Draft Preliminary Response to Review of ISA for Lead

Susan Korrick

7/17/2011:

Charge Question 2:

Is this a useful and effective summary presentation?
Generally, yes.

Is the framework for causal determination appropriately applied?
Causal determination framework seems reasonable.

Comment on approaches that may improve the communication of key ISA findings to varied audiences. Comment on the approach used (integrating scientific evidence across disciplines of health and ecology); e.g., is this a useful and effective integration of scientific evidence?

Application of mechanistic studies (from in vitro and animal experimentation) to ecologic outcomes optimizes the use of available data which is commendable. As a number of biological processes relevant to Pb toxicity are well conserved across human systems, ecologic systems, and experimental animal models, integrating across disciplines makes sense as it can address at least some data gaps and uncertainties that would be present if only one discipline was assessed in isolation.

Page-specific comments:
Page 2-11, lines 17-21: The logic behind an apparent differential relationship of blood vs. cumulative (bone?) Pb measures and neurocognitive outcomes in adults is unclear to me per the following text: "Studies of adults without occupational Pb exposure have not provided consistent evidence for associations between blood Pb and…neurological effects…[as] cognitive reserve may compensate for the effects of Pb…Compensatory mechanisms may become less effective with increasing age, explaining the consistent associations between measures of cumulative Pb exposure and neurocognitive deficits."

Page 2-13, Fig 2-1: what's the blood Pb at which decreased neurite outgrowth is seen in rodents?

Page 2-15, lines 3-4: "…concentration-response relationships of blood Pb with BP or mortality….information is inconclusive (Section 2.8.2)" Does this refer to uncertainty about the shape of the dose-response (e.g., linear vs. non-linear) or uncertainty about the general association? It seems to imply the latter but I believe intends the former. Needs clarification.

Page 2-16, lines 6-7: prospective studies are also key evidence against reverse causality as an explanation for observed Pb-renal function associations.

Page 2-26, table 2-3: Delayed puberty is a health outcome in children, not adults. Why does decreased hematocrit occur at 30 mcg/dL vs. decreased hemoglobin at 10 mcg/dL? If hemoglobin is decreased, so is hematocrit.

Page 2-42, table 2-5: Growth is not covered in human health review; is this because there have been no new studies following up earlier findings of Pb-related decrements in childhood stature? (e.g., Schwartz et al., Pediatrics 1986;77:281-8; Ballew et al., J Pediatr 1999;134:623-30)

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Charge Question 4b:
How well does Section 4.3 reflect the current state of knowledge of Pb biomarkers and their interpretation as it relates to exposure and dose?
The section reflects current knowledge. However, see page-specific comments for areas that could be expanded or clarified.

Is the focus on blood Pb and bone Pb appropriate, given that the epidemiologic literature largely assesses exposure through these two biomarkers?
This focus is appropriate.

Is there sufficient and accurate discussion of the relationship between blood Pb and bone Pb? Are relationships between blood Pb and Pb in soft tissues and urine Pb adequately described?
Section 4.3 relies heavily on the ICRP Pb biokinetics model to demonstrate relationships among biomarkers of Pb exposure under different exposure scenarios and at different ages. This is useful for demonstrating the theoretical kinetic differences between, and relationships among, bone and blood/soft tissue compartments. However, it is unclear how much this contributes to understanding and interpreting the epidemiologic literature. Also, the underlying model assumptions are not explained. E.g., the models do not demonstrate any increase in blood Pb after an exposure period despite a persistent increase in bone Pb. Based on observational epidemiology data, once the exposure period ends, I would expect the blood Pb to increase somewhat above the baseline as bone and blood reach a new equilibrium. Rather than these theoretical descriptors, more empiric information about the relationship among markers (e.g., estimated correlations, prediction models, half-lives, etc.) from epidemiologic studies of non-occupationally exposed populations, including both men and women would be useful. E.g., see: Nie et al., J Occup Environ Med 2009;51:848-57; Korrick et al., Am J Epidemiol 2002;156:335-43 ; Kim et al., Am J Epidemiol 1997;146:586-91.

Page-specific comments:
Page 4-35, lines 3-4: The patella may be preferred over the calcaneous as a trabecular bone site but the tibia has advantages over both in terms of likely measurement error and is the most commonly used bone Pb measurement site in the literature.

Page 4-35, lines 5-9: The mix of technologies described for measuring bone Pb seem to include both non-invasive in vivo measures like XRF but also ex-vivo chemical measures. Making this distinction explicit would be helpful since the use of non-invasive in vivo measures is applicable to most epidemiologic studies.

Page 4-35, lines 11-12: Although it is not necessary to repeat detailed information on precision, accuracy, and variability in bone Pb reviewed in the 2006 Pb AQCD, summarizing the data here would be useful especially as this technology has relatively

poor reproducibility especially in populations with lower bone Pb content or low bone density (For example, Hoppin et al., Environ Health Perspect 2000;108:239-42; Hoppin et al., Environ Health Perspect 1995;103:78-83).

