

Preliminary Comments on the ISA from 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.

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

<i>Undersocialized Aggressive Conduct Disorder</i>
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
<i>Socialized Aggressive Conduct Disorder</i>
“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
<i>Attention Deficit Hyperactivity Disorder</i>
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

b.

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 Preamble Table 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 “spermatogenesis” 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).

02-03-13 Preliminary Draft Comments from Clean Air Scientific Advisory Committee (CASAC) Lead Review Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

- 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 line 20: 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.

02-03-13 Preliminary Draft Comments from Clean Air Scientific Advisory Committee (CASAC) Lead Review Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

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?