Preliminary Comments on the ISA from Dr. Michael Kosnett

The following are initial preliminary comments on the 3rd external draft Integrated Science Assessment for Lead (February 2012) prepared prior to CASAC Lead Review Panel meeting of February 5-6, 2013. They will be subject to expansion and revision as I continue my review and analysis of the document. These preliminary comments focus on the Preamble, Executive Summary (Chapter 1), and Integrative Summary (Chapter 2).

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 was 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

[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.

many aspects of behavior (such as attention disorders) are highly heritable traits.[2] This is acknowledged 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 notable, however, that mention of such limitations and inconsistencies does not appear in the integrated summary in Chapter 2.

The optimal solution to this issue will be a useful topic of discussion for the CASAC lead review panel. 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)."

[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. 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.

This would appear to be 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."

Certainly there is an extensive body of published literature and CERCLA remedial actions that have documented elevated levels of lead in soil and dust in the vicinity of a variety of sources that have emitted lead into the atmosphere. While the soil and dust concentrations may not correlate well with contemporary air levels (which are often lower than they were in the past), the contribution of historical air emissions to the ecosystem (including human receptors) in the vicinity of these areas has often been well established. Moreover, given the well-documented secular trend between leaded gasoline usage and human lead exposure, it appears discordant to suggest that there is only "limited evidence" for the impact of air lead concentration on nonhuman ecosystems. Accordingly, it is suggested that section 2.9.7 be expanded and revised. New language should identify key studies and links to other sections of the ISA that discuss major supporting studies.

Although the 3rd draft ISA has appropriately downgraded the determination 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.

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, supportive references are cited in Chapter 2, and in Chapter 5, it may be seen 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. A new section of the

3rd draft ISA, "5.5.2.4 Reverse Causality" represents a welcome addition, in that it highlights the hypothesis that reverse causality may account for the inverse relationship between BLL and renal function in populations with low-level lead exposure. The discussion in section 5.5.2.4, which overall expresses doubt regarding this hypothesis would benefit from being more objective, and will be addressed by additional reviewer comments to be submitted in the near future. However, it is my preliminary opinion that the uncertainties regarding reverse causality and the inconsistent observations in environmental and occupational studies, acknowledged in the narrative, merit downgrading the relationship to "suggestive of a causal relationship" as it concerns low level environmental lead exposure.

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.

Re 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.

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). This suggests that lead induced cognitive deficits associated with early childhood exposure may be reversible to a certain extent provided that the exposure is reduced.

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.

Additional preliminary 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 <u>for the past twenty years</u>" 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.