Page 4-35, lines 20-23: An important consequence (not mentioned here) of expressing bone Pb measures relative to bone mineral content is that lower bone mineral density is associated with greater measurement uncertainty in bone Pb. This can have important implications for studies in older women for whom low bone mineral density is more common than in other populations including men and younger adults.

Page 4-50, lines 10-11: I think it's important to acknowledge that the NAS is an all male cohort; the relationship of bone Pb with blood Pb can be very different in women, especially across an age range that includes menopause.

Page 4-50, lines 32-33: If applicable, the increased calcium demands of lactation (relative to pregnancy) may explain the significantly greater %change in blood Pb observed post pregnancy vs. in the $2^{nd}/3^{rd}$ trimesters.

Page 4-54, lines 4-5: I don't follow the logic that faster Pb uptake kinetics in the brain during infancy/childhood is reflected as *slower* brain Pb accumulation in children?

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Charge Question 5d:

What are the views of the panel on the integration of epidemiologic and toxicologic evidence, in particular, on the balance of emphasis placed on each discipline? And on the accuracy with which the evidence is presented? Considering the Pb exposure concentrations and durations in toxicological studies and the potential for confounding in epidemiologic studies, please comment on the conclusions drawn about the coherence of the evidence and biological plausibility.

General comments:
Chapter 5 provides a comprehensive review of the human epidemiologic and toxicologic evidence of lead's health effects with the addition of studies published since the last AQCD (January 2006 forward). The Chapter is organized by health outcome with human and related toxicologic studies for a given outcome presented in tandem. The approach works well and, depending on the health outcome, there is more or less emphasis on epidemiologic vs. toxicologic evidence. Overall, a focus on human evidence is reasonable assuming human health effects are the primary interest. For some sections of the review, the encyclopedic nature of the research summaries fails to provide the reader with any perspective or prioritization of data vis-à-vis its quality. For example, some studies have more robust designs than others but this distinction is rarely explicit. Similarly, numbers of epidemiologic studies on a topic are often enumerated again, without commenting on relative value. Oftentimes there is an appearance of multiple studies on a topic when, in fact, studies represent slight variants on analyses in the same population such as NHANES or the Normative Aging Study (NAS). In these cases, most information on a particular topic may actually be coming from a relatively limited number of study populations samples. This is generally not discussed or acknowledged.

The juxtaposition of epidemiologic and toxicologic data on a given health outcome is useful but often the two data streams are not well integrated. For example, section 5.3 reviews Neurological Effects. The epidemiologic review focuses on enumerating effect estimates associating biomarkers of Pb exposure with specific neurologic outcomes ranging from childhood IQ and behavior to neurodegenerative disease in the elderly. But for studies relating to childhood cognition and behavior, e.g., the toxicologic evidence does not review complementary (where relevant) effect estimates in animal models. Instead, the emphasis is on the interaction between Pb exposure and stress in animal models. This provides a reasonable basis for discussion about mechanisms whereby Pb might effect neuropsychological functions but means there is minimal direct overlap with the epidemiologic review. Although Figure 5-29 provides some dose-response comparisons between animal and human data, toxicologic studies described in the text, tables, and other figures are often not directly analogous to the human studies described.

Admittedly, the lack of animal data that more directly parallels human data is, at least in part, a consequence of differences in study design (and necessary differences in outcomes) between the epidemiologic and toxicologic literature. Given these differences, providing additional synthesis (beyond Figure 5-29) of the two information streams would be helpful. E.g., a table listing neurobehavioral outcomes studied in humans and, where applicable, their animal analogue with an indication of the general pattern of Pb associations observed in the two disciplines could be useful.

Also, the integration between the two disciplines would benefit from summary statements discussing: (1) exposure dose (level and chronicity) comparability between animal and human studies; (2) the dose-response relationship in animal models (e.g., is there a threshold?). This is discussed in the "Neurological Effects" section as its own topic (p. 5-139 to 146) but not integrated into the description of specific studies; (3) animal exposure route (oral, iv, ip, etc.) and its implications for relevance of toxicological studies to human exposures; (4) choice of Pb form for animal dosing (Pb acetate, Pb chromate, Pb nitrate, or Pb chloride, e.g.). This is important in a number of ways to interpretation of findings (as happens in carcinogenicity studies where Pb chromate was used and findings attributable to Cr but not Pb could be discerned); and (5) specific outcomes that are roughly comparable between animal models and human studies. Otherwise, there is minimal discussion of issues of exposure comparability between human and animal studies and how this may, or may not, impact the integration of information from the two fields. Although the animal studies often have discrete dosing regimens that make it difficult to assess thresholds, where possible, noting threshold for effects, where relevant, would be helpful to integrating the two data sources and applying results for risk assessment. In addition to generally higher exposures (higher blood Pb levels) in animal models compared with contemporary U.S. population levels, there are also differences in the route of exposure which may be particularly important to consideration of population Pb exposure from air pollution which likely involves multiple pathways. Acknowledgement of this issue is lacking. Similarly, discussion of studies with exposure routes unrelated to human circumstances (studies in which Pb is injected directly into the hippocampus of an animal – e.g., page 5-76, Jett et al., 1997 or Pb is administered via intraperitoneal (IP) bolus, page 5-110, lines 4-5) should be done with caveats regarding generalizeability to humans. In mechanistic study reviews, acknowledgement of potential differences between in vitro and in vivo mechanisms would be useful. E.g., the Cardiovascular Effects section seems to assume that in vitro mechanistic studies are applicable to the in vivo setting but, where in vivo and in vitro study findings are in conflict, does not acknowledge that these differences in study type may being determining such differences (e.g., page 5-182, lines 12-20).

