious why the figure changed? Also, in listing the elements with low to moderate correlations (p 3-107, lines 2-3), it seems somewhat arbitrary to exclude K which is barely lower than Br and is followed by a much larger step reduction in correlation with K^+. It can also be noted in the seasonal correlation plots in Figures 3-66 and 3-67 of the Chapter 3 Appendix, K exhibited the 2nd, 3rd, 4th and 2nd highest correlations with Pb (in Winter, Spring, Summer and Fall, respectively) – and so it seems odd that it would have only the 8th highest correlation on an annual basis.

These relatively high correlations of Pb with K and K^+ - as well as with EC & OC – suggest a possible influence from wood smoke. Fireworks are another occasional large source of K, OC and EC which have been identified as an occasional Pb source (more so in past years, but occasionally in recent measurements). See for example:

DePaolo, D.J. (2012) Using Pb and Sr Isotopes to Assess Asian Aerosol Impacts in Urban and Interior California, Final Report to the California ARB and the California EPA, Contract No. 07-318. http://www.arb.ca.gov/research/apr/past/07-318.pdf

Licudine, J.A., H. Yee, W. L. Chang and A. C. Whelen (2012) Hazardous Metals in Ambient Air Due to New Year Fireworks During 2004–2011 Celebrations in Pearl City, Hawaii, *Public Health Reports*, Volume 127, 440-450. http://hawaii.gov/health/laboratories/sld-forms/np-2012_PHR_127_4_Licudine.pdf

Liu, D-Y. D. Rutherford, M. Kinsey and K.A. Prather (1997) Real-Time Monitoring of Pyrotechnically Derived Aerosol Particles in the Troposphere, *Analytical Chemistry*, 69 (10), 1808-1814.

Perry, K. D. (1999): Effects of Outdoor Pyrotechnic Displays on the Regional Air Quality of Western Washington State, *J. Air & Waste Manage. Assn.*, 49:2, 146-155.

In addition to wood smoke and fireworks, soil is another well-known source of K in $PM_{2.5}$ measurements. The fact that K correlates better with Pb than other soil elements do suggests that other sources of K and Pb are important, but possibly the consistently high Pb:K correlations in all seasons indicates that soil, smoke and fireworks may all be occasional contributors.

Dr. Joel G. Pounds

Comments on Chapter 4 – Exposure, Toxicokinetics, and Biomarkers

General Comments

The third draft of this chapter is very well organized and well written. I am particularly pleased with the lucid description of topic strengths, weaknesses, and limitations found in the introductory and concluding paragraphs of many sections. The authors of Chapter 4 have done a very nice job of explaining and applying both mechanistic and empirical models to illustrate scenarios of changing exposure levels, duration of Pb exposure, and other Pb exposure scenarios to the interpretation of blood and bone Pb levels as biomarkers of Pb exposure.

I believe the principle purpose of computational models is to organize existing data and knowledge. The current mechanistic models are out-dated and fail to organize much information that we know to modulate the relationship between exposure and blood Pb. The Chapter 4 authors should anticipate the next ISA iteration and the inadequacy of the current mechanistic model to accurately simulate Pb exposure levels appropriate to 21st century Pb exposure. All existing mechanistic models are parameterized based on blood, tissue, or skeletal Pb levels associated with Pb exposure during periods of much higher levels of Pb exposure. Moreover, the mechanistic models are poorly calibrated to growth, exposure patterns, etc. of adolescents. The last ten or fifteen years has seen numerous studies that incorporate blood or urine biomarkers of bone formation with dual energy x-ray absorptiometry (DEXA) characterization of bone mineral density, especially during ages of skeletal growth or aging. These data provide a significant opportunity to improve the biological accuracy and relevance of mechanistic models for individuals and populations.

Page 58. The review and analysis of the potential contribution of ALAD alleles to blood Pb levels is fair and complete. However, this paragraph needs to draw a more explicit conclusion because ALAD polymorphisms are the most widely recognized genetic determinants of blood Pb. This conclusion may be little more than the contribution of ALAD alleles is inconclusive and the underlying causes of discrepancies among studies remains to be elucidated.

