

Preliminary Comments on the ISA from Dr. Michael Rabinowitz

Comments on the Preamble

The general methodology and approach are clearly presented. The diagrams do help. Overall, in this draft, the Preamble does provide a more useful and effective introductory format.

Page lvii line 13 This raises the issue of increased confidence from replicating studies, not only from using different subjects, but also different patterns of exposure. I suspect this is generally true, particularly if the strength of un-measured confounders were some-how randomly distributed across studies. There always are un-measured confounder (micro-nutrient level such as iodine, zinc, iron, omega-3 fatty acids or educational opportunities, or exposure to co-pollutants, for example). If they are not measured in any study, using more studies will not remove their influence, particularly if the disadvantaged sub-groups are also the more lead exposed group. What is attributed to a lead-effect after adjustment for measured covariates, may still contain the effects of any un-measured covariates. We should not become over-confident. As stated in line 15, intervention studies avoid this issue.

Comments on Chapters 1 (Executive Summary)

Regarding the relative strength of the air pathway compared to lead ingestion from water, food and other sources, perhaps on page 1-3 or in the figure 1-1, is there any way to show how small the air input is relative to these other inputs? I realize the figure is conceptual, but it might be taken too literally. I just want to stress more how relatively small current air inputs.

page 1-2 two minor comments line 20, average lead in soil was about 20 ug/g. That would be accurate enough. line 26 maybe just 1 decade, 1970 and 1980

page 1-3 line 9 , to put air lead in perspective, why not offer a general summary statement something like: most of us get most of our lead not from air, but we get it from the ingestion of food, water, dust, and other consumer products.

page 1-5 line 8, add fever as a factor that moves lead from bone to blood, it is fairly common.

page 1-12 lines 6 and 12 do you want to say here that these (BP and IQ) were the driving basis of the earlier standards?

page 1-13 line 27 the source of the airborne Pb (combustion or smelting, for example) effects the chemical form and the particle size. maybe mention that... examined and the chemical and physical form of the airborne Pb, which varies according to its source (leaded fuel, smelter, or re-suspended soil). It is the form of the lead, not the source, per se, that matters.

page 1-14 line 3 "larger effect" may be misleading to some. The effect of lead is greater at higher doses. More lead equates to more badness. What you may want to say is that it is a larger rate of change, or larger bad effect from a small incremental increase in lead, at lower than at higher lead levels. again in line 10 larger incremental effect.....

Comments on Chapter 2 (Integrative Overview)

page 2-8 line 5 please say measurable increase in lead concentrations (or detectable lead pollution) , not just measurable lead.

2-28 line 4 can you give an example or two of the potential confounding in this context

Table 2-8 I liked it, although it is massive, and not without room for improvement

page 2-63 Figure 2-1 Regarding population shifts and the magnified effects seen in the tails. I have some problems with this abstraction. Does health-outcome mean Pb level here? Is this about IQ or BP? In theory it is correct if the shape of the population does not change as different Pb groups are considered, but in practice that may not be the case. For example, different remediation measured will impact the curve differently. Lowering air or water Pb levels will move population curves more uniformly than Pb-paint remediation, which would affect the higher lead groups more, changing the shape of the curve. I would prefer a figure based on real data.

page 2-71 Regarding the reversibility of low-level lead induced neurotoxicity, we know from longitudinal studies that concurrent blood lead levels are often better predictors than earlier blood samples, in young children. So, some effects of earlier exposure can become un-detectable, much as heme-formation disruptions disappear when blood lead levels are lowered. The problem with relying on the failure of chelation to produce reversibility (line 25-26) may be related to chelation's change in the bodily distribution of lead. Any good from getting rid of the whole-body lead stores may well be offset by putting more lead into the brain.

Generally, I wish there were a place to express overall uncertainty or confidences in our ability to predict blood lead levels, let alone lead induced effects, at these exposure levels of interest.

Overall, this draft is adequate, and the suggested changes minor.