Additional issues for <u>Neurological Effects</u>: (1) emphasis on stress/Pb interactions in animal toxicologic literature raises issue of how stress of animal handling (for purposes of neurocognitive/neurobehavioral assessments) may be impacting demonstrated Pb associations in animal models. Although handling stress is mentioned, its role as a modifier of experimental systems is not. (2) how to interpret findings for areas with primarily animal data and ~no human data (e.g., vision effects?) where animal models generally have relatively high exposure (e.g., blood Pb 25 mcg/dL). (3) how to interpret

findings with supportive mechanistic toxicologic data but inconclusive or null human studies (e.g., Pb related neuronal plaque formation in prenatally exposed animals vs. AD in aging humans). (4) how to identify meaningful susceptibility factors (sex perhaps more consistent in animal models, genotypes inconsistent findings for ALAD & VDR, e.g.).

Issues for Cardiovascular Effects: the data for non-BP-related CVD outcomes is limited and largely based on either NHANES or NAS (men only). Some acknowledgement of the limited variation in study populations would be useful.

Page-specific comments:
Page 5-44, lines 2-5: in describing the relation of Pb with neuroimaging, references are summarized as showing "…associations of childhood blood Pb levels with decreased neuronal density and neuronal loss measured in adulthood, as assessed by magnetic resonance imaging techniques…". One of the referenced studies is a case-control assessment of 9-13-year-olds, another is a case report in a young boy and thus these do not address adult outcomes. Furthermore, two of the referenced studies used functional MRI to measure regional neuronal activity and lateralization of activity which is not the same as either neuronal density or loss but is an important phenomenon in understanding Pb effects on neuroanatomical functional correlates but was overlooked in the summary text.

Page 5-48-49, figure 5-2, table 5-3: What do Baghurst exposure measures mean (21.7 (25-50%))? In table 5-3, 25-50% is given as 17. 4 (vs. 50-75% is 21.7)? Are there no exposure measures available ('NR') for Dietrich 1993 and Ris 2004? It seems footnotes a and b are reversed?

Page 5-51, figure 5-3: the original manuscript being referenced is inconsistent on this point but it seems the Mn threshold should be in units of mcg/L so the cut point would be 1.4 mcg/dL rather than 14 mcg/dL; similarly, the blood Pb concentrations are log transformed (it would be helpful to say so in the figure).

Page 5-77, lines 1-2: the statement that 'Deficits in working memory are thought to underlie associations between blood Pb levels and ADHD in humans' is an unfamiliar concept to this reader. Unless there is a reference to support this statement, it should be deleted.

Page 5-76, lines 19-20: it is unclear what 'new study' is being referred to as the apparent reference is from 1997.

Throughout the "Neurologic Effects" section, table and figure footnotes have errors in them and some of the figure graphic symbols are incorrect (e.g. wrong color coding for exposure periods).

Also, it is common throughout this section for associations to be described without indicating the direction of effect, direction needs to be consistently indicated, e.g.:

Page 5-77, line 8: "…early life Pb…contributes to response inhibition…" – does this mean that it contributes to *impaired* response inhibition?

Page 5-101, lines 2-3: "They found positive associations, suggesting that blood Pb…may have an independent effect on behavior." Because higher scores on behavioral indices typically indicate worse behavior, making this explicit would be useful, e.g., by adding, "may have an independent *adverse* effect on behavior".

Page 5-105, lines 8-9: "…DRD4.7 also has been associated with sustained attention, response inhibition, and quicker response time…" Shouldn't this be "…DRD4.7 also has been associated with *better* sustained attention, *better* response inhibition, and quicker response time"?

Page 5-109: lines 33+: How does rodent performance on the rotarod (endurance, balance & coordination measure) relate to human neurobehavior?

Page 5-122, line 2: PD should be ET.

Page 5-147, lines 22-31: This is a recurring theme mentioned in the Neurological Effects section that for animals in utero/early postnatal period is the most sensitive for Pb-related neurologic effects but that stronger effect estimates are generally observed for concurrent blood Pb in epidemiologic studies of children. Can this observation be related to mechanistic issues and dose-response relationships?

Page 5-167, Figure 5-33: where's the "arrow line"?

Page 5-177, lines 10-11: discussion of heart rate variability (HRV) is important but out of place in this section otherwise entirely devoted to BP and hypertension. Should be placed in the following paragraph (page 5-178).

Page 5-191, lines 1-2: Weisskopf (2009) null blood Pb relationship with mortality "could have been affected if the majority of the hypothesized non-linear effect was contained…in the…(reference) blood Pb tertile" Is this referring to an hypothesized 'superlinear' dose-response between Pb and mortality? Needs to be clearer.

Page 5-197, line 9: 5th-9th percentile should be 5th -95th