April 21, 2020

To: Hugh Barton, PhD, Chair AALM Review Panel

From: Michael Kosnett, MD, MPH, AALM Review Panel Member

Response to April 7, 2020 draft report "Review of the All Ages Lead Model External Review Draft 2.0" in advance of April 23, 2020 Review Panel Meeting.

I. Suggestions regarding revision of the Draft Transmittal Letter

I recommend that two parts of paragraph 5 of the draft transmittal letter be reconsidered. I suggest that the third sentence of the paragraph be revised to read:

"…This effort would include modifications of the existing model or its parameters, such as provision of occupational exposure to inhaled lead, adjustment for postmenopausal changes in bone lead kinetics, input of typical lead dust loading measurements as opposed to dust lead concentration, and consideration of pregnancy and lactation. Risk assessors would benefit from revisions of the model that facilitate determination of the amount of lead in various exposure media (air, soil, or water) that are associated with benchmark changes in blood lead (e.g. a 1 µg/dL increment). Offer model outputs that include not just central tendency estimates of the amount of lead in blood or bone but also lower and upper bound estimates (e.g. 95th percentile) will be useful for risk assessment."

It appears that the point of the last sentence of the fifth paragraph is that more review and real-world testing is needed before AALM outputs become the basis for risk assessment or risk management decisions that are currently based on other models, particularly IEUBK, that have enjoyed extensive use, validation, and stakeholder acceptance. I suggest we discuss this further and consider a more explicit revision of the sentence.

II. Suggestions regarding revision of the Draft Committee Report

Charge Question 2 recommendations Page 14, pdf page 19..

Insert as a Tier 1 recommendation:

• *Revise the model to allow for different user defined bioavailability (RBA) for multiple different ingested media encountered by a receptor at different times and locations (e.g. Pb in soil, Pb in dust, Pb in water). Currently a single RBA applies to all intake relative to that medium.*

Accordingly, delete as a Tier 2 recommendation the sentence:

Explain why with respect to relative bioavailability (RBA) for most media, (e.g. Pb in soil, Pb in dust, Pb in water) only a single RBA applies to all intake relative to that medium.

Charge Question 3a recommendations: Page 24, pdf page 24:

Change the following Tier 3 recommendations to Tier 2 recommendations:

• *Evaluate relationships between indoor dust loading and indoor dust Pb concentration for application in AALM.*

• Evaluate any available data to reconsider the recommendation to apply outdoor soil Pb concentration as a surrogate for indoor dust Pb in situations where no indoor Pb source is known to exist.

Charge Question 3b Recommendations (Inhalation)

The Committee's narrative provides a detailed discussion of how the AALM.FOR approach to modeling lead absorption from the respiratory tract may not be adequate for occupational exposures (including occupational exposure to waste site remediation workers that are of particular interest to EPA). Accordingly, I suggest revising the recommendation that currently appears on Page 32, pdf page 37, line 1, that reads, "•Clarify that MPPD deposition fraction and fraction of total lead are very different for different air sampling methods and size of particles and how this should be addressed in modeling." My suggested revision of the recommendation, which can remain Tier 2, would read:

" • The TSD should acknowledge that the current default modeling approach of the AALM.FOR for absorption of lead in the respiratory tract may be best suited to scenarios associated with exposure to low concentrations of soluble submicron lead particulate. Use of the model for scenarios with exposure to higher concentrations of larger, sometimes less soluble lead particles (e.g. at outdoor remediation sites or other occupational settings) is also desirable, and accordingly future development of the AALM should examine the utility of adapting the Multi-Path Particle Dosimetry Model (MPPD2 or subsequent iterations) to revise the respiratory tract model."

[Note: The narrative response to Charge Question 3b did not address the impact of air sampling methodology and as such the topic should not be referred in a bulleted recommendation]

A similar critique applies to the Tier 2 recommendation pertaining to RBA and the GI tract model. The Committee's discussion pertaining to relative bioavailability and the GI tract model is also extensive. In light of this, the current recommendations seem too understated, i.e.

"Tier 2 •Provide model users with guidance to address differences in lead bioavailability of different media from multiple sources.

Tier 3 • Add more discussion about active and passive absorption

• Gut absorption needs further discussion and potentially update the model (see Leggett et al. 2007 intro to new ICRP GI model)

• Add discussion on bioavailability of suspended particle versus water soluble lead"

I respectfully suggest these be replaced by:

"Tier 1 (the same recommended in response to charge Question 2):

• Revise the model to allow for different user defined bioavailability (RBA) for multiple different ingested media encountered by a receptor at different times and locations (e.g. Pb in soil, Pb in dust, Pb in water). Currently a single RBA applies to all intake relative to that medium.

