

Preliminary Comments on the ISA from Dr. Susan Korrick

Comments on Chapter 5: Integrated Health Effects of Lead Exposure

1. *"...Causal determinations for health effects were drawn for more specific groups of related outcomes instead of major organ systems. Please comment on the appropriateness of new endpoint groupings..."*

The Nervous System Effects section, in particular, has been re-organized into more specific outcomes. E.g., Cognitive function in children has been divided into sections focused on specific tests and/or cognitive domains such as "full scale IQ", Bayley Scales of Infant Development, Learning and Memory, Executive Function and Academic Performance and Achievement. Similarly, the previous draft's "Behavioral Effects" section has been divided according to behavioral phenotypes -- Attention-related behavioral problems, Conduct problems, Internalizing problems, etc. In general, this a much better approach than in the previous draft and facilitates a more focused and critical discussion of the literature. This, in turn, makes the causal determinations clearer and better justified.

The only limitation of this approach is that some specific groups of related outcomes may not have been optimal. In addition, the choice of studies to include in each specific group was sometimes confusing. E.g., on p. 110 and Table 5-9, the summary of studies of academic achievement includes a study of the WRAML Verbal Learning test. This is an odd choice as it is a pure memory task (the child is asked to recite a simple word list from memory after hearing it read); this task is unrelated to vocabulary or other acquired verbal skill. These are not critical limitations but it is useful to keep in mind that there is still some misclassification among the health groupings.

2. *"...Further, please comment on the extent to which the text and new summary tables support the application of the causal framework in deriving causal determinations?"*

This draft provides clearer and better documented support for the application of the causal framework than was the case in the previous draft. Especially helpful in this regard are the new summary tables that parallel the text summaries of causal determination for each health measure.

3. *"...How consistently and appropriately was the causal framework applied across endpoint groups?"*

In general, this draft applied a more balanced approach to reviewing the literature. The approach included giving prospective studies priority over those with cross-sectional designs, explicitly acknowledging potential for residual confounding where applicable, and commenting on the likelihood (or not) of participation bias affecting results. In addition, the generalizeability of specific study populations to the U.S. general population was considered. In keeping with this approach, tables summarizing study findings provided more detail (study size, design, participation rates, confounders considered, modeling approach, etc.) than previously which is a valuable update. But there were a number of basic issues that were vague. E.g., summary tables indicated that nervous system studies were listed in order of strength of study design. Aside from prospective studies being listed before cross-sectional ones, the additional 'ordering' criteria were unclear and never explicitly explained. E.g., large cross sectional studies were often listed as lower priority than very small ones. On p. 5-123 the BMS (Baltimore Memory Study) did not adjust for potential confounding by smoking and etoh which seems

like a potentially important weakness in studies of adult cognitive function and Pb, yet BMS is 1st in Table 5-10. Was adjustment for smoking and etoh considered over-adjustment since these can be important correlates of exposure? Some discussion of this would have been useful. Lack of adjustment for parental caregiving quality seemed to play a disproportionately large role in prioritizing child nervous system outcomes although the role of this covariate in confounding for some nervous system outcomes was unclear. For behavioral outcomes, there was repeated emphasis on whether or not parental behavioral disorders were accounted for and whether parental psychopathology correlated with parenting quality. This was an issue of concern in the previous draft given that many behavioral disorders (e.g., ADHD) have strong familial components. Also, "representativeness" of study populations was emphasized as a limitation in a number of nervous system studies (e.g., studies with a high prevalence of maternal pregnancy alcohol consumption or drug use appeared to be downgraded because of this issue). Although generalizability is important in interpreting study findings, unless there is effect measure modification by the unique features of the study population that has not been accounted for, it should not impact the internal validity of a study's findings. Examples of studies down weighted because of this issue include IQ studies in cohorts in Detroit, MI (e.g., Chiodo et al., 2004; 2007) and null findings in the prospective Cleveland, OH cohort (e.g., Greene et al. 1992). In fact, the Cleveland cohort's null associations were described as having "weaker implications" because of its "lack of representativeness" (see p. 69-70,75, etc.) The reasoning here is presumably not based on the validity of the findings? It's a bit unclear.

4. *"Please comment on the adequacy of the discussion of the strengths and limitations of the evidence in the text and tables within Chapter 5 and in the evaluation of the evidence in the derivation of causal determinations..."*

As in charge #3 above. There were a few cases, where causal determination needed refinement. E.g., (p. 272), in nervous system effects, Pb's relationship with sensory findings are most consistent for hearing, not vision, but conclusions seem to encompass all sensory functions. Conclusions should be more clearly focused on hearing alone. Conversely, the causal analysis for renal effects was carefully updated to be more nuanced than in the previous draft, acknowledging uncertainties re. reverse causality and methodologic concerns in prospective epidemiologic studies in which change in serum creatinine was assessed after adjustment for baseline Cr. Thus, the conclusion of "likely causal" (rather than "causal") is an appropriate change.

