

## Preliminary Comments from Dr. Joel G. Pounds

### Comments on Chapter 4 of EPA's Integrated Science Assessment for Lead (First External Review Draft – May 2011)

**Page 21. Section 4.2.1.** Absorption. This section defines the terms “absorption”, “bioavailability”, and “bioaccessibility”. The working definitions of absorption and bioavailability do not make the terms very distinct. Absorption refers to the fraction of Pb absorbed from respiratory or gastrointestinal tract while bioavailability refers to the amount of lead ingested or inhaled that enters systemic circulation. Is it the units (fraction vs. amount or the specificity of absorption into ‘systemic circulation’ that distinguishes the two terms? This ambiguity is furthered by the apparent interchangeable (or incorrect by these definitions) use of the absorption and bioavailability. I suspect that most of these inconsistent uses result from carry-over usage from the original paper. Some of these inconsistent uses are identified below in my “editorial suggestions” I recommend that these definitions be revisited and that the document be reviewed for use consistent with the definitions.

**Sections 4.3 and 4.7.3.** The definition, application, and limitations of biomarkers. Section 4.3 should be expanded (and carried into section 4.7.3). The section introduction would be well served by defining the distinction between, validation and application of, biomarkers for Pb exposure, body burden, internal dose, and risk. The ISA clearly recognizes as recognition that the Pb biomarkers are not equally valid when applied to different exposure scenarios. Experimental validation of biomarkers of exposure and are

It is easy to use and interpret Pb markers in a facile manner without communicating the ‘biomarker for what’ and limitations. The Chapter 4 text contains cogent, but scattered discussions (including figures) illustrating this point. Because blood and bone Pb levels are used for risk assessment and management, this discussion is important enough to bring up to section 4.0 or at least 4.3 and the summary.

Sections 4.2 and 4.3 (Kinetics and lead biomarkers) should recognize that adolescents are poorly defined by all existing PBPK and biokinetic models. Individuals undergo rapid changes in growth, food and water intake, bone growth and turnover, behavior, etc. during adolescence. There is a paucity of experiment measurements of Pb biomarkers during this time. And, the individual biological and kinetic parameters are largely interpolated rather than based on solid experimental and toxicological measurements. These deficiencies limit the validity of model predictions.

**Relationship between Air Pb and PbB** is not completely described. Literature review is good, but not complete and generalizations (conclusions) are not clearly made. Respiratory tract deposition and clearance are reported in the context of a specific study, but the ISA does not give a sense of the breath of the issue. Perhaps a table that summarizes relationships between PM size, Pb content, PbB, etc would be helpful.

**Page 34. 4.3. Biomarkers.** This section nicely introduces the topic but could be improved by slightly more extended rationale for selection of the Leggett model.

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4.2.2.3. Soft tissues. While the statement that soft tissue Pb “exists predominately bound to protein” may be true and may be logical, the state of Pb in tissues is more conjecture than experimentally derived conclusion. Pb is no doubt, in equilibrium with proteins and complexed with many other ligands including glutathione, amino acids and small organic acids.

#### **Editorial Suggestions.**

P 4-1, L6 It was reported in → The 2006

P 4-1, L7 2006) that → 2006) reported that

P4.1, L10 It was also observed that Pb → Pb

P4-3, L3 Could you list a couple susceptibility factors that influence exposure?

P4.3, L8-10. Sentence beginning “it is plausible” is not clear

P4-4, L4. Delete ‘shown to be’

P4.8, L1. Studies have demonstrated → studies demonstrated

P4-9, L4. This indicates → This result indicates

P4-9, L23. Delete ‘found to be’

P4-9, L24. Change ‘It was’ → Sill surface was...

P4-10, L20. in Pb → in water Pb”

P4-10, L24. To what does “This” refer?

P4-11, L15. this would → this substitution would

P4-11, L16. To what does “this” refer?

P4-11, L22. Delete “potentially”

P4-11, L35. It was found that blood Pb level was → Blood Pb levels were

P4-12, L11 & 13 Does “Pb(II)” in line 13 meant to convey information distinct from line 11?

P4-13, L10. “enriched the Pb content...” of what?

P4-13, L19. median Pb → median fertilizer Pb...

P4-13, L22. this remains → this source remains...

P4-13, L26. Delete ‘found to be’

P4-13, L28. was observed to have → had

P4-14, L6-7. were demonstrated to have high → had high

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## **Challenge to CASAC**

### **a. How well do the choice and emphasis of topics provide a useful context for the evaluation of human health effects of Pb in the ISA?**

- Is the current organization of the chapter clear and logical?
- Are there ways that information on exposure and toxicokinetics can be more clearly integrated throughout the chapter?
- Does the ISA adequately describe and balance air-related and non-air related pathways of lead exposure?

### **b. Biological markers of lead exposure and body burden**

- How well does this section reflect the state of knowledge of lead biomarkers and their interpretation as it relates to exposure and dose?
- Is the focus on blood and bone lead appropriate given the epidemiologic literature large assess exposure through these two biomarkers?
- Is there sufficient and accurate discussions of the relationship between blood and bone lead?
- Are relationships between blood Pb and Pb in soft tissues and urine adequately described?

### **c. Section 4.5.1. Discusses empirical models of air Pb – blood Pb relationships from new and old studies.**

- This was an important policy issue in the last Pb NAAQS review.
- Does this section accurately reflect what is known about air Pb – blood Pb relationships?
- Are there particular studies that should receive less or greater emphasis?