Tier 2

• Future revisions of the AALM should address non-linear aspects of gastrointestinal lead absorption that account for active and passive absorption mechanisms, the impact of food in the gastrointestinal tract (i.e. fasting vs. non-fasting states),the absorption of particulate lead in

water compared to soluble lead in water, and lead concentration in the gut on lead absorption fraction."

Charge Question 3c Recommendations:
On page 36, pdf pager 41, I suggest we upgrade the following recommendation from Tier 3 to Tier 2:
"•Revise AALM to account for postmenopausal changes in bone turnover and age-sex interactions in bone lead and release of lead from bone."

Charge Question 3 continued Recommendations
A recommendation now states, page 36, pdf 41, line 43: "•Each of the two models underlying the AALM appear to be overly sensitive to *two* of their parameters. This dependence needs to be investigated." The narrative called attention to four (rather than two) parameters: C1 and C2 (pertaining to urinary clearance of lead), and TEVF and TORBC. TEVF is the deposition fraction for lead transfer from plasma to the extravascular fluid. As the TSD narrative notes (TSD page 101, pdf page 113,) diffusible plasma is the central distribution compartment for the AALM.LG model. Plasma is in rapid equilibrium with extravascular fluid, which is in contract with all tissues in the body. Accordingly, it is not surprising that TEVF has a major impact on blood lead. This is also the case with TORBC, which controls the transfer rate (deposition fraction) of lead from plasma into red blood cells. (At low whole blood lead concentrations, less than 1% of blood lead is in the plasma). The TSD acknowledges that TEVF is highly influential on blood lead in AALM.LG (TSD page 101, pdf page 112), as is BIND (an equivalent parameter in AALM.OF). The TSD refers to evidence to support a nonlinear, saturable uptake of lead from plasma into red blood cells. Figure 4-15 (TSD page 174, pdf page 185) indicates that the AALM.FOR performed well in modeling actual blood lead – plasma lead relationship from multiple studies. In order for the committee report to imply that the AALM.LG and AALM.OF are "overly sensitive" to parameters that govern diffusion of lead from plasma, it would seem important to provide a more detailed discussion of the scientific basis for this opinion. Otherwise, it may be reasonable to draw attention to the influence of these parameters in the narrative without describing the AALM.FOR as being "overly sensitive" to their contribution.

Narrative response to Charge Question 4.
Page 38 (pdf page 43). The paragraph beginning at line 28 states, "d. AALM appears to underestimate the ratio of trabecular bone Pb:cortical bone Pb." The paragraph further states, "Currently, the AALM ratio of trabecular to cortical bone lead (µg/g bone mineral basis) is much lower than observed in Nie et al.., Hernandez-Avila et al.. and Cake et al." A related statement regarding the AALM estimation of trabecular to cortical bone lead ratios appears on page 42 (pdf page 47, line 20). In order for these critiques to be included in the Committee's report, it would seem important to point out the basis for these observations (e.g. calling attention to a published figure or presenting a simulation of AALM output). I may have missed it, but the current TSD does not appear to compare AALM outputs to findings in these data-sets regarding trabecular and cortical bone lead.

Page 39 (pdf page 44), line 3: The narrative contains a paragraph that begins with the sentence: "Calibration of the model to historic empirical data may introduce a high bias in predicted blood lead concentrations for current day occupational exposure scenarios…." The paragraph suggests that the development of the O'Flaherty and Leggett models using some older occupational datasets to relate air lead to blood lead may cause the current version of the AALM to overestimate the slope of air lead: blood lead relationships in contemporary workplaces. The paragraph infers this might occur because lead-exposed workers in the past had more hand to mouth exposure to lead as a result of less stringent workplace hygiene, and therefore part of what was attributed to inhalation exposure was actually ingestion exposure. A problem with this comment is that no specific data are cited and discussed in support of the supposition that the current version of the AALM will overestimate blood lead associated with air lead exposure in occupational settings. It may be noted that the empiric data used in the Leggett and O'Flaherty lead models to "calibrate" air lead: blood lead relationships were not all drawn from occupational settings, but rather included human exposure studies (chamber studies) or studies of populations with lower level environmental lead exposure. For example, the Leggett+ model developed by OEHHA provided a reasonable fit to data obtained by Griffin et al (1975) that examined changes in blood lead over with time in 31 healthy adult male volunteers who were exposed to elevated levels of airborne lead concentration for 23 hours/day for about 16 weeks in an environmentally controlled exposure chamber. Accordingly, I respectfully suggest that this paragraph as currently written be deleted, along with the Tier 2 recommendation on page 39, (pdf page 44) line 35 that reads, "Discuss the potential uncertainties associated with model calibration and evaluation from historical data as compared to likely contemporary exposures."