5. *"Please also comment on the extent to which the nervous system outcomes have been grouped into appropriate constructs and the extent to which appropriate parallels were drawn between nervous system endpoints examined in humans and animals..."*

In general, the nervous system outcomes have been grouped into appropriate outcomes and constructs with reasonable parallels drawn between human and animal endpoints. Also, pairing the toxicology summaries with the specific relevant epidemiology rather than summarizing the two literature streams separately, was helpful for assessing coherence of findings across disciplines. A few specifics could be clearer. E.g., on p. 92, Pb-associated impaired animal FI (Fixed Interval) operant conditioning is used to support effects of Pb on attention-related problems. Is FI attention, or impulse control? Also, as per charge question #1, there are some nervous system groupings for the human literature that could be improved. Also, e.g., per Dr. Canfield's suggestion that Externalizing Behavior would be a better umbrella to describe a number of the behaviors currently subsumed under attention-related outcomes.

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Specific Comments:

Mechanisms:

p 30: not sure why heterogeneity of species, exposure duration, and metrics precluded assessing role of non-linearities in dose-response as a source of inconsistent findings....is the issue whether or not the D-R is a threshold?

p 37: How do gonadal cells have decreased plasma IGF1?

p 39: It is good that Pb-chromate studies are not included for genotoxic effects

Nervous system:

p 55: Description "attention-related behavioral problems" is good

p 57: This is a good overview of exposure across childhood (later periods as well as cumulative) likely being detrimental (FSIQ) in epidemiologic literature (not just focused on prenatal/perinatal periods per some animal literature). Also, acknowledged issue of correlation of exposures over time and persistence of effects is useful.

p 68: Emphasis on attenuated adjusted effect estimates not "losing precision" (ie still statistically significant) doesn't preclude residual confounding given evidence of reasonably strong confounding among known/measured covariates considered in models. Text seems to imply otherwise.

p. 75: Table 5-4: It would be good to indicate that Hu et al. is also same Mexican study population (different subset?) as Telez-Rojo and Claus Henn.

p. 77 & 80: Uncertainty re. exposure scenarios contribute to associations btw cord blood Pb and MDI since there is increased mobilization of Pb from bone to blood in pregnancy. What does this mean? How would a given cord blood Pb level mean something different because of bone Pb mobilization?

p. 84: Use of the WCST as a memory/learning task seems odd.

p. 90: Seems an odd definition of working memory ("info that changes frequently and is not stored permanently")

p.101: line 23: "Stoop" should be "Stroop"

p. 103, Table 5-8: Bellinger et al. 1994a (need to adjust signs for 95% CI; scores reversed so negative is worse but 95% CI are all positive values)

p. 104, Table 5-8: For 3 studies on this page, can't tell if test scores were 'adjusted' (as in 1st half of table on previous page) so negative effect estimate means worse performance. Otherwise, looks as if Pb is associated with better performance as, e.g., fewer WCST errors, shorter Stroop time?

p. 105: Can't tell why some studies mentioned briefly in text but results not summarized in any table or specifics (Nelson and Espy 2009, e.g.)

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p. 110: Table 5-9: WRAML Verbal Learning is not a test of academic performance or achievement. Other odd choices in this table which includes KABC at age 4 yrs (or PPVT at age 7 yrs), etc. Aren't those more measures of innate intelligence rather than explicit school achievement especially in a 4-year-old?

p. 110: Table 5-9: Fergusson – what does it mean to leave school with no qualifications?

p. 111: Table 5-9: Leviton for Reading/BTQ, what does RR estimate reflect?

p. 116: Leviton *did* or *did not* adjust for SES/parenting quality?

p. 118-119: In summary language, text sometimes reverts back to using “cognitive function” effects while also discussing specifics such as FSIQ, memory/learning, executive function where available studies and strength of associations may be more variable....Unfortunately, not fully making use of the outcome specificity that was addressed with new review organization

p. 120: Bone Pb does not contribute to childhood blood Pb to the same degree as in adults because bone is such a rapidly growing compartment in children. Still, it is true that concurrent blood Pb may reflect past exposures in children but it's perhaps a more subtle issue. Also, concurrent blood Pb may reflect past exposure in as much as exposures are childhood correlated over time.

p. 5-128: Table 5-10: looks as if Gao et al. (2008) saw beneficial Pb effects?

p. 5-131: Tendency to be overly broad -- enhanced Pb effect on MMSE in NAS with HFE variant "firm conclusions are not warranted" means what? Conclusions about mechanism behind effect modification by HFE cannot be made? Conclusions need to be cautious because of increased type 1 error with subgroup analyses?