Specific Comments

Page 4-41 – Bioaccessibility is a key factor in defining bioavailability of Pb. The ISA authors might consider speculating (I'm not aware of any data) on the potential role of the human microbiome in modulating Pb bioassessibility. There are many reports in the environmental microbiology literature of microbes oxidizing or reducing minerals and using diverse minerals as electron sources. Characterization of the role of the gut microbiome accessibility including the age- or diet- or ethnic-

dependent differences in microbiome composition and function. Perhaps this issue should be identified as a data gap?

Page 4-60. Figure 4-7 Legend is a little confusing. Is Child B "elevated" Pb intake of 5.5 µg per day on top of the baseline 10 µg/d? Should be 55µg/d? Is there a reason this simulation used a 10 µg/d baseline when several other simulations in this chapter used 3.2 µg/d?

Page 4-70 Figures 4-9. Is "bone" total skeletal Pb? See also comment on Figure 4-7 above. Blood Pb peaks at ~ 8 µg/dL with a simulated intake of ~38 µg/d, while Child B (Figure 4-7) peaks at ~20 µg/dL with a smaller simulated Pb intake?

Figures 9-15. The plots which show time-dependent decreases in blood Pb are potentially misleading because they compress many decades, even a simulated lifetime blood Pb into a single plot. This time compression supports the conclusion that the decrease in blood Pb is "very rapid" especially when viewed in contrast to changes in blood Pb over a few months or a couple years human occupational studies. This potential confusion or interpretation could be minimized by (a) fitting the blood Pb curve (e.g. Figure 4-11 or 4-12) after reduction in intake to a three-term sum of exponential equation, (b) then calculating the size and half-time for each blood Pb kinetic pool, and (c) incorporating this information into the text. These calculated half-times for blood Pb will be consistent with half-time measurements in human populations and help mitigate these potential interpretation that model simulated decline in blood Pb is inappropriate rapid.

Page 4-83. Figure 4-15 legend. This legend might also include the Leggett model inputs for this simulation. That is, that the "switch" for RBC saturation is turned on, and the RBC concentration used for saturation. Question, How was RBC saturation handled in Figure 12- (high exposure in adults)?

Page 4-88. Figure 4-17. Can you clarify the meaning of "at baseline" for this figure.

Table 4-9. This table could be modified to note how the papers cited handled censored data. The related text includes a nice description of the issues related to the application of XRF measurements to population studies. But, how the authors dealt with frequent missing or negative data affects the readers' inference of the distribution of bone Pb that might be drawn from this table using the tabulated mean and SD. Not a problem with data presented as quintiles.

Add citations for Pb model papers from David Fleming and Anna Steen out for completeness?

<u>Editorial comments</u>

Consider renaming, "Exposure, Toxicokinetics, and Biomarkers" to "Exposure, Toxicokinetics, and Biomarkers of Exposure".

P4-63 Teeth. I recall a couple papers describing the heterogeneity of Pb in longitudinal sections of teeth using PIXE or SRIXE. Joel will look for those papers.

P4-65 Line 26. Contribute 40- → contribute as much as 40% (because relative contribution depends on all sources of Pb to blood, including soft tissue and skeletal Pb.

P4-68 Line 28. by resorption → by bone resorption

P4-65 Line 29. This sentence, Half-times for the release of Pb in bone are dependent on age and intensity of exposure" is a little confusing. Bone Pb half-times depend on bone turnover rates, bone resorption, age. Why intensity? Perhaps, when Pb exposure is extremely high and osteoclast function is inhibited the bone half-time may be increased. In general, the bone Pb half-time will be far more dependent on the rates of bone formation and resorption than the 'intensity' of Pb exposure.

Page 4-45.

