Preliminary Comments from Dr. Joel Pounds on EPA's Integrated Science Assessment for Lead (Second External Review Draft – February 2012)

Comments on Chapter 4

Comments on accuracy of the interpretation of the science:

In general, the literature results presented in Section 4.1 (dietary lead exposure) is clearly written and faithfully presented. However, the text of individual paragraphs provide little interpretation, context, or summary. That is data are merely presented without evaluation, thus the reader must guess the importance and impact of the reviewed data to the ISA. For example, the point of paragraph beginning on P4-20-L12 is unclear without inclusion of a summary sentence that helps the reader understand why these two studies were reviewed. The paragraph identifies an "important problem" but does not convince the reader as to the importance of the problem or the insights offered by the reviewed studies. In contrast, most paragraphs of 4.2 are summarized with an evaluative sentence that places the reviewed data in context of the ISA.

Are uncertainties and limitations of relevant data, methodologies and approaches adequately discussed:

P4-30-L-23.

P4-33. Organic Lead Section. Suggest ISA include sentence or two that summarizes the importance, or lack thereof, of organic lead compounds to the lead body burden or blood lead.

P4-50, L3. Very nice paraphagrh describing uses and limitations of mechanistic models. P4-100 is a parallel nice paragraph describing the use and limitations of empirical models.

I have several comments related to blood Pb simulations P4-48; P4-8, 4-9, 4-11; and other figures and text. The ISA authors are commended for their efforts to provide lucid simulations that collectively illustrate relationships between blood Pb and selected tissue. These simulations are very helpful to provide an interpretative context for blood lead and bone lead measurements in human individuals and populations.

1. It would be helpful to include a little more information in the "Note" for each simulation. For example, how much lead was "administered"? When Pb administration to the model was changed, was input set to zero Pb or some baseline?

2. I'm unclear why "time-averaging" of urine Pb, blood Pb etc. was used in many of the Figures in this Section. I think of time-averaging as a method to decrease variability of experimental in addition to experimental error. However, the simulations have no variability in this sense. Over what time scale are

the data averaged? The time-averaged data could be more useful if compared and contrasted with experimental data, yet this comparison is not provided.

Specific recommendations to refine interpretation / representation of the science:

P4-30-L24-28. The text states "If properly measured (e.g. time-integrated blood Pb), under most conditions Pb bioavailability is equivalent (or nearly equivalent) to Pb absorption". This statement seems conceptually incorrect. Agreed, blood lead is the central compartment of biological reality and the models that describe these biological processes. However, blood lead also includes inputs from soft tissues and bone. Thus, time-integrated blood lead will over-estimate Pb bioavailability/absorption.

P4-34-35→ The role of "nutritional deficiencies" in lead metabolism is more complex than summarized here. The papers reviewed are interpreted correctly but the review is necessarily superficial or not well organized. Good summary however on P35-L20-24. It would be helpful to include a paragraph on the ISA that summarizes the complexity of nutritional interactions as these interactions may be physiological (deficiency programs homeostatic regulators to absorb and retain needed elements), biochemical (competition between Pb and other elements for transport and binding sites), macronutrients may alter Pb bioassessibility, genetic variants may modify all of the above.

P4-38,L36-37. "Factors that may affect in vitro predictions of RBA of interior dust Pb could include…" Suggest clarify sentence for potential ambiguity. The 'prediction' is for in vivo RBA. In vitro RBA is measured. Secondly, while the in vitro measurements will be affected by factors such as particle size and composition, etc. the 'predictions' should hold as the in vitro → in vivo predictions are particle dependent.

P4-46, L19-21. "Approximately 7-39% of the maternal Pb burden transferred to the fetus was derived from the maternal skeleton…" The relative contribution of maternal skeletal lead stores and contemporaneous environmental lead exposures to the fetal skeleton is not easily generalized as the maternal skeletal burden on the environmental exposure may vary significantly – independent of each other. Moreover, I believe the skeletal lead levels of these cynomologus monkeys were quite high diminishing the human relevance of these studies (Joel will check literature)

P4-39,L23 vs. L4-49,L12. Contradiction → Page 39 reports that 1% of body burden is in blood; Page 49 reports 5%.

P4-49,L15 vs. P4-54, L7. Contradiction → variously report either hemoglobin or ALAD as the major lead binding protein in blood.

P4-53,L22-30. Most proteomic and metabolomics data are highly left censored and statistical strategies have been developed to deal with this issue, with and without imputation. It may be appropriate to revisit this issue using newer methods.

P4-61,L9-18. Although Mitchell et al, and Hernberg et al. discussed blood Pb, and blood ALAD activity in the context of lead exposure I suggest the their use as a "biomarker of lead exposure" (L11) is vague and potentially mislead in the context of the ISA. This limitation is due to the effects of ALAD alleles on Pb binding and ALAD activity that confound relationship to lead exposure.

P4-65, Figure 4-9, 4-11. Remove "upper", "middle" , lower" labels . Suggest remove panel with time-averaged blood Pb

Comments related to clarification:

P4-21-L20. Define the model used my Miranda et al.

P4-30. Section 4.2. Consider moving (burying) the "dermal absorption" text at the end of 4.2.1 rather than leading with the section with this less important route.

P4-32-L10-13. I believe that "bioavailable' should be "bioaccessible"

P4-34, L14. Sentence "Eating breakfast…" is not clear. Is breakfast proportional to blood lead? Inversely proportional? Is lead found in breakfast foods or is breakfast a bioavailability/bioassessibility issue?

P4-36, L13. Relative bioavailability (RBA) is defined as fraction (L13) but presented as percentage.

P4-40, L28. 'toxicologically' → kinetically

P4-41, L3 clarify to 'limited capacity of Pb-binding proteins in RBCs…"

P4-44, L13 – clarify to "nonexchangeable" (except by bone resorption/bone remodeling) pool of Pb in bone…"

P4-45, L13. "A key factor affecting Pb uptake into bone the fraction of bone surface in trabecular and cortical bone adjacent to active bone marrow." This paragraph does not convinceably describe why this fraction is a "key factor".

P4-47, L32. "Estimates of urinary filtration of Pb from serum" → Estimates of urinary filtration of plasma

P4-62,L28. "…measure of Pb dose." → "…measure of long-term lead exposure.

P4-67,L25. "…the effects of bone Pb…" → "the correlation of bone Pb…"

P4-99, Figure 4-20. Note is confusing. What is the solid line?