p. 5-124, Table 5-10: Effect estimates expressed as SD scores not always specified...it would be helpful to label these consistently.

p. 5-140: I don't usually think of response inhibition/impulse control as part of attention but distinct behavioral skills

p. 5-148: 'Not clear how adjustment for parental psychopathology self-report (in studies of attention-related behaviors) relates to caregiving quality...' This was a recommended adjustment because of the familial component of some behaviors and the theoretical possibility that parental psychopathology could affect caregiving and thus not only be a predictor of outcome but a confounder of the Pb-behavior association. This same comment repeats throughout the sections on behavior-type outcomes (e.g., p-157). It's not clear what it means.

p. 4-149: Per last review request, it's good that Wasserman and Canfield null attention studies are now included (lower BPb, smaller n, younger age kids; prospective cohorts but looked at concurrent exposure)

p. 5-150: Problem with using case-ctrl design (ADHD cases) to study continuous measures is NOT related to the potential for biased participation by Pb exposure but to the non-representativeness of the outcome measures. Specifically, it is biased to do analyses assessing continuous outcomes related to the outcome upon which case-control selection was based. The way to account for this bias is to do analyses weighted by sampling probability. This study is listed relatively high among the cross-sectional ones despite this important limitation.

p. 5-158: There is the potential for reporting bias in parental report of ADHD diagnosis in NHANES. But text says, “however...examination of multiple risk factors and outcomes in NHANES reduces...likelihood of biased...reporting of ADHD by parents of children with higher Pb exposure”. This type of statement repeats throughout the chapter. Issue of parent-reported ADHD dx in NHANES has potential biases that are completely unrelated to the breadth of the study’s outcomes and risk factors. E.g., regional/SES/cultural differences in dx may correspond to regional/SES/cultural differences in exposure risk. Indeed the text goes on to say, “states with higher Pb poisoning have lower ADHD rates...and these data reduce potential for confounding of associations in NHANES...by regional differences in BPb levels and ADHD prevalences...” The lower ADHD rates in more exposed states could be related to diagnostic bias, not true differences in rates. In this case, there could be negative confounding by region so that failure to adjust for region could lead to an underestimation of Pb-ADHD associations.

p. 179: Frequent comment that cross-sectional studies make “temporal sequence btw Pb exposure and development of a health outcome uncertain” [approx quote]. It's even a more basic issue than that since the direction of the association is potentially unclear or unknown in a cross sectional study. An indeterminant temporal sequence can be a problem in a longitudinal study too depending on frequency, timing, and type (blood vs bone, e.g.) of exposure assessment relative to outcome assessment.

p. 183: “Epidemiologic evidence of Pb-assoc’d schizophrenia is inconclusive...” I would say it’s almost non-existent. One cited study used δ -ALA levels, not Pb measures, making interpretation difficult.

p.235: Schnaas et al. 2006 is not reported in Table 5-15 despite text referring to it there

p. 238: It's good that distinction btw inverted U-shaped dose-response and supralinear D-R is made clear as, with the latter, one still sees adverse effects with increasing exposure

pp. 254-55: Public health significance does a good job explaining the hypothetical nature of this analysis and defining the assumptions made in estimating changes in proportions of individuals in tails of the IQ distribution with Pb-associated shifts in mean IQ.

p. 256: In this public health analysis, one may even underestimate the adverse population effect given, e.g., at least some evidence of potential (Miranda et al. 2009 greater Pb-related decrements in children with poorer performance (see Miranda et al. 2009 with greater Pb-related decrements in EOG achievement test results for kids with lower EOG scores).

p. 264: Use of parental hx psychopathology not intended for caregiving quality alone (as text seems to imply) but as a confounder based on strong familial component to some behavioral disorders. Its role as a confounder would depend on its relation with Pb exposure risk which may not be completely clear....

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p. 264+: Challenge with evidence for attention-related behaviors is that there may be stronger effects at higher Pb levels than relevant currently, more likely seen in older kids (e.g., null Canfield and Wasserman studies in younger children (4-5 yrs)). Evidence for ADHD itself is weaker (case-control studies)

p. 273: Motor seems smaller body of literature so inconsistencies more noticeable; +/- agree with “likely causal association”

p. 278: Limited studies on adult psychopathology, +/- agree with “likely causal association”

p. 279: Evidence is suggestive for Pb and adult sensory function (limited past evidence now enhanced by just one NAS study and weak case-control study) – perhaps would consider it “inadequate to determine....”

p. 421+: It is noted that "treatment" (with antioxidants & chelators) sections have been removed from Renal Effects section which is appropriate.