Line 14 this… → this limited binding capacity
Line 16. This… → This process…

Page 4-55 Line 22 This… → This uncertainty…

Page 4-69 line 4. This… → This concept…

Page 4-84 Line 84. This… → This observation…

Page 4-84 Title Studies of Pb Biomarker Levels → Studies of Biomarkers of Pb Exposure

Page 4-139 Line 18 They… → These models…

Page 4-139 Line 21 They… → These models

Page 4-139 Line 23 confidence in… → confidence in individual…

Page 4-142 Line 12 diffuses to… → diffuse to kinetically…

Page 4-142 Title for 4.7.3 Pb Biomarkers → Biomarkers of Pb Exposure

Dr. Michael Rabinowitz

Comments on the Preamble

The general methodology and approach are clearly presented. The diagrams do help. Overall, in this draft, the Preamble does provide a more useful and effective introductory format.

Page lvii line 13 This raises the issue of increased confidence from replicating studies, not only from using different subjects, but also different patterns of exposure. I suspect this is generally true, particularly if the strength of un-measured confounders were some-how randomly distributed across studies. There always are un-measured confounder (micro-nutrient level such as iodine, zinc, iron, omega-3 fatty acids or educational opportunities, or exposure to co-pollutants, for example). If they are not measured in any study, using more studies will not remove their influence, particularly if the disadvantaged sub-groups are also the more lead exposed group. What is attributed to a lead-effect after adjustment for measured covariates, may still contain the effects of any un-measured covariates. We should not become over-confident. As stated in line 15, intervention studies avoid this issue.

Comments on Chapters 1 (Executive Summary)

Regarding the relative strength of the air pathway compared to lead ingestion from water, food and other sources, perhaps on page 1-3 or in the figure 1-1, is there any way to show how small the air input is relative to these other inputs? I realize the figure is conceptual, but it might be taken too literally. I just want to stress more how relatively small current air inputs.

page 1-2 two minor comments line 20, average lead in soil was about 20 ug/g. That would be accurate enough. line 26 maybe just 1 decade, 1970 and 1980

page 1-3 line 9 , to put air lead in perspective, why not offer a general summary statement something like: most of us get most of our lead not from air, but we get it from the ingestion of food, water, dust, and other consumer products.

page 1-5 line 8, add fever as a factor that moves lead from bone to blood, it is fairly common.

page 1-12 lines 6 and 12 do you want to say here that these (BP and IQ) were the driving basis of the earlier standards?

page 1-13 line 27 the source of the airborne Pb (combustion or smelting, for example) effects the chemical form and the particle size. maybe mention that... examined and the chemical and physical form of the airborne Pb, which varies according to its source (leaded fuel, smelter, or re-suspended soil). It is the form of the lead, not the source, per se, that matters.

page 1-14 line 3 "larger effect" may be misleading to some. The effect of lead is greater at higher doses. More lead equates to more badness. What you may want to say is that it is a larger rate of change, or larger bad effect from a small incremental increase in lead, at lower than at higher lead levels. again in line 10 .... larger incremental effect.....

Comments on Chapter 2 (Integrative Overview)

page 2-8 line 5 please say measurable increase in lead concentrations (or detectable lead pollution) , not just measurable lead.

2-28 line 4 can you give an example or two of the potential confounding in this context

Table 2-8 I liked it, although it is massive, and not without room for improvement

page 2-63 Figure 2-1 Regarding population shifts and the magnified effects seen in the tails. I have some problems with this abstraction. Does health-outcome mean Pb level here? Is this about IQ or BP? In theory it is correct if the shape of the population does not change as different Pb groups are considered, but in practice that may not be the case. For example, different remediation measured will impact the curve differently. Lowering air or water Pb levels will move population curves more uniformly than Pb-paint remediation, which would affect the higher lead groups more, changing the shape of the curve. I would prefer a figure based on real data.

page 2-71 Regarding the reversibility of low-level lead induced neurotoxicity, we know from longitudinal studies that concurrent blood lead levels are often better predictors than earlier blood samples, in young children. So, some effects of earlier exposure can become un-detectable, much as heme-formation disruptions disappear when blood lead levels are lowered. The problem with relying on the failure of chelation to produce reversibility (line 25-26) may be related to chelation's change in the bodily distribution of lead. Any good from getting rid of the whole-body lead stores may well be offset by putting more lead into the brain.

Generally, I wish there were a place to express overall uncertainly or confidences in our ability to predict blood lead levels, let alone lead induced effects, at these exposure levels of interest.

Overall, this draft is adequate, and the suggested changes minor.

Dr. Ian von Lindern

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

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

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

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

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

Please comment on the adequacy of these and other changes to the chapters and recommend any revisions to improve the discussion of key information. Please recommend any revisions that may further improve the clarity of discussion.

The revisions to Chapter 1 have improved the readability for a non-technical audience. The call-outs added to Chapters 1 and 2 are a distinct improvement and convenience in reviewing the document. The updates are reflective of the critical revisions in the individual chapters. The introduction, however, could perhaps reflect a bit more of the Preamble, and the criteria for determining "Policy Relevant Considerations" if the Executive Summary is intended to be a stand-alone section.

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

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

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

Comments on Chapter 4 – Exposure, Toxicokinetics, and Biomarkers

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

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

Both Chapters 3 and 4, however, remain biased toward the gasoline phase down in this regard and should note the significant emission and air lead reductions achieved in the vicinity of point sources. The major reductions in point source emissions were achieved through a combination of pollution control and relocation of the industry. The export of the mineral processing operations had profound

effects with respect to risk co-factors in the US and exposures abroad. Also important in the US were effects associated with decreases in other metal-related pollutant concentrations decreases in other media and levels of ecological risk, both locally and regionally. These effects were both attendant to and independent of the phase down and curtailments in industrial emissions.

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

Dr. Gail Wasserman

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

Preamble

This section reads well and is clearly presented.

Smaller edits:
P lvi L 32 perhaps should read: "methods is completely satisfactory"
P lxiv L 18 extra word? "the ISA evaluates results from across epidemiologic studies that characterize"

Chapter 2

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

P 63 The Weiss Hypothetical model. In a document that is so packed with actual real DATA, I don't really agree that this hypothetical model needs to be presented here and then again in Chapter 5.

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

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

(2) Other conclusions

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

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

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

P 75 L 16 typo: increased[d]

Comments on Chapter 5

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

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

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

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

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

P 221 L 27 schizophrenia is NOT a mood disorder

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

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

(2) Concerns about discussion of appropriate parallels across species for nervous system endpoints largely met.
(3) Merging discussion of epidemiologic and toxicologic evidence by outcome is a useful integration.

(4) Expanded discussions that provide additional details on strengths and limitations of the evidence is very helpful.

Two concerns about presentation of confounding remain:

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

Subcategories within cognitive and behavioral functioning are usually substantially intercorrelated, making examination of specificity complicated, and this should be noted somewhere. For example P 174 the text should point out that externalizing and internalizing (and indeed, most forms of mental health problems) are positively correlated. This is the case for cognitive outcomes as well, where intelligence is related to working memory, executive function, etc.

P 227 L 9 This is not a limitation of the prospective studies, but of studies, in general, that examine development

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

Other edits

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

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

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

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

Smaller edits

5-74 L 26. Should read “not necessarily STRONGLY correlated” Bayley and later IQ are generally positively (and significantly) correlated, but the strength is less than for relationships across later ages.
5-101 L 23 should be STROOP test
5-139, last para: the decision about which studies of inattention were most weighted seems sound
5-140. L 22: should read “evidence in both”
L. 26 The proper spelling is Somerville
5-141 L 3: “responses”
P 160 L26 typo
P 170 L 34 provide citation for “the authors….”
P 181 L 15 what are the three self-reported disorders?
P 197 L 10 did
P 264 L 10 The proper spelling is Somerville

Comments on Chapter 6

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

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

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

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

Smaller edits
P 1 L 27-28 not a sentence
P 5 L 13 confounders?
L 24-25 since this section considers both human and non-human studies, it would be clearer if for each point, the text could clarify which species is studied
P 8 provide units for Table
P 18 Section 6.2.6. It would be better if here the text mentioned the direction of associations
P 26 L 18 interaction(s)
P 26 L 13-14 species
The last paragraph on this page should reword its conclusions to be clearer.

Dr. Michael Weitzman

Comments on Chapter 6 - Potentially At-Risk Populations

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

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

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

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

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

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

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